Anticancer Plants

Deepa P.

Anticancer Plants

Deepa P.

Post Graduate Department of Botany
Korambayil Ahamed Haji Memorial Unity Women's College,
Manjeri, Narukara (PO), PIN: 676122, Malappuram (DT), Kerala, India.

Edited by:

Deepa P.

Assistant Professor (Ad-hoc)

Post Graduate Department of Botany

Korambayil Ahamed Haji Memorial Unity Women's College, Manjeri, Narukara (PO),

PIN: 676122, Malappuram (DT), Kerala, India.

Email: deepapsaj@gmail.com

First Edition: March 2023

ISBN: 978-93-5701-654-4

Published by:

Deepa P.

Assistant Professor (Ad-hoc)

Post Graduate Department of Botany

Korambayil Ahamed Haji Memorial Unity Women's College, Manjeri, Narukara (PO),

PIN: 676122, Malappuram (DT), Kerala, India.

Price: ₹750/-

Date of publication: March 2023

Design & layout: Aneesh C. S.

Printed at: Right Click, Manjeri, Malappuram (DT), Kerala, India.

Foreword

Cancer is one of the leading causes of death worldwide, and conventional therapies such as chemotherapy, radiation therapy, and surgery often have significant side effects. Medicinal plants, on the other hand, offer a promising alternative with fewer adverse effects. This book 'Anticancer Plants' has made a comprehensive exploration, to the scientific evidences behind the use of medicinal plants in cancer prevention and treatment. It covers a broad range of plants from various parts of the world that have been traditionally used to combat cancer. Each plant is presented with a detailed description of its properties, phytochemical constituents, and pharmacological actions. In addition to the plant based remedies, this book also discusses the use of herbal supplements, including their potential benefits and risks in cancer treatment. The book is intended for researchers, and by researchers, in the field of oncology and pharmacology.

In the present global scenario, where the world needs to work together on achieving the Sustainable Development Goals (SDGs), this compilation on anticancer plants helps to support SDG 1 - No Poverty, SDG 2 - Zero Hunger, as many of the plants with anticancer properties are found in low income countries, and the traditional knowledge of their use has been passed down through generations. By supporting research and development of these plants, economic opportunities for communities and promotion of food security through sustainable harvesting and cultivation, can be accomplished. Further it addresses SDG 3 - Good Health and Well being, as medicinal plants offer a promising alternative to conventional therapies, and research on their properties and mechanisms of action can contribute to the development of new and improved treatments for cancer, thereby improving global health outcomes. The knowledge shared can contribute to SDG 13- Climate Action and SDG 15 - Life on Land as the development of plant based therapies reduces the need for chemical based treatments, which can have harmful effects on the environment.

The book has the potential to inspire further research and innovation in the field of anticancer plant-based therapies, contributing to the advancement of cancer treatment. It is an important resource for those interested in exploring the potential of medicinal plants in the fight against cancer and has the potential to improve patient healing outcomes and quality of life, and a comprehensive guide to the various medicinal plants that possess anticancer properties, highlighting their traditional use, chemical constituents, pharmacological actions, and clinical applications. By supporting improvement of global health outcomes, we can create economic opportunities, promote sustainable practices, and contribute to a healthier planet.

This book, edited by Dr. Deepa P., with 17 chapters, from information on diverse groups of plants, is an elaborate attempt to provide a comprehensive and evidence based resource for researchers, clinicians and scientists, interested in exploring the therapeutic potential of medicinal plants in the global fight against cancers. I congratulate Dr. Deepa P., for this compilation, with a mine of information, which would soon serve as a reference point, for scientists and healers alike.

Prof. (Dr.) Minoo Divakaran, FLS
Professor (Botany)
Providence Women's College
Kozhikode, Kerala, India

Preface

Compounds which are characteristic to the plant kingdom are necessary for plant survival and "housekeeping" of humans. Production of naturally derived phytocompounds influences on the human welfare by providing major sources of molecules with nutritional and medicinal properties. For thousands of years, herbal medicines have been used by 80% of the world population to control the chronic or life-threatening diseases. As free from side effects, there is the need of conservation of locally available medicinal plants in the medicinal plant repository of our country. In many countries, cancer ranks the second most common cause of death. Hence, the prevention of this silent killer by natural remedies is more predominant to avoid the health problems regarding chemotherapy. The anticancer activities of many of the plants have identified and checked in different cancer cell lines in many research institutes. Pooling of these anticancer plants in a single document is more useful to the society in the present era for quick identification and analysis.

The introductory part of the book provides the details on different cancer types and mechanism, causes and preventory remedies of the cancer, followed by the detailed morphology and cancer preventive activities of species coming under algae, bryophytes, pteridophytes and angiosperms included in families such as Menispermaceae, Simaroubaceae, Fabaceae, Rubiaceae, Asteraceae, Apocynaceae, Acanthaceae, Lamiaceae, Amaranthaceae, Orchidaceae, Zingiberaceae and Musaceae. One of the genus, *Inula* L. incorporated in Asteraceae. At the end, the common plants used in Siddha System of Medicine are discussed followed by index to the scientific names. Photographs of seventeen important anticancer plants included in the book in which each plants placed at the beginning of every chapters. A total of 175 anticancer plant genera and their antiproliferative activities in different human cancer cell lines make the book as good source of medicinal information to the society and also to the students and researchers who are interested in this field.

Deepa P.

In memory of Korambayil Ahamed Haji Sahib

The founder, Korambayil Ahamed Haji Memorial Unity Women's College, and the visionary leader who could see beyond the current situation and imagine a better future which could inspired others to dream big and work hard to turn those dreams in to reality.

Contents

Cancer: A Silent Killer

Soumya K. K.

Department of Zoology, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: soumyasathyan94@gmail.com

Abstract: Cancer is the most prevalent life threatening disease worldwide. The burden of cancer in society is growing day by day. It is due to uncontrolled growth and spread of abnormal cells which can be cured if diagnosed in early stage of life. The disease is caused by many external factors and some internal factors. Different types of cancer are present based on the tissues and organs affected. Various screening tests and a number of treatments such as chemotherapy, gene therapy, radiation therapy, immunotherapy, surgery etc. are now available for the detection of cancer. Apart from these, the treatments with medicinal herbs also provide a feasible alternative against cancer.

Keywords: Cancer, oncogenes, carcinoma, colorectal cancer, histone deacetylases

Cancer is a major healthcare threat worldwide. Every year the incidence of cancer will continue to rise. In India about 11 lakh new cancer patients are diagnosed every year. There are more than two hundred different types of cancer that affects human beings. The symptoms shown by each type of cancer is different and their required treatment also differs. Cancer is not a single disease but a group of diseases characterized by uncontrolled growth and spread of abnormal cells. The causes of cancer are diverse and complex. External factors like tobacco use, chemicals, radiations and infectious organisms and internal factors such as inherited mutations, random mutations, hormones and immune conditions contribute to cancer. The current lifestyle including lack of physical activity, obesity, dietary factors and environmental pollutants increase the risk of cancer (Mathur et al., 2015). Cancer can be detected by the symptoms like pain, skin changes, unusual bleeding, fatigue, lump formation etc. There are mainly two types of cancers, namely benign and malignant. Malignant tumor has the ability to invade the parts of the body and has a property known as metastasis. Benign tumor is a mass of cells which cannot invade to the parts of the body and are not cancerous (Ferlay et al., 2008).

According to GLOBOCAN data, there were an estimated 18.1 million new cases of cancer and 9.6 million deaths from cancer worldwide in 2018 (Ferlay et al., 2012). The most frequently diagnosed cancers are breast, colorectal, prostate and lung cancer. In this, the highest percentages of cancer types present in men are prostate, lung, bronchus, colon, rectum and urinary bladder cancer. In women, the most commonly found cancers are breast,

lung, bronchus, colon, rectum, uterine corpus and thyroid (http://refhub.elsevier.com). In case of children, blood cancer and cancers related to the brain and lymph nodes are more common. Cancer incidence worldwide is higher in men than in women. The global burden of cancer is increasing day by day (Moscow et al., 2011).The lack of effective prevention and awareness leads to the development of cancer.

1. Diversity in cancer

More than 100 types of cancers are diagnosed till date. Cancers are named according to the tissues or organs affected. There are different types of cancer that begins in specific types of cells. Carcinoma, sarcoma, leukemia, lymphoma, multiple myeloma, melanoma, carcinomas and brain and spinal cord tumors are some among them.

Carcinoma: Carcinoma is the most common type of cancer formed by epithelial cells. Adenocarcinoma forms in the glandular tissue, which lines certain internal organs and makes and releases substances in the body such as mucus, digestive juices and other fluids. Cancers in breast, prostate and colon are adenocarcinomas. Cancer that begins in the lowest layer of epidermis is called basal cell carcinoma. Squamous cell carcinoma forms in squamous cells, which lines the organs such as stomach, intestine, lungs, bladder and kidneys. Some cancers of the bladder, ureters and kidneys are transitional cell carcinomas which form in transitional epithelium. Different types of cancer includes bladder cancer, breast cancer, cervical cancer, colorectal cancer, gynecologic cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, prostate cancer, skin cancer, thyroid cancer, uterine cancer, vaginal and vulvar cancers, lymphoma, mesothelioma and myeloma. ***Sarcoma:*** It is a type of cancer which forms in bones and soft tissues like cartilage, muscle, fat, fibrous tissue, blood vessels and lymph vessels. More than 70 types of sarcoma are found. The most common types of sarcoma are angiosarcoma, Kaposi's sarcoma, dermafibrosarcoma protuberans, epitheloid sarcoma etc.. ***Leukemia:*** It is the cancer of blood forming tissues including bone marrow. In leukemia patients, the bone marrow produces abnormal functionless white blood cells. There are four common type of leukemia like acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia and chronic myelogenous leukemia. ***Lymphoma:*** The cancer forms in lymphatic system and begins in T or B cells. The main subtypes of lymphoma include Hodgkin lymphoma and Non-Hodgkin lymphoma. ***Melanoma:*** It begins in cells that become melanocytes which produces melanin. This is most dangerous type of skin cancer. ***Multiple myeloma:*** In this condition, the plasma cells in bone marrow become cancerous and spreading to other parts. These abnormal plasma cells are called myeloma cells that can damage the kidneys, bones, immune system and red blood cell count. ***Brain and spinal cord tumors:*** Main reason of the cancer is the DNA changes inside the cell. Growth of abnormal cells in brain causes brain tumor and also cancer in the body can spread to the brain. A spinal cord tumor develops within spinal cord, also called intradural tumor. Intramedullary tumors and extramedullary tumors are the main types of intradural tumors (https://www.cdc.gov; https://www.cancer.org).

The most common cancers reported in 2020 are breast (2.26 million cases), lung (2.21 million cases), colon and rectum (1.93 million cases), prostate (1.41 million cases), skin (1.20 million cases) and stomach cancer (1.09 million cases) (https://www.who.int/news-room/fact-sheets/detail/cancer).

1.1. Breast cancer

The second most common cancer found in females is breast cancer. It is also found in men too. It accounts for about 22% of all female cancers and 15% of cancer related death among females (Edward et al., 2003; Stewart, 2004). The most breast lumps are benign not malignant. The spreading of breast cancer occurs when the cancer cells get in to the blood or lymph system. These cancer cells

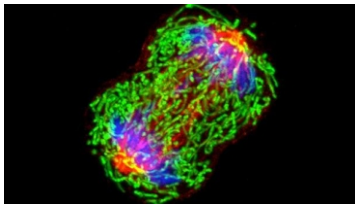

Fig.1. A dividing breast cancer cell (Credit: National Cancer Institute / Univ. of Pittsburgh Cancer Institute)

are carried to other parts of the body (https://www.cancer.org). Statistically each year breast cancer is about 30% of all new female cancer. It mainly affects middle aged and older women. The incidence of breast cancer is increasing rapidly in developing countries. Breast cancer is caused by changes in many different genes. Intraductal epithelial cells account for the majority of breast cancer (Russo et al., 2001). Weight gain and obesity increase are the risk of breast cancer. High penetrance of breast cancer is caused by the mutations in genes like BRCA1, BRCA2, p53, PTEN and ATM.

1.2. Lung cancer

Lung cancer is a common cause of cancer deaths worldwide. It is the most often diagnosed cancer with an incident rate of 22.5 per 100,000 persons-years worldwide in 2018. The chance of lung cancer is higher in males than females. Tobacco smoking, earlier lung diseases, exposure to carcinogens and air pollutants, and any family history of malignancy are the typical risk factors of lung cancer. Generally the survival of lung cancer patient is low.

1.3. Liver cancer

In liver cancer, the malignant cells form in the tissues of the liver. The main types of adult primary liver cancer include hepatocellular carcinoma and bile duct cancer. In this, hepatocellular carcinoma is high risky pathological types of liver cancer. Both adults and children are prone to primary liver cancer. Abdominal pain, weight loss, ascites and hypertension are common symptoms of liver cancer. It is most commonly found in males with liver disease caused by alcohol consumption, hepatitis or hemochromatosis. The best treatment choice for liver cancer is chemotherapy because of its capability to completely kill the cancerous cells.

1.4. Leukemia

The cancer focuses in blood forming cells. It may be acute or chronic. The risk factors of leukemia include genetic history, environmental factors and exposure to radiations. Fever, fatigue, weight loss, body pain and bleeding are some of the symptoms of leukemia (Amanda et al., 2014). Generally

the prevalence of leukemia is higher in males and white. Incidence will also increase with the age (NCI, 2014).

1.5. Colorectal cancer

The cancer begins in the last part of digestive tract colon or rectum. It is reported as the second leading cause of cancer death in US.

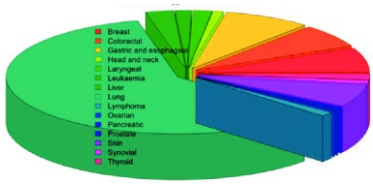

Fig.2. Different types of cancer that analyzed in humans

CRC is the third most diagnosed type of cancer worldwide. In the prevalence rate males rank third and females rank second (Sung et al., 2020, Duan et al., 2022). It is more related to environmental factors, diet and lifestyle. The cancer risk increases with age and considered as a multifactorial disease. Carcinogenic factors initiate the epithelial cells of colorectal mucosa to undergo hyperplasia and adenomas which will eventually transforms in to carcinomas (Bu et al., 2018).

1.6. Prostate cancer

Cancer origins in prostate gland, a part of male reproductive system. Prostate cancer causes blood in urine and semen, painful ejaculation and erectile dysfunction. Almost all prostate cancers are recognized to be adenocarcinomas. There are other types of cancers that can start in prostate including small cell carcinomas, neuroendocrine tumors, transitional cell carcinomas and sarcomas.

2. Cancer causing agents

Cancer is a disease caused when cells divide uncontrollably and spread in to surrounding tissues. It is a genetic disease caused by changes to genes that control the way our normal cells function. Normal cells only grow when they receive the appropriate signals, but cancer cells ignore those signals that tell cells to stop dividing. The changes in the DNA cause cancer and it transforms the genes involved in the normal cell growth to become oncogenes. A normal cell contains genes which help to control cell growth and cell division. Those genes are known as proto oncogenes. The mutated proto oncogene becomes an oncogene (https://www.cancer.org). Oncogenes cause uncontrolled cell growth. Tumor suppressor genes present in normal cells prevents cancer by stopping the cell growth. In cancer cells, the DNA changes inactivate the tumor suppressor genes that lead to uncontrollable cell growth. Three main types of genes are affected by the genetic changes of cancer namely proto oncogenes, tumor suppressor genes and DNA repair genes. The process by which cancer cells spread to other parts of the body is called metastasis. In metastatic cancer, cancer cells divide and move away from their originally formed position and spreads to other parts of body to form new tumors.

The risk of developing certain cancer depends on the changes in certain inherited genes. For example, if any mutations happen in tumor suppressor genes like BRCA genes (BRCA1 and BRCA2) it will lose its ability to suppress abnormal cell growth. Thus it will increase the risk of cancer (https://www.cancer.

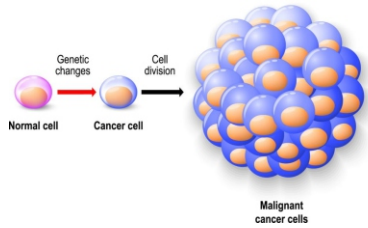

Fig.3. The formation of cancer cells from a normal cell

org). The causes of cancer are too many and some are preventable. Smoking, heavy alcohol consumption, obesity, poor nutrition, lack of exercise, unhealthy diet and lifestyle contribute to the cancer risk.

The causes of cancer include the person's genetic factors and also environmental factors. The external agents of cancer include physical carcinogens (UV and ionizing radiation), chemical carcinogens (tobacco smoke, alcohol, asbestos etc.) and biological carcinogens (infections from virus, bacteria or parasites) (https://www.who.int/news-room/fact-sheets/detail/cancer). Cancer mortality can be decreased by the early detection and effective treatment. Early diagnosis can avoid the delays in care given to the patient. Screening test like HPV test for cervical cancer and mammography screening for breast cancer helps in cancer diagnosis. The treatments include chemotherapy, radiation therapy, gene therapy and immunotherapy.

3. Mechanism behind cancer

Gene mutations have a pivot role in the abnormal cell proliferation. The generation of oncogenes and genetic disorders are caused by the DNA changes. This leads to deletion, point mutation, amplification and chromosomal translocation. An unusual protein is formed by the mutation of p53 gene. This will trigger the molecular process related to p53. It is reported that p53 abnormality leads to the formation of cancer cells (https://doi.org/10.1016/j.jcrpr.2017.07.001). Hypomethylation activates the ectopic expression of oncogenes. This is found in MASPN as a tumor suppressor gene in breast and prostate cancer. Another example for hypo methylation includes L1 from the LINE family which contributes for breast, lung and bladder cancer. Deacetylation by Histone deacetylases (HDACs) is involved in the formation of different tumors. The expression of HDAC can be controlled by microRNA. The suppression of HDAC-1 expression can be regulated by miR-449a during prostate cancer. Many cancers like colon cancer, lung and leukemia involve the deletion of HAT genes and trigger in histone acetylation

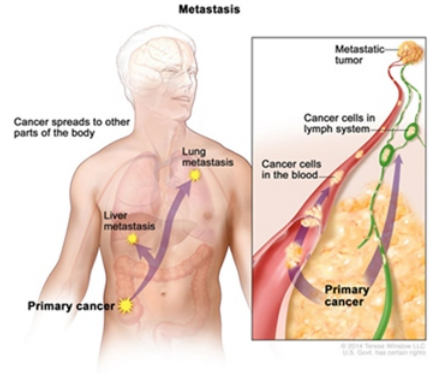

Fig.4. The process of spreading of cancer cells (metastasis) (Credit: © Terese Winslow)

(Noonan et al., 2021). The studies also show that the exposure to asbestos, pesticides, benzene and chlorinated hydrocarbons may increase the risk of pancreatic cancer (Antwi et al., 2015).

4. Cancer prevention by plant derived compounds

The increasing incidence of cancer worldwide calls for alternative treatment solution. Herbal medicines are one of such alternative against cancer. Anticancer plants which contain the plant sources of anticancer agents can be used for the treatment of cancer. This type of herbal medicine is safe, non toxic and easily available. Many anticancer medicinal plants, *Phaleria macrocarpa* (Mahkota dewa) and *Fagonia indica* (Dhamasa) have been used traditionally for the anticancer properties of their active ingredients. In cancer cells, apoptosis can be induced by the metabolites extracted from plant material. Gallic acid extracted from *P. macrocarpa* has role in inducing apoptosis in lung and colon cancer. Gallic acid which act as a natural antioxidant is also extracted from grapes, strawberries, bananas, green tea and vegetables. In addition to gallic acid, *Vinca* alkaloids, podophyllotoxin and camptothecin obtained from various plants are used for the treatment of cancer (Khan et al., 2019). The researchers have tested anticancer activity of many plants and proved that many of such plants and plant based compounds can be used effectively against one or more types of cancers. Thus more researches should be carried out to find out the mechanism of anticancer actions of many explored and unexplored plants.

5. Outlook

The risk of cancer can be reduced by maintaining a healthy lifestyle, avoiding the exposure to known carcinogens and taking medicines. As per the data of World Health Organization, between 30-50 % of all cancer cases are preventable. Tobacco smoke is one of the major causes of many severe cancer types. Avoiding the use of tobacco and alcohol will decrease the risk of cancer. Cancer causing infections like hepatitis and human papilloma virus can be prevent by taking vaccines. Many cancer screening tests and treatment methods are now available. Apart from that future research works may focus on alternative methods like use of anticancer plants along with other treatments in order to achieve effective cancer therapy.

References

1. Antwi, S.O., Eckert, E.C., and Sabaque, C.V. (2015). Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer. *Cancer Causes Control*. 26:1583-1591.
2. Bu, H., and Li, Y. (2018). People's Medical Publishing House. *Pathology*.
3. Davis, A. S., Viera, A. J., and Mead, M. D. (2014). Leukemia: an overview for primary care. *Am. Fam. Physician*. 89(9):731-8.
4. Duan, B., Zhao, Y., and Bai, J. (2022). Colorectal Cancer: An Overview. In: Morgado-Diaz JA, editor. Gastrointestinal Cancers (Internet). Brisbane (AU): *Exon Publications.*
5. Edwards, B.K., Howe, H.L., Ries, L.A., Thun, M.J., Rosenberg, H.M., Yancik, R., Wingo, P.A., Jemal, A., Ergul, E., Sazci, A., Utkan, Z., and Canturk, N.Z. (2003). Polymorphisms in the MTHFR gene are associated with breast cancer. *Tumour Biol*. 24:286-290.
6. Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C., and Parkin, D.M. (2008). Cancer Incidence and Mortality Worldwide. *IARC.GLOBOCAN*. 1:2.
7. Ferlay, J., Soerjomataram, I., and Dikshit, R. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. *Int. J. Cancer*. 136:59-86.

8. Khan, Ali, Khan, Nisar, Jan, Afridi, and Shinwari. (2019). Anticancer Plants: A Review of the active phytochemicals,applications in animal models, and regulatory aspects. *Biomolecules.* 10(1):47.

9. Mathur, G., Nain, S., and Sharma, P.K. (2015). Cancer: An Overview. *AJCR.* 8(1): 01-09.

10. Moscow, J.A., Cowan, K.H., Goldman, L., and Schafer, A.I. (2011). *Biol. canc.* 116:544-573.

11. Noonan, E., Robert, F.P., Shashwati, B., Deepa, P., and Long-Cheng L. (2009). miR-449a targets HDAC-1 and induces growth arrest in prostate cancer. *Oncogene.* 28:1714-1724.

12. Russo, J., and Russo, I.H. (2001). The pathway of neoplastic transformation of human breast epithelial cells. *Radiat. Res.* 155:151-154.

13. Stewart, S.L., King, J.B., Thompson, T.D., Friedman, C., and Wingo, P.A. (2004). Cancer mortality surveillance-United States, 1990-2000, MMWR. *SurveillSumm.* 53:1-108.

14. Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., and Jemal, A. (2020). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *Canc. J. Clin.* 71(3):209-49.

15. http://www.medicalnewstoday.com/info/cancer.oncology

16. https://www.cdc.gov/cancer/dcpc/research/articles

17. https://www.cancer.org/content/dam/cancer-org/research/cancer

18. http://refhub.elsevier.com/S2311-3006(17)30012-5/sref4

19. https://doi.org/10.1073/pnas.92.12.5258

20. https://www.cancer.gov/types/breast/research/articles

21. https://www.cancer.org/cancer/breast-cancer/about.html

22. https://doi.org/10.1016/B978-012088393-6/50077-4

23. http://seer.cancer.gov/statfacts/html/leuks.html

24. https://www.who.int/news-room/fact-sheets/detail/cancer

25. https://doi.org/10.1016/j.jcrpr.2017.07.001

Prolific Anticancer Bioactivity of Algal Species

Febina Thasneem K., *Deepa P.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
*Corresponding author: deepapsaj@gmail.com

Abstract: Algae play major role in global primary productivity and act as excellent sources of lipids, polysaccharides, vitamins and secondary metabolites. Both marine and fresh water micro or macro algae have antibacterial, anticancer, antioxidant, antifungal and antiviral properties due to the presence of secondary metabolites including terpenoids, flavonoids, sterols, sulfated polysaccharides, polyphenols, sargaquinoic acids, sargachromenol etc. The specific phytochemical compounds of multicellular and unicellular algae which are effective against tumour growth and metastasis in turn help to synthesize antiproliferative pharmaceutical drugs in future. Some of the algae that show anticancer activities are *Laurencia, Padina, Ulva, Caulerpa, Chaetomorpha, Gracilaria, Gelidium* etc..

Keywords: Microalgae, cancer therapy, antiproliferative, seaweeds, metastasis

Algae, the photosynthetic organisms, are growing in an aquatic environment and able to grow alone or concurrently with other organisms. The organism can be classified into red algae (Rhodophyta), green algae (Chlorophyta) and brown algae (Phaeophyta). According to the size, it can be classified into macroalgae or microalgae. Macroalgae, seaweeds, are large sized multicellular group that visible by the naked eye; while the microscopic single celled microalgae may be prokaryotic or eukaryotic.

Fresh water and marine microalgae are a great source of several useful byproducts like medicines, cosmetics and pharmaceuticals. Major constituents in this lower group are lipids, proteins, polysaccharides, vitamins and antioxidants. It enhances the defense mechanism by increasing natural killer cell activity, activation of the immune system and inhibition of the cancer cell growth. The natural potent antimalignant activity of algae derived compounds is very useful in drug industry now. One of the carotenoid, fucoxanthin, present in microalgae like diatom and brown seaweeds, shows potent anticancer properties via growth prevention of malignant cells and stimulation of cancer suppressor genes.

Macroalgae grown in fresh and marine water also contribute to the proapoptotic, antiangiogenic and antiinvasive activities due to their derived compounds. Among them, with less than 3% of world's marine macroalgal species are assessed for anticancer activities. Normally, the macroalgae contain different types of flavonoids which are assumed to have unique chemical structures and bioactivities. These flavonoids are not only good

antioxidants but also have the abilities to kill cancer cells by inducing apoptosis and autophagy.

Chemotherapy is usually the first line treatment to cure cancers such drugs are able to destroy or at least inhibit the growth of cancerous cells. These drugs are allied through noxiousness that ranges from a mild reaction to severe life threatening illness. Many side effects of chemotherapeutic drugs comprised baldness and loss of appetite. To avoid or reduce the side effects, new anticancer agents should be investigated from various natural resources. Plants have been an essential source of conventional and clinically valuable drugs for the treatment of numerous forms of tumours. Investigating plants for their effective anticancer agents with moderately low side effects seem to give an attractive strategy of anticancer drug development. A lot of natural antitumour amalgams or their byproducts are generally produced by algae are very helpful in treating different human cancers.

1. Medicinally significant compounds in algae

The aquatic life is producing various and distinctive chemical components essential for the human survival. Due to the harsh conditions such as high salinity and deficiency of nutrients, light and space, which make the marine environment competitive, organisms adapt to the environment by producing various chemicals and metabolites to help them survive under such conditions. The secondary metabolites produced by algae are the source of fatty acids, fibers, antioxidants, carotenoids, sterols, proteins, phytocolloids, lectins, oils, amino acids, unsaturated fatty acids and vitamins which could be commercially utilized.

Laurencia claviformis and *L. tasmanica* are the source of pacifenol, terpenoid isolated from seaweeds. *Stypopodium* is a rich source of polycyclic meroditerpenoids such as stypodiol, epistypodiol, stypotriol, taondiol, epitaondiol, 2β,3α-epitaondiol, flabellinol, flabellinone, stypotriolaldehyde, stypohydroperoxide, isoepitaondiol and 14-ketostypodiol. Epitaondiol is a terpenoid present in brown algae, *Stypopodium flabelliforme* which is the source of derivative of 14-keto-stypodiol diacetate (SDA). *Dunaliella salina* is one of the richest sources of natural β-carotene. The green algae, *Chlorella vulgaris* has produced canthaxanthin and astaxanthin in fairly high yields. *Ecklonia cava*, edible brown algae, has effective antioxidant activity due to the high phenolic content production (Alassali et al., 2016). Many biologically active compounds like terpenoids, flavonoids, sterols, sulfated polysaccharides, polyphenols, sargaquinoic acids, sargachromenol and pheophytine include in different *Sargassum* species. *Spirulina* presents with nutritional benefits including 50 to 70% protein, 5 to 10% lipids, 10 to 20% carbohydrates, 10% vitamins especially vitamin B12 and pro vitamin A (β-carotene) and minerals such as iron and one of the few sources of dietary γ-linolenic acid (GLA). The bioactive compounds in the crude extract of *Caulerpa* are 2-(-3-bromo-1-adamantyl) acetic acid methyl ester and chola-5, 22-dien-3-ol. The marine green alga, *Ulva lactuca*, contains 3-O-β-D glucopyranosyl-stigmasta-5,25-dien. *Padina* is the source of oleic, palmitoleic, 9-cis-hexadecenoic, linoleic, αlinolenic, arachidonic and elaidic acid. *Gracilaria bursa-pastoris* contains a high total phenolic content, vitamin E and vitamin C. It

also included *mycosporines* and *mycosporine* like amino acids. Majority of the algae are the rich source of primary and secondary metabolites in turn will become the major source of nutrient supplements in future. The secondary metabolites will ameliorate the opportunities in drug industry and pharmacology.

2. Anticancer algae

2. 1. *Caulerpa* J.V. Lamouroux

Caulerpa is a genus of seaweeds in the family Caulerpaceae among the green algae. They are the macroalgae found in a variety of shallow water marine habitats. These are unique in that they are made up of just one cell, but it has several nuclei, making it one of the largest single cells in the world. The *Caulerpa* genus has a variety of growth patterns. They have a stolon with downward growing rhizoids that anchor the plant to the substrate. Assimilators or erect fronds or leaves are supported by the stolons. The assimilator's structure can be ligulate as in the case of *C. prolifera*, or it can have a central axis known as a rachis. The rachis may possess lateral branchlets called ramuli, which can be arranged in a variety of ways and take diverse shapes including terete, turbinate, clavate, peltate, falcate and vesiculate. The distichous ramuli are uniformly spaced out in opposition to one another (*C. taxifolia*), irregular vesiculate ramuli with no distinct arrangement (*C. racemose*) or verticillate whorled ramuli (*C. cuppresoides*). *Caulerpa* species can be eaten in some cases. *C. lentillifera* and *C. racemosa*, both known as 'Sea grapes' are most frequently consumed in Southeast Asia, Oceania and East Asia. They are traditionally gathered from the wild and marketed there. The species have a distinctive 'sea' flavour and a crunchy texture and are used in salads. *Caulerpa* has other uses besides as a food source including bioremediation, fertilizer and health and wellness. Well researched *Caulerpa* antioxidant chemicals are utilized to treat a variety of illnesses and health concerns including cancer and cardiovascular conditions. It has been demonstrated that *Caulerpa* is efficient at filtering the water used to cultivate fish, mollusks and shrimp (*C. lentillifera*). Invasive plants of a different species, *C. taxifolia*, have been found in the Mediterranean Sea, Australia and Southern California where it has since been eradicated.

Anticancer activities: *C. taxifolia* is excellent marine green algae which produces enormous bioactive compounds with more biological activities. The species mediated Ag NPs has superior anticancer activity against A549 lung cancer cells. Moreover, the nanoparticles show increased bioactivities including antibacterial, antiviral, antimalarial, antioxidant, larvicidal and wound healing properties (Zhang et al., 2020). More interestingly, *C. lentillifera* is novel bioresource agents for anticancer drugs especially for hepatoma, leukemia and breast and colorectal cancers (Nurkolis et al., 2023). *C. microphysa* pepsin digested extracts inhibit myelomonocytic leukaemia (WEHI-3) and human promyelocytic leukaemia (HL-60) cell lines (Lin et al., 2012).

2. 2. *Laurencia* J.V. Lamouroux

Laurencia is a genus of Rhodophyta that can be found at temperate and tropical shorelines, in habitats from the littoral to the sublittoral and at depths up to 65 meters. Thalli of the macroalgae can branch and spread in both

bilateral and omnidirectional patterns. On stoloniferous holdfasts, its appendages might have rhizoidal or discoidal appearances. According to morphology, branches have a flat or cylindrical shape. Branchlets can have a shape that is blunt, truncate or claviform, and they might be slightly stiff. As a genus, *Laurencia* has demonstrated significant diversity, with species having distinctive characteristics that may be quickly identified within the *Laurencia* complex. Using rbcL, the molecular research has identified the genus *Laurenciella*, which has similar morphology to *Laurencia* but differs in several ways. During 2015, 1047 secondary metabolites from *Laurencia* and *Aplysia* species have been collected. *Laurencia*'s complex chemical make up is primarily related to both environmental and hereditary causes. Humans have used the genus for many years as food, medicines and fertilizers.

Anticancer activities: *Laurencia* terpenoid extract has negative effects on tumour growth and immune modulation; while positively influence on apoptosis of sarcoma 180 cell lines. The ethanolic extracts of *L. catarinensis* and *L. majuscula* show antimicrobial, antioxidant and anticancer activities. The ethanol or chloroform extract of *L. papillosa* exhibits the highest levels of cytotoxicity against Jurkat cancer cell line (acute lymphoblastic leukemia) compared with the ethanol or water extract (Tannoury et al., 2017). The methanol extract of *L. obusta* shows antiproliferative effects and inhibiting the human cancer cell lines, A549, HCT15 and MCF-7 (Dellai et al., 2013). *L. caspica* extract includes dodecane, undecane and dodecane, 2, 6, 11- trimethyl as predominant compounds, in turn inhibit proliferation of breast cancer T47D and HEK293 cells (Moshfegh et al., 2019). *L. okamurai* extract containing laurinterol induces apoptosis in melanoma cells (B16F1) (Kim et al., 2008).

2.3. *Sargassum* C. Agardh

Sargassum is a genus of brown algae in the class Phaeophyceae, a macroalgae in the order Fucales. The genus is well known for its planktonic species, which are widely distributed throughout the temperate and tropical oceans of the world. The species typically live in shallow water and on coral reefs. *Sargassum* appears to be an exception to the rule that most species in Phaeophyceae are primarily cold water organisms that benefit from nutrients upwelling. Due to the abundance of *Sargassum*, the Sargasso Sea in the Atlantic Ocean was given its name. The algae reach the lengths of several metres. They have a holdfast, stipe and frond and are often brown or dark green in colour. Oogonia and antheridia are found in conceptacles that are integrated into receptacles. Certain species fronds include berry like gas filled bladders that aid in flotation. Many are resistant to strong water currents because of their rough, sticky texture and sturdy flexible bodies.

Anticancer activities: The extract from *S. oligocystum* shows the most effective antitumour activity against Daudi and K562 cell lines (Zandi et al., 2010). Similarly, the deacetylated fucoidans from *S. feldmannii* inhibit colony formation of human colon cancer cells, DLD-1, HT-29 and HCT-116 (Usoltseva et al., 2019). Fucoidan isolated from *S. hornery* plays an inhibitory role in colony formation in human melanoma and colon cancer cells in turn act as effective antitumour agents

(Ermakova et al., 2011). The cytotoxicity effect of fucoidan from *S. polycystum* shows a higher percentage of inhibition against the MCF-7 cell line (Palanisamy et al., 2017). *S. mcclurei* includes SmF1, SmF2 and SmF3 fucoidans which are sulfated heteropolysaccharides that contain fucose, galactose, mannose, xylose and glucose and act as anticancer agents. The isolated fucoidan SdF from *S. duplicatum* also exhibit anticarcinogenic activity in colon cancer cells (Usoltseva et al., 2017). However, fucoidan from *S. cinereum* expresses the anticancer activity against Caco-2 cell line. Moreover, the silver nanoparticles from *S. incisifolium* display cytotoxic activity against cancerous cell lines, HT-29 and MCF-7.

2.4. *Chaetomorpha* Kutzing

Caetomorpha is a macroalgae belongs to the genus of green algae in Cladophoraceae family. Common name of this genus is 'Sea emarald'. The genus is composed of microscopic filaments of cylindric cells. It is distinguished by its unbranched filaments which give it a characteristic appearance. Thallus is bright to dark green, filamentous, rigid and gregarious. Filaments are unbranched, rough, twisted, loosely knotted with 10-40 cm long. Cells are cylinder shaped in the lower half and with mild constrictions at joints. Basal cell has a lobed attachment. It grows epiphytically on big algae in the middle intertidal to subtidal zones on rocky, sandy-muddy bottoms with stones and shells, and producing floating and free lying interwoven masses in calm shallow pools.

Anticancer activities: The silver nanoparticles from *C. linum* show anticancer effectiveness against colorectal carcinoma cells (HCT-116) by an increase in the expression of apoptotic caspase 3, caspase 9, BH3 and Bax, along with a decrease in the antiapoptotic protein like Bcl-2 and Bcl-xl (Acharya et al., 2021). *C. ligustica* exhibits antiproliferative effect against colon cancer cell lines, HT29 and HCT116. The biosynthesized AgNPs from *C. ligustica* extract also shows anticancer potential. Many of the bioactive compounds identified from *C. brachygona* are well known for significant anticancer activities against cervical cancer cells (Bcl-2) by the enhanced expression of Beclin 1 and LC3BII (Majumder et al., 2020). Docking studies in *C. antennina* confirms the occurrence of carpesterol dehydrate and triazines as an anticancer component; hence it can serve as a promising antioxidant and anticancer agent (Dubey et al., 2022).

2.5. *Turbinaria* J.V. Lamouroux

Turbinaria is a macroalgae belongs to brown algae (Phaeophyceae) found in tropical marine waters. It is generally seen in rocky substrate. The genus has an upright thallus with blade bearing radially branching axes having rough texture. The blades might be stipitate, turbinate, crowned or obpyramidal, among other shapes. It's shape is similar to a long pinecone. A holdfast made up of widely spaced branches sprouting from the major axis holds the thallus erect. Receptacles, the mature thalli's reproductive organs, protrude from the tips of the stalks on the blades. *Turbinaria* is used for its alginate extracts which is used in food and drink, cosmetics, and pharmaceutical goods as thickening, gelling and stabilizing agents. In Indonesia, the young thalli of *T. ornata* are eaten fresh, salted or with curry sauce. Due to their ability to enhance growth and serve as nutritional supplements, brown

algae are frequently utilized in animal feed. Prawn feeds with supplements of *T. ornata* boost growth, survival and digestion. In many Asian nations, *Turbinaria* is also applying as a pesticide and fertilizer.

Anticancer activities: The fucoidan isolated from *T. conoides* shows the anticancer activity. The extracted fucoidan contains 53 ± 0.69% of fucose and 38 ± 0.42% of sulphate in turn causes antiproliferative effect on A549 cell line (Marudhupandi et al., 2015). The ZnO nanoparticles from the hydroethanolic extract of *T. conoides* are effective against a murine model of Dalton's lymphoma ascites. Treatment with ZnO-NPs and hydroethanolic extract decrease the tumour volume, in turn increasing the lifespan of DLA-bearing mice. The anticancer activity of polysaccharides and modified derivatives of fucoidan ToF2 in *T. ornata* against several cancer cell lines are prominent in pharmacology. Usually, the fucoidan ToF2 and its derivative obtained by enzymatic hydrolysis inhibit colony formation of human colorectal, breast adenocarcinoma and malignant melanoma cell lines (Ermakova et al., 2016). Hexadecanoic acid (HA) of *T. ornata* also shows inhibitory effect on HT-29 human colon cancer cells. The α-amylase inhibitory activity of native fucoidan from *T. ornata* is the basic of NIDDM therapy. The synthesized AuNPs using hydromethanolic extract of *T. decurrens* show anticancer effect and cytotoxicity against human cancer cell lines.

2.6. *Padina* Adanson

Padina is a macroalgae belongs to the brown algae in the family Dictyotaceae. The genus is seen in tropical regions, although they are seen in cooler temperate waters from South America to South East Asia. They have a characteristic shape resembling a peacock tail structure and are attached to hard substrate or growing as epiphytes on larger seaweeds. With a brownish off-white colouring, the thalli have a flabellate look. The thallus is made up of cells that are fan shaped, 2-8 layers thick and have hairs covering the edges. It has a stipe attached to its rhizoidal holdfast, and the blades of the stipe prominently resemble several layers of cells thick. The thalli appear to have apparent zonations that produce coextensive rows of rigid segments of hair. The number of cell layers, the placement of sporangial sori in relation to hair bands and the presence or absence of hair bands on the lower thallus surface is used to distinguish between different species of *Padina*. The group is ecologically significant macroalgae which function as excellent bioindicators of aquatic pollution and remediation in marine ecosystems.

Anticancer activities: The sulfated and acetylated fucoidan fraction of *P. boryana* contains fucose, galactose, mannose, glucose and uronic acid. The native and modified fucoidan fractions show anticancer effect against the colorectal carcinoma cells, DLD-1 and HCT-116 (Usoltseva et al., 2018). Pd-NPs induce antiproliferation of breast cancer MCF-7 cells and enhance mRNA expression of apoptotic marker genes in the order of p53 > bax > caspase 3 > caspase 9 at 125 µg/mL. Hence, the PB extract capped Pd-NPs can be used for successful clinical management of MDR pathogens and breast cancer cells. The polysaccharide, fucoidan, isolated from *P. tetrastromatica* acts as capping and reducing agent which exhibits antiproliferative activity on HepG2 and A549 cell lines. The methanolic

extract of *P. pavonica* shows anticancer activity against lung carcinoma. Extract includes phenols, terpenes, amino acids, alkaloids, flavones, alcohols and fatty acids, induces antibiofilm, antibacterial, antioxidant and anticancer activities (Makhlof et al., 2023). The methanol extract of *P. pavonica* possesses cytotoxic activity against human cervix (HeLa) and breast cancer (MDA-MB-453) cell lines; while the extracts did not exert any significant cytotoxicity toward normal human fetal lung fibroblast cells (MRC-5). Often, the extract reduces the number of cells with distorted shapes and condensed cytoplasm. Similarly, fucoidan from *P. distromatica* shows inhibitory effect against A-431, A-549, HL-60, HT-29 and MCF-7 cell lines (Stanojkovic et al., 2013).

2.7. *Gracilaria* Greville

Gracilaria is a macroalgae belong to Rhodophyta. It is notable for its economic importance as an agarophyte and food for humans and various species of Jellyfish. They are found in warm waters throughout the world and occur seasonally in temperate waters. It has been traditionally cultivated as a source of agar. A little discoid holdfast gives rise to an erect thallus. The thalli typically have lateral, alternating or subdichotomous branches which are cylindrical, depressed or blade shaped. Occasionally a single plant will have a variety of branches. Many species have varied branch apex and base styles. The thalli of some species like *G. eucheumaides*, grow horizontally along the substrate and develop secondary holdfasts from the margin of branches.

Anticancer activities: *Gracillaria* extracts with different solvents include bioactive components as anticancer agents and antiplatelet aggregations. The n-hexane, ethyl acetate, chloroform and ethanol extracts of *G. verrucosa* act as anticolorectal cancer agent that inhibits the proliferation of HCT-116 cells (Kurniasari et al., 2018). *G. corticata* normally shows cytotoxicity against HeLa, K-562 and MDA-MB cell lines. Butanolic extract of *G. corticata* shows greater anticancer activity than hexane and methanolic extracts. The species exhibit anticancer activity against different cancer cell lines including human promyelocytic leukemia (HL-60), a human lung carcinoma (A549) and a mouse melanoma (B16F10). The alcoholic extract shows antiproliferative activity against five important human cancer cell lines (MCF-7, MDA-MB-231, HeLa, HepG2 and HT-29) proliferation, apoptosis and cell cycle arrest. The methanol extract of *G. edulis* exhibits antiproliferative and apoptotic activities against human rhabdomyosarcoma (RD) and breast adenocarcinoma (MCF-7) cells by activating the caspase 3/7 pathway (Gunathilaka et al., 2020).

2.8. *Gelidium* J.V. Lamouroux

Gelidium is a genus of Rhodophyta in the family Gelidiaceae. It is a macroalgae found in tropical to temperate regions but lacking in polar region. In the ocean they are seen in intertidal to subtidal zone. Thalli branching are irregular and producing tertaspores. Irregular branching occurs in rows on either side of the main stem. Thalli are cartilaginous, blackish-red color when slightly dry and forming turf. Many of the algae in this genus are harvested for agar.

Anticancer activities: Matrix metalloproteinase-9 (MMP-9) from *G. crinale* is a proteolytic metalloenzyme that degrades the central part of the extracellular matrix (ECM)

and promotes tumour metastasis. Sulfated polysaccharide from *G. crinale* influences on tumour metastasis and MMP-9 expression of human fibrosarcoma (HT1080) cells in turn influence excellent activity in inhibition on migration and invasion (Zheng et al., 2022). The compounds of *G. latifolium* inhibit the growth of human cancer cells by causing cytotoxicity in HeLa and Caco2 in turn cause apoptosis and boost the immune system (Prasedya et al., 2018).

2.9. *Ulva* Linnaeus

Ulva is an edible macroalgae belongs to Chlorophyta and the family Ulvaceae which are widely distributed along the coasts of the world's oceans. They are commonly called as 'Sea lettuce'. It has light to dark green in colour and thallus attached by disc holdfast. They have a leaf like flattened structure and eaten by different sea animals like manatees and sea hares. Many species of *Ulva* are food source for humans in China, Japan and Ireland. Humans use sea lettuce raw in salads or use to prepare soups. It is high in protiens, dietary fibres, vitamins and minerals like iron. *Ulva* also causes a major public health scare as it decomposed. The rotting leaves of this produce a toxic gas hydrogen sulphide.

Anticancer activities: *U. rigida* exhibits the most potent antiproliferative effect on EAC cell line in a dose dependent manner. Treatment with methanol or chloroform extract of *U. rigida* results in significant reductions in the level of lipid peroxidation (salem & Ibrahim, 2011). Sulfated polysaccharides isolated from *U. fasciata* show in vitro antioxidant and antitumour activities. The concentrated extract of *U. lactuca* exhibits anticancer activity against breast MCF-7 and colorectal HCT-116 cells with IC_{50} ranging from 21 µg/mL to 99 µg/mL due to the presence of metabolites including steroids, glycosides, flavonoids and tannins. Biogenic silver nanoparticles (U-AgNPs) using marine green macroalga, *U. lactuca* extract exhibits the mechanism behind its anticancer activity against the human colon cancer (HCT-116). The cytotoxicity reveals the dose dependent cell death in colon cancer cells with no loss of viability in normal human colon epithelial cells. AgNPs treated cancer cells show the rise in proapoptotic markers (P53, Bax, and P21) and decline in antiapoptotic markers (Bcl-2), thus confirming the p53 dependent apoptosis mediated cell death in HCT-116 (Acharya et al., 2022).

2.10. *Chara* Linnaeus

Chara is a macroalgae belongs to Chlorophyta in the family Characeae. Because of their stem like and leaf like structures, it resembles to land plants. They are found in fresh water where they grow submerged or attached to the muddy bottom. The genus prefers less oxygenated and hard water and not found in waters where mosquito larvae present. They are also known as 'Stoneworts' because of the covering with calcium carbonates. Nitrogen fixing cyanobacteria found growing as epiphytes on surface of *Chara*. The plant is a gametophyte which consists of the main axis that differentiated into nodes and internodes. The branches are dimorphic, long branch of unlimited growth and short branches of limited growth. The rhizoids are multicellular with oblique septa and stipuloides form needle shaped structures at the base of secondary laterals.

Anticancer activities: About 89 chemical

constituents identified in ethanol extract of *C. baltica*. The extract shows anticancer activity against cancer cell lines MCF-7, DLD-1, HeLa, FADU, A549 and SKOV3 (Tatipamula et al., 2019). The cytotoxicity of the aqueous extract and crude alcohol extract of *C. elegans* clearly visible on the cancer cells line, Hela. Hence, it is a promising alga in treatment of cancer through its inhibition of the proliferation on cancer cells (Mohammed et al., 2018).

2.11. *Spirulina* Turpin ex Gomont

Spirulina is symbiotic, multicellular and filamentous blue green microalgae. The aquatic organisms inhabit in fresh water alkaline lakes. However some species are found in marine ecosystem. They are mesophilic and are able to survive over a wide range of temperatures. They are filamentous, undifferentiated and rod or disc shaped. The main photosynthetic pigment is blue coloured phycocyanin, also contain chlorophyll a and carotenes. Gas vesicles give them buoyancy in the aquatic environment. They reproduce by fission. *Spirulina* is consumed by humans and animals. They have significantly high macro and micronutrient value; hence used as food supplement in the dietary or whole food, aquaculture, poultry and aquarium.

Anticancer activities: *S. neglecta* exhibits the anticarcinogenicity. The cytotoxic effects of *S. platensis* hot methanolic extracts on L20B and MCF-7 human cancer cell lines are prominent. The phytochemical compounds from extracts including alkaloids, phenols, terpenes, steroids, flavones, resins, saponines, proteins, amino acids and tannins cause the cytotoxicity (Fayyad et al., 2019). Polysaccharides from *S. platensis* with the highest degree of sulfation demonstrate maximum anticancer activity against MCF-7 breast cancer cell line. The anticancer activity of the commercial *Spirulina* product against lung cancer cells strongly supports the knowledge of the chemo preventive properties of *Spirulina* species. *Spirulina* product reduces the phosphorylation of Akt and Rb proteins and the expression of cyclin D1 and CDK4, while increasing the Bax to Bcl-2 ratio in the A549 cells (Czerwonka et al., 2018).

2.12. *Spirogyra* Link

Spirogyra is a macroalgae belongs to filamentous Chlorophyta of order Zygnematales. They have helical or spiral arrangement of chloroplasts, characteristics of the genus. It is commonly known as 'Sare water silk', 'Mermaids tresses' and 'Blanket weed'. The vegetative structure of *Spirogyra* is filamentous that is branched or unbranched. Multicellular thallus with each cylindrical cell attached end to end to form a ring structure. It has a cell wall, nucleus, pyrenoid and spiral chloroplast. The freshwater genus found as green slimy patches on the ground near ponds and other water bodies having stagnant water.

Anticancer activities: The galloyl glucose derivates in methanol extract of *Spirogyra* varians could be used as antimicrobial and anticancer agents. *S. porticalis* methanol extract provides protection from hypoxia-induced oxidative stress. The extract shows cytotoxic activity on human hepatocellular carcinoma HepG2 and colon carcinoma RKO cell lines due to the presence of fatty acid esters, sterols, unsaturated alcohols and alkynes having substantial phyto pharmaceutical importance (Kumar et al., 2015).

Methanolic extract of *S. triplicata* exhibits anticancer proliferative activity against MCF-7, A549, HEPG2, REH and MOLT4 cell lines. In the extract, GC-MS clearly indicates the presence of nineteen major components and twenty three minor components which have more or less bioactivity and would help in therapeutics in future (Mridha et al., 2020).

2.13. *Chlorella* Beyerinck (Beijerinck)

Chlorella is a green unicellular microalga belongs to Chlorophyta in the family Chlorellaceae. It is the single celled genus. The cells are spherical in shape and are without flagella. Their chloroplast has green photosynthetic pigments, chlorophyll a and chlorophyll b. *Chlorella* is a best food source due to its high protein content and essential nutrients. The dried form contains 45% protein, 20% fat, 20% carbohydrates, 5% fibre, and 10% minerals and vitamins; hence, they are considered as super foods.

Anticancer activities: Au/cellulose nanocomposite synthesized from *Chlorella* species shows anticancer activity against A549 cancer lung cells and HEL299 normal lung fibroblasts by increasing the relative expression of tumour suppressor 53 (p53) (Hamouda et al., 2021). *C. vulgaris* showed marked cytotoxicity against breast cancer, MCF-7 cell lines due to the presence of phenol and flavonoid conte-nts. *C. vulgaris* exhibits antioxidant and anticancer activity against Hela cancer cell lines by the activity of (2E,7R,11R)-3,7,11,15-tetramethyl-2-hexadecenol (Jayshree et al., 2016). The silver nanoparticles (AgNPs) synthesized from the chloroform extract have anticancer activity against MCF-7 and 4T1 cells by the presence of hexanedioic acid, bis (2-ethylhexyl) ester, neophytadiene, eicosane, hexatria-contane and 13-Docosenamide, (Z). The formu-lation could lead to the development of potent therapeutic agents against breast cancer with reduced or no side effect (Hussein et al., 2020).

2.14. *Nostoc* Vaucher ex Bornet & Flahault

Nostoc is the most common species of cyanobacteria that may form colonies made up of filaments of moniliform cells encased in a gelatinous sheath of polysaccharides and found in a various environments. It is a genus of gram negative, photosynthetic cyanobacteria that can be found in both aquatic and terrestrial settings. The algae develop symbiotically within the tissues of plants, supplying its host with nitrogen via the activity of terminally differentiated cells known as heterocysts. *Nostoc* is occasionally found in aquatic environments, on moist rocks, in soil, and at the bottom of lakes and springs. Many species have an outer layer and a thick inner matrix of polysaccharides that give them their "jelly-like" or gelatinous appearance. These polysaccharides also serve as a layer of defense against their surroundings and can aid in the absorption of moisture. This enables them to endure challenging circumstances like erratic temperatures, drought, salt stress, desiccation, UV radiation and pathogen invasion. Depending on the species, the colonies can be found as mats or gelatinous masses that range in colour from brown to yellow to green and are made up of aggregated trichomes. Certain *Nostoc* species can also go into quiescent states that help them to survive harsh environments and enables them to start their metabolism again when rehydrated.

Anticancer activities: Phycobiliprotein, phenolic compounds, flavonoids, tannins etc.

are present in *Nostoc* species. *N. linckia* extract shows anticancer activity against the cell lines like A549, Hela, HCT 116, and MCF-7. Moreover, the species can resist under heavy metal stress and it can act as the strategy to reduce the water pollution (Ramadan et al., 1972). Methanolic extract of *Nostoc* sp. N42 shows cytotoxicity against liver and lung cancer cells. The polysaccharides isolated from *N. commune* exhibit strong antimicrobial and antioxidant activities against growth and proliferation of MCF-7 and DLD1 cells. Similarly, *N. entophytum* has effective anticancer properties against tumour cells (Guo et al., 2015).

3. Outlook

Algae are rich in phytochemicals and show diversity depends to species. They are a promising source of secondary metabolites that useful in drug industry in future to prevent different diseases due to their antioxidant, antibacterial, anticancer, antifungal and antiviral properties. Moreover, in medical and pharmaceutical biotechnology, algae are used for the synthesis of growth factors, hormones, antibodies, vaccines and immune regulators that promote the human health. Similarly, algae can speed up the decomposition of plastics and promote the biofilm formation. It can also act as the important blue carbon sink in turn save the world.

References

1. Acharya, D., Satapathy, S., Somu, P., Parida, U. K., and Mishra, G. (2021). Apoptotic effect and anticancer activity of biosynthesized silver nanoparticles from marine algae *Chaetomorpha linum* extract against human colon cancer cell HCT-116. *Biol. Trace Elem. Res.* 199:1812-1822.
2. Acharya, D., Satapathy, S., Yadav, K. K., Somu, P., and Mishra, G. (2022). Systemic evaluation of mechanism of cytotoxicity in human colon cancer HCT-116 cells of silver nanoparticles synthesized using marine algae *Ulva lactuca* extract. *J. Inorg. Organomet. Polym. Mater.* 1-10.
3. Alassali, A., Cybulska, I., Brudecki, G. P., Farzanah, R., and Thomsen, M. H. (2016). Methods for upstream extraction and chemical characterization of secondary metabolites from algae biomass. *Adv. Exp. Med.* 1-16.
4. Czerwonka, A., Kaławaj, K., Sławińska-Brych, A., Lemieszek, M. K., Bartnik, M., Wojtanowski, K. K., and Rzeski, W. (2018). Anticancer effect of the water extracts of a commercial *Spirulina* (*Arthrospira platensis*) product on the human lung cancer A549 cell line. *Biomed. Pharmac.* 106:292-302.
5. Dellai, A., Laajili, S., Le Morvan, V., Robert, J., and Bouraoui, A. (2013). Antiproliferative activity and phenolics of the Mediterranean seaweed *Laurencia obusta*. *Ind. Crops Prod.* 47: 252-255.
6. Dubey, A., and Sivaraman, J. (2022). Unravelling the antioxidant and anti-cancerous properties of the chemical constituents present in methanol extract of green algae *Chaetomorpha antennina*. *Bull. Pharm. Sci. Assiut.* 45(1):75-87.
7. Ermakova, S. P., Menshova, R. V., Anastyuk, S. D., Zakharenko, A. M., Thinh, P. D., Ly, B. M., and Zvyagintseva, T. N. (2016). Structure, chemical and enzymatic modification, and anticancer activity of polysaccharides from the brown alga *Turbinaria ornata*. *J. Appl. Phyc.* 28:2495-2505.
8. Ermakova, S., Sokolova, R., Kim, S. M., Um, B. H., Isakov, V., and Zvyagintseva, T. (2011). Fucoidans from brown seaweeds *Sargassum hornery, Eclonia cava, Costaria costata*: structural characteristics and anticancer activity. *Appl. Biochem. Biotech.* 164:841-850.
9. Fayyad, R. J., Ali, A. N. M., Dwaish, A. S., and Al-Abboodi, A. K. A. (2019). Anticancer activity of *Spirulina platensis* methanolic extracts against

L20B and MCF7 human cancer cell lines. *Plant Arch.* 19(1):1419-26.

10. Gunathilaka, T. L., Samarakoon, K., Ranasinghe, P., and Peiris, D. C. (2020). Antiproliferative and apoptotic activity of polyphenol-rich crude methanol extract of *Gracillaria edulis* against human rhabdomyosarcoma (rd) and breast adenocarcinoma (mcf-7) cell lines. In *Proceedings*. 79(1):6. MDPI.

11. Guo, M., Ding, G. B., Guo, S., Li, Z., Zhao, L., Li, K., and Guo, X. (2015). Isolation and antitumor efficacy evaluation of a polysaccharide from Nostoc commune Vauch. *Food Funct*. 6(9): 3035-3044.

12. Hamouda, R. A., Abd El Maksoud, A. I., Wageed, M., Alotaibi, A. S., Elebeedy, D., Khalil, H., and Abdella, A. (2021). Characterization and anticancer activity of biosynthesized Au/cellulose nanocomposite from *Chlorella vulgaris. Polymers.* 13(19):3340.

13. Hussein, H. A., Mohamad, H., Ghazaly, M. M., Laith, A. A., and Abdullah, M. A. (2020). Anticancer and antioxidant activities of *Nannochloropsis oculata* and *Chlorella sp.* extracts in co-application with silver nanoparticle. *J. King Saud Univ. Sci.* 32(8):3486-3494.

14. Jayshree, A., Jayashree, S., and Thangaraju, N. (2016). *Chlorella vulgaris* and *Chlamydomonas reinhardtii*: effective antioxidant, antibacterial and anticancer mediators. *Indian J. Pharm. Sci.* 78(5): 575-581.

15. Kim, M. M., Mendis, E., and Kim, S. K. (2008). *Laurencia okamurai* extract containing laurinterol induces apoptosis in melanoma cells. *J. Med. Food*. 11(2): 260-266.

16. Kumar, J., Dhar, P., Tayade, A. B., Gupta, D., Chaurasia, O. P., Upreti, D. K., and Srivastava, R. B. (2015). Chemical composition and biological activities of trans-Himalayan alga *Spirogyra porticalis* (Muell.) Cleve. *PloS One.* 10(2), e0118255.

17. Kurniasari, K. D., Arsianti, A., AzIzA, Y. A. N., Mandasari, B. K. D., Masita, R., Zulfa, F. R., and Putrianingsih, R. I. S. T. A. (2018). Phytochemical analysis and anticancer activity of seaweed *Gracilaria verrucosa* against colorectal HCT-116 cells. *Orient. J. Chem.* 34(3): 1257.

18. Lin, H. C., Chou, S. T., Chuang, M. Y., Liao, T. Y., Tsai, W. S., and Chiu, T. H. (2012). The effects of *Caulerpa microphysa* enzyme-digested extracts on ACE-inhibitory activity and in vitro anti-tumour properties. *Food Chem.* 134(4):2235-2241.

19. Majumder, I., Paul, S., Nag, A., and Kundu, R. (2020). Chloroform fraction of *Chaetomorpha brachygona*, a marine green alga from Indian Sundarbans inducing autophagy in cervical cancer cells in vitro. *Sci. Rep.* 10(1):1-12.

20. Makhlof, M. E., El-Sheekh, M. M., and El-Sayed, A. I. (2023). In vitro antibiofilm, antibacterial, antioxidant, and antitumor activities of the brown alga *Padina pavonica* biomass extract. Int. *J. Environ. Health Res.* 1-18.

21. Marudhupandi, T., Kumar, T. T. A., Lakshmanasenthil, S., Suja, G., and Vinothkumar, T. (2015). In vitro anticancer activity of fucoidan from *Turbinaria conoides* against A549 cell lines. *Int. J. Biol. Macromol.* 72:919-923.

22. Mohammed, I. H., Abed, A. K., and Nsaif, Q. H. (2018). The Cytotoxic Activity *Chara elegans* on Growth of same Cell Lines. *DJM.* 14(2):9-16.

23. Moshfegh, A., Salehzadeh, A., Sadat Shandiz, S. A., Shafaghi, M., Naeemi, A. S., and Salehi, S. (2019). Phytochemical analysis, antioxidant, anticancer and antibacterial properties of the Caspian Sea red macroalgae, *Laurencia caspica. Iran J. Sci. Technol. Trans. A. Sci.* 43: 49-56.

24. Mridha, A., Gopal, P. K., and Paul, S. (2020). Screening data reveals that *Spirogyra triplicata*, a fresh water algae induces robust anti-proliferative activity against A549 cells. *Pharmacog. J.* 12(3).

25. Nurkolis, F., Taslim, N. A., Qhabibi, F. R., Kang, S., Moon, M., Choi, J., and Kim, B. (2023). Ulvophyte green algae *Caulerpa lentillifera*: Metabolites profile and antioxidant, anticancer, anti-obesity, and in vitro cytotoxicity properties. *Molecules*. 28(3):1365.

26. Palanisamy, S., Vinosha, M., Marudhupandi, T., Rajasekar, P., and Prabhu, N. M. (2017). Isolation of fucoidan from *Sargassum polycystum* brown algae: Structural characterization, in vitro antioxidant and anticancer activity. *Int. J. Biol. Macromol.* 102:405-412.

27. Prasedya, E., Hamdin, C., Riandinata, S., Rosidah, S., Susumu, Y., Miyake, M., and Sunarpi, H. (2018). Antiproliferative and immunomodulatory activity of edible seaweed *Gelidium latifolium. Sci. Pharm.* 1-14.

28. Ramadan, K., El-Beltagi, H. S., Shanab, S. M., El-fayoumy, E. A., Shalaby, E. A., and Bendary, E. S. (2021). Potential antioxidant and anticancer

activities of secondary metabolites of *Nostoc linckia* cultivated under Zn and Cu stress conditions. *Processes.* 9(11): 1972.

29. Salem, T. A., and Ibrahim, A. M. (2011). Anticancer activity of Egyptian marine alga *Ulva rigida. Inter. J. Health Sci.* 5(2):6.

30. Stanojkovic, T. P., Savikin, K., Zdunic, G., Kljajic, Z., Grozdanic, N., and Antic, J. (2013). In vitro antitumoral activities of *Padina pavonia* on human cervix and breast cancer cell lines. *J. Med. Plants Res.* 7(8):419-424.

31. Tannoury, M. Y., Saab, A. M., Elia, J. M., Harb, N. N., Makhlouf, H. Y., and Diab-Assaf, M. (2017). In vitro cytotoxic activity of *Laurencia papillosa*, marine red algae from the Lebanese coast. *J. Appl. Pharm. Sci.* 7(3):175-179.

32. Tatipamula, V. B., Killari, K. N., Prasad, K., Rao, G. S. N. K., Talluri, M. R., Vantaku, S., and Srilakshmi, N. (2019). Cytotoxicity studies of the chemical constituents from marine algae *Chara baltica. Ind. J. Pharm. Sci.* 81(5):815-823.

33. Usoltseva, R. V., Anastyuk, S. D., Ishina, I. A., Isakov, V. V., Zvyagintseva, T. N., Thinh, P. D., and Ermakova, S. P. (2018). Structural characteristics and anticancer activity in vitro of fucoidan from brown alga *Padina boryana. Carbohydr. Polym.* 184:260-268.

34. Usoltseva, R. V., Anastyuk, S. D., Shevchenko, N. M., Surits, V. V., Silchenko, A. S., Isakov, V. V., and Ermakova, S. P. (2017). Polysaccharides from brown algae *Sargassum duplicatum*: the structure and anticancer activity in vitro. *Carbohydr. Polym.* 175:547-556.

35. Usoltseva, R. V., Anastyuk, S. D., Surits, V. V., Shevchenko, N. M., Thinh, P. D., Zadorozhny, P. A., and Ermakova, S. P. (2019). Comparison of structure and in vitro anticancer activity of native and modified fucoidans from *Sargassum feldmannii* and *S. duplicatum*. *Int. J. Biol. Macromol.* 124:220-228.

36. Zandi, K., Ahmadzadeh, S., Tajbakhsh, S., Rastian, Z., Yousefi, F., Farshadpour, F., and Sartavi, K. (2010). Anticancer activity of *Sargassum oligocystum* water extract against human cancer cell lines. *Eur. Rev. Med. Pharmacol. Sci.* 14:669-673.

37. Zhang, D., Ramachandran, G., Mothana, R. A., Siddiqui, N. A., Ullah, R., Almarfadi, O. M., and Manoharan, N. (2020). Biosynthesized silver nanoparticles using *Caulerpa taxifolia* against A549 lung cancer cell line through cytotoxicity effect/morphological damage. *Saudi J. Biol. Sci.* 27(12):3421-3427.

38. Zheng, H., Pei, Y., He, Y. L., Liu, Y., Chen, M., Hong, P., and Qian, Z. J. (2022). A Sulfated Polysaccharide from Red Algae (*Gelidium crinale*) to Suppress Cells Metastasis and MMP-9 Expression of HT1080 Cells. *Foods.* 11(15):2360.

An Insight in to Potential Anticancer Activity of Bryophytes

Anjana K.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: anjanaanju241@gmail.com

Abstract: Bryophytes, "amphibians of plant kingdom", are primitive group of non vascular land plants which inhabit damp, shaded and humid localities. Exceptionally, a few are floating in water even though they are with gametophytic and sporophytic phases. The plant group is intermediate between algae and pteridophytes that broadly classified into 3 lineages viz. Marchantiophyta (Liverworts), Bryophyta (Mosses) and Anthocerophyta (Hornworts). About 18500 species are identified till date which distributed all over the world. These are poorly studied plant groups in turn using in many of the traditional medicines due to the presence of secondary metabolites having pharmaceutical activities. To date, by conducting an extensive screening for anticancer activity in approximately 35,000 plants species, the National Cancer Institute (NCI) has built a database of 3,000 plant species with reproducible anticancer activity. Most commonly, the liverwort and moss metabolites including phenolic compounds, terpenoids, bibenzyls and (bis) bibenzyls show cytotoxic activity against many of the cancer cell lines. Various secondary metabolites extracted from bryophytes such as marchantin A, marchantin C, bisbibenzyls, riccardin, 2 alpha 5 beta- dihidroxyboranane-2-cinnamate, costunolide, tulipinolide, jungermannenone, Radulapin, (–)-ent-Arbusculin B, (–)-entcostunolide, eudesmanolides, germacranolides and guaianolides shows tumour suppressing activity towards various cancer cell lines.

Keywords: Anticancer, bryophytes, phenols, terpenoids, bibenzyls

Cancer is a broad collection of illnesses that can begin in practically any organ or tissue of the body. These illnesses are brought on when abnormal cells grow out of control, cross their normal boundaries to infect nearby body parts and spread to other organs. Plants are a source of anticancer chemicals, and it has been demonstrated that their derivatives can be used to cure or prevent cancer in people. The prevention of cancer depends heavily on plant secondary metabolites such as flavonoids, polyphenols, anthraquinones, triterpenoids, alkaloids, terpenoids and quinones. Even if some natural chemicals have specific anticancer effects according to their physicochemical characteristics, a number of new secondary metabolites are derived from plants every year, offering a supply of possibilities to study against malignant disorders. When aberrant cells proliferate uncontrollably, cross their normal borders to infiltrate other body parts and move to other

organs in turn result in cancer, a broad category of disorders which can begin in nearly any organ or tissue of the body.

Generally, the bryophytes are nonvascular, small, green, simple, spore bearing plants and having relatively large perennial, photosynthetic, free living, haploid gametophytes and unbranched diploid sporophytes that remain attached to the maternal gametophyte throughout their lifespan. Thus it is heteromorphic in their lifespan (Shaw & Beer, 1999). The primitive group of land plants inhabits damp and shaded and humid localities, while a few of them are floating in water. The term 'Bryophyta' drived from Greek words Bryon (moss) and Phyton (plants). These non vascular plants commonly called "Amphibians of plant kingdom" which occurs intermediate position between algae and pteridophytes. Bryophytes are broadly classified into 3 lineages viz. Marchantiophyta (Liverworts), Bryophyta (Mosses) and Anthocerophyta (Hornworts) and that include about 18500 species, distributed all over the world. Among them, some of the species show anticancerous properties.

1. Anticancer plants in Marchantiales

1.1. *Marchantia* L.

Marcantia is the most common highly differentiated genus grows in large mats. Thallus is dichotomously branched, green to dark green coloured with broad and distinct midrib bearing saucer shaped gemma cups. The rhizoids are two kinds, smooth walled and tuberculate. Sexually matured thallus bears gamatangiophores, antheridiophores and archegoniophores (Vasishta, 1963).

