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.