Fabaceae: A Boon for Cancer Therapy

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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.

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