Anticancer activities: Marchantin A, a cyclic bis (bibenzyl ether), isolated from the liverwort, *M. emarginata* subsp. *tosana*, induces apoptosis in human MCF-7 breast cancer cells (Huang et al., 2010). Marchantin A, (cyclic bis (bibenzyl ether) and plagiochin E (macrocyclic bis (bibenzyl) isolated from *M. polymorpha* which are responsible for its anticancer and antifungal activity respectively (Jantwal, 2019). The ethyl acetate extract of *M. convoluta* is most cytotoxic against human non small cell lung carcinoma cell lines, H1299 and human liver carcinoma, HepG2 (Chen, 2006). Marchantin A obtained from *M. paleacea, M. polymorpha* and *M. tosana*, has shown cytotoxicity against the leukemic KB cells (Jantwal, 2019). Marchantin A from *M. emarginata* sub sp. *tosana* which effectively actuates cell development restraint in human breast cancer cells (MCF-7) (Jantwal, 2019).

1.2. *Plagiochasma* Lehm. & Lindenb.

Plagiochasma species grow on exposed conditions and prefer calcium as rich substrate. The gametophytic plant body is thalloid with ill defined midrib. Ventral surface bears 2 rows of ventral scales. Both smooth walled and tuberculate rhizoids are present (Vasishta, 1963).

Anticancer activities: *P. appendiculatum* shows the presence of alkaloids, flavonoids, carbohydrates, phenols, terpenes, steroids, glycosides and lipids. The liverwort is a rich source of bisbibenzyls including marchantin A-C, riccardin C, riccardin D and neomarchantin A. The bisbibenzyls isolated from *P. appendiculatum* show excellent antitumour and antifungal activities (Zhao, 2022).

1.3. *Dumortiera* Nees

Monoicous or dioicous, dark greenish

thallus of the species is formed in dense overlapping patches as mats in comparatively less illuminated areas along streamside or on wet rocks. The dorsal surface is smooth without air pores. The ventral scales are in two rows, sex organs formed on stalked receptacles, involucres tubular, pseudoperianth absent, seta short, capsule wall single layered, dehiscence of capsule by the splitting of wall into irregular longitudinal valves, elaters long and 2-3 spiral (Mufeed, 2021).

Anticancer activities: Riccardin D is a novel macrocyclic bisbibenzyl compound extracted from Chinese liverwort plant, *D. hirsuta*. The compound is a DNA topo II inhibitor and has therapeutic potential for treatment of cancers. It displays the anticancer effect on growth of human lung carcinoma cells by the inhibitory activity of riccardin D and related angiogenesis (Xue, 2012).

1.4. *Conocephalum* Hill

The thalli are flat, smooth and have a pungent odour. They have dark green, leathery surfaces and purplish edges. The surface of the thalli is covered with a series of lines and air pores that may be seen in the spaces in between the lines. Thallus is dichotomously branched, dorsal surface with elongated polygonal areas with elevated air pores in the middle and margin hyaline. Airpores are simple and surrounded by 4-6 concentric rings of 6-8 cells. Ventral scales are large, hyaline or slightly purplish and one row on either side of midrib. Air chambers are in single row and photosynthetic filaments vestigial. The male receptacle is terminal, sessile, discoid and unlobed. The female receptacle is stalked, carpocephalum conical, not deeply lobed, pseudoperianth absent, peduncle with single rhizoid furrow, involucres tubular, 7-8 per receptacle and each bear single sporogonium. The capsule wall is unistratose, cells with annular thickening, dehiscence by splitting in to 4-8 valves and spores with lamellate ornamentation (Mufeed, 2021).

Anticancer activities: Presence of monoterpenes has been recorded from the liverwort *C. conicum*. A monoterpene ester, 2 alpha, 5 beta-dihidroxyboranane-2-cinnamate, from Chinese *C. conicum* is cytotoxic against human HepG2 cells (Adam, 1998).

1.5. *Asterella* P. Beauv

Thallus is prostrate, aromatic and dichotomously branched. Fleshy thallus is leathery, dorsal surface smooth with air pores, ventral surface and scales usually purplish, rhizoids smooth or pegged. Thallus differentiated into photosynthetic region and storage region. Photosynthetic region is aerenchymatous, usually with empty air chambers in many rows, storage region broad. Midrib is absent (Mufeed, 2021).

Anticancer activities: Marchantin C, isolated from *Asterella angusta*, strongly inhibits the growth of human cervical tumour. It is a novel microtubule inhibitor that induces mitotic arrest of tumour cells and suppresses tumour cell growth (Nandy, 2020).

2. Anticancer plants in Metzgeriales

2.1. *Riccardia* L.

The monoecious or dioicous thallus is narrow, delicate, irregularly or pinnately branched. Rhizoids are scarce in nature. The oil bodies present in the epidermal cells; antheridial branches once or twice arched, archegonial branches short, antheridial branches branched; calyptra cylindrical or

clavate, seta elongated; capsule blackish-brown, ovoid or slightly cylindrical, dehiscing by 4 valves; spores spherical or globose, pale yellow or brown, elaters unispiraled, broad in the middle, sometimes branched (Mufeed, 2021).

Anticancer properties: The majority of Hepaticae have been shown to primarily consist of lipophilic mono-, sesqui- and diterpenoids, aromatic compounds (bibenzyls, bis-bibenzyls, benzoates, cinnamates, long-chain alkyl phenols, naphthalenes and phthalides) and lipids. Riccardins A and B from *R. multifida* inhibit KB cells. *R. perrottetii* contained plagiochiline and perrottetin E shows cytotoxicity against KB cell (Alam, 2012).

3. Anticancer plants in Jungermanniales

3.1. *Frullania* Raddi

The gametothallus is dorsiventral and differentiated into a branched, prostrate, central stem like axis and leaves. The stem is pinnately or bipinnately branched. The leaves on the stem are inserted in three rows. There are two rows of dorsal leaves arranged laterally on the stem. A third row of smaller leaves arranged on the lower or ventral side of the stem, known as the underleaves or amphigastria. The closely set lateral (dorsal) leaves are almost transversely inserted on the stem with the anterior edge of each leaf covering the posterior edge of the leaf in front. Such an overlapping arrangement of the leaves is described as incubous. Each lateral leaf is bilobed (Vasishta, 1867).

Anticancer activities: The sesquiterpenoids, costunolide and tulipinolide, isolated from *F. monocera* show the anticancer activity against human carcinoma of the nasopharynx (Chandra, 2017). An extract from *F. nisquallensis* exhibits anticancer activity against lung cancer cells.

3.2. *Porella* L.

Porella (Madotheca) is generally found in the moist, shady places growing flat on logs, tree trunks and rocks over which water trickles. It grows in dense layers forming large mats closely covering substratum. The plant body is greenish, leafy and fairly large up to 15 cm or even more in length. It consists of a branched central axis or stem that bears leaf like expansions. The stem is thin and cylindrical and bears branches in a bipinnate or tripinnate manner. The branching is monopodial. The branch primordium lies close to the apical cell. The stem and branches bear two kinds of leaves, large dorsal and small ventral. They are arranged in three rows .The dorsal leaves are closely set in two lateral rows (Vasishta, 1963).

Anticancer activities: *P. cordeuna* consisted of sesquiterpenes, pinguisanin, norpinguisone methyl ester, porella pinguisanolide, porella pinguisenone, spiropinguisan and striatenone. Pinguisanin and porella pinguisenone show selective activity against the RAD52 strain RS322YK of *Saccharomyces cerevisiae* and inactive against the wild type strain RS188N (RAD). The compound, drimenin 111, is inactive in P388 (Murine leukemia) and CHO (Chinese hamster ovary) cytotoxicity assays. The extract shows cytotoxicity against breast, colon and lung cancer cells (Harrigan, 1993).

3.3. *Jungermannia* L.

The majority of the species can be found in temperate climates with succubus leaves. The leaves are unlobed with a smooth edge. The perianth is terminal on the leading

shoot. When the plants branched, the branches do not emerge from the base of stem. Rhizoids are found all over the underside of stem, not just in a few concentrated areas close to the under leaves (Vasishta, 1963).

Anticancer activities: Ent-kaurane diterpenoids, jungermannenone A and B, exhibit the highest cytotoxic activity against several cancer cell lines. Jungermannenone A and B are able to arrest the cell cycle, induce apoptosis and cause mitochondrial damage. Jungermannenone A (1.5 µmol/L) causes a significant increase in PC-3 apoptotic cells (Cianciullo, 2022).

3.4. *Radula* Dumort.

It is a leafy liverwort. In a protected wet outdoor setting, the plants appear as a scaly, green surface on the trunk of a tree, log or rock. The leaves have two uneven lobes and are rounded with overlap. Folded beneath the bigger lobe is the smaller one (Mufeed, 2021)

Anticancer activities: The prenylated bibenzyls, radulapin A-H, from *R. apicata*, 2-carbomethoxy-3,5dihydroxystilbene and 3, 5-dimethoxybibenzyl from *R. amoena* exhibit cytotoxic activity against several cancer cell lines (Zhang, 2019). The extract of *R. marginata* is cytotoxic against breast, lung and colon cancer cells.

3.5. *Diplophyllum* (Dumort.) Dumort.

In hilly areas with base poor acid soils, *D. albicans* is one of the commonest leafy liverworts. Oddly for such a distinctive looking liverwort, it is quite variable in size, colour and growth form. Plants are usually in thin flat patches or mats. Stems are with few intercalary and axillary branches, usually with subfloral innovations; cortex in 3-5 layers, cells somewhat to strongly flattened, smaller, more strongly thick walled than medullary cells; branches few; rhizoids scattered, colorless. Leaves are complicate 2 lobed with smaller dorsal and larger ventral lobes, not decurrent, the most proximal leaves usually smaller, rounded to apiculate, sheathing, nearly or almost parallel to the stem (Redfearn, 2008).

Anticancer activities: Diplophyllin from *D. albicans* and *D. taxifolium* has methylene- lactone unit that shows significant activity against human epidermoid carcinoma (Marko, 2001).

3.6. *Hepatostolonophora* J. J. Engel & R. M. Schust.

It is a taxonomic genus having a group of leafy liverworts forming mats. Branches are mostly of lateral-intercalary type; *Frullania* type branches less common; *Andrewsianthus* type present in *Evansianthus*; ventral-intercalary branches much less frequent, present in some taxa. Rhizoids are typically from stem in a sharply defined region at under leaf base, in *Leptophyllopsis* from cells of underleaf. Leaves are alternate to subopposite (Engel & Briscoe, 2021).

Anticancer activities: (–)-ent-Arbusculin B and (–)-entcostunolide from *H. paucistipula* show cytotoxic activity against P388 murine leukemia cells, with IC_{50} values of 1.1 and 0.7 µg/mL, respectively (Baek et al., 2003).

3.7. *Lophocolea* (Dumort.) Dumort.

Plants are yellowish green to light green, sparingly branched, prostrate, delicate, branches lateral or intercalary; stem usually undifferentiated, rarely outer layers thick walled; leaves closely imbricate or distant, alternate, ovate to oblong, quadrate or rectangular,

usually entire at margins, rarely toothed; apex acute, retuse or obtuse; cells thin walled, with or without trigones; under leaves remote, free or narrowly united at base with leaves, usually deeply bilobed; dioecious or monoecious, male and female inflorescence terminal or intercalary on main branches or lateral branches, perianth oblong or campanulate, usually triplicate; capsule ovoid or dark brown, spores granulate, elaters bispiral (Mufeed, 2021).

Anticancer activities: Several sesquiterpene lactones such as eudesmanolides, germacranolides and guaianolides isolated from liverworts exhibit cytotoxic activity against KB nasopharyngeal and P-388 lymphocytic leukemia cells. However, *L. heterophylla* shows cytotoxicity against P-388 cells (Cianciullo, 2022).

4. Anticancer plants in Porellales

4.1. *Lepidolaena* Dumort.

The leaves of leafy forms lack a midrib and often have lobes, flaps or pockets. Thalloid liverworts form a flat growth (thallus) on the substrate. Some have pores. Liverworts are attached to the substrate with single celled filaments, rhizoids. The sporophyte, consisting of a stalk or seta and capsule, is very delicate, short lived and often greatly reduced in size. The capsule opens by splitting into segments.

Anticancer activities: 8, 9-Secokauranes, rabdoumbrosanin and 8,14-epoxyrabdoumbrosanin, isolated from a New Zealand *L. taylorii* show in vitro and in vivo model system for antitumour activity (Bandyopadhyay, 2022).

5. Anticancer plants in Ptilidiales

5.1. *Ptilidium* Nees

The plants grow in dense mats, with stems growing either prostrate or ascending. Individual stems are once or twice pinnate, rarely with branches and only a few short rhizoids. The leaves are incubous and divided deeply into three to five portions, and edges of the leaf divisions are fringed with cilia. The under leaves are similar to the lateral leaves, but are slightly smaller. All species are dioecious, producing antheridia and archegonia on separate plants. The archegonia are terminal on a main stem. Mature sporophytes develop from a large perianth with three distal folds.

Anticancer properties: Cytotoxicity of different secondary metabolites isolated from the liverwort *P. pulcherrimum* have been reported against the PC3, MDA-MB-231 and Hela cell lines of which ursane triterpenoids had shown moderate cytotoxicity against PC3 Cells (Guo, 2009).

6. Anticancer plants in Polytrichales

6.1. *Polytrichum* Hedw.

Polytrichum is one of the largest mosses. It is commonly called the hairy cap moss because of the luzzy calyptra enclosing the mature capsule. The genus comprises over 100 species found all over the world. *P. commune* is a cosmopolitan perennial woodland moss which occurs in clonal groupings. Many aerial leafy stems are interconnected by underground rhizomes. The erect aerial shoots may attain a length up to 45 cm and the rhizomes may reach a depth of about 30 cm. The conspicuous part of the plant body is an erect leafy shoot, but it is not the entire gametophyte. In fact the leafy shoots arise from the haploid branched, alga like, green filamentous structure called the protonema

(Vasishta, 1963).

Anticancer activities: *P. commune* plays very significant role especially for the therapy of lymphocytic leukemia. It has been found that *P. ohioense* and *P. pallidisetum* show cytotoxicity against the 9PS murine leukemia and several other tumour cell lines (Chandra, 2017).

7. Anticancer plants in Bryales

7.1. *Bryum* Hedw.

Plants usually short, up to 2 cm high; pure white, silver green, yellow, yellowish green and green with red tints; stem julaceous or gemmiform; leaves usually shorter, 1.5 mm long, ovate-lanceolate, base not decurrent; apex broadly rounded to acute; costa percurrent or excurrent; alar cells usually absent or somewhat differentiated in juxta costal region; sporophytes seen on tip of the plant, seta long twisted when dry, capsule inclined to pendent, ovate or clavate to pyriform, spores finely papillose, pale brown or yellow brown in colour (Mufeed, 2021).

Anticancer activities: Plants have the ability to synthesize aromatic substances such as phenolic and nitrogen containing compounds, vitamins, terpenoids and some other endogenous metabolites, which are active against herbivores, insects, bacteria and fungi. The extract inhibits the genotoxic activity of H_2O_2. Methanol extract of *B. argenteum* inhibits the growth of breast, liver and lung cancer cells (Onbasli, 2021).

8. Oulook

Bryophytes are nonvascular plants, small, green, simple, spore bearing and unique among land plants. These are poorly studied plant groups in turn using in many of the traditional medicines due to the presence of secondary metabolites having pharmaceutical activities. Anticancer agents discovered from primitive plant group such as bryophytes have played a major role in cancer treatment. Studies reveal many bryophytes have antitumour and cytotoxic activities, which inhibit the growth of tumour. Among the plants, *Marchantia, Plagiochasma, Dumortiera, Conocephalum, Asterella, Riccardia, Frullania, Porella, Jungermannia, Radula, Diplophyllum, Hepatostolonophora, Lophocolea, Lepidolaena, Ptilidium, Polytrichum* and *Bryum* show anticancerous activities. Various secondary metabolites extracted from bryophytes such as marchantin A, marchantin C, bisbibenzyls, riccardin A, D, 2 alpha, 5 beta-dihidroxyboranane-2-cinnamate, costunolide, tulipinolide, jungermannenone A and B, radulapin A-H, (–)-ent-arbusculin B and (–)-entc-ostunolide, eudesmanolides, germacranolides and guaianolides show tumour suppressing activity towards various cancer cell lines.

References

1. Adam, K.P., and Croteau, R. (1998). Monoterpene biosynthesis in the liverwort *Conocephalum conicum*: demonstration of sabinene synthase and bornyl diphosphate synthase. *Phytochem.* 49(2):475-480.
2. Alam, A. (2012). Some Indian bryophytes known for their biologically active compounds. *Int. J. Appl. Biol. Pharm.* 3(2):239-246.
3. Bandyopadhyay, A., and Dey., A. (2022). The ethno-medicinal and pharmaceutical attributes of Bryophytes: A review. *Phytomed. Plus.* 2(2): 100255.

4. Asakawa, Y., and Ludwiczuk, A. (2017). Chemical constituents of Bryophytes: Structures and Biological activity. *J. Nat. Prod.* 81(3):641-660.

5. Chandra, S., Chandra, D., Barh, A., Pandey, R. K., and Sharma, I. P. (2017). Bryophytes: Hoard of remedies, an ethno-medicinal review. *J. Tradit. Complement. Med.* 7(1):94-98.

6. Chen, X., and Xiao, J. (2006). In vitro cytotoxic activity of extracts of *Marchantia convoluta* on human liver and lung cancer cell lines. *Afr. J. Tradit. Complement Altern. Med.* 3(3):32-36.

7. Zhang, C., Gao, Y., Zhu, R., and Qiao, Y. (2019). Prenylated Bibenzyls from the Chinese Liverwort *Radula constricta* and their Mitochondria-Derived Paraptotic Cytotoxic Activities. *J. Nat. Prod.* 1741-1751.

8. Cianciullo, P., Cimmino, F., Maresca, V., Sorbo, S., Bontempo, P., and Basile, A. (2022). Anti-tumour activities from secondary metabolites and their derivatives in bryophytes: A brief review. *J. Appl. Biosci.* 1(1):73-94.

9. Guo D. X., Du Y., Wang Y. Y., Sun L. M., Qu J. B., Wang X. N., and Lou H. X. (2009) Secondary metabolites from the liverwort *Ptilidium pulcherrimum. Nat. Prod. Commun.* 4(10):1319-22.

10. Harrigan, G. G., Ahmad, A., Baj, N., Glass, T. E., Gunatilaka, A. A. L., and Kingston, D. G. I. (1993). Bioactive and other sesquiterpenoids from *Porella cordeana. J. Nat. Prod.* 56(6):921-925.

11. Huang, W. J., Wu, C. L., Lin, C. W., Chi, L. L., Chen, P. Y., Chiu, C. J., and Chen, C. N. (2010). Marchantin A, a cyclic bis (bibenzyl ether), isolated from the liverwort *Marchantia emarginata* subsp. t*osana* induces apoptosis in human MCF-7 breast cancer cells. *Cancer Lett.* 291(1):108-119.

12. Jantwal, A., Rana, M., Rana, A. J., Upadhyay, J., and Durgapal, S. (2019). Pharmacological potential of genus *Marchantia: Rev. J. pharmacogn. phytochem.* 8(2):641-645.

13. Mufeed,B., Manju, C. N., and Rajesh, K. P., (2021). Bryophytes of Anamudi Shola National Park in the Western Ghats of Kerala. Centre for Research in Indigenous Knowledge, *Science and Culture and Malabar Natural History Society*. 214-252.

14. Nandy, S., and Dey, A. (2020). Bibenzyls and bisbybenzyls of bryophytic origin as promising source of novel therapeutics: Pharmacology, synthesis and structure-activity. *Daru: DARU J. Pharm. Sci.* 28(2):701-734.

15. Onbasli, D., and Yuvali, G. (2021). In vitro medicinal potentials of *Bryum capillare*, a moss sample, from Turkey. *Saudi. J. Biol. Sci.* 28(1):478-483.

16. Sun, C. C., Zhang, Y. S., Xue, X., Cheng, Y. N., Liu, H. P., Zhao, C. R., and Qu, X. J. (2011). Inhibition of angiogenesis involves in anticancer activity of riccardin D, a macrocyclic bisbibenzyl, in human lung carcinoma. *Eur. J. Pharmacol.* 667(1-3):136-143.

17. Vasishta, B. R. (1867). Botany for Degree students-Bryophyta. *S.Chand & Company Pvt. Ltd.* 74-75.

18. Xue X., Qu X. J., Gao Z. H., Sun C. C., Liu H. P., Zhao C. R., Cheng Y. N., and Lou H. X., (2012). Riccardin D, a novel macrocyclic bisbibenzyl, induces apoptosis of human leukemia cells by targeting DNA topoisomerase II. Invest. New Drugs. 30(1):212-22.

19. Zhao, Y., Wen, X., Ni, R., Cheng, A., and Lou, H. (2022). Tissue Culture of *Plagiochasma appendiculatum* and the Effect of Callus Differentiation on Types and Content of Bisbibenzyls. *Nat. Prod. Commun.* 17(9).

Pteridophytes as a Potential Treasury of Anticancer Agents

Unaisudheen T. P.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College, Manjeri, Malappuram, 676122, Kerala, India.

Corresponding author: unaisbotany@gmail.com

Abstract: Human has been interacting with plants from the beginning of human existence. Plants have provided humans with basic needs such as sustenance, firewood, livestock feed, and wood. Approximately there are over 3 million vascular plants on the earth. As the first vascular plants, pteridophytes are an ancient lineage, and human beings have been exploring and using taxa from this lineage for over 2000 years because of their beneficial properties. About 13,600 species of ferns are distributed in worldwide. In India, Himalayas, Western and Eastern Ghats, and Pachmarhi Biosphere Reserve are major distribution of pteridophytes. They remain underexplored in ethno botanical aspects, than any other vascular plants despite being regarded as a valuable component of healthcare. Cancer is one of the leading causes of death and globally the numbers of cases on cancer are increasing gradually. Among the anticancer drugs, about 50% come from natural products as isolated or semisynthetic or related synthetic compounds and plants represent important source of these substances. Among all the pteridophytes examined, taxa from the Polypodiaceae, Pteridaceae, Davalliaceae and Aspleniaceae contain more anticancer compounds like taxol, *Vinca* alkaloids, camptothecin, podophyllotoxins etc.

Keywords: Anticancer, pteridophytes, ethno botany, Western-Ghats, alkaloids

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. There are many types of cancer including lung, breast, prostate and colon cancer. Risk factors for cancer include smoking, excessive alcohol consumption, exposure to chemicals and toxins, certain infections and inherited genetic mutations. Symptoms of cancer include fatigue, pain, changes in the skin and unexplained weight loss. Treatment options for cancer consists surgery, radiation therapy, chemotherapy and targeted therapy. Early detection and prevention are keys to managing cancer and improving outcomes.

Pteridophytes are a group of vascular plants that include ferns, horsetails and club mosses. They have been used in traditional medicine for centuries, and several species have been found to have medicinal properties. Some of the medicinal pteridophytes are the following. Maidenhair fern (*Adiantum capillus-veneris*): The fronds of the ferns have been traditionally used to treat respiratory problems such as asthma, bronchitis and coughs. Horsetail (*Equisetum arvense*): It has been

traditionally used to treat a variety of ailments including kidney and bladder problems, wounds and bone fractures. Club moss (*Lycopodium clavatum*): The fern is used to treat a variety of conditions including diarrhea, indigestion and rheumatism. Ferns have been found to have potential anticancer properties. Some studies have shown that compounds found in ferns such as flavonoids and polysaccharides, can inhibit the growth of cancer cells and induce apoptosis in certain types of cancer cells. Additionally, they have also been found to have antiinflammatory and antioxidant properties, which may also contribute to their potential as anticancer agents. However, more research is needed to fully understand the mechanisms of action and potential therapeutic uses of ferns in cancer treatment. Some studies have shown that extracts from certain ferns have the ability to inhibit the growth of cancer cells in lab tests. However, more research is needed to determine the effectiveness and safety of these plants in humans. Some examples of ferns that have been studied for their potential anticancer properties include *Dryopteris crassirhizoma, Polypodium leucotomos* and *Pteris cretica*.

1. Anticancer compounds in pteridophytes

Plants including pteridophytes are most common source of anticancer agents like apigenin, chrysoeriol, luteolin and tricin as well as their O-glycosylated or C-glycosylated forms. A majority of the anticancer activity of ferns is reported to be attributed to phenolic compounds, particularly flavonoids and their O-glycosides. In vivo as well as in vitro flavonoids are powerful antioxidants with anticancer properties. Flavonoids from different ferns show both of these properties. Amentoflavone found in Psilotaceae and its monomer apigenin is primarily contained in this family of plants has only been discovered that biflavonoids occur in Osmundaceae and Cyatheaceae so far. Flavonols are the main constituents of Ophioglossaceae. Several flavonoids derived from ferns along with their O-glycosides can be found in most plant kingdoms. These are quercetin and kaempferol; the flavanone naringenin; the flavones apigenin, isoorientin, tricetin, vicenin-2 and vitexin; and the 3-deoxyanthocyanins, apigenidin and luteolinidin etc. Among the mechanisms by which they work are a reduction in DNA polymerase activity, suppression of NF-κB, decreasing of Bcl-2 expression as well as suppression of MMP-1, p38 MAPK and c-Jun N-terminal kinase.

2. Anticancer plants in pteridophytes

2.1. *Microsorum* Link

Microsorum belongs to family Polypodiaceae, is a terrestrial epiphytic fern. Rhizomes are long or short creeping. Rhizome scales are clathrate, squarrose or appressed. Fronds are monomorphic or dimorphic and articulated to short stalks called phyllopodia. Laminae are undivided, variously lobed or deeply pinnatifid. Veins are reticulated, areoles with free included veinlets. Sori are round or slightly elongate, superficial or impressed into the lamina and bulging on upper surface. Paraphyses absent or sometimes present as simple uniseriate hairs. Spores are monolete, bilaterally symmetrical, granulate to tuberculate.

Anticancer activities: The genus includes two important species that shows anticancer properties. *M. pustulatum* uses by people of Dayak Tribes in Central Kalimantan for antitumour medicines. Hexane extract of *M. pustu-*

latum rhizomes is potential to inhibit tumour growth in mice (Neneng et al., 2020). *M. grossum* has been used to cure liver cancer (Petard & Raau, 1972; Defilpps et al., 1988).

2.2. *Drynaria* (Bory) J.Sm.

It is commonly known as 'Basket fern' which are epiphytes or lithophytes coming under family Polypodiaceae with creeping, branched and densely scaly rhizome. Scales are dark brown, linear or lanceolate and acuminate at end. Fronds are dimorphic, sterile and fertile. Sterile bracket fronds are simple; leaf lamina is elliptic in outline, cordate at base. Fertile fronds are simply pinnate; stipes grooved above, rounded beneath; leaf lamina is broadly elliptic in outline. Sori are dark brown, many on vein endings. Sporangial capsule is subglobose. Spores are brown, ellipsoid with spinous perine.

Anticancer activities: *D. fortunei* is used in Traditional Chinese medicine "Gu-Sui-Bu" against cancer (Punzon et al., 2003). *D. quercifolia* shows anticancer property against lung and prostate cancer cells through Brine Shrimp lethality bioassay (Milan et al., 2013)

2.3. *Aglaomorpha* Schott

Aglaomorpha is a member of the Polypodiaceae and is related to the oak fern which is found in the wild throughout Northern Europe. The natural habitat is in Indochina, Taiwan and the southern islands of Japan. Plants are epiphytic, epilithic or terrestrial. Rhizome is thick, shortly to long creeping. Scales on rhizome are appressed or spreading and margins are toothed or ciliated. Fronds not articulate, monomorphic, usually internally dimorphic, sessile with a dilated base, frond bases imbricate or separate, forming individual nests. Fertile parts similar to sterile or usually narrower. Sori are small, in rows along connecting veins or veinlets, or distinctly enlarged to form soral patches between midrib and margin. Sporangia are glabrous or sometimes with acicular hairs. Spores are with spines or small globules.

Anticancer activities: In the Chinese traditional medicine system, "Gusuibu" has been used for its anticancer and antiinflammation activity. It is prepared from the rhizomes of various ferns, namely *A. coronans* (Cai et al, 2004; Chang et al., 2007a)

2.4. *Phlebodium* (R.Br.) J.Sm.

They are epiphytic ferns, with a creeping, densely hairy or scaly rhizome bearing fronds at intervals along its length. Rhizome is broad with densely toothed scales. The fronds are evergreen, persisting for 1-2 years and pinnatifid. Apex of pinnae attenuate and acuminate. Leaf lamina is glabrous on underside. The sori or groups of spore cases, sporangia, are borne on the back of the frond.

Anticancer activities: *P. decumanum* has been used for anticancer and ulcer treatment. Extracts of the species show anticancer activity. Testing of HL-60 and MCF-7 cells shows the inhibition of proliferation and the induction of cell death. Western blot and FACS analyses elucidate the underlying mechanisms (Punzon et al., 2003).

2.5. *Polypodium* L.

They are terrestrial or epiphytic ferns, with a creeping, densely hairy or scaly rhizome bearing fronds at intervals along its length. The species differs in size, general appearance and

in the character of the fronds which are evergreen. The sori or groups of sporangia are borne on the back of the frond; they are globose and naked, not covered with a membrane.

Anticancer properties: *P. nipponica* is an anticancer plant by testing in vivo two stage carcinogenesis on mouse skin papillomas. *P. formosanum, P. vulgare, P. fauriei* and *P. virginianum* contain triterpenes with oxygenated functional group which reduce the inhibitory effects on EBV-EA activation. This strongly suggests that these compounds are strong anticancer promoters (Konoshima et al., 1996).

2.6. *Pteris* Gled. Ex Scop.

The genus *Pteris* belongs to family Pteridaceae is a terrestrial herb. Rhizome is erect with dense scales, and scales are lanceolate, entire and pale brown in colour. Leaves are simple pinnate, pale green; stipe is long, green, scaly and grooved. Lamina is simple pinnate, pale green in colour. Pinnae are oblong, acuminate gradually reduced towards base; basal pinnae are ovate or oblong. Sori are linear along the margins, covered by translucent reflexed margins; spores are trilete, pale brown.

Anticancer properties: *P. polyphylla* and *P. multifida* contain antimutagenic factors against both picrolonic acid and benzo[a]pyrene induced mutation using the *Salmonella/* microsomal system. Each crude drug is extracted with boiling water for 2h, the method which is commonly used by Chinese people to prepare the drug for oral intake (Lee et al., 1998). From aerial part of the fern *P. multifida*, two diterpenes, entkaurane-2 beta, 16 alpha-diol and ent-kaur-16-ene-2 beta, 15 alpha-diol isolated by repeated column chromatography using silica gel and silica gel impregnated with silver nitrate. Both compounds show a moderate cytotoxicity to Ehrlich ascites tumour cells (Woerdenbag, 1996). *P. semipinnata* shows cytotoxicity against HL-60 cell line in combination with genistein. In *P. vittata*, protoapigenone is a unique flavonoid showing potent antitumour activity against a broad spectrum of human cancer cell lines. RY10-4, a modified version of protoapigenone, manifested better anti proliferation activity in human breast cancer cell line MCF-7. The cytotoxicity of RY10-4 against MCF-7 cells is exhibited in both time and concentration dependent manners (Li et al., 1998).

2.7. *Hemionitis* L.

Hemionitis is a genus of small terrestrial, soft herbaceous ferns. Rhizomes are short creeping to erect. Thin scales intermixed with pericellular hairs present on rhizome. Fronds are somewhat dimorphic. The sterile fronts are tending to be short stalked and spreading; fertile ones long stalked and erect. Leaf blades are palmately or pedately lobed or else pinnately compound; sporangia in many superficial lines, following the course of veins throughout the lower side of fertile blades. Indusium and paraphyses are absent. Spores of *Hemionitis* are globose or tetrahedral globose, trilete and the surface cristate is echinate or tuberculate.

Anticancer activities: Leaf and rhizome of *H. arifolia* show properties of antidiabetic, antimicrobial and anticancer (Santhosh et al., 2014).

2.8. *Adiantum* L.

Adiantum is terrestrial herb with erect rhizome. Scales are lanceolate, acuminate, pale

brown coloured. Fronds are dichotomously branched. Stipe is dark brown to black in colour. Pinnules are dimidiate, obovate, elliptic or rhomboid, shortly stipitate and truncate to cuneate at base. Sterile pinnae are serrate; fertile pinnae serrate to lobed; hispid is coriaceous. Sori are along the reflexed margins, reniform, dark brown to black. Sporangial capsules are subglobose. Spores are yellow, trilete and tetrahedral.

Anticancer activities: The whole plant of *A. capillus-veneris* is anticancerous, antiviral and hypoglycaemic (Santhosh et al., 2014). Neohopane 12 ene, adianane and secoadianane are isolated from *A. monoclamys*, exhibit inhibitory effect on EBV-EA activation at higher concentration (Konoshima et al., 1996). Preliminary phytochemical screening and anticancer evaluation of *A. venustum* against Ehrlich Ascites Carcinoma in animal model is valuable. The findings indicate that ethanolic extract of *A. venustum* possesses significant anticancer activity and also reduces elevated level of lipid peroxidation due to the presence of terpenoids and flavonoids. Thus, ethanolic extract could have vast therapeutic application against cancer (Viral et al., 2011).

2.9. *Pityrogramma* Link

It is terrestrial herb with erect, densely scaly rhizome. Scales are brownish, linear and entire. Fronds are bipinnate. Stipe is dark-pinkish brown coloured. Lamina is triangular in outline and pinnae lanceolate, acuminate in outline. Pinnules are rhomboidal to lanceolate in shape, rachi and costa grooved above, raised below; lower surface of pinnules white crusted. Sori are acrostichoid. Sporangial capsule is globose. Spores are triangular in outline, yellowish with pinkish thickenings.

Anticancer activities: In vitro cytotoxicity of the extracts and isolated components observed in Dalton's lymphoma ascites tumour cells (DLA cells) and Ehrlich ascites tumour cells (EA cells) using the trypan blue exclusion method (Sukumaran & Kuttan, 1991).

2.10. *Angiopteris* Hoffm.

Angiopteris belongs to family Marattiaceae. It is a terrestrial herb with erect, massive rhizome. It densely covered with dark brown to black hairs. Fronds are bipinnate. Stipe is long and hairy. Lamina is broadly elliptic, acute in outline. Pinnae are oblong-lanceolate, acute in outline. Pinnules are oblong, acuminate, serrulate to entire and rounded at base. Costa raised above and below, veins indistinct above, prominent below, rarely forked.

Anticancer activity: For sarcoma, the leaves are crushed together with leaves of "agakai" (plant species not stated), and the sap applies twice a day (Defilpps et al., 1988).

2.11. *Davallia* Sm.

The plant rhizome is long creeping, white-waxy and appressed to substrate. Black peltate bases of rhizome scales usually persistent, and remaining portion is deciduous. Fronds are not always markedly dimorphic, and chartaceous. Stipe bearing scattered reduced scales with a minute peltate base and marginal crisped hairs. Rachis and lower surface of lamina contain scattered reduced scales. Sori present on the marginal portion, indusium often projecting beyond margin and very tightly attached along both sides.

Anticancer activities: *D. divaricata* and *D.*

solida are used in Traditional Chinese medicine and Korean folk medicine (Cui et al., 1990). *Pteridium aquilinum* and *D. cylindrica* show the anticancer potentials in A549 cells (Chiu et al., 2009; Sarker et al., 2011).

2.12. *Marsilea* Necker

It is terrestrial or aquatic herbs with long creeping rhizome. Fronds are simple and stipe is slender, glabrous or softly pubescent. Lamina is quadrifid and each lobe is obovate or obtriangular, lobed to serrate along the outer margins. Sporocarps are oblongoid; hispid is less hairy at maturity, with stalk and produced in clusters.

Anticancer activities: The methanolic extracts of *M. quadrifolia* show an antiproliferative activity with IC_{50} value of MCF-7 cells at 39.06 µg/ml. Ethylacetate and aqueous extracts of *M. quadrifolia* exhibit antiproliferative activity with an IC_{50} value of 47.825 and 187.5 µg/ml respectively (Uma & Pravin, 2013). Among the species, the highest percentage of tumour inhibition induce by *M. minuta* (82.32%) at 1000ppm, and significant tumour inhibition observed at 10, 100 and 1000 ppm of plant extracts on potato disc induced by *Agrobacterium tumefaciens* indicating their presence of tumour inhibitor metabolites. These metabolites may serve an important role in developing antitumour drugs for human beings, as there is a similarity between human and plant tumour formation mechanism (Sarker et al., 2011).

2.13. *Blechnum* L.

Blechnum is a terrestrial herb with suberect rhizome. Apex of rhizome is densely scaly and scales are lanceolate, pale brown, apex acuminate with entire margin. Stipes are tufted, dark brown at the very base, pale or grey-brown above, sparsely scaly at the base and glabrous above. Lamina is falcate lanceolate, apex acuminate, base truncate, basal few pinnae pairs are sessile, slightly reduced or not, subopposite. Largest pinna oblong-lanceolate, apex acuminate, base truncate, margin apparently entire but bearing very minute pale brown spinules. veins obscure above and below, forked once or twice, free, reaching the margin; pinnae dark green, glabrous above and below; texture coriaceous. Sori linear along the costa, not reaching the base and apex, parallel, indusiate; indusia pale brown, firm, margin serrate; spores reniform, yellowish-brown, exine with faint thin, reticulate thickenings.

Anticancer activities: In the evaluation on the anticancer property of this fern, selective cytotoxicity exhibits against human colon cancer cells HT-29 and HCT-116, human colonic adenocarcinoma HT-29, human colonic carcinoma HCT-116, human breast adenocarcinoma MCF-7 and human leukemia K562 (Lai & Lim, 2010).

2.14. *Dryopteris* Adans.

The genus is terrestrial herb with erect rhizome. Dense scales are present at the apex and scales are ovate-lanceolate. The characters of lamina include ovate-lanceolate shape, bipinnatifid, acuminate apex. Primay pinnae are ascending, falcate, subopppposite at the basal part of the lamina. Largest pinna ovate-lanceolate, apex acuminate, base cuneate; basal pairs usually bear an accessory branch; pimary pinna of the largest frond, subopposite or alternate, anadromous below, isodromous above; basal few pairs shortly stalked, others

sessile or adnate, ovate-lanceolate, decurrent on the basal basiscopic side, apex acute, basiscopic base broadly cuneate, acroscopic base truncate or broadly cuneate, margin lobed onesixth to five-sixth way to the costules; lobes oblong, apex acute or rounded, margin entire or toothed; rachules narrowly winged on either side, shallowly grooved and dark brown above, stramineous below; veins indistinct above, slightly distinct below, up to five pairs, forked once or twice, not reaching the margin; pinnae dark green; texture herbaceous; scattered small scales borne on rachis and costa. Sori median on the veinlets; pale brown, glabrous with thin membraneous border; spores dark brown, with prominently winged, irregularly folded perispore.

Anticancer activity: Fernane 9(11)-ene and 22-hydroxy hopane are the two anticancer compounds found in *D. crassirhizoma* (Konoshima et al., 1996).

2.15. *Oleandra* Cav.

Rhizome is creeping and white waxy in the older parts, and long leafless parts alternating with more or less dense clusters of very short phyllopodia. Branches usually in opposite pairs; in cross section is with weak sclerenchyma sheath and without sclerified strands; roots scattered, usually with long unbranched parts. Scales persistently covering the rhizome, peltate base appressed, with dark centre and lighter margin, acumen brown, usually recurved, with ciliate margin, apex twisted and with frizzy cilia. Fronds monomorphic; stipe with dark coloration on abaxial side, often distinctly bicolorous, with catenate hairs; lamina base truncate to rounded, apex often abruptly caudate, texture thin herbaceous, translucent, both surfaces densely set with catenate hairs, costa on lower surface in basal half of lamina with dark coloration, with copious long pale scales. Sori close to costa, indusium thin, glabrous or hairy. Sporangial stalk without glands below the sporangium. Spores are echinate and ridged, perispore solid.

Anticancer activity: Gammacerane is an anticancer compound present in *O. wallichii* that inhibits in vivo two stage carcinogenesis in mouse skin papillomas (Konoshima et al., 1996).

2.16. *Asplenium* L.

The genus is a terrestrial herb with creeping rhizome. Scales are brownish, clathrate, lanceolate, margins fimbriate with glandular hairs. Fronds simply pinnate; scaly beneath, sparsely above; lamina lanceolate in outline; pinnae, lanceolate, long-acuminate, crenulate, coriaceous, veins forked near the costa, veinlets again forked, not reaching the margin; terminal pinna smaller, gemmiparous. Sori are linear, reddish brown; indusia linear, paler. Sporangial capsule is globose. Spores yellowish, elliptic or planoconvex with thickly folded perine.

Anticancer activity: Two species from this genus, *A. polyodon* and *A. nidus*, have anticancer, antidiabetic and antiviral activity. (Singh, 1999; Lee et al., 2003)

2.17. *Ophioglossum* L.

Terrestrial herbs are with fleshy small, sub-globose, subterranean rhizome. Fronds bipartite; sterile blade, oblong or elliptic, obtuse or apiculate, subcoriaceous, veins anastomosing; fertile spike arising from the base of the sterile blade, oblong, acute, flattened, fleshy

with wavy margins. Sporangia globose sunken and arranged in a row on either side of the stalk.

Anticancer activity: *O. gramineum* and *Hexastylis arifolia* have anticancer, antidiabetic and antiviral activities (Singh, 1999; Lee et al., 2003)

2.18. *Pteridium* Gleditsch; Scopoli

Common bracken is herbaceous perennial plant, deciduous in winter. The large, roughly triangular fronds are produced singly, arising upwards from an underground rhizome. It dies back to ground level in autumn. The rhizome grows up to deep, because it regrows in the spring from an underground rhizome. *P. aquilinum* tends to be found in dense colonies on genetically identical fronds. In the spring as the plant enters its growing cycle, fiddle heads are first sent up from the rhizome. The density and area covered by a single rhizome maximizes that rhizome's chance of biological success when sending up new growth. The new growth presents as vertical stalks, coiled and covered in silver-gray hairs, that can be several feet in height before unfurling into fronds.

Anticancer activity: β-caryophyllene, linalool, geranial and γ-terpinene in the genus exhibit anticancer and antioxidative activities (Nwiloh et al., 2014)

2.19. *Dicranopteris* Bernh.

The genus *Dicranopteris* means two branched. Species name of *D. linearis* means narrow and parallel sided and refers to the fronds. Large fern, sprawling up to 3 metres, has characteristic forking stems growing along the ground with compound stalked fronds. The main rachis is divided into two distinct rachis branches. Trilete shaped spores in sporangia lack indusium. The sporangia are found on the underside of lobes of the ultimate two branches.

Anticancer activities: *D. linearis* has anticancer property proved through in vitro MTT assay on MCT-7, HeLa, HT-29, HL-60, K-562 and MDA-MB-231 cell lines (Sukumaran & Kuttan, 1991).

2.20. *Sellaginella* P. Beauv.

Terrestrial herbs are with erect cylindrical green stem, branched from base. Branches are many, erecto-patent and compound. Rhizophores are in tufts towards basal portion, slender, cylindrical. Leaves pale green, green or light brownish, heteromorphic, distant on main stem, closely arranged in four rows on branches; median leaves membranous, ovate, aristate, margin dentate or denticulate; lateral leaves membranous, ovate-lanceolate, acute, proximal margin serrate at base, serrulate to towards apex; axillary leaves membranous, ovate-lanceolate, acute, oblique at base, margin dentate towards apex. Strobili are terminal, sessile; sporophylls monomorphic, spiral, ovate, aristate, oblique, dentate or denticulate. Megasporangia are towards base, microsporangia towards apex. Megaspores are orange-red, trilete, tetrahedral, papillate. Macrospores are creamy white, globose, tetrahedral, reticulate.

Anticancer activities: Bioactivity guided fractionation of the leaves of *S. willdenowii* affords three known biflavones, 4',7"-di-*O*-methylamentoflavone, isocryptomerin and 7"-*O*-methylrobustaflavone, that are significantly cytotoxic against a panel of human cancer cell lines (Silva et al., 1995). In vitro MTT assay on

human colon cancer cell lines gives idea of anticancer property of *S. lepidophyla* (Lee & Lin, 1988). *S. willdenowii, S. lepidophyla, S. labordei, S. moellendorffii, S. delicatula, S. tamariscina,* and *S. doederleinii* are shown to have cytotoxic and antimutagenic effects due to the presence of bioflavonoids (Silva et al., 1995; Sun et al., 1997; Lee et al, 1999). *S. moellendorffii* exhibits in vitro cytotoxic activity on human ovarian adenocarcinoma cells, cervical carcinoma (HeLa) and foreskin fibroblast (FS-5) (Lin et al., 2000; Su et al., 2000). *S. tamariscina* shows in vitro antiproliferative activity in leukemia cells (Chen et al., 2005; Gayathri et al., 2005). *S. doederleinii* induces antimutagenic activity against picrolonic acid induced mutation and exhibits antiproliferative activity against human cancer cells (Woo et al., 2005; Gao et al., 2007).

2.21. *Odontosoria* (C.Presl) Fee

Odontosoria from family Lindsaeaceae is terrestrial herb with creeping, branched rhizome. Dense dark brown hairs cover the rhizome. Fronds are quadripinnate and finely dissected. Stipe is long, yellow and hairy at the very base. Fronts have oblong or elliptic-lanceolate shaped lamina. Primary pinnae triangular or ovate-acuminate in outline and show alternate stalk arrangement. Secondary pinnae are rhomboid or elliptic in outline with alternate phyllotaxy. Tertiary pinnae are obovate or obtriangular in outline. Quaternary pinnae obtriangular shaped, truncate at apex, cuneate at base, entire. Sori are elliptic at the apex of the quaternary pinnae, dark brown. Sporangial capsule is subglobose and a stalk present. Spores are yellow, hyaline, smooth.

Anticancer activities: In traditional Chinese medicine, *O. chinensis*, either alone or in combination with other ingredients, is considered effective in cancer treatments, detoxification and hemostasis, resulting in its reputation as an "all-purpose antidote" (Wu et al., 2017).

2.22. *Macrothelypteris* (H.Ito) Ching

The terrestrial plant is under the family Thelypteridaceae. Creeping rhizome is with dense scales. Scales are dark brown, linear, densely acicular and hairy. Fronds are bipinnate; stipe, scaly at base; lamina ovate-lanceolate in outline, rachis grooved above, pinnae elliptic-lanceolate, acuminate; pinnules alternate, lanceolate, acuminate, cuneate to decurrent at base, thin membranous, progressively reduced to both ends, deeply lobed to costa; lobes oblong, serrate, obtuse to rounded, falcate; costules grooved above, raised below, hispid on both sides, veins pinnate, forked free. Sori are circular, yellow color present on median of veins. Sporangial capsule is subglobose. Spores are ellipsoid with thinly folded perine.

Anticancer activities: Protoapigenone is an antitumour compound isolated from root of *M. torresiana*. It is a main constituent of the total flavonoid fraction that exhibits in vitro antitumour activity against lung cancer (Huang et al., 2010).

3. Outlook

Pteridophytes, a group of plants that includes ferns and their allies, have been shown to possess various anticancer properties. Several studies have investigated the cytotoxicity of extracts and compounds derived from different parts of pteridophytes, and have found them to be effective against a range of cancer cells. Some of the mechanisms through which

pteridophytes exhibit their anticancer properties include inducing cell cycle arrest, promoting apoptosis, and inhibiting angiogenesis. Furthermore, some pteridophyte compounds have been shown to enhance the efficacy of chemotherapy drugs. Several researchers have studied the phytochemical and medicinal uses of lycophytes and ferns in recent years that demonstrate the importance of ferns and their allies in plant science fields. The medicinal uses of pteridophytes are specifically due to their antioxidant, antidiabetic, anticancer, antiviral, antiinflammatory, wound healing, antimicrobial and anti-Alzheimer activities. The main medicinal pteridophytes belong to the following families: Davalliaceae, Equisetaceae, Lygodiaceae, Ophioglossaceae, Polypodiaceae, Psilotaceae, Pteridaceae, Salviniaceae, Selaginellaceae, Lindsaeaceae, Woodsiaceae, Aspleniaceae, Marattiaceae, Blechnaceae, Polypodiaceae and Thelypteridaceae. Present data may contribute to a better understanding of the uses of fern beyond ornamental purposes; especially those that promote the use and development for medicinal purposes.

References

1. Cai, Y., Luo Q., and Sun, M., et al., 2004. Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anti-cancer. *Life Sci.* 74(17):2157-2184
2. Chang, H.C., Huang, G.J., and Agrawal, D.C. (2007). Antioxidant activities and polyphenol contents of six folk medicinal ferns used as "Gusuibu". *Bot. Stud.* 48:397-406.
3. Cui, C.B., Tezuka, Y., and Kikuchi, T., (1990). Constituents of fern, *Davallia mariesii* Moore. I. Isolation and structures of Davallialactone and a new flavanone glucuronide. *Chem. Pharm. Bull.* 38:3218-3225
4. Defilpps, R.A., Maina, S.L., and Pray L.A., (1988). The Palauan and Yap Medicinal Plant Studies of Masayoshi okabe. The National Museum of Natural History Smithsonian Institution, Washington DC, USA. 1941-1943.
5. Gao, L.L., Yin, S.L., and Li, Z.L. (2007). Three novel sterols isolated from *Selaginella tamariscina* with antiproliferative activity in leukemia cells. *Plant Med.* 73:1112-1115.
6. Woerdenbag, H.J., Lutke, L.R., and Bos, R., (1996). Isolation of two cytotoxic diterpenes from the fern *Pteris multifida. Z. Naturforsch.* 51(9-10):635-638.
7. Huang, X.H., Xiong, P.C., and Xiong, C.M. (2010). In vitro and in vivo antitumor activity of *Macrothelypteris torresiana* and its acute/sub-acute oral toxicity. *Phytomedicine.*17:930-934.
8. Konoshima, T., Takasaki, M., and Tokuda, H., (1996). Antitumor-promoting activities of triterpenoids from ferns. *Biol. Pharm. Bull.* 19(7):962-965.
9. Lai, H.Y., Lim, Y.Y., and Kim, K.H. (2010). *Blechnum orientale* Linn. - A fern with potential as antioxidant, anti-cancer and antibacterial agent. BMC Complement. *Alternat. Med.* 10(15):1-8.
10. Lee, H., and Lin, J.Y., (1988). Antimutagenic activity of extracts from anti-cancer drugs in Chinese medicine. *Mutat. Res.* 204(2):229-234.
11. Li, J.H., He, C.W., and Liang, N.C. (1999). Effects of antitumor compounds isolated from *Pteris semipinnata* L. on DNA topoisomerases and cell cycle of HL-60 cells. *Acta. Pharmacol. Sin.* 20(6):541-545.
12. Neneng, L., Pujirahadju, A., Ferayani, F., and Widayat, T. (2020), Anti-tumor Potential Ethnomedicinal Plants from Dayak Tribes in Central Kalimantan, *J. Biol. Biol. Ed.* 12(3): 422-430
13. Milan, C.M., Avijit, D., and Abdur, R. (2013). Evaluation of antioxidant, cytotoxic and antimicrobial properties of *Drynaria quercifolia. Int. Res. J. Pharm.* 4(7):46-4
14. Petard, P., and Raau, T. (1972). The Use of Polynesia Medicinal Plants in Tahitian Medicine. South Pacific Commission. Noumea, New Caledonia.
15. Punzon, C., Alcaide, A., and Fresno, M. (2003). In vitro anti-inflammatory activity of *Phlebodium decumanum.* Modulation of tumor necrosis factor

and soluble TNF receptors. *Int. Immonopharmacol.* 3(9):1293-1299.

16. Santhosh, K.S., Samydurai, P., and Nagarajan, N. (2014). Indigenous knowledge on some medicinal pteridophytic plant species among the Malasar tribe's in Valparai Hills, Western Ghats of Tamil Nadu. *Am. J. Ethnomed.* 1(3):164-173.
17. Sarker, M.A.Q., Mondol, P.C., and Alam, M.J. (2011). Comparative study on antitumor activity of three pteridophytes ethanol extracts. *Int. J. Agric Tech.* 7(6):1661-1671.
18. Silva, G.L., Chai, H., and Gupta, M.P. (1995). Cytotoxic biflavonoids from *Selaginella willdenowii. Phytochem.* 40(1):129-134.
19. Wu, S., Li, J., Wang, Q., Cao, H., Cao, J., and Xiao, J. (2017). Seasonal dynamics of the phytochemical constituents and bioactivities of extracts from *Stenoloma chusanum* (L.) Ching, *Food Chem.* Toxicol. 18:458-466.
20. Sukumaran, K., and Kuttan, R. (1991). Screening of 11 ferns for cytotoxic and antitumor potential with special reference to *Pityrogramma calomelanos. J. Ethnopharmacol.* 34(1): 93-96.
21. Uma, R., and Pravin, B. (2013). In vitro cytotoxic activity of *Marsilea quadrifolia* Linn. of MCF-7 cells of human breast cancer. *Int. Res. J. Med. Sci.* 1(1): 10-13.
22. Viral, D., Shivanand, P., and Jivani N.P. (2011). Anticancer evaluation of *Adiantum venustum* Don. *J. Young Pharm.* 3(1):48-54.
23. Woo, E.R., Lee, J.Y., and Cho I.J. (2005). Amentoflavone inhibits the induction of nitric oxide synthase by inhibiting NF-κB activation in macrophages. *Pharm. Res.* 51(6):539-546.
24. Singh, H.B. (1999). Potential medicinal pteridophytes of India and their chemical constituents. *J. Econ. Tax. Bot.* 23(1):63-78.

Menispermaceae Members as Sources of Anticancer Compounds

Karthika T., *Anoop K.

PG & Research Department of Botany, The Zamorin's Guruvayurappan College
Kozhikode, 673014, Kerala, India.
*Corresponding author: anoopkuttiyil@gmail.com

Abstract: Cancer is one of the major health problems in both developed and developing countries. Cancer treatments including surgery, chemotherapy, radiation therapy and immunotherapy, are expensive and reported to have side effects. Many medicinal plants possess anticancer activity and act as rich source of medicines in cancer therapy. Pharmaceutical properties of medicinal plants are mainly attributed to the presence of several potential secondary metabolites such as alkaloids, phenols, flavonoids, quinones, tannins, saponins and sterols. Many active compounds from such groups of metabolites have resulted in the development of highly effective plant derived clinical drugs. Menispermaceae members of flowering plants are dioecious climbing plants. Majority of the members show wide distribution in tropical climates, and have long been used worldwide in traditional medicine to treat various ailments. Most species have been identified as a reservoir of bioactive metabolites with potent antipyretic, antimalarial, antimicrobial, antidepressant, antifertility, antiallergic, antiulcer, anticancer, antioxidant, antidiabetic, antiinflammatory and antivenom activities.

Keywords: Anticancer plants, Menispermaceae, medicinal plants, cancer therapy, cytotoxicity

Uncontrolled growth and proliferation of normal cells by the loss of control over the cell cycle causes the dreadful human disease, commonly called cancer (Pandey & Madhuri, 2009; Chanda & Nagani, 2013). It is one of the leading causes of death across the globe. According to the World Health Organization (WHO, 2020), about 19.3 million cancer cases and 9 million cancer deaths are reported to occur in the year 2020. The number of new cancer cases is estimated to go up to 28 million and cancer death is expected to cross 16 million by the year 2040. Several drugs are available to treat cancer but no medicines are found to be safe and effective to cure the disease. Current treatments available for patients diagnosed with cancer include surgery, chemotherapy, radiation therapy and immunotherapy which cause adverse effects like paresthesia, paralysis, ataxia, spasm, coma, infertility and also seriously affect the skin, hair, bone marrow, blood, gastrointestinal tract, kidney, lung, heart and brain (Schirrmacher, 2019). Therefore, the alternate treatments and therapies with less or no side effects are necessary to cure the disease. Herbal plants have been used as the primary source of medicine since ancient times. The advancement in the analytical and separation techniques helps to identify potential novel drug

candidates from plants (Dias & Urban, 2009). The secondary metabolites from many plants are reported to have anticancer properties and have long been used to treat cancer (Raina et al., 2014). About 60% of the chemotherapeutic agents are derived from natural sources (Cragg & Newman, 2005). Plant and plant based products have proved to be effective to treat cancer without side effects. Secondary metabolites produced by some medicinal plants including *Catharanthus roseus, Podophyllum peltatum, P. hexandrum, Taxus brevifolia, Ochrosia elliptica* and *Campototheca acuminata*, have been reported to be used as anticancer drugs to treat advanced stages of malignancies (Jagetia & Rao, 2006). Podophyllotoxin, camptothecin, taxol, vinblastine, vincristine etc. are some of the plant derived anticancer drugs that are in clinical applications all over the world. Plant derived anticancer drugs have largely contributed to the development of new drugs in cancer treatment (Cragg & Newman, 2005; Chanda & Nagani, 2013).

The Menispermaceae family of flowering plants consists of approximately 70 genera and 450 species (Maroyi, 2019). Majority of the plants belonging to this family are climbers and are widely distributed in tropical climates. They have long been used worldwide in traditional medicine for the treatment of various diseases such as fever, asthma, tuberculosis, dysentery, hyperglycemia, malaria and cancer. They are reservoirs of several potential secondary metabolites such as alkaloids, phenols, flavonoids, quinones, tannins, saponins and sterols. Most species in this family contain a wide range of pharmacologically active metabolites with potent antipyretic, antimalarial, antimicrobial, antidepressant, antifertility, antiallergic, antiulcer, anticancer, antioxidant, antidiabetic, antiinflammatory and antivenom activities (Jahan et al., 2010; Meenu & Radhakrishnan, 2020). Secondary metabolites produced by the members of Menispermaceae have already been reported as a potential source of chemotherapeutic agents against cancer treatment (Kupchan et al., 1961; Meenu & Radhakrishnan, 2020). Hence, an attempt has been made to review some medicinal plants belonging to Menispermaceae used for the prevention and treatment of cancer.

1. Anticancer plants in Menispermaceae

1.1. *Anamirta* Colebr.

A. cocculus (L.) Wight & Arn. is large woody climber, and widely distributed throughout India as well as South-East Asia. Leaves are large, simple, alternate, petiolate, sub coriaceous, cordate or truncate at the base and tufts of hairs present in the axils of the nerves except the basal ones. Small yellowish-white flowers are in long panicles that drooping from the nodes of the old wood (Jijith et al., 2016; Viswan et al., 2020).

Anticancer activities: The 50% ethanolic extract of *A. cocculus* has anticancer activity against leukemia cancer cell line in mice (Dhar et al., 1974).

1.2. *Cissampelos* L.

C. pareira is a perennial climbing herb that is commonly known as 'Malathangi', 'Karanakody' or 'Pambuveru'. It is distributed throughout tropical and subtropical India (Manu et al., 2012; Wimpy et al., 2016; Maroyi,

2019). The plant species is used to treat various diseases like inflammation, pain, hemorrhage, gastro toxicity, cancer, diarrhea, diabetes and cardiotoxicity (Wimpy et al., 2016). *C. pareira* secretes secondary metabolites such as alkaloids, flavonoids, tannins, volatile oils and glycosides. These metabolites are known to have potent bioactivities including antidiarrhoeal, antiprotozoal, antifertlity, antihelminthic, antiulcer, antioxidant, antileukemic, antihemorrhagic, hepatoprotectant, antihyperglycemic, antiplasmodial, antidengue, antitumour, antinociceptive and antiarthritic activity (Manu et al., 2012; da Silva Mendes et al., 2020).

C. sympodialis, Eichler, commonly called 'Bindweed' is herbaceous climbing plant species endemic to Brazil and secretes a wide range of secondary metabolites such as bisbenzylisoquinoline alkaloids (warifteine, methylwarifteine, roraimine and simpodialine), morphinic alkaloids (milonine), aporfinic alkaloids (laurifoline) and oxoaporphinic alkaloid (liriodenine). The medicinal herb is used for the treatment of asthma, bronchitis, influenza, rheumatism, cold, flu, arthritis, cough and urinary tract infection (Vieira et al., 2013; de Sales et al., 2015; da Silva Mendes et al., 2020).

Anticancer activities: Alkaloids isolated from roots of *C. pareira* include tropoloisoquinoline alkaloids such as pareirubrine A, pareirubrine B, azafloranthene, norimeluteine, norruffscine, tropone-isoquinoline and pareitropone that show antileukemic activities against P-388 cancer cell line (Morita et al., 1993a, 1993b, 1995). A bisbenzylisoquinoline alkaloid, cissampareine exhibits cytotoxicity against nasopharynx cancer cell line, KB (Kupchan et al., 1961). A chalcone flavone dimeric compound, cissampeloflavone isolated from *C. pareira* has low toxicity towards human KB cell line (Ramirez et al., 2003). The ethanolic extract of *C. pareira* shows protective effects against benzo(a)pyrene induced gastric cancer, tumour multiplicity and micronucleus polychromatic erythrocytes in mice (Amresh et al., 2007a). The hydro ethanolic root extract of *C. pareira* is active against stomach cancer and carcinogen metabolizing phase I and phase II enzymes along with antioxidant enzymes. The increase in glutathione S-transferase level and the enzyme activities involved in xenobiotic metabolism and maintaining the antioxidant status of cells show the chemo preventive potential of the root extract of *C. pareira* against chemotoxicity (Amresh et al., 2007b). The hydro ethanolic extract fractions, isoquinoline alkaloids, of *C. pareira* roots show cytotoxic effect against human oral squamous carcinoma (KB cells), human lung carcinoma (A549 cells) and human cervical cancer (SiHa cells) (Bala et al., 2019). The n-butanol fractions exhibit cytotoxic activity against KB cells. Among the isoquinoline alkaloids, cycleanine shows maximum activity against KB cells whereas hayatinine has a maximum cytotoxic effect against KB and A549 cell lines.

A bisbenzylisoquinoline compound, warifteine and a novel 8,14-dihydromorphinandienone alkaloid, milonine isolated from the leaves of *C. sympodialis* exhibit cytotoxic activity against rat hepatocytes and V79 fibroblasts. Milonine is less toxic than warifteine in both hepatocytes and V79 fibroblasts (Melo et al., 2003). The hydroalcoholic extract of *C. sympodialis* leaves inhibits in vitro proliferative

effect on resting B cells induced by lipopolysaccharide, antidelta- dextron and anti IgM. Similarly, the alcoholic extract blocks the function of B cell proliferation and immunoglobulin secretion through an increase in intracellular cAMP levels (Alexandre-Moreira et al., 2003).

1.3. *Cocculus* DC.

C. hirsutus is a perennial climbing shrub distributed in tropical and subtropical areas. It is commonly known as 'Broom Creeper' and in malayalam it is named as 'Pathalagarudakodi', 'Pathalamuli', etc. Leaves are simple, alternate, ovate, subdeltoid, obtuse and mucronate. Petiole is short, dark green, usually sub auriculate at the base. Flowers are small green in color, later develop to drupe (Das et al., 2016; Logesh et al., 2020). The root of *C. hirsutus* is used to treat various diseases such as eczema, gonorrhea, ophthalmia, neuralgia and leucorrhoea (Thavamani et al., 2014).

Anticancer activities: The crude alkaloid extract of *C. hirsutus* has shown cytotoxicity against breast (MCF-7), melanoma (UACC62) and renal (TK10) cell lines (De Wet et al., 2009). With an IC_{50} value of 78.5 µg/mL, the methanolic extract shows in vitro cytotoxic activity against the breast cancer cell line (MCF-3). Similarly, the extract has cytotoxicity against human cervical cancer cell line (HeLa) with IC_{50} value of 111 µg/mL; and exhibits in vivo antitumour activity against Dalton's Lymphoma Ascites cells in mice at doses of 200 and 400 mg/kg body weight (Thavamani et al., 2013; Thavamani et al., 2014).

1.4. *Coscinium* Colebr.

C. fenestratum is a woody climbing plant widely distributed in the Western Ghats of India and Sri Lanka. It is commonly known as 'Tree turmeric' and is considered as a critically endangered medicinal plant (Tushar et al., 2008). Wood is yellow with simple, alternate, deltoid, ovate, apex acuminate and base truncate leaves with entire margin. Inflorescence has supra axillary or cauliflorous nature. Female flowers are mostly from old wood (Tushar et al., 2008; Sasidharan, 2013). The stem is used to treat several diseases like diabetes, wounds, ulcers, fever, jaundice, snake bite, piles etc. (Sudharshan et al., 2010). The major alkaloid, berberine, along with protoberberine, jatrorrhizine, oxypalmatine, berberrubine etc. are the secondary metabolites produced by this plant (Tushar et al., 2008; Rai et al., 2013).

Anticancer activities: Methanol and hydro methanolic extracts of *C. fenestarum* induce antiproliferative activity against two lung cancer cell lines, A549 and LLC. Methanolic extract of *C. fenestratum* shows EC50 value of 1.65 µg/-mL against LLC; whereas the hydro-methanolic extract of 2.88 µg/mL and 2.84 µg/mL against A549 and LLC respectively (Ueda et al., 2002). The antiproliferative activity of 80% ethanolic extract, dichloromethane and aqueous fraction, reveals against human colorectal cancer cell lines (HCT-116 and SW480). DCM fraction exhibits antiproliferative activity through the activation of proapoptotic proteins and peroxisome proliferator activated receptor γ (PPARγ) (Rojsanga et al., 2010). The methanolic extract of *C. fenestratum* shows cytotoxic activity against ten cancer cell lines and one normal cell (PMBC). Berberine isolated from methanolic extract of *C. fenestratum* stem

shows the most cytotoxic activity against the acute promyelocytic leukemia cell line (HL-60) with an IC_{50} of 1.41 0.7 µg/mL (Tungpradit et al., 2010). The crude water extract of *C. fenestratum* exhibits anticancer activity against human head and neck cancer cell lines with IC_{50} value of 0.12 mg/mL after 48 h incubation through inhibiting the phosphorylation of P38 MAPK and pAkt and by reducing the expression of tumour suppressor protein P53 (Potikanond et al., 2015).

1.5. *Cyclea* Arn. ex Wight

C. peltata is locally known as 'Padathali' or 'Padakizhangu'. It is a dioecious climbing shrub, found throughout India and Sri Lanka. The plant is a well known medicinal plant used in traditional medicine to treat various ailments. It is a twining shrub with pilose stem and branches bearing simple alternate leaves. The flowers are small greenish yellow in axillary panicle (Shine et al., 2020). The plant secretes a wide variety of secondary metabolites such as flavonoids, tannins, alkaloids, diterpenes and saponins with potent antioxidant, antidiabetic, antiulcer, anticancer, diuretic and hepatoprotective activities (Kupchan et al., 1961; Odaya Kumar et al., 2016).

Anticancer activities: Tetradine isolated from the methanolic root extracts of *C. peltata* suppresses MDA-MB-231 (breast cancer cell lines) and PANC-1 (pancreatic cancer cell lines) through the activation of ROS and Caspase 8, 9 and 3 (Bhagya et al., 2019). Leaf extract of *C. peltata* shows anticancer activity against the human colon carcinoma cell line (HCT-116) with IC_{50} value of 800 µg/mL, 100 µg/mL and 50 µg/mL after 24, 48 and 72 h of incubation respectively (Jayaraman & Variyar, 2019).

1.6. *Diploclisia* Miers

D. glaucescens are woody climbers distributed in Indo-Malaysia and china. It is locally known as 'Vattavalli' or 'Vattoli'. Leaves are simple, alternate, broadly ovate to orbicular with obtuse apex and truncate base. Bright yellow flowers present in large drooping panicles (Sasidaran, 2013; Sagayaraj et al., 2014).

Anticancer activities: A novel dimeric proaporphine alkaloid, distepharinamide extracted from *D. glaucescens* stem inhibits the differentiation and proliferative expansion of CD4+Foxp3+ regulatory T cells; thereby, enhancing the antitumour immune responses in mice cells (Chen et al., 2022).

1.7. *Stephania* Kuntze

S. elegans is a woody or herbaceous climbing plant found in India, China, Nepal and Thailand. Petiolated leaves are simple, alternate, peltate, thin, dark green and glabrous on both surfaces. Axillary inflorescence is compound panicle of umbelliform cymes which possesses light green to dark purple flowers (IBP, 2020). It secretes secondary metabolites including epihernandolinol, N-methylcorydalmine, hasubanonin, aknadinin, cyclanoline, magnoflorine, isotetrandrine, isochondodendrine and cycleanine in turn use in treatment of boils and dysentery (Singh et al., 1981; Acharya & Pokhrel, 2006).

Anticancer activities: The methanol extract of *S. elegans* has cytotoxic activity against MCF-7 cells with IC_{50} value of 158.7±0.13 µg/mL (Sharma et al., 2017).

1.8. *Tinospora* Miers

T. cordifolia is a climbing deciduous shrub distributed in tropical part of India, Sri

Lanka, Bangladesh and China. It is known as 'Heart leaved moonseed plant' in english and 'Amirthavalli' or 'Chittamruthu' in malayalam. Leaves are simple, alternate, exstipulate, heart shaped with long, round and pulvinate petiole. Aerial adventitious roots arise from the branches to downward. Flowers are small, yellow which situated in axillary panicles. Male flowers are in clusters and female flowers are solitary. Seed curved in fleshy fruit (Saha & Ghosh, 2012; Spandana et al., 2013; Mittal et al., 2014). *T. cordifolia* produces a lot of secondary metabolites including alkaloids, diterpenoid lactones, steroids, glycosides, aliphatic compounds and polysaccharides (Mishra & Kaur, 2013; Spandana et al., 2013). The plant is used to treat various ailments such as fevers, diabetes, dyspepsia, jaundice, urinary problems, skin diseases, chronic diarrhea, dysentery, heart diseases, leprosy and helminthiasis (Reddy & Reddy, 2015).

T. crispa is a dioecious climbing plant distributed in South East Asia including Vietnam, Thailand, Malaysia, Indonesia and India (Koay & Amir, 2013). The plant is used extensively in the treatment of jaundice, rheumatism, urinary infections, fever, malaria, diabetes, internal inflammation, fracture, scabies, hypertension, reducing thirst, increasing appetite and cooling down the body temperature (Ahmad et al., 2016). The plant contains secondary metabolites such as alkaloids, diterpenes, flavones, phenolics, triterpenes, lactones, sterols, lignans and nucleosides with pharmacologically potent bioactivities like antibacterial, antiparasitic, antiinflammatory, antioxidant, immunomodulatory, cytotoxic, antimalarial, cardioprotective, antihyperglycemic and antidiabetic activities (Koay & Amir, 2013; Lekshmipriya et al., 2021).

