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