Anticancer activities: The anticancer activity of palmatine, an alkaloid extracted from *T. cordifolia* against 7,12-dimethylbenz(a)anthracene (DMBA) which induces skin cancer in Swiss albino mice (Ali & Dixit, 2013). The enhanced glutathione (GSH), superoxide dismutase (SOD) and catalase and reduced level of lipid peroxidase show the role of palmatine in the detoxification pathway. Further, palmatine acts as an oral supplement that provides protection against skin cancer in Swiss albino mice. Ethanolic extract (50 %) of *T. cordifolia* (TCE) has antibrain cancer activity against C6 glioma cells (Mishra & Kaur, 2013). The TCE reduces the proliferation in dose dependent manner and induces differentiation in C6 glioma cells. The 50% methanolic extract of *T. cordifolia* stem exhibits cytotoxic activity against human breast cancer cell line MDA-MB-231 with IC_{50} value of 59 ± 4.05 µg/mL and 50± 2.01 µg/mL in 0.25% and 0.5% DMSO respectively (Ahmad et al., 2015). Different extracts, fractions and isolated compounds of *T. cordifolia* promisingly show anticancer activity against four different human cancer cell lines, KB (human oral squamous carcinoma), CHOK-1 (hamster ovary), HT-29 (human colon cancer) and SiHa (human cervical cancer) respectively. All extracts and fractions exhibit cytotoxic activity against KB and CHOK-1 cells. Among the isolated compounds, tinocordiside has maximum cytotoxic activity against KB and CHOK-1; while, yangambin is found to be cytotoxic against KB cell line and palmatine has cytotoxicity against KB and HT-29 cell lines

(Bala et al., 2015). Berberine extracted from *T. cordifolia* induces anticancer activity against colon cancer cells by inhibiting the expression of several genes responsible for the development, progression, proliferation, differentiation, cell motility and epithelial mesenchymal transition of colon cancer (Palmieri et al., 2019).

Methanol, water and chloroform extracts of *T. crispa* stem show antiproliferative activity against MCF-7, MDA-MB-231, HeLa and 3T3 normal fibroblast cell lines (Ibahim et al., 2011). The methanolic extract has maximum antiproliferative activity against MCF-7 with an IC_{50} value of 33.75 ± 4.65 µg/mL. Methanolic extract, (petroleum ether, chloroform and aqueous fraction) of *T. crispa* is evaluated for cytotoxic activity using brine shrimp lethal assay. In Brine shrimp lethality bioassay, the LC_{50} values of methanolic crude extract and petroleum ether, chloroform and aqueous fractions are found to be 6.43, 0.8. 4.58 and 7.46 g/mL respectively (Islam et al., 2013).

1.9. *Tiliacora* Colebr.

T. acuminata is a large twinning woody shrub distributed throughout India. Stem is twining, ribbed, woody, solid, green when young and brownish in older parts. Leaves are long, alternate, simple, exstipulate, cordate, truncate or rounded at the base with long, ribbed and twisted petiole. The plant secretes secondary metabolites such as alkaloids, anthraquinones, catechins, coumarins, flavonoids, phenols, quinones, saponins, steroids, sugar, glycosides, tannins and xanthoproteins (Kundu & Guha, 1975; Nishanthini et al., 2016).

T. triandra is a woody climbing shrub, commonly known as 'Bai Yanang' or 'Yanang' in Thai. It is an indigenous plant distributed in South East Asia including Cambodia, India, Laos, Malaysia, Myanmar, Thailand and Vietnam. Leaves are simple, alternate, lanceolate, broadly ovate, coriaceous, dark green, glabrous above and glaucous beneath. Inflorescence is axillary panicle, pseudoracemes or cauliflorous (IBP, 2020). The plant species is a rich source of alkaloids, fatty acids, essential oils and polyphenolic compounds which is used in the treatment of fever, gastrointestinal diseases, hypertension, diabetes, skin diseases and malaria (Makinde et al., 2019).

Anticancer activities: Hydro alcoholic extract/fractions of *T. acuminata* have cytotoxic activity against five different cell lines including A-549 (Human small cell lung carcinoma), MCF-7 (Human breast cancer), HepG2 (Human hepatic cancer), HT29 (Human colon cancer) and L6 (Rat normal skeletal muscle). The alkaloid fractions of *T. acuminata* is found to be maximum cytotoxic against HT-29 cell line (Rodrigues et al., 2020).

Oxoanolobine isolated from methanol extract of *T. triandra* shows cytotoxic activity against the lung cancer cell line (NCI-H187); whereas, the water extract found to be active against oral cavity cancer (KB) cell line (Rattana et al., 2016). Moreover, the ethanolic extract of *T. triandra* exhibits cytotoxicity against five different cancer cell lines of the respiratory system including oropharynx cancer (KB), larynx cancer (Hep2) and human lung cancer (A549, COR-L23, NCI-H226) cancer cell lines with an IC_{50} value ranging from 19.5 to 45.2 µg/mL (Juckmeta et al., 2019).

2. Outlook

Medicinal plants are rich sources of

novel pharmaceutical compounds with potent bioactivities. These compounds are known to possess promising therapeutic effects to treat various ailments including cancer. Anticancer agents derived from plants have gained much attention because plant derived anticancer drugs are safe, effective, non toxic and economical, and are used as an alternate source of modern medicine against cancer. Plant derived anticancer agents will remain to serve as lead molecules for anticancer drug development. Most species of Menispermaceae have long been used in ayurvedic preparations to cure various diseases. The members of Menispermaceae have been recognized as effective anticancer agents to fight against various cancers including breast cancer, leukemia, colon cancer, oral cancer, hepatic cancer and cervical cancer. Warifteine, methylwarifteine, roraimine, simpodialine, tetradine, tinocordiside and palmatine are some of the important bioactive metabolites produced by Menispermaceae members that are responsible for the anticancer activity to prevent different cancer types. Further efforts are now necessary to explore more plants having anticancer properties to develop novel chemotherapeutic drugs that can save humans from cancer.

References

1. Acharya, E., and Pokhrel, B. (2006). Ethnomedicinal plants used by Bantar of Bhaudaha, Morang, Nepal. *Our Nature*. 4(1):96-103. https://doi.org/10.3126/on.v4i1.508
2. Ahmad, R., Srivastava, A. N., Khan, M. A., and Khan, A. (2015). Evaluation of in vitro anticancer activity of stem of *Tinospora cordifolia* against human breast cancer and Vero cell lines. *J. Med. Plants Stud.* 3(4):33-37.
3. Ahmad, W., Jantan, I., and Bukhari, S. N. A. (2016). *Tinospora crispa* (L.) Hook. f. & Thomson: A review of its ethnobotanical, phytochemical, and pharmacological aspects. *Front. Pharmacol.* 7(3):1-19. https://doi.org/10.3389/fphar.2016.00059
4. Alexandre-Moreira, M. S., Piuvezam, M. R., and Pecanha, L. M. T. (2003). Modulation of B lymphocyte function by an aqueous fraction of the ethanol extract of *Cissampelos sympodialis* Eichl (Menispermaceae). *Braz. J. Med. Biol. Res.* 36(11): 1511-1522. https://doi.org/10.1590/S0100-879X2003001100010
5. Ali, H., and Dixit, S. (2013). Extraction optimization of *Tinospora cordifolia* and assessment of the anticancer activity of its alkaloid palmatine. *Sci. World J.* 2013. https://doi.org/10.1155/2013/376216
6. Amresh, G., Kant, R., Rao, C. V., and Singh, P. N. (2007). Chemomodulatory influence of *Cissampelos pareira* (L.) *hirsuta* on gastric cancer and antioxidant system in experimental animal. *Acta Pharm. Sci.* 49:71-83.
7. Amresh, G., Rao, C. V., and Singh, P. N. (2007). Evaluation of *Cissampelos pareira* against gastric cancer and enzymes associated with carcinogen metabolism. *Pharm. Biol.* 45(8):595-603. https://doi.org/10.1080/13880200701538641
8. Bala, M., Kumar, S., Pratap, K., Verma, P. K., Padwad, Y., and Singh, B. (2019). Bioactive isoquinoline alkaloids from *Cissampelos pareira. Nat. Prod. Res.* 33(5):622-627. https://doi.org/10.1080/14786419.2017.1402319
9. Bala, M., Pratap, K., Verma, P. K., Singh, B., and Padwad, Y. (2015). Validation of ethnomedicinal potential of *Tinospora cordifolia* for anticancer and immunomodulatory activities and quantification of bioactive molecules by HPTLC. *J. Ethnopharmacol.* 175:131-137. https://doi.org/10.1016/j.jep.2015.08.001
10. Bhagya, N., Chandrashekar, K. R., Prabhu, A., and Rekha, P. D. (2019). Tetrandrine isolated from *Cyclea peltata* induces cytotoxicity and apoptosis through ROS and caspase pathways in breast and pancreatic cancer cells. In Vitro Cell. *Dev. Biol. Animal.* 55(5):331-340. https://doi.org/10.1007/

s11626-019-00332-9

11. Chanda, S., and Nagani, K. (2013). In vitro and in vivo methods for anticancer activity evaluation and some Indian medicinal plants possessing anticancer properties: an overview. *J. pharmacogn. phytochem.* 2(2):140-152.

12. Chen, F. Y., Geng, C. A., Chou, C. K., Zheng, J. B., Yang, Y., Wang, Y. F., Li, T. Z., Li, P., Chen, J. J. and Chen, X. (2022). Distepharinamide, a novel dimeric proaporphine alkaloid from *Diploclisia glaucescens*, inhibits the differentiation and proliferative expansion of CD4+ Foxp3+ regulatory T cells. *Phytomedicine.* 107:154482.

13. Cragg, G. M., and Newman, D. J. (2005). Plants as a source of anti-cancer agents. *J. Ethnopharmacol.* 100(1-2):72-79. https://doi.org/10.1016/j.jep.2005.05.011

14. da Silva Mendes, J. W., Cunha, W. E. M., Rodrigues, F. F. G., Silveira, E. R., de Lima, R. D. P., and da Costa, J. G. M. (2020). *Cissampelos* genus: biological activities, ethnobotanical and phytochemical aspects. *Phytochem Rev.* 19(4):955-982. https://doi.org/10.1007/s11101-020-09695-4

15. Das, A., and Bondya, S. L. (2016). *Cocculus hirsutus* (L.) Diels: Diverse uses by the tribal population of Dumka. *The Biobrio*, 3(3):190-193.

16. de Sales, I. R. P., Machado, F. D. F., Marinho, A. F., Lúcio, A. S. S. C., Filho, J. M. B., and Batista, L. M. (2015). *Cissampelos sympodialis* Eichl. (Menispermaceae), a medicinal plant, presents antimotility and antidiarrheal activity in vivo. B*MC Complement Altern. Med.* 15(1):1-6. https://doi.org/10.1186/s12906-015-0578-7

17. De Wet, H., Fouche, G., and Van Heerden, F. R. (2009). In vitro cytotoxicity of crude alkaloidal extracts of South African Menispermaceae against three cancer cell lines. *Afr. J. Biotechnol.* 8(14): 3332-3335. https://doi.org/10.1016/j.sajb.2007.07.001

18. Dhar, M. L., Dhawan, B. N., Prasad, C. R., Rastogi, R. P., Singh, K. K., and Tandon, J. S. (1974). Screening of Indian plants for biological activity: Part V. *Indian J. Exp. Biol.* 12:444-467.

19. Dias, D. A., and Urban, S. (2009). Application of HPLC-NMR for the rapid chemical profiling of a Southern Australian Sponge, *Dactylospongia* sp. *J. Sep. Sci.* 32(4):542-548. https://doi.org/10.1002/jssc.200800548

20. Ibahim, M. J., Wan-Nor I'zzah, W. M. Z., Narimah, A. H. H., Nurul Asyikin, Z., Siti-nur Shafinas, S. A. R., and Froemming, G. A. (2011). Anti-proliperative and antioxidant effects of *Tinospora crispa* (Batawali). *Biomed. res.* 22(1):57-62.

21. India Biodiversity Portal. (2020). Online portal of India Biodiversity Portal. https://indiabiodiversity.org/species/list

22. Islam, A., Mahmud, Z. A., Rahman, S. M. A., Monirujjaman, and Saha, S. K. (2013). Evaluation of thrombolytic activity and brine shrimp lethality bioassay of methanol extract of stems of *Tinospora crispa. Int. J. Pharm. Sci.* 4(3):1148.

23. Jagetia, G. C., and Rao, S. K. (2006). Evaluation of the antineoplastic activity of guduchi (*Tinospora cordifolia*) in Ehrlich ascites carcinoma bearing mice. *Biol. Pharm. Bull.* 29(3):460-466. https://doi.org/10.1248/bpb.29.460

24. Jahan, R., Khatun, M. A., Nahar, N., Jahan, F. I., Chowdhury, A. R., Nahar, A., Seraj, S., Mahal, M. J., Khatun, Z., and Rahmatullah, M. (2010). Use of Menispermaceae family plants in folk medicine of Bangladesh. *Adv. Nat. Appl. Sci.* 4(1):1-9.

25. Jayaraman, S., and Variyar, E. J. (2019). Immunomodulatory, anticancer and antioxidant activities of *Cyclea peltata* (Lam.) Hook. F. & Thomson. *Int. J. Pharm. Pharm. Sci.* 11(10): 40–46.

26. Jijith, U. S., Nair, C. R. S., Ajithkumar, K. C., and Pramod, K. (2016). Phytochemistry and Pharmacology of *Anamirta cocculus* Willd. *Res. J. Pharmacogn. Phytochem.* 8(2). 90. https://doi.org/10.5958/0975-4385.2016.00017.0

27. Juckmeta, T., Pipatrattanaseree, W., Jaidee, W., Dechayont, B., Chunthorng-Orn, J., Andersen, R. J., and Itharat, A. (2019). Cytotoxicity to five cancer cell lines of the respiratory tract system and anti-inflammatory activity of Thai traditional remedy. *Nat. Prod. Commun.* 14(5). https://doi.org/10.1177/1934578X19845815

28. Koay, Y. C., and Amir, F. (2013). A review of the secondary metabolites and biological activities of *Tinospora crispa* (Menispermaceae). *Trop. J. Pharm. Res.* 12(4):641–649. https://doi.org/10.4314/tjpr.v12i4.30

29. Kundu, B. C., and Guha, S. (1975). *Tiliacora acuminata* (Lam.) Miers. *Nelumbo*, 17:147–156.

30. Kupchan, S. M., Yokoyama, N., and Thyagarajan, B. S. (1961). Menispermaceae Alkaloids II: The Alkaloids of *Cyclea peltata* Diels. *J. Pharm. Sci.* 50(2):164-167.

31. Lekshmipriya, S., Pandya, M. R., and Prajapati, B. (2021). Analytical profile of an unparalleled drug *Tinospora crispa* W.R.T Guduchi. *J. Pharm. Res. Int.* 33:195–203. https://doi.org/10.9734/jpri/2021/v33i49b33356

32. Logesh, R., Das, N., Adhikari-devkota, A., and Devkota, H. P. (2020). *Cocculus hirsutus* (L.) W. Theob. (Menispermaceae): A review on traditional uses, phytochemistry and pharmacological activities. *Medicines*. 7(11):69. doi:10.3390/medicines7110069

33. Makinde, E. A., Ovatlarnporn, C., Adekoya, A. E., Nwabor, O. F., and Olatunji, O. J. (2019). Antidiabetic, antioxidant and antimicrobial activity of the aerial part of *Tiliacora triandra*. *S. Afr. J. Bot.* 125: 337–343. https://doi.org/10.1016/j.sajb.2019.08.012

34. Manu, A., Tanvi, S., Anu, D., Neeraj, B., and Ahmad, S. A. (2012). An inside review of *Cissampelos pareira* Linn: A potential medicinal plant of India. *Int. Res. J. Pharm.* 3(12):38–41.

35. Maroyi, A. (2019). *Cissampelos torulosa* (Menispermaceae): a synthesis and review of its botany, medicinal uses and biological activities Alfred. *J. Pharm. Sci. Res*. 11(9):3385–3390.

36. Meenu, M. T., and Radhakrishnan, K. V. (2020). Menispermaceae family of plants and its action against infectious diseases: A review. *Mapana J. Sci.* 19(2):33–71. https://doi.org/10.12723/mjs.53.4

37. Melo, P. S., De Medeiros Cavalcante, H. M., Barbosa-Filho, J. M., De Fátima Formiga Melo Diniz, M., De Medeiros, I. A., and Haun, M. (2003). Warifteine and milonine, alkaloids isolated from *Cissampelos sympodialis* Eichl: Cytotoxicity on rat hepatocyte culture and in V79 cells. *Toxicol. Lett.* 142(1–2):143–151. https://doi.org/10.1016/S0378-4274(03)00064-X

38. Mishra, R., and Kaur, G. (2013). Aqueous ethanolic extract of *Tinospora cordifolia* as a potential candidate for differentiation based therapy of glioblastomas. *PLoS ONE*, 8(10).

39. Mittal, J., Sharma, M. M., and Batra, A. (2014). *Tinospora cordifolia*: a multipurpose medicinal plant-A. Review. *J. Med. Plants Stud.* 2:32–47.

40. Morita, H., Matsumoto, K., Takeya, K., and Itokawa, H. (1993). Azafluoranthene alkaloids from *Cissampelos pareira*. *Chem. Pharm. Bull.* 41(7):1307–1308.

41. Morita, H., Matsumoto, K., Takeya, K., Itokawa, H., and Iitaka, Y. (1993). Structures and solid state tautomeric forms of two novel antileukemic tropoloisoquinoline alkaloids, pareirubrines A and B, from *Cissampelos pareira*. *Chem. Pharm. Bull.* 41(8):1418–1422.

42. Morita, H., Takeya, K., and Itokawa, H. (1995). A novel condensed tropone- isoquinoline alkaloid, pareitropone,from *Cissampelos pareira*. *Bioorg. Med. Chem. Lett.* 5(6):597–598.

43. Nishanthini, A., Mohan, V., Jeeva, S., and Ramasamy Mohan, V. (2016). Phytochemical, in vitro antioxidant and antibacterial activity of flower extracts of *Tiliacora acuminata* (Lam.) Hook. f. & Thoms (Menispermaceae). *Chem. Sci. Rev. Lett.* 5(17):120–131.

44. Odaya Kumar, P., Srinivasu, K., Venkata Rao, V., Onchweri, A. N., and Muchiri, J. N. (2016). Antifungal activities of *Cyclea peltata* leave extracts in Tirunelveli, Tamilnadu. India. *Spec. Fung. Pathog. J.* 1(1):28–31.

45. Palmieri, A., Scapoli, L., Iapichino, A., Mercolini, L., Mandrone, M., Poli, F., Giannì, A. B., Baserga, C., and Martinelli, M. (2019). Berberine and *Tinospora cordifolia* exert a potential anticancer effect on colon cancer cells by acting on specific pathways. *Int. J. Immunopathol. Pharmacol*. 33:1–10. https://doi.org/10.1177/2058738419855567

46. Pandey, G., and Madhuri, S. (2009). Some medicinal plants as natural anticancer agents. *Pharmacogn. Rev.* 3(6):259–263.

47. Paudel, H. R., Bhattarai, S., and Kunwar, R. M. (2020). *Tinospora crispa* (L.) Hook. f. & Thomson (Menispermaceae): a new record for Nepal. *Feddes. Repert.* 131(3):159–162. https://doi.org/10.1002/fedr.202000001

48. Potikanond, S., Chiranthanut, N., Khonsung, P., and Teekachunhatean, S. (2015). Cytotoxic effect of *Coscinium fenestratum* on human head and neck cancer cell line (HN31). *Evid. Based Complementary Altern. Med.* https://doi.org/10.1155/2015/701939

49. Rai, R. V., Rajesh, P. S., and Kim, H. M. (2013). Medicinal use of *Coscinium fenestratum* (Gaertn.) Colebr.: An short review. *Orient. Pharm. Exp. Med.* 13(1):1–9. https://doi.org/10.1007/s13596-012-0094-y

50. Raina, H., Soni, G., Jauhari, N., Sharma, N., and Bharadvaja, N. (2014). Phytochemical importance of medicinal plants as potential sources of anticancer agents. *Turk. J. Bot.* 38(6): 1027–1035.

https://doi.org/10.3906/bot-1405-93

51. Ramírez, I., Carabot, A., Meléndez, P., Carmona, J., Jimenez, M., Patel, A. V., Crabb, T. A., Blunden, G., Cary, P. D., Croft, S. L., and Costa, M. (2003). Cissampeloflavone, a chalcone-flavone dimer from *Cissampelos pareira*. *Phytochemistry*. 64(2): 645–647. https://doi.org/10.1016/S0031-9422(03)00241-3

52. Rattana, S., Cushnie, B., Taepongsorat, L., and Phadungkit, M. (2016). Chemical constituents and in vitro anticancer activity of *Tiliacora triandra* leaves. *Pharmacogn. J.* 8(1): 1–3. https://doi.org/10.5530/pj.2016.1.1

53. Reddy, N. M., and Reddy, R. (2015). *Tinospora cordifolia* chemical constituents and medicinal properties: A review. *Sch. Acad. J. Pharm.* 4(8): 364–369.

54. Rodrigues, J., Hullatti, K., Jalalpure, S., and Khanal, P. (2020). In-vitro cytotoxicity and in silico molecular docking of alkaloids from *Tiliacora acuminata*. *Indian J. Pharm. Educ. Res*. 54(2):S295–S300. https://doi.org/10.5530/ijper.54.2s.86

55. Rojsanga, P., Sukhthankar, M., Krisanapun, C., Gritsanapan, W., Lawson, D. B., and Baek, S. J. (2010). In vitro anti-proliferative activity of alcoholic stem extract of *Coscinium fenestratum* in human colorectal cancer cells. *Exp. Ther. Med.* 1:181–186. https://doi.org/10.3892/etm

56. Sagayaraj, M. I., Britto, S. J., Arulappan, M. T., Krishnakumar, J., Thomas, S., and George, M. (2014). Antimicrobial studies and phytochemical screening of the leaves in *Tiliacora acuminata* (Lam.) Hook. & Thomson and *Diploclisia glaucescens* (Blume) Diels. (Menispermaceae). *Asian J. Pharm. Res.* 4(2):82–86.

57. Saha, S., and Ghosh, S. (2012). *Tinospora cordifolia*: One plant, many roles. *Ancient Science of Life.* 31(4):151–159. https://doi.org/10.4103/0257-7941.107344

58. Sasidharan, N. (2013), Flowering plants of Kerala: CD- ROM ver 2.0. Kerala Forest Research Institute, Peechi, Kerala.

59. Schirrmacher, V. (2019). From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review). *Int. J. Oncol.* 54(2):407–419. https://doi.org/10.3892/ijo.2018.4661

60. Sharma, R., Chandan, G., Chahal, A., and Saini, R. V. (2017). Antioxidant and anticancer activity of methanolic extract from *Stephania Elegans*. *Int. J. Pharm. Pharm. sci.* 9(2):245. https://doi.org/10.22159/ijpps.2017v9i2.16204

61. Shine, V. J., Anuja, G. I., Suja, S. R., Raj, G., and Latha, P. G. (2020). Bioassay guided fractionation of *Cyclea peltata* using in vitro RAW 264.7 cell culture, antioxidant assays and isolation of bioactive compound tetrandrine. *J. Ayurveda Integr. Med.* 11(3):281–286. https://doi.org/10.1016/j.jaim.2018.05.009

62. Singh, R. S., Kumar, P., and Bhakuni, D. S. (1981). The alkaloids of *Stephania elegans*. *J. Nat. Prod.* 44(6):664–667. https://doi.org/10.1021/np50018a006

63. Spandana, U., Ali, S. L., Nirmala, T., Santhi, M., and Sipai Babu, S. D. (2013). A review on *Tinospora cordifolia*. *Int. J. Curr. Pharm. Rev. Res.* 4(2):61–68.

64. Sudharshan, S. J., Prakash Kekuda, T. R., and Sujatha, M. L. (2010). Antiinflammatory activity of *Curcuma aromatica* Salisb. and *Coscinium fenestratum* Colebr.: A comparative study. *J. Pharm. Res.* 3(1):24–25.

65. Thavamani, B. S., Mathew, M., and Dhanabal, S. (2013). In vitro cytotoxic activity of Menispermaceae plants against HeLa cell line. *Anc. Sci. Life.* 33(2):79. https://doi.org/10.4103/0257-7941.139040

66. Thavamani, B. S., Mathew, M., and Palaniswamy, D. S. (2014). Anticancer activity of *Cocculus hirsutus* against Dalton's lymphoma ascites (DLA) cells in mice. *Pharm. Biol.* 52(7): 867–872. https://doi.org/10.3109/13880209.2013.871642

67. Tungpradit, R., Sinchaikul, S., Phutrakul, S., Wongkham, W., and Chen, S.-T. (2010). Anti-cancer compound screening and isolation: *Coscinium fenestratum, Tinospora crispa* and *Tinospora cordifolia*. *Chiang Mai J. Sci.* 37(3):476–488.

68. Tushar, K. V., George, S., Remashree, A. B., and Balachandran, I. (2008). *Coscinium fenestratum* (Gaertn.) Colebr. -A review on this rare, critically endangered and highly-traded medicinal species. *J. Plant Sci.* 3(2):133–145.

69. Ueda, J. Y., Tezuka, Y., Banskota, A. H., Le Tran, Q., Tran, Q. K., Harimaya, Y., Saiki, I., and Kadota, S. (2002). Antiproliferative activity of Vietnamese medicinal plants. *Biol. Pharm. Bull.* 25(6):753–760. https://doi.org/10.1248/bpb.25.753

70. Vieira, G. C., De Lima, J. F., De Figueiredo, R. C. B. Q., Mascarenhas, S. R., Bezerra-Santos, C. R., and Piuvezam, M. R. (2013). Inhaled *Cissampelos sympodialis* down-regulates airway allergic reaction by reducing lung CD3+T cells. *Phytother. Res.* 27(6):916–925. https://doi.org/10.1002/ptr.4791

71. Viswan, A. K., Pushapalatha, E., Arivudainambi, S., and Selvamuthukumaran, T. (2020). Fractional extraction, isolation and identification of biologically active compounds from *Anamirta cocculus* (L.) Wight & Arn to control *Culex quinquefasciatus* Say and *Aedes albopictus* Skuse. *J. Commun. Dis.* 52(3):53–57. https://doi.org/10.24321/0019.5138.202031

72. WHO (2020) Fact sheet. World Health Organisation Committee.

73. Wimpy, K., Yadav, S. K., Kumkum, M., and Manoj, G. (2016). Phytochemical and pharmacological review on *Cissampelos pareira. Indian J. Pharm. Pharmacol.* 3(4):152–154. https://doi.org/10.18231/2393-9087.2016.0002

Potential Anticancer Agents in Simaroubaceae

Shirin P.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: shirinvaseem28@gmail.com

Abstract: The family Simaroubaceae includes a number of plants with anticancer properties which can be used in future for drug designing against cancer. Cancer is a disease in which some of the body cells grow and divide uncontrollably and spread to other parts of the body. It is the second most leading cause of death in the world. But survival rates are now improving due to the application of modern pharmacology. Plant derived medicines are now using extensively in the treatment of cancer.

Keywords: Simaroubaceae, anticancerous, cytotoxicity, antiproliferative, drug designing

Simaroubaceae is a small mostly tropical family in the order Sapindales. The family includes 32 genera and more than 170 species of trees and shrubs having pantropical distribution. The main distribution hot spots are located at tropical areas of America, extending to Africa and Madagaskar. The family is characterised by the presence of many quassinoides, secondary metabolites responsible for a wide range of biological activities such as antitumour, antimalarial, antiviral, insecticidal, deterrant, antiparasitic and herbicidal. Due to the chemical diversity, it is worth noting that it can be characterized as a promising source of bioactive molecules with remarkable research potential. Since 1961, when the first quassinoid structure was elucidated, the growing interest on various species of Simaroubaceae family resulted in the isolation and identification of more than 200 currently known quassinoides (Vieira, 2006). Many species of Simarubaceae display prominent anticancer properties. The main genera include *Ailanthus, Brucea, Simarouba, Quassia, Picrolemma, Simaba* and *Picrasma.* Nevertheless, many of it's species have not been studied or remain unexplored.

1. Anticancer plants in Simaroubaceae

1.1. *Ailanthus* Desf.

The genus is known as 'Tree of Heaven' and native from East Asia to northern Australasia. It is rapidly growing deciduous tree, becomes a widespread invasive species across North America. It can grow rapidly to 25-30 meters. Leaves are odd-pinnately compound with 11-41 leaflets. Twigs are light brown, very stout and covered with fine hairs when young. Bark is smooth, striped, grey-brown or light brown which cracks with age and exhibits light coloured grooves. Inflorescence is terminal panicles. Flowers are radially symmetrical with 5-6 petals. Fruits are 3-8cm long schizocarp with 2-5 samaroid mericarps.

Anticancer activities: *A. altissima* plays major role in tumour therapy in which the bark of the plant is used in the treatment of colonic, cervical, rectal and breast cancer (Effereth et al., 2007). Ailanthone, a quassinoid extract from the plant exhibits in vitro growth inhibitory effects against several cancer cell lines including HepG2, Hep3B, R-HepG2, HeLa and A549 cells. Ailanthone could induce mitochondrial membrane depolarization and caspase-3 activation in Jurkat cancer cells (Rosati et al., 2004). There are three cell cycle regulation points in G_1, S and G_2 phases which can modulate cell cycle progression. Induction of tumour cell cycle arrest in G_0/G_1 phase is a target for the development of antitumour therapy (Chen et al., 2010). Certain molecules, including tumour protein p53. serve a role in cell cycle inhibition and induction of apoptosis. The cells may be arrested in the G_1 phase and apoptosis may be induced by p53. Analysis of the cell cycle demonstrates an increase in the number of MCF-7 cells in G_0/G_1 phase following treatment with ailanthone and a decrease in the number of cells in S phase, indicating that the cells arrests in the G_0/G_1 phase by so that the cells could not enter S phase or perform DNA synthesis, thus inhibiting proliferation. This checkpoint involves in the effects of ailanthone on the cell cycle of MCF-7 cells. Caspases are mediators of apoptosis, of which caspase 3 are frequently activated death protease that catalyzes specific cleavage of numerous cellular proteins. Ailanthone can induce apoptosis in tumour cells. Apoptosis is an active cell suicide process that is regulated by p53. The effect of Bcl-2 depends on the ratio of its expression with Bax; this ratio determines whether cells undergo apoptosis or survival upon signal stimulation. Excessive Bax expression in cells promotes apoptosis, whereas excessive Bcl-2 expression promotes survival.

The treatment of MCF-7 cells with 0.5, 1.0, 2.0, 4.0 or 8.0 μg/ml ailanthone for 48 h increases Bax expression whereas Bcl-2 decreases markedly. The mechanism underlying ailanthone induces MCF-7 cell apoptosis which is associated with the adjusting of the Bax and Bcl2 family proteins. The ailanthone exhibits an inhibitory effect on cellular proliferation and induces apoptosis. The promotion of Bax and the inhibition of Bcl2 proteins may further enhance the antitumour effect. Genetic abnormalities in the phosphatidylinositol 3-kinase (PI3K)/RAC serine/threonine-protein kinase (AKT) signalling pathway are common in human tumours. The role of the PI3K/AKT pathway and its potential as a therapeutic target for tumour treatment has been investigated in a number of tumour types including lung, breast and renal cancer, neuroblastoma and glioblastoma. The PI3K/AKT signaling pathway and the downstream are potential targets for therapeutic intervention. The PI3K/AKT pathway serves a role in apoptosis, cell cycle progression and tumourigenesis; therefore, ailanthone induced apoptosis may involve the PI3K/AKT pathway, demonstrating that the ailanthone treatment of Huh7 cells results in a decrease in the expression of PI3K and AKT phosphorylation at threonine 408 and serine 473.

Treatment of MCF-7 cells with ailanthone causes cell apoptosis. The antitumour effect of ailanthone promises that the compound may be beneficial for the

treatment of breast cancer. Ailanthone, isolated from *A. altissima*, exhibits an inhibitory effect on MCF-7 cells and promotes cell apoptosis by upregulating Bax protein and mRNA. The compound inhibits the protein and mRNA expression of Bcl-2 and in turn expresses potential antitumour activity. Hence, it may be a new phytomedicine for tumour therapy.

1.2. *Brucea* J.F.Mill.

The shrubby plant, *B. javanica*, is commonly known as 'Macassar kernals', 'Java brucea' or 'Kosam'. It grows in the forests of India, Sri Lanka, Burma, China, Malaysia, Indonesia, Philippines and Australia. The wood is extremely bitter and the leaves are compound. The leaflets are lanceolate, rounded at the base, asymmetrical, with serrate margines and acuminate apex. The inflorescence is axillary panicle with minute unisexual flowers with four sepals and petals each. Androecium is with four stamens around a four lobed disc. Gynoecium made of four tiny apocarpous carpels. Fruit is small black, glossy and oblong drupe. The plant is widely used as an antipyretic, antimalarial, antiinflammatory, antiviral and detoxifying plant. It also used in the treatment of lung, prostate and gastro intestinal cancer.

Anticancer activities: *B. javanica* exerts anticancer effect on various types of cancer lines through inhibiting cell proliferation, inducing apoptosis and autophagy and restraining angiogenesis. *B. javanica* oil extracted from the plant by using petroleum ether has antiinflammatory, antimalarial, antiviral and antitumour properties (Zhang et al., 2011; Huang et al., 2017). The oil contains saturated and unsaturated fatty acids. Oleic acid and linoleic acid are the predominant components which have high anticancer activity and specific affinity for tumour cell membrane. It could inhibit the oxygen uptake of cancer cell during tumourigenesis. The unsaturated fatty acids also affect the oxygen free radical level and the lipid peroxidation rate of tissue.

Various extracts from this plant is effective on inhibiting different cancer types. These are proved to be useful against myeloma, glioma, laryngeal neoplasms, bowel cancer, lymphoma, epidermoid carcinoma, nasopharyngeal carcinoma, bladder cancer, osteosarcoma, prostate cancer, leukemia, oesophageal cancer, ovarian cancer, oral cavity cancer, colon cancer, cervical cancer, breast cancer, gastric cancer, hepatoma, pancreatic cancer and lung cancer (Guo, 2022). *B. javanica* triggers the generation of reactive oxygen species, release of cytochrome C, activation of mitochondrial apoptosis pathway and regulation of a series of signal pathways and proteins related to cancer. The molecular mechanism involved are inhibiting the PI3K/Akt/mTOR, NF-κB and Nrf2-Notch1 pathways, up or down modulating the levels of p53, p62, p21, Bax, and Bcl-2 and inhibiting the expression of matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) (Li et al., 2021).

1.3. *Simarouba* Aubl.

S. glauca is a native flowering tree of Florida, South America and the Caribean. It is commonly known as 'Paradise tree', 'Dysentery bark' and 'Bitter wood'. In India, the plant is known as 'Lakshmitaru'. The tree is well grown in warm humid tropical regions. It is an ever

green small to medium sized tree. Leaves are odd pinnately compound and leaflets are dark green above, light green below with entire margin and rounded leaf tip. Yellow flowers are arranged in panicle inflorescence. Fruits are oval in shape with inferior quality and bearing the seeds containing edible oil. The wood is generally insect resistant and used to prepare furniture, toys, matches and paper pulp. The plant is a potential oil seed tree with wide scope for biodiesel production.

Anticancer activities: Parts of *S. glauca* have been used extensively from ancient times to treat cancer. The leaves are the potential source of anticancer agents in traditional medicine. Decoction prepared by using leaves of this plant has been reported to be effective in treating various cancers. Quassinoids are thought to be the molecule that imparts anticancer properties to the plant. Bioactivity guided fractionation of chlorophorm extract of *S. glauca* found 6 alkaloid derivatives including a limonoid, an acyclic squalene type triterpanoid, two coumarins and two triglycerides. Of these 2 alkaloid derivatives, canthin-6-one, 2-hydroxycanthin-6-one, limonoid and melianodiol are found to have anticancer properties (Rivero-Cruze, 2005). Tricaprion extracted from the plant induces apoptosis in colorectal carcinoma cells. Induction of caspase -3/7 mediated apoptosis is a characteristic of HDAC inhibitors (Jose et al., 2018).

Moreover, the plant is able to treat leukemia. Among the extracts used, petroleum ether extract shows a higher order of in vitro anticancer activity by strongly inhibiting the proliferation of cancer cell lines (Vikas et al., 2021).In vitro anticancer activity of leaf extract is effective against three leukemic cell lines including K-562, MOL-3 and KG-1. Hence, the plants help to isolate pure compounds from *S. glauca* for anticancer drug designs (Prajapathi et al., 2018).

1.4. *Quassia* L.

The genus *Quassia* is mainly of tropical and subtropical distribution. It is a small tree growing mainly on sandy soils in lowland, forest and along the riverbanks. The plant is native to Northern-south America, Africa, Asia, Malasia and North-eastern Australia. The shrub grows upto 4-6 cm with compound leaves having winged midrib. Flowers are bright red with lanceolate petals. Fruits are aggregate of five black, elliptic or obovate drupes, attached to a fleshy red receptacle. Wood is yellow to white with severely bitter taste.

Anticancer activities: *Quassia* is extensively used as an antipyretic from ancient times. In some parts of the world, it is used for the treatment of malaria and fevers. It is also used as antiviral, antianaemic, antibiotic, cytotoxic and antiamoebic agent in different parts of the world. Qussinoids are the major phytochemical compound of the plant which gives bitter taste; while, quassin is a white crystalline substance that extensively used in herbal medicines.

1.5. *Picrolemma* Hook.f.

Picrolemma is small dioecious slender flowering shrubs, native to Southern and South-eastern Amazons and Peru. It is primarily grows in wet tropical zones and used as herbal medicines. Inflorescence is elongate and stamens opposite to the petals. Fruit are with ellipsoid fruitlets.

Anticancer activities: Quassinosides from the areal parts of the plant is significantly cytotoxic against MCF-7 and PC3 cell lines. Neosergeolide, isolated from the plant is effective against HL60 leukemia cell line which leads to apoptosis by damaging DNA in intrinsic path ways. Extracts from the aerial parts of *P. sprucei* is cytotoxic against breast and prostate human cancer cell lines (de Sousa et al., 2019). Natural quassinoids, isobrucein B, neosergeolide, semisynthetic derivative 1,12-diacetylisobrucein B, and a new semi-synthetic derivative, 12-acetylneosergeolide are found to have cytotoxic effects against human cancer cell lines. First two compounds have greater effect against all the tumour cell lines (Silva et al., 2009). The alkaloids including canthin-6-one, huberine, 1-hydroxy-canthin-6-one, canthin-6-one and stigma sterol isolated from the bark of *P. huberi* have antitumour activities. Canthin-6-one has antiviral, antiinflammatory, antiproliferative and aphrodisiacal properties additional to antitumour activities (Lopez et al., 2018). Leaf extract of *P. pseudocoffea* contains quassinoid which has been found antileukemic effects. This antileukemic quassinoid is similar to 15-deacetylsergeolide that induces strong antileukemic activity in P-388 test system (Polonsky et al., 1984).

1.6. *Picrasma* Blume

Picrasma is a genus with six to nine species which are native to temperate and tropical zones of Asia and tropical regions of Americas. The species are shrubs or trees growing upto 20 meter in height. The plant is deciduous with smooth dark grey brown bark. Leaves are pinnately compound with 7-15 leaflets. Flowers are green to yellow with four or five sepals and petals produced in cymose inflorescence. Fruits are ovoid to globose, red to black drupe with 6-7 mm diameter. *P. quassioides* is a species native to temperate regions of Southern Asia, Northeast of Pakistan, Taiwan and Japan. It is a deciduous shrub or small tree growing to 10-15m tall with a trunk upto 50cm in diameter. The leaves are 15-40 cm long, pinnate, with 7-15 leaflets having coarsely and irregularly toothed margin. The fruit is an ovoid to globose drupe with 6-7 mm diameter.

Anticancer activities: *P. quassioides* is widely used in traditional medicines of Asia. The chemical composition of the plant is complex. The plant contains quassinodes, alkaloids and triterpanoids. Among the triterpanoids, tirucallane type triterpenoid called kumuquassin C is found to have anticancer properties. The plant extracts induces cervical cancer cell apoptosis by upregulating proapoptotic protein Bad and t-Bad expression. Ethanolic extract of the plant found to induce H-Ras liver cancer cell apoptosis and n-butanol extract induces HT-29 colon and NCI-N87 gastric cancer cell apoptosis. Among the alkaloids, β-carboline alkaloids are found to be cytotoxic against human ovarian cancer cell lines. β-carboline-1-carboxylic acid, isolated from the stem is moderately cytotoxic against K562 leukemia cancer cells and SGC-7901 gastric cancer cells. Besides, carboline alkaloids, carthinone, also exhibit anticancer properties. In this category, 9-methoxy-canthin-6-one and canthin-6-one show that these compounds have cytotoxic activity against A549 lung cancer and MCF-7 breast cancer cells (Lee et al., 2021).

2. Outlook

Cancer is a threatening disease for

human population. Various kinds of researches and studies are going on to prevent and treat different types of cancers. Plant based medicines have a great demand in this field due to its less toxic side effect compared to current treatments like chemotherapy. The plant kingdom produces active secondary metabolites which have potential anticancer effects. Some species of Simaroubaceae shows potent anticancer properties against various cell lines. The main group of secondary metabolites, quassinoids, play major role in cancer treatment. Among the various types of alkaloids, carboline and canthinone, are of great priority. *Simarouba* is the only genus abundantly available in our area, and majority of the genus are yet to be studied.

References

1. Chen, M., Xu, X. Y., Xu, D. Y., Zhao, F. Z., and Xu, Q. Y. (2010). Inhibiting Bcl-2 gene expression enhance radiosensitivity of non-small cell lung cancer NCI-H460 cells. *Chin. Oncol.* 20(9):641-645.
2. de Sousa, S. R. N., Díaz, I. E. C., Younes, R. N., Frana, S. A., Bernardi, M. M., and Suffredini, I. B. (2019). *Picrolemma sprucei* quassinosides inhibits breast and prostate cell growth and impairs behavioral phenotype in mice. *Pharmacogn. Mag.* 15(60):1-11.
3. Efferth, T., Li, P. C., Konkimalla, V. S. B., and Kaina, B. (2007). From traditional Chinese medicine to rational cancer therapy. *Trends Mol. Med.* 13(8):353-361.
4. Guo, H., Chen, Y., Wang, J., Ma, H., and Liu, Y. (2022). A critical review: anti-cancer effects of *Brucea javanica* and the mechanisms. *Pharmacol. Res. Modern Chin. Med.*100133.
5. Huang, Y. F., Zhou, J. T., Qu, C., Dou, Y. X., Huang, Q. H., Lin, Z. X., and Su, Z. R. (2017). Anti-inflammatory effects of *Brucea javanica* oil emulsion by suppressing NF-κB activation on dextran sulfate sodium-induced ulcerative colitis in mice. *J . Ethnopharmacol.* 198:389-398.
6. Jose, A., Chaitanya, M. V., Kannan, E., and Madhunapantula, S. V. (2018). Tricaproin isolated from *Simarouba glauca* inhibits the growth of human colorectal carcinoma cell lines by targeting class-1 histone deacetylases. *Front. Pharmacol.* 9:127.
7. Lee, J., Gong, Y. X., Jeong, H., Seo, H., Xie, D. P., Sun, H. N., and Kwon, T. (2021). Pharmacological effects of *Picrasma quassioides* (D. Don) Benn for inflammation, cancer and neuroprotection. *Exp. Ther. Med.* 22(6):1-16.
8. Li, K. W., Liang, Y. Y., Wang, Q., Li, Y., Zhou, S. J., Wei, H. C., and Wan, X. H. (2021). *Brucea javanica:* A review on anticancer of its pharmacological properties and clinical researches. *Phytomedicine.* 86:153560.
9. López, C., Pastrana, M., Ríos, A., Cogollo, A., & Pabón, A. (2018). Huberine, a new canthin-6-one alkaloid from the bark of *Picrolemma huberi. Mol.* 23(4):934.
10. Polonsky, J., Bhatnagar, S., and Moretti, C. (1984). 15-deacetylsergeolide, a potent antileukemic quassinoid from *Picrolemma pseudocoffea. J. Nat. Prod.* 47(6):994-996.
11. Prajapati, C., Reddy, M., and Bhatt, M. (2018). Evaluation of anticancer activity using leaf extract of *Simarouba glauca* on leukemic cancer cell lines. *Eval.* 3(2):52-56.
12. Rivero-Cruz, J. F., Lezutekong, R., Lobo-Echeverri, T., Ito, A., Mi, Q., Chai, H. B. and Kinghorn, A. D. (2005). Cytotoxic constituents of the twigs of *Simarouba glauca* collected from a plot in Southern Florida. *Phytother. Res.: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives.* 19(2): 136-140.
13. Rosati, A., Quaranta, E., Ammirante, M., Turco, M. C., Leone, A., and De Feo, V. (2004). Quassinoids can induce mitochondrial membrane depolarisation and caspase 3 activation in human cells. *Cell Death. Differ.* 11(2):S216-S218.
14. Silva, E. C., Cavalcanti, B. C., Amorim, R. C., Lucena, J. F., Quadros, D. S., Tadei, W. P., and

Pohlit, A. M. (2009). Biological activity of neosergeolide and isobrucein B (and two semi-synthetic derivatives) isolated from the Amazonian medicinal plant *Picrolemma sprucei* (Simaroubaceae). *Mem. Inst. Oswaldo Cruz,* 104:48-56.

15. Vieira, I. J. C., and Braz-Filho, R. (2006). Quassinoids: structural diversity, biological activity and synthetic studies. *Stud. Nat. Prod. Chem.* 33:433-492.

16. Vikas, B., Kunjiraman, S., Rajam, S. S. N., and Anil, S. (2021). The Apoptotic Properties of Leaf Extracts of *Simarouba glauca* against Human Leukemic Cancer Cells. *APJCP.* 22(4):1305.

17. Zhang, H., Yang, J. Y., Zhou, F., Wang, L. H., Zhang, W., Sha, S., and Wu, C. F. (2011). Seed oil of *Brucea javanica* induces apoptotic death of acute myeloid leukemia cells via both the death receptors and the mitochondrial-related pathways. *Evid. Bas. Compl. Altern. Med.* https://doi.org/10.1155/2011/965016.

Fabaceae: A Boon for Cancer Therapy

Bhasura K.

Department of Life Sciences, University of Calicut
Thenhipalam, Malappuram, 673635, Kerala, India.
Corresponding author: bhasura96@gmail.com

Abstract: Cancer is a severe health problem that continues to be a leading cause of death worldwide. The advent of modern drug targeted therapies has undeniably improved cancer patient's cares; while the advanced metastasized cancer remains untreatable. The continued searching for a safer and more effective chemoprevention and treatment is clearly needed for the improvement of the efficiency and to lower the treatment cost for cancer. Cancer chemoprevention with natural phytochemical compounds is an emerging strategy to prevent, impede, delay or cure cancer. In cancer chemoprevention and treatment, the bioactive components from natural plants of Fabaceae play significant role.

Keywords: Fabaceae, anticancerous, phytochemicals, medicinal, antiproliferative

Cancer is a condition in which cells grow abnormally with the potential to spread to other parts of the body. Among several factors that are involved in cancer initiation include changes in the genes that regulate normal functions of the body. With the steady increase in cancer incidence around the globe, various strategies for cancer prevention is also increasing. Stem cell transplantation, chemotherapy, radiotherapy, immunotherapy and surgery are various methods used to treat cancer among which chemotherapy is the most effective method. But various side effects are associated with this treatment. Due to the reason, other treatment methods with no or few side effects are required for the prevention and treatment of cancer. Recently, researchers around the globe have focused their efforts on discovering novel drugs from natural sources such as plants with authentic medicinal importance. Natural compounds are found to be good sources for the development of new remedies for different diseases. Several medicinal plants and herbal ingredients have been found to show anticancer activity. The plant derived compounds are widely used for chemotherapy of cancerous patients. Phytochemicals isolated from medicinal plants have been shown to decrease cell proliferation, apoptosis, metastasis and inhibit angiogenesis. Taxol analogues, *Vinca* alkaloids (vincristine and vinblastine), and podophyllotoxin analogues are some of the drugs used to treat cancer.

Kingdom Plantae is characterized by approximately 250,000 plant species; while, only 10% of all plant species has been tested for the anticancer activity (Tariq et al., 2017). Leaf, flower, fruit, root, stigma, pericarp, embryo,

rhizome, seed, stem, sprout and bark are various plant parts where anticancer compounds occur and these phytochemicals derived from plants has a huge role in pharmacology (Subramanian et al., 2019). Different phytochemicals such as alkaloids, flavonoids, glycosides, saponins, terpenes, lignin, vitamins, minerals, taxanes, gums, biomolecules, oils and various other metabolites are found to show anticancer activities (Subramanian et al., 2019). These compounds can activate enzymes and proteins, regulate cellular and signaling events in growth and improve anti-inflammatory and antioxidant action; thus play a pivotal role in cancer prevention (Tariq et al., 2017).

The family Fabaceae is a rich source of phytochemicals including flavonoids, lectins, saponins, alkaloids, carotenoids and phenolic acids which have anticancer properties and the use of these phytochemicals is increasing over time (Sebastian et al., 2020). Phytochemicals of the family have industrial and pharmacological importance (Pastorino et al., 2018). However, these phytochemicals have not been explored massively for their anticancer activity. Therefore, more research is needed in the future to explore the potential of phytochemicals in Fabaceae members against cancer and to discover novel drugs against the disease. It is an attempt to explore the potential effects of phytochemicals against cancer cell growth, development and associated mechanisms giving emphasis on eight major genera of Fabaceae.

1. Anticancer plants in Fabaceae

1.1. *Astragalus* L.

Astragalus is the largest genus of vascular plants in the world that comprises an estimated number of 2900 annual and perennial species. The members of this genus have been used as medicine, food, fodder, fuel, ornamental plants etc. *A. membranaceus*, a commonly used herb in china, has a long history of use in Traditional Chinese Medicine. It is now commonly used as an immunomodulating agent in mixed herbal decoctions.

Anticancer activities: *A. membranaceus* is found to possess phytochemicals like polysaccharides, saponins and flavonoids (Max et al, 2002). Basic research indicates that *Astragalus* saponins could induce growth inhibition and apoptosis in human colon cancer cells and tumour xenografts (Tim et al., 2007). Total saponins normally possess potential antitumourigenic effects in human colon cancer cells and tumour xenografts through modulation of both mTOR and ERK signaling pathways (Auyeung et al., 2010). Astragalus polysaccharides (APS) show immune potentiating properties. It promotes dendritic cell maturation and acts as an effective adjuvant in vaccines (Du et al., 2012). APS could increase the effectiveness of platinum based chemotherapy and improve the quality of life in patients with advanced non small cell lung cancer (NSCLC) (Cullock et al., 2006; Guo et al., 2012). Moreover, the antitumour activity of APS may depend on its function of immune regulation (Liu et al., 2010).

1.2. *Acacia* Mill.

Acacia is one of the largest species of Fabaceae, rich of bioactive compounds with significant medicinal properties. *Acacia* possesses several secondary metabolites including amines, flavonoids, alkaloids, fluoroacetate, cyanogenic glycosides,

diterpenes, hydrolyzable tannins, seed oils, cyclitols, gums, non protein amino acids, fatty acids, terpenes and condensed tannins. These compounds are found to show different pharmacological activities such as antiinflammatory, antioxidant, antidiarrheal, antidiabetic, anticancer, antiviral, liver protective effects. The leaves and bark of *Acacia* plants contain highest amount of tannin as well as polyphenolic compounds such as dicatechin, quercetin and gallic acid (Said, 1997; Asolkar et al., 2005). Pods of the *Acacia* plant contain various polyphenolic compounds like gallic acid, catechin, robidandiol and chlorogenic acid (Gulco, 2001). The root and flowers contain several biologically important constituents like hentriacontane, sitosterol, betulin, β-amyrin, kaempferol-3 glucoside and isoquercetin (Chatterjee & Pakrashi, 2000).

Anticancer activities: *A. nilotica* extract obtained from wood are found very impressive in preventing the disease caused by the overproduction of radicals and illustrates the high cytotoxic potential against MCF-7, a breast cancer cell line (Barapatre et al., 2016). *A. nilotica* is used to treat cancers and tumours of ear and eye and also to treat infections such as diarrhea, dysentery, leprosy, cancers, ulcer and diabetes (Aliyu, 2006; Ahmad et al., 2008). *A. salicina* leaf extracts possess significant antimutagenisity against *Salmonella typhimurium* TA98 and *S. typhimurium* TA 1535 strains (Chatti et al., 2011). A phytoconstituent, isorhamnetin 3-O-neohesperidoside isolated from *A. salicina* leaves protects the cells against oxidative stress by inhibiting xanthine oxidase and superoxide anion scavengers (Bouhlel et al., 2010). Aqueous and methanol extracts of *A. karroo* bark inhibit virus HIV-type 1 reverse transcriptase significantly; while the *A. salicina* leaves extracts show significant antioxidant activities against superoxide radicals and also found to protect pKS plasmid DNA from hydroxyl radicals (Mulaudzi et al., 2011; Boubaker et al., 2012). The aqueous extract of *A. tortilis* polysaccharide (AEATP) is very effective in reducing the blood glucose at high doses (Kumar & Singh, 2014). Aqueous extract of *A. tortilis* at low doses induces potential anxiolytic activity and at high doses it exhibits antidepressant, sedative as well as anticonvulsant property which might be due to inhibitory mechanism of glycine and the action of constituents present in the extract on BZD or 5-HT(1A) receptor (Alharbi & Azmat, 2015). The diverse pharmacological properties possessed by various *Acacia* species (*Acacia salicina, Acacia laeta, Acacia hamulosa* and *Acacia tortilis*) motivate us to compare the cytotoxicity against HepG2, HEK-293, MCF-7 and MDA-MB 231, and antimicrobial activity against *Staphylococcus aureus, E. coli, P. aeruginosa* and *C. albicans*. Several antimicrobial and cytotoxic biomarkers such as rutin and β-amyrin have been quantitatively estimated in different species of genus *Acacia* by HPTLC method (Alam et al., 2015; Alam et al., 2017). The different fractions of *A. etbaica, A. laeta, A. origena* and *A. pycnantha* are found very active against Klebsiella oxytocain, *Staphylococcus aureus* and *Klebsiella pneumoniae* strains (Mahmoud et al., 2016).

1.3. *Indigofera* L.

Indigofera is a large genus of over 750 species of flowering plants belonging to Fabaceae. They are widely distributed throu-

ghout the tropical and subtropical regions of the world. Ayurveda has already described this plant as a stimulant, alternative and deobstruent (Chunekar & Nighatu, 1993). In the traditional systems of Indian medicine, the extract of the plant is used for the management of several hepatic and nervous disorders (Chatterjee & Pakrashi, 1992). Plants have remarkable pharmacological properties of which the aerial parts of *I. tinctoria* possess antihepatoxic activities. The alcoholic extract of the leaves possess antihepatoxic effect against D-galactosamine and carbon tetrachloride induced damage in liver (Sreepriya et al., 2001). Indigtone, an active compound isolated from the leaves possesses hepatoprotective activity (Singh et al., 2004). Further, the plant has proved to be more effective against chronic myelogenous and other leukemias (Steriti, 2002). Indiubin, the active constituent from the leaves is a promising anticancer drug (Han, 1994). Juice of the leaves has a great repute as a cure for hydrophobia being administered both internally and externally (Chopra, 1956).

Anticancer activities: Indirubin, the component responsible for the anticancer activity in *I. tinctoria* yields marked inhibition of Lewis lung carcinoma and walker carcinoma; hence the plant possesses significant antineoplastic activity (Xiujuan, 1981; Rui, 1995). *I. suffruticosa* aqueous extracts by infusion and maceration exhibit the antitumour effect against sarcoma 180 in mice (Jeymesson et al., 2006). *I. aspalathoides*, the under shrub with copiously terete spreading branches, is traditionally used in treating various skin disorders and tumours (Kirtikar & Basu, 2000). It is found to be active against transplantable tumours and inflammations (Rajkapoor et al., 2005). The aqueous extract of *I. aspalathoides* contains mainly saponins, tannins, carbohydrates and steroids that have the ability to counteract the adverse biological effects of carcinogens. The aqueous extract of *I. aspalathoids* also induces antitumour potency against fibrosarcoma in rats (Kumar et al., 2011).

1.4. *Mimosa* L.

The genus *Mimosa* consists of about 400 species distributed all over the world. The plants range from herbs to trees. Several species of the genus play important roles in folk medicine. *Mimosa* species are nutritionally very important and several species are used as feed for different varieties of chickens. The species of *Mimosa* have promising pharmacological properties including antimicrobial, antioxidant, anticancer, antidiabetic, wound healing, hypolipidemic, antiinflammatory, hepatoprotective, antinociceptive, antiepileptic, neuropharmacological, toxicological, antiallergic, antihyperurisemic, larvicidal, antiparasitic, molluscicidal, antimutagenic, genotoxic, teratogenic, antispasmolytic, antiviral and antivenom activities. Hence, the genus could be the future of the medicinal industry for the treatment of various diseases, although in the future more research should be carried out to explore its ethnopharmacological, toxicological and nutritional attributes.

Anticancer activities: The biocomposite films made from *M. tenuiflora* cortex and chitosan show cytotoxicity against 3T3 fibroblasts (Valencia-Gomez et al., 2016). Similar to this, bark ethanol extract exhibits cytotoxicity against four human cancer cell lines including

HL-60, HCT-116, PC-3 and SF-295 (Silva, 2020). Different extracts (petroleum ether, ethanol and aqueous) of *M. pudica* leaves induce in vitro anticancer activity against three human cancer cell lines derived from lung (CHAGO), liver (HepG2) and colon (SW620) (Chimsook, 2014). While the Hy-EtOH extracts of *M. pudica* whole plant and L-mimosine show anticancer activity against the Daudi cell line (Parmar et al., 2015). The cell viability and proliferation of smooth muscle in male Wistar rats reduce by HyMeOH extract of *M. pigra* leaves. No significant effects were observed by the extract at a concentration of 0.01 to 1 mg/mL on smooth muscle cell proliferation or cell viability (Rakotomalala et al., 2013). *M. pigra* fruit extract has been used by Sudanese healers against tumours due to the anticancer activity (Saeed et al., 2015)

The EtOH extract of *M. caesalpiniifolia* leaves induces the anticancer activity against the human breast cancer cell line MCF-7 (Silva et al., 2014). The anticancer activity of EtOH extract and fractions (n-Hex, DCM, EtOAc and Aq.) of *M. caesalpiniifolia* stem bark detected against HCT-116, OVCAR-8, and SF-295 cancer cells (Moncao et al., 2015). The MeOH extract of *M. rubicaulis* stem exhibits cytotoxicity against an Ehrlich ascites carcinoma (EAC) tumour model in Swiss albino mice against cancer cell lines such as EAC, MCF-7, and MDA-MB 435S (Nandipati et al., 2014). *M. verrucosa* and *M. pteridifolia* bark EtOH extracts are highly cytotoxic against four human cancer cell lines including HL-60, HCT-116, PC-3 and SF-295 (Silva, 2020).

1.5. *Phaseolus* L.

Phaseolus is the herbaceous to woody annual and perennial vines containing about 70 plant species native to Americas, primarily Mesoamerica. Various constituents of *P. vulgaris* have beenstudied regarding their antigenotoxic potential. Phenols are shown to have this effect in strains of *Salmonella typhimurium* damaged with aflatoxin B1 or benzo (a) pyrene, as well in the cells of mice treated with cyclophosphamide (De Mjiaa et al., 1999; Martinez et al., 2002). Moreover, a correlation between the antimutagenic and antioxidant effects is evident for phenolic compounds obtained from a methanolic extract of the bean seed coat in *Salmonella* exposed aflatoxin B1 (Martinez et al., 2006).

Anticancer activities: A number of antioxidant properties have been reported with respect to *P. vulgaris*. The methanolic extract, proanthocyanidin rich fraction and whole bean consumption, has significant antiradical capacity (Martinez et al., 2006; Fernandez et al., 2007; Mbenza et al.; 2013). In addition, with regard to cancer chemoprevention, epidemiologic studies have suggested that the consumption of beans is associated with a reduction in the rate of breast, prostate and colon cancers (Correa et al., 1981; Hayat et al., 2013). Several parts or specific compounds of *P. vulgaris* are known to experimentally act on various types of cancers; however, no studies about the antigenotoxic and chemopreventive effects of phaseolin have been reported. Epidemiologic data suggests that colon cancer may be reduced in populations consuming beans (Hayat et al., 2013). The cooked Bayo Madero variety of *P. vulgaris* and its non-digestible fraction suppress CAC formation in rats induced with azoxymethane (AOM) (Vergara et al. 2010). Similarly, the polysac-

charide extract from cooked beans decreases the number of precarcinogenic CAC lesions in AOM treated rats and modifies the transcriptional expression of various genes (Feregrino et al., 2008). Additional beneficial effects from the consumption of different varieties of *P. vulgaris* include reduction in the glycemic index, cardiovascular diseases, stomach and prostate cancer, weight control and obesity (Chavez et al., 2017). Kaempferol and quercetin are the main flavonoids in *P. vulgaris* that reduce cardiovascular disease. Genistein, the isoflavonoid, may inhibit the growth of carcinogenic cells including breast and prostate cancer, and anthocyanins, cyanidin 3-glucoside, exhibit antioxidant activity (Espino et al., 2006). Besides, some varieties of *P. vulgaris* contain ferulic acid as their main phenolic acid in turn causes antioxidant activity in treated organisms (Chavez et al., 2017).

1.6. *Glycyrrhiza* Tourn. ex L.

Glycyrrhiza is a genus of about 20 species with a subcosmopolitan distribution in Asia, Australia, Europe and America. The plant bears compound leaves that consist of 4 to 7 leaf pairs with an end leaflet that is sticky due to secretion of juice. Flowers are blue and fruit contains 5 to 6 brown seeds.

Anticancer activities: *G. glabra* is a species native to Eurasia and North Africa and well known in pharmacology, from which most confectionery liquorice is produced. The root and stem of the species have higher medicinal use to treat different diseases (Khanahmadi et al., 2013). Extract contents of the root lead to morphological changes in the mammary cell line (4T1) and reduce the viability; beyond this, it induces BCL2 phosphorylation (Hamta et al., 2014). The root extract promotes apoptosis in HT29 cells; therefore useful in the treatment of colon cancer (Nourazarian et al., 2015). Glycyrrhizin, a triterpene glycoside, is the main compound in root extract and acts as an anti-proliferative agent against tumour cells especially breast cancer cell lines (MCF-7 & HEP2) and plays major role in induction of apoptosis (Bartina et al., 2003). *G. uralensis* is one of the commonly prescribed herbs in Traditional Chinese Medicine that is associated with immune modulating and antitumour potential. Cytotoxic activity guided fractionation studies on *G. echinata* roots led to the isolation of eight compounds. Among the molecules, retrochalcones, licochalcone B and tetra hydroxyl methoxy chalcone are the most active ones against PC3, MCF-7 and HepG2 cells.

1.7. *Medicago* L.

Medicago is commonly known as 'Medick' or 'Burclover'. It contains at least 87 species and is distributed mainly around the Mediterranean basin. The best known member of the genus is alfalfa, *M. sativa*, an important forage crop. It is usually found in most parts of the world and has been used in traditional medicine for the treatment of various diseases such as hepatic disorders (Servatyari et al., 2017).

Anticancer activities: Phytoestrogen in the plant has strong estrogenic activity and useful in treating hormone dependent cancers. Alfalfa contains large amount of almost all vitamins, flavonoids, digestive enzymes, coumarin, alkaloids, amino acids and trepans. Hence, it is more useful for breast cancer and the breast milk enhancement. Triconlin plays major role in

plant development and bears the pharmacological properties like anticancer effects (Huyghe et al., 2007). Moreover, the two flavonoids namely millepurpan and medicarpin, isolated from *M. sativa* suppress cancer cell proliferation. Millepurpan and medicarpin can be utilized as chemopreventive agents for breast cancer as well as cervical cancer (Bora et al., 2011). The role of flavone, tricin as a chemopreventive agent sourced from *M. truncatula* is also investigated (Stochmal et al., 2007). It is noticed that tricin in humans causes cell cycle arrest or a growth inhibitory effect on MDA-MB-468 breast cancer. It majorly inhibits the cyclooxygenase enzyme activity in turn regulates the cyclooxygenase mediated prostaglandin production. Due to this effect, tricin can be exploited as a chemopreventive agent for prostate and intestinal carcinogenesis.

1.8. *Sophora* L.

Sophora is deemed as one of the most remarkable genera of Fabaceae. The genus comprises approximately 52 species of small trees and shrubs that are widely distributed in Asia and mildly in Africa.

Anticancer activities: Sophoraflavanone G from *S. flavescens* reveals cytotoxicity for several tumour cells which is similar to cisplatin, commonly used as a recent chemotherapy drug to treat different cancers (Long et al., 2020). The compound induces apoptosis in triple negative breast cancer cells (Huang et al., 2019). Kurarinone induces apoptosis in small cell lung carcinoma (SCLC) cells via multiple mechanisms and delays SCLC-cell's migration and invasion (Chung et al., 2019). By it's underlying mechanism, Kurarinone promotes Fas and TRAIL receptor1 and 2 expression via the caspase 8 / Bid pathway. A prenylated flavanone from the roots of *S. flavescens* has antiproliferative activity against human hepatoma cells (HepG2) (Yang et al., 2021). This lavandulyl flavonoid, 2-methoxy-2', 4', 4, 6-tetrahydroxy -5- lavanduly dihydrochalcone, significantly activates autophagic flux and trigger reactive oxygen species (ROS) release in HepG2. The compound mediates it's antiproliferative effects through autophagic cell death which is an apoptosis independent event. This prenylated flavanone could also activate the key signaling protein of autophagy and ROS, while it does not affect the main protein of the apoptosis signaling pathway (Yang et al., 2021).

Oxysophoridine is an alkaloid extracted from *S. alopecuroides* with various pharmacological activities. It suppresses the growth of hepatocellular carcinoma and colorectal cancer cells by regulating apoptosis associated with the Bcl-2/Bax/caspase-3 signalling pathway and alleviation of spinal cord injury via antiinflammatory, antioxidative stress and antiapoptosis effects (Yao et al., 2012; Jin et al., 2017; Cao et al., 2018). HPLC fingerprint of chloroform extract from *S. tonkinensis* reveals the presence of ononin, genistin, genistein, isosophoranone, trifolirhizin, isotrifolirhizin and maackiain (Chen et al., 2020; Song et al., 2021). The extract suppresses the tumours of nasopharyngeal carcinoma cells; beyond, the extract inhibits the cell viability, clonal growth and induces cell apoptosis in a dose dependent manner by silencing the PI3K/AKT/mTOR signaling pathway which is associated with upregulation of cleaved PARP, caspase 3/7/8/9 and Bax and

downregulation of PI3K, P-PI3K, PARP, AKT,P-AKT, mTOR, P-mTOR and Bcl-2 (Ao et al., 2019; Cao & He, 2020; Chen et al., 2020). The mechanism of allomatrine, isolated from the bark of *S. japonica*, shows the inhibition of invasion and proliferation in human lung cancer A549 cell line by promoting apoptosis, inducing ROS production, inhibiting ubiquitin proteasome, arresting cell cycle and regulating tumour related gene expression (Liu et al., 2020). Evaluation of anticancer activity of isolated compounds from *S. mollis* including scopoletin and β-sitosterol glucoside has weak effect against HeLa and 3T3 cell lines (Quradha et al., 2021).

2. Outlook

Species of Fabaceae are a rich source of phytochemicals including flavonoids, lectins, saponins, alkaloids, carotenoids and phenolic acids. The consumption of various species lowers the risk of cancer, as the phytochemicals from the members are effective in the prevention and treatment of cancer. Some of the phytochemicals have already been utilized against cancer worldwide; however, other phytochemicals are also gaining importance. Despite many reports about the efficacy of different anticancer phytochemicals, most of these reports are under in vitro or in vivo experiment conditions and very few clinical trial reports are available. Therefore, more clinical trial reports confirming the efficacy of phytochemicals from Fabaceae members with responsible mechanisms will be indispensable in future studies.

References

1. Alam, P., Alajmi, M.F., Siddiqui, N.A., Al-Rehaily, A.J., Alharbi, H., Basudan, O.A., and Hussain A. (2015). Densitometric validation and analysis of biomarker β-amyrin in different Acacia species (leaves) grown in Kingdom of Saudi Arabia by high performance thin-layer chromatography. *Pak. J. Pharm. Sci.* 28:1485–1491.
2. Ao, M., Xiao, X., and Li, Q. (2019). Efficacy and safety of compound Kushen injection combined with chemotherapy on postoperative patients with breast cancer: a meta-analysis of randomized controlled trials. *Medicine.* 98
3. Aparicio-Fernández, X., Reynoso-Camacho, R., Castaño-Tostado, E., García-Gasca, T., de Mejia, E., Guzmán-Maldonado, S.H., Elizondo, G., Yousef, G.G., Lila, M.A., and Loarca-Pina, G. (2007). Antiradicalcapacity and Induction of Apoptosis on HeLa Cells by a *Phaseolus vulgaris* Extract. *Plant Foods Hum. Nutr.* 63:35–40.
4. Asolkar, L.V., Kakkar, K.K., and Chakre, O.J. (2005). Glossary of Indian medicinal plants with active principles. Part I (A-K). *New Delhi NISCAIR and CSIR*, 10-11.
5. Auyeung, K.K., Mok, N.L., Wong, C.M., Cho, C.H., and Ko, J.K. (2010). Astragalus saponins modulate mTOR and ERK signaling to promote apoptosis through the extrinsic pathway in HT-29 colon cancer cells. *Int. J. Mol. Med.* 26:341–349
6. Azevedo, L., Gomes, J.C., Stringheta, P.C., Gontijo, A.M.M.C., Padovani, C.R., Ribeiro, L.R., and Salvadori, D.M.F. (2003). Black bean (Phaseolus vulgaris L.) as a protective agent against DNA damage in mice. *Food Chem. Toxicol.* 41: 1671–1676.
7. Aliyu, B. S. (2006). Some ethno medicinal plants of the Savannah regions of West Africa: description and phytochemicals. *Triumph publishing company.* 1:135-152.
8. Baltina, L.A. (2003). Chemical modification of glycyrrhizic acid as a route to new bioactive compounds for medicine. *Curr. Med. Chem.* 10: 155–171.
9. Barapatre, A., Meena, A.S., Mekala, S., Das, A., and Jha, H. (2016). In vitro evaluation of antioxidant

and cytotoxic activities of lignin fractions extracted from *Acacia nilotica. Int. J. Biol. Macromol.* 86:443–453.

10. Bora, K.S., and Sharma, A. (2011). Phytochemical and pharmacological potential of *Medicago sativa*: *A Rev. Pharm. Bio.* 49:211–220.

11. Boubaker, J.B., Mansour, H., Ghedira, K., and Chekir, G.L. (2012) Polar extracts from (Tunisian) *Acacia salicina* Lindl. Study of the antimicrobial and antigenotoxic activities. *BMC Complement. Altern. Med.* 12:37.

12. Bouhlel, I., Limem, I., Skandrani, I., Nefatti, A., Ghedira, K., Dijoux-Franca, M.G., and Leila, C.G. (2010). Assessment of isorhamnetin 3-O-neohesperidoside from *Acacia salicina*: protective effects toward oxidation damage and genotoxicity induced by aflatoxin B1 and nifuroxazide. *J. Appl. Toxicol.* 30:551–558.

13. Cao, X., He, Q., (2020). Anti-tumor activities of bioactive phytochemicals in *Sophora flavescens* for breast cancer. *Can. Manag. Res.*12:1457–1467.

14. Cao, Z., Chen, L., Liu, Y., and Peng, T. (2018). Oxysophoridine rescues spinal cord injury via antiinflammatory, antioxidative stress and antiapoptosis effects. *Mol. Med. Rep.*17:2523 –2528.

15. Cardador-Martínez, A., Albores, A., Bah, M., Calderón-Salinas, V., Castaño-Tostado, E., Guevara-González, R., Shimada-Miyasaka, A., and Loarca-Piña, G. (2006). Relationship among Antimutagenic, Antioxidant and Enzymatic Activities of Methanolic Extract from Common Beans (*Phaseolus vulgaris* L) *Plant Foods Hum. Nutr.* 61:161–168.

16. Cardador-Martínez, A., Castaño-Tostado, E., and Loarca-Piña, G. (2002) Antimutagenic activity of natural phenolic compounds present in the common bean (*Phaseolus vulgaris*) against aflatoxin B 1. *Food Addit. Contam.* 19:62–69.

17. Chatterjee, A., and Pakrashi, S.C. (2000). The Treatise on Indian Medicinal Plants. NISCAIR Press; New Delhi: 51–53.

18. Chatterjee, A., and Pakrashi, S.C. (1992). The Treatise on Indian Medicinal Plants. CSIR, Publication, New Delhi.

19. Chatti, I.B., Boubaker, J., Skandrani, I., Bhouri, W., Ghedira, K., and Chekir, G.L. (2011). Antioxidant and antigenotoxic activities in Acacia salicina extracts and its protective role against DNA strand scission induced by hydroxyl radical. *Food Chem. Toxicol.* 49(8):1753–1758.

20. Chávez-Mendoza, C., and Sánchez, E. (2017). Bioactive compounds from Mexican varieties of the common bean (*Phaseolus vulgaris*): Implications for health. *Molecules.* 22:1360.

21. Chen, N., Qiao, Z., Xu, J., Wei, K., and Li, M. (2020). Physiological mechanism and developmental events in differentiating floral buds of *Sophora tonkinensis* gagnep. *Pharmacogn. Mag.* 16(67):83.

22. Chen, Y., Luo, Q., Li, S., Li, C., Liao, S., Yang, X., Zhou, R., Zhu, Y., Teng, L., Chen, H., and Yang, Y. (2020). Antiviral activity against porcine epidemic diarrhea virus of Pogostemon cablin polysaccharide. *J. Ethnopharmacol.* 259:113009.

23. Chimsook, T. (2014). Bioactivities of *Mimosa pudica* and *Phyllanthus niruri* crude extracts collected from the locality of Chaiyaphum, Thailand. *Adv. Mat. Res.*12–15

24. Chopra (1956). A review of medicinal plants from India. *Ind. J. Pharmacol.* 8: 416-420.

25. Chunekar, K.C., and Nighatu, B. (1993). Ayurveda Series 28. In: Chukambha Bharathi Academy, Pandey, G.S. (Ed.). Varanasi, India. 406

26. Chung, TW., Lin, C.C., Lin, S.C., Chan, H.L., and Yang, C.C., (2019). Antitumor effect of kurarinone and underlying mechanism in small cell lung carcinoma cells. *Onco. Targ. Ther.* 12:6119.

27. Correa, P. (1981). Epidemiological correlations between diet and cancer frequency. *Can. Res.* 41:3685–3690.

28. De Mejıía, E.G., Castaño-Tostado, E., and Loarca-Pina, G. (1999). Antimutagenic effects of natural phenolic compounds in beans. *Mutat. Res. Toxicol. Environ. Mutagen.* 441:1–9.

29. Du, X., Zhao, B., Li, J., Cao, X., Diao, M., and Feng, H. (2012). Astragalus polysaccharides enhance immune responses of HBV DNA vaccination via promoting the dendritic cell maturation and suppressing Treg frequency in mice. *Int. Immunopharmacol.* 14:463–470.

30. Dymock, W., Warden, C.J.H., and Hooper, D. (2005). A History of the Principal Drugs of Vegetable Origin. Shrishti book distributors; New Delhi: *Pharmacographica Indica.* 556.

31. Espinosa-Alonso, L.G., Lygin, A., Widholm, J.M., Valverde, M.E., and Paredes-Lopez, O. (2006). Polyphenols in wild and weedy Mexican common

beans (*Phaseolus vulgaris* L.) *J. Agric. Food Chem.* 54:4436–4444.

32. Feregrino-Perez, A.A., Berumen, L.C., Garciía-Alcocer, G., Guevara-Gonzalez, R.G., Ramos-Gómez, M., Reynoso-Camacho, R., Acosta-Gallegos, J.A., and Loarca-Pinña, G. (2008). Composition and Chemopreventive Effect of Polysaccharides from Common Beans (*Phaseolus vulgaris* L.) on Azoxymethane-Induced Colon Cancer. *J. Agric. Food Chem.* 56:8737–8744

33. Gulco, P. (2001). CCRUM. New Delhi. Medicinal Plants in Folklores of Bihar and Orissa. 25.

34. Guo, L., Bai, SP., Zhao, L., and Wang, X.H. (2012). Astragalus polysaccharide injection integrated with vinorelbine and cisplatin for patients with advanced non-small cell lung cancer: effects on quality of life and survival. *Med. Oncol.* 29:1656–1662.

35. Hamta, A., Shariatzadeh, S.M.A., Soleimani, Mehranjani, S.M.A., Fallah, Huseini, H., and Hosseinabadi, F. (2014). The cytotoxic effects of *Glycyrrhiza glabra* L. root extract on 4T1 cell line derived from BALB/c mice mammary tumors. *J. Med. Plant.* 2(50):92–103.

36. Han, R., (1994). Highlight on the studies of anticancer drugs derived from plants in china. *Stem. Cells.* 12: 53-63.

37. Harwansh, R.K., Patra, K.C., Pareta, S.K., and Singh, J. (2011). Pharmacological studies on *Glycyrrhiza glabra*. *Pharmacologyonline.* 2:1032 –1038.

38. Hayat, I., Ahmad, A., Masud, T., Ahmed, A., and Bashir, S. (2013). Nutritional and Health Perspectives of Beans (*Phaseolus vulgaris* L.): An Overview. *Crit. Rev. Food Sci. Nutr.* 54:580–592.

39. Huang, W.C., Gu, P.Y., Fang, L.W., Huang, Y.L., Lin, C.F., and Liou, C.J. (2019). Sophoraflavanone G from *Sophora flavescens* induces apoptosis in triple-negative breast cancer cells. *Phytomedicine.* 61:152852.

40. Huyghe, C., Bertin, E., and Landry, N. (2007). Medicinal and nutraceutical uses of alfalfa (*Medicago sativa* L). A review In: Acharya SN, Thomas JE, eds. *Advances in Medicinal Plant Research.* Trivandrum, India: Research Signpost. 147–172.

41. Jin, S.J., Yang, Y., Ma, L., Ma, B.H., Ren, L.P., Guo, L.C., Wang, W.B., Zhang, Y.X., Zhao, Z.J., and Cui, M. (2017). In vivo and in vitro induction of the apoptotic effects of oxysophoridine on colorectal cancer cells via the Bcl-2/Bax/caspase-3 signaling pathway. *Oncol. Lett.* 14(6):8000–8006.

42. Joy, P.P., Thomas, J., Mathew S., and Skaria, P. (2013). Medicinal. Plants Kerala Agricultural University Publications; Kerala, India

43. Khanahmadi, M.M., Naghdi, Badi, H., and Akhondzadeh, S. (2013). A review on medicinal plant of *Glycyrrhiza glabra* L. *JMP.* 2(46):1–12

44. Kirtikar, K. R., and Basu, B.D. (2000). Illustrated Indian medicinal plants. Sir Satguru's Publications, Delhi. 2271

45. Kritikar, K.R., and Basu, B.D. (2003). Indian Medicinal Plants with Illustrations. Uttaranchal Oriental Press. 2:1289–1292.

46. Kumar, B.P., and Singh, R. (2014). Antidiabetic activity of Acacia tortilis (Forsk.) Hayne ssp. raddiana polysaccharide on streptozotocin-nicotinamide induced diabetic rats. *Biomed. Res. Int.*

47. Liu, J., Guo, Y., and Cao, J. (2020). Matrine triggers colon cancer cell apoptosis and G0/G1 cell cycle arrest via mediation of microRNA-22. *Phytother. Res.* 34(7):1619-1628.

48. Liu, L.M., and Zhang, L.S. (2010). Effect of *Astragalus* polysaccharide on the function and maturation of plasmacytoid dendritic cells from chronic myelogenous leukemia before and after treatment. *Zhonghua Xue Ye Xue Za Zhi.* 31:740 –743.

49. Long, G.Q., Wang, D.D., Wang, J., Jia, J.M., and Wang, A.H. (2020) Chemical constituents of *Sophora flavescens* Ait. and cytotoxic activities of two new compounds. *Nat. Prod. Res.* 36(1): 108-113.

50. Longo-Mbenza, B., and Muaka, M. (2013. The protective effect of *Phaseolus vulgaris* on cataract in type 2 diabetes: A profitable hy-pothesis. *Med. Hypothesis Discov. Innov. Ophthalmol.* 2:105–108

51. Ahmad, M. (2008). Antidiabetic and hypolipidemic effects of aqueous methanolic extract of *Acacia nilotica* pods in alloxan-induced diabetic rabbits. *Scand. J. Lab. Anim. Sci.*

52. Ma, X.Q., Duan, J.A., Dong, T.T., and Tsim, K.W. (2002). Chemical analysis of Radix astragali (Huangqi) in China: a comparison with its adulterants and seasonal variations. *J. Agric. Food Chem.* 50:4861–4866.

53. Mahmoud, M.F., Alrumman, S.A., and Hesham, Ael-L. (2016). Biological activities of some Acacia

spp. (Fabaceae) against new clinical isolates identified by ribosomal RNA gene-based phylogenetic analysis. *Pak. J. Pharm. Sci.* 29:221 –229.

54. McCulloch, M., See, C., Shu, X.J, Broffman, M., Kramer, A., and Fan, W.Y. (2006). Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. *J. Clin. Oncol.* 24:419–430.

55. Mohammad, Alharbi, W.D., and Azmat, A. (2015). Anticonvulsant and neuroprotective effects of the *Acacia tortilis* growing in KSA. *Pak. J. Pharm. Sci.* 28:531–534.

56. Monção, B.N., Araújo, Q.B., Silva, D.J., Lima, J.D., Ferreira, M.P., Airoldi, P.F., Pessoa, C., Cito. (2015). Assessing Chemical Constituents of *Mimosa caesalpiniifolia* Stem Bark: Possible Bioactive Components Accountable for the Cytotoxic Effect of *M. caesalpiniifolia* on Human Tumour Cell Lines. *Molecules.* 20:4204–4224.

57. Mulaudzi, R.B., Ndhlala, A.R., Kulkarni, M.G., Finnie, J.F., Van, and Staden J. (2011). Antimicrobial properties and phenolic contents of medicinal plants used by the Venda people for conditions related to venereal diseases. *J. Ethnopharmacol.* 135:330–337.

58. Nadkarni, K.M. (2005). The Indian Plants and Drugs. New Delhi: Shrishti Book Distributors.

59. Nandipati, M.C., Sumalatha, G., Baburao, C., Babu, J.R., and Sridevi, C. (2014). Antitumor activity of *Mimosa Rubicaulis* Lam against *Ehrlich Ascites* carcinoma in swiss albino mice. *Int. J. Pharm. Sci. Res.* 5:1514.

60. Nourazarian, S.M, Nourazarian, A., Majidinia, M., and Roshaniasl, E. (2015). Effect of root extracts of medicinal herb *Glycyrrhiza glabra* on HSP90 gene expression and apoptosis in the HT-29 colon cancer cell line. *Asian. Pac. J. Cancer Prev.* 16:8563–8566.

61. Parmar, F., Kushawaha, N., Highland, H., and George, L.B. (2015). In vitro antioxidant and anticancer activity of *Mimosa pudica* L. extract and L-mimosine on lymphoma daudi cellsl. *Int. J. Pharm. Pharm. Sci.* 7:100–104

62. Pastorino, G., Cornara, L., Soares, S., Rodrigues, F., and Oliveira, M.B.P. (2018). Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. *Phytother. Res.* 32:2323 –2339.

63. Quradha, M.M., Khan, R., Adhikari, A., Rauf, A., Rashid, U., Bawazeer, S., Al-Awthan, Y.S., Bahattab, O., and Mubarak, M.S. (2021). Isolation, biological evaluation, and molecular docking studies of compounds from *Sophoramollis* (Royle) Graham Ex Baker. *ACS Omega.* 6(24):15911–15919.

64. Rajkapoor, N., Murugesh, D., Chodon., and Sakthisekaran, D. (2005). Chemoprevention of Nitosodiethylamine induced phenobarbitol promoted liver tumors in the rat by extract of *Indigofera aspalathoids*. *Biol. Pharm. Bull.* 28:364-366

65. Rakotomalala, G., Agard, C., Tonnerre, P., Tesse, A., Derbré, S., Michalet, S., Hamzaoui, J., Rio, M., Cario-Toumaniantz, C., and Richomme, P. (2013). Extract from *Mimosa pigra* attenuates chronic experimental pulmonary hypertension. *J. Ethnopharmacol.* 148:106–116

66. Kumar, S.S., Rao, M.R.K., and Balasubramanian, M.P. (2011). Anticarcinogenic effects of *Indigofera aspalathoides* on 20-Methylcholanthrene induced fibrocarcinoma in rats. *Res. J. Med. plant.* 5(6):747-755.

67. Saeed, M.E.M., Abdelgadir, H., Sugimoto, Y., Khalid, H.E., and Efferth, T. (2015). Cytotoxicity of 35 medicinal plants from Sudan towards sensitive and multidrug-resistant cancer cells. *J. Ethnopharmacol.* 174:644–658

68. Said, H.M., Hamdard (1997). Pharmacopeia of Eastern Medicine. New Delhi Sri Satguru Publications; 2:353

69. Sebastian, R., Jaykar, B., and Gomathi, V. (2020). Current status of anticancer research in Fabaceae family. *Pathways.* 6:7.

70. Servatyari, K., Ahmadi., A, Kashefi, H., Menbari, M.N., Rostami, R., and Moloudi, M.R. (2017). The effects of hydroalcoholic extract of *Medicago sativa* on liver functional test, blood biochemical and coagulation system parameters in male rat. *Sci. J. Kurdistan. Univ. Med. Sci.* 21(6):16–26.

71. Silva, S.A., Barros, A.B., Souza, J.M.T., Moura, A.F., Araújo, A.R., Mendes M.G.A., Daboit T.C., Silva D.A., Araújo, A.J., Marinho, and Filho, J.D.B. (2020). Phytochemical and biological prospection of *Mimosa* genus plants extracts from Brazilian northeast. *Phytochem. Lett.* 39:173–181

72. Silva, M., Carvalho, A., Rocha, C., Vilegas, W., Silva, M., and Gouvêa, C. (2014). Ethanolic extract of *Mimosa caesalpiniifolia* leaves: Chemical characterization and cytotoxic effect on human

breast cancer MCF-7 cell line. *S. Afr. J. Bot.* 93:64 –69.

73. Singh, B., Saxena, A.K., Chandan, B.K., Bhardwaj, V., Gupta, V.N. , Suri, O.P. , and Handa, S.S. (2004). Hepatoprotective activity of indigtone - a bioactive fraction from *Indigofera tinctoria* Linn. *Phytother. Res.* 115:274-277.

74. Song, Z., Gong, X., Ou, C., Zhang, W., Wang, J., Yao, C., Qin. S., Yan, B., Li, Q., Wei, K., and Hou, X. (2021). Chloroform extract from *Sophora tonkinensis* Gagnep. inhibits proliferation, migration, invasion and promote apoptosis of nasopharyngeal carcinoma cells by silencing the PI3K/AKT/mTOR signaling pathway. *J. Ethnopharmacol.* 271:113879.

75. Sreepriya, H., Devaki T, and Nayeem, M., 2001. Protective effects of *Indigofera tinctoria* against D-galactosamine and carbon tetra chloride on in situ perfused in liver. *Ind. J. Physiol. Pharmacol.* 45:28-34.

76. Steriti, R., (2002). Nutritional support for chronic myelogenous and other leukemia's: A review of scientific literature. *Altern. Med. Rev.* 7:404-409.

77. Stochmal, A., Kowalska, I., and Oleszek, W. (2007). Medicago sativa and *Medicago truncatula* as plant sources of the chemopreventive flavone tricin. *Planta Med.* 73:304.

78. Subramaniam, S., Selvaduray, K.R., and Radhakrishnan, A.K. (2019). Bioactive compounds: Natural defense against cancer? *Biomol.* 9:758.

79. Sutthivaiyakit, S., Thongnak, O., Lhinhatrakool, T., Yodchun, O., Srimark, R., Dowtaisong, P., (2009). Cytotoxic and antimycobacterial prenylated flavonoids from the roots of *Eriosema chinense* . *J. Nat. Prod.* 72:1092–1096.

80. Tariq, A.S, Adia S., Pan, K., Ullah, I., Mussarat, S., Sun, F., Abiodun, O.O., Batbaatar, A., Li, Z., and Song, D. (2017). A systematic review on ethnomedicines of anti-cancer plants. *Phytother. Res.* 31: 202–264.

81. Tin, M.M., Cho, C.H., Chan, K., James, A.E., and Ko, J.K. (2007). *Astragalus saponins* induce growth inhibition and apoptosis in human colon cancer cells and tumor xenograft. *Carcinogenesis.* 28:1347–1355.

82. Valencia-Gomez, L.E., Martel-Estrada, S.A., Vargas-Requena, C., Rivera-Armenta, J.L., Alba-Baena, N., Rodriguez-González, C., and Olivas-Armendariz, I. (2016). Chitosan/*Mimosa tenuiflora* films as potential cellular patch for skin regeneration. *Inter. J. Biol. Macromol.* 93:1217–1225.

83. Vergara-Castañeda, H.A., Guevara-González, R.G., Ramos-Gómez, M., Reynoso-Camacho, R., Guzmán-Maldonado, H., Feregrino-Pérez, A.A., Oomah, B.D., and Loarca-Pina, G.(2010). Non-digestible fraction of cooked bean (*Phaseolus vulgaris* L.) cultivar Bayo Madero suppresses colonic aberrant crypt foci in azoxymethane-induced rats. *Food Funct.* 1:294–300

84. Xiujuan, (1981). Role of *Indigofera tinctoria* against Lewis lung carcinoma. *Carcinogenesis.* 9: 431-438.

85. Yang, Y.N, Zhu, H., Yuan, X., Zhang, X., Feng, Z.M., Jiang, J.S., and Zhang, P.C. (2021). Seven new prenylated flavanones from the roots of *Sophora flavescens* and their anti-proliferative activities. *Bioorg Chem.* 109:104716.

86. Yao, X.Q., Zhang, Y.H., Long, W., and Liu, P.X. (2012). Oxysophoridine suppresses the growth of hepatocellular carcinoma in mice: in vivo and cDNA microarray studies. *Chin. J. Integr. Med.* 18:209-213.

Traditionally Used Anticancer Plants in Rubiaceae

Sahla P.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: mailstosahla@gmail.com

Abstract: By considering the family Rubiaceae, there is many species with valuable secondary metabolites which can be used as anticancer and cytotoxic agents. Some of the plants are well known for camptothecin, genipin, genipodide, cisplatin, kaempterol, erithrodiole, quinine, caffeine, polyphenole, ursolicacid and phenolic compounds as anticancer agents. Cancer is a dreadful disease, and combating this disease is of great importance to public health. Phytochemical examination has been making rapid progress, and herbal products are becoming popular as sources of plausible anticancer compounds. The Rubiaceae members inhibit cancer in different human cell lines including A549, MCF-7, HeLa etc. by suppressing cell cycle and promoting apoptosis. The major plants which show the property are *Anthocephalus, Gardenia, Cinchona, Ixora, Chassalia, Coffea, Morinda* etc..

Keywords: Rubiaceae, anticancer, bioactive compounds, camptothecin, apoptosis

Globally cancer is one of the commonly life threatening diseases which severely affect the human being. It is recognized by the uncontrollable division of cells. There is a demand for new methods to prevent this disease. Conventional therapies have several adverse effects on the healthy cells; therefore, the alternative and effective medications are required to combat this disease. Benefits of using plant derived products over synthetic medicine have increased the importance of medicinal plants in the field of healthcare. Many plants derived products are potent in cancer treatment by inhibiting cancer activating enzymes, stimulating DNA repair mechanism, inducing antioxidant action and promoting protective enzymes production. As chemotherapy and radiation therapy causes various side effects, so there is a necessity to discover novel agents for the treatment of the disease; it could be possible with the use of naturally occurring compounds (Arpita & Navaneeta, 2017).

The chapter provides significant information regarding the plant resources of the family which can provide bioactive compounds for cancer treatment. The family is the main group of angiosperm represents one of the most species rich flowering plants with13, 548 species under 617 genera in Gentianales. The members are herbs, shrubs and trees, distributed primarily in tropical areas of the world. Several species are of economic

importance as sources of useful chemicals and a number are cultivated as ornamentals. The leaves are opposite each other with stipules or in whorls, unbroken leaf margins, and leaf like appendages at the base of the leafstalks. The plants may bear a single flower or many small flowers clustered together. The fruits can be berries, drupes, capsules or schizocarps (Michael, 2010).

The members of Rubiaceae as well as their isolated compounds possess diverse biological activities including antiinflammatory, antitumour, antimicrobial, larvicidal, antioxidant, gastrointestinal, antiulcer and hepato protective, with alkaloids and iridoids as the major active principles. About 3000 plants has anticancer properties are subsequently used as potent anticancer drugs (Srigiri, 2015). The members such as *Morinda, Gardenia, Ixora, Neurocalyx, Cinchona, Anthocephalus* etc., have shown potent cytotoxic activities in the previous studies.

About 12 species with anticancerous property which are almost common including the phytochemicals such as camptothecin, genipin, genipodide, cisplatin, kaempterol, erithrodiole, quinine, caffeine, polyphenole, ursolicacid and phenolic compounds. This can inhibit cancer in different cell lines. So the demand of natural pharmaceuticals made investigation in different plant groups of the family and also helps in conservation of them.

1. Anticancer plants in Rubiaceae

1.1. *Anthocephalus* A. Rich.

A. cadamba is one of the most precious medicinal evergreen tropical trees, native to South and Southeast Asia. It is a large tree with a broad crown and may reach a height of 45 m. The bark is gray, smooth in young trees, rough and longitudinally fissured in old trees. Leaves are glossy green, opposite, simple more or less sessile to petiolate, ovate to elliptical. Inflorescence is in clusters; terminal globose heads without bracteoles, subsessile, fragrant with orange or yellow flowers. Flowers are bisexual and 5 merous. Calyx tube is funnel shaped, corolla gamopetalous, saucer shaped with a narrow tube, the narrow lobes imbricate in bud. Stamens 5, inserted on the corolla tube, filaments short, anthers basifixed. Ovary is inferior, bilocular, sometimes 4 locular in the upper part, style exserted with a spindle shaped stigma. Fruitlets are numerous with their upper parts containing 4 hollow or solid structures. Seeds are trigonal or irregularly shaped.

Anticancer activities: The phytochemical screening of Cadamba reveals the presence of lupeol and betulinic acid type triterpene which have antineoplastic activity. It also has antitumour activity on Ehrlich ascites carcinoma (EAC) by defatted methanol extract of Cadamba (MEC). The antitumour potential of MEC shows influence on tumour volume, viable and nonviable tumour cell count, tumour weight, hematological parameters and biochemical estimations (Dwevedi, 2015). Despite several known pharmacological properties of *A. cadamba*, only few studies are available on antiproliferative activity of bark. The bark methanol extract shows the antiproliferative activity against human cervical cancer HeLa cells. By comparing with standard cisplatin drug, *A. cadamba* bark methanol extract have significant antiproliferative activity against

human cervical cancer cells due to induction of apoptosis which is credited to the phenolic contents. The phytochemical potency of the plant is due to high amount of total phenolic content.

1.2. *Borreria* G. Mey.

B. hispida is a creeping herb with tropical and subtropical distribution. Much branched prostrate perennial herb forms mats up to 23-40 cm wide; stems 10-20 cm long, tinged reddish, covered with spreading white hairs, with short internodes and rather congested foliage. Leaf blades are elliptic or oblong elliptic with white hairs on upper surface and particularly along the margins, also with hairs on midrib and nerves beneath. Flowers are 1-several, sessile, in most leaf axils. Calyx tube is oblong-ovoid, densely hairy; lobes 4, lanceolate, hairy along the margins. Corolla is pale blue or lilac; tube narrowly cylindrical; lobes oblong, hairy at the apex. Filaments exserted. Style exserted; stigma shortly bifid. Capsule is obovoid with spreading white hairs. Seeds are chestnut brown, oblong ellipsoid, sometimes narrowed to one end, finely reticulate, ventrally grooved.

Anticancer activities: The methanolic extract of the seeds of *B. hispida* shows the anticancer activity due to the presence of some bioactive elements like kaempterol and erythrodiol. The methanolic extract of seeds inhibits the growth of A549 and MCF-7 cells at the IC_{50} concentration of 3.125µg/mL and 1.56µg/mL respectively which show the anticancer activity of the extract against human lung carcinoma (A549) and breast carcinoma (MCF-7) cell lines. The F3 fraction cytotoxic protein of methanolic extraction of seed exhibits growth inhibition (in vitro cytotoxicity assay) and cell cycle arrest in sub-G0 population of human lung (A549) and cervical (HeLa) cancer cells (Rupachandra & Sarada, 2013).

1.3. *Cinchona* L.

C. officinalis is commonly known as 'Peruvian bark', native to South America specifically from the Andes mountain range. It can also be found in India, Java, Cameroon and Vietnam and in some other Asian and African countries. In India, it is mainly found in hilly areas. *Cinchona* is a 10 to 20 m tall tree with straight trunk about 30 cm in diameter. It has a dense and irregular globular crown; darkly green, oval shaped leaf with a thick central nerve with full margin. The color of flower is white or pinkish with white hairs found in panicles. The fruit is dark brown 2-4 cm long with 3-4 seeds. The brown bark of *Cinchona* is looked like a tube which is arched or curved during aging. Barks are usually visible in trunk or branches and after immediate collection the outside has a brown grayish color while the inside has a reddish brown.

Anticancer activities: The phytochemical screening of bark and leaves shows the presence of alkaloids known as quinine, cinchonine, quinidine, quinoline and cinchonidine. Quinine is more potent to inhibit the cell proliferation and induces apoptotic cell death in cancer cell line in a dose and time dependent manner (Krishnavedi & Suresh, 2015). ROS (Reactive oxygen species) is critical for the metabolic and signal transduction pathways associated with cell growth and apoptosis. Several anticancer agents including anthracyclines, cisplatin and bleomycin, currently used for cancer treatment have been shown to cause increased intrace-

llular ROS generation. Quinine also increases the intracellular ROS levels at time and dose dependent manner (Pranay & Puspal, 2017). Induction of cell death through indirect activation of the mitochondria dependent pathway is the conventional anticancer treatment but sometimes it is altered in drug resistant cancer cells. Effect of quinine induces typical morphological changes as the signal of apoptosis like cell shrinkage, membrane blebbing, chromatid condensation, nuclear fragmentation, apoptotic bodies and loss of adhesion. So quinine may be a strong anticancer agent in future due to its huge apoptotic activities in cancer.

1.4. *Chassalia* Comm. ex Poir.

The genus, commonly known as Curved flower Chasalis' or 'Curved flower woody *Chassalia*', consists of more than 110 species with paleotropic distribution, mainly in open areas forest edges in North East India. The plant erect, 1-2 m tall; branches weakly flattened to sub terete. Leaves opposite; petiolate, oblong-elliptic, glabrous; stipules persistent, united shortly around stem, with interpetiolar portion. Inflorescence cymose, pyramidal to rounded, several to many flowered, puberulent; bracts lanceolate to triangular or usually multifid. Flowers subsessile, trimorphic with anthers exserted and stigmas included, with anthers included and stigmas exserted or with anthers and stigmas both exserted. Calyx with hypanthium portion ellipsoid to obovoid. Corolla white with pink, violet on lobes, outside glabrous to sparsely puberulent; tube shallowly to markedly curved, straight or bent at base; lobes 4 or 5, ovate-triangular. Infructescence axes becoming swollen and red. Fruit purple, oblate to globose or weakly didymous.

Anticancer activities: The plant has various phytoconstituents such as steroids, terpenoids, alkaloids, tannins, phenolic compounds, flavonoids, carbohydrates, amino acids and other many bioactive compounds with medicinal property (Savitha et al., 2019). Ethanolic extract of leaves and roots of *C. curviflora* were possesses antiinflammatory, analgesic and hepatoprotective activity, and phytochemical analysis reveals that roots have high content of alkaloid. The antiinflammatory and immunomodulatory properties of a plant may contribute to its anticancer properties. Main alkaloid present in the plant is camptothecin. It can be treated against the 3 human cancer cell lines; breast cancer (MCF-7), lung cancer (A549), cervix cancer (HeLa) and normal fibroblast cell (3T3L1). The cytotoxic effect of the alkaloid rich extract (Chr-alk) on cancer cell lines shows a concentration and time dependent increase in the percentage of cytotoxicity. There is more cell death treatment of extract on in A549 lung cancer cells. The Chr-alk induces less toxicity in normal cells compared to cancer cells showing its specificity to cancer cells (Rajeswari et al., 2020).

1.5. *Coffea* L.

Members of the genus *Coffea* are evergreen shrubs or small trees and often inhabit the understory of tropical forests. The elliptical waxy leaves are borne oppositely along the stems and often feature prominent venation. Many species have a characteristic growth habit in which the upright trunks branch horizontally and may then repeat the pattern on secondary and tertiary branches. The small fragrant white or pink flowers

frequently open after a dry period and may last only a few days. The fruit, known as a "Coffee cherry," is a one or two seeded drupe and can be red, purple, yellow, orange, blue or black when mature, depending on the species. The "Coffee beans" are the rounded oblong seeds, each with a flat face marked by a lengthwise groove.

Anticancer activities: The epidemiological evidence consistently indicates that coffee protects against liver cancer, and also point toward protective effects for risk of colorectal cancers, overall risk of breast and prostate cancer. However, for subgroups such as postmenopausal breast cancers, advanced prostate cancers, and breast and prostate cancer survivors, an inverse association with coffee intake is indicated. Basically the coffee contains caffeine, chlorogenic acid (CGA) (which is caffeic acid bound to quinic acid), cafestol, kahweol, p-coumaroylquinic and feruloylquinic acid. Potential mechanisms for chemopreventive effects of coffee phytochemicals include inhibition of oxidative stress and oxidative damage, regulation of DNA repair, phase II enzymatic activity, apoptosis, inflammation, as well as having antiproliferative, antiangiogenetic and antimetastatic effects. The antiproliferative effect can be found as in human cancer cell line viability (breast carcinoma) significantly decreases in a concentration dependent manner. Similarly, the plant shows a comparable effect in cancer lines from colon (CHT116), brain (T98G) and bone (U2OS). Both green and dark coffee extracts inhibit the proliferation of MCF-7 and MDA-MB-231human breast cancer cell lines.

The two coffee lipids, cafestol and kahweol, are antigenotoxic compounds that prevent the deleterious effects of reference carcinogens such as N-nitrosodimethylamine, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, ferric ion-nitrilotriacetic acid and H_2O_2 in human hepatoma HepG2 cells. The ability of the caffeine and chlorogenic acids, 5-O-caffeoylquinic acid (5-CQA) and 3,5-O-dicaffeoylquinic acid (3,5-DCQA), to protect against ROS induced oxidation has investigated in HepG2 cancer cells (Ayelene et al., 2021). Both cafestol and kahweol are the inhibitors of cytochrome P450, an enzyme responsible for the activation of carcinogens and thus DNA damage (Jose et al., 2012).

1.6. *Gardenia* J. Ellis

Gardenia is a genus of more than 140 species of shrubs and trees in the Madder family, native to tropical and subtropical Africa, Asia, and Pacific islands. The plants have glossy evergreen leaves that usually are arranged oppositely or in whorls. The tubular flowers are white or yellow and are borne singly or in small clusters; the flowers are often strongly scented. The large berrylike fruits contain a sticky orange pulp. The fruits are used in Japan and China for dyeing food yellow. The colouring matter in the fruits contains glycoside, a compound similar to crocetin which is found in Saffron. The dye is also used to colour textiles yellow or scarlet. The flowers contain fragrant essential oils and are used in perfumery. It is also used in China for flavouring tea.

Anticancer activities: *G. jasminoides* is a natural plant, has many biological activities. Plant has the ability of apoptosis in HepG2 human hepatoma cells. It contains 1.03% genipin gentiobioside, 5.90% gardenoside,

1.26% crocin 1 and 0.17% crocin 2 in turn show significantly strong HepG2 cell inhibitory effects. Usually, species has the ability to increase the mRNA expression of caspase 3, caspase 8, caspase 9, Bax, TRAIL, Fas, Fas/FasL, p53, p21 and IκB-α, and decrease the Bcl-2, Bcl-xL, XIAP, cIAP-1, cIAP-2, survivin, NF-κB expression in HepG2 cells. The higher concentration of *G. jasminoides* shows the higher increasing or decreasing mRNA expression effects in HepG2 cells. So *G. jasminoides* had a strong anticancer effect through its apoptosis inducing abilities in hepatic cancer; it could be used for the treatment as a medicine or health product in daily human life for good liver health (Sook et al., 2012).

1.7. *Ixora* L.

I. coccinea is a small shrub. Stem is herbaceous, aerial, erect, branched, cylindrical, and differentiating into nodes and internodes. Leaves are cauline, simple, opposite, decussate, stipulate, sessile, ovate to elliptical, entire and acute with unicostate reticulate venation. Inflorescence is corymbose cyme. Flowers are bracteate, pedicellate, complete, hermaphrodite, actinomorphic, tetramerous, epigynous, large, showy with long corolla tube. Calyx made up of 4 sepals, gamosepalous, green, valvate, very short in comparison to corolla. Corolla made up of 4 petals, gamopetalous, twisted, long, slender, corolla tube with abruptly expanded corolla limbs. Androecium made up of 4 stamens, polyandrous, epipetalous and alternipetalous, anthers sagitate, dithecous, dorsifixed, introrse. Gynoecium composed of bicarpellary, syncarpous, bilocular, two ovules in each locule on axile placentation. The style is long and passes through the long corolla tube. Stigma is bilobed and simple. Fruit is berry with small endospermic seeds.

Anticancer activities: *I. coccinea* flowers show cytotoxic activity. The flower extract contains terpenoids, flavonoids, phenols, tannins and lupeol which have cytotoxic activity and kaempferol with antiplatelet aggregation potential. The compounds show cytotoxic activity against cancer cell lines namely, NCI H-460 (large cell carcinoma, lung), MCF-7 (adenocarcinoma, breast), HeLa and Hep3B (liver tumour) cell line.

The flower extract is effective against MCF-7, HeLa and NCI H-460 human cancer cell lines. 17 metabolites identified from *I. coccinea* flowers (yellow), which are mostly responsible for its cytotoxicity and growth inhibitory actions preferably towards cervical cancer cell line (Lubna et al., 2018). The flowers and leaves contain an anticancer drug camptothecin which having anticancer activity against Dalton's lymphoma (ascitic and solid tumours) and Ehrlich ascites carcinoma (EAC) tumours (Saravanan & Boopalan, 2011).

1.8. *Morinda* L.

M. citrifolia is a small, glabrous tree with straight trunk; smooth, yellowish white bark; branchlets obtusely quadrangular. Leaves are broadly elliptic, acute, acuminate or obtuse, bright green, glabrous, shining, one of the pair next the prominent peduncle, petiolate; stipules connate, short, broad, obtuse, membranous. Flowers are white in dense ovoid heads, peduncles solitary (rarely 2-3 together), usually leaf opposed. Calyx limb is truncate. Corolla is infundibuliform tube with hairy mouth, lobes 5, lanceolate, acute. Stamens are 5 in number,

filaments hairy, anthers about half exerted. Fruit is white when ripe, smooth, glossy, about a size of a small egg.

Anticancer activities: The ethyl acetate extract of noni fruit juice strongly inhibits the proliferation of MCF-7, MDA-MB-231 and HEK-293 cell lines with IC_{50} values of 25, 35, 60 µg/mL respectively. The extract shows increase in apoptosis of MCF-7 and MDA-MB-231 cells and arresting of the cell in the G1/S phase of MCF-7 and G0/G1 phase of MDA-MB-231 cells. Noni extract also decreases the intracellular ROS generation and mitochondrial membrane potential (Sharma et al., 2015). Concentrated components in noni juice may stimulate the immune system to 'possibly' assist the body fight to cancer, and kill a small percentage (0-36%) of cancer cells depending on the type (Amy, 2017).

The noni juice inhibits the A549 cells proliferation, migration and invasion. It also promotes cell apoptosis in A549 cells as well as effectively suppresses tumour formation of A549 cells in nude mice. The phosphorylation level of AKT, p50 and STAT3 proteins inhibits to different extents after noni juice treatment. It can be inhibited the expression of Ki67, PCNA and Bcl-2 protein in the tumour; while promoted the expression of caspase-3 protein. Additionally, the noni juice treatment could restrain the activity of AKT/NF- κ B signaling pathway in the tumour tissue (Ma et al., 2020).

More than 160 phytochemicals have been isolated from the plant Noni (Steroids, glycosides, phenol, tannins, terpenoids, alkaloids, resins, carbohydrates, flavanoids, anthraquinones, phylobatannins, saponins and protein) which makes it an amazing herbal remedy for the treatment of numerous disorders including cancer. Recently, the Noni juice has been in high demand in market as Complementary and Alternative Medicine (CAM) for its multidimensional health benefits. It is a potent antibacterial, antiviral, antifungal, antihelminthic, anticancer, analgesic, antiinflammatoiy, antioxidant, hypotensive, cardiovascular protective, wound healer, anxiolytic, sedative, antigout, antiobesity and immune enhancing agent. Anticancerous activity of *M. citrifolia* is attributable to its antiinflammatoiy, antioxidant and apoptosis inducing effects. Based on toxicological and mutagenicity assessment, Noni juice has been considered as safe.

1.9. *Neurocalyx* Hook.

N. calycina is a large herb endemic to South West India, found in evergreen forest. These are large pubescent herbs. Leaves are simple, whorled at tip, oblanceolate, acute at apex, rusty puberulus; nerves to 18 pairs, prominent below; stipule 2 cm long, obovate, 2 fid at apex. Racemes are 10-13 cm long, axillary, rarely branched; bracts lanceolate. Flowers white, pedicelled. Calyx tube is hemispherical, lobes 5, ovate. Corolla tube is absent, lobes 5 x 3 mm, ovate, twisted. Stamens are 5 in number, anthers connate into a conical tube. Ovary 2 celled, ovules many, style slender. Capsule irregularly bursting; seeds many, pitted.

Anticancer activities: The plant has wound healing, burn healing, anticancer, analgesic, antiinflammatory, immune enhancing, platelet augmentation and antioxidant effects. *N. calycina* has significant concentration of anticancer

alkaloid camptothecin, in the plant parts. Roots of *N. calycina* produce the highest content of camptothecin (CPT) and followed by stem and leaves. Plant derived monoterpene pyrrolidine alkaloid camptothecin, possessed to have unique antitumour activity. CPT inhibits the cell cycle at various stages and finally induces the cell death. Continuous exploration on the action of mechanisms of CPT, researchers have found out the compound inhibits the DNA replication in association of Topoisomerase I (Karuppuswami & Mohanaraj, 2021). Camptothecin and its derivatives are used as second or third line treatment for patients with endocrine resistant breast cancer (BC). These drugs convert nuclear enzyme DNA topoisomerase I (TOP1) to a cell poison with the potential to damage DNA by increasing the half life of TOP1-DNA cleavage complexes, ultimately resulting in cell death (Tesauro et al., 2019).

1.10. *Ophiorrhiza* L.

O. mungos is an annual erect herb form roots at lower nodes. Leaves 7-15 x 3-6 cm, elliptic or elliptic-lanceolate, base attenuate, apex acuminate, chartaceous, hirsute on veins below; petiole to 1.5 cm; stipules subulate, 3-5 mm long, 2 fid at tip. Flowers in dense terminal branched, scorpioid cymes. Peduncle is to 2.5 cm long, rusty pubescent. Calyx tube c. 1 mm long; lobes obscure. Corolla is 0.8-1 cm long, white with pink shades on lobes. Capsule 2.5-3 mm long, 4-6 mm wide, obcordate, laterally compressed, glabrous, dehiscence loculicidal. Seeds are many, angular.

Anticancer activities: *O. pumila* and *O. mungos* produce camptothecine in small quantity. The four other derivatives of CPT, which are currently in use, including topotecan, irinotecan, belotecan and trastuzumab deruxtecan, are also produced. The mode of action of CPT involves inhibition of topoisomerase 1 (TOP 1), which is known to be present in higher amounts in cancer cells when compared to normal tissues. The formation of TOP I-CPT complex leads to an irreversible strand breaks in the DNA eventually causing the death of cells. The initial usage of CPT and its derivatives are targeted to gastrointestinal tumours, and further slowly explored in the treatment of breast, ovarian, colon, lung and stomach cancers. It's low solubility and resistance by the cancer cells has reduced its usage (Madihalli et al., 2021).

1.11. *Pavetta* L.

P. indica, 'Indian *Pavetta*', is an erect, nearly smooth or somewhat hairy shrub, 2 to 4 meters or more in height. The leaves are elliptic-oblong or elliptic-lanceolate, 6-15 cm long, and pointed at both ends. The flowers are white, rather fragrant, and borne in considerable numbers in hairy terminal panicles which are 6-10 cm long. The sepals are very small and toothed. The flower tube is slender and about 1.5 cm long, with obtuse petals about half the length of the tube. The flowers attract butterflies and insects. The fruit is berry, black when dry, somewhat rounded, and about 6 mm in diameter.

Anticancer activities: Methanol extract of the leaves and branches of *P. indica* (MEPI) causes cell cycle arrest at the sub-G1 phase and induces apoptosis, as indicated by the activation of caspase 8, 3, 7, and c-PARP. The MEPI significantly reduces the expression of multidrug resistance associated protein 1 in triple negative breast cancer (TNBC). MEPI

causes nuclear fragmentation and chromatin condensation; thus, MEPI induces caspase dependent apoptosis of MDA-MB-231 cells. Moreover, the co-treatment with MEPI and doxorubicin results in a synergistic reduction in cell viability. MEPI also induces radiation sensitization of TNBC cells. The major constituent of MEPI is 5,6-dehydrokawain (DK). Doxorubicin (DOX) has enhanced the expression of MRP1 in breast cancer cells, leading to resistance. DOX significantly induces MRP1 expression levels in different non small cell lung cancer cells (H1299, A549, and CH27 cells) in a time dependent manner. Use of chemotherapeutics in combination with natural compounds can increase efficacy, reduce the dosage, minimize side effects and overcome resistance (Yen et al., 2019).

1.12. *Psychotria* L.

P. leptothyrsa is under shrubs up to 1 m tall with striate stem. Leaves are simple, opposite decussate; stipules 2x0.3 cm, foliaceous, linear-lanceolate; petioles 1.5-4 cm long, shallow-grooved; lamina 10-25x4-17 cm, ovate-lanceolate to elliptic-lanceolate, narrowed at base, acuminate at apex, obscurely crenate at margin; secondary nerves 10-15 paired. Inflorescences are in axillary or terminal 4-6 cm long umbellate cymes. Flowers are pale yellow; peduncles 2-3 cm long, slender puberulous; bracts subulate, 0.3 cm; pedicels 0.5 cm long; calyx lobes linear-lanceolate, 2x0.5 mm, ciliate; corolla tube very short; throat villous within. Fruits are 1x0.8 cm, ellipsoid with persistent calyx teeth, orange-yellow.

Anticancer activities: *P. leptothyrsa* var. *longicarpa* contains a suite of different cyclotides. Cyclotides, the largest known family of head to tail cyclic peptides, have approximately 30 amino acid residues with a complex structure containing a circular peptide backbone and a cystine knot. It displays cytotoxic, antiHIV, antimicrobial and inhibition of neurotensin binding activities and also has cytotoxic activity toward the human lymphoma cell line U937-GTB (Samantha et al., 2010). The another species, *P. serpens*, shows powerful activity against H460, HepG2, Hela and PC9/GR cell lines, and no toxic effects against normal 16HBE cell lines. The anticancer activity leading compounds are sevenetin, rutin, kaempferol-3-flavonoids, quercetin, tamarixetin-3-O-rutinoside, quercetin 3-O-(2G-β-D-xylopyranosyl-rutinoside), kaempferol and tamarixO- rutinoside. It can be often used as a substitute for *Caulis trachelospermi* to treat cancer in China (Chao-Zhang et al., 2015).

2. Outlook

The demand of bioactive plant derived compounds in pharmaceutical market is ever increasing due to its cancer potential and with their pharmacological efficacy of diverse natural chemical derivative. It is urged the identification of alternative source to meet out the pharmaceutical demand and conservation of high valued plant species. Total of 12 different species of family Rubiaceae have been reported in this chapter with bioactive compounds as their secondary metabolites which are active as anticancer molecules in different cell lines with different physiological properties. The major plant derived compouds, used as anticancer drug are camptothecin, lupiol, kaempterol, doxorubin, genipion, quinone, cyclotides etc., will become great demanded product in future.

References

1. Amy, C.B. (2012). Anticancer activity of *Morinda citrifolia* (Noni) fruit: a review. *Phytother. Res.* 26 (10):1427-40.
2. Arpita, R., and Navneeta, B. (2017). Medicinal Plants in the Management of Cancer: A Review. *Int. J. Compl. Alt. Med.* 9(2):311-17.
3. Ayelen, N., Deborah, B., Cesar, P., Otniel, F.S., Anderson., and Prucca, G.G. (2021). Antitumour effects of freeze-dried Robusta coffee (*Coffea canephora*) extracts on Breast Cancer cell lines. *Oxid. Med. Cell. Long.* 1-16.
4. Chao-Zhan, L., Ai-Zhi, W., Ying, Z., Yu-Mei, W., Guang-Tian, P., Xian-Jun, S., Bing-Xin L., Yun, D., Chen-Chen, Z., and Cui-Xian, Z. (2015). Flavonoids from *Psychotria serpens* L., a Herbal Medicine with Anti-Cancer Activity. *J. Cancer Res. Updates.* 4:60-64
5. Dwevedi, A., Sharma, K., and Sharma, Y. K. (2015). Cadamba: A miraculous tree having enormous pharmacological implications. *Pharmacogn. Rev.* 9(18):107-113.
6. Eun- sook, K., Choon-sik, J., and Areemoon. (2012). Genipin, a constituent of *Gardenia jasminoides* Ellis, induces apoptosis and inhibits invasion in MDA-MB-231 breast cancer cells. *Oncol. Rep.* 27: 567-572.
7. Fatima, N., Ahmad, M. K., J. A. Ansari1, H. J. Khan, H. J., Rastogi, N., Srivastava, S. K., Ahmad, S., and Ali, Z. (2016). Antiproliferative and antioxidant studies of *Anthocephalus cadamba* Rox. Miq. Bark. *Indian J. Pharm. Sci.* 78(4):525-531.
8. Jose, S. A., Nuno, B., Alejandro, S., and Arminda, A. (2012). Method validation for Cafestol and Kahweol quantification in Coffee brews by HPLC-DAD. *Food Anal. Meth.* DOI 10.1007/s12161-012-9387-5.
9. Karuppuswami, S., and Mohanraj, R. (2021). New plant sources of the anticancer alkaloid camptothecin from two genera of Rubiaceae in southern Western Ghats of India. *Int. J. Herb. Med.* 9(4):129-136.
10. Krishnaveni, M., and Suresh, K. (2015). Induction of apoptosis by quinine in human laryngeal carcinoma cell line. *Int. J. Curr. Res. Aca. Rev.* 3(3):169-178.
11. Lubna,. Rahat, A. A., Faheema, S., Perveen, F., Ahsana, D. F., Amna, J. S., and Syed, G. M. (2018). Cytotoxic activitiy of extracts of *Ixora* species and their GC-MS analysis. *J. Chem. Soc. Pak.* 40(5):941-952.
12. Ma, L. D., Lin, G. B., Yang, L. B., Cao, J. L., Wang, J., Chen, Q. D., Li, W. Q., and Zhong, W. J. (2021). *Morinda citrifolia* (Noni) Juice Suppresses A549 Human Lung Cancer cells via Inhibiting AKT/Nuclear Factor-κ B Signaling Pathway. *Chin. J. Integr. Med.* 27(9):688-695.
13. Madihalli, S. C., Abhijit, D., and Mallapa, K. S. (2022). Introduction to cancer and treatment approaches, Camptothecin and its derivatives. *Paclitaxel.* 1-27.
14. Michael, G. (2010). Diversity and Classification of Flowering Plants: Eudicots, Plant Systematics. Academic Press. 2:275-448.
15. Pranay, G., and Puspal, D. (2017). Spectrum of biological properties of *Cinchona* alkaloids: A brief review. *J. Pharmacogn. Phytochem.* 6(4): 162-166.
16. Rajeswari, G., Lakshmi, S., Jayakumaran, N. A., Gangaprasad, A., Sudhakaran, P. R Muraleedharan, D., and Nair, G. M. (2020). Antiproliferative effects of total alkaloid extract of roots of *Chassalia curviflora* (Wall.) Thwaites on cancer cell lines. *Indian J. Exp. Bio.* 58:389-395.
17. Rupachandra, S., and Sarada, D. V. L. (2013). Anticancer activity of methanol extract of the seeds of *Borreria hispida* and *Momordica dioica. J. Pharm. Res.* 6(5): 565-568.
18. Samantha, G., Robert, B., Lars, B., Debasis, M., and Ulf, G. (2010). Isolation, characterization, and bioactivity of cyclotides from the Micronesian plant. *J. Nat. Prod.* 73(7):1207-1213.
19. Saravanan, P., and Boopalan, E. (2011). Occurrence of Camptothecin an Anticancer Drug From *Ixora coccinea* Linn. *Intl. J. Appl. Biol.* 2(2): 30-34.
20. Savitha, T., Elamaran, T. J., and Amritha, C. K. (2019). *Chassalia curviflora* (Wall. ex Kurz) Thwaites: a review. *Asian J. Res. in Chem. Pharm. Sci.* 7(2): 759-765.
21. Sharma, K., Pachauri, S. D., Khandelwal, K., Ahmad, H., Arya, A., Biala, P., Agrawal, S., Pandey, R. R., and Srivastava, A. (2015). Anticancer Effects of Extracts from the Fruit of *Morinda Citrifolia* (Noni) in Breast Cancer Cell Lines. *Drug Res.* 6(3):141-147.
22. Sirigiri, C. (2015). Medicinal attribute of family

Rubiaceae. *Int. J. Pharm. Bio. Sci.* 5(2): 179-181.

23. Tesauro, C., Simonsen, A.K., and Andersen, M.B. (2019). Topoisomerase I activity and sensitivity to camptothecin in breast cancer-derived cells: a comparative study. *BMC Cancer*. 19:1158

24. Yen, T. N., Jeong, Y. M., Ji, Y. and Sangmi, E. (2019). Methanol Extract of Aerial Parts of *Pavetta indica* L. Enhances the Cytotoxic Effect of Doxorubicin and Induces Radiation Sensitization in MDA-MB-231 Triple-Negative Breast Cancer Cells. *Molecules*. 24(12): 2273.

The Genus *Inula* (Asteraceae) as Source of Anticancer Agents

Gouthami V.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: gouthamimanjeri@gmail.com

Abstract: Cancer is a group of more than 100 distinct diseases characterized by the uncontrolled growth of abnormal cells in the body. The World Health Organization has estimated that the global cancer burden could be reduced by as much as 30 to 50% through prevention strategies, particularly through the avoidance of known risk factors. Medicinal plants have a role in curing and avoiding such cell proliferation. The local people used the plants in a traditional way for all health problems from the ancient period. One of the plant genera, *Inula*, belongs to the tribe Inuleae and the family Asteraceae with about 100 species. Diverse biological activities have been attributed to this genus including anticancer, antibacterial, hepatoprotective, cytotoxic and antiinflammatory. The species growing in East Asia are widely used by the local people for varied medicinal properties which have prompted many workers to study the phytochemistry of these species that ultimately resulted in the extraction of a number of novel bioactive molecules. This emphasizes the need for extensive study for revealing the medicinal importance of the other species of *Inula*.

Keywords: *Inula*, anticancer agents, secondary metabolites, antiproliferative, Asteraceae

Over a decade the number of cancer patients is increasing in the world. The research field always seeks new medicines and treatments for different cancer. Plants take place a vital role in the manufacturing of medicines because plants produce lots of secondary metabolites that are beneficial to major biological activities of organisms. Moreover, 80% of the population depends on traditional medicinal plants. We have a glorious history of traditional medicines. Our cultural legacies like the Vedas and Upanishads show the plethora of wisdom on the plant kingdom. The largest group of the plant kingdom is angiosperms, in which the Asteraceae family is one of the larger families.

Asteraceae is commonly known as the sunflower family and is under the Asterales order. The family included 1600 genera and 2500 species. Many species are used for diet and medicinal purposes. Most species are great sources of inulin, a natural polysaccharide with solid prebiotic properties. It has potent antioxidant, antiinflammatory, antimicrobial activity, anticancer, diuretic and wound healing properties. All species of the family have phytochemical compounds including polyphenols, phenolic acids, flavonoids, acetylene and

terpenoids. The genus *Inula* contains more than one hundred species in temperate region of Europe and Asia. The genus first described by Linnaeus in 'Species Plantarum' (1753). In India total 17 species and two varieties are represented (Karthikeyan et al., 2009). The genus comprises annual or perennial herbs in India. Characters of the genus is flowering heads (capitula), which are heterogamous and with both ray and disc florets. The capitula are usually arranged in terminal corymbs or cymes but in some taxa, they are solitary and pedunculate or sessile and densely congested at the center of the rosulate leaves. *Inula* members have some ethnomedicinal uses, while some members face habitat loss. Hence, some species are endemic including *I. racemosa* and *I. rhizocephala* (Rao & Datt, 1996).

1. Anticancer species in the genus *Inula*

1.1. *Inula viscosa* (L.) Aiton

This is a highly branching perennial plant common throughout the Mediterranean Basin. It has long, narrow leaves that are pointed at both ends and have teeth along the edges and glandular hairs on the surfaces. One plant can produce many yellow flower heads each with as many as 16 ray florets and 44 disc florets.

Anticancer activities: It is a generally used folk medicine with antiinflammatory and antiseptic activities. The plant contains twenty one components; among them, patchulane, 3-ethyl-3hydroxy-5alpha-androstan-17-one and γ-gurjunene are prominent. The species shows high antioxidant capacity, high rate of secondary metabolites and demonstrated neuroprotective activities (Qneibi et al., 2021). Tomentosin is considered a traditional remedy for the treatment of different types of cancers, which is present in the species. Traditionally, the plant is used for lung cancer.

1.2. *Inula helenium* Hook.f. & Thomson

The plant is a rhizomatous, sunflower like composite of the aster family that is native to Europe and northern Asia, but has naturalized in fields, clearings, disturbed sites, roadsides, and waste places in parts of eastern North America from Nova Scotia to Minnesota, South to North Carolina and Missouri. It typically grows to 3-6' tall. It is noted for having coarse, toothed, rough hairy leaves. Ovate-elliptic basal leaves typically grow to 1-2' long on petioles extending to as much as 1' long. Ovate-lanceolate stem leaves are much shorter and sessile, decreasing in size from the bottom to the top of the central rigid hairy stalk. Sunflower like flowers (2-3" diameter) subtended by broad floral bracts, feature numerous very thin, scraggly yellow rays which surround a central disk of darker yellow tubular flowers. Flowers bloom July-September.

Anticancer activities: The plant has a long and interesting history as a medicinal herb wherein the rhizomes and roots are at one point, using in a large variety of medical applications primarily in the treatment of respiratory type ailments. The plant widely used in folk medicine to treat many diseases including bronchitis, cough, lung disorder, tuberculosis, intestinal ulcers etc. The major component of the plant extract is sesquiterpene lactones and eudesmanolides, exhibiting diverse bioactivities such as antitumour, antiinflammatory, antimicrobial, antiproliferative and antibacterial

(Konishi et al., 2002). The plant is an efficient inhibitor of the human U87 MG glioma cells. Therefore, the aerial parts are a valuable source for the development of a new chemotherapeutic drug for brain cancer.

1.3. *Inula britannica* L.

The common names of the plant are 'British Elecampane', 'British Yellowhead' or 'Meadow Fleabane'. It is an erect, rhizomatous, sunflower like, herbaceous biennial or perennial in the composite family. Once established in the landscape, the plant will spread aggressively and rapidly by seeds, rhizomes or root fragments.

Anticancer activities: Flowers of the plant are used as traditional Chinese and Kampo Medicines which are rich source of secondary metabolites. These consist of terpenoids like sesquiterpene lactones and dimmers, diterpenes, triterpenoids and flavonoids. The isolated compounds have shown diverse biological activities like anticancer, antioxidant, antiinflammatory, neuroprotective and hepatoprotective. The sesquiterpenoids, OABL and OODABL isolated from the species induce phosphorylation of BCl-2 in breast, ovary and prostate cancer cell lines.

1.4. *Inula falconeri* Hook.

The plant is annual herbaceous that vary greatly in size from small species of few centimeters tall. They carry yellow daisy like composite flower heads often with narrow ray florets.

Anticancer activities: Alantolactone and sesquiterpene lactone help cytotoxic activity against solid tumours and several acute myeloid leukemia stem cell lines.

1.5. *Inula royleana* DC.

Kashmir *Inula* is found in the Himalayas, from Pakistan to Kashmir, at altitudes of 2100-4000 m. It is common and prominent in Kashmir. The plant is stout erect with very large handsome golden-yellow flower heads of 10-12.5 cm across, much larger than those of showy *Inula*. Ray florets are numerous, up to 5 cm long. Leaves are large, elliptic-lance shaped. Lower leaves are elliptic-blunt, 15-25 cm, with an equally long winged leaf stalk. Upper stem leaves are elliptic, up to 20 cm, with enlarged stem clasping base. The stem is unbranched 1-2 feet tall. Flowering period is July-September.

Anticancer activities: The plant is an ethno medicine, used as antiinflammatory and antitumour agent due to the presence of diterpene alkaloids, alantolactone and sesquiterpene lactone. The plant shows antiproliferative activity against different cancer cell lines of lung cancer (Stojakowska & Malarz, 2004).

1.6. *Inula racemosa* Hook.

The plant is a critically endangered Himalayan herb. The species is a perennial herb up to 1.5 m tall with fragrant prominent root and root stock. Stems are many in number, ascending from the base of the rootstock. Leaves are leathery, rough above and densely hairy below, 25-50 cm long, 10-12 cm broad and elliptic-lanceolate in shape.

Anticancer activities: Alantolactone, sesquiterpene lactone, β–sitosterol, isoalantolactone, dihydroalantolactone and other secondary metabolites are present in leaf and root of the plant. Anticancer activity detected in this plant but further research is not investigated. Normally, the plant is using by the ethnic comm-

unities for breathlessness, asthma and lung cancer.

1.7. *Inula rhizocephala* var. *rhizocephaloids* (Clarke) Kitam

The species is endemic to Nubra and adjacent ranges of Ladakh. It is a stemless species and easily distinguished by its rosette of leaves flat on the ground and a domed stalkless cluster of yellow flower heads at its center. Flower heads are 1.9-2.5 cm across, ray florets yellow, about 8 mm, involucral bracts linear pointed, outer ones green with curled tips, inner ones purplish. Leaves are pressed to the ground, long spoon shaped, blunt, narrowed into a broad stalk, bristly haired, usually 3-5 cm long. The plant is usually 7-12 cm across. Fruits are brown, round, longitudinally finely ribbed, covered with appressed short fox-red hairs or hairless. Pappus is as long as achene, with numerous bristles. Flowering period is June-August.

Anticancer activities: It is ethnomedicine used for treating colds, cough, chest complaints and lung cancer. Alantolactone and sesquiterpene lactone are extracted from the plant which induce the medicinal properties. It can be used as anticancer drugs in future, if the research proved the cancer inhibition potentials of the plant extracts.

1.8. *Inula grantioides* Boiss

The plant is a perennial herb, up to 50 cm high, moderately branched. Cortex is green, striped, glandular-hairy. Leaves are linear to spoon shaped, entire to 3 lobed at tip, flattened, fleshy, 6 x 2 cm, gradually narrowing towards the base, glandular-hairy. Flower heads are more or less solitary, radiate with herbaceous bracts externally. Involucre is cup shaped, involucral bracts about 70 in several rows, linear to oblong, pointed, dorsally glandular, spreading at anthesis. Ray florets are 5-13, 9-20 x 2-5 mm, blade oblong to almost linear, apically 2-3 finely toothed. Disc florets are 40-90; flower 6-11 x 1.5-2 mm, style about 7 mm long. Flowering period is November-May.

Anticancer activities: A new flavonol, grantioidin, has been isolated from *Inula grantioides* and it's structure determined as 5-hydroxy-3,6,7,2',5'-pentamethoxyflavone. β-Sitosterol, lupeol, taraxasterol, taraxasterol acetate and triacontanol also isolated for the first time from this plant. This plant is used for pancreatic cancer treatment (Ahmad & Ismail, 1991).

1.9. *Inula helianthus-aquatica* C. Y. Wu

The plant is herbaceous perennials or subshrubs, mostly with large basal leaves and daisy like yellow flower heads, often with narrow ray florets. Many of the species are popular for the garden, with cultivation going back to antiquity. The smaller species are used in rock gardens and the more common larger ones, which tend to have very coarse foliage in borders. The plant includes different secondary metabolites having medicinal activities like alkaloids, flavonoids, saponins, terpenoids, steroids, glycosides etc.; hence the plant shows antioxidant, antitumour, antibacterial, antiviral, antidiabetic and antiinflammatory properties. It makes the species highly medicinal in pharmacology.

Anticancer activities: Seven compounds were isolated and elucidated from the plant namely inuchinenolide B, 8-epi-florilenalin-2-O-acetate,

neogaillardin, tomentosin, atractyligenin, β-sitosterol and β-hydroxypropiovanillone. from the plant. All the compounds are isolated from the flower of *Inula helianthus-aquatica* for the first time which is used against lungs, stomach, intestines, uterine neck, nasopharynx and bladder cancer cells.

2. Outlook

Asteraceae is one of the largest families of flowering plants with key character of head inflorescence. The plants bear numerous trichomes which also exhibit the characteristic flavour due to the presence of secondary metabolites that are not essential for the primary growth and development of the plant. But they possess different biological activities such as antioxidant, antidiabetic, antitumour, antimicrobial etc. due to the presence of these compounds. Hence, the family members may contribute more in the field of medicinal industry in future, especially in cancer prevention and controlling drug designing areas.

References

1. Adebayo, A.H., Tan, N.H., Akindahunsi, A.A., Zeng, G.Z., and Zhang, Y.M. Anticancer and antiradical scavenging activity of *Ageratum conyzoides* L. (Asteraceae). (2010). *Pharmacogn Mag.* 6(21):62-6. doi: 10.4103/0973-1296.59968.
2. Ahmad, V.U., and Ismail, N. (1991). 5-Hydroxy-3,6,7,2',5'-pentamethoxyflavone from *Inula grantioides. Phytochem.* 30(3):1040-1041.
3. Al-Snafi, A. (2018). Traditional uses of Iraqi medicinal plants. IOSR *J. Pharm.* 32–96.
4. Hamedi, A., Bayat, M., Asemani, Y., and Amirghofran, Z. (2022). A review of potential anticancer properties of some selected medicinal plants grown in Iran. *J. Herb. Med.* 33:100557.
5. Karthikeyan, S., Sanjappa, M., and S. Moorthy. (2009). Flowering Plants of India, Dicotyledons (Acanthaceae – Avicenniaceae). Botanical Survey of India, Kolkata. 1.
6. Kauroo, S., Govinden-Soulange, J., and Ranghoo-Sanmukhiya, V.M. (2021). Antiproliferative sesquiterpene lactones from the roots of *Inula helenium. Biol. Pharm. Bull.* 25:1370-2.
7. Qneibi, M., Hanania, M., Jaradat, N., Emwas, N., and Radwan, S. (2021). *Inula viscosa* (L.) Greuter, phytochemical composition, antioxidant, total phenolic content, total flavonoids content and neuroprotective effects. *Eur. J. Inte. Med.* 42: 101291.
8. Nesterova, I.V., Zelenskaia , K.L., Vetoshkina, T.V., Aksinenko, S.G., Gorbacheva, A.V., and Gorbatykh, N.A. (2003). Mechanisms of antistressor activity of *Inula helenium* preparations. *Eksp. Klin. Farmakol.* 66:63-5.
9. Guo, Q.L., and Yang, J.S. (2005). Sesquiterpenes in *Inula* L. plants and their pharmacological activities. *Nat. Prod. Res. Dev.* 17:804
10. Rao, R, R., and Datt, B. (1996). Diversity and phytogeography of Indian Compositae. In: Hind, D.J.N., and Beentje H.J. (Eds.), Compositae: Systematics. *Proc. Intern Compos. Conf. Royal Bot. Gard.,* Kew. 1:445-461.
11. Rolnik, A., and Olas, B. (2021). The plants of the Asteraceae family as agents in the protection of human health. *Int. J. Mol. Sci.* 22(6):3009. doi: 10.3390/ijms22063009.
12. Saeidnia, S., Gohari, A.R., Mokhber-Dezfuli, N., and Kiuchi, F. (2011). A review on phytochemistry and medicinal properties of the genus *Achillea*; DARU *J. Pharmaceut. Sci.* 19(3):173-186.

Apocynaceae Species with Anticancer Activities

Muhsina K. K.

Department of Botany, H. M. College of Science and Technology
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: muhsinahabeeb25@gmail.com

Abstract: Apocynaceae is a family of flowering plants that includes trees, shrubs, herbs, succulents and vines. The members of this family have wide variety of medicinal uses both traditionally and in conventional. The medicinal properties of the plants are due to the presence of alkaloids which is either indoline or steroidal. The anticancer bioactivities of Apocynaceae species are well known in barks and roots due to the accumulation of secondary phytocompounds, in turn lead the production of anticancer drugs in future.

Keywords: Apocynaceae, anticancer plants, phytochemical compounds, antiproliferation, cytotoxic

The family Apocynaceae consists of about 366 genera and 5100 species of tropical trees, shrubs and vines. With the inclusion of species of Asclepiadaceae, the family has now been enlarged from two to five subfamilies. Characteristic features of the family are that almost all species produce milky sap; leaves are simple, opposite or whorled; flowers are large, colourful and slightly fragrant with five contorted lobes; and fruits are in pairs. Several members of the family had various economic uses and are source of important natural products.

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. The most common cancers are breast, lung, colon, rectum and prostate cancers. Around one-third of deaths from cancer are due to tobacco use, high body mass index, alcohol consumption, low fruit and vegetable intake, and lack of physical activity. Many cancers can be cured if detected early and treated effectively. Vast numbers of naturally derived compounds from medicinal plants are targets for potential anticancer treatments. Apocynaceae plants are presented as a new hope for cancer patients as the plants have toxic secondary metabolites.

1. Anticancer plants in Apocynaceae

1.1. *Catharanthus* G. Don

C. roseus (Nithyakalyani or Shavamnari) is an evergreen subshrub or herbaceous plant growing 1 m tall. The leaves are oval to oblong, 2.5-9 cm long and 1-3.5 cm wide, glossy green, hairless with a pale midrib and a short petiole of 1-1.8 cm long. Leaves are arranged in opposite pairs. The flowers range from white with a yellow or red center to dark pink with a darker red center, having a basal tube 2.5-3 cm long and a corolla 2-5 cm diameter with five petal like lobes. The fruit is a

pair of follicles 2-4 cm long and 3 mm wide.

The species has long been cultivated for herbal medicine. In Ayurveda, the extracts of roots and shoots are used against several diseases including diabetes, malaria and Hodgkin's lymphoma. Other traditional uses include against dengue fever, diarrhea, cancer, skin diseases, menorrhagia/leucorrhea, indigestion, dyspepsia, dysentery, toothache, lower blood pressure, headache and antiatherosclerotic. In 1950s, *Vinca* alkaloids, including vinblastine and vincristine, were isolated from *C. roseus* and screened for antidiabetic drugs. Alkaloids also possess hypertensive, sedative and tranquillizing properties and cause relaxation of plain muscles and depression of the central nervous system.

Anticancer activities: The species is one of the most important and high value medicinal plants known for its anticancer alkaloids. It is the iota of the isolated secondary metabolites used in chemotherapy to treat diverse cancers. Moreover, they have hypoglycemic as well as cytotoxic effects. *Vinca* alkaloids are the second most used class of cancer drugs and stay among the original cancer therapies. Several high performance liquid chromatography (HPLC) methods have been developed to quantify the active alkaloids in the plant. There are four major *Vinca* alkaloids in clinical use including vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). VBL has been used as an integral part of medicinal treatment regimens for testicular carcinoma and both Hodgkin and non-Hodgkin lymphomas. It is also used in breast cancer and germ cell tumours. VRL is same to VBL. It has significant antitumour activity in patients with breast cancer and can be affected on bone tumour cells, osteosarcoma. In addition, VRL decreases the stability of lipid bilayer membranes. In the United States, VRL has been approved for the initial treatment of patients with advanced lung cancer. VCR has been approved to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumour, Hodgkin's disease and other lymphomas. Another characteristic of VCR that has been reported is treating several non-malignant hematologic disorders such as refractory autoimmune thrombocytopenia, hemolytic uremic syndrome and thrombotic thrombocytopenia purpura. VDS has similar effects to VBL. Antineoplastic activity of VDS has been reported in acute lymphocytic leukemia, blast crisis of chronic myeloid leukemia, malignant melanoma, pediatric solid tumours and metastatic renal, breast, esophageal and colorectal carcinomas.

In chemotherapy medications, vincristine and vinblastin used to treat several types of cancers and are biosynthesised from the coupling of the alkaloids catharanthine and vindoline. The newer semi synthetic chemotherapeutic agent vinorelbine, used in the treatment of non small cell lung cancer, can be prepared either from vindoline and catharanthine or from the *Vinca* alkaloid leurosine, in both cases via anhydrovinblastine. The insulin stimulating vincoline is also isolated from the plant. Vinflunine is a synthetic *Vinca* alkaloid which has been in use recently for the treatment of second line transitional cell carcinoma of the urothelium and other malignancies. Mauritianin, a flavonoid, enhances the 12-O-tetradecanoylphorbol-13-acetate (TPA),

which suppresses delayed type hypersensitivity reaction in mice, indicating that mauritianin may augment the resistance of the immune system to cancer. The 2, 3-dihydroxybenzoic acids from periwinkle show a strong radical scavenging activity which is associated with a lower risk of cancer.

1.2. *Nerium* L.

Oleander (Red Arali) grows to 2–6 metres tall, with erect stems that splay outward as they mature. The first year stems have a glaucous bloom, while mature stems have a grayish bark. The leaves are in pairs or whorls of three, thick and leathery, dark green, narrow lanceolate, 5–21 cm long and 1–3.5 cm broad, and with an entire margin filled with minute reticulate venation. The leaves are light green and very glossy when young, at maturity it becomes dull dark green. The flowers grow in clusters at the end of each branch; they are white, pink to red, 2.5–5 cm diameter, with a deeply 5-lobed fringed corolla round the central corolla tube. They are often, but not always, sweet scented. The fruit is a long narrow pair of follicles, 5-23 cm long, which splits open at maturity to release numerous downy seeds. Even though all parts of the plants are poisonous, it has been traditionally used in the treatment of cardiac illness, asthma, diabetes mellitus, corns, scabies, cancer, epilepsy and in wound healing as an antibacterial or antimicrobial. Leaf decoction is used to reduce swellings. Macerated leaves are used for itch and fall of hair. The flowers are good for inflammations, chronic pains in the muscles and joints, lumbago and headache.

Anticancer activities: Various Research findings prove that *N. oleander* can induce cell death in human cancer and inhibit fibroblast growth factor-2 (FGF-2) in prostate cancer cell lines PC-3 and DU-145. Oleandrin may stimulate apoptosis through activation-suppression of nuclear factor-kB (NF-kB), activator protein-1 (AP-1) and c-Jun NH2-terminal kinase in Hela cell line. Oleandrin treated cells irradiated with 6 Gy of γ-ray, can increase the activation of caspase 3 in humanprostate carcinoma cell line (PC-3); thus inhibit the process of tumourigenesis and inflammatory processes. It is also able to inhibit the growth of myeloma cells in a dose1, 74 x 10-5 M, proportional to the dose of vincristine sulfate 3,4 x 10-5 M.

1.3. *Plumeria* L.

P. alba (Pala) is a shrubby or small plant with a vase shaped canopy. It is grown in rich, dry to medium moisture, coastal thickets and limestone forests. The leaves are strap like and clustered at the end of branches. Flowers are white and fragrant in corymbose fascicles. The fruit is edible. Their medicinal properties are often due to their latex which is frequently drastic and corrosive. Latex is applied to ulcers, herpes and scabies. Seeds possess hemostatic properties. Moreover, its bark is bruised and applied as plaster over hard tumours; whereas the others can be used as purgative, cardiotonic, diuretic and hypotensive. The medicinal value of *Plumeria* species in the treatment of a large number of human ailments is mentioned in Ayurveda, Charaka Samhita, and Sushrita Samhita. In addition, the flowers are edible and eaten as fritters, while the heart of the wood is part of a traditional medical preparation taken as a laxative. The root bark is depurative and purgative, causing thirst. It is

used in the treatment of herpes and syphilis. The root bark is used externally as a lotion on syphilitic ulcers. The latex from the stem is caustic and used for treating ulcers, dartre and scabies. The seeds are using in the treatment of dysentery.

Anticancer activities: The synthesis of silver nanoparticles (AgNPs) from the leaf extract act as an anticancer and antimicrobial agent (Muthuraj et al., 2022). Moreover, it has effective anticancer activity against the glioma U118 MG cancer cell line with an IC_{50} value of 9.77 µg/mL AgNPs by initiating apoptosis as identified by a staining study with flow cytometric annexin V–fluorescein isothiocyanate (FITC) and propidium iodide (PI).

1.4. *Tabernaemontana* L.

T. divaricata is generally known as 'Nanthyarvattam' and grows to a height of 1.5–1.8 metres with dichotomous branches. The large shiny leaves are deep green and about 15 cm in length and 5 cm in width. The waxy blossoms are found in small clusters on the stem tips. The flowers have the characteristic 'pinwheel' shape. Both single and double flowered forms are cultivating type, the flowers of both forms being white. The plant blooms in spring but flowers appear sporadically all year. The flowers have a pleasing fragrance. More than 66 alkaloids are found in the shrub. Its habitat includes montane brush woods and sparse forests. Crape jasmine is widely used as a medicinal herb in the tropics and the plant may well be classified as a panacea for gastro-intestinal and skin affections. The roots are astringent and the decoction is used in the treatment of diarrhoea and abdominal complaints. The roots, leaves and flowers are all used in the treatment of snake and scorpion poisoning. An infusion is applied as a remedy for jungle fever. The roots are used in modern medicine to treat hypertension, headache and scabies.

Anticancer activities: Hydroalcoholic extract of flowers of *T. divaricata* possesses a moderate amount of anticancer activity and the IC_{50} value is greater than100 µg/mL (Akhila et al., 2012). The cytotoxic activity of the extracts assessed on THP-1 leukemia cell line using MTT assay and the plant demonstrated potential cancer cell inhibitory activity (Rebecca et al., 2013). The gold nanoparticles synthesized from *T. divaricata* demonstrated potent anticancer activity against MCF-7 cell line (Preetam et al., 2016). *Taberinamonatana* leaf extracts exhibit antioxidant and anticancer activity against T-24 human bladder cancer cell lines (Sridevi et al., 2018). The compound, 3'-R/S-hydroxyvoacamine, a potent acetyl cholinesterase inhibitor present in the stem of *T. divaricata* (Chaiyana et al., 2013). The alkaloid acts as non competitive inhibitor of AChE and has IC_{50} value of 7.00 ± 1.99µg/mL. The plant consisted of five novel vobasinyl ibogan type bisindole alkaloids named as tabernaricatines A-E (Bao et al., 2013). About 24 known indole alkaloids isolated from the plant; among them, conophylline has significant anticancer activities with IC_{50} values of 0.17, 0.35, 0.21, 1.02, and 1.493 µg/mL on HL-60, SMMC-7721, A- 549, MCF-7 and SW480 cell lines respectively.

1.5. *Alstonia* R.Br.

A. scholaris (Ezhilampala, Devil's tree) is a glabrous tree that grows up to 40 m tall. Its mature bark is grayish and young branches are copiously marked with lenticels. One unique

feature of this tree is that in some places, such as New Guinea, the trunk is three sided. The upper side of the leaves is glossy, while the underside is greyish. Leaves occur in whorls of three to ten; petioles are 1-3 cm; the leathery leaves are narrowly obovate to very narrowly spathulate, base cuneate, apex usually rounded and up to nine inches long by up to three inches in width. The lateral veins occur in 25 to 50 pairs at 80-90° to midvein. Cymes are dense and pubescent; peduncle is 4-7 cm long. Pedicels are usually as long as or shorter than calyx. The corolla is white and tube like, 6-10 mm long; lobes are broadly ovate or broadly obovate. The ovaries and follicles are distinct and pubescent. The fragrant flowers bloom in the month of October. Seeds are oblong with ciliated margins, and ends with tufts of hairs. The bark is almost odorless and very bitter with abundant bitter and milky sap.

Anticancer activities: Ezhilampala is an important medicinal plant in the various folk and traditional systems of medicine in Asia, Australia and Africa. The decoction, mostly prepared from the bark, is used to treat a variety of diseases of which the most important is malaria. Furthermore, the ethnomedicinal practices also suggest it to be of use in treating cancer. Additionally, the phytochemicals like echitamine, alstonine, pleiocarpamine, O-methylmacralstonine, macralstonine and lupeol are also reported to possess antineoplastic effects. In addition to the cytotoxic effects, the plant is observed to possess radiomodulatory, chemomodulatory and chemopreventive effects and free radical scavenging, antioxidant, antiinflammatory, antimutagenic and immunomodulatory activities, all of which are properties efficacious in the treatment and prevention of cancer.

The anticancer effect of various doses of an alkaloid fraction of *A. scholaris* studied in vitro in cultured human neoplastic cell lines (HeLa, HepG2, HL60, KB and MCF-7). The ASERS treatment results in a dose dependent elevation in the median and average survival time up to 240 mg/kg ASERS. Chemopreventive potential of the bark extract in DMBA induced skin tumourigenesis in Swiss albino mice was assertive.

1.6. *Carissa* L.

C. carandas (Karanta) is a woody shrub to a small tree with long, stout, sharp, horizontal spines at the base of the branchlets. It can grow up to 5m tall. Leaves are broadly ovate to oblong in shape, broadly cuneate to rounded base and apiculate apex, measuring up to 7cm long and 4cm wide. Stem has spines which are simple to slightly forked, measuring about 5cm. Flowers are red, yellow and pink in colour. It produces berry sized fruits that are commonly used as a condiment in Indian pickles and spices. It is a hardy, drought tolerant plant that thrives well in a wide range of soils. The major bioactive constituents, which impart medicinal value to the herb, are alkaloids, flavonoids, saponins and large amounts of cardiac glycosides, triterpenoids, phenolic compounds and tannins. Roots are reported to contain volatile principles including 2-acetyl phenol, lignan, carinol, sesquiterpenes (carissone and carindone), lupeol, β-sitosterol, 16β-hydroxybetulinic acid, α-amyrin, β-sitosterol glycoside and des-Nmethylnoracronycine; whereas leaves contains triterpenoids as well as tannins. The fruits consisted of carisol, epimer

of α-amyrin n, linalool, β-caryophyllene, carissone, carissic acid, carindone, ursolic acid, carinol, ascorbic acid, lupeol and β-sitosterol. Ethnopharmacological significance of the plant has been ascribed due to anticancer, anticonvulsant, antioxidant, analgesic, antiinflammatory, antiulcer, anthelmintic, cardiovascular, anti-nociceptive, antidiabetic, antipyretic, hepatoprotective, neuropharmacological, diuretic and antimicrobial activities.

Anticancer activities: The leaves and unripe and ripe fruits of *C. carandas* extract has anticancer activity using n-hexane, chloroform and methanol as the solvent systems against a three step extraction on the human ovarian carcinoma cells and lung cancer cells. The extracts exhibit good anticancerous activity (Sulaiman et al., 2008). The aqueous leaf extracts show the anticancerous efficiencies and antioxidant potentials by analyzing different antioxidant enzymes such as catalase, superoxide dismutase and glutathione-s-transferase, and non-enzymatic antioxidant, glutathione on MCF-7 cancer lines (Dua & Srivastav, 2013). Hence, the extract has the potential for future development of therapeutic drugs against breast cancer. Further, its fruits can be a good source of natural antioxidants for both pharmaceutical and dietary requirements and appears to be useful in relieving oxidative stress. The DNA damage inhibition potential of methanolic extract of *C. carandas* leaves show significant dose dependent DPPH radical scavenging, H_2O_2 scavenging and reducing power activity (Verma et al., 2015).

1.7. *Allamanda* L.

A. schotti (Manja kolambi) is an erect shrub to 2 m tall with clear sap. Leaves in whorls of 3-5 and subsessile; leaf blade elliptic or narrowly obovate, minutely hispid along veins and lateral veins elevated on abaxial surface. Corolla tube is rather narrowly funnel form, distinctly swollen at base, lobes pale yellow, ovate or orbicular. Fruits are capsules with long spines.

Anticancer activities: *Allamanda* species have been used in systems of traditional medicine for various purposes. *A. schottii* has been used to treat liver tumours, jaundice, splenomegaly and malaria. In analyses, some species have shown some activity against carcinoma cells, pathogenic fungi and HIV. The root extract of the species is the most active. The root extracts show a cytostatic effect on K562 due to the strong cytotoxic effect. Similar cytostatic and cytotoxic effects are seen in the endothelial cells, but at lower doses. Parts of *A. schottii* are assayed against three different cultured cells: K-562, a cell line derived from chronic myeloid leukemia in blastic crisis; BMEC, primary bone marrow endothelial cells; and HUVEC, primary human umbilical cord endothelial cells.

1.8. *Holarrhena* R.Br.

'Kallippala' is a deciduous shrub or small tree which grows well on open wastelands and uplands. Stems are short pale bark with several branches. Leaves are opposite, ovate, obtusely acuminate and long with short stalks. Flowers white and turn creamish yellow at maturity, appear at the end of the branch in corymb like cymes and have oblong petals. Fruits are thin and cylindrical with two follicles which attached together at distal ends and contain 25-30 seeds. Most of the known chemical constituents in *H. antidysenterica* have been found in the stem, bark,

leaves and a few in the seeds as well. The major constituents are steroidal alkaloids, flavonoids, triterpenoids, phenolic acids, tannins, resins, coumarins, saponins and ergostenol. The plant is widely used in traditional medical system for treatment of constipation and diarrhea; hence, proved usefulness in gut motility disorders. The alkaloids present in the ethanolic extract have significant antibacterial and diarrhoeal properties. The plants consist of antidiabetic activities and are used to treat fever, bleeding piles, vomiting, leprosy and herpes.

Anticancer activities: The extracts from leaves of *H. antidysenterica* show cytotoxicity against fourteen human cancer cell lines including A-549, COLO-205, DU-145, HeLa, HEP-2, IMR-32, KB, MCF-7, NCI-H23, OVCAR-5, SiHa, SK-N-MC, SW-620 and ZR-75-1 from nine different tissues like breast, colon, cervix, CNS, lung, liver, oral, ovary and prostate. The cytotoxic activity is found in the chloroform soluble fraction of 95% ethanolic extract at 100 µ/mL and inhibits the growth in the range of 71-99% of seven human cancer cell lines from five different tissues via. OVCAR-5, HT-29, SK-N-MC, HEP-2, COLO-205, NIH-OVCAR-3 and A-549. The cytotoxic activity of chloroform soluble fraction found to be higher than 5-flurouracil, adriamycin, mitomycin-c and paclitaxel.

1.9. *Ichnocarpus* R.Br.

I. frutescens (Vettyar valli) is a woody shrub with lianas sprawling to 10 m in maximum length and 6 cm in diameter. The bark produces a creamy white sap. The leaves are up to 11 cm long by 4.5 cm wide. The inflorescence is a head of several flowers. Each flower has a calyx of densely hairy sepals and a five lobed corolla just under a centimeter long. The fruit is a follicle which may be over 14 cm long. The plant has a large number of traditional medicinal uses because of the presence of alkaloids, flavonoids, terpenoids and glycosides which act against rheumatism, asthma, cholera and fever. The extracts of the plant inhibit tumours, protect liver cells from damage in acetaminophen overdose and reduce complications of hyper lipidemia in diabetic rats.

Anticancer activities: The residue from methanolic extract of roots of *I. frutescens* (MIF) and isolated triterpenes show anticancer activity against MCF-7, BEL-7402, SPC-A-1 and SGC-7901 cancer cell lines. MIF exhibits significant anticancer activity on four cancer cell lines with IC_{50} values 163.5±3.58, 156.3±2.95, 142.6±2.60 and 112.4±1.85 respectively. It effectively inhibits in vitro proliferation of U-937 monocytoid leukemia and K-562 erythroleukemia cell lines, U-937 and K-562.

1.10. *Kopsia* Blume

K. fruticosa is a shrub or a tall bush with simple leaves. It is an evergreen shrub growing upto 4m tall. Leaf blade is narrowly elliptic or narrowly oblong, tip sharp or blunt. The plant is hairless except for inflorescence. Flower occurs in bunches of a few. Beautiful light pink flowers, which may also be almost white, have 5 petals that are oblong. *Kopsia* monoterpene alkaloids present in various skeletons, but aspidofractinines, eburnamines and chanofruticosinates are the three major backbones. Mersinines and pauciflorines are new chemical classes of monoterpene alkaloids. With the rich content of monoterpene alkaloids, *Kopsia* constituents are the main objects in pharmacological studies, since the

plant extracts and isolated compounds are proposed for antimicrobial, antiinflammatory, antiallergic, antidiabetic, antimanic, antinociceptive, acetylcholinesterase (AChE) inhibitory, cardiovascular and vasorelaxant activities.

Anticancer activities: Extracts of *K. fruticosa* had the highest TAC against MCF-7 cells. Ten new indole alkaloids of the aspidofractinine type in the leaf and stem-bark extract of the Malayan *K. singapurensis*, include kopsimalines A-E (1-5), kopsinicine (6), kopsofinone (7), and kopsiloscines H-J (8-10). Kopsimalines A (1), B (2), C (3), D (4), and E (5) and kopsiloscine J (10) found to reverse multidrug resistance in vincristine resistant KB cells, with 1 showing the highest potency. Valpacrinine isolated from Malayan *K. arborea* shows pronounced cytotoxic effects against KB and Jurkat cells.

1.11. *Ochrosia* Juss.

O. elliptica (Ochrosia) is an evergreen shrub or small tree usually growing 4-6 m tall but sometimes reaching 12 m. It has leathery dark green elliptic to obovate leaves up to 8-20cm long and 4-8cm wide. The leaves occur in whorls of 3 or 4. The flowers occur in axillary clusters and are small, yellow or white and fragrant. They are followed by pairs of striking red fruit with 5-6 cm long and 2-3 cm diameter. The fruits are poisonous and plants bleed white sap copiously when wounded.

Anticancer activities: The plant is well known as a promising anticancer agent. Carbohydrates, sterols, catechol tannins, flavonoids and alkaloids are present in all the organs of the plant. Ellipticine, a cytotoxic plant alkaloid, is known to inhibit topoisomerase II in human breast MCF-7 cancer cells. Treatment of cells with ellipticine results in inhibition of growth, and G2/M phase arrests of the cell cycle. This effect associates with a marked increase in the protein expression of p53 and, p21/WAF1 and KIP1/p27. Ellipticine treatment increases the expression of Fas/APO-1 and its ligands (mFas ligand and sFas ligand), and subsequent activation of caspase 8. The mitochondrial apoptotic pathway amplifies the Fas/Fas ligand death receptor pathway by Bid interaction in turn result in a significant increase in activation of caspase 9.

1.12. *Rauvolfia* L.

R. vomitoria is a small tree or large shrub growing to 8 m high. The branches grow in whorls, and the leaves grow from swollen nodes in groups of three. The leaf blades are broadly lanceolate or elliptical and tapering to a long point. The small, fragrant flowers follow by globular red fruit. All parts of the plant, except the mature wood, contain latex. *R. vomitoria* has been used across its range in traditional medicine. A decoction or extract of the roots is used for diarrhea, jaundice, rheumatism, snake bites, fever, to calm people with anxiety or epilepsy, and to lower blood pressure. The macerated root or sometimes the pulped fruit is used for a variety of skin conditions. The bark, twigs and leaves are used as a purgative and emetic. The plant contains a number of chemical compounds used by the pharmaceutical industry including reserpine, reserpinine, deserpidine, ajmalicine and ajmaline.

Anticancer activities: The β-carboline alkaloids from *R.vomitoria* are using against human LNCaP prostate cancer cell to block the metastasis. *Rauwolfia* extract decreases in vitro

cell growth in a dose dependent manner and induces the accumulation of G1 phase cells. PARP cleavage demonstrates that apoptosis is induced only at the highest concentration tested which was confirmed by detection of cells containing sub genomic DNA. The expression of genes associated with DNA damage signaling pathway upregulates by *Rauwolfia* treatment including that of GADD153 and MDG. Moreover, the expression of a few cell cycle genes like p21, cyclin D1 and E2F1 modulates by the plant extracts. tumour volumes decrease by 60%, 70% and 58% in the groups fed the 75, 37.5 or 7.5 mg/kg *Rauwolfia*, respectively. *R. vomitoria* has potent antitumour activity against ovarian cancer.

1.13. *Thevetia* L.

T. peruviana (Manjarali) is an evergreen tropical shrub or small tree. The leaves are willow like, linear-lanceolate and glossy green in color. They are covered in waxy coating to reduce water loss. The stem is green turning silver or gray as it ages. The flowers are long funnel shaped, fragrant and yellow in terminal clusters. Its fruit is deep red-black in color encasing a large seed that bears some resemblance to a 'Chinese lucky nut'. Moreover, the plant is rich in phytochemicals like alkaloids, phenolic compounds, tannins, glycosides, cardiac glycosides, flavonoids, diterpenes, steroids and saponins.

Anticancer activities: *T. peruviana* methanolic extract exhibits cytotoxic activity on four human cancer cell lines like colorectal adenocarcinoma (HTB-38), lung carcinoma (HTB-177), prostate adenocarcinoma (HTB-81) and breast adenocarcinoma (HTB-22) with values of IC_{50} 1.91 ± 0.76, 5.78 ± 2.12, 6.30 ± 4.45 and 12.04 ± 3.43 µg/mL respectively. The extract causes a significant reduction of cell motility and colony formation on all cancer cell lines. In addition, the morphological examination displays cell size reduction, membrane blebbing and detachment of cells, compared to non treated cancer cell lines. The *T. peruviana* extract induces apoptotic cell death, which was confirmed by DNA fragmentation and AO/EB double staining. Cardiac glycosides from seeds of *T. peruviana*, are cytotoxic toward cancer cell lines P15, MGC-803, SW1990 and normal hepatocyte cell, LO2. They selectively inhibit the proliferation of cancer cell lines with IC_{50} from 0.05 to 0.15 µM.

1.14. *Wrightia* R.Br.

W. tomentosa (Ayyappala) is a deciduous tree with a rounded crown. It can grow up to 20 m tall and the unbuttressed bole can be up to 35cm in diameter. The plant contains four uncommon sterols, desmosterol, clerosterol, 24-methylene-25-methylcholesterol and 24-dehydropollinastanol in turn help to treat snake bites, scorpion stings and renal complaints.

Anticancer activities: The plant extract exhibits antiproliferative activity against MDA-MB-231 and MCF-7 cancer cells. The CH_2Cl_2 extracts of the leaves and twigs of *W. pubescens* exhibit varying cytotoxic activities. The ethanolic extract, subsequent hexane fractions and fraction F-4 of *W. tomentosa* inhibit the proliferation of human breast cancer cell lines, MCF-7 and MDA-MB231. The fraction F-4 obtained from hexane extract inhibits proliferation of MCF-7 and MDA-MB-231 cells in concentration and time dependent manner with IC_{50} of 50µg/mL and 30µg/mL for 24h, 28µg/mL and 22µg/mL for 48h and 25µg/mL

and 20µg/mL for 72h respectively. The fraction F-4 induced G1 cell cycle arrests reactive oxygen species generation, loss of mitochondrial membrane potential and subsequent apoptosis. Normally, the apoptosis is indicated in terms of increased Bax/Bcl ratio, annexin-V positivity, caspase 8 activation and DNA fragmentation. The active molecule isolated from fraction F4, oleanolic acid and urosolic acid, inhibites cell proliferation of MCF-7 and MDA-MB-231 cells at IC_{50} value of 7.5µM and 7.0µM respectively; whereas there is devoid of significant cell inhibiting activity in non cancer originated cells like HEK-293. Different extracts of *W. tinctoria* leaves have negative impact on replication of HIV-1(IIIB) in MT-4 cells and HCV in Huh 5.2 cells.

1.15. *Beaumontia* Wall.

B. brevituba is often rampant climber. Leaves are large, smooth and opposite with sticky white sap from petiolar glands. The large white fragrant flowers are borne in terminal corymbs and in the leaf axils. The calyx is 5-lobed and the corolla is dark funnel or bell shaped with 5 lobes. Stamens are attached near the base of the corolla tube and have slender filaments with arrow shaped anthers. They are very showy when in full bloom and are regarded as among the most outstanding vines of the world. The fruits comprise a pair of thick woody follicles. The seeds are compressed and apex gradually narrows with a silky coma.

Anticancer activities: Five known cardenolides, digitoxigenin, oleandrigenin, digitoxigenin alpha-L-cymaroside, digitoxigenin beta-gentiobiosyl-alpha-L-cymaroside, and delta 16-digitoxigenin beta-D-glucosyl-alpha-L-cymaroside isolated from the stems of *B. brevituba* show cytotoxicity against cultured human lung cancer cell line. The compounds have cytotoxic activity on human and murine cancer cell lines. The lignan glycoside, syringaresinol beta-D-glucoside, isolated for the first time in the form of its levo-enantiomer from the species which is also anticancerous.

1.16. *Cerbera* L.

C. odollam (Othalanga) is a tree species commonly known as the 'Suicide tree'. The branchlets are whorled about the trunk and leaves are terminally crowded, with tapering bases, acuminate apices and entire margins. The plant as a whole yields a milky white latex. Fruit, when still green, looks like a small mango, with a green fibrous shell enclosing an ovoid kernel measuring approximately 2 cm × 1.5 cm and consisting of two cross matching white fleshy halves. On exposure to air, the white kernel turns violet, then dark grey and ultimately brown or black.

Anticancer activities: The cytotoxicity of the leaf of *C. odollam* against two breast cancer cell lines (T47D and MCF-7), two ovarian cancer cell lines (SKOV3 and CaOV3) and a normal (Vero) cell line was investigated. It shows potent anticancer activity with IC_{50} values of 17, 21, 28, 32 and 24 mM, respectively. Tanghinin, isolated from *C. odollam*, exhibits cytotoxic activities against oral human epidermoid carcinoma (KB), human breast cancer cell (BC) and human small cells lung cancer line (NCI-H187).

1.17. *Chonemorpha* G. Don.

C. fragrans, the 'Frangipani vine' or 'Climbing frangipani' is a vigorous, generally

evergreen, climbing shrub producing stems 30 m or more long that can climb to the tops of the tallest trees in the forests of Southeast Asia. It has scented white flowers and large shiny leaves.

Anticancer activities: The plant is commonly used as medicine in Ayurveda and contains alkaloids including camptothecin, chonemorphine and funtumafrine. Camptothecin is a monoterpene indole alkaloid and several synthetic drugs which are analogs of captothecin are used in chemotherapy for various cancer types. MTT assay shows that the chloroform extract of callus has potent anticancer potential. The plant has a promising anticancer activity against human colon epithelium, lung carcinoma and epidermoidal carcinoma cell lines.

1.18. *Strophanthus* DC.

The genus name is a compound of the Greek words '*Strophes*' (twisted) and '*Anthos*' (flower) in reference to the corolla lobes. In *S. petersianus*, corolla resembles long twisted ribbons or threads and can reach a length of 30-35 cm. *Strophanthus* has been used medicinally as a cardiac stimulant and in the treatment of peptic ulcer and snake bites. The extract possesses antimicrobial, wound healing, antioxidant, analgesic and anticarcinogenic properties. The plant contains toxic alkaloids and cardiac glycosides including g-strophanthin (ouabain), k-strophanthin and e-strophanthin.

Anticancer activities: Six new compounds, cardenolide glycosides boivinides 1–6 as well as the four known cardenolide glycosides, digitoxigenin 3-O-[β-d-glucopyrananosyl-(1→4)-α-l-acofriopyranoside], corotoxigenin 3-O-β-d-boivinoside, 17α-corotoxigenin 3-O-β-d-sarmentoside and uzarigenin 3-O-α-l-rhamnoside from *Stropanthus* show significant antiproliferative activity against the A2780 human ovarian cancer cell line, with boivinide A being the most active at IC_{50} of 0.17 μM. *S. Wallichii* has very good antitubercular, antioxidant and anticancer effect against renal cell carcinoma induced by DEN and Fe-NTA in male Wistar Albino rats.

1.19. *Vallaris* Burm.f.

V. glabra is a moderate growth woody climber with clusters of fragrant white flowers, which can grow up to about 2-3 m tall. Leaves are light green, glossy, opposite, elliptic or ovate with wavy leaf margin. Leaf apex is acute or has a distinct drip tip. Stems are thin, woody, light grey and having smooth bark.

Anticancer activities: Sequential extracts of leaves, flowers and stems, and fractions and isolated compounds from dichloromethane (DCM) leaf extract of *V. glabra* show anticancer effect against MDA-MB-231 cancer cells. Both DCM extracts of leaves and flowers possess broad spectrum APF activity against HT-29, MCF-7, MDA-MB-231 and SKOV-3 cancer cells and the apoptotic effect is due to the activation of caspase 8, 9 and 3. Thirteen cardenolide glycosides consist in CH_2Cl_2 and MeOH extracts of *V. glabra* leaves that induce cytotoxic activity against human cervix adenocarcinoma, lung carcinoma and colorectal adenocarcinoma cell lines.

1.20. *Calotropis* R.Br.

C. gigantea is a large shrub growing to 4 m tall. It has clusters of waxy flowers that are either white or lavender in colour. Stem is erect, branched, cylindrical, solid and contains

milky latex. Leaves are 100–200 mm long, decussate, obovate or elliptic-oblong, shortly acute, subsessile, cordate or often amplexical at the base. Flowers are in umbellate cymes, large, white, not scented and peduncles arising between the petioles. Calyx lobes 5, divided to the base and corolla broadly rotate, valvate, lobes 5, deltoid ovate, reflexed, coronate appendages broad, obtusely 2 auricled below the rounded apex which is lower than the stamina column. Stamens 5, anthers short with membranous appendages, inflexed over the depressed apex of the pentagonal stigma. Pollinium is one in each cell with pendulous caudicles slender. Carpels and styles are two in number which unite to the single pentagular stigma. Fruit is a pair of follicles with many hairy seeds. Given the potent bioactivity of calotropin, *C. gigantea* has been used as a folk medicine in India for many years and has been reported to have a variety of uses. In Ayurveda, Indian practitioners have used the root and leaf of *C. procera* in asthma, bacterial infection, swelling with redness, boils and shortness of breath. The plant is effective in treating skin, digestive, respiratory, circulatory and neurological disorders and also to treat fevers, elephantiasis, nausea, vomiting and diarrhea.

Anticancer activities: Recent studies have displayed the use of calotropin as a contraceptive and promising cancer medication. In study of the cancer fighting properties of *C. gigantea*, DCM extracts demonstrate to be strongly cytotoxic against non small cell lung carcinoma (A549), colon carcinoma (HCT116) and hepatocellular carcinoma (HepG2). These extracts show promise as cancer medications and warrant further clinical research. The extract from the stem bark of *C. gigantea* exhibits potent anticarcinogenic effects against DEN induced hepatic cancer, including a reduction in apoptosis induced cancer progression (Suphunwadee et al., 2022). Eight different cardenolides from *C. gigantea* have been shown to inhibit transcription by hypoxia-inducible factor-1 transcription. Interestingly, these cardenolides exhibit strong cytotoxic effects against MCF-7 cells, but less on normal cells. The cardenolides present in *C. gigantea* able to induce transcription of pro apoptotic genes, while repressing antiapoptotic gene expression and impart apoptosis in MCF-7 cells (Kiran & Arun, 2019).

The antitumour activity of ethyl acetate extract from the flower of the *C. gigantea* against EAC in Swiss mice is very prominent. The flower extract exhibits a significant decrease in both viable tumour cells and body weight gain induced by the tumour burden and prolonged survival time. The PUMA family proteins involve apoptosis pathways through controlling mitochondrial membrane permeability and cell death. The BH3 proteins only promote apoptosis through neutralizing apoptosis inhibitory proteins (Bcl-2 and Bcl-xL) and also by promoting the opening of mitochondrial pores comprised by the death-promoting members of the Bcl-2 family, Bax and Bak. The root extracts from *C. gigantea* has antiproliferative activity against human hepatocellular carcinoma cells, HepG2 and MCF-7 cells. Gene expression studies of Bcl-2 family of genes (Bax, Bcl-2, and p53) show significantly increased expression in Bax and p53; but significantly reduced Bcl-2 expression. The ratio of Bax/Bcl-2 is a decisive factor and plays an important role in determining apop-tosis under experimental conditions promoting cell death.

2. Outlook

Cancer is becoming a high profile disease in developed and developing worlds. Even though chemically derived drugs have been developed and other cancer treatments pre-exist, there is a demand for alternative treatments with naturally derived anticancer agents with plants being the desired source. The secondary metabolites in the plant kingdom such as polyphenols, flavonoids and brassinosteroids have been studied for their potential use as anticancer agents. Among them, anticancer and antiproliferative properties of Apocynaceae members will play significant role in future anticancer drug designing.

References

1. Kiran, R.K., and Arun, S.K. (2019). The *Calotropis gigantea* Methanolic extract induces apoptosis in human breast Carcinoma cells. *Iran J. Med. Sci.* 44(6):483-492.
2. Kupchan, S.M., Dessertine, A.L., Blaylock, B.T., and Bruan, R.F. (1974). Isolation and structural elucidation of allamandin, an antileukemic iridóide lactone from *Allamanda cathartica*. *J. Org. Chem.* 39 (21):2477-2484.
3. Schmidt, D., Yunes, R.A., Schaab, E.H., Malheiros, A., Cechinel Filho, V., Franchi, G. C. Jr., Nowill, A.E., Cardoso, A.A., and Yunes, J. (2006). Evaluations of the anti-proliferative effect the extracts of *Allamanda blanchetti* and *A. schottii* on the growth of leukemic and endothelial cells. *J. Pharm. Pharmaceut Sci.* 9(2):200-208.
4. Fabiana, G.N., Amanda F., Jessica F.W., Carolina W., Folvi D.T., Sheila L.B., Rosendo A. Y., Gilberto C.F., and Alexandre, E.N. (2014). Seasonal influence and cytotoxicity of extracts, fractions and major compounds from *Allamanda schottii.* Revista Brasileira de Farmacognosia. *Rev. Bras. Farmacogn.* 24(5).
5. Jahan, S., Chaudhary, R., and Goyal, P.K. (2009). Anticancer activity of an Indian medicinal plant, *Alstonia scholaris*, on skin carcinogenesis in mice. *Integ. Canc. Therap.* 8(3):273-279.
6. Ganesh, C.J., and Manjeshwar, S.B. (2004). Treatment with *Alstonia scholaris* enhances radiosensitivity in vitro and in vivo. *Canc. Biother. Radiopharm.* 917-929.
7. Baliga, M.S. (2010). *Alstonia scholaris* Linn R Br in the treatment and prevention of Cancer: Past, present, and future. *Integr. Canc. Therap.* 9(3): 261–269.
8. Keawpradub, N., Houghton, P. J., Eno-Amovquay, E., and Burke, P. J. (1997). Activity of extracts and alkaloids of Thai *Alstonia* species against human lung cancer cell lines. *Planta Med.* 63:97-101.
9. Jagetia, G.C., and Baliga, M.S. (2006). Evaluation of anticancer activity of the alkaloid fraction of *Alstonia scholaris* (Sapthaparna) in vitro and in vivo. *Phytother. Res.* 20:103–9.
10. Kaneda, N., Chai, H., Pezzuto, J.M., AKinghorn, A.D., Farnsworth, N.R., Tuchinda, P., Udchachon, J., and Santisuk, V.R. (1992). Cytotoxic activity of cardenolides from *Beaumontia brevituba* stems. *Planta Med.*
11. Gupta, P., Bhatnagar, I., Se-Kwon Kim., Verma, A.K., and Sharma, A. (2014). In-vitro cancer cell cytotoxicity and alpha amylase inhibition effect of seven tropical fruit residues. *Asian Pacif. J. Trop. Biomed.* 4(2):665–671.
12. Bodakhe, S.H., Devi, N., Gupta, S.K., Namdeo, K.P., and Jain, S.K. (2014). Hepatoprotective Activity of *Carissa carandas* Linn. fruit ethanolic extract in carbon tetrachloride intoxicated rats. *Adv. Pharmacol. Toxicol.* 15(3):51-58.
13. Begum, S., Syed, S.A., Siddiqui, B.S., Sattar, S.A., and Iqbal, C. (2013). Carandinol: First isohopane triterpene from the leaves of *Carissa carandas* L. and its cytotoxicity against cancer cell lines. *Phytochem. Lett.* 6(1):91-95.
14. Sahreen, S., Khan, M.R., Khan, R.A., and Shah, N.A. (2013). Estimation of flavoniods, antimicrobial, antitumor and anticancer activity of *Carissa opaca* fruits. *BMC Compl. Altern. Med.* 27(13): 372.

15. Nisa, S., Bibi, Y., Zia, M., Waheed, A., and Chaudhary, M.F. (2013). Anticancer investigations on *Carissa opaca* and *Toona ciliata* extracts against human breast carcinoma cell line. *Pak. J. Pharm. Sci.* 26(5):1009-12.

16. Eric Wei, C.C., Siu, K.W., Hung, T.C., Shigeyuki, B., and Mio Kezuka. (2016). *Cerbera* are coastal trees with promising anticancer properties but lethal toxicity: A short review. *J. Chin. Pharm. Sci.* 26(3): 161-169.

17. Suphunwadee, S., Dumrongsak, P., Pennapha, S., Thanwarat, W., Worasak, K., Julintorn, S., Chaidan, I., Supawadee, P., and Piyarat, S. (2022). *Calotropis gigantea* stem bark extracts inhibit liver cancer induced by diethylnitrosamine. *Scient. Rep.* 12.

18. Sarot, C., Chatchanok, K., Yanisa, R., Chanita, P., and Kan, C. (2004). New Cytotoxic cardenolide glycoside from the Seeds of *Cerbera manghas. Chem. Pharm. Bull.* 52(8):1023-1025

19. Syarifah, M. M., Nurhanan, M. Y., Muhd Haffiz, J., Mohd, I., Getha, K., Asiah, O., Norhayati, I., Lili, S.H., and Anees. (2011). Potential Anticancer compounds from *Cerbera odollam. J. Trop. Forest Sci.* 23(1):89-96.

20. Chang, L.C., Gills, J.J., Bhat, K.P., Luyengi, L., Farnsworth, N.R., Pezzuto, J.M., and Kinghorn, A. D. (2000). Activity-guided isolation of constituents of *Cerbera manghas* with antiproliferative and antiestrogenic activities. *Bioorg Med. Chem. Lett.* 10(21):2431-2434.

21. Mohd, M.S., Nurhanan, Y., and Muhd Haffiz. (2011). Potential anticancer compound from C*erbera odollam. J. Trop. Forest Sci.* 23(1):89-96.

22. Shah, V. C., Adolf, S.D., and Souza, N. J. (1989). Chonemorphine, stigmasterol, and ecdysterone: Steroids isolated through bioassay-directed plant screening programs. *Steroids.* 53(3-5): 559-565.

23. Kedari, P.P., and Malpathak, N.P. (2013). Quantification of Camptothecin in Different Plant Parts of *Chonemorpha fragrans. Adv. Zool. Bot.* 1(2):34-38.

24. Kedari, P.P., and Malpathak, N.P. (2016). Screening of *Chonemorpha fragrans* bioactive extracts for cytotoxicity potential and inhibition studies of key enzymes involved in replication. *Pharmacog. Mag.* 12(46):297-302.

25. Kedari, Malpathak, P., and Nutan P. (2014). Hairy root cultures of *Chonemorpha fragrans* (Moon) Alston. A potential plant for camptothecin production. *IJBT.* 13(2):231-235.

26. Poornima, K., and Gopalakrishnan, V.K. (2014). Anticancer Activity of *Tabernaemontana coronaria* against carcinogen induced clear cell renal cell carcinoma. *Chin. J. Biol.* 8.

27. Sarath, P., Gunasekera, Geoffrey, C., and Norman, R.F. (1980). Anticancer indole alkaloids of *Ervatamia heyneana. Phytochem.* 19(6):1213-1218.

28. Akhila S.D., Shankarguru, P., Ramya D.D., and Vedha, H.B.N. (2012). Evaluation of in vitro anticancer activity of hydroalcoholic extract of *Tabernaemontana divaricata. Asian. J. Pharm. Clin. Res.* 5(3):59-61.

29. Habib, M.R., and Karim, M.R. (2011). Evaluation of antitumour activity of *Calotropis gigantea* L. root bark against Ehrlich ascites carcinoma in Swiss albino mice. *Asian Pac. J. Trop. Med.* 4:786-790.

30. Shamas-Din, A., Kale, J., Leber, B., and Andrews, D.W. (2013). Mechanisms of action of Bcl-2 family proteins. *Cold Spring Harb Perspect Biol.* 5

31. Fink, S.L., and Cookson, B.T. (2005). Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. *Infect Immun.* 73:1907-1916.

32. Habib, M.R., and Karim, M.R. (2013). Effect of anhydrosophoradiol-3-acetate of *Calotropis gigantea* (Linn.) flower as antitumoric agent against Ehrlich's ascites carcinoma in mice. *Pharmacol. Rep.* 65:761-7.

33. Kirankumar, H., Namrata, P., Yuvaraj, M., Ashok, G., and Mahesh, B. (2013). Bioactivity-guided isolation of cytotoxic constituents from three medicinal plants. *Pharm. Biol.* 51(5): 601-606.

34. Kumar, A., and Selvakumar, S. (2015). Antiproliferative efficacy of *Tabernaemontana divaricata* against HEP2 cell line and Vero cell line. *Pharmacogn. Mag.* 11:46-52.

35. Sim, D.S., Teoh, W.Y., Sim, K.S., Lim, S.H., Thomas, N.F., Low, Y.Y., and Kam, T. S. (2016). Vobatensines A-F, cytotoxic iboga-vobasine bisindoles from *Tabernaemontana corymbosa. J. Nat. Prod.* 2279(4):1048-55.

36. Pereira, P.S., França, S.C., Oliveira, P.V.A., Breves, C.M.S., and Pereira, S.I.V. (2008). Chemical constituents from *Tabernaemontana catharinensis* root bark: A brief NMR review of indole alkaloids and in vitro cytotoxicity. *Química Nova.* 31(1):20-24.

37. Cheenpracha, S., Boapun, P., Thunwadee, L.,

Surat, L., and Stephen, G.P. (2017). Antimalarial and cytotoxic activities of pregnene-type steroidal alkaloids from *Holarrhena pubescens* roots. 10:14786419-1408108. *Nat. Prod. Res.* 33(6): 782-788.

38. Sharma, V., Hussain, S., Bakshi, M., Bhat, N., and Saxena, A.K. (2014). In vitro cytotoxic activity of leaves extracts of *Holarrhena antidysenterica* against some human cancer cell lines. *Indian J. Biochem. Biophys.* 51(1):46-51.

39. Badmus, J.A., Ekpo, O.E., Hussein, A.A., Meyer, M., and Hiss, D.C. (2015). Antiproliferative and Apoptosis Induction Potential of the Methanolic Leaf Extract of *Holarrhena floribunda* (G. Don). *Evid. Based Compl. Alternat. Med.* 11:756482.

40. Sharma, V., Hussain, S., Bakshi, M., Bhat, N., and Saxena, A.K. (2014). In vitro cytotoxic activity of leaves extracts of *Holarrhena antidysenterica* against some human cancer cell lines. *Ind. J. Biochem. Biophys.* 51(1):46-51.

41. Singh, N.K., and Singh, V.P. (2012). Phytochemistry and pharmacology of *Ichnocarpus frutescens. Chin. J. Nat. Med.* 10(4):241-246.

42. Thangarajana, S., Perumal, S., Chinthamony, A.R., Ragavendran, P., Vidya, B., Sunitha, M., and Velliyur K. G. (2013). Chemomodulatory effects of *Ichnocarpus frutescens* R. Br against 4-vinylcyclohexane induced ovarian cancer in swiss albino mice. *J. Acute Dis.* 2(2):151-155.

43. Kumarappan, C.T., and Mandal, S.C. (2007). Antitumor activity of polyphenolic extract of *Ichnocarpus frutescense. Exp. Oncol.* 29(2):94-101.

44. Singh, N.K., and Singh, V.P. (2014). Anticancer activity of the roots of *Ichnocarpus frutescens* R. Br. and isolated triterpenes. *Pak. J. Pharm. Sci.* 27(1):187-91.

45. Chidambaram, K., and Subhash, C. M. (2007). Antitumor activity of polyphenols extracts of *Ichnocarpus frutescens. Exper. oncol.* 29(2):94-101.

46. Lee, Y.S., Tee, C.T., Tan, S.P., Khalijah, A., Najihah, M.H., Mohd A.N., Kartini A. (2014). Cytotoxic, antibacterial and antioxidant activity of triterpenoids from *Kopsia singapurensis* Ridl. *J. Chem. Pharm. Res.* 6(5):815-822.

47. Lim, K. H., Hiraku, O., Komiyama, K., Koyano, T., Hayashi, M., and Kam, T. S. (2007). Biologically active indole alkaloids from *Kopsia arborea. J. Nat. Prod.* 70(8): 1302-1307.

48. Subramaniam, G., Hiraku, O., Hayashi, M., Koyano, T., Komiyama, K., and Kam, T. S. (2008). Biologically active aspidofractinine alkaloids from *Kopsia singapurensis. J. Nat. Prod.* 71(1):53-57.

49. Lim, S.H., Sim, K.M., Abdullah, Z., Hiraku, O., Hayashi, M., Komiyama, K., and Kam, T.S. (2007). Leuconoxine, kopsinitarine, kopsijasmine, and kopsinone derivatives from *Kopsia. J. Nat. Prod.* 70(8):1380-1383.

50. Priya, V., Jain, P., Vanathi, B.M., Raj, P.V., Kamath, B.V., and Rao, J.V. (2015). Methanolic root extract of *Calotropis gigantea* induces apoptosis in human hepatocellular carcinoma by altering Bax/Bcl-2 expression. *Am. J. Pharmacol. Sci.* 3:13–7.

51. Juncker, T., Schumacher, M., Dicato, M., and Diederich, M. (2009). UNBS1450 from *Calotropis procera* as a regulator of signaling pathways involved in proliferation and cell death. *Biochem. Pharmacol.* 78:1–10.

52. Seeka, C., and Sutthivaiyakit, S. (2010). Cytotoxic cardenolides from the leaves of *Calotropis gigantea. Chem. Pharm. Bull.* 58:725–8.

53. Wong, S.K., Lim, Y.Y., Abdullah, N.R., and Nordin, F.J. (2011). Assessment of antiproliferative and antiplasmodial activities of five selected Apocynaceae species. *BMC Compl. Altern. Med.*11: 3.

54. Wang, Z.N., Wang, M.Y., Mei, W.L., Han, Z., and Dai, H.F. (2008). A new cytotoxic pregnanone from *Calotropis gigantea. Molecules*. 13: 3033–3039.

55. Wahyuningsih, M.S.H., Mubarika, S., Mark, T., Hamann G.I.G., and Wahyuono, S. (2008). Structure identification of potential compound as selective renal anticancer isolated from *Nerium Indicum* Mill. Leaves, Indon. *J. Pharm.* 19(2):57-64.

56. Siddiqui, B.S., Begum, S., Siddiqui, S., and Lichter, W. (1995). Two cytotoxic pentacyclic triterpenoids from *Nerium oleander. Phytochem.* 39:171-4.

57. Pathak, S., Multani, A.S., Narayan, S., Kumar, V., and Newman, R.A. (2000). Anvirzel™, an extract of *Nerium oleander*, induces cell death in human but not murine cancer cells. *Antican. Drug.*11:455-63.

58. Heinz, H., Fiebig, G., Kelter, A., Maier, T., Metz, and Luay, J. (2013). Rashan. Breastin a natural product from *Nerium Oleander* exhibits high activity in a panel of human tumor cell lines. *A. Exp. Mol. Therap.* 73(8).

59. Turan, N., Akgün, K., Kuruca, S. E., Kiliçaslan, A.T., Seyhan, V. G., and Atasever, B. (2006). Cytotoxic effects of leaf, stem and root extracts of *Nerium oleander* on leukemia cell lines and role of the p-glycoprotein in this effect. *J. Exp. Ther. Oncol.* 6: 31–8.

60. Siddiqui, B.S., Khatoon, N., Begum, S., Farooq, A.D., Kehkashan, Q., Huma, A.B., and Syed K. A. (2012). Flavonoid and cardenolide glycosides and a pentacyclic triterpene from the leaves of *Nerium oleander* and evaluation of cytotoxicity. *Phytochem.* 77:238-244.

61. Rashan, L.J., Franke, K., Khine, M.M., Gerhard K., Heinz, H.F., Joachim N., and Ludger, A. W. (2011). Characterization of the anticancer properties of monoglycosidic cardenolides isolated from *Nerium oleander* and *Streptocaulon tomentosum*. *J. Ethnopharmacol.* 134:781-788.

62.Qamar, K.A., Farooq, A.D., Siddiqui, B.S., Kabi,r N., Khatoon, N., Ahmed, S., Erum, S., and Begum, S. (2018). Antiproliferative effects of *Nerium oleander* stem and mitotic arrest induced by Cardenolide Odoroside B on NCI-H460 cancer cells. *Lett. Drug Des. Discov.* 15(1):84-94.

63. Su J.S., Cheng Y.J., Yung H.C., and Won D. H. (2011). Induction of Apoptosis by Ethanol Extract of *Nerium indicum* Stem Is Associated with Activation of JNK in Human Renal Carcinoma Caki-1 Cells. *Cancer Prev. Res.* 16:269-279.

64. Nagwa, M.E., Neveen, S.G., Safaa, Q., Mohamed, M., and Kamel, A. (2010). Cytotoxicity and antimicrobial activity of *Nerium oleander* extracts. *J. Appl. Anim. Res.* 37:25-31.

65. Garbett, N.C., and Graves, D.E. (2004). Extending nature's leads: the anticancer agent ellipticine. *Curr. Med. Chem. Anticancer Agents.* 4(2):149-172.

66. Po-Lin, K., Ya-Ling, H., Cheng-Hsiung, C., and Chun-Ching, L. (2005). The mechanism of ellipticine-induced apoptosis and cell cycle arrest in human breast MCF-7 cancer cells. *Cancer Lett.* 223:293-301.

67. Parhira, S, Zhu, G.Y., Chen, M., Bai, L.P., and Jiang, Z.H. (2016). Cardenolides from *Calotropis gigantea* as potent inhibitors of hypoxia-inducible factor-1 transcriptional activity. *J. Ethnopharmacol.* 194: 930–936.

68. Riham, A.E., Dalia, A.A., Mohamed, S. H., Tzvetomira T., Emilie E., Stéphanie, P., Denyse, B., and Essam, A.A. (2017). Chemical and Biological Investigation of *Ochrosia elliptica* Labill. Cultivated in Egypt. *Rec. Nat. Prod.* 11(6): 552-557.

69. Periyasamy, G., Gupta, M., Mazumder, U. K., Gebrelibanos, M., and Sintayehu. (2013). Antioxidant and Antitumor Activity of *Plumeria acuminata* in Ehrlich Ascites Carcinoma Bearing Swiss Albino Mice. *Brit. J. Pharm. Res.* 3(4):671-685.

70. Leonardus, B.S., Soefjan, T., Kosasih, P., John, M.P., and Douglas, K. (1990). Cytotoxic constituents of the bark of *Plumeria rubra* collected in Indonesia. *J. Nat. Prod.* 53(6):1447-1455.

71. Periyasamy, G., Gupta, M., Mazumder, U.K., Mebrahtom, G. and Biruk, S. (2007). Antioxidant and Antitumor Activity of *Plumeria acuminata* in Ehrlich Ascites Carcinoma Bearing Swiss Albino Mice. *British J. Pharm. Res.* 3(4):671-685.

72. Guevara, A.P., Amor, E., and Russell, G. (1996). Antimutagens from *Plumeria acuminata Ait. Mutat. Res.* 361(2-3):67-72.

73. Bemis, D.L., Capodice, J.L., Gorroochurn, P., and Katzand R.B. (2006). Anti-prostate cancer activity of a β-carboline alkaloid enriched extract from *Rauwolfia vomitoria. Inter. J. Onc.* 29:1065-1073.

74. Jun, Y., Yan, M., Jeanne, D., and Qi Chen. (2013). Antitumor Activities of *Rauwolfia vomitoria* Extract and Potentiating of carboplatin effects against ovarian Cancer. *Curr. Ther.. Res. Clin. Exp.* 75:8-14.

75. Rong-Fu, C., Fumiko, A., Tatsuo, Y., and Masakatsu, T. (1987). Cardenolide glycosides of *Strophanthus divaricatus. Phytochem.* 26(8):2351-2355.

76. Pezzani, R., Rubin, B., Redaelli, M., Radu, C., Barollo, S., Maria, V. C., Monica, S., Caterina, M., Carla, M. C., Paolo, S., Maurizio I., and Franco, M.. (2014). The antiproliferative effects of ouabain and everolimus on adrenocortical tumor cells. *Endocr. J.* 61(1):41-53.

77. Karkare, S., Adou, E., Cao, S., Brodie, P., James, S., Miller, N. M., Andrianjafy, J., Razafitsalama, R., Andriantsiferana, V. Rasamison, E. David, G., and Kingston, I. (2007). Cytotoxic Cardenolide Glycosides of *Roupellina (Strophanthus) boivinii* from the Madagascar Rainforest. *J. Nat. Prod.* 70(11):1766–1770

78. Tamiris, C.B., Cássio, P.S., Suely, V.S. and Mateus, A.B. (2012). Evaluation of Anticancer Activity Promoted by Molecules Contained in the Extracts

of *Thevetia peruviana Toxicon.* 60(2):179-180.

79. Huo, Y.C., Dan, M.T., Jin, S.T., Wei, Z.S., and Xin, S.Y. (2016). Cardiac glycosides from the seeds of *Thevetia peruviana* and their pro-apoptotic activity toward cancer cells. Mar2016. *J. Asian Natural Prod. Res.* 18(9): 837-847.

80. Ramos, S. A., Tavares, C.F., Figueroa, M., Susana, T.Z., Argel, G.A., Aída, R.G., Luis, J., Galán, W. and Hamlet A. A. (2017). Anticancer potential of *Thevetia peruviana* fruit methanolic extract. *BMC Compl. Altern. Med.* 17:241.

81. Salama, M., Hawary, E.S., Mousa, O., Askari, E.N. and Esmat, A. (2012). In vivo TNF-α and IL-1β inhibitory activity of Phenolics isolated from *Trachelospermum Jasminoids* (Lindl.) Lem. *J. Medi. Plants Res.* 9 (2): 30-41.

82. Xing, O.T., Liang, J.G., Hua, Y.Q., Sheng, H.C. and Chang H. T. (2009). Chemical constituents of *Trachelospermum jasminoides. Natural Prod. Res. Form. Nat. Prod. Lett.* 24(13):1248-1252.

83. Fatima, T., Ijaz, S., Crank, G., and Wasti, S. (1987). Indole Alkaloids from *Trachelospermum jasminoides. Planta Med.* 53(1):57-59.

84. Siu, K.W., and Eric, W.C. (2013). Botany, uses, phytochemistry and pharmacology of *Vallaris*: A short review. *Pharmacog. J.* 5:242-246.

85. Wong, S.K., Lim, Y.Y., Ling, S.K., and Chiang, E.W. (2014). Antiproliferative activity of *Vallaris glabra* Kuntze (Apocynaceae). *Phcog. Mag.* 10(38):232-239.

86. Kruakaew, S., Seeka, C., Thitima, L., Sanit, T., Jantana, Y., Suratsawadee, P., Pongpun, S., and Somyote, S. (2017). Cytotoxic Cardiac Glycoside Constituents of *Vallaris glabra* Leave. *J. Nat. Prod.* 80(11):2987–2996

87. Karmakar, U.K., Ghosh, D., and Sadhu, S.S. (2010). Assessment of Analgesic, Cytotoxic and Antioxidant activities of *Vallaris solanacea* (Roth) Kuntze. *Stamford. J. Pharm. Sci.* 4(1):64-68.

88. Siddiqui, M. J., Ismail, Z., Aisha, A.F., and Majid, A. M. (2010). Cytotoxic activity of *Catharanthus roseus* (Apocynaceae) crude extracts and pure compounds against human colorectal carcinoma cell line. *Int. J. Pharmacol.* 6:43–47.

89. Robert L.N. (1990). The discovery of the vinca alkaloids—chemotherapeutic agents against cancer. *Biochem. Cell Biol.* 68(12):1344-1351

90. Maryam, M., Rusea, G., Christina, Y.S., and Mohd, N. (2013). *Vinca* Alkaloids. *Int. J. Prev. Med.* 4(11):1231-1235.

91. El-Sayed, A., Handy, G.A., and Cordell, G.A. (1983). *Catharanthus* alkaloids XXXVIII. Confirming structural evidence and antineoplastic activity of the bisindole alkaloids leurosine-N'b-oxide (pleurosine) roseadine and vindolicine from *Catharanthus roseus. J. Nat. Prod.* 46:517-27

92. Antony, J., Saikia, M., Vinod, V., Nath, L. R., Katiki, M.R., Murty, M. S., Paul, A., Shabna, A., Chandran, H., Joseph, S. M., Nishanth, K.S., Panakkal, E.J., Sriramya, I., Sridivya, I., Ran, S., Sanka,r S., Rajan, E., and Anto, R.J. (2015). DW-F5: A novel formulation against malignant melanoma from *Wrightia tinctoria. Sci. Rep.* 10(5):12662.

93. Selvam, P., Murugesh, M., Witvrouw, M., Keyaerts, E., and Neyts, J. (2009). Studies of antiviral activity and cytotoxicity of *Wrightia tinctoria* and *Morinda citrifolia. Indian J. Pharm. Sci.* 71(6):670–672.

94. Ramalakshmi, S., Edaydulla, N., Ramesh, P., and Muthuchelian, K. (2012). Investigation on cytotoxic, antioxidant, antimicrobial and volatile profile of *Wrightia tinctoria* (Roxb.) R. Br. Flower used in Indian medicine. *Asian. Pac. J. Trop. Dis.* 68-75.

95. Chakravarti, B., Maurya, R., Siddiqui, J.A., Bid, H.K., Rajendran, S.M., Yadav, P.P., and Konwar, R. (2012). In vitro anti-breast cancer activity of ethanolic extract of *Wrightia tomentosa*: Role of pro-apoptotic effects of oleanolic acid and urosolic acid. *J. Ethnopharm.* 142(1):72-79.

96. Chaudhary, S., Devkar, R.A., Bhere, D., Setty, M. M., and Ranganath, K.S. (2015). Selective cytotoxicity and pro-apoptotic activity of stem bark of *Wrightia tinctoria* Roxb. *Pharmacog. Magaz.* 11(44):481-487.

97. Fatima, N., Ahmad, M.K., Ansari, J.A., Ali, Z., Khan, A.R., and Mahdi, A.A. (2016). Anticancer, antioxidant potential and profiling of polyphenolic compounds of *Wrightia tinctoria* Roxb. (R.Br.) bark. *J. Adv. Pharm. Tech. Res.* 7(4):159-165.

98. Chakravarti, B., Maurya, R., Siddiqui, J. A., Bid, H.K., Rajendran, S.M., Yadav, P. P., and Konwar, R. (2012). In vitro anti-breast cancer activity of ethanolic extract of *Wrightia tomentosa*: Role of pro-apoptotic effects of oleanolic acid and urosolic acid. *J. Ethnopharm.* 142(1):72–79.

99. Mariquit, M.R., Glenn, G.O., Vincent, A.S., Chien-Chang Shen, and Consolacion, Y R. (2018). Cytotoxic Compounds from *Wrightia pubescens* (R.Br.). *Phcog. Res.* 10(1):9-15.

100. Kupchan, S. M., Dessertine, A. L., Blaylock, B. T., and Bruan, R. F., (1974). Isolation and structural elucidation of allamandin, an antileukemic iridóide lactone from *Allamanda cathartica. J. Org. Chem.* 39(21):2477-2484.

101. Navarro, S.D., Yunes, R.A., Schaab, E.H., Malheiros, A., Cechinel, F.V., Franchi, G.C., Nowill, A.E., Cardoso, A.A., and Yunes, J. (2006). Evaluations of the anti-proliferative effect the extracts of *Allamanda blanchetti* and *A. schottii* on the growth of leukemic and endothelial cells. *J. Pharm. Pharmaceut. Sci.* 9(2):200-208.

102. Fabiana, G.N., Amanda, F., Jessica, F.W., Carolina, W., Folvi, D.T., Sheila, L.B., Rosendo, A.Y., Gilberto, C.F., and Alexandre, E.N. (2014). Seasonal influence and cytotoxicity of extracts, fractions and major compounds from *Allamanda schottii. Revista Brasileira de Farmacognosia Rev. Bras. Farmacogn.* 24(5).

103. Riham, A.E., Dalia A.M., Mohamed S.H., and Essam A.A. (2019). Pharmacognostical study of *Ochrosia elliptica* Labill. (Apocynaceae). *J. Appl. Pharm. Sci.* 9(05):49-57.

104. Sulaiman, S.F., Wong, S.T., Ooi, K.L., Yusof, S.R., Muhammad, T., and Sifzizul, T. (2008). Anticancer study of *Carissa carandas* extracts. Project Report, Monograph Universiti Sains Malaysia.

105. Dua, D., and Srivastav, N.S. (2013). Anti-cancerous and antioxidant potential of aqueous extracts of *Annona reticulata, Podophyllum peltatum, Psidium guajava, Ananas comosus, Carissa carandas* on MCF-7 cancer cell line. *Int. J. Integr. Sci. Innov. Technol. Sec.* 2(4):15-19.

106. Sadek, Y.B., Choudhury, N., and Shahriar, M. (2013). Biological investigations of the leaf extracts of *Carissa Carandas. Int. J. Pharm. Res. Technol.* 5(2):97-105.

107. Verma, K., Shrivastava, D., and Kumar, G. (2015). Antioxidant activity and DNA damage inhibition in vitro by a methanolic extract of *Carissa carandas* (Apocynaceae) leaves. *J. Taibah. Univ. Sci.* 9(1):34-40.

108. Manjeshwar, S.B. (2010). *Alstonia scholaris* Linn R Br in the treatment and prevention of cancer: past, present, and future. *Integr. Canc. Ther.* 9(3):261-9.

109. Gosh, M., and Ganesh, M.S. (2014). Studies on anticancer agents from natural sources. The *Tabernaemontana divaricata* (L.)R. Br. Ex Roem. & Schult., Munich, *GRIN Verlag.*

110. Sridevi, I.P., Murigendra, B.H., Rajendra, B.N., and Shridhar, C.G. (2018). Evaluation of in vitro antioxidant and anticancer activity of *Tabernamontanea divaricata* leaf extract against T-24 human baldder cancer cell lines. *Inter. J. Canc. Res.*14(2): 100-108.

111. Raj P.J.P., Purushothaman, M., Ameer, K., and Shirly, G.P. (2016). In-vitro anticancer and antioxidant activity of gold nanoparticles conjugate with *Tabernaemontana divaricata* flower SMs against MCF -7 breast cancer Cells. *Korean Chem. Eng. Res.* 54(1):75-80.

112. Rebecca, T., Rajshree, J., and Neeta, P. (2013). Evaluation of phytoconstituents, antibacterial, antioxidant and cytotoxic activity of Vitex negundo and *Tabernaemontana divaricata. Int. J. Pharm. Bio. Sci.* 4(1):389 -396.

113. Akhila, S.D., Shankarguru, P., Ramya, D., and Vedha, H. (2012). Evaluation of in vitro anticancer activity of hydroalcoholic extract of *Tabernaemontana divaricata. Asian J. Pharm. Clin. Res.* 5(4).

114. Heijden, R., Jacobs, D., Snoeijer, H.D., and Verpoorte, R. (2004). The *Catharanthus* Alkaloids: Pharmacognosy and Biotechnology. *Curr. Med. Chem.* 11(5): 607-628.

115. Gansäuer, A., Justicia, J., Fan, C.A., Worgull, D., Piestert., and Frederik. (2007). "Reductive C-C bond formation after epoxide opening via electron transfer". In Krische, Michael J. (ed.). Metal Catalyzed Reductive C—C Bond Formation: A Departure from Preformed Organometallic Reagents. Topics in Current Chemistry. *Springer, Sci. Bus. Media.* 279:25–52.

116. Cooper, R., and Deakin, J.J. (2016). "Africa's gift to the world". Botanical Miracles: *Chemistry of Plants That Changed the World.* CRC Press.46–51.

117. Keglevich, P., Hazai, L., Kalaus, G., and Szántay, C. (2012). Modifications on the basic skeletons of vinblastine and vincristine. *Molecules.* 17(5):5893-5914.

118. Raviña, E. (2011). "Vinca alkaloids". The evolution of drug discovery: From traditional medicines to modern drugs. *John Wiley & Sons.* 157–159.

119. Faller, B.A., and Pandi, T.N. (2011). "Safety and efficacy of vinorelbine in the treatment of non-small cell lung cancer". Clinical Medicine Insights: *Oncol.* 5:131-144.

120. Ngo, Q.A., Roussi, F., Cormier, A., Thoret, S.,

Knossow, M., Guénard, D., and Guéritte, F. (2009). "Synthesis and biological evaluation of *Vinca* alkaloids and phomopsin hybrids". *J. Med. Chem.* 52 (1):134-142.

121. Hardouin, C., Doris, E., Rousseau, B., Mioskowski., and Charles. (2002). "Concise synthesis of anhydrovinblastine from leurosine". *Org. Lett.* 4 (7):1151–1153.

122. Sini, S., and Malathy, N.S. (2006). Phytochemical characteristics of *Ichnocarpus frutescens*. (L) R.Br. *Anc. Sci. Life*. 25:71–75.

123. Aynilian, G.H., Weiss, S.G., Cordell, G.A., Abraham, D.J., Crane, F.A., and Farnsworth, N.R. (1974). "*Catharanthus* alkaloids. XXIX. Isolation and structure elucidation of vincoline". *J. Pharm. Sci.* 63(4):536–8.

124. Yao, X.G., Chen, F., Li, P., Quan, L., Chen, J., Yu, L., Ding, H., Li, C., Chen, L., Gao, Z., Wan, P., Hu, L., Jiang, H., and Shen, X. (2013). Natural product vindoline stimulates insulin secretion and efficiently ameliorates glucose homeostasis in diabetic murine models. *J. Ethnopharmacol.* 150(1):285–97.

125. Siddiqui, M.J., Ismail, Z., Aisha, A. F., and Majid, A.M. (2010). Cytotoxic activity of *Catharanthus roseus* (Apocynaceae) crude extracts and pure compounds against human colorectal carcinoma cell line. *Int. J. Pharmacol.* 6:43–47.

126. Robert, L.N. (1990). The discovery of the *vinca* alkaloids-chemotherapeutic agents against cancer. Biochem. *Cell Biol.* 68(12):1344-1351

127. Maryam, M., Rusea, G., Christina, Y.S.Y., and Mohd., N. (2013). *Vinca* Alkaloids. *Int. J. Prev. Med.* 4(11):1231–1235.

128. El-Sayed, A., Handy, G.A., and Cordell, G.A., (1983). *Catharanthus* alkaloids XXXVIII. Confirming structural evidence and antineoplastic activity of the bisindole alkaloids leurosine-N'b-oxide (pleurosine) roseadine and vindolicine from *Catharanthus roseus. J. Nat. Prod.* 46:517-27.

129. Nirmala, D., Ajay, K.G., and Sunil, K.P. (2019) Prospects of Traditionally important Apocynaceae plants of India in Cancer Remediation. *J. Drug Deliv. Therap.* 9(1):293-302

130. Wahyuningsih, M.S.H., Mubarika, S., Mark, T.H.G., and Wahyuono, S. (2008). Structure identification of potential compound as selective renal anticancer isolated from *Nerium Indicum* Mill. Leaves. *Indones. J. Pharm.* 19(2):57-64.

131. Siddiqui, B. S., Begum, S., Siddiqui, S., and Lichter, W. (1995). Two cytotoxic pentacyclic triterpenoids from *Nerium oleander. Phytochem.* 39:171–4.

132. Pathak, S., Multani, A.S., Narayan, S., Kumar, V., and Newman, R.A. (2000). Anvirzel™, an extract of *Nerium oleander*, induces cell death in human but not murine cancer cells. *Anticanc. Drug.* 11:455–63.

133. Heinz, H.F., Gerhard, K., Armin, M., Thomas, M., and Luay, J.R. (2013). Breastin a natural product from *Nerium Oleander* exhibits high activity in a panel of human tumor cell lines. *Exp. Molecul. Therap.* 73(8).

134. Turan, N., Akgün-Dar, K., Kuruca, S.E., Kiliçaslan-Ayna, T., Seyhan, V.G., and Atasever, B. (2006). Cytotoxic effects of leaf, stem and root extracts of *Nerium oleander* on leukemia cell lines and role of the p-glycoprotein in this effect. *J. Exp. Ther. Oncol.* 6:31–8.

135. Siddiqui, B.S., Khatoon, N., Begum, S., Farooq, A.D., Kehkashan, Q., Huma, A.B., and Syed K.A. (2012). Flavonoid and cardenolide glycosides and a pentacyclic triterpene from the leaves of *Nerium oleander* and evaluation of cytotoxicity. *Phytochem.* 77:238.

136. Rashan, L. J., Franke, K., Khine, M. M., Gerhard, K., Heinz, H. F., Joachim, N., and Ludger, A. W. (2011). Characterization of the anticancer properties of monoglycosidic cardenolides isolated from *Nerium oleander* and *Streptocaulon tomentosum. J. Ethnopharmacol.* 134:781-788.

137. Qamar, K. A., Farooq, A. D., Siddiqui, B. S., Kabir, N., Khatoon, N., Ahmed, S., Erum, S., and Begum, S. (2018). Antiproliferative effects of *Nerium oleander* stem and mitotic arrest induced by Cardenolide Odoroside B on NCI-H460 cancer cells. *Lett. Drug Desig. Discov.* 15(1):84-94.

138. Su, J.S., Cheng, Y.J., Yung, H.C., and Hwang. (2011). Induction of Apoptosis by Ethanol Extract of *Nerium indicum* Stem Is Associated with Activation of JNK in Human Renal Carcinoma Caki-1 Cells. *Cancer Prev. Res.* 16:269-79.

139. Nagwa, M., Sawi., Neveen S., Geweely., Safaa Qusti., Mohamed, M., and Kamel, A. (2010). Cytotoxicity and antimicrobial activity of *Nerium oleander* extracts. *J. Appl. Animal Res.* 37:25-31.

140. Jagdish, S., Sumeet, D., and Raghvendra, D. (2022). Pharmacological, phytochemical, and traditional uses of *Plumeria alba* L. *Indian Med. Plant.*

141. Muthuraj, R., Hassan, A.R., Rasha, A.A., Asmatanzeem, B., Dhanyakumara, S., Basavarajappa, Shashiraj, K.N., Bidhayak, C., Pallavi, S.S., Shekappa, N.A., Shaik, K. N., and Sreenivasa, N. (2022). *Plumeria alba*: Mediated green synthesis of silver nanoparticles exhibits antimicrobial effect and anti-oncogenic activity against Glioblastoma U118 MG cancer cell line. *Nanomat. (Basel).* 12(3):493.

142. Bemis, D.L., Capodice, J.L., Gorroochurn, P., and Katzand, R.B. (2006). Anti-prostate cancer activity of a β-carboline alkaloid enriched extract from *Rauwolfia vomitoria. Int. J. Oncol.* 29:1065-1073.

143. Jun, Yu., Yan, Ma., Jeanne, Drisko., and Qi, Chen. (2013). Antitumor Activities of *Rauwolfia vomitoria* Extract and potentiating of carboplatin effects against ovarian cancer. *Curr. Ther. Res. Clin. Exp.*75:8-14.

A Green Anticancer Approach on Acanthaceae

Chithra M.

Department of Botany, Kottakkal Farook Arts and Science College
Kottakkal, Malappuram, 676503, Kerala, India.
Corresponding author: chithra@kottkkalfarookcollege.edu.in

Abstract: Medicinal plants play an important role in the development of new drugs both for humans and animals which act as a potential material for maintaining health. Almost 3/4th of the herbal medicines used worldwide are discovered from local medicinal plants. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. According to WHO in 2020 nearly 10 million deaths are reported worldwide due to cancer. Many people seek alternative complementary methods of cancer treatment because of high death rate and serious side effects of chemotherapy and radiation therapy. Herbal medicine has become a very safe, non toxic and easily available source of cancer treating compounds. Some plant species belonging to Acanthaceae are useful for treatment of cancer. These species with active anticancer activity due to phytocompounds have to be investigated for future to improve cancer therapy.

Keywords: Cancer, Acanthaceae, herbal medicines, metastasis, apoptosis

Cancer is a generic term for a large group of diseases that can affect any part of the body and is one of the most common leading causes of death worldwide. According to WHO, cancer is a serious health problem in all populations. The global response to cancer has been uneven and inequitable. In 2020, one in five people globally will face a cancer diagnosis during their life time. Chemotherapy, radiation therapy, immunotherapy, stem cell therapy etc. are commonly recommended to overcome the disease. But most of them prefer traditional medicines due to its safety, efficacy and cost effectiveness. Traditional herbs are effective for the treatment of cancer and have less toxic side effects (Rajeshkumar et al., 2015).

Plant species belonging to family Acanthaceae have abundant medicinal properties and are rich source of phytochemicals. For instance, among the many anticancer medicinal plants, *Andrographis paniculata, Justicia gendarussa, Justicia adhatoda, Acanthus ilicifolius, Avicennia alba, Avicennia marina, Barleria prionitis, Odontonema strictum, Rhinacanthus nasutus, Thunbergia grandiflora, T. laurifolia* etc. of Acanthaceae have been used traditionally for the anticancer properties of their active ingredients.

1. Anticancer plants in Acanthaceae

1.1. *Acanthus* L.

A. ilicifolius is commonly known as 'Sea holly', 'Chullikandal', 'Harikusa', 'Holly mangrove', 'Nivagur' etc. This plant is a mangrove with spiny holly leaves. It contains wide

range of secondary metabolites and has traditional usage in Indian and Chinese system of medicine. Mangrove survives in the most hostile environment with fluctuating tidal and saline regime. Hence, these plants are considered to be rich sources of steroids, triterpenoids, saponins, flavonoids, alkaloids and tannins. Traditionally, the plant has been used for dyspepsia, paralysis, asthsma, headache, rheumatism and skin diseases (Singh & Aeri, 2013). Several classes of polyphenolic compounds such as phenolics, flavonoids and tannins contribute to plant defense mechanism in resisting pathogenic microorganisms (Vani et al., 2018).

Anticancer activities: The plant extract prevents DNA alterations in a transplantable ehrlich ascites carcinoma bearing murine model (Chakraborty et al., 2007). The administration of *A. ilicifolius* reduces viable tumour cell count and brought about a marked increase in mean survival of tumour bearing hosts, suggesting the tumour combating efficacy of the extract under investigation. Anticancer efficacy of root tissue and callus of *A. ilicifolius* is evident on Benzo (A) Pyrene induced pulmonary carcinoma in *Mus musculus* (Singh & Kathiresan, 2013). The plant is potent to have chemoprotective, antimutagenic, antioxidant and anticancer effects against Benzo (a) Pyreneinswiss albino rat. Moreover, the plant is found to be a natural preventive source of pulmonary carcinoma. Anticancer activity of leaf and root extracts of *A. ilicifolius* reveals that the ethyl acetate extract reduces cellular viability in MCF-7 and PA-1 cells (Smitha et al., 2014).

1.2. *Andrographis* Wall. ex Nees

A. paniculata is an important medicinal plant and widely used around the world. It is also known as 'Indigenous king of bitter' and uses as a traditional herbal medicine in India, Bangladesh, China, Hong Kong, Pakistan, Philippines, Malaysia, Indonesia and Thailand. The plant is ethnobotanically used for the treatment of snake bite, bug bite, diabetes, dysentery, fever and malaria.

Anticancer activities: Extracts of *A. paniculata* reduce the risk of cancer due to the presence of flavonoids. The aerial part of the plant is most commonly using in medicines because of the presence of diterpenoids, diterpene glycosides, lactones, flavonoids and flavonoid glycosides in the extracts. Leaves have many phytochemical constituents like phenols, tannins, alkaloids, saponins, flavonoids and reducing sugars. These phytochemicals actively involved in the medicinal uses for treating various diseases. The plant has been reported to have a broad range of pharmacological effects including anticancer, antidiarrheal, antihepatitis, antiHIV, antihyperglycemic, antiinflammatory, antimicrobial, antimalarial, antioxidant, cardiovascular, cytotoxic, hepatoprotective, immunostimulatory and sexual dysfunctions (Sadhana et al., 2020). The in vitro anticancer activities of different solvent derived extracts of *A. paniculata* leaves are against different human cancer cell lines, neuroblastima (IMR-32) and human colon (HT-29) (Rajeshkumar et al., 2015). Andrographolide exhibits both direct and indirect effects on cancer cells by inhibiting proliferation of cancer cells, cell cycle arrests or cell differentiation that enhancing body's own immune system against cancer cells and inducting apoptosis and necrosis of diseased cells (Hossain et al., 2014). The presence of

various chemical constituents in the aerial parts of *A. paniculata* is andrographolide which is diterpene lactone, colourless, crystalline and bitter in taste (Nyeem et al., 2017). Ethanol extract of *A. paniculata* contains 2.13 ppm neoandrographolide and shows an inhibitory effect in MCF-7 cells with higher doses (Sholihah et al., 2019).

1.3. *Avicennia* L.

A. alba is also known as 'Api Api Putih', and considers as the iconic tree of the mangrove forest. The height may be up to 20 m and bearing the salt excreting leaves in presence of salt glands. The tree develops pneumatophores that protrude out of the soil allowing root respiration in the anaerobic muddy soil. *A. marina* is commonly known as 'Grey mangrove' or 'Cheru uppatty'. They are generally 10-4 m long and have light gray or whitish bark with stiff, brittle and thin flakes. Their leaves are thick, glossy and bright green on the upper side and gray or silvery white with small hairs on the lower side. The pneumatophores can grow up to 20 cm (Baishya et al., 2020).

Anticancer activities: Polyisoprenoids from *A. alba* show anticancer activity (Lllian et al., 2019). Isoprenoids as well as polyisoprenoids identified from the leaves and roots of the mangrove which possesses various pharmacological activities including anticancer and anti-inflammatory. Bioactive compounds in leaf extract exhibit in vitro anticancer potential against MCF-7 and Hela cell lines (Eswaraiah et al., 2020). It could be used as a potential alternative for the development of bioactive leads in the treatment of cancer. The leaves of plants include flavonoids, steroids, saponins and tannins; whereas in roots, flavonoids and steroids / triterpenoid compounds are present (Rahmania et al., 2018). *A. marina* plant extracts show anticancer and antiproliferative activity (Albinhassan et al., 2021). The hexane extract of leaves is helpful for anticancer drug development due to the presence of highest phenolic and flavonoid contents. Polyphenol rich leaf extracts induce apoptosis in human breast and liver cancer cells (Huang et al., 2016).

1.4. *Barleria* L.

B. prionitis is commonly known as 'Yellow nail dye', 'Chemmulli', 'Manjakanakambaram', 'Shemmuli', 'Vennkurinjiveru' etc. It is an indigenous herb of Southern Asia and some regions of Africa. The various parts including leaf, flower, stem, seed, shoot and root are with therapeutic effects against numerous disorders including cough, fever, jaundice, asthma, severe pain and cut wound (Banerjee et al., 2021).

Anticancer activities: *B. prionitis* leaf ethanol extract shows anticancer and antimicrobial potential. The anticancer effect against lung cancer cell line, breast cancer cell line, breast metastatic cell line, colon cancer cell line and lung metastatic cell line is statistically significant at particular concentration (Panchal et al., 2018). Assessment of stem ethanol extract potential to kill pathogenic microbial strains and in vitro inhibitory effect on human cancer cell lines is prominent (Panchal et al., 2021). Several bioactive compounds isolated from *Barleria* species, such as iridoids, phenolics, flavonoids, terpenoids, phytosterols and phenylethanoid glycosides possess various biological properties of medicinal importance.

Moreover, both extracts and bioactive compounds from *Barleria* have demonstrated several biological activities including antioxidant, antibacterial, antifungal, antiinflammatory and anticancer properties and the ability to synthesize silver nanoparticles (Gangaram et al., 2022).

1.5. *Justicia* L.

J. adhatoda is a widespread plant throughout the tropical regions of Southeast Asia and commonly known as 'Vasaka' or 'Malabar nut'. The species is a perennial, evergreen and highly branched shrub with unpleasant smell and bitter taste. It has opposite ascending branches with white, pink or purple flowers. It is a highly valuable ayurvedic medicinal plant used to treat cold, cough, asthma and tuberculosis. The major alkaloids of the plant, vasicine and vasicinone, have been found to be biologically active and are the area under discussion of many chemical compounds and pharmacological studies. *J. gendarussa* is commonly known as 'Black adusa'. The species is a shade loving, quick growing, evergreen shrub found throughout India and also in all Asian countries like Malaysia, Indonesia, Sri Lanka and Bangladesh.

Anticancer activities: *J. adathoda* shows in vivo anticancer activity against dal cell lines (Jiju, 2019). It has potent phytochemical, antimicrobial and antiinflammatory activity. The qualitative analysis of the extracts from the leaf sample of *J. adathoda* reveals the presence of tannins, saponin, flavonoids, steroid, lipids, amino acids and terpenoids. The active compounds such as amino acids, flavonoids, alkaloids and lipids have antiinflammatory activity and can be considered as a resource for a potential anticancer agent. A compound "vasicine" isolated from n-butanol fraction is found potent in inhibiting proliferation of prostate cancer cells (Batoo et al., 2017). *J. adhatoda* leaf extract showed a potential anticancer effect in MCF-7 cells (Kumar et al., 2022).

Phytochemical screening of *J. gendarussa* plant extracts show higher yield of phenolic and flavonoid content (Ramees et al., 2019). *Jendarussa* crude extracts exhibit cytotoxicity against human cancer cell lines (Ayob et al., 2013). The leaf extracts have potential cytotoxic activity on human cancer cell lines particularly BxPC-3 cells. Usually, the plant is used in traditional medicinal practice for chronic rheumatism, inflammations, bronchitis, vaginal discharges, dyspepsia, eye diseases and fever.

1.6. *Odontonema* Nees

O. strictum is commoly known as 'Fire spike', 'Cardinal guard' and 'Scarlet flame', native to semi-forested areas in Central America. Fire spike is attractive evergreen shrub with sparse stiff branches that grow mostly straight up to about 6 feet tall. It has shiny dark green leaves with wavy margins and long pointed tips. The leaves are oblong and arranged opposite each other on the stem. From late summer through winter, fire spike produces abundant 9-12 m upright panicles of brilliant red tubular flowers. The individual flowers are about an inch long and two lipped.

Anticancer activities: The silver nanoparticles isolated from *O. strictum* leaf extract show antioxidant activity (Luhata et al., 2022). Their antioxidant properties in the management of

oxidative stress are found in several acute and chronic pathological processes such as hypertension, cancer, diabetes and neurodegenerative diseases (Luhata et al., 2016). A qualitative phytochemical screening of the extracts obtained from the leaves of *O. strictum* indicates the presence of flavonoids, saponins, glycosides, tannins, steroids and terpenoids (Luhata & Usuki, 2021).

1.7. *Rhinacanthus* Nees

R. nasutus is commonly known as 'Snake jasmine', 'Dainty sprus', 'Nagamulla' or 'Kaurasago'. It is a small slender shrub growing to a height of about 0.6 to 1.2 m with sparsely branched club shaped fruit and four seeds. The whole plant is widely used in traditional medicinal practices for the treatment of diverse disease conditions. Medicinal preparations of the plant in the form of decoctions and herbal tea have been given internally to the people for the treatment of hepatitis, diabetes and hypertension; while the external application in the form of paste has been used by the people who suffer from psoriasis, eczema, ringworm as well as inflammation. Traditionally seeds, roots and leaves of the plant have been used against scabies, eczema and various skin conditions. Leaves are used for prickly heat as well as scurf and roots are being boiled along with milk which is used as an aphrodisiac (Brimson et al., 2020).

Anticancer activities: The phytochemical analysis of *R. nasutus* reveals the presence of alkaloids, phenols, saponins, flavonoids, tannins, steroids and terpenoids. The aqueous extract possesses a higher concentration of phenolic compounds and flavonoids. The anticancer activity of *R. nasutus* is significant in pharmacology (Nirmala & Savitha, 2021). *R. nasutus*, a Chinese medicinal herb, is rich in carotenoids and possesses vital biological activities such as anti-cancer. Carotenoids reduce the risk of cancer and cardiovascular diseases. Utilization of microemulsions from *R. nasutus* helps to improve carotenoid bioavailability (Ho et al., 2016). The leaf extracts exhibit cytotoxic activity against oral human carcinoma (KB), human breast cancer (MCF-7) and lung cancer (NCI-H187) cell lines (Boonyaketgoson et al., 2018).

1.8. *Thunbergia* Retz.

T. grandiflora is also known as 'Blue *Thunbergia*' or 'Bengal clock vine'. It is native to India, southern China and Myanmar. It thrives predominantly on tropical and subtropical regions, and the habitat preference is exhibited by its morphological characteristics. The species has the medicinal properties such as antibacterial, antifungal, antidiabetic, antipyretic, antiinflammatory, anthelmentic, antioxidant, antinociceptive, antidrug, antidote, antimutagenic, detoxifying, cytotoxic and hepatoprotective activities; hence, it can be considered as potential alternative herbal medicine to treat different types of diseases (Sultana et al., 2015).

T. laurifolia is commonly known as 'Blue trumpet vine' or 'Laurel clock vine', a popular ornamental vine in the tropics. Leaves are heart shaped with a pointed tip and slightly serrated leaf margin. Flowers are attractive with pale purplish blue petals and a yellow throat. In Thailand, the leaves of *T. laurifolia* are believed to have detoxifying effects. They are used as an antidote for poisons and drugs including the treatment of drug addiction. It has reported to

have antioxidant, antidiabetic, antiinflammatory and antipyretic properties (Chan et al., 2011).

Anticancer activities: *T. grandiflora* is the agent of in vivo acute toxicity and anticancer and antioxidant properties (Thorat & Jain, 2020). The plant extracts inhibit lung cancer effectively (Jain, 2020). The extract contains phenolic acid, flavonoid, kaempferol and quercetin. It's presence indicates the significant antioxidant, antidiabetic, antimicrobial and hepatoprotective activities which give the plant a great potential and supporting the use of the plant as a source of natural raw material for phytopharmaceutical preperations (Ibrahim et al., 2017).

Radical intermediate generation and cell cycle arrest by an aqueous extract of *T. laurifolia* detected in human breast cancer cells (Jetawattana et al., 2015). The plant possesses antioxidant, antiinflammatory and anticancer activities (Wonkchalee et al., 2012). *T. laurifolia* leaf extract increases the levels of antioxidant enzymes and protects human cell lines in vitro against cadmium (Junsi et al., 2020). The aqueous extract of leaves significantly increases antioxidant enzyme activities in human embryonic kidney and human liver cells; and significantly decreases malondialdehyde levels in vitro. Crude dried extract of *T. laurifolia* leaves can protect against Cd induced oxidative stress in cells possibly due to it's antioxidant properties. Cytotoxicity of *T. laurifolia* crude extracts investigated in L929, BHK (21) C13, HepG2 and Caco-2 cell lines (Oonsivila et al., 2008).

Two novel iridoid glucosides of 8-epi-grandifloric acid and 3'-O-β-glucopyranosyl-stilbericoside have been isolated from *T. laurifolia* leaves along with seven known compounds of grandifloric acid, benzyl β-glucopyranoside, benzyl β-(2'-O-β-glucopyranosyl) glucopyranoside, 6-C-glucopyranosyl apigenin, 6,8-di-Cglucopyranosyl apigenin, (E)-2-hexenyl-β-glucopyranoside and hexanol-β-glucopyranoside. Leaves and flowers have been found to contain other bioactive phenolic constituents including delphinidin-3, 5-di-O-β-D-glucopyranoside, apigenin, apigenin-7-O-β-D glucopyranoside and chlorogenic acid. A phenolic profiling of water extract of leaves shows the presence of apigenin and apigenin glucosides, as well as phenolic acids of caffeic, gallic and protocatechuic (Chan et al., 2011).

2. Outlook

The purpose of this review is to brief the plants' literature survey via internet sources and to explain various anticancer plants belonging to the family Acanthaceae. Plant species belonging to the family Acanthaceae have abundant source of anticancer compounds. It is beneficial for drug industry to find out this compouds.

References

1. Albinhassan, T. H., Saleh, K.A., Barhoumi, Z., Alshehri , M.A., and Al-Ghazzawi, A.M . (2021). Anticancer, anti-proliferative activity of *Avicennia marina* plant extracts. *J. Cancer Res. Ther.* 17(4): 879-886

2. Ayoba, Z., Samada, A.A., and Boharia, S.P.M. (2013). Cytotoxicity Activities in Local *Justicia gendarussa* crude extracts against Human Cancer cell lines. *J. Teknolog.* 64(2):45–52.

3. Baishya, S., Banik, S.K, Choundhury, M.D, Talukdar, D.D and Talukdar, A.D. (2020). Chapter 11 - Therapeutic potentials of littoral vegetation: an antifungal perspective. Biotechnological utilization of mangrove resources. *Sci. direct.* 275-292.

4. Banerjee, S., Banerjee, S., Ja, G.K., and Bose, S. (2021). *Barleria Prionitis* L.: An illustrative traditional, phytochemical and pharmacological review. *J. Nat. Prod.* 11(3):258-274.

5. Batoo, R., Salahuddin, H., Mahmood, T., and Ismail M. (2017). Study of anticancer and antibacterial activities of Foeniculum vulgare, *Justicia adhatoda* and *Urtica dioica* as natural curatives. *CMB.* 63(9): 109-114.

6. Boonyaketgoson, S., Rukaschaisirikul, V., Phongpaichit, S., and Trisuwan, K. (2018). Naphthoquinones from the leaves of *Rhinacanthus nastus* having acetylcholinesterase inhibitory and cytotoxic activities. *Fitoterapia.* 124:206-210.

7. Brimson, J.M., Prasanth, M.I., Malar, D.S., Brimson, S. and Tencomnao, T. (2015). *Rhinacanthus nasutus* "Tea" Infusions and the Medicinal Benefits of the Constituent Phytochemicals. *Nutrients*. 12(12):3776.

8. Chakraborty. T., Bhuniya, D., Chatterjee, M., Rahaman, M., Singha, D., Chatterjee, B.N., Datta, S., Rana, A., Samanta, K., Srivastawa, S., Maitra, S.K., and Chatterjee. (2007). *Acanthus ilicifolius* plant extract prevents DNA alterations in a transplantable ehrlich ascites carcinoma-bearing murine model. *World J. Gastroenterol.* 13(48): 6538-6548.

9. Chan, E .W. C., Eng, S. Y., Tan, Y.P., and Wong, Z. C. (2011). Phytochemistry and Pharmacological Properties of *Thunbergia laurifolia*: A Review. *Pharmacogn. J.* 3(24):1-6.

10. Corrêa, G.M., Antonio, F., and de C.A. (2011). Chemical constituents and biological activities of species of *Justicia* - a review. *Rev. Bras. Farmacogn.* 22(1):220-238.

11. Eswaraiah, G., Peele, K.A, Kumar, R.B, and Venkateswarulu, T.C. (2020). Identification of bioactive compounds in leaf extract of *Avicennia alba* by GC-MS analysis and evaluation of its in-vitro anticancer potential against MCF7 and hela cell lines. *J. King. Saud. Univ. Sci.* 32(1):740-744.

12. Gangaram, S., Naidoo, Y., Dewir, Y.H, and Hendawy, S.E. (2022). Phytochemicals and biological activities of *Barleria* (Acanthaceae). *Plants.* 11(1).

13. Ho, N.H., Inbaraj, B.S., and Chen, B.H. (2016). Utilization of microemulsions from *Rhinacanthus nasutus* (L.) Kurz to improve carotenoid bioavailability. *Scientific Rep.* 6.

14. Hossain, S. M., Urbi, Z., Sule, A., and Rahman, K.M. H. (2014). *Andrographis paniculata* (Burm. f.) Wall. ex Nees: A Review of Ethnobotany, Phytochemistry, and Pharmacology. *Sci. World J.* 1-28.

15. Huang, C., Lu, C K., Tu, M.C., Chang, J.H., Chen, Y.J., Tu, Y.H., and Huang, H.C. (2016). Polyphenol-rich *Avicennia marina* leaf extracts induce apoptosis in human breast and liver cancer cells and in a nude mouse xenograft model. *Oncotarget.* 7(24):35874-35893.

16. Ibhrahim, M. T., El wafa, A.A., and Sleem, A.A. (2017). Phytochemical and biological Investigation of *Thunbergia grandiflora. J. pharmacogn. Phytochem.* 6(2):43-51.

17. Jain, N.K. (2020). Extraction phytochemical screening and anticancer activity of *Thunbergia grandiflora* using in vitro and in vivo models of lung cancer. *http://hdl.handle.net/10603/325898.*

18. Jetawattana, S., Boonsirichai, K., Charoen, S., and Martin, S.M. (2015). Radical intermediate generation and cell cycle arrest by an aqueous extract of *Thunbergia laurifolia* Linn. in human breast cancer cells. *APJCP.* 16(10):4357-4361.

19. Jiju, V. (2019). Assessment of in vivo Anticancer Activity of *Justicia adathoda* Using Dal Cell Lines. *East Afr. Sch. J. Med. Sci.* 2(7):438-442.

20. Jinsi,M., Yupanqui,C.T., Usawakesmanee, W., Slusarenko, A., and Siripongvutikorn, S. (2020). *Thunbergia laurifolia* leaf extract increased levels of antioxidant enzymes and protected human cell-lines in vitro against cadmium. *Antioxidants (Basel).* 9(1):47.

21. Kumar, S., Singh, R., Dutta, D., Chandel, S., Bhattacharya, A., Ravichandiran, V., and Sukla S. (2022). In vitro anticancer activity of methanolic extract of *Justicia adhatoda* leaves with special emphasis on Human Breast Cancer Cell Line. *Molecules.* 27(23):8222.

22. Llian, D.N., Hasibuan, P.A.Z., Sumardi, S., Nuryawan, A., Wati, R., and Basyuni, M. (2019). Anticancer Activity of Polyisoprenoids from *Avicennia alba* Blume. in WiDr Cells. *Iran. J. Pharm. Res.* 18(3):1477-1487.

23. Luhata, L.P., and Usuki, T. (2021). Antibacterial

activity of β-sitosterol isolated from the leaves of *Odontonema strictum* (Acanthaceae). *Bioorg Med. Chem. Lett.* 48.

24. Luhata, L.P., Chick, C.N., Mori, N., Tanaka, K., Uchida, H., Hayashita, T., and Usuki, T. (2022). Synthesis and antioxidant activity of silver nanoparticles using the *Odontonema strictum* leaf extract. *Molecules*. 27(10):3210.

25. Luhata, L.P., Munkombwe. N.M., Cheuka, P.M., and Sikanyika, H. (2016). Phytochemical and Pharmacological Profiles of the genus *Odontonema* (Acanthaceae). *BJPR.* 14(1):1-7.

26. Nadeem, N., Khan, K.M., Koala, M., Islam,M., Chohan, T.A., Khan, S.A., Fatima, N., Bashir,K., Qamar, S., Chaman, S., Tahir, M.A., and Mannan, A.(2023). Cytotoxic, in vitro enzyme inhibitory potential and phytochemical profiling of *Odontonema Strictum. Pharmacogn. Mag.* 1–8.

27. Nirmala, A., and Savitha, D. (2021). Phytochemical analysis and anticancer activity of *Rhinacanthus nastus. AJBLS.* 10(3):694-699.

28. Nyeem, M.A.B, Mannan, M.A., Nuruzzaman, M., Kamarujjaman, K.M., and Das S.K. (2017). Indigenous king of bitter (*Andrographis paniculata*): A review. *JMPS*. 5(2):318-324.

29. Oonsivilai, R., Ferruzzi, M. G., and Ningsanond, S. (2008). Antioxidant activity and cytotoxicity of Rang Chuet (*Thunbergia laurifolia* Lindl.) extracts. *As. J. Food Ag-Ind.* 1(02):116-128

30. Panchal, P.K, Singh, K., Sharma, N., Deepak, K. K., and Meena, S.K. (2022).Assessment of *barleria prionitis* stem ethanol extract potential to kill pathogenic microbial strains and in-vitro inhibitory effect on human cancer cell lines. *WJPR*. 11(8):818-828.

31. Panchal, P.K., Meena, S.K., Singh, K., and Sharma, N. (2018). Anticancer and antimicrobial potential of Barleria prionitis leaves ethanol extract. *Int. J. Pharm. Sci.* 10(10):100-103.

32. Prasad, N., Singh, B., and Puri, D. (2017). Pharmacognostic screening studies of *Justicia gendarussa* leaves found in Dehradun district of Uttarakhand. *Asian J. Pharm. Clin. Res.* 83-87.

33. Rahmania, N., Herpandi., and Rozirwan. (2018). Phytochemical test of Mangrove *Avicennia alba*, *Rhizophora apiculata* and *Sonneratia alba* from Musi River Estuary, South Sumatera. *BIOVALENTIA*. 4(2).

34. Rajeshkumar, S., Nagalingam M., Ponnaanikajamideen, M., Vanaja, C., and Malarkodi, C. (2015). Anticancer activity of *Andrographis paniculata* leaves extract against neuroblastima (imr-32) and human colon (ht-29) cancer cell line. *WJPPS*. 4(6):1665-1675.

35. Ramees, M., Nileena, F., Rosemery, K., Sinju, P., Nobin, C., and Suresh, J. (2019). Phytochemical Screening of *Justicia gendrussa. Int. J. Pharmacogn. Chinese Med.* 3(1).

36. Sadhana, H.M, Joghee, S., and Hamsalakshmi (2020). *Andrographis paniculata* - A review. I*nt. J. Res. Pharm. Sci.* 11(4):5395-5400.

37. Sholihah, M.M., Indarto, D., and Pramana, T.Y. (2019). The inhibitory effect of *Andrographis paniculata* extract on proliferation of breast cancer cell line. *IOP Conf. Ser.: Mater. Sci. Eng.* 546 062029.

38. Singh, C.R., and Kathiresan, K. (2013). Anticancer efficacy of root tissue and root-callus of *Acanthus ilicifolius* l., on Benzo (A) Pyrene induced pulmonary carcinoma in musmusculus. *WJPPS*. 2(6):5271-5283.

39. Singh, D., and Aeri, V. (2013). Phytochemical and pharmacological potential of *Acanthus ilicifolius. J. Pharm. Bioallied. Sci.* 5(1):17-20.

40. Smitha,R.B., Madhusoodanan, P.V., and Prskashkumar, R. (2014). Anticancer activity of *Acanthus ilicifolius* Linn. from Chettuva Mangroves, Kerala, India. *Int. J. Bioassays*. 3(11): 3452-3455

41. Sudevan, S., Parasivam, R., Sundar, S., Velauthan, H., and Ramasamy, V. (2019). Investigation of anti-inflammatory and anti-cancer activity of *Justicia adathoda* metabolites. *Pak. J. Pharm. Sci.*, 32: 1555-1561.

42. Sultana, K.W., Chatterjee, S., Roy, A., and Chandra. (2015). An Overview on ethnopharmacological and phytochemical properties of *Thunbergia* sp.. *Med. Aromat. Plants*. 4:5.

43. Thorat, M.B., and Jain, N.K. (2020). In vivo acute toxicity, anticancer and antioxidant assay evaluation of *Thunbergia grandiflora. EJMCM*. 7(1):3483-3498.

44. Uddin, R., Sinha, S., Hossain, A., Kaisar, A., Hossain, K., and Rashid, M. A. (2011). Chemical and Biological Investigations of *Justicia gendarussa* (Burm. f). *Dhaka Univ. J. Pharm. Sci.* 10(1):53-57.

45. Vani, M., and Manikandan, T. (2018). Phytochemical analysis and antioxidant activity of *Acanthus ilicifolius. IJCR.* 10(12):76891-76896.

46. Wonkchalee, O., Boonmara, T., Aromdee, C., Laummaunawai, P., Khunkitti, W., Vaeteewoottacharn, K., Sriraj, P., Aukkanimart, R., Loilome, W., Chamgramol, Y., Pairojkul, C., Wu, Z., Juasook, A., and Sudsarn, P. (2012). Anti-inflammatory, antioxidant and hepatoprotective effects of *Thunbergia laurifolia* Linn. on experimental opisthorchiasis. *Parasitol. Res.* 111(1):353-9.

Exploration of Lamiaceae Members in Cancer Treatment

***Deepa P., Anjana K.**

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
*Corresponding author: deepapsaj@gmail.com

Abstract: The members of Lamiaceae are aromatic with a number of phytochemical compounds having anticancer properties against different human cancer cells. The major compounds in plants include menthol, geraniol, eucalyptol, camphor and thymol in turn consider as a source of anticancer drugs. The reduction of tumours and inhibition of metastasis by arresting cell cycle are due to the antiproliferative bioactivities of phytocompounds.

Keywords: Anticarcinogenic, Lamiaceae, cytotoxicity, chemoresistance, cell proliferation

Cancer is a worldwide public health problem, which involves uncontrolled growth of cells and the main reason for cancer today is life style. The cells lose their interaction with each other, invade neighboring tissues and finally spread to distant tissues of the body. It is one of the leading causes of death in both developed and developing countries. It has been reported that in India there will be 19 to 20 lakhs death in 2022 due to cancer. The anticancer properties of plants have been recognized many years ago. The natural compounds in plants and microbes fight against cancer. Recent researches in the field of plant based natural compounds have move towards advanced and molecular level understandings, leading to the development of potent anticancer agents and also plants have been accepted as abundant and rich sources for the development of novel therapeutic agents for the management and prevention of different cancer types.

The Lamiaceae is a family of flowering plants commonly known as the mint, deadnettle or sage family. Many of the members of the family are aromatic due to the presence of secondary metabolites. Many members have demonstrated considerable efficiency in inhibiting cancer cell growth through synergistic effects. Lamiaceae is among the largest families of flowering plants with about 250 genera and over 7,000 species distributed around the world. It is considered as the important source of essential oils such as menthol, geraniol, eucalyptol, camphor and thymol; therefore, it is widely used in various medicines. In addition to proven biological activities, essential oils have recently been evaluated for anticancer activities and considered as a source of anticancer drugs. The present chapter helps to assess the anticancer properties of essential oils obtained from different members of Lamiaceae and also we can understand which plants are used as anticancer agents.

1. Anticancer plants in Lamiaceae

1.1. *Anisochilus* Wall. ex Benth.

The genus, *Anisochilus* is commonly known as 'Kapuri'. The native place of the genus is China, the Indian Subcontinent and Indochina. The plants are herbs or under-shrubs with opposite or whorled leaves. Flowers are usually small in whorled spike inflorescence. The calyx is 2-lipped or 5-lobed with 2-lipped corolla tube of slender below and inflated above. Stamens are four in number and didynamous with free filaments. The ovary is 4-partite and style bifid at apex. Fruit are 4 ovoid dry nutlets. The plant has healing qualities that help with dermal problems and address conditions like stomach ulcers. Additionally, it contains active ingredients such as apigenin, leutiolin and camphor (Bhagat, 2014). Moreover, the secondary metabolites like alkaloids, flavonoids, saponins, glucosides, tannins, lignin, pectin, starch, cellulose and carbohydrates are abundant in the plant (Reshi, 2015).

Anticancer activities: *A. carnosus* extracts play a significant role in lowering of tumour volume, tumour weight and cell viability in EAC induced organisms. It helps in considerable prolongation of host life span and restoration of hematological parameters to almost normal levels. The ethanol extracts and fractions of the plant include luteolin along with phytosterols, terpenoids and flavonoids that induce anti-tumour potential in the plant (Gupta et al., 2015). Petroleum ether and ethanolic extracts show higher cytotoxic effect against BT-549 compared to the aqueous extracts. Because, the ethanol extract contains the highest concentration of luteolin than the aqueous extract. Due to the reason, the petroleum ether and ethanolic extracts induce promising anticancer activity and has the potential to be developed into a therapeutic option for the treatment of cancer (Bhagat et al., 2014).

1.2. *Leucas* R.Br.

The genus includes herbs, under-shrubs or shrubs with pubescent four angled branches showing opposite or whorled phyllotaxy. Flowers are white in colour and in axillary inflorescence. Bracts are many, linear or lanceolate. Calyx is tubular, 10-ribbed, equally or unequally 6-10-toothed. Bilipped corolla has upper erect and lower spreading lip. Stamens are four in number and didynamous. The ovary has four carpels that form dry nutlets after fertilization.

Leucas is mostly distributed over Africa, Iran, India, China, Japan, Indonesia and with a few species in Queensland and on various islands in the Indian Ocean. The plant is used traditionally as an antipyretic and insecticide. It possesses various pharmacological activities like antifungal, antioxidant, antimicrobial and cytotoxicity. Plant is the rich source of various phytochemical constituents viz. triterpenoids, oleanolic acid, ursolic acid, b-sitosterol, nicotine, sterols, glucoside, diterpenes, phenolic compounds etc. (Prajapati, 2010).

Anticancer activities: The presence of diverse bioactive compounds makes *Leucas* sp. more demandable for curing several diseases such as inflammatory diseases, diabetes and cancer. The different phytochemicals in methanol extract of *L. indica* leaves show remarkable antioxidant and anticancer activities (Susmi et al., 2022). The crude methanol extracts of

flowers exhibit antioxidant and anticancerous properties due to the cytotoxic effects against the selected cancerous cell lines viz. HeLa, HCT116, HL-60 and MCF-7. The important bioactive compound responsible for anticancer activity is 6-hydroxy-3-(4-hydroxyphenyl)-7-(3,4,5-trihydroxy-6-)(hydroxymethyl)tetrahydro-2H-pyran-2yl)-4H-chromen-4-one. Based on the antioxidant and anticancerous properties, *L. indica* might be a promising source of useful natural products and the newly bioactive compound might offer opportunities to develop new anticancerous drugs (Sowjanya et al., 2022). Presence of DPPH, flavoinds, FRAPS and phenol contents in water and methanol extracts of *L. aspera* induces antioxidant and anticancer activities as well as cytotoxicity in treated cells (Suruthi et al., 2016). The silver nanoparticles synthesized from aqueous leaf extract exhibit potent cytotoxic effect on cervical cancer cells and induce cell death through apoptosis (Chavata et al., 2019). Silver-copper bimetallic nanoparticles (Ag-Cu BNP) synthesized from the leaf extract act as a bioreducing agent that shows significant alveolar anticancer and antioxidant activity against human alveolar cancer cell line A549 than aqueous leaf extract (Yang et al., 2022). Moreover, ethyl acetate fraction shows cytotoxic effects in Dalton's lymphoma cell lines results in significant decrease in ascites tumour volume and viable cell count (Augustine et al., 2014).

L. biflora leaf extract fabricated silver nanoparticles (LbLE-Ag-NPs) act as a potential anticancer agent. LbLE-AgNPs exhibits an effective dose dependent anticancerous activity on MDA-MB-231 breast cancer cell line (Chitra et al., 2022). The leaf extract of *L. zeylanica* is mitodepressive and may be considered as a potential antitumour promoting agent (Sinha & Kumar, 2014). The methanolic extract contains phenol, flavonoid and tannin that are also responsible for cytotoxicity related antitumour activity (Abdullah et al., 2021). Ethanolic extract of *L. lanata* includes reducing sugars, alkaloids, cardiac glycosides, flavonoids and tannins. The plant also has 6-octadecenoic acid, cis-13-octadecenoic acid and l-(+)-ascorbic acid 2,6-dihexadecanoate as dominant phytochemicals in turn cause anticancer properties (Vijisaral & Arumugam, 2014; Vermaa et al., 2020). *L. martinicensis* has high inhibition of the cyclooxygenase-2 (COX-2) enzyme with IC_{50} values ranging from 3.79–25.80 µg/ml in turn induce anticancer activity against cervical and epidermoid cancer (Twilley et al., 2017).

1.3. *Leonotis* (Pers.) R.Br.

Leonotis is commonly called 'Lion's tail' and 'Wild dagga'. The plants may be herbs or shrubs with 4 angled stems having opposite phyllotaxy. The flowers with numerous bracts are yellow and axillary in position. Calyx is 10-ribbed while corolla bear 2 lips in which the upper lip is long and concave with a villous crown; and the lower lip is small 3 lobed with the largest mid lobe. Stamens are four in number and didynamous. The 4 partite ovary is end with subulate style that forms 4 dry nutlets after pollination and fertilization. The plants are the rich source of phenols, flavonoids, carotenoids, fatty acids and steroids (Oliveira, 2015). It is used in the treatment of haemorrhoids, eczema, skin rashes, boils, itching, muscular cramps, headache, epilepsy, chest infections, constipation, spider and snake bites due to the

presence of secondary metabolites (Nsuala, 2015).

Anticancer activities: *L. nepetifolia* root methanolic extract acts as a source of bioactive compounds with cytotoxic, genotoxic and proapoptotic activity against human melanoma cells (Merecz-Sadowska et al., 2022). It shows in vitro cytotoxic effects on HepG2 cell line. The methanol extract of leaves is to be more significant in scavenging free radicals that causes dose dependent damage to the breast and laryngeal cancer cell lines, MCF-7 and Hep2 (Veerabadran et al., 2013). While the ethanolic extract of the plant includes 1,3 propanediamine N (3- aminopropyl)-N-methyl, 1,3-methyl-2-(3,7,11-trimethyl dodecyl thiophene and benzoquinoline (n) quinoline 2,4-dimethyl shows cytotoxicity against Ehrlich Ascites carcinoma by activating the apoptotic pathway (Gurunagarajan & Pemaiah, 2011). Leaf extracts have various bioactive components including λ-sitosterol in methanol extract, 1-nonadecanol in petroleum extract and eicosane in hexane extract. Due to this, the leaves are significant in scavenging free radicals and causing damage to proliferative cells. Similarly, the different solvent extracts of flower buds contain a significant amount of various bioactive phytochemicals with antioxidant and anticancer activities; thus, the plant could serve as a potential source of pharmacological applications (Nagaraja et al., 2022).

1.4. *Isodon* (Schrad. ex Benth.) Spach

Isodon is native to the tropics and subtropics, especially in China. They are pubescent herbs with 4 angled branchlets with ovate leaves having truncate base and crenate-serrate margin. Panicled inflorescence is slender and terminal in position. Calyx is campanulate and 2 lipped with 3+2 condition. Corolla is white and 2 lipped with 4 + 1 condition. Stamens are four in number. Fruit is ovoid nutlets. The plants are used for treatment of acute hepatitis, trauma, dysentery, enteritis, bacterial infections and inflammation, treatment of sore throats, malaria, jaundice, pneumonia, gastrointestinal disorders and cholecystitis (Lianzhu et al., 2011).

Anticancer activities: The methanolic extract of *I. coetsa* treated DLA and EAC cell lines reveals cytotoxic activity that varies on basis of concentration. It induces cell death in dividing cells, an essential phenomenon in anticancer therapy (Neelamkavil & Thoppil, 2016). Melissoidesin G (MOG) is a diterpenoid purified from *I. melissoides*, uses in Chinese traditional medicine as antitumour and antiinflammatory agents. MOG specifically inhibits the growth of human leukemia cell lines and primary acute myeloid leukemia blasts via induction of apoptosis, with the evidence of mitochondrial ΔΨm loss, reactive oxygen species production, caspases activation and nuclear fragmentation (Yu et al., 2007). Water soluble flavanoids in *I. lophanthoides* var. *gerardianus* inhibit cell growth in HepG2 cells. It stimulates to increase the amount of iROS, mitochondrial membrane potential and the apoptotic relevant factors (cytochrome c, caspase-3) in HepG2 cells in turn induce apoptosis through downregulating apoptosis antagonizing protein (Bcl-2, Survivin, mcl-1) and upregulating apoptosis promoting proteins (Bax) (Feng et al., 2016). The ent-kaurene diterpenoid melissoidesin isolated from the leaves of *I. wightii* shows significant cytotoxicity against lung cancer and neurobla-

stoma cell lines. The prevention of DNA degradation activity of melissoidesin is prominently significant that promoting the anticarcinogenic activity in a dose dependent manner (Thirugnanasampandan & Jayakumar, 2009).

Diterpenoids isolated from *I. wightii* exhibits antibacterial, antiacetylcholinesterase, antioxidant and anticarcinogenic activities. Cytotoxic activity of ABA against cervical cancer cells (HeLa) promising it as a natural compound for herbal anticancer drug preparation (Ramnath et al., 2016). The compound, 3,4-*seco*-isopimarane isoamethinol D (4), isolated from *I. amethystoides* has toxicity to the cervical Hela cancer (Hela) cells and the lung (A549) cancer cells (Zhao et al., 2022).

Oridonin is the main bioactive constituent of *I. rubescens* which has anti-neoplastic effects against hepatocarcinoma HepG2 cells in a dose dependent manner. Treatment with oridonin induces apoptosis and G2/M cell cycle arrest. In addition, the up regulation of Hsp70.1, STRAP, TCTP, Sti1 and PPase as well as the down regulation of hnRNP-E1 by oridonin could be responsible for the apoptotic and G2/M arresting effects suppress the liver cancer cells (Wang et al., 2011).

1.5. *Hyptis* Jacq.

Hyptis is commonly known as 'Bushmints' and widespread in tropical North and South America as well as parts of West Africa. They are herbs or shrubs with opposite leaves and small or medium sized flowers. Calyx is tubular with 5 lobes and the five lobbed corolla tube is cylindrical. Didynamous stamens are 4 in number with free filaments. Ovary is 4 partite with sub-entire or shortly bifid stigma on the style. Fruit is dry nutlet. The plant shows antimicrobial, antidiabetic, antiulcer and antiinflammatory effects due to the presence of flavonoids and terpinoids.

Anticancer activities: Ethanolic leaf extract of *H. capitata* shows anticancer potential on T47D cells. The extract contains neophytadiene, hexadecanoic acid, methyl ester, ethyl ester and heptadecanoic acid, 16-methyl-, methyl ester that work synergistically to inhibit cell proliferation (Tobungan et al., 2022). *H. suaveolens* shows in vitro anticancer activity due to the occurrence of the major compounds of sabinene, trans caryophyllene, E-spathulenol, rimuene, 1,8 cineole, β-elemene, eucaliptol, bergamotol, α-selinene, caryophyllene oxide, γ-elemene and α-humulene. The compounds are very effective against human breast cancer cell line, MCF-7 (Poonkodi et al., 2017). *H. pectinata* hydro ethanolic extract includes a greater proportion of monoterpenes, cymene, thymol and β-terpinene in the essential oil and of a 2(5H)-furanone and α-pyrones in a dichloromethane extract. Thus shows moderate cytotoxicity against HCT-8 line cells and inhibits the sarcoma 180 (Barbosa et al., 2012). Isoquercitrin isolated from the aerial parts of *H. fasciculata* is effective to interfere with glioblastoma (Gbm) cell growth. Quercetin and rutin in the extract negatively affect Gbm cell proliferation after treatment times of longer than 24 h. Isoquercitrin did not induce Gbm cell death, but in turn cause marked reduction in cyclin D1 levels and an increase in p27 levels. Therefore, the compound reduces Gbm cell growth without inducing apoptosis, possibly by modulating the control of the cell cycle (Amado

et al., 2009). The extract of *H. mutabilis* leaves with different polarities viz. hexane, methanol, water and hot water; are against sarcoma 180 and Ehrlich solid tumour due to the anticancer activity. The extract includes steroids, saponins, flavonoids and catechins. The aqueous extract shows strong inhibition of tumour growth compared to other extracts (Ximenes et al., 2012). Moreover, *H. verticillata* and *H. tomentosa* are strongly effective against different cancer cell proliferation due to the effective secondary metabolites (Kingston et al., 1979; Picking et al., 2013).

1.6. *Gomphostemma* Wall. ex Benth.

The plant is native to Southeast Asia, China and the Indian subcontinent. The plants are herbs or undershrubs with salient morphological characters. The leaves are opposite, large, entire, dentate or crenate. Flowers are rather large, usually yellow with cymose inflorescence. Calyx is campanulate, equally 5 lobed, 10 ribbed; while corolla 2 lipped with slender tube. Didynamous stamens are four in number and ovary 4 partite with slender style and bifid stigma. After fertilization, the ovary forms nutlets. Normally, the plant is used to prepare medicines for rheumatism, dysentery and diorrohea by kurichia, kuruma and kattunaika tribes of Kerala due to the presence of alkaloids, flavonoids, terpenoids, phenols, tannins and saponins in the species.

Anticancer activities: The methanol extracts of selected species of *Gomphostemma*, viz., *G. heyneanum* and *G. eriocarpum*, consists a total of 72 volatile phytoconstituents belonging to various classes like terpenoids, flavonoids, phenolics, fatty acids, aldehydes etc.. Among them, the major components identified with prominent biological activities include α-thujene, neophytadiene, β-caryophyllene, limonene, eucalyptol, phytol, stearic acid, stigmasterol, quinic acid and tocopherol (Sajitha Menon & Thoppil, 2022). The cytotoxic potential of aqueous extract of *G. heyneanum* is the sign of apoptotic induction. Cytogenetic aberrations with apoptotic signs together with reduction in metabolic activity due to mitochondrial disfunction and cell death caused by the membrane damage are all indications of possible apoptotic potential of *G. heyneanum* extract (Sajitha Menon & Thoppil, 2018).

1.7. *Clinopodium* L.

Clinopodium is a genus of flowering plants in the mint family. It is commonly known as 'Wild basil' or 'Savory'. The genus includes several species of perennial herbs that are native to Europe, Asia and Africa. *Clinopodium* plants are typically low growing, bushy herbs with woody stems and small, oval shaped leaves that are arranged opposite each other on the stem. The leaves often have a pleasant aroma when crushed. The flowers of *Clinopodium* species are small and typically arranged in dense clusters at the tips of the stems or in the axils of the leaves. The flowers are usually tubular in shape, with a slightly curved or bent corolla that is typically two lipped. The corolla tube is often hairy or glandular, and the upper lip may be concave or hooded, while the lower lip is often three lobed. The flowers come in a variety of colors including white, pink, purple and blue. They are often used in traditional medicine to treat a range of ailments, including digestive issues, headaches and respiratory problems. Some species of *Clinopodium*, such

as *C. douglasii*, is also used as culinary herbs in certain cuisines.

Anticancer activities: The acidified, alkalized and lipophilic extracts of *C. vulgare* are very effective on the cell viability of cancer cell lines like CaOV (human testis cystadenocarcinoma), HeLa (human cervical adenocarcinoma), HT-29 (human colorectal adenocarcinoma) and FL (human amnion normal). The acidified and lipophilic extracts exert selective dose dependent cytotoxic activity against CaOV and HeLa cells, while the cytotoxicity of the alkalized extract against these cell lines is less pronounced. All extracts show very weak or lack of cytotoxic actions towards HT-29 and the normal FL cells. *C. vulgare* extracts possess selective anticancer activity and could serve as a source for isolation and development of new therapeutic anticancer agents (Batsalova et al., 2017). The petroleum ether, chloroform and methanol extracts of *C. umbrosum* have cytotoxic activity on HN-5 oral cancer cells after 24 h of treatment. The cytotoxicity of buddlejasaponin IVa and buddlejasaponin IV shows that buddlejasaponin IV possesses superior cytotoxicity. Both compounds show their cytotoxicity through the apoptotic pathway with increasing *Bax/Bcl2* ratio and the level of caspase 9. Similarly, HN-5 cells migration reduces with two saponin compounds (Sharifi et al., 2022). The essential oil from *C. sericeum* includes 73 compounds in which major components of the oil are -germacrene-D, caryophyllene and sabinene. The essential oil displays antibacterial activity against gram negative and gram positive bacterial strains in a dose range close to standard antibiotics. The antiproliferative activity in healthy non tumourigenic cells (HEK-293) and in three human cancer cell lines (T24, DU-145 and MCF-7) is positive by the essential oil (Benites et al., 2021).

1.8. *Ocimum* L.

Ocimum is a genus of aromatic annual or perennial herbs, undershrubs or shrubs native to the tropical and warm temperate regions of all 6 inhabited continents with the greatest number of species in Africa. It has strong aroma because of the presence of oil glands. Leaves are opposite or whorled, usually toothed and petioled. The flowers are small in whorls of 6-10 on the axis of elongate spikes or racemes which are sometimes panicled. The bracts are small and caducous. Calyx is 2 lipped in which upper lip broad and lower lip with 4 mucronate teeth. Corolla tube is short and 2 lipped. The upper lip is subequally 4 lobed and lower lip hardly longer than the upper. The didynamous stamens are four in number in which the filaments are free and connate below. Ovary is 4 partite with slender style and bifid stigma. A number of secondary metabolites such as nerol, eugenol, terpinene pinene and carvacrol are present in whole plant. The leaves are rich with ursolic acid, apigenin, luteolin and orientin which are used for the treatment of bronchitis, bronchial asthma, malaria, diarrhea, dysentery and skin diseases.

Anticancer activities: *O. gratissimum, O. basilicum, O. canum, O. kilimandscharicum, O. tenuiflorum* and *O. citriodorum* are found to reduce the proliferation of human breast cancer cells (Anusmitha et al., 2022). The ethanolic extract of *O. sanctum* induces cytotoxicity in human fibrosarcoma (HFS) cells. Biochemically

the extract treated HFS cells show depleted intracellular glutathione and increased levels of lipid peroxidation products. Administration of aqueous and ethanolic extracts in mice bearing Sarcoma-180 solid tumours mediates a significant reduction in tumour volume and an increase in lifespan (Karthikeyan et al., 1999).

Antioxidants and other bioactive compounds in *O. basilicum* leaves show important potential anticancer activity regards to cell death and viability inhibition, cytotoxicity, apoptosis, cell cycle arrest etc. Additionally, rosmarinic acid shows inhibition in DNA and protein synthesis in hepatoma derived cell line (HepG2) by lowering the suppression on caspase-3 activation to block apoptosis (Perna et al., 2022). Methanolic extract of *O. basilicum* contains ursolic acid which induces anticancer activity in HT-144, MCF-7, NCI-H460 and SF-268 cell lines. Ursolic acid induces a significant decrease in the percentage of cells in anaphase or telophase stages along with F actin aggregation and mitotic spindle distortion (Arshad Qamar et al., 2010). Beyond, the methanol extract of basil seeds is anticancerous due to the presence of potential source of stable bioactive compounds (Gajendiran et al., 2016). *O. tenuiflorum* essential oil significantly decreases AGS cell viability in a dose dependent manner and effectively inhibits cell migration and invasion. Essential oil induces cell shrinkage, chromatin condensation and fragmentation that are considered typical morphologies of apoptotic cell death. Proapoptotic genes including TP53, BAX and BAK significantly upregulate, while antiapoptotic genes like BCL2 and BCLxL significantly downregulate in presence of essential oil. In addition, significant increase of expressions of CASP8, CASP9 and CASP3 in AGS cells occurs when expose to the oil, rich with caryophyllene and α-pinene (Boonyanugomol et al., 2021).

1.9. *Mentha* L.

The plants are widely grown in temperate areas around the world, particularly in Europe, North America, North Africa, Asia Minor and Northern parts of Iran. Nowadays, it is cultivated throughout all regions of the world. The genus is strongly aromatic perennial herbs which is used remedy for respiratory diseases like bronchitis, sinusitis, tuberculosis and cold. Quadrangular stem is with opposite leaves of ovate-lanceolate shape and rounded or acute base bearing verticillaster inflorescence. Calyx of the flowers is glabrous with 13 nerves and corolla pale purple or pink in colour. Presence of the components like menthol, isomenthone, limonene, iso-menthanol, menthol acetate, carvone, β-pinene, α-pinene, 1,8-cineole, α-terpineol, isopulegol, pulegone, piperiton, piperitone oxide and β-phellandrene are boosting the antioxidant activities of the plant (Stefanaki, 2021).

Anticancer activities: *M. piperita* leaf extracts in petroleum ether, benzene, chloroform, ethyl acetate, methanol and water show anticancer effects on human cancer cell lines (HeLa, MCF-7, Jurkat, T24, HT-29, MIAPaCa-2). All the extracts show significant dose and time dependent anticarcinogenic activity leading to G1 cell cycle arrest and mitochondria mediated apoptosis, perturbation of oxidative balance, upregulation of Bax gene, elevated expression of p53 and p21 in the treated cells (Jain et al., 2011). The methanolic and aqueous extracts of whole plants of *M. arvensis, M. longifolia, M.*

spicata and *M. viridis* exhibit anticarcinogenic effect against eight human cancer cell lines like A-549, COLO-205, HCT-116, MCF-7, NCI-H322, PC-3, THP-1 and U-87MG from six different origins of breast, colon, glioblastoma, lung, leukemia and prostate. Beyond, the methanolic extracts display antiproliferative effect in the range of 70-97% against four human cancer cell lines namely COLO-205, MCF-7, NCI-H322 and THP-1; however, the aqueous extracts are found to be active against HCT-116 and PC-3 (Sharma et al., 2014).

M. piperita essential oil contains five major ingredients of menthol, menthone, camphane, menthofuran and iso-menthone. The essential oil has anticancer activity at various incubation periods against three human breast cancer cell lines. *M. piperita* possesses an antiemetic effect and green nanoemulsion could be used as an anticancer agent (Abedinpour et al., 2021). The cytotoxicity reveals considerable anticancer activity of AgNPs on HeLa and MCF-7 cancer cells (Kelkawi et al., 2017). The silver nanoparticles (NP) synthesized using an aqueous extract of *M. spicata* leaves show cytotoxicity and anticancer activity. The NP decreases cell viability and generation of reactive oxygen species in Chang and SiHa cells (Torres-Martinez et al., 2019). The anticancer and antioxidant activity confirmed in *M. citrata* and *M. longifolia* aerial parts. The extracts inhibit the growth of three tested cancer cells of liver, cervix and colon carcinoma due to the presence of phytosterols, phenolic compounds, unsaturated fatty acids and specific volatile constituents (Al-Okbi et al., 2015).

1.10. *Plectranthus* L. Her.

Plectranthus (Spur flower) is a genus of about 85 species mostly found in southern and tropical Africa and Madagascar. The species are herbs, undershrubs or shrubs with the 4 angled stem. Leaves are opposite with small flowers in panicle or raceme of 6-8 flowered cymes. Bracts are usually small, sometimes large and caducous. Two lipped calyx and corolla are with 5 lobes. The didynamous stamens are with free filaments. Tetra partite ovary ends with slender style and 2 fid stigma at the tip. Usually, the fruits are 4 orbicular ovoid or oblong nutlets. The plant is widely used in folk medicine to treat conditions like cold, asthma, constipation, headache, cough, fever and skin diseases due to the presence of 76 volatiles and 30 non volatile compounds belonging to different classes of phytochemicals such as monoterpenoids, diterpenoids, triterpenoids, sesquiterpenoids, phenolics, flavonoids, esters, alcohols and aldehydes. It has antimicrobial, antiinflammatory, antitumour, wound healing, antiepileptic, larvicidal, antioxidant and analgesic properties.

Anticancer activities: *P. ornatus* includes the phytochemicals viz. halimane (11R*,13E)-11-acetoxyhalima-5,13-dien-15-oic acid (HAL), the labdane diterpenes 1α,6β-diacetoxy-8α,13R*-epoxy-14-labden-11-one (PLEC) and forskolin like 1:1 mixture of 1,6-di-O-acetylforskolin and 1,6-di-O-acetyl-9-deoxyforskolin (MRC) that show anticancer properties in MCF-7 and FaDu cancer cell lines by increasing ROS production and mitochondrial damage in the ND1 and ND5 gene regions (Sitarek et al., 2022). The methanolic extract of *P. stocksii* leaf and stem shows higher concentrations of total phenolics and tannins that defend against MCF-7, Caco-2

and RAW 264.7 cancerous cell lines (Muniyandi et al., 2017). *P. amboinicus* treated TiO2 nanoparticles have better anticancer properties to treat oral cancer (Maheswari et al., 2021). The phytocompounds namely carvacrol, thymol, alpha pinene, limonene, vanillin, cineole and syringic acid include in *P. amboinicus* interact with the cancer target proteins (Sindhu et al., 2022). Moreover, the essential oil of the plant exhibits the potent chemotherapeutic or chemopreventive effect (Manjamalai et al., 2013). *P. strigosus* consists active ingredient of parvifloron D, a strongest antimicrobial and cytotoxic agent (Garcia et al., 2019).

1.11. *Pogostemon* Desf.

The plants are native to the island region of Southeast Asia including Sri Lanka, Indonesia, Malay Peninsula, New Guinea and Philippines. The plants are grown as herbs, under shrubs or shrubs, often aromatic with opposite leaves. The small flowers are in clusters of elongate spikes or raceme inflorescence. Calyx is more or less tubular and equally 5 lobed while the 2 lipped corolla tube includes the 3 lobed upper lip and the lower narrower and longer 2 lobed lower lip. The sub-equal four stamens and 4 partite ovary with slender style and 2 fid stigmatic lobes are prominent in flowers. The plant is used to treat colds, headaches, fever, nausea, vomiting, diarrhea, abdominal pain, insect and snake bites by the detection of secondary metabolites such as terpenoids, phytosterols, flavonoids, organic acids, lignins, alkaloids, glycosides, alcohols and aldehydes in plants (Swamy et al., 2015).

Anticancer activities: The aqueous leaf extract of *P. heyneanus* is effective cytotoxic agent inducing various clastogenic and non clastogenic aberrations including chromosome gaps, bridges, multipolar anaphase, fragments, nuclear budding and lesions, hyperchromasia, laggards and mitotic pairing in turn induce anticancer activity (Sheela & Thoppil, 2017). Patchouli alcohol (PA) is one of the important compounds isolated from the essential oil of *P. cablin* that exerts an anticancer activity by decreasing cell growth and increasing apoptosis in human colorectal cancer cells (Jeong et al., 2013). The methanol extract of *P. cablin* inhibits the growth of various cancer cells such as A549, HepG2, MCF-7 and HT29 by arresting the G1 phase of cell cycle (Yun et al., 2015).

1.12. *Salvia* L.

The genus shows maximum diversity in Central America and Mediterranean region. The plants are herbs or shrubs of various habits with small or large showy flowers having variously sized bracts. Calyx and corolla tubes are tubular with 3 lobbed upper lip and 2 lobbed lower lip. The lower pair of stamens shows fertility and the upper pair reduced to staminodes. The four partite ovary ends with bifid style. The plant normally uses for the treatment of different kinds of disorders including seizure, ulcers, gout, rheumatism, inflammation, dizziness, tremor, paralysis, diarrhea and hyperglycemia (Ghorbani et al., 2017).

Anticancer activities: The extracts of *S. africana-caerulea, S. africana-lutea, S. albicaulis, S. aurita, S. chamelaeagnea, S. disermas, S. lanceolata, S. muirii, S. namaensis, S. radula, S. repens, S. runcinata, S. schlechteri, S. stenophylla* and *S. verbenaca* have cytotoxic

effects on human colon cancer cells (HT-29) (Kamatou et al., 2008). Liposoluble compounds like tanshinone IIA [1,6,6-trimethyl-8,9-dihydro-7H-naphtho[1,2-g] [1] benzofuran-10,11-dione] and tanshinone I [1,6-dimethylphenanthro[1,2-b]furan-10,11-dione] are rich in *S. miltiorrhiza* and related species regards as having phytoestrogenic effects with antiproliferation of human breast cancer MCF-7 (Zhao et al., 2007). Daucosterol, a β-sitosterol glycoside, present in *S. sahendica* inhibits cell proliferation by inducing apoptosis (Esmaeili & Farimani, 2014). *S. miltiorrhiza* and *S. officinalis* contain the hydrophilic phenolic acids and the lipophilic tanshinones both show anticancer effects. *S. miltiorrhiza* and related species have specific effects on lung cancer cell lines. The methanol crude extracts of *S. menthaefolia, S. sclarea, S. dominica, S. spinos* and *S. palestina* exhibit antiproliferative activity against prostate cancer cell MDA Pca2b (Fiore et al., 2006). The protocatechualdehyde, a polyphenol in *S. miltiorrhiza* suppresses proliferation of breast cancer cell lines like MCF-7 and MDA-MB-231 via an estrogen dependent manner. The neo-tanshinlactone isolated from *S. miltiorrhiza* is active against ER positive human breast cancer cell lines (MCF-7 and ZR-75-1) and HER-2-overexpressing breast cancer cell lines (SK-BR-3, HER-2+) (Choi et al., 2014). Moreover, the aqueous extract from *S. miltiorrhiza* strongly inhibits the proliferation of hepatocellular carcinoma cells (HepG2). Linalyl acetate, α-terpineol and camphor, the main components of the essential oil of *S. libanotica* synergistically induces cell arrest and apoptosis resulting in the inhibition of the growth of two isogenic human colon cancer cell lines HCT-116 (p53+/+ and p53−/−) (Lee et al., 2014). Beyond, the acetone extract of *S. hypargeia* roots shows the highest activity against the human ovarian cancer cell line, A2780 (Topcu et al., 2008). Taxodione, ferruginol and 6-hydroxysalvinolone isolated from *S. chorassanica* exhibit cytotoxic and apoptotic effectiveness against the leukemic cancer cells, K562 and HL-60 (Tayarani-Najaran et al., 2013). The essential oils of *S. bracteata* and *S. rubifolia* from Lebanon exhibit an inhibitory effect on the human melanoma cells M14 through induction of apoptotic cell death (Cardile et al., 2009). Saprorthoquinone and taxodione of *S. hypargeia* show cytotoxic activity on human colon cancer, Col 2 (Ulubelen et al., 1999).

1.13. *Scutellaria* L.

The genus is commonly known as 'Skullcaps'. The generic name derived from the Latin word “Scutella” meaning "a small dish, tray or platter" or "Little dish". The plants may be mostly herbs or under shrubs with opposite leaves and small bract like floral leaves. Inflorescence is normally terminal raceme. Calyx and Corolla are 2 lipped in which the upper lip entire or notched and lower lip is broad and three lobed. Two paired didynamous stamens arranged as the lower longest pair and upper shortest pair in which anthers are connivent. Ovary is four partite on a curved gynophore with slender style and bifid stigma. The plants are usually using in the treatment of diarrhea, dysentery, hypertension, hemorrhaging, insomnia, inflammation and respiratory infections. Flavones such as baicalin, wogonoside and their aglycones baicalein wogonin are the major bioactive compounds. The flavones have pharmacological functions like anticancer, hepatoprotective, antibacterial,

antiviral, antioxidant, anticonvulsant and neuroprotective effects (Zhao et al., 2016).

Anticancer activities: The bioactive components of *Scutellaria* include flavones in which the major constituents are wogonin, baicalein and baicalin. These are cytostatic and cytotoxic to various human tumour cell lines in turn inhibit tumour growth (Li-Weber, 2009). The anticancer activity of the flavones in *S. baicalensis* extract is well known in human leukemia cell lines that connected with reduction of high level reactive oxygen species, inflammatory reaction and NFκB activation. The extract also shows antiprostate and antibreast cancer activity (Lamer-Zarawska et al., 2010). The gold nanoparticles synthesized from the *S. barbata* by green route method exhibits anticancer activity against pancreatic cancer cell lines (PANC-1) that may lead to the development of novel anticancer drugs to combat pancreatic cancer (Wang et al., 2019). The cytotoxic properties of methanol extract of *S. litwinowii* roots lead to the inhibition of different cancer cell lines including AGS, HeLa, MCF-7, PC12 and NIH 3T3 (Tayarani-Najaran et al., 2011). The methanol extract of *S. orientalis* contains apigenin, baicalein, chrysin, luteolin and wogonin which correlate with cyclin D1 and Cdc25A suppression and p21 induction in turn cause potent antileukaemic properties through the antiproliferative effect of baicalein and the genotoxic property of wogonin (Ozmen et al., 2010).

2.14. *Teucrium* L.

Teucrium is a wild growing flowering herb or shrubs found in various regions such as Europe, North Africa and South Western Asia. The leaves show opposite phyllotaxy. Flowers usually small in whorls of 2-6 in axillary or terminal spike, raceme or head inflorescence. Calyx may be 2 lipped, 10 ribbed and 5 toothed. Corolla tube is not annulate with 1 lipped limb. In didynamous stamens, the lower pair is longest with exserted and reniform anthers. The four lobed ovary ends with bifid style. The genus is used for treating different diseases such as diabetes, rheumatologic diseases, inflammation and gastrointestinal disorders. The antioxidant property of *T. polium* is due to the presence of ortho-dihydroxy substitutions in the flavone B ring (Rafieian-Kopaei, 2014).

Anticancer activities: Crude extracts with the phytochemicals show potential anticancer properties. A methanolic extract obtained from *T. persicum* potently inhibits viability of PC-3 cells. The viability of SW480 colon and T47D breast cancer cells significantly decreases in presence of the extract (Tafrihi et al., 2014). *T. polium* shows the identification of 29 phytochemical compounds belonging to 13 classes of compounds and 20 tripeptides. In the species, 13R-hydroxy-9E,11Z octadecadienoic acid, dihydrosamidin, valtratum and cepharantine are the main compounds. Using the malignant Walker 256/B and MatLyLu cell lines, *T. polium* methanolic extract shows a dose or time dependent antitumour activity (Noumi et al., 2020). The phenolic compounds of the *T. chamaedrys* and *T. arduini* show best cytotoxic effects in HCT-116 cells and also the high apoptotic percentage (Stankovic et al., 2011). The stable silver nanoparticles synthesized using the leaf extract of *T. polium* exhibits significant anticancer activity against MNK45 human gastric

cancer cell line helps for further development of anticancer drugs (Hashemi et al., 2020).

1.15. *Rosmarinus* L.

Rosmarinus is a small taxonomic clade of woody, perennial herbs or subshrubs with fragrant evergreen needle like leaves. It is native to the Mediterranean and Asia, but is reasonably hardy in cool climates. Calyx is densely white stellate and tomentose type. The flowers are white, pink, purple or blue in colour with upper bilobed lip and trilobed lower lip. *Rosmarinus* uses in folk medicine to cure several diseases including headache, dysmenorrhea, stomach ache, epilepsy, rheumatic pain, spasms, nervous agitation, memory boosting, hysteria, depression as well as physical and mental fatigue. The main constituents in the plants are carnosic acid, carnosol, rosmarinic acid etc. that in turn results in antiinflammatory, antioxidant, antinociceptive, neuroprotective, antidepressant and antihysteric properties (Rahbardar, 2020).

Anticancer activities: *R. officinalis* includes a variety of phenolic compounds essential for basic cellular processes or macro and micro nutrient metabolisms. The main compounds are carnosic acid and carnosol. The extracts are very effective in treatment of different cancers affecting various parts like human colon, gastric areas, pancreatic gland, hepatic cells, lungs, cervical cells, skin, mouth, breast, kidney etc. (Allegra et al., 2020).

2. Outlook

The species of the family Lamiaceae with active compounds have the potential to inhibit the growth of different human cancer cell lines of lung, breast, prostate, colon etc.. The whole extracts and essential oils effect at the molecular level and reduce the proliferation of the tumour cells by checking the cell cycle in turn inhibit the metastasis. Therefore, the members of Lamiaceae are the sources of crucial phytochemicals that may be important modulators of cancer related molecular targets and can be used as effective factors to support antitumour treatment in present era.

References

1. Abdullah, F., Salleh, N. A. F., and Selahuddeen, M. L. (2021). Phytochemical and Toxicity Analysis of *Leucas zeylanica* crude extracts. *Environ. Toxicol. Manag.* 1(2):1-8.
2. Abedinpour, N., Ghanbariasad, A., Taghinezhad, A., and Osanloo, M. (2021). Preparation of nanoemulsions of *mentha piperita* essential oil and investigation of their cytotoxic effect on human breast cancer lines. *BioNanoScience.* 11:428-436.
3. Allegra, A., Tonacci, A., Pioggia, G., Musolino, C., and Gangemi, S. (2020). Anticancer activity of *Rosmarinus officinalis* L.: mechanisms of action and therapeutic potentials. *Nutrients.* 12(6):1739.
4. Al-Okbi, S. Y., Fadel, H. H., and Mohamed, D. A. (2015). Phytochemical constituents, antioxidant and anticancer activity of *Mentha citrata* and *Mentha longifolia. Res. J. Pharm. Biol. Chem. Sci.* 6(1):739-751.
5. Amado, N. G., Cerqueira, D. M., Menezes, F. S., da Silva, J. F. M., Neto, V. M., and Abreu, J. G. (2009). Isoquercitrin isolated from *Hyptis fasciculata* reduces glioblastoma cell proliferation and changes β-catenin cellular localization. *Anti-cancer drugs.* 20(7):543-552.
6. Anusmitha, K. M., Aruna, M., Job, J. T., Narayanankutty, A., Benil, P. B., Rajagopal, R. and Barcelo, D. (2022). Phytochemical analysis,

antioxidant, anti-inflammatory, anti-genotoxic, and anticancer activities of different *Ocimum* plant extracts prepared by ultrasound-assisted method. *Physiol. Mol. Plant Pathol.* 117:101746.

7. Arshad Qamar, K., Dar, A., S Siddiqui, B., Kabir, N., Aslam, H., Ahmed, S., and Begum, S. (2010). Anticancer activity of *Ocimum basilicum* and the effect of ursolic acid on the cytoskeleton of MCF-7 human breast cancer cells. Lett. *Drug Des. Discov.* 7(10):726-736.

8. Augustine, B. B., Dash, S., Lahkar, M., Sarma, U., Samudrala, P. K., and Thomas, J. M. (2014). *Leucas aspera* inhibits the Dalton's ascitic lymphoma in Swiss albino mice: A preliminary study exploring possible mechanism of action. *Pharmacog. Magazine.* 10(38): 118.

9. Barbosa, C. V., Aquino, P. G. V., Ribeiro-Júnior, K. A. L., Moura, F. B. P., Alexandre-Moreira, M. S., Sant'Ana, A. E. G., and Araujo-Júnior, J. X. (2012). Cytotoxic and antitumor activities of *Hyptis pectinata* (Sambacaitá) extract. *Pharmacologyonline.* 3:70-4.

10. Batsalova, T., Bardarov, K., Bardarov, V., Moten, D., and Dzhambazov, B. (2017). Cytotoxic properties of *Clinopodium vulgare* L. extracts on selected human cell lines. *Comptes rendus l'Academie Bulg. des Sci.* 70.

11. Benites, J., Rios, D., Guerrero-Castilla, A., Enriquez, C., Zavala, E., Ybanez-Julca., and Calderon, P. B. (2021). Chemical Composition and Assessment of Antimicrobial, Antioxidant and Antiproliferative Activities of Essential oil from *Clinopodium sericeum*, a Peruvian Medicinal Plant. *Records Nat. Prod.* 15(3).

12. Bhagat, J., Lobo, R., Kumar, N., Mathew, J. E., and Pai, A. (2014). Cytotoxic potential of *Anisochilus carnosus* (Lf) wall and estimation of luteolin content by HPLC. *BMC Compl. Altern. Med.* 14(1):1-9.

13. Boonyanugomol, W., Rukseree, K., Prapatpong, P., Reamtong, O., Baik, S. C., Jung, M., and Lee, W. K. (2021). An In Vitro Anti-Cancer Activity of *Ocimum tenuiflorum* Essential Oil by Inducing Apoptosis in Human Gastric Cancer Cell Line. *Medicina.* 57(8):784.

14. Cardile V., Russo A., and Formisano C. (2009). Essential oils of *Salvia bracteata* and *Salvia rubifolia* from Lebanon: Chemical composition, antimicrobial activity and inhibitory effect on human melanoma cells. *J. Ethnopharmacol.* 126:265–272.

15. Chavata, R., Datchanamurthy, S., and Kotteeswaran, V. (2019). Biofabrication of silver nanoparticles from aqueous leaf extract of *Leucas aspera* and their anticancer activity on human cervical cancer cells. *Advances in Natural Sciences: Nanosci. Nanotechnol.* 10(4): 045008.

16. Chitra, K., Sureshkumar, M., Vijayakumar, N., Ajarem, J. S., Allam, A. A., Kim, W., and Kumar, P. (2022). Synthesis of silver nanoparticles using *Leucas biflora* (Vahl) Sm. Leaf extracts and their activity on breast cancer (MDA-MB-231) cells. *Mat Lett.* 312:131706.

17. Choi J., Jiang X., Jeong JB., and Lee, S. H. (2014). Anticancer activity of protocatechualdehyde in human breast cancer cells. *J. Med. Food.* 17:842-848.

18. Esmaeili M. A., and Farimani M. M. (2014). Inactivation of PI3K/Akt pathway and upregulation of PTEN gene are involved in daucosterol, isolated from *Salvia sahendica*, induced apoptosis in human breast adenocarcinoma cells. *S. Afr. J. Bot.* 93:37-47.

19. Feng, C. P., Tang, H. M., Huang, S., Hou, S. Z., Liang, J., Huang, W., and Lai, X. P. (2016). Evaluation of the effects of the water-soluble total flavonoids from *Isodon lophanthoides* var. *gerardianus* (Benth.) H. Hara on apoptosis in HepG2 cell: investigation of the most relevant mechanisms. *J. Ethnopharmacol.* 188:70-79.

20. Fiore, G., Nencini, C., and Cavallo, F. (2006). In vitro antiproliferative effect of six *Salvia* species on human tumor cell lines. *Phytother. Res.* 20:701-703.

21. Gajendiran, A., Thangaraman, V., Thangamani, S., Ravi, D., and Abraham, J. (2016). Antimicrobial, antioxidant and anticancer screening of *Ocimum basilicum* seeds. *Bull. Pharm. Res.* 6(3):114-119.

22. Garcia, C., Ntungwe, E., Rebelo, A., Bessa, C., Stankovic, T., Dinic, J., and Rijo, P. (2019). Parvifloron D from *Plectranthus strigosus*: Cytotoxicity screening of *Plectranthus* spp. extracts. *Biomol.* 9(10): 616.

23. Gupta, N., Lobo, R., Kumar, N., Bhagat, J. K., and Mathew, J. E. (2015). Identity-based High-performance thin layer chromatography fingerprinting profile and tumor inhibitory potential of *Anisochilus carnosus* (Lf) wall against ehrlich ascites carcinoma. *Pharmacog. Magazine.* 11(3):S474.

24. Gurunagarajan, S., and Pemaiah, B. (2011). Comparative studies on cytotoxic effect of *Hyptis suaveolens* Poit. and *Leonotis nepeatefolia* R. Br. against EAC cell lines. *J. Pharm. Resear.* 4(4): 1222-1224.

25. Hashemi, S. F., Tasharrofi, N., and Saber, M. M. (2020). Green synthesis of silver nanoparticles using *Teucrium polium* leaf extract and assessment of their antitumor effects against MNK45 human gastric cancer cell line. *J. Mol. Stru.* 1208:127889.

26. Jain, D., Pathak, N., Khan, S., Raghuram, G. V., Bhargava, A., Samarth, R., and Mishra, P. K. (2011). Evaluation of cytotoxicity and anticarcinogenic potential of *Mentha* leaf extracts. *Inter. J. Toxicol.* 30(2):225-236.

27. Jeong, J. B., Choi, J., Lou, Z., Jiang, X., and Lee, S. H. (2013). Patchouli alcohol, an essential oil of *Pogostemon cablin*, exhibits anti-tumorigenic activity in human colorectal cancer cells. *Inter. Immunopharmacol.* 16(2):184-190.

28. Kamatou, G. P. P., Van Zyl, R. L., Davids, H., Van Heerden F. R., Lourens A. C. U., and Viljoen AM. (2008). Antimalarial and anticancer activities of selected South African *Salvia* species and isolated compounds from *S. radula. S. Afr. J. Bot.* 74:238 –243.

29. Karthikeyan, K., Gunasekaran, P., Ramamurthy, N., and Govindasamy, S. (1999). Anticancer activity of *Ocimum sanctum. Pharm. Biol.* 37(4):285-290.

30. Kelkawi, A. H. A., Abbasi Kajani, A., and Bordbar, A. K. (2017). Green synthesis of silver nanoparticles using *Mentha pulegium* and investigation of their antibacterial, antifungal and anticancer activity. *IET Nanobiotech.* 11(4):370-376.

31. Kingston, D. G., Rao, M. M., and Zucker, W. V. (1979). Plant anticancer agents. IX. Constituents of *Hyptis tomentosa. J. Nat. Prod.* 42(5):496-499.

32. Kumar, S. N., Yanadaiah, J. P., Ravindrareddy, K., and Kumar, K. M. (2011). Analgesic activity of aqueous ethanolic extract of whole plant of *leucas hirta* in Swiss albino mice. *J. Pharm. Resear.* 4(3): 874-876.

33. Lamer-Zarawska, E., Wisniewska, A., and B ach-Olszewska, Z. (2010). Anticancer properties of *Scutellaria baicalensis* root in aspect of innate immunity regulation. *Adv. Clin. Exp. Med.* 19(4): 419-428.

34. Lee J. R., Lee M. H., and Eo H. J. (2014). The contribution of activating transcription factor 3 to apoptosis of human colorectal cancer cells by protocatechualdehyde, a naturally occurring phenolic compound. *Arch. Biochem. Biophys.* 64: 203–210.

35. Li-Weber, M. (2009). New therapeutic aspects of flavones: the anticancer properties of *Scutellaria* and its main active constituents Wogonin, Baicalein and Baicalin. *Cancer Treat. Rev.* 35(1):57-68.

36. Maheswari, P., Harish, S., Ponnusamy, S., and Muthamizhchelvan, C. (2021). A novel strategy of nanosized herbal *Plectranthus amboinicus, Phyllanthus niruri* and *Euphorbia hirta* treated TiO2 nanoparticles for antibacterial and anticancer activities. *Bioprocess Biosyst. Eng.* 44:1593-1616.

37. Manjamalai, A., and Grace, V. B. (2013). The chemotherapeutic effect of essential oil of *Plectranthus amboinicus* (Lour) on lung metastasis developed by B16F-10 cell line in C57BL/6 mice. *Cancer Investig.* 31(1):74-82.

38. Merecz-Sadowska, A., Sitarek, P., Sliwinski, T., Zajdel, K., Malinowska, K., Zielinska-Blizniewska, H., and Zajdel, R. (2022). In Vitro and In Silico Studies on *Leonotis nepetifolia* (L.) R. Br. Root Extract against Cancer Cells. *Current Pharm. Biotechnol.*

39. Muniyandi, K., George, E., Mudili, V., Kalagatur, N. K., Anthuvan, A. J., Krishna, K., and Natarajan, G. (2017). Antioxidant and anticancer activities of *Plectranthus stocksii* Hook. f. leaf and stem extracts. *Agri. Nat. Resources.* 51(2):63-73.

40. Nagaraja, S. K., Nayaka, S., and Kumar, R. S. (2022). Phytochemical Analysis, GC–MS Profiling, and In Vitro Evaluation of Biological Applications of Different Solvent Extracts of *Leonotis nepetifolia* (L.) R. Br. Flower Buds. *Appl. Biochem. Biotech.* 1-19.

41. Neelamkavil, S. V., and Thoppil, J. E. (2016). Evaluation of the anticancer potential of the traditional medicinal herb *Isodon coetsa. South Ind. J. Biol. Sci.* 2:41-45.

42. Noumi, E., Snoussi, M., Anouar, E. H., Alreshidi, M., Veettil, V. N., Elkahoui, S., and Badraoui, R. (2020). HR-LCMS-based metabolite profiling, antioxidant, and anticancer properties of *Teucrium polium* L. methanolic extract: Computational and in vitro study. *Antioxidants.* 9(11): 1089.

43. Ozmen, A., Madlener, S., Bauer, S., Krasteva, S.,

Vonach, C., Giessrigl, B., and Krupitza, G. (2010). In vitro anti-leukemic activity of the ethno-pharmacological plant *Scutellaria orientalis* ssp. carica endemic to western Turkey. *Phytomedicine.* 17(1):55-62.

44. Perna, S., Alawadhi, H., Riva, A., Allegrini, P., Petrangolini, G., Gasparri, C., and Rondanelli, M. (2022). In Vitro and In Vivo Anticancer Activity of Basil (*Ocimum* spp.): Current Insights and Future Prospects. *Cancers.* 14(10):2375.

45. Peron, G., Hosek, J., Prasad Phuyal, G., Raj Kandel, D., Adhikari, R., and Dall'Acqua, S. (2020). Comprehensive Characterization of Secondary Metabolites from *Colebrookea oppositifolia* (Smith) Leaves from Nepal and Assessment of Cytotoxic Effect and Anti-Nf-κB and AP-1 Activities in Vitro. *Inter. J. Mol. Sci.* 21(14):4897.

46. Picking, D., Delgoda, R., Boulogne, I., and Mitchell, S. (2013). *Hyptis verticillata* Jacq: A review of its traditional uses, phytochemistry, pharmacology and toxicology. *J. Ethnopharmacol.* 147(1):16-41.

47. Poonkodi, K., Karthika, J., Tamilselvi, V., Anitha, R., and Vasanthamani, S. (2017). Chemical composition of essential oil of *Hyptis suaveolens* (L) Poit and its invitro anticancer activity. *J. Pharm. Resear.* 11(5):410-413.

48. Ramnath, M. G., Thirugnanasampandan, R., Mathusalini, S., and Mohan, P. S. (2016). Hepatoprotective and cytotoxic activities of abietic acid from *Isodon wightii* (bentham) *H. hara. Pharm. Res.* 8(3):206.

49. Rahbardar, M. G., and Hosseinzadeh, H. (2020). Therapeutic effects of rosemary (*Rosmarinus officinalis* L.) and its active constituents on nervous system disorders. *Iran. J. Bas. Med. Sci.* 23(9): 1100.

50. Sajitha Menon, K., and Thoppil, J. E. (2022). Metabolite Profiling of Bioactive Compounds in Selected Species of *Gomphostemma* Wall. ex Benth. from the Western Ghats by GC-MS Analysis. In *Natural Product Experiments in Drug Discovery.* New York, NY: *Springer US.* 97-107.

51. Sajitha, M. K., and Thoppil, J. E. (2018). Screening of cytotoxicity, metabolic inhibition and possible apoptotic cell death induced by *Gomphostemma heyneanum* Wall. ex Benth. var. *heyneanum* using *Allium cepa* root tips. *Int. J. Pharm. Biol. Sci.* 8(2): 56-64.

52. Sharifi, S., Naseri, N., Fathiazad, F., Asnaashari, S., and Hamedeyazdan, S. (2022). Anticancer effect of buddlejasaponin IV and buddlejasaponin IVa from *Clinopodium umbrosum* on oral cancer cells (HN-5). *Toxicon.* 220:106939.

53. Sharma, V., Hussain, S., Gupta, M., and Saxena, A. K. (2014). In vitro anticancer activity of extracts of *Mentha* spp. against human cancer cells. *NISCAIR-CSIR*, India. 51(5):416-419

54. Sheela, A., and Thoppil, J. E. (2017). Evaluation of cytotoxicity of the aqueous leaf extract of *Pogostemon heyneanus* Benth.(Java Patchouli). *Biotropia-The Southeast Asian J. Trop. Biol.* 24(1):28-34.

55. Sindhu, M. S., Poonkothai, M., and Thirumalaisamy, R. (2022). Phenolic and terpene compounds from *Plectranthus amboinicus* (Lour.) Spreng act as promising hepatic anticancer agents screened through in silico and in vitro approaches. *South Afr. J. Bot.* 149: 145-159.

56. Sinha, V. S., and Kumar, N. (2014). Genotoxic effects of *Ocimum basilicum* L and *Leucas zeylanica* L. in root tip cells of *Allium cepa* L. *J. Ind. Bot. Soc.* 93(2):135-139.

57. Sitarek, P., Synowiec, E., Kowalczyk, T., Bangay, G., Sliwinski, T., Picot, L., and Rijo, P. (2022). Anticancer Properties of *Plectranthus ornatus*-Derived Phytochemicals Inducing Apoptosis via Mitochondrial Pathway. *Int. J. Mol. Sci.* 23(19):11653.

58. Sowjanya, M., Venkata Sandeep, B., Venkaiah, K., Dirisala, V. R., Reddy, M. H., Pradeepkiran, J. A., and Sainath, S. B. (2022). Purification, Structural Elucidation, and Anticancerous Properties of a Novel Flavonoid from Flowers of *Leucas indica. Processes.* 10(11):2341.

59. Stankovic, M. S., Curcic, M. G., Zizic, J. B., Topuzovic, M. D., Solujic, S. R., and Markovic, S. D. (2011). *Teucrium* plant species as natural sources of novel anticancer compounds: antiproliferative, proapoptotic and antioxidant properties. *Int. J. Mol. Sci.* 12(7):4190-4205.

60. Suruthi, M., Sivabalakrishnan, S., Yuvasri, G., Ragunathan, R., and Johney, J. (2016). Antioxidant anticancer activity of *Leucas aspera* plant extract and its dna damage study on he-la cell lines. *Res. J. Lif. Sci. Bioinf. Pharm. Chem. Sci.* 2(2):1-9.

61. Susmi, T. F., Khan, M. M. R., Rahman, A., Mahmud, S., Saleh, M. A., Reza, M. A., and Rahi, M. S. (2022). In vitro antioxidant and cytotoxicity activities and *in silico* anticancer property of

methanolic leaf extract of *Leucas indica*. *Informatics in Medicine Unlocked*. 100963.

62. Tafrihi, M., Toosi, S., Minaei, T., Gohari, A. R., Niknam, V., and Arab Najafi, S. M. (2014). Anticancer properties of *Teucrium persicum* in PC-3 prostate cancer cells. *Asian Pac. J. Cancer Prev.* 15(2):785-791.

63. Tayarani-Najaran Z., Mousavi S. H., Tajfard F. (2013). Cytotoxic and apoptogenic properties of three isolated diterpenoids from *Salvia chorassanica* through bioassay-guided fractionation. *Food Chem. Toxicol.* 57:346–351.

64. Tayarani-Najaran, Z., Emami, S. A., Asili, J., Mirzaei, A., and Mousavi, S. H. (2011). Analyzing cytotoxic and apoptogenic properties of *Scutellaria litwinowii* root extract on cancer cell lines. *Evidence-Based Complementary and Alternative Medicine*.

65. Thirugnanasampandan, R., and Jayakumar, R. (2009). Cytotoxic and anticarcinogenic activity of the ent-kaurene diterpenoid, melissoidesin, from *Isodon wightii* (Bentham) H. Hara. *Nat. Prod. Res.* 23(16):1499-1506.

66. Tobungan, N., Jati, W. N., and Zahida, F. (2022). Acute toxicity and anticancer potential of knobweed (*Hyptis capitata*) ethanolic leaf extract and fraction. *Plant Sci. Today.* 9(4):955-962.

67. Topcu G., Turkmen Z., Schilling J. K., Kingston DGI., Pezzuto J. M., and Ulubelen A. (2008) . Cytotoxic activity of some *Anatolian Salvia* extracts and isolated abietane diterpenoids. *Pharm. Biol.* 46:180–184.

68. Torres-Martinez, Y., Arredondo-Espinoza, E., Puente, C., González-Santiago, O., Pineda-Aguilar, N., Balderas-Renteria, I., and Ramírez-Cabrera, M. A. (2019). Synthesis of silver nanoparticles using a *Mentha spicata* extract and evaluation of its anticancer and cytotoxic activity. *Peer. J.* (7):8142.

69. Twilley, D., Langhansova, L., Palaniswamy, D., and Lall, N. (2017). Evaluation of traditionally used medicinal plants for anticancer, antioxidant, anti-inflammatory and anti-viral (HPV-1) activity. *South Afr. J. Bot.* 112:494-500.

70. Ulubelen A., Topçu G., Chai HB., and Pezzuto JM. (1999). Cytotoxic activity of triterpenoids isolated from *Salvia hypargeia. Pharm. Biol.* 37:148–151.

71. Veerabadran, U., Venkatraman, A., Souprayane, A., Narayanasamy, M., Perumal, D., Elumalai, S., and Perumal, A. (2013). Evaluation of antioxidant potential of leaves of *Leonotis nepetifolia* and its inhibitory effect on MCF7 and Hep2 cancer cell lines. *Asian Pac. J. Trop. Dis.* 3(2):103-110.

72. Vermaa, R., Tapwalb, A., Kumara, D., and Puria, S. (2020). Phytochemical profiling and biological activity of *Leucas lanata* Benth. An important ethnomedicinal plant of Western Himalaya. *Ecol. Environ. Conserv.* 26:169-175.

73. Wang, H., Ye, Y., Pan, S. Y., Zhu, G. Y., Li, Y. W., Fong, D. W., and Yu, Z. L. (2011). Proteomic identification of proteins involved in the anticancer activities of oridonin in HepG2 cells. *Phytomedicine.* 18(2-3):163-169.

74. Wang, L., Xu, J., Yan, Y., Liu, H., Karunakaran, T., and Li, F. (2019). Green synthesis of gold nanoparticles from *Scutellaria barbata* and its anticancer activity in pancreatic cancer cell (PANC-1). *Artif. Cells Nanomed. Biotechnol.* 47(1):1617-1627.

75. Ximenes, R. M., Melo, A. M., Magalhães, L. P. M., de Souza, I. A., and de Albuquerque, J. F. C. (2012). Antitumor activity of leaves from *Hyptis mutabilis* (A. Rich.) Briq. (Lamiaceae) in mice bearing tumor. *Dataset Papers in Pharmacol.*

76. Yang, H., Zhang, X., Velu, P., Liu, X., and Vijayalakshmi, A. (2022). Enhanced green mediated synthesis of optimized Ag-Cu bimetallic nanoparticles using *Leucas aspera* and its application in Anti-cancer activity against alveolar cancer. *Mater. Lett.* 313:131645.

77. Yu, Z. Y., Liang, Y. G., Xiao, H., Shan, Y. J., Dong, B., Huang, R., and Cong, Y. W. (2007). Melissoidesin G, a diterpenoid purified from Isodon melissoides, induces leukemic-cell apoptosis through induction of redox imbalance and exhibits synergy with other anticancer agents. *Inter. J. Cancer.* 121(9):2084-2094.

78. Yun, S. G., Jin, S., Jeong, H. Y., Yun, H. J., Kim, B. W., and Kwon, H. J. (2015). Anti-oxidant, anti-inflammatory and anti-cancer effect of methanol extract of *Pogostemon cablin. J. Life Sci.* 25(1):44-52.

79. Zhao P. W., Niu J. Z., Wang D. W., Chen J. X., and Wang L. Q. (2007). Phytoestrogenic effects of six active components in Chinese medicine. *Chin. Pharm. J.* 42:1852–1855.

80. Zhao, C., Zhou, L., Xie, W., Zhao, L., Zhang, C., He, K., and Zhang, H. (2022). Bioactive isopimarane and 3, 4-seco isopimarane diterpenoids from *Isodon amethystoides. BMC chem.* 16(1):1-11.

Evaluation of Anticancer Activity in Amaranthaceae Members

***Jaseela M.P., Janeesha A.P.**

PG Department of Botany, PSMO College
Tirurangadi, Malappuram, 676306, Kerala, India.
*Corresponding author: jaseelamp10@gmail.com

Abstract: Cancer, one of the dreadful diseases, is a rising burden for the worldwide. The people look for an alternative treatment solution to avoid the side effects that causing by chemical or radiation therapies. Herbal medicine provides a very feasible alternative to modern medicine against cancer. The herbal plants in Amaranthaceae play predominant roles in medicines against different types of human cancer by inhibiting the proliferation, metastasis and apoptosis of cell lines.

Keywords: Amaranthaceae, medicinal, anticancerous, cytotoxicity, ethnobotany

The dreadful disease, Cancer, severely affects the human population. The available medical treatments like chemotherapy can damage the health of the patient. From ancient time itself, the herbal medicines have been used as the source of medicines for various diseases. According to the World Health Organization (WHO), some nations still reply of plant based treatment as their main source of medicine and developing nations are utilizing the benefits of naturally sourced compounds for therapeutic purposes (Rao et al., 2002). Keeping this fact, an attempt has been made to analyze the work being carried out all over the world about the plants which are used as anticancerous agents. Since the naturally derived plant products are less toxic, scientists and researchers starts to pay more attention in this field now.

The presence of secondary metabolites is the reason behind the medicinal properties of all the plants. Thus researchers have developed in to investigating the potential properties and uses of terrestrial plant extracts for the preparation of nanomaterial based drugs for diseases including cancer (Sivaraj et al., 2014). Many plant species are already being used to treat or prevent development of cancer. Multiple researchers have identified species of plants that have demonstrated anticancer properties with a lot of focus on those that have been used in herbal medicine in developing countries (Frieburghaus et al., 1996; Ochwang et al., 2014). Over 60% of anticancer agents have been derived from natural sources (Cragg & Newman, 2005). Amaranthaceae is such a family with lots of potential as medicine, and also many members are reported to have anticancer properties.

Amaranthaceae contains annual or

perennial, dioecious, monoecious or polygamous herbs, shrubs or rarely trees. It is composed of approximately 800 species of 60 genera with two sub families, Amaranthoideae with Gomphrenoideae (Iamonico, 2020). The family has a largely worldwide distribution and the members are common in deserts, estuarine or alkaline regions, tropical areas and some temperate regions (Simpson, 2010). The members of the family which are commonly used as a medicine for cancer treatment are *Achyranthes, Aerva, Amaranthus, Alternanthera, Celosia* and *Cyathula.*

1. Anticancer plants in Amaranthaceae

1.1. *Achyranthes* L.

Achyranthes is also known as 'Chaff Flower' which are mostly perennial or annual herbs. Stem is erect to ascending with opposite leaves. Inflorescences are terminal and axillary, pedunculate, elongate, many flowered, simple spikes or few branched panicles. Flowers crowded together at tips, becoming more widely spaced toward base. The bisexual flowers often become deflexed with age and bear 4 or 5 tepals. Utricles are indehiscent and one seeded (Robertson, 1981). The plants are distributed in Central and South-East United States, Mexico, West Indies, Central America, South America, tropical, subtropical and warm-temperate regions of the Old World.

The genus includes two famous medicinal species namely *A. bidentata* and *A. aspera. A. bidentata* which has used for the treatment of various diseases including amenorrhea, dysmenorrhea, lumbago, gonalgia, paraplegia, edema, stranguria, headache, dizziness, odontalgia, oral ulcer, hematemesis and epistaxis (He et al., 2017). *A. aspera* is a well known medicinal plant used commonly in ayurvedic, Unani-Tibbi, Siddha, allopathic, homeopathic, naturopathic and home Remedies (Dhale & Bhoi, 2013). Different parts of the plant and the plant as a whole are used for medicinal purpose. The plant is bitter, pungent, heating, laxative, stomachic, carminative, and traditionally it is used to treat fever, dysentery, diabetes, vomiting, bronchitis, heart disease, piles, itching, abdominal pains, ascites, dyspepsia, blood diseases, tooth ache, gonorrhoea, cough and stomachic and digestive problems (Girach et al., 1992; Chopra, 1933; Rangari, 2006; Dwivedi et al., 2007). The addition of *A. aspera* would enhance the efficacy of any drug of plant origin and can used as a supporting agent (Hasan, 2014).

Anticancer activities: *A. aspera* suppresses the cell proliferation and increases cytotoxicity in colon cancer cells. This ability could be attributed to the induction of apoptosis via the mitochondria mediated pathway and arresting the cells in S phase of cell cycle in COLO-205 cells. They could promote the release of cytochrome c by regulating Bcl-2 family proteins and activate caspase-9/-3 to trigger cell apoptosis, decrease Akt-1transcription (Subbarayan et al., 2012; Arora & Tandon, 2014; Omidiani et al., 2020). The extract from *A. aspera* has cytotoxic effects against VERO (monkey healthy kidney epithelial) cells, AGS (human stomach cancer cells), MCF-7 (human breast cancer cell line), A549 (human lung cancer cells) and COLO 320 DM (human colon cancer cell line) (Baskar et al., 2012). The leaves of *A. aspera* contain anti-proliferative compounds with specific activity against

pancreatic cancer (Subbarayan et al., 2012). At the same time, in Dalton's Lymphoma (DL) cells treated with methanolic extract, the protein kinase Cα (PKCα) pathway inhibits in a concentration-dependent manner. (Singh et al., 2021). *A. aspera* roots extract in acetone has the maximum cytotoxicity against HeLa, colon and liver cancer cell lines (Singh et al., 2017; Omidiani et al., 2020).

1.2. *Aerva* Forssk.

Aerva species are perennial herbs with salient morphological characters. They constitute prostrate to erect stem, alternate branches and leaves with entire margins, hermaphrodite flowers, oval or oblong perianth and membranous and margined sepals. Flowers usually bear five stamens which are shortly monadelphous at the base. The single pendulous ovule containing ovary possesses slender and distinct short style. Two stigmas are present which are short to long and thread like. The seeds are compressed which are reniform, firm and black (Alwadie, 2005). There are approximately 28 species of *Aerva* species, but only a few are medicinal of which *A. persica, A. lanata* and *A. javanica* exhibit great medicinal values. A number of flavonol glycosides including aervanone, kaempferol-3-galactoside and isorhamnetin-3-O-β-D-glucoside, are the major phytoconstituents in *A. persica* and the minor constituents include β-cyanins (glycine betaine and trigonelline), sterols and carbohydrates (Chawla et al., 2012). *A. lanata* is an important medicinal plant widely used in traditional systems of medicine like ayurveda and Siddha. It belongs to the Pashanbheda group of plants used to cure urinary stones. The plant possesses a wide variety of healing applications in traditional and folklore medicines of various geographical locations. It comprises of an extensive range of phytochemicals such as canthin-6-one, β-carboline alkaloids, flavonoids, phenolic acids, steroids and terpenoids. Due to the presence of the phytocompounds, the plant bears anti-urolithiatic, diuretic, hepatoprotective, anticancer, immunomodulatory, antioxidant, antimicrobial and numerous other pharmacological activities (Mandal & Madan, 2016).

Anticancer activities: Ethanolic extract of whole plant of *A. lanata* exhibits immunomodulatory and antitumour activity. It enhances the total WBC count, bone marrow cellularity and number of α-esterase-positive cells (Siveen & Kuttan, 2012; Kumar et al., 2013). Treatment also shows enhanced proliferation of splenocytes, thymocytes and bone marrow cells both in the presence and absence of specific mitogens in vitro and in vivo. Both aqueous and ethanolic extracts decrease the average increase in body weight, reduce the packed cell volume and viable tumour cell count and increase the life span of Dalton's Ascitic Lymphoma (DAL) treated mice in turn brought back the haematological parameters, serum enzyme and lipid profile near to normal values (Rajesh et al., 2011).

1.3. *Alternanthera* Forssk.

The members of the genus are annual or perennial herb with prostrate or ascending stems and simple leaves. Inflorescence is axillary and terminal, sessile or peduncled, many flowered cylindric spikes or spheric heads with persistent bracts and bract lets. Flowers are bisexual, white, glabrous or woolly with 3-5 stamens fused at base into short tube and 5

pseudo staminodes alternate with stamens. The plants have an ovoid to spheric ovary with short style and stigma. Fruits are indehiscent with one seed. The genus comprises about 170 species worldwide and generally distributed in tropical America (Iamonico & Pino, 2016).

Anticancer activities: Some members of *Alternanthera* are widely using in the treatment of cancer. The cytotoxicity of *A. sessilis* plant parts induces anticlonogenic property on the HT 29 cancer cells and causes cell growth inhibition and activation of apoptosis (Hanahan et al., 2014). The plant parts act in a dosage dependent manner and the ethanolic leaf extracts become active for the treatment of colon cancer (Gothai et al., 2018). Similar to this, the ethyl acetate extract of *A. brasiliana* shows significant decrease in tumour volume, viable cell count, tumour weight and life span of EAC tumour bearing mice in a dose dependent manner (samudrala, 2015). At the same time, the hematological profile count of RBC, hemoglobin and WBC revert to normal level. The cytotoxic, antiproliferative and antimigratory properties of ethanol based extracts of the aerial portions of *A. bettzickiana* inhibit the cell growth and proliferation of breast (MCF-7), liver (HepG2) and cervical (HeLa) cancer cells (Saengha et al., 2022).

1.4. *Amaranthus* L.

The plants are typically annuals or short lived herbs. The stem of monoecious or dioecious is armed with spines and bears simple alternately arranged leaves. The small flowers arranged in dense showy inflorescences. A single plant can produce hundreds or thousands of seeds, borne singly in dry capsule fruits. The plants utilize a photosynthetic pathway known as C4 carbon fixation, which largely prevents photorespiration and thus increases drought tolerance. Several species of Amaranth utilize for food as well as medicines by native tribal people in many countries.

Anticancer activities: Methanolic extracts of *Amaranthus* spinosus have the ability to inhibit cell proliferation and induce apoptosis in cancers of breast (MCF-7), colorectal (HT-29), liver (HEP-G2) and normal cell lines (Rajashekaran et al., 2014). The upregulation of p53, Bax and caspase-3 and downregulation of Bcl-2 mRNA in *Amaranthus* treated mice indicates the mitochondria mediated apoptosis of EAC cells (Al-Mamun, 2016). The ethyl acetate extracts of *A. viridis* and *A. spinosus* show greater anticancer activities against HT-29 and Hep G2 cancer cells (Jin et al., 2013).

1.5. *Cyathula* Blume

The species under *Cyathula* are prickly chaff flowering plant. It is a small sized weed, reaching height up to 10-20 cm height. Stems are violetish red in colour and the leaves are simple, opposite, exstipulate, short petioled, rhomboid or ovate (Vijayakumar et al., 2014).

Anticancer activities: Of the members of the genus, *C. prostrata* has high potential as an anticancer drug. Methanolic extract of *C. prostrata* leaves has antitumour activity which reduces the tumour growth, viability of tumour cells and raising life span by preventing the lipid peroxidation in turn promoting the antioxidant systems in Dalton's lymphoma ascites induced mice (Priya et al., 2013). The extract of *C. prostrata* induces apoptosis via the extrinsic pathway, and this activation is

independent of the mitochondria. The extract acts through multiple targets by inducing cell cycle arrest in the G1 phase through an unknown mechanism, apoptosis through an extrinsic death receptor pathway and replicative senescence through inhibition of telomerase (Schnablegger, 2010).

1.6. *Celosia* L.

Celosia species are annual or perennial herbs, edible and ornamental plants, consisting of about 60 species worldwide, is native to subtropical and temperate zones of Africa, South America, and South East Asia. The flowers are edible and ornamental. The generic name is derived from the Greek word kelos, meaning "burned," and refers to the flame like flower heads. If the flower heads are crested by fasciation; it is called as 'Velvet flower' (Thorat, 2018)

Anticancer activities: *C. argentea* consists of 2 important phytoconstituents; a flavonoid, luteolin-7-O-glucoside (Compound 1), and a phenolic compound, 1-(4-hydroxy-2-methoxy-benzofuran-5-yl)-3-phenylpropane-1,3-dione (Compound 2). Presence of benzopyran and hydroxyl groups in compound 1 and benzofuran, dione, and hydroxyl groups in compound 2 serve a basis for their anticancer potential (Rub et al., 2016).

2. Outlook

Anticancer agents discovered from medicinal plants have played a major role in cancer treatment. It is documented that medicinal herbs have rich anticancer potential due to their immunomodulatory and antioxidant properties. Many studies have reported inhibition of enzymes that stops tumour growth. Studies are needed to highlight the mechanism of anticancer action of many already explored and many unexplored plants. Among the family Amaranthaceae, the members of the genera *Achyranthes, Aerva, Alternanthera, Amaranthus* and *Cyathula* are widely using for the treatment.

References

1. Al-Mamun, M.A., Husna, J., Khatun, M., Hasan, R., Kamruzzaman, M., Hoque, K.M.F., Reza, M.A., and Ferdousi, Z. (2016). Assessment of antioxidant, anticancer and antimicrobial activity of two vegetable species of *Amaranthus* in Bangladesh. *BMC Compl. Alt. Medicine.* 16(1):1-11.
2. Alwadie, H.M. (2005). Morphology and distribution of three genera of *Amaranthaceae* in the south western area of Saudi Arabia. *J. King Saud Uni. Sci.* 18:51-62.
3. Arora, S., and Tandon, S. (2014). *Achyranthes aspera* root extracts induce human colon cancer cell (COLO-205) death by triggering the mitochondrial apoptosis pathway and S phase cell cycle arrest. *Sci. World J.*
4. Baskar, A.A., Al. Numair, K.S., Alsaif, M.A., and Ignacimuthu, S. (2012). In vitro antioxidant and antiproliferative potential of medicinal plants used in traditional Indian medicine to treat cancer. *Red. Report.* 17(4):145156.
5. Bitasta, M., and Madan, S. (2016). *Aerva lanata*: A blessing of Mother Nature. *J. Pharmaco. Phytochem.* 5(1):92.
6. Chawla, P., Chawla, A.M.I.T., Vasudeva, N.E.E.R.U., and Sharma, S.K. (2012). A review of chemistry and biological activities of the genus *Aerva* - a desert plant. *Acta. Pol. Pharm.* 69(2):171-177.
7. Chopra, R N. (1933). Indigenous drug of India. The Art Press, Calcutta.
8. Cragg, G.M., and Newman, D.J. (2005). Plants as a

source of anti-cancer agents. *J. Ethnopharm.* 100(1-2):72-79.

9. Dhale, D.A., and Bhoi, S. (2013). Pharmacognostic Characterization and Phytochemical Screening of *Achyranthes aspera* Linn. *Curr. Agric. Res. J.* 1(1):51.
10. Dwivedi, S.N., Satyaendra, S., Sangeeta, D., Abhishek, D., Sumeet, D., and Shefali, K. (2007). Relevance of medicinal herbs used in traditional system of medicine. *Farmavita. Net.*
11. Freiburghaus, F., Kaminsky, R., Nkunya, M.H.H., and Brun, R. (1996). Evaluation of African medicinal plants for their in vitro trypanocidal activity. *J. Ethnopharmacol.* 55(1):1-11.
12. Girach, R.D., Ahmad, A., and Ahmad, M. (1998). Medicinal ethnobotany of Sundargarh, Orissa, India. *Pharm. Biol.* 36(1):20-24.
13. Gothai, S., Muniandy, K., Esa, N.M., Subbiah, S.K., and Arulselvan, P. (2018). Anticancer potential of *Alternanthera sessilis* extract on HT-29 human colon cancer cells. *Asian Pac. J. Trop. Biomed.* 8(8):394.
14. Hanahan, D., and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. *Cell.* 144(5): 646-674.
15. Hasan, S. (2014). Pharmacological and medicinal uses of *Achyranthes aspera. Int. J. Sci. Environ. Tech.* 3(1):123-129.
16. He, X., Wang, X., Fang, J., Chang, Y., Ning, N., Guo, H., Huang, L., and Huang, X. (2017). The genus *Achyranthes*: A review on traditional uses, phytochemistry, and pharmacological activities. *J. Ethnopharmacol.* 203:260-278.
17. Iamonico, D. (2020). A nomenclatural survey of the genus *Amaranthus* (Amaranthaceae) 7: names published by Willdenow. *Willd.* 50(1):147-155.
18. Iamonico, D., and Pino, S.I. (2016). Taxonomic revision of the genus *Alternanthera* (Amaranthaceae) in Italy. *Plant Biosyst.* 150(2):333-342.
19. Kumar, S., and Pandey, A.K. (2013). Chemistry and biological activities of flavonoids: an overview. *Sci. World J.*
20. Ochwangi, D.O., Kimwele, C.N., Oduma, J.A., Gathumbi, P.K., Mbaria, J.M., and Kiama, S.G. (2014). Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya. *J. Ethnopharmacol.* 151(3):1040-1055.
21. Omidiani, N., Datkhile, K.D., and Barmukh, R.B. (2020). Anticancer potentials of leaf, stem, and root extracts of *Achyranthes aspera* L. *Not. Sci. Biol.* 12(3):546-555.
22. Priya, K., Krishnakumari, S., and Vijayakumar, M. (2013). *Cyathula prostrata*: A potent source of anticancer agent against daltons ascites in Swiss albino mice. *Asian Pac. J. Trop. Med.* 6(10):776-779.
23. Rajasekaran, S., Dinesh, M.G., Kansrajh, C., and Baig, F.H.A. (2014). *Amaranthus spinosus* leaf extracts and its anti-inflamatory effects on cancer. *Ind. J. Res. Pharm. Biotech.* 2(1):1058.
24. Rajesh, R., Chitra, K., Paarakh, P.M., and Chidambaranathan, N. (2011). Anticancer activity of aerial parts of *Aerva lanata* Linn Juss ex Schult against Dalton's Ascitic Lymphoma. *Eur. J. Integr.Med.* 3(3):245-250.
25. Rangari, V.D. (2006). Pharmacognosy and Phytochemistry. Part II. Carrer publication. 179-180.
26. Rao, Y.V., Govinda, R.D., Babu, G.S., and Rao, R.A. (2002). Immunomodulatory activity of *Achyranthes aspera* on the elicition of antigen-specific murine antibody response. *Pharm. Biol.* 40(3): 175-178.
27. Robertson, K.R. (1981). The genera of Amaranthaceae in the southeastern United States. *J. Arnold Arbor.* 62(3):267-313.
28. Rub, R. A., Pati, M. J., Siddiqui, A. A., Moghe, A. S., and Shaikh, N. N. (2016). Characterization of anticancer principles of *Celosia argentea* (Amaranthaceae). *Pharmacognosy research.* 8(2):97.
29. Saengha, W., Karirat, T., Buranrat, B., Katisart, T., Ling, N., and Luang-In, V. (2022). Antioxidant properties and cytotoxic effects of *Alternanthera sissoo* and *Alternanthera bettzickiana* extracts against cancer cells. *Not. Bot. Horti. Agrobo.* 50(3):12776-12776.
30. Samudrala, P.K., Augustine, B.B., Kasala, E.R., Bodduluru, L.N., Barua, C., and Lahkar, M. (2015). Evaluation of antitumor activity and antioxidant status of *Alternanthera brasiliana* against Ehrlich ascites carcinoma in Swiss albino mice. *Pharmacog. Res.* 7(1):66.
31. Schnablegger, G. (2011). The anticancer activity of *Cyathula prostrata* on two malignant cell lines (Doctoral dissertation). Nelson Mandela Metropolitan University.

32. Simpson, M.G. (2010). Plant systematics. Academic Press, Elsevier. 301-302

33. Singh, R.K., Verma, P.K., Kumar, A., Kumar, S., and Acharya, A. (2021). *Achyranthes aspera* L. leaf extract induced anticancer effects on Dalton's Lymphoma via regulation of PKCα signaling pathway and mitochondrial apoptosis. *J. Ethnopharmac.* 274:114060.

34. Singh, S., Verma, S.K., and Singh, S.K. (2017). In-vitro anticancer activity of *Achyranthes aspera* root extract against different human cancer cell lines. *Biolife.* 5(1):119-122.

35. Sivaraj, R., Rahman, P.K., Rajiv, P., Narendhran, S., and Venckatesh, R. (2014). Biosynthesis and characterization of *Acalypha indica* mediated copper oxide nanoparticles and evaluation of its antimicrobial and anticancer activity. *Spectrochim. Acta Mol. Bio.* 129:255-258.

36. Siveen, K.S., and Kuttan, G. (2011). Immunomodulatory and antitumor activity of *Aerva lanata* ethanolic extract. *Immunopharmacol.* 33(3):423-432.

37. Subbarayan, P.R., Sarkar, M., Rao, S.N., Philip, S., Kumar, P., Altman, N., Reis, I., Ahmed, M., Ardalan, B., and Lokeshwar, B.L. (2012). *Achyranthes aspera* (Apamarg) leaf extract inhibits human pancreatic tumor growth in athymic mice by apoptosis. *J. Ethnopharmacol.* 142(2):523-530.

38. Thorat, B. R. (2018). Review on *Celosia argentea* L. Plant. *Res. J. Pharmacog. Phytochem.* 10(1):109-119.

39. Vijayakumar, M., Priya, K., Krishnakumari, S., and Noorlidah, A. (2014). Anticancer activity of *Cyathula prostrata* (L.) blume against dalton's lymphomae in mice model. *Pak. J. Pharm. Sci.* 27(6): 1911-1917.

Anticancer Activities of Selected Members in Family Orchidaceae

***Jusna Fairooz P. K.[1], Anu Krishna K.[2]**

[1]PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
[2]MCT Teacher Training College, Melmuri, Malappuram, 676519, Kerala, India
*Corresponding author: pkjfairooz@gmail.com

Abstract: Orchidaceae is one of the largest families among angiosperm monocots and the members commonly known as orchids. They are cultivated worldwide for their beautiful flowers with variety of colours, shapes and sizes. Many plants are medicinally important and extensively using in drugs for treating various human diseases. Likewise, most of the species contain antibacterial, antiinflammatory, antimicrobial, antioxidative and antitumour compounds. Recently there are a number of investigations going on revealing the anticancerous properties and antitumour compounds of different orchids, as a solution to treat various types of cancers in human beings.

Keywords: Orchids, secondary metabolites, cancer, anticancerous, cytotoxicity

All living organisms are made up of many microscopic cells, irrespective of their size. Some are unicellular and others are multicellular forms. The growth and development of these organisms mainly relies upon the controlled division and multiplication of these cells. Cancer occurs when the cellular reproduction process become out of control. Nowadays cancer is one of the major threats facing by human population which will ultimately leads to death. Any cell in any part of the body may become cancerous by several environmental and genetic factors.

The cancer burden continues to grow globally, exerting tremendous physical, emotional and financial strain on individuals, families, communities and health systems. Various treatment options such as surgery, chemotherapy, hormone therapy, biological therapy etc. developed by modern medical systems are highly expensive. Moreover, all these treatments had its own difficulties and side effects in the patients. In this scenario, the herbal medicines play an important role to replace with the expensive and side effects creating allopathic medicines.

Medicinal plants continue to play a central role in the healthcare system of large proportions of the world's population. Human beings are using medicinal plants to treat many diseases today. Recognition and development of the medicinal and economic benefits of plants are on the increase in both developing and industrialized nations. The plant or plant parts are using for its scent, flavour or therapeutic properties (Jain et al., 2016). Many

herbs have been evaluated in clinical studies and are currently being investigated phytochemically to understand their antitumour actions against various cancers (Harpreet et al., 2011).

The family Orchidaceae includes about 1000 genera and more than 25,000 species. They are cultivated and protected worldwide for their attractive flowers. The information regarding their medicinal properties especially the anticancerous secondary metabolites are not much known. Orchids are traditionally used in folk medicine for the cure of various infectious diseases and tumours (Hu et al., 2008). Based on recent investigations, many of the orchids contain antibacterial, antiinflammatory, antimicrobial, antioxidative and antitumour compounds. Extract investigation of different species confirms the presence of anticancer compounds. Moreover, the isolates from various plant parts exhibit cytotoxic activity against leukemia and melanoma as well as against brain, breast, cervical, gastric, liver and lung cancer cells (Sliwinski et al., 2022).

1. Anticancer plants in Orchidaceae

Several orchid species contain a large number of potential anticancerous secondary metabolites (Pant et al., 2021). Alkaloids, terpenes, stilbenoids, bibenzyls, phenanthrenes, flavonoids and polysaccharides isolated from Orchidaceae indicate their potential medical usefulness. Gigantol and batatasin III are the main bibenzyls occurring in orchids with cytotoxic activity (Chen et al., 2008). Most of the orchids are cytotoxic and kill human cancer cell lines which possess antiallergic, antimicrobial, antiinflammatory and antioxidant properties (Toth et al., 2017). Beyond this, antitumour properties are reported for monomeric phenanthrenes, biphenanthrenes and triphenanthrenes which include in orchids (Teoh et al., 2016). Bibenzyl derivatives of phenanthrenes are effective antitumour chemicals and using in the preparation of anticancer drugs (Wang et al., 2014). The secondary metabolite present in some genera, denbinobin, triggers apoptosis of numerous human cancer cell lines (Chen et al., 2013). Interestingly, some bioactive compounds of orchids are produced by symbiotic microbes within them which carry excessive cytotoxic effects (Favre-Godal et al., 2020). The main genera which are possessing potential anticancerous and antitumour properties include *Dendrobium, Vanda, Bulbophyllum, Vanilla, Spathoglottis, Eulophia, Nervilia, Malaxis, Luisia* and *Habenaria*.

1.1. *Dendrobium* Sw.

The genus *Dendrobium* includes about 1,500 species of epiphytic orchids. Many are cultivated as ornamentals and some are important in the floral industry. They are native to tropical and subtropical Asia, many Pacific islands and Australia. Species are sympodial herbs with cylindrical roots usually arising from the base of a pseudobulb. The pseudobulbs are hard, cylindrical, cone shaped and more or less covered with the bases of the leaves.

Anticancer activities: The extracts of several species of *Dendrobium* have cytotoxic effects and are inhibitors of the growth of cervical cancer and glioblastoma brain tumour cells (Paudel et al., 2020). The extracts in different solvents consists a number of bioactive constituents having medicinal values. Major macromolecules include lectins, chalcone

synthase, sucrose synthase, cytokinin oxidase and polysaccharides. The polysaccharides mainly display immunomodulatory and hepatoprotective activities; while the alkaloids exhibit antioxidant, anticancer and neuroprotective activities (Ng et al., 2012).

D. longicornu carries extremely beautiful flowers and native to warm-temperate, subtropical and tropical regions of Asia and Australia. The whole plant of *D. longicornu* contains bibenzyl and phenanthrene as well as minimal amounts of monoaromatics, steroid and flavonoid derivatives in turn causes antiproliferative activity (Paudel et al., 2017). Protocorm is a special organ induced from seed culture that belongs to the somatic embryo and undergoes growth and differentiation into plants. They are highly proliferated tissues which accumulate high content of secondary metabolites (Cui et al., 2015). Anticancer effect of the protocorm extract from *D. longicornu* toward human cervical cancer (HeLa) and brain tumour (U251) cell lines determined using MTT colourimetric assay (Paudel et al., 2019). The ethanolic extract of *D. chrysanthum* and *D. venustum* perturbs cell cycle progression and results in a delay in the growth of cells; moreover, it exerts anticancer activity (Prasad et al., 2017; Phiboonchaiyanan et al., 2018). *D. crepidatum* is significantly cytotoxic against both cervical cancer (HeLa) and glioblastoma brain tumour (U251) cell lines (Paudel et al., 2018). The medicinally active compounds like stilbenoids and phenolic derivatives in the extract have high cytotoxic effects. Similarly, the extract of *D. transparens* shows high cytotoxic effect towards the HeLa and U251 cell lines (Joshi et al., 2020). The stem extract of wild pineapple orchid, *D. densiflorum*, inhibits the growth of 50% cervical cancer cells (HeLa) and glioblastoma cells (U251). Chloroform extract of *D. lasianthera* stem demonstrates cytotoxicity against T47D cancer cells that can be considered as a potential anticancer natural product (Pant et al., 2022). *D. nobile* is a good source of anticancer compounds in which denbinobin and 4, 7-Dihydroxy-2-methoxy-9, 10-dihydrophenanthrene show cytotoxicity against human lung carcinoma, ovary adenocarcinoma and promyelocytic leukemia cell lines (Lee et al., 1995).

1.2. *Vanda* Jones ex R.Br.

The genus *Vanda* includes about 50 species of colourful orchids distributed from East Asia to Australia. Most species are epiphytic and have long sturdy stems that bear closely spaced strap like leaves. Some species have cylindrical leaves in a form known as terete. The long lasting fragrant flowers usually are flat and have a short spur on the lip. The plants grow well in warm temperatures with high humidity and require a well draining potting medium.

Anticancer activities: The methanolic leaf extract of *V. spathulata* has anticancer action in breast cancer MCF-7 cells via producing cell toxicity and apoptosis (Jeline Rani et al., 2022). *V. bensonii* is a promising source of bioactive molecules with anticancer potential, which can be developed further as pharmaceutical products to optimize the future pharmacotherapy of lung cancer (Jimoh et al., 2022). Four phytochemicals including phloretic acid methyl ester, cymbinodin-A, ephemeranthoquinone B and protocatechuic acid in whole plant

methanolic extract demonstrates varying bioactivities to inhibit growth and metastasis of NCI-H460 cells. The whole plant methanol extracts of wild orchid, *V. cristata*, show significant cytotoxic activity against cervical cancer and brain tumour cell lines (Joshi et al., 2020).

1.3. *Bulbophyllum* Thouars

Bulbophyllum, one of the largest genera of orchids, composed of more than 2,000 species of flowering plants. The genus is found in warm climates throughout Africa, Asia and the Americas. Some species are of horticultural interest due to their unusual flowers. Several species are endangered and are threatened by habitat loss. *Bulbophyllum* species have creeping rhizomes and rounded pseudobulbs. Most species have a single leaf per pseudobulb, and the leaves are often succulent and usually are folded along the midrib. The genus displays a wide diversity of growth forms, ranging from small epiphytes to large cane like. Many of the orchids have small flowers with coloured sepals that are often larger than the petals. Some species are pollinated by flies and give off an offensive odour.

Anticancer activities: *B. kwangtungense* shows antitumour activity against cervical cancer (HeLa) and leukemia (K562) cell lines (Wu et al., 2006). Beyond, *B. odoratissimum* is cytotoxic against leukemia cell lines (K562, HL-60), hepatoma (BEL-7402), lung adenocarcinoma (A549) and stomach cancer (SGC-7901) cell lines (Xu et al., 2009). Extracts of *B. sterile* bulbs and roots cause apoptosis in human colon cancer (HCT116) cell lines by arresting the G2/M phase of the cell cycle (Biswas et al., 2016).

1.4. *Vanilla* Plum. ex Mill.

Vanilla is tropical climbing orchids with the flavouring agent vanillin, extracted from the pods. *Vanilla* plants have a long, fleshy climbing stem that attaches to trees by aerial rootlets. Moreover, the roots also penetrate the soil for nutrient absorption. Numerous flowers open a few at a time and last a single day during the blooming season, which lasts about two months.

Anticancer activities: *Vanilla* leaf extract has a dose dependent antiproliferative effect in human beings. The extract might contain the lead molecule which may be developed as chemotherapeutic agent for treating skin cancer of squamous cell carcinoma type (Vijaybabu et al., 2019). Essential oil of *Vanilla* has ability to inhibit the growth of cancerous cells due to anticarcinogenic and antioxidant properties by killing free radicals in the body and inhibiting the growth of cancerous cells. The bioactive compound, 3-hydroxy-4-methoxybenzaldehyde, present in *Vanilla* plays great role in anticancer activity and inhibits migration of human lung cancer cells which are induced by the hepatocyte growth factor (Hanif et al., 2020).

1.5. *Spathoglottis* Blume

The genus *Spathoglottis* consisting of 49 species with evergreen plant body which are terrestrial orchid plants with pseudobulbs just below the soil and large narrow leaves above the surface. The flowering stem arising from the pseudobulb bears medium sized colourful flowers. Because of their attractive flowers they are extensively cultivated in outdoor gardens.

Anticancer activities: Even though there are

many species under this genus, only one species is reported to contain anticancer agents. Chloroform extracts of leaf and whole plant, *S. plicata* have moderate potency to develop as anticancer agents, especially on breast cancer (Holle et al., 2015).

1.6. *Eulophia* R.Br.

Eulophia covers more than 200 species which spread throughout tropical Americas, Asia and South Africa. They are characterized by being terrestrial, rarely epiphytic and are tall having globose corms, short stalks and long plicate leaves. The basal inflorescence can attain a length of' 5 meters with a raceme of several medium sized flowers. The flowers are with upwardly arched lateral sepals, deeply concave basal lip and longitudinal crests on its blade. There is a long foot on the column carrying two pollina with a stipe.

Anticancer activities: The ethanolic extract of *E. macrobulbon* roots and its components show notable cytotoxic effects on the human cervical adenocarcinoma cell line HeLa, the human colorectal adenocarcinoma cell line CaCo-2 and the human breast adenocarcinoma cell line MCF-7 (Schuster et al., 2017).

1.7. *Nervilia* Comm. ex Gaudich.

The genus includes terrestrial orchids, commonly known as shield orchid which has about 80 species. The plant body is perennial, sympodial and deciduous with one or two flowers born on an erect fleshy leafless stalk.

Anticancer activities: *N. fordii* is a species using in Chinese folk medicine. Both petroleum ether and ethyl acetate extracts of the species show anticancerous properties and can prolong the life of cancer induced mices. The exact phytochemicals which are responsible for anticancerous properties is not known yet (Prakash et al., 2013).

1.8. *Malaxis* Sol. ex Sw.

The genus is commonly known as 'Adder's Mouth' and consisting of terrestrial and semi epiphytic orchids with a variety of vegetative growth. It shows worldwide distribution except in Africa.

Anticancer activities: Cytotoxicity of methanol extract of the whole plant of *M. rheedii* toward MCF-7 suppresses the cell proliferation and it shows good cytotoxicity than HeLa cell line (Haridas et al., 2016).

1.9. *Luisia* Gaudich.

The genus is commonly known as 'Velvet Orchids'. Some members are epiphytic and others show lithophytic nature. The plant body has thick flattened roots and long fibrous leafy stem branching near the base. The leaves are narrow, thick and leathery. Inflorescences are very short recemes having a number of flowers.

Anticancer activities: The ethyl acetate and methanol extracts of shade dried leaves of *L. zeylanica* show cytotoxicity against HeLa and MCF-7 cell lines. The viability of these cell lines decreases considerably with increasing concentrations of extracts. Nowadays, the phytochemicals present in the leaves are using to develop anticancer drugs (Khasim et al., 2019).

1.10. *Habenaria* Willd.

Habenaria is a large terrestrial genus with more than 800 species having colourful flowers. They are commonly known as 'Ghost

Orchids'. The species have small to large underground root tubers with erect stem of 20 to 80 cm. Some members have two flat leaves and others are with many leaves. The small or large flowers in the inflorescence are green, yellow or white in colour.

Anticancer activities: *H. digitata* is a species with a wide range of cytotoxic properties due to the presence of phytochemical compounds present like flavonoids and phenolic compounds having potential antitumour properties (Alshehri et al., 2022).

2. Outlook

Medicinal plants have important roles in curing various diseases of human beings. In different parts of the world, a wide variety of herbs are using as folk medicines. Cancer treatment aiming at reducing the risks of using allopathic methodologies in patients and replacing them by medicinal plants is very interesting in the present scenario. Recent studies reveal that there are many plants which contain cytotoxic secondary metabolites and their extracts can be used to kill or control the cancer cells. Especially, the Orchidaceae members are rich in anticancerous metabolites according to modern research. But we are not much aware of many orchids and investigations carried out only in very few members. In future, Orchids will become as a very good source of antitumour compounds and in turn can produce plant derived anticancer drugs to treat various types of human cancers.

References

1. Alshehri, O. M., Alshamrani, S., Mahnashi, M. H., Alshahrani, M. M., Khan, J. A., Shah, M., and Sadiq, A. (2022). Phytochemical Analysis, Total Phenolic, Flavonoid Contents, and Anticancer Evaluations of Solvent Extracts and Saponins of *H. digitata*. *Biomed. Res. Int.*
2. Biswas, S., Pardeshi, R., Reddy, N. D., Shoja, M. H., Nayak, P. G., Setty, M. M., and Pai, K. S. R. (2016). *Bulbophyllum* sterile petroleum ether fraction induces apoptosis in vitro and ameliorates tumor progression in vivo. *Biomed. Pharmacother.* 84:1419-1427.
3. Chen, J., Zhang, L. C., Xing, Y. M., Wang, Y. Q., Xing, X. K., Zhang, D. W., and Guo, S. X. (2013). Diversity and taxonomy of endophytic xylariaceous fungi from medicinal plants of *Dendrobium* (Orchidaceae). *PloS one.* 8(3):e58268.
4. Chen, T. H., Pan, S. L., Guh, J. H., Chen, C. C., Huang, Y. T., Pai, H. C., and Teng, C. M. (2008). Denbinobin induces apoptosis by apoptosis-inducing factor releasing and DNA damage in human colorectal cancer HCT-116 cells. *Naunyn-Schmiedeb. Arch. Pharmacol.* 378:447-457.
5. Cui, H. Y., Murthy, H. N., Moh, S. H., Cui, Y. Y., and Paek, K. Y. (2015). Establishment of protocorm suspension cultures of *Dendrobium candidum* for the production of bioactive compounds. *J. Hortic. Sci. Biotechnol.* 56:114-122.
6. Favre-Godal, Q., Gourguillon, L., Lordel-Madeleine, S., Gindro, K., and Choisy, P. (2020). Orchids and their mycorrhizal fungi: an insufficiently explored relationship. *Mycorrhiza.* 30:5-22.
7. Hanif, M. A., Nawaz, H., Khan, M. M., and Byrne, H. J. (2020). Medicinal Plants of South Asia. *Amsterdam: Susan Dennis.*
8. Haridas, R., Manorama, S., and Thekkan, S. (2016). In vitro cytotoxicity activity of *malaxis rheedii* sw methanol extract against hela cell line and mcf7 cell line. *Asian J. Pharm. Clin. Res.* 9(6):1-3.
9. Harpreet, S., Leena, P., and Pradeep P. (2011). Review on cancer and anticancerous properties of some medicinal plants. *J. Med. Plants Res.* 5(10):1818-35.
10. Holle, M. J. M., Puspitasari, H. D., Satryo, A., Ningrum, W. D. A., Sudigyo, D., and Nuriliani, A. (2015). Cytotoxic effect of aquadest, ethanolic, and chloroform extracts of *Spathoglottis plicata* Blume on breast cancer cells line (t47d cells). *KnE Life Sci.* 64-69.

11. Hu, J. M., Chen, J. J., Yu, H., Zhao, Y. X., and Zhou, J. (2008). Five new compounds from *Dendrobium longicornu*. *Planta medica.* 74(05):535-539.

12. Jain, S., Dwivedi, J., Jain, P. K., Satpathy, S., and Patra, A. (2016). Medicinal plants for treatment of cancer: A brief review. *Pharmacogn. Mag.* 8(2).

13. Jeline Rani, J., and Nandagopalan, V. (2022). In vitro anticancer activity of methanolic leaf extract of *Vanda Spathulata* (L.) Spreng-A medicinally important Orchid. *In Vitro.* 15(1).

14. Jimoh, T. O., Nuamnaichati, N., Sungthong, R., Chansriniyom, C., Chanvorachote, P., Likhitwitayawuid, K., and Sritularak, B. (2022). Phytochemicals from *Vanda bensonii* and Their Bioactivities to Inhibit Growth and Metastasis of Non-Small Cell Lung Cancer Cells. *Molecules.* 27(22):7902.

15. Joshi, P. R., Paudel, M. R., Chand, M. B., Pradhan, S., Pant, K. K., Joshi, G. P., and Pant, B. (2020). Cytotoxic effect of selected wild orchids on two different human cancer cell lines. *Heliyon.* 6(5):e03991.

16. Khasim, S. M., Jhansi, K., and Venkatesh, R. (2019). Anticancer efficacy of *Luisia zeylanica* Lindl., an epiphytic orchid from Eastern Ghats of Andhra Pradesh, India-an in vitro approach. In *International Symposium on Botanical Gardens and Landscapes*. 371-376.

17. Lee, Y. H., Park, J. D., Beak, N. I., Kim, S. I., and Ahn, B. Z. (1995). In vitro and in vivo antitumoral phenanthrenes from the aerial parts of *Dendrobium nobile*. *Planta Medica.* 61(02):178-180.

18. Ng, T. B., Liu, J., Wong, J. H., Ye, X., Wing Sze, S. C., Tong, Y., and Zhang, K. Y. (2012). Review of research on *Dendrobium*, a prized folk medicine. *Appl. Microbiol. Biotechnol.* 93:1795-1803.

19. Nugroho, L. H., Pratiwi, R., Susandarini, R., Wardoyo, E. R. P., Megawati, O., and Handayani, S. (2016). Isolation of bioactive compounds from two orchid species and preliminary test of their cytotoxicity against T47D breast cancer cells. *Int. J. Pharmacogn. Phytochem.* 8(1):150-155.

20. Pant, B., Chand, K., Paudel, M. R., Joshi, P. R., Thapa, B. B., Park, S. Y., and Rajbhandari, P. (2022). Micropropagation, antioxidant and anticancer activity of pineapple orchid: *Dendrobium densiflorum* Lindl. *J. Plant Biochem. Biotechnol.* 1-11.

21. Pant, B., Paudel, M. R., and Joshi, P. R. (2021). Orchids as potential sources of anticancer agents: Our experience. *Annapurna J. Health Sci.* 1(1):42-51.

22. Paudel, M. R., Bhattarai, H. D., and Pant, B. (2020). Traditionally used medicinal Dendrobium: a promising source of active anticancer constituents. *Orchids Phytochemistry, Biology and Horticulture: Fund. Appl.* 1-26.

23. Paudel, M. R., Chand, M. B., Pant, B., and Pant, B. (2017). Cytotoxic activity of antioxidant-riched *Dendrobium longicornu*. *Pharmacogn. J.* 9(4).

24. Paudel, M. R., Chand, M. B., Pant, B., and Pant, B. (2018). Antioxidant and cytotoxic activities of *Dendrobium moniliforme* extracts and the detection of related compounds by GC-MS. *BMC Complement. Med. Ther.* 18:1-9.

25. Paudel, M. R., Chand, M. B., Pant, B., and Pant, B. (2019). Assessment of antioxidant and cytotoxic activities of extracts of *Dendrobium crepidatum*. *Biomol.* 9(9):478.

26. Phiboonchaiyanan, P. P., Petpiroon, N., Sritularak, B., and Chanvorachote, P. (2018). Phoyunnanin E induces apoptosis of non-small cell lung cancer cells via p53 activation and down-regulation of survivin. *Anticancer Res.* 38(11):6281-6290.

27. Prakash, O. M., Kumar, A., and Kumar, P. (2013). Anticancer potential of plants and natural products. *Am. J. Pharmacol. Sci.* 1(6):104-115.

28. Prasad, R., Rana, N. K., and Koch, B. (2017). *Dendrobium chrysanthum* ethanolic extract induces apoptosis via p53 up-regulation in HeLa cells and inhibits tumor progression in mice. *J. Complement. Integr. Med.* 14(2).

29. Schuster, R., Zeindl, L., Holzer, W., Khumpirapang, N., Okonogi, S., Viernstein, H., and Mueller, M. (2017). *Eulophia macrobulbon* - an orchid with significant anti-inflammatory and antioxidant effect and anticancerogenic potential exerted by its root extract. *Phytomedicine.* 24:157-165.

30. Shukla, M. K., Thakur, A., Verma, R., Lalhlenmawia, H., Bhattacharyya, S., Bisht, D., and Kumar, D. (2022). Unravelling the therapeutic potential of orchid plant against cancer. *S. Afr. J. Bot.* 150:69-79.

31. Siegel, R. L., Miller, K. D., and Jemal, A. (2019). Cancer statistics, 2019. *CA Cancer J. Clin.* 69(1):7-34.

32. Śliwiński, T., Kowalczyk, T., Sitarek, P., and

Kolanowska, M. (2022). Orchidaceae-derived anticancer agents: *A review. Cancers.* 14(3):754.

33. Teoh, E. S., and Teoh, E. S. (2016). Secondary metabolites of plants. *Med. orchids Asia.* 59-73.
34. Tóth, B., Hohmann, J., and Vasas, A. (2017). Phenanthrenes: A promising group of plant secondary metabolites. *J. Nat. Prod.* 81(3):661-678.
35. Vijaybabu, K., and Punnagai, K. (2019). In-vitro anti-proliferative effects of ethanolic extract of V*anilla planifolia* leaf extract against A431 human epidermoid carcinoma cells. *BPJ.* 12(3):1141-1146.
36. Wang, C., Han, S. W., Cui, B. S., Wang, X. J., and Li, S. (2014). Chemical constituents from *Pleione bulbocodioides. Zhongguo Zhong yao za zhi Zhongguo Zhongyao Zazhi. Chin. Med. J.* 39(3):442-447.
37. Wu, B., He, S., and Pan, Y. J. (2006). New dihydrodibenzoxepins from *Bulbophyllum kwangtungense. Planta medica.* 72(13):1244-1247.
38. Xu, J., Yu, H., Qing, C., Zhang, Y., Liu, Y., and Chen, Y. (2009). Two new biphenanthrenes with cytotoxic activity from *Bulbophyllum odoratissimum. Fitoterapia.* 80(7):381-384.
39. Zhen, H. S., Zhou, Y. Y., Yuan, Y. F., Zhong, Z. G., Liang, C. Y., and Qiu, Q. (2007). Study on anticancer effect in vivo of active fraction from *Nervilia fordii. Zhong yao cai Zhongyaocai. Chin. Med. J.* 30(9):1095-1098.s as a

Zingiberaceae as the Family of Potential Anticancer Plants

Faseela P.

PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
Corresponding author: faseela8888@gmail.com

Abstract: The increasing number of cancer patients worldwide has encouraged developing effective and affordable anticancer drugs due to the limitations and drawbacks of chemotherapy and radiotherapy. The exploration of potential medicinal plants constitutes a common alternative for cancer treatment in many countries around the world as it is a rich source of bioactive compounds. Zingiberaceae is one of the most explored families for anticancer herbal medicine identification and characterization. The common genera in the family which have the anticancer properties are *Ginger, Curcuma, Hedychium, Boesenbergia, Alpinia, Etlingera, Kaempferia, Globba, Amomum* and *Elettaria*.

Keywords: Anticancer, bioactive, phytochemicals, therapeutic, Zingiberaceae

Cancer is one of the diseases that threaten human death and important cause of death worldwide, accounting for almost 10 million deaths recently (Sung et al., 2021). Conventional methods such as chemotherapy and radiotherapy are used to treat cancer patients. These methods can cause unpleasant side effects and toxicity since they can destroy both normal cells and cancer cells. To reduce the side effects, there is a tremendous clinical need for the development of effective anticancer drugs with low toxicity. Medicinal plants have become a source of anticancer compounds because they are safe, with low side effects and are easily accessible. Natural products play an essential role in the discovery and development of anticancer agents, especially plant sourced anticancer drugs have made significant contributions to cancer treatment and successfully used for the benefits of human health (Atanasov et al., 2021).

Zingiberaceae or Ginger family is a large family containing approximately 1600 aromatic plant species in 52 genera, most of which are rich in essential oils. The family is an important natural resource providing many useful products for food, spices, medicines, dyes, perfumes and aesthetics. Among this high number of representatives, some species have been reported for their therapeutic properties both in classical and ethno medicine. Most of the genera are widely used as traditional medicine for many treatments, such as to relieve stomachache and hemorrhoids, as a herbal compress for massage, to improve blood circulation, to relieve muscular pain, and

as a honey balm. Moreover, the rhizomes of these plants are used as spices and ingredients for cooking. Essential oils from Zingiberaceous plants have been used for mosquito control. They have demonstrated various bioactivities such as antimycobacterial, immunomodulatory, antineoplastic and anticancer (Alolga et al., 2022). The common genera in Zingiberaceae which have the anticancer potential are *Ginger, Curcuma, Hedychium, Boesenbergia, Alpinia, Etlingera, Kaempferia, Globba, Amomum* and *Elettaria*.

1. Anticancer plants in Zingiberaceae

1.1. *Zingiber* Mill.

Ginger is herbaceous plant widely distributed throughout the tropical and subtropical regions and it is equally reputed for its medicinal properties. The perennial plant has annual pseudostem of about one meter tall bearing narrow leaf blades. The inflorescences bear flowers having pale yellow petals with purple edges, and arise directly from the rhizome on separate shoots. Different types of extract from the rhizome of ginger have been used in Ayurvedic and traditional herbal medicine in order to treat various disorders such as indigestion, vomiting, arthritis, rheumatism, pains, cramps, fever and infection. The main pharmacological actions of active compounds extracted from ginger root reported by in vitro and in vivo test attributed to its active phytocompounds were antiinflammatory, antioxidant, antiemetic, anticancer, anticoagulant, immunomodulatory and cardioprotective. The main phytochemical constituents of the root, the vegetal product of this plant, responsible for the therapeutic action are gingerols, shogaols, paradols, gingerdiols and zingerone. Regarding its anticancer properties, recent studies have indicated a beneficial effect in case of liver, endometrial, ovarian and prostate cancer. Furthermore, ginger was described as an antiemetic agent in cancer chemotherapy. Moreover, the ginger extracts show promising anticancer activity against cholangiocarcinoma (Plengsuriyakarn et al., 2012).

Anticancer activities: *Z. officinale* is the main representative of Zingiberaceae family studied for a wide range of therapeutic properties. The antitumour activity of *Z. officinale* rhizome on B164A5 murine melanoma cell line regarding both proliferation and apoptosis and the increased anticancer activity may be correlated with the higher amount of polyphenols and antioxidant capacity (Dancio et al., 2015). Moreover, *Z. ottensii* is a plant with less than 2 m in height and it is widely cultured in Southeast Asian countries including Thailand, Malaysia, Indonesia, Loas and Vietnam. It has been used as traditional medicinal herb for the treatment of gastrointestinal diseases like peptic ulcers, stomachache and constipation as well as myalgia, sprain and wounds. Crude extracts of *Z. ottensii* exhibit its cytotoxicity in HEK293T/17 cells and reduce IL-6 levels in HeLa cells. The extracts in different solvents induce anticancer activity against four strains of cancer cells, A549 cells (lung carcinoma cell lines), MCF-7 cells (breast cancer cell lines), HeLa cells (cervical carcinoma cell lines), and K562 (chronic myelogenous leukemia cell line). Among the four cancer cells, extracts of *Z. ottensii* shows the most effective in inhibiting MCF-7 (Panyajai et al., 2022).

Z. cassumunar is commonly known as

'Cassumnar Ginger'. The root is perennial, tuberous with long, white fleshy fibres, deep yellow when fresh and possessing a strong camphoraceous odour with bitterish taste. The plant has been used in folk medicine for the treatment of inflammation, sprains, rheumatism, muscular pain, wounds and asthma. Moreover, it acts as mosquito repellent, carminative, mild laxative, antidysenteric, radical scavenging and anti-malarial activity. A major part of the pale amber colour oil obtained from *Z. cassumunar* consists of terpenoids, flavonoids, alkaloids, steroids and benzenoids. It is often used as traditional medicine for inflammation, sprains, rheumatism, muscular pain, wounds and asthma (Singh et al., 2015).

1.2. *Curcuma* L.

Curcuma is a perennial, herbaceous plant that can reach a height of 1 meter and it emits numerous, edible rhizomes whose interiors are yellow or orange. The rhizomes are reduced to a powder, which is the spice called *curcuma*. The lanceolate leaves are oblong or elliptical and uniform green coloured. *C. longa,* (Turmeric), popular name-turmeric, is an aromatic, nutraceutical plant have been intensively used under different pharmaceutical formulations in Indian traditional medicine for different ailments namely wounds, acne, parasitic infection, cold and urinary tract and liver diseases. Numerous experimental studies regarding the therapeutic activity of turmeric reported a plethora of pharmacological properties of the vegetal extract including antioxidant, antiinflammatory, antiangiogenic, antibacterial, analgesic, immunomodulatory, proapoptotic, and antihuman immunodeficiency properties. The major active compound responsible for the pharmacodynamic action is the polyphenol curcumin. Additionally, this natural polyphenol has been described as an anticancer agent both in vitro and in vivo on a wide range of cancer types such as colon, pancreatic, liver, cervical, pulmonary, thymic, brain, breast and bone cancer. Recent studies intensively support the role of polyphenols in the prevention of degenerative diseases like cardiovascular affections and cancers. The antioxidant activity of polyphenols induces the antiproliferative and proapoptotic effect of *Curcuma* rhizome on B164A5 murine melanoma cell line (Danciu et al., 2015).

Anticancer activities: *C. zedoaria*, 'White Turmeric', is one of the important crude drugs possesses many biological activities for many therapeutic actions due to the presence of wide range of phytochemicals such as curcumin, ethyl p-methoxycinnamate, β-turmerone, β-eudesmol, zingiberene, dihydrocurcumin, furanodiene, α-phellandrene, 1–8 cineole, β-elemense and germacrone. White turmeric extract has the antitumour activity against various human cancerous cell lines of breast, cervical and lungs. Moreover, sesquiterpene compounds in white turmeric are highly active against human gastric cancer cells lines (Lee et al., 2019).

1.3. *Alpinia* Roxb.

The genus is commonly known as 'Shell ginger' which is native to Asia, Australia and the Pacific Islands. Several species are cultivated as ornamental plants in tropical and subtropical climates. It shows thick rhizome from which the lance shaped to oblong leaves are arising. The inflorescence is spike, panicle or raceme and hooded in bracts and bracteoles. The plants are generally aromatic due to the

presence of essential oils. *A. coriandriodora*, a widely cultivated perennial edible plant with the odor of coriander, is widely cultivated for its medicinal value and used as a condiment. The rhizome of *A. coriandriodora* has been used in Chinese folk medicine to treat indigestion, stomachache, cold, asthma and fever.

Anticancer activities: Phytochemical compounds like diarylheptanoids and flavonoids isolated from *A. coriandriodora* are responsible for the antioxidant and anti-inflammatory activities. Moreover, the most predominant component of *A. coriandriodora* rhizome essential oil, (E)-2-decenal, inhibits the migration and invasion ability of A549 cells via down regulation of MMP-2 and N-cadherin as well as upregulation of E-cadherin (Hong et al., 2022). *A. officinarum* is a tropical perennial species native to China. It is used to flavor food and to treat a variety of diseases. It bears long, narrow green leaves and produces white flowers and dark brown rhizomes. The phytochemical compounds of *A. officinarum* extracts have antiinflammatory, antibacterial, antioxidant, antiobesity, anticancer, enzyme inhibitory and remarkable antiviral properties. The effectiveness of leaves and rhizome extracts induces apoptosis against acute monocytic leukemia cells and breast cancer cells (MCF-7) (Ghil 2013; Omoregie et al., 2013).

A. purpurata, a traditional herbal medicinal plant, shows antidermatophytic, hepatoprotective, antimicrobial, immunostimulatory and anticancer properties. The rhizomes are used to improve appetite, taste and voice; in addition, it is used to treat headache, rheumatism, sore throat and renal infection. The leaves and rhizomes have antioxidant, antibacterial, larvicidal, cytotoxic and vasodilator activities. The plant extracts exhibit anticancer activities against prostate cancer cells (Palanirajan et al., 2022). Likewise, *A. elegans*, 'Tagbak', is an endemic herbaceous species found at low to medium altitudes in Luzon, Polilio Islands, Mindoro and Leyte. It possesses therapeutic properties including hemoptysis, paralysis extremities, urticarial etc. The leaf extract of *A. elegans* significantly inhibits the cellular proliferation and migration at high concentrations in turn exhibits antiproliferative activity against lungs, liver and colorectal cancer cells (Lintao & Medina, 2021).

A. galanga, 'Greater galangal', is a perennial rhizomatous herb, widely cultivated in tropical areas as an essential source of cosmetics, medicines and culinary products. The species includes various bioactive compounds like diarabinoside, steroldiglucosyl caprate, galangoflavonoside and acetoxychavicol acetate. The essential oils and extracts from different parts of *A. galanga*, especially from flower, rhizome, leaf and fruit, have been used for the treatment of various diseases including stomach ache, vomiting, diarrhea, diabetes, microbial infections, bronchitis, fever and headache. The ethanolic extract of *A. elegans* contained bioactive compounds which inhibit the proliferation of breast cancer cell lines (MCF-7) with the involvements of apoptosis or programmed cell death (Samarghandian et al., 2014).

1.4. *Hedychium* J. Koenig

The genus *Hedychium* is distributed in Asia and Madagascar, and native to India, Southeast Asia and Madagascar. There are

approximately 70-80 known species that grows as herb of perennial tuberous rootstocks. Members of the genus are commonly growing up to 120-180 cm height. Some species are cultivated for the exotic foliage and fragrant spikes of flowers in shades of white, yellow and orange. Various species are used in traditional medicines for the treatment of asthma, bronchitis and gastric and eye diseases.

Anticancer activities: The ornamental ginger, *H. coronarium* (Butterfly Ginger) has the pharmacological properties including antioxidant, antibacterial, antifungal, cytotoxic, chemopreventive, antiallergic, larvicidal, antiinflammatory, neuropharmacological, fibrinogenolytic, coagulant and hepatoprotective (Chan & Wong, 2015). *H. spicatum* rhizome is described as medicine in Ayurvedic and the plant has been used in various treatments of stomachache, cough, wound ulcer, fever, respiratory problems, cancer, AIDS etc. The species also shows the antioxidant, antimicrobial, antidiabetic, hepatoprotective, antidiarrheal, analgesic, expectorant, antiinflammatory, emmenagogue, antifungal, hypoglycaemic, insect repellent, hypotensive, pediculicidal and cytotoxic activities (Bhatt et al., 2008).

1.5. *Boesenbergia* Kuntze

Genus contains more than 70 species that native to China, the Indian Subcontinent, and Southeast Asia. *B. rotunda* or 'Finger Root' is a herb with medicinal properties which grows in Southeast Asia, India, Sri Lanka and southern China. The species uses as a traditional medicine to treat rheumatism, muscle pain, gastrointestinal disorders, flatulence, stomach ache, dyspepsia and peptic ulcer.

Anticancer activities: The whole plant extract of *B. rotunda* is effective towards breast, colon, prostate, liver and lung cancers. Moreover, the rhizome possesses antileukemic property due to the occurrence of various bioactive compounds having high anticancer potential. Sakuranetin has a cytotoxic effect on B16BL6 melanoma cells, while cardamonin and pinostrobin chaconne isolated from rhizome have a cytotoxic effect on the H-29 colon cancer cell line. The anticancer activity of *B. rotunda* is strong cytotoxic and induces apoptosis of breast cancer cell lines through insilico and in vitro approaches (Widyananda et al., 2022). *B. pandurata* is known to have various pharmacological activities, mainly the anticancer property. The ethanolic extract of the plant shows strong inhibitory effects on the growth of cancer cells. Panduratin A, a chalcone derivative isolated from *B. pandurata*, inhibits the growth of MCF-7 human breast cancer and HT-29 human colon adenocarcinoma cells. In addition, rhizomes of *B. pandurata* contain active compounds with anticancer activities and have antiproliferative and apoptotic induction against HeLa and PANC-1 pancreatic cancer cell lines. Recently, the species is known to inhibit the growth of breast cancer cells and the anti-breast cancer activity is significantly influencing by the inhibition of two receptors, ER-α and HER2 (Pratama et al., 2022).

1.6. *Etlingera* Giseke

The genus *Etlingera* consists of more than 100 perennial herbaceous species distributed mainly in tropical regions. Some of the larger species have leafy shoots reaching almost 10 metres high, and the bases of the shoots are so stout as to seem almost woody.

Other species grows as clumps of leafy shoots; while some have long creeping rhizomes with leafy shoots, more than a metre apart. Unique and distinctive to the species is a tube that forming above the point where the base of the flower petals joins onto the plant. The main phytochemical compounds of *Etlingera* are phenolics, diarylheptanoids, flavonoids, steroids, alkaloids and terpenoids. Eight species in the genus namely *E. elatior, E. pavieana, E. brevilabrum, E. pyramidosphaera, E. megalocheilos, E. coccinea, E. fimbriobr-acteata,* and *E. corneri* are potential anticancer agents to treat human cancer.

Anticancer activities: The rhizome of *E. elatior* provides the anticancer activity; similarly the rhizome essential oil has potential against the cell lines MCF-7, HeLa and Hl 60. The aqueous extract of flowers shows anticancer activity against the breast and colon cancer cell lines. Presence of lapachol, apigenin, methylated chrysin, 6,2'-dihydroxyflavanone, 3-Hydroxy3, 4'-dymethoxyflavone and 4'-Hydroxy-5,7-dimethoxyflavanone compounds contained in *E. elatior* provide the anticancer effect in turn help to suppress different human cancers. Moreover, *E. pavieana* rhizome extract provides an antiproliferative effect against breast adenocarcinoma MDA-MB-231, hepatoma HepG2 and cervical carcinoma HeLa and C33A. The trans-4-methoxycinnamaldehyde (4-MCA) compound blocks the cell proliferation and cancer cell colony formation by inducing apoptosis and cell cycle arrest (Wahyuni et al., 2021).

The essential oil from *E. brevilabrum* shows cytotoxic activity and inhibits cell proliferation against MCF-7, HeLa, P388 and HL 60 cancer cell lines due to the presence of α-fenchol, elemicin, borneol, methyl isoeugenol, β-farnesene etc. similarly, the essential oil from the rhizomes of *E. pyramidosphaera* inhibits cell proliferation of MCF-7 and P388 cancer cell lines due to the presence of lauricaldehyde, 1-dodecanol, lauryl acetate, 1-tetradecanol etc. (Vairappan et al., 2012). Due to the presence of terpineol oxide, aromadendrene, aromadendrene oxide and caryophyllene, the essential oil from the rhizomes of *E. megalocheilos* obstructs cell proliferation of MCF-7, HeLa, P388 and HL 60 cells. Likewise, the essential oil derived from the rhizome of *E. coccinea* demonstrates the cytotoxic activity against the MCF-7, P388 and HL 60 cell lines with the presence of 2-Methyl-1-undecanol, 1-Dodecanol, Lauryl acetate, etc. The polyphenolic content in leaf extract of *E. fimbriobracteata* has antiproliferative effect against cervical cancer cells; beyond, rhizome of *E. corneri* hinders the growth and proliferation of MCF-7 cells (Ghazaly et al., 2020).

1.7. *Kaempferia* L.

Kaempferia is native to China, India and Southeast Asia. These gingers grow from small globular rhizomes bearing fleshy roots. The herbaceous plant has pronounced dormancy period. The short stem with two to a few colourfully marked broad leaves often carries large showy flowers. Various species of the genus are used in traditional medicines for the treatment of cold, dry cough, toothache, rheumatism and hypertension. In addition, it has been used widely as spices due to highly aromas.

Anticancer activities: *K. parviflora* is commonly known as 'Black Ginger' grown in

tropical Asia and traditionally plays an important role in treating all kinds of everyday ailments including general pains, abscess, allergy and ulcer. Extracts of *K. parviflora* also suppresses gastrointestinal ulcer formation and cancer cell growth. It inhibits cervical cancer HeLa and ovarian cancer SKOV3 cells (Paramee et al., 2018). Likewise, *K. galanga*, 'Aromatic Ginger', is one of the most economically important species known for its broad ethnomedicinal use. It has been used as a spice and traditional medicine in local communities of Southeast Asia. The rhizome extract of *K. galanga* exhibits the antiproliferative activities against various cancer cell lines. The anticancer effects have been attributed to enhanced cytotoxic T lymphocyte responses and the upregulation of proapoptotic genes (Elshamy et al., 2020).

K. rotunda is also known as an ornamental plant with silver patterned leaves and a purplish flower. It is used as ethnomedicines in wide area spreading from India to Indonesia. Some of the polyoxygenated cyclohexane derivatives of the plant have moderate cytotoxic activity and acts against pancreatic and breast cancer cell lines. Lectin in *K. rotunda* induces cell cycle arrest in colon cancer cells and Ehrlich-Lettre ascites carcinoma cells via the caspase-3-dependent pathways. Likewise, anticancer compounds, kaempulchraol F and kaempulchraol L, extracted from *K. pulchra* exhibit antiproliferative activities against human pancreatic cancer cells (Win et al., 2016). Moreover, the anticancer properties of kaempfolienol and zeylenol derivatives from *K. angustifolia* acts against human promyelocytic leukemia (HL-60) and human breast adenocarcinoma (MCF-7) cell lines (Yeap et al., 2017).

1.8. *Globba* L.

Globba ('Dancing Ladies') is the third largest genera in the Zingiberaceae family with over 100 species, distributed in tropical and sub-tropical Asia. Many of the species have the peculiar habit of producing bulbils on the inflorescence in place of the lower flowers. In some species, the bulbils are spicy and occasionally eaten. Different *Globba* species have been used for centuries to treat a variety of diseases including mouth ulcers, conjunctivitis, eye infections, asthma, leucoderma, cough, stomachache, fever and heart disease. Phytochemical compounds including humulen-6,7-epoxide, β – caryophyllene, terpineol, heptadecane, 2,6-dimethyl1,5,7-octa trien-3-ol and alloaromadendrene are prominent in *G. marantina* extract which could be a potential source of natural antioxidants for use in food, cosmetics and pharmaceuticals industries. Moreover, the main compounds of the rhizome extract of *G. candida* are levoglucosan, allylhydrazone acetaldehyde, trans-2,3-epoxybutane, butan-3-enoic acid methyl ester, 2-methylcyclopentanone and 2-n-propyl-oxetan. While the dominant contents of the leaves extract of *G. candida* are pinostrobin chalcone.

Phytochemical studies of *G. reflexa* rhizomes afford main compounds namely stearyl palmitate, villosin, coronarin D and stigmasterol that have anticancer activity against the human breast cancer, human oral epidermoid carcinoma and human small cell lung cancer cell lines. Likewise, the essential oil from *G. pendula* possesses significant cytotoxic

activity against MCF-7 and Hep3B cell lines and *G. bulbifera* ethanolic tuber extract shows good activity for protease inhibition to block the proliferation of breast cancer cell lines (Rao & Kaladhar, 2014).

1.9. *Amomum* L.

The genus *Amomum* consists of over 90 species extensively distributed in Africa, Tropical Asia, Australia and the Pacific Islands. These are mostly terrestrial rhizomatous herbs showing elongate pseudostems that arise from widely creeping rhizomes. The densely flowered spike, spike like raceme or panicle type inflorescence arises from rhizomes. The seeds of *Amomum* are used as spices; similarly, other plant parts are used in traditional medicine in healing of toothache, dysentery, diarrhea, rheumatism and lung diseases (Dutta et al., 2000).

Anticancer activities: *Amomum* consumption is beneficial to health as it possesses antioxidant, cytotoxic and immunosuppressive properties. The volatile oil from *A. kravanh* induces anticancer activity in human beings (Chaothanaphat et al., 2022). The hexane and ethyl acetate extracts of *A. subulatum* exhibit maximum cytotoxic activity against human breast cancer and cervical cancer cell lines. Aculeatin A extracted from *A. aceleatum* is active against human breast cancer cells, MCF-7. Moreover, acetone extract of *A. compactum* has anticancer activity against breast cancer cells (Alkandahri, 2021); while the ethanolic extract of *A. subulatum* fruits shows cytotoxic activity against cervical cancer cell line due to the presence of proteins, terpenoids, tannins, steroids, phenols and flavonoids (Yadav, 2014).

1.10. *Elettaria* Maton

The genus is commonly known as 'Green Cardamom' or 'Queen of Spices'. The dried fruit of herbaceous perennial plant *E. cardamomum* is spicy and ethnomedicinal. It is the third most expensive spice behind vanilla and saffron. Cardamom has three sided fruits with a rough, thin and delicate outer layer and small deep-brown aromatic seeds that arranged in vertical order. It exhibits many medicinal and pharmacological activities like antiseptic, antispasmodic, anthelminthic, cephalic, antibacterial and stomachic (Singhal et al., 2022).

Anticancer activities: Cardamom phytochemicals are well known inhibitors of cancer. The plant is also able to treat or inhibit different stages of breast cancer from Stage 0 to Stage 4 due to the occurrence of cancer fighting compounds. It is not only inhibits the progression of the disease, but also prevents the breast cancer when consumed at the appropriate dosage level. Cardamom based therapy has very few side effects in turn increases the levels of tumour suppressor p53, inhibits tumour proliferation initiating cells, decreases expression of the metastasis promoter Snail1 and inhibits the epithelial mesenchymal transition. Chemical compounds in cardamom, diindolylmethane and indole-3-carbinol, prevent the growth of cancer cells including breast cancer cells. Moreover, phytochemicals such as cineole and limenonene have the protective role against cancer progression (Vutakuri & Somara, 2018). Moreover, cardamom could serve as an apoptotic stimulator agent presenting a novel and potentially curative approach for cancer

treatment, inducing fewer side effects than those of the commercially used anticancer drugs (Almeer et al., 2021).

2. Outlook

Phytochemical investigations in medicinal plants reveals that many plant species have anticancer activity due to the presence of broad range of secondary metabolites or bioactive compounds. Among the genus of Zingiberaceae, the most notable members include *Ginger, Curcuma, Hedychium, Boesenbergia, Alpinia, Etlingera, Kaempferia, Globba, Amomum* and *Elettaria* which possess various biological activities towards different human cancer cell lines. Nowadays, these species play major role in pharmaceutical and therapeutic approaches towards anticancer drug development to inhibit cancer cell proliferation and metastasis.

References

1. Abha Yadav, L. (2014). Evaluation of anticancer activity of various extracts of fruit of *Amomum subulatum* Roxb. using cervical cancer cell line by invitro methods. Doctoral dissertation, College of Pharmacy, Madras Medical College, Chennai.
2. Alkandahri, M. Y. (2021). Pharmacological Studies on *Amomum compactum. Current Aspects in Pharma. Res. Develop.*4:46-55.
3. Almeer, R. S., Alnasser, M., Aljarba, N., and AlBasher, G. I. (2021). Effects of Green cardamom (*Elettaria cardamomum* Maton) and its combination with cyclophosphamide on Ehrlich solid tumors. *BMC Complement. Med. Ther.* 21(1):1-13.
4. Alolga, R. N., Wang, F., Zhang, X., Li, J., Tran, L. S. P., and Yin, X. (2022). Bioactive compounds from the Zingiberaceae family with known antioxidant activities for possible therapeutic uses. *Antioxidants.* 11(7):1281.
5. Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., and Supuran, C. T. (2021). Natural products in drug discovery: advances and opportunities. *Natu. Rev. Drug Discov.* 20(3):200-216.
6. Bhatt, I. D., Prasad, K., Rawat, S., and Rawal, R. S. (2008). Evaluation of antioxidant phytochemical diversity in *Hedychium spicatum*: a high value medicinal plant of Himalaya. *Pharmacog. Mag.* 4(16):202-205.
7. Chan, E. W. C., and Wong, S. K. (2015). Phytochemistry and pharmacology of ornamental gingers, *Hedychium coronarium* and *Alpinia purpurata*: a review. *J. Integr. Med.* 13(6):368-379.
8. Chaothanaphat, N., Weerapol, Y., Manmuan, S., Limmatvapirat, S., and Tubtimsri, S. (2022). Anticancer activity of nanoemulsions loading biomaterial *Amomum kravanh* oil against oral cancer cells. In *Key Engineering Materials.* Trans Tech Publications Ltd. 914:31-36.
9. Danciu, C., Vlaia, L., Fetea, F., Hancianu, M., Coricovac, D. E., Ciurlea, S. A., Şoica, C.M., Marincu, I., Vlaia, V., Dehelean, C.A., and Trandafirescu, C. (2015). Evaluation of phenolic profile, antioxidant and anticancer potential of two main representants of Zingiberaceae family against B164A5 murine melanoma cells. *Biol. Res.* 48(1):1-9.
10. Dutta, S., Ahmed, R., and Pathak, M.G. (2000). Essential oil composition of *Amomum linguiforme* Benth. from north-east India. *Indian Perfum.* 44:11-13.
11. Elshamy, A. I., Mohamed, T. A., Swapana, N., Yoneyama, T., Noji, M., Efferth, T., Hegacy, M.E.F., and Umeyama, A. (2020). Cytotoxic polyoxygenated isopimarane diterpenoids from the edible rhizomes of *Kaempferia galanga* (kencur). *Ind. Crops Prod.* 158:112965.
12. Ghazaly, M., Lee, G. E., Athifah, N., Salam, R., Lau, K. H., Iff, A. L., Tajuddin, S. A., and Razali, R. A. (2020). Short communication attenuation of mcf-7 breast cancer cell growth: a comparison between the inflorescence and rhizome extract of *Etlingera Corneri. J. Sustain. Sci. Manag.* 15(5):279-283.
13. Ghil, S. (2013). Antiproliferative activity of *Alpinia officinarum* extract in the human breast cancer cell line MCF-7. *Mol. Med. Rep.* 7(4):1288-1292.

14. Hong, Y., Liu, X., Wang, H., Zhang, M., and Tian, M. (2022). Chemical composition, anticancer activities and related mechanisms of the essential oil from *Alpinia coriandriodora* rhizome. *Ind. Crops Prod*. 176:114328.

15. Lee, T. K., Lee, D., Lee, S. R., Ko, Y. J., Kang, K. S., Chung, S. J., and Kim, K. H. (2019). Sesquiterpenes from *Curcuma zedoaria* rhizomes and their cytotoxicity against human gastric cancer AGS cells. *Bioorg. Chem*. 87:117-122.

16. Lintao, R. C., and Medina, P. M. B. (2021). Screening for anticancer activity of leaf ethanolic extract of *Alpinia elegans* ("tagbak") on human cancer cell lines. *Asian Pac. J. Cancer Prev*. 22(12):3781-3787.

17. Omoregie, S. N., Omoruyi, F. O., Wright, V. F., Jones, L., and Zimba, P. V. (2013). Antiproliferative activities of lesser galangal (*Alpinia officinarum* Hance Jam1), turmeric (*Curcuma longa* L.), and ginger (*Zingiber officinale* Rosc.) against acute monocytic leukemia. *J. Med. Food* 16(7):647-655.

18. Palanirajan, A., Kannappan, P., and Kanniappan, G. V. (2022). Anticancer activity of *Alpinia purpurata* (Vieill) K. Schum. against MNU and testosterone induced prostate cancer in male Wistar albino rats. *Pharmacol. Res. Modern Chinese. Med.* 3:100105.

19. Panyajai, P., Chueahongthong, F., Viriyaadhammaa, N., Nirachonkul, W., Tima, S., Chiampanichayakul, S., Anuchapreeda, S., and Okonogi, S., (2022). Anticancer activity of *Zingiber ottensii* essential oil and its nanoformulations. *PloS one.* 17(1):e0262335.

20. Paramee, S., Sookkhee, S., Sakonwasun, C., Na Takuathung, M., Mungkornasawakul, P., Nimlamool, W., and Potikanond, S. (2018). Anticancer effects of *Kaempferia parviflora* on ovarian cancer SKOV3 cells. *BMC complement. Altern. Med.* 18(1):1-13.

21. Plengsuriyakarn, T., Viyanant, V., Eursitthichai, V., Tesana, S., Chaijaroenkul, W., Itharat, A., and Na-Bangchang, K. (2012). Cytotoxicity, toxicity, and anticancer activity of *Zingiber officinale* Roscoe against cholangiocarcinoma. *Asian Pac. J. Cancer Prev*. 13(9):4597-4606.

22. Pratama, M. R. F., Praditapuspa, E. N., Kesuma, D., Poerwono, H., Widiandani, T., and Siswodihardjo, S. (2022). *Boesenbergia Pandurata* as an anti-breast cancer agent: molecular docking and ADMET study. *Lett. Drug Des. Discov*. 19(7):606-626.

23. Rao, V. N., and Kaladhar, D. S. V. G. K. (2014). Inhibition of proteases and anti-cancer activities of ethanolic tuber extract of *Globba bulbifera*. *WJPPS*. 2(6):6579-6588.

24. Samarghandian, S., Hadjzadeh, M. A. R., Afshari, J. T., and Hosseini, M. (2014). Antiproliferative activity and induction of apoptotic by ethanolic extract of *Alpinia galanga* rhizhome in human breast carcinoma cell line. *BMC complement. Altern. Med*. 14(1):1-9.

25. Singh, C. B., Manglembi, N., Swapana, N., and Chanu, S. B. (2015). Ethnobotany, phytochemistry and pharmacology of *Zingiber cassumunar* Roxb.(Zingiberaceae). *J. Pharmacogn. Phytochem.* 4(1):01-06.

26. Singhal, P. K., Gautam, G. K., Kumar, R., and Kumar, G. (2022). A review on *Amomum subulatum* and *Elettaria cardamomum* with their pharmacological activity. *RTPSR*. 4(1):1-6.

27. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J. Clin.* 71(3):209-249.

28. Vairappan, C. S., Nagappan, T., and Palaniveloo, K. (2012). Essential oil composition, cytotoxic and antibacterial activities of five *Etlingera* species from Borneo. *Nat. Prod. Commun.* 7(2):237-242.

29. Vutakuri, N., and Somara, S. (2018). Natural and herbal medicine for breast cancer using *Elettaria cardamomum* (L.) Maton. *Int. J. Herbal Med. 6(2):91-96.*

30. Wahyuni, W., Diantini, A., Ghozali, M., and Sahidin, S. (2021). *Etlingera* genus: phytochemical screening and anticancer activity. *J. Farm. Sains Praktis* 7(3):343-355.

31. Widyananda, M. H., Wicaksono, S. T., Rahmawati, K., Puspitarini, S., Ulfa, S.M., Jatmiko, Y.D., Masruri, M., and Widodo, N., (2022). A Potential anticancer mechanism of finger root (*Boesenbergia rotunda*) extracts against a breast cancer cell line. *Scientifica*. 9130252.

32. Win, N. N., Ito, T., Matsui, T., Aimaiti, S., Kodama, T., Ngwe, H., Okamoto, Y., Tanaka, M., Asakawa, Y., Abe, I., and Morita, H. (2016). Isopimarane diterpenoids from *Kaempferia pulchra* rhizomes collected in Myanmar and their Vpr inhibitory activity. *Bioorganic. Med. Chem. Lett.* 26(7):1789-

1793.

33. Yeap, Y. S. Y., Kassim, N. K., Ng, R. C., Ee, G. C. L., Saiful Yazan, L., and Musa, K. H. (2017). Antioxidant properties of ginger (*Kaempferia angustifolia* Rosc.) and its chemical markers. *Inter. J. Food Prop.* 20:1158-1172.

Cancer Preventive Potential of Musaceae Members

***Deepa P.[1], Sanoj E.[2], Sreejith P.E.[3]**

[1]PG Department of Botany, Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, 676122, Kerala, India.
[2&3]PG & Research Department of Botany, The Zamorin's Guruvayurappan College
Kozhikode, 673014, Kerala, India.
*Corresponding author: deepapsaj@gmail.com

Abstract: The genera of Musaceae are well known due to the secondary metabolite induced medicinal properties. Anticancer potential of *Musa* and *Ensete* species are better remedy to suppress the cancer initiation, proliferation and metastasis related apoptosis in different human cell lines without interfering the healthy cells.

Keywords: *Musa, Ensete,* antiproliferative, cytotoxicity, secondary metabolites

The monocotyledonous family, Musaceae, consists rhizhomatous plants that growing commonly in humid areas. The members are distributed in South East Asia and African countries. The plants may be perennial or monocarpic rhizomatous herbs with terminal large inflorescence on huge pseudostem. This ancient family consists of three genera viz. *Musa* L., *Ensete* Horan. and *Musella* (Franch.) H.W.Li; while Indian wild Musaceae represented by two genera, *Ensete* and *Musa*. Both genera are economically important due to the presence of a number of medicinal, nutritious and aesthetic values. The wild genus, *Ensete*, can easily identify from *Musa* by the presence of non stoloniferous pseudostem with seeded fruits which consists a number of phytochemical compounds (Sabu et al., 2013).

The fruits of cultivated or wild genus, *Musa*, are rich with starch, sugar, potassium, calcium, sodium and magnesium (Doymaz, 2010). Moreover, it shows the antioxidant, antibacterial, antifungal, antidiarrheal and antiulcer properties due to the presence of phytochemical compounds. Presence of secondary metabolites in *Musa* sp. includes alkaloids, flavonoids, terpenoids, coumarins, phenols, tannins, steroids, glycosides and saponins which in turn improve the medicinal properties. Various parts of the plant including leaves, flowers, pseudostem and fruit and fruit peel are using in various industries nowadays that makes the edible members as one of the major cultivated crops in India. Applications in bio fuelproduction, biosorbents, pulp and paper, cosmetics, organic fertilizer, environmental clean-up etc. are very popular from the ancient time onwards.

In recent decades, advanced medicines have replaced by traditional medicines for treating human illnesses. Extensive phytoch-

emical studies in plants promise the anticancer properties which interfere the cancer initiation and proliferation by modulating various pathways in cells. Cancer is a hyper proliferative disorder and the second most frequent cause of morality. According to the Global Observatory Report, the number of newly diagnosed cancer cases is projected to increase to 29.5 million per year and projected cancer related deaths are expected to increase to 16.4 million per year by 2040. Currently, many of the anticancer medications destroy both cancer and healthy cells. In addition, the cancer therapy causes non specific targeting and induction of drug resistance. To overcome the present obstacles, the more effective anticancer medications with improved safety profiles are urgent to defeat the dangerous disease. Because of this reason, the use of medicinal plants for health promotion and disease prevention has increased now. In Musaceae members, the phytochemicals are being extensively investigated and demonstrated that promising anticarcinogenic properties by interfering with cancer modulating pathways.

1. Anticancer plants in Musaceae

1.1. *Musa* L.

The genus *Musa* comprises of 65 species including both wild and cultivated taxa. At present, the different cultivars of the species, *Musa paradisiaca*, cultivated around the world and the significant producers of fruits are India, China, Philippines and Brazil. But *M. acuminata* has been discovered from the native habitats of India historically. The species are perennial herb with large fruit bearing pseudostem that emerges from the rhizome. The stem is a compact assembly of wrapping with spirally arranged leaf sheaths. The leaf arising from the centre of pseudostem by elongating the distal end of the leaf sheath in to a petiole, in turn split the lamina in to two equal halves. Inflorescence is a spike which turning downward towards the soil and consists both male and female flowers. The fruits are normally parthenocarpic fleshy berry without seeds. In each cultivar, the fruits vary in their arrangement, position, number per hand, size, shape, colour, nature etc.

Anticancer activities: The phytochemical analysis of *Musa* spp. reveals the presence of numerous secondary metabolites including polyphenols, terpenoids, alkaloids, steroids, anthocyanins, tannins etc. The plant extract with the phytochemical compound is better strategy to prevent cancer cell proliferation in human beings. The aqueous methanol extract of *Nendran* banana peel exhibits significant antitumour activity against MCF-7 breast cancer cell line (Durgadevi et al., 2019). Through induction of apoptosis, the anthocyanin from methanol extract of *M. acuminata* bract and *M. cavendish* green peel hydroalcoholic extract suppresses the proliferation of MCF-7cells (Jenshi & Aravindhan, 2011; Barroso et al., 2019). The hexane extract of *M. sapientum* peel and pulp blocks the proliferation of MCF-7 cells (Dahham et al., 2015); meanwhile, the acetone extract of *M. acuminata* leaves exhibits prominent activity against breast tumour cell lines (Salama et al., 2020). *M. paradisiaca* floral extracts has shown the potent antitumourigenic activity in MCF-7 and MDA-MB-231 breast cancer cell lines (Lavudi et al., 2022).

By the increased activity of caspase enzyme, the ethanol extract of *M. paradisiaca*

flower exhibits anticancer activity against HeLa cervical cancer cell line (Nadumane & Timsina, 2014). Due to the effect of eugenol and phytol, ethyl acetate extract shows anticervical carcinoma in HeLa cell lines (Deep et al., 2020). By enhancing DNA fragmentation, ferulic acid isolated from banana peel using *Staphylococcus aureus* induces antiproliferative and cytotoxic activities against HeLa cervical cancer cells (Srinivasan et al., 2017). The methanol extract of *M. acuminata* flower reveals antiproliferative and cytotoxic potential against HeLa cells (Das et al., 2020). An ethyl acetate fraction of *M. x paradisiaca* leaves also indicates strong cytotoxic and anticancer activity against HeLa and A375 cervical cancer cell lines. At a concentration of 100 µg/mL, *M. cavendish* green peel hydroalcoholic extract demonstrates antiproliferative and cytotoxic activity against A-375 human malignant melanoma cells (Barroso et al., 2019). Due to the presence of eugenol and phytol, ethyl acetate extract of *M. paradisiaca* leaves prevents malignant melanoma (Deep et al., 2020).

By arresting cell growth, the hexane fraction of *M. sapientum* peel and pulp exhibits in vitro anticancer activity against HCT-116 colon carcinoma cell line (Dahham et al., 2015). *M. cavendish* green peel hydroalcoholic extract suppresses the proliferation of Caco-2 human colorectal adenocarcinoma cells (Barroso et al., 2019). Protocatechualdehyde (PCA, 3,4-dihydroxybenzaldehyde) from green cavendish bananas promises antiproliferative activity by triggering apoptosis in human colorectal carcinoma cells, HCT116 and SW480, through histone deacetylase 2 (HDAC2) initiated cyclin D1 suppression. The compound, 2-pentanone present in banana ameliorates antiproliferative action by inhibiting the prostaglandin (PGE2) production and cyclooxygenase 2 (COX-2) protein expression in colon cancer cells, HT29 (Pettersson et al., 2008).

By decreasing the level of mitochondrial membrane potential (MMP) and increasing the reactive oxygen species (ROS) level, *M. cavendish* green peel hydroalcoholic extract exhibits antiproliferative activity against HepG2 human hepatocellular carcinoma cell lines (Barroso et al., 2019). Various extracts of banana (*Musa* AAB var. Nanjanagudu Rasabale) pseudostem and rhizome demonstrates cytotoxicity against HepG2 cell lines. Crude chloroform and acetone extracts of the banana pseudostem and rhizome express substantial cytotoxicity against the cell lines (Kandasamy et al., 2016). The isolated bioactive compounds, 4-epicyclomusalenone, cycloeucalenol acetate and chlorogenic acid, from banana rhizome exhibit potent cytotoxicity against HepG2 cell lines. Acetone extract of *M. acuminata* leaves possesses a high content of phenolics, flavonoids and tannins of which vanillic and ferulic acids are more intensive in turn shows vigorous activity against liver hepatocellular tumour cell lines (Salama et al., 2020).

Ethyl acetate subfraction of the ethanol extract of *M. paradisiaca* soft piths exhibits potent cytotoxic and antiproliferative activity against the human oral squamous cell carcinoma cell line (HSC-4) (Ghafar et al., 2019). Aqueous banana flower extract shows anticancer activity against benign prostatic hyperplasia in vitro. The extract at a concentration of 2 mg/mL normally reduces the viability of BPH-1 cells through cell cycle

arrest at the G_1 phase (Liu et al., 2018). By inhibiting 5α-reductase activity, the methanol fraction of the banana peel inhibits testosterone induced cell growth in the androgen responsive LNCaP human prostate carcinoma cell line (Akamine et al., 2009). In MG-63 cell lines, the hexane extract of *M. acuminata* promotes the anticancer activity (Agustine et al., 2020).

1.2. *Ensete* Bruce ex Horan.

The genus *Ensete* (False Banana) was first named by Horaninow (1862) and later 25 species of *Ensete* were included by Cheesman (1947). Later, the number of species under the genus has shrunken and recorded as seven species viz. *Ensete gilletii, E. homblei, E. perrieri, E. ventricosum, E. glaucum, E. lasiocarpum* and *E. superbum.* Among the species, *E. superbum* and *E. glaucum* are commonly distributed in North-East and Whestern Ghats of India.

E. superbum is commonly known as Wild Banana. It is monocarpic and non stoloniferous perennial shrub found in Dindigul and Anaimalai Hills, Western Ghats and some parts of peninsular India. The species is well documented for the medicinal and nutritional purposes for the local peoples in India and Ethiopia. It is well recorded in different regions of the world for ailments such as dog bite, semen production, abortion, leucorrhoea, stomachache, immune response, diabetes, psychosomatic, contraceptive, umbilical cord care, pneumonia, cholera, labor and delivery pain, dehydration, appendicitis, chickenpox, measles, urinary problems, food poisoning, snake bites, diarrhoea, dysentery, jaundice, bone fracture, fever, asthma and leucoderma. Plant is the source of many phytochemical compounds like triterpenoid esters, proanthocyanidin, propelargonidin glucosides, pelargonidin, anigorufone, hydroxyanigorufone, β-carboline alkaloids etc. Pharmacologically, *E. superbum* possesses antiurolithiatic, antidiabetic, antifertility, antiestrogenic, antiviral, cardiovascular and antiinflammatory activities (Sethiya et al., 2019).

Naturally, *Ensete glaucum* is distributed in Burma, Thailand, China, Laos, Viet Nam, Philippine, Papua New Guinea and Solomon Islands up to Java; and its probable existence in North-East India was reported by Simonds (1960). The species is monocarpic nonstoloniferous herb with pseudostem, persistant bracts, hermaphrodite flowers and large seeds. Seeds are black, smooth and asymmetrically subglobose to irregular due to the pressure in packed fruit. Long dormancy period of seed make it unique habitat and limited distribution (Majumdar et al., 2013).

The fruits have been used in folk medicine to treat kidney stones, diabetes, perforated edema, stomach ulcers and skin allergies. The seeds contain flavonoids, saponins and tannins; meanwhile, the presence of amino acids, flavonoids and terpenoids in peel and flavonoids, tannins, saponins and amino acids in pulp is also confirmed. The total content of polyphenols and flavonoids is higher in the seeds than in peel and pulp (Ly et al., 2022). Presence of secondary metabolites induces the antioxidant and antimicrobial properties of the species (Tuan, 2021).

Anticancer activities: The ripe peel aqueous extract of *E. superbum* exhibits higher cytotoxic, antiinflammatory and antimutagenic activities compared to the aqueous extracts of

seed, flower and bract. The active compounds like quercetin-3-*O*-rutinoside, 3,5-dimethoxy-4-hydroxybenzoic acid and 4',5,7-trihydroxyflavone present in the species possesses the antiproliferative potential in colorectal cell lines (Mathew et al., 2021).

2. Outlook

Two genera in Musaceae, *Musa* and *Ensete*, are naturally distributed in India which show nutritious, medicinal, aesthetic and religious values. The parthenocarpic fruits of wild and cultivated species of *Musa* play significant role in diet. In addition, the plant parts viz. leaf, pseudostem, flower, corm etc. prevent a number of human diseases due to the properties including antimicrobial, antioxidant, anticancer etc. The wild genus, *Ensete*, is nonstoloniferous herb with seeded fruits rich with secondary metabolites in turn improves medicinal values. Nowadays, the production of natural medicines from plants becomes very relevant and safe strategy to prevent cancer initiation and proliferation. The identified Musaceae members are better source of anticancer compounds. Hence, it will be helpful in production of natural anticarcinogenic medicines in present decades without causing any side effects in human beings.

References

1. Akamine, K., Koyama, T., and Yazawa, K. (2009). Banana Peel Extract Suppressed Prostate Gland Enlargement in Testosterone-Treated Mice. *Biosci. Biotechnol. Biochem.* 73:1911–4. doi: 10.1271/bbb.80770
2. Barroso, W.A., Abreu, I.C., Ribeiro, L.S., da Rocha, C.Q., de Souza, H.P., and de Lima, T.M. (2019). Chemical composition and cytotoxic screening of *Musa Cavendish* green peels extract: Antiproliferative activity by activation of different cellular death types. *Toxicol. In Vitro.* 59:179-86. doi: 10.1016/j.tiv.2019.04.020
3. Dahham, S.S., Mohamad, T.A., Tabana, Y.M., and Majid, A.M.S.A. (2015). Antioxidant activities and anticancer screening of extracts from Banana fruit (*Musa Sapientum). Acad. J. Cancer Res.* 8:28–34. doi: 10.5829/idosi.ajcr.2015.8.2.95162
4. Das, A., Bindhu, J., Deepesh, P., Priya, G.S., and Soundariya, S. (2020). In Vitro Anticancer study of bioactive compound isolated from *Musa* extract (*Musa Acuminata*). *Indian J. Public. Health Res. Dev.* 11:340-6. doi: 10.37506/v11/i1/2020/ijphrd/193841
5. Deep, A., Upadhyay, O.N., Nandal, R., Kumar, S., Sharma, A.K., and Wadhwa, D. (2021). Anticancer Potential of *Musa×Paradisiaca* as Cervical Carcinoma and Malignant Melanoma. *Res. Square.* 1-16. doi: 10.21203/rs.2.20790/v1
6. Do Lai Tuan, L. (2021). Contribution to pharmacognostical standardization and evaluation of antioxidant activity of seed extracts of *Ensete glaucum* (Roxb.) cheesman (Doctoral dissertation, International University-HCMC).
7. Durgadevi, P.K.S., Saravanan, A., and Uma, S. (2019). Antioxidant potential and antitumour activities of Nendran Banana peels in breast cancer cell line. *Indian J. Pharm. Sci.* 81:464–73. doi: 10.36468/pharmaceutical-sciences.531
8. Ghafar, S.A.A., Fikri, I.H.H., and Eshak, Z. (2019). Antioxidant activity of *Musa Paradisiaca* (Banana) soft pith and its cytotoxicity against oral squamous carcinoma cell lines. *Malaysian J. Sci. Health Technol.* 3:1–11.
9. Jenshi Roobha, J., and Aravindhan, M.S.K. (2011). In vitro evaluation of anticancer property of anthocyanin extract from *Musa acuminate* Bract. *Res. Pharm.* 1:17–21.
10. Kandasamy, S., Ramu, S., and Aradhya, S.M. (2016). In Vitro functional properties of crude extracts and isolated compounds from Banana pseudostem and rhizome. *J. Sci. Food Agric.* 96:1347–55. doi: 10.1002/jsfa.7229
11. Lavudi, K., Hemalatha, S., Kokkanti, R. R., Harika, G. V. S., Patnaik, S., and Penchalaneni, J. (2022).

Anti-tumour efficacy of *Musa paradisiaca* flower extracts on DMBA induced mammary carcinogenesis in female wistar rats. *S. Afr. J. Bot.* 151:200-207.10.1016/j.jep.2018.12.048

12. Liu, L.C., Lin, Y.H., Lin, Y.C., Ho, C.T., Hung, C.M., and Way, T.D. (2018).Banana flower extract suppresses benign prostatic hyperplasia by regulating the inflammatory response and inducing G1 cell-cycle arrest. *In Vivo.* 32:1373–9. doi: 10.21873/invivo.11389
13. Ly, H. T., Khuong, H. T., Do, T. G., Nguyen, T. P., and Phan, T. A. D. (2022). Extraction and Phytochemical Composition of *Ensete glaucum* (Roxb.) Cheesman Fruits in Bu Gia Map National Park, Binh Phuoc Province. *J. Tech. Education Sci.* 70B:116-120.
14. Majumdar, K., Sarkar, A., Deb, D., Majumder, J., and Datta, B. K. (2013). Distribution record of *Ensete glaucum* (Roxb.) Cheesm. (Musaceae) in Tripura, Northeast India: a rare wild primitive banana. *Asian J. Conserv. Biol.* 2:164-7.
15. Mathew, N. S., Kurrey, N. K., Bettadaiah, B. K., and Negi, P. S. (2021). Anti-proliferative activity of *Ensete superbum* Roxb. Cheesman extract and its active principles on human colorectal cancer cell lines. *J. Food Sci.* 86(11):5026-5040.
16. Nadumane, V.K., and Timsina, B. (2004). Anticancer potential of Banana flower extract: An in vitro study. *Bangladesh J. Pharmacol.* 9:628–35. doi: 10.3329/bjp.v9i4.20610
17. Pettersson, J., Karlsson, P.C., Goransson, U., Rafter, J.J., and Bohlin, L. (2008). The flavouring phytochemical 2-Pentanone reduces prostaglandin production and COX-2 expression in colon cancer cells. *Biol. Pharm. Bull.* 31:534–7. doi: 10.1248/bpb.31.534
18. Sabu, M., Joe, A., and Sreejith, P. E. (2013). *Musa velutina* subsp. *markkuana* (Musaceae): a new subspecies from northeastern India. *Phytotaxa.* 92(2): 49-54.
19. Srinivasan, S., Valarmathi, S., Illanchezian, S., and Dhanalakshmi, K.G. (2017). Anticancer activity and DNA fragmentation of ferulic acid from Banana peel using HeLa cell line. *Int. J. Res. Dev. Technol.* 7:631–5.

Antimetastatic Plants in Siddha System of Medicine

***Neethu Kannan B., Ghanthi Kumar S., Lekha G. S., Kanagarajan A.**

Siddha Regional Research Institute, Under CCRS and Ministry of AYUSH
Thiruvananthapuram, 695012, Kerala, India.
*Corresponding author: neethusamhitha@gmail.com

Abstract: Siddha system of medicine is a traditional system practiced in South India. The plant based formulations as well as plant derived phytochemicals possessing therapeutic potential have drawn considerable attention in recent years. Cancer is one of the major Non-Communicable Disease and remains one of the leading causes of morbidity and mortality. As a number of undesired side effects occur during chemotherapy, natural therapies involving the plant derived products are used in cancer treatment, may reduce adverse side effects. A plethora of many plant products that has shown very promising anticancer activity in vitro, but have yet to be evaluated in clinical trials. Prominently using anticancer plants in Siddha medicine include *Plumbago indica, Taxus baccata, Asparagus racemosa, Glycyrriza glaba* and *Ocimum gratissimum*. The compound formulations or single drugs in Siddha literature shall be subjected to retrospective analysis for the exploration of scientific background behind the therapeutic aspects.

Keywords: Anticancer, natural sources, chemical constituents, Siddha medicine

For many years herbal medicines have been used and are still used in developing countries as the primary source of medicines to treat various ailments. Plants have been used in medicine for their natural therapeutic properties. In line with this, the research has developed into investigating the potential properties and uses of terrestrial as well as marine plant extracts for the preparation of potential nanomaterial based drugs for various dreadful diseases including cancer (Kuppuswamy et al., 2016; Siddique & Chow, 2020). Many plant species are already being used to treat or prevent development of cancer. Multiple researchers have identified species of plants that have demonstrated anticancer properties with a lot of focus on those that have been used in herbal medicine in developing countries. The National Cancer Institute (NCI) has screened approximately 35,000 plant species for potential anticancer activities. Among them, about 3,000 plant species have demonstrated reproducible anticancer activity. The untapped structural diversity of natural compounds is having major importance in drug discovery.

Cancer is a dreadful as well as a high profile disease in developing countries. The alarming and frightening rise in the number of people dying from various types of cancer has prompted researchers to search for alternative anticancer drugs with fewer side effects to

battle the illness in an effective manner (Cai et al., 2006; Ochwangi et al., 2014). The great potential of plant based compounds for the treatment and prevention of cancer is attributed to their safety, low cost and oral bioavailability; while a few plant based compounds induce some side effects. The side effects can be overcome by dose dependent administration and usage of plant extracts (Raina et al., 2014). The already available expensive conventional therapies for cancer like chemotherapy and radiotherapy have a number of side effects such as myelo-suppression and neurological, cardiac, pulmonary and renal toxicity, which pose

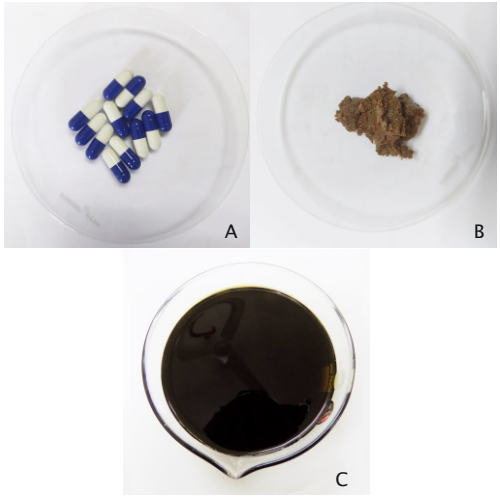

Fig.1. A. Rasagandhi Mezhugu Capsules, B. Gandhaka, C. Rasayanam Megathennai

serious harm to the quality of life (Alonso-Castro et al., 2011). Siddha system of medicine is a traditional system of medicine practised by saint from ancient period. It is getting more attention nowadays due to its less toxicity rendered by plant based drugs. According to Siddha system, Vippuruthinoi (carcinoma like illness) is being classified into seven types based on the pathogenicity and site, stages and severity of lesions developed on a particular part of body (Lekha et al., 2018). The therapeutic aspect in Siddha system is based on the body constitution of the subjects and pathogenesis of the disease.

1. Plant derived anticancer agents

1.1. *Clerodendron inerme* (L.) Gaertn.

The species belongs to family Verbenaceae with a lot of ethnomedicinal properties. The plant contains some important phytoconstituents viz. pentadecanoic acid–β-D-glicoside, stigmasterol, 4α-methyl-24βethyl-5α-cholesta-14, 25-dien-3β-ol, 24β-ethylcholesta-5, 9(11), 22-trien-3β-ol and betulinic acid. Anticancer potential of *C. inerme* has been proved on lung cancer, Burkitt's lymphoma cancer and human colon cancer cell line (Chouhan et al., 2018; Kumar et al., 2018; Trieu, 2019).

1.2. *Plumbago indica* L.

It is a well-known medicinal plant belongs to the family Plumbaginaceae. The potential phytoconstituent, Plumbagin, is known to exert various bioactivities. The plant extract exhibits selective cytotoxic and anti-proliferative effects in human skin cancer SK MEL-28 cells (Anuf et al., 2014). A significant synergy of cytotoxicity towards cancer cells demonstrated in the use of *P. rosea* extract due to interactions among plumbagin and other components present in the herb. In addition to plumbagin, several other potential bioactive components such as sitosterol, stigmasterol, campesterol, napthaquinone, 5, 6-dihydroxy-2-methyl-1,4-naphthoquinone (6-hydroxyplumba-

gin) α-amyrin and β-sitosterol are present in plant (Checker et al., 2010; Hafeez et al., 2012).

1.3. *Smilax chinensis* L.

It is a climbing plant species belonging to Smilacaceae. The ethanol extract of *S. chinensis* proved to be effective in arresting the proliferation and migration of MDA-MB-231 human breast cancer cells (Nho et al., 2015). A flavonoid, glycoside that isolated from *S. chinensis* rhizome effects against human cancer cell lines (HeLA) (Li et al., 2007).

1.4. *Morinda tinctoria* Roxb.

It is an evergreen shrub or small tree in the family Rubiaceae commonly known as Indian mulberry. GC-MS analysis shows the presence of compounds like scopolamine, a secondary metabolite and Malvidin-3, 5-diglucoside, an anthocyanin and a glycoside, as main constituents (Arunachalam et al., 2015). Significant anticancer and cytotoxic effect found in the methanolic extract against EAC and human cancer cell lines (Kumar et al., 2017).

1.5. *Trapa natans* L.

The small free-floating plant grows mainly in shallow water or swampy regions and belongs to family Trapaceae. The plant contains carbohydrates, minerals, calcium, phosphate, iron, copper, manganese, magnesium, sodium and potassium. The kernels contain some vitamins like thiamine, riboflavin, nicotinic acid, vitamin C, vitamin A, D-amylase and considerable amount of phosphorylases. Even though not many studies and formulations of *T. natans* are documented, the plant has been indicated for cancer (Bharthi et al., 2015).

1.6. *Taxus baccata* L.

The tree species belongs to the family Taxaceae, has both toxic and medicinal properties. Identifying the chemical components of different parts of the tree can be useful in the better understanding of toxicity and medicinal effects. A large number of chemical constituents have been reported from the Himalayan yew, *T. baccata* or *T. wallichiana* in which the main constituents are taxoids and phenolics. Taxol and paclitaxel are important anticancer constituents using to prepare the anticancer drugs (Das & Anjani, 1998). These alkaloids interrupt mitosis by promoting and stabilizing microtubule formation. Methanolic extract of *T. baccata* displays significant anticancer activity on MDA-MB-231 and HCT-116 cell lines (Milutinovic et al., 2015).

1.7. *Allium sativum* L.

It is a bulbous perennial plant coming under the family Alliaceae, which is characterized by its peculiar aroma and pungent taste. The species is rich in sulphur containing compounds such as allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, alliin, S-allylcysteine and S-allylmercaptocysteine that impact various stages of carcinogenesis. The anticancer actions by these garlic derived phytochemicals include altering the mitochondrial permeability, inhibiting angiogenesis, enhancing antioxidative and proapoptotic properties and regulating cell proliferation. The effects of various garlic-derived products, the phytoconstituents and nanoformulations has negative impact on skin, prostate, ovarian, breast, gastric, colorectal, oral, liver and pancreatic cancers. The constituents inhibit different stages of cancer including initiation, promotion and progression. Besides, these bioactive metabolites alter the lipid peroxidation, activity of nitric oxide synth-

etase, nuclear factor-κB and protein kinase C, cell cycle and survival signalling (Greef et al., 2021; Mondal et al., 2022).

1.8. *Erythrina variegata* L.

It is a showy, spreading, deciduous tree legume that can reach a height of 18-25 m and involving in Fabaceae. The plant is a rich source of alkaloids like 3- Demethoxyerythratidinone, erythraline, erythramine, erythrinine, erythratidinone, erysonine and erysotine. Species acts as a potential source of anticancer agent by MTT assay, nucleoprotein assay and cell morphology studies on MDA-MB-231 cells (Rai et al., 2017).

2. Outlook

The poly herbal formulations or formulations consisting of metals or minerals possessing a tremendous potential for a cancer cure are being used in Siddha System. These formulations are deemed to work on multiple biochemical pathways and are capable of influencing several organ systems simultaneously. Siddha medicine can be useful in the management of cancer, besides being safe, non-toxic, cost effective and non-invasive. Owing to the high antioxidative potential, most

1. Plants used in Siddha system of medicine as anticancer agents

Plant species	Mode of administration	Formulation
Clerodendron inerme (L.) Gaertn.	The leaves are indicated for cancerous lesions. The intake of leaf/ root juice twice a day is beneficial in treatment of tumours in neck region. The leaves roasted in castor oil can also be used for the external application in cancerous legion.	Vippuruthi ennai
Plumbago indica L.	*Plumbago* root barks are generally indicated for tumours.	Kodiveli ennai, Kodiveli tailam, Megathennai Chitramoola kuligai
Smilax chinensis L.	Root tuber of *S. chinensis* is indicated for cancerous growths.	Parangipattai rasayananm
Morinda tinctoria Roxb .	The root bark of *M. tinctoria* is indicated for tumours, ulcers and cancer.	Nunappattai thylam
Trapa natans L.	The tender leaves and stem of *T. natans* can be grinded and applied externally for the treatment of cancers.	-
Taxus baccata L.	The leaves of *Taxus buccata* grinded in vinegar can be applied externally for cancerous lesions.	Nanti Mezhuku, Rasaganthi melugu, Kantaki Rasayanam
Allium sativum L.	Garlic paste is being used externally for the treatment of tumours.	Megathennai
Erythrina variegata L .	The leaves of *E . variegata* can be applied externally for cancerous lesions	-

(Ref.: Classical Siddha Literature, Gunapadam)

of the Siddha medicines confer nutrition and reduce the side effects imposed by conventional cancer therapy. The compound formulations or single drugs in Siddha literature shall be subjected to retrospective analysis for the scientific validation behind the therapeutic aspects.

References

1. Alonso-Castro, A. J., Villarreal, M. L., Salazar-Olivo, L. A., Gomez-Sanchez, M., Dominguez, F., and Garcia-Carranca, A. (2011). Mexican medicinal plants used for cancer treatment: pharmacological, phytochemical and ethnobotanical studies. *J. Ethnopharm.* 133(3):945-972.
2. Anuf, A. R., Ramachandran, R., Krishnasamy, R., Gandhi, P. S., and Periyasamy, S. (2014). Antiproliferative effects of *Plumbago rosea* and its purified constituent plumbagin on SK-MEL 28 melanoma cell lines. *Pharmacog. Res.* 6(4):312.
3. Arunachalam, K. D., Kuruva, J. K., Hari, S., Annamalai, S. K., and Baskaran, K. V. (2015). HPTLC Finger print analysis and Phytochemical Investigation of *Morinda tinctoria* Roxb. Leaf extracts by HPLC and GS MS. *Int. J. Pharm. Sci.* 7(2):360-366.
4. Bharthi, V., Kavya, B., Shantha, T. R., Prathapa Reddy, M., Kavya, N., Rama Rao, V., and Venkateshwarlu, G. (2015). Pharmacognostical evaluation and phytochemical studies on Ayurvedic nutritional fruits of *Trapa natans* L. *Int. J. Herb. Med.* 3(5):13-19.
5. Cai, Y. Z., Sun, M., Xing, J., Luo, Q., and Corke, H. (2006). Structure–radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. *Life Sci.* 78(25):2872-2888.
6. Checker, R., Sharma, D., Sandur, S. K., Subrahmanyam, G., Krishnan, S., Poduval, T. B., and Sainis, K. B. (2010). Plumbagin inhibits proliferative and inflammatory responses of T cells independent of ROS generation but by modulating intracellular thiols. *J. Cell. Biochem.* 110(5):1082-1093.
7. Chouhan, M. K., Hurakadle, P. J., and Hegde, H. V. (2018). *Clerodendrum inerme* (L.) Gaertn. extract exerts anticancer activity on lung cancer cells. *Dhaka University J. Pharma. Sci.* 17(2):191-196.
8. Curcic Milutinovic, M., Stankovic, M., Cvetkovic, D., Topuzovic, M., Mihailovic, V., and Markovic, S. (2015). Antioxidant and anticancer properties of leaves and seed cones from European yew (*Taxus baccata* L.). *Arch. Biolog. Sci.*
9. Das, B., and Anjani, G. (1998). Chemical Constituents of the Himalayan Yew, A Review. *Nat. Prod. Sci.* 4(4):185-202.
10. De Greef, D., Barton, E. M., Sandberg, E. N., Croley, C. R., Pumarol, J., Wong, T. L., and Bishayee, A. (2021). Anticancer potential of garlic and its bioactive constituents: A systematic and comprehensive review. In *Seminars in cancer biology*. 73:219-264. Academic Press.
11. Hafeez, B. B., Zhong, W., Mustafa, A., Fischer, J. W., Witkowsky, O., and Verma, A. K. (2012). Plumbagin inhibits prostate cancer development in TRAMP mice via targeting PKCε, Stat3 and neuroendocrine markers. *Carcinogenesis*, 33(12):2586-2592.
12. Kumar, C. M., Jayadevappa, H. P., and Vasudev, H. H. (2018). Evaluation of *Clerodendrum inerme* (L.) Gaertn. on Burkitt's lymphoma cancer. *Indian J. Pharm. Educ. Res.* 52(2):241-7.
13. Kumar, R. S., Kumar, S. V., and Sudhakar, P. (2017). Anticancer activity of methanolic leaf extract of *Morinda tinctoria* Roxb. against ehrlich ascites carcinoma in mice. *Bull. Pharm. Res.* 7:146.
14. Kuppusamy, P., Yusoff, M. M., Maniam, G. P., and Govindan, N. (2016). Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications - An updated report. *Saudi Pharm. J.* 24(4):473-484.
15. Lekha, G. S., Aparna, S., Kanagarajan, A. (2018). Diagnosis and Treatment of Cancer – Siddha Perspective. *J. Res. Siddha Med.* 1(1):3-14.
16. Li, Y. L., Gan, G. P., Zhang, H. Z., Wu, H. Z., Li, C. L., Huang, Y. P., and Liu, J. W. (2007). A flavonoid glycoside isolated from *Smilax china* L. rhizome in vitro anticancer effects on human cancer cell lines. *J. Ethnopharm.* 113(1):115-124.
17. Mondal, A., Banerjee, S., Bose, S., Mazumder, S.,

Haber, R. A., Farzaei, M. H., and Bishayee, A. (2022). Garlic constituents for cancer prevention and therapy: From phytochemistry to novel formulations. *Pharm. Res.* 175:105837.

18. Nho, K. J., Chun, J. M., and Kim, H. K. (2015). Anti-metastatic effect of *Smilax china* L. extract on MDA-MB-231 cells. *Mol. Med. Rep.* 11(1):499-502.
19. Ochwangi, D. O., Kimwele, C. N., Oduma, J. A., Gathumbi, P. K., Mbaria, J. M., and Kiama, S. G. (2014). Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya. *J. Ethnopharm.* 151(3):1040-1055.
20. Rai, V., Pai, V. R., Kevin, S., and Kedilaya, H. P. (2021). Could Methanol Leaf Extracts of *Erythrina variegata* L. be a Potential Source of Anticancer Molecule against Breast Cancer Cell Lines? - A Preliminary in vitro Investigation. *Current Aspect. Pharmaceut. Res. Develop.* 1:30-44.
21. Rai, V., Pai, V. R., Kevin, S., and Kedilaya, H. P. (2021). In vitro evaluation of anticancer potential of *Erythrina variegata* L. on breast cancer cell lines. *Asian J. Pharmaceut. Clinical Res.* 10(7):305-310.
22. Raina, H., Soni, G., Jauhari, N., Sharma, N., and Bharadvaja, N. (2014). Phytochemical importance of medicinal plants as potential sources of anticancer agents. *Turk. J. Bot.* 38(6):1027-1035.
23. Siddique, S., and Chow, J. C. (2020). Gold nanoparticles for drug delivery and cancer therapy. *Appl. Sci.* 10(11):3824.
24. Trieu, L. H. (2019). Phytochemical screening and cytotoxic evaluation from leaf extracts of *Combretum quadrangulare* and *Clerodendrum inerme* on MCF-7 and HEPG2 cancer cell lines. *UED J. Soc. Sci. Hum. Edu.* 9(5):26-31.

Index to Anticancer Plants

With the academia and higher education tuned towards achieving Sustainable Development Goals and holistic education, it's indeed an honour to see a publication that explores a comprehensive exploration of plants that can combat cancer, a terminal disease that has become a challenge to humanity as one of the leading causes of death worldwide. Finding time to edit and compile these chapters as a book must have been a herculean task for a teacher with innumerable responsibilities and challenges for which Dr. Deepa P. deserves great appreciation. We, at Korambayil Ahamed Haji Memorial Unity Women's College, sincerely wish that this book becomes a great contribution to the academia and the world of medicine, and in turn for global wellbeing.

Prof. (Dr.) Muhammed Basheer Ummathur
Principal
Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Malappuram, Kerala

Published by:
Deepa P.; M.Sc., B.Ed., Ph.D.
Assistant Professor (Ad-hoc)
Post Graduate Department of Botany
Korambayil Ahamed Haji Memorial Unity Women's College
Manjeri, Narukara (PO), PIN: 676122, Malappuram (DT), Kerala, India.

ISBN: 978-93-5701-654-4

MRP : ₹750/-