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Nutritional and therapeutic potential of *Ailanthus excelsa* - A Review.

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ABSTRACT

Over the past decade, herbal medicine has become an item of global importance, with both medicinal and economic implications. Widespread use of herbs throughout the globe has raised serious concerns over their quality, safety and efficacy. Thus, accurate scientific assessment has become a prerequisite for acceptance of herbal health claims. *Ailanthus excelsa* Roxb is a tree, indigenous to central and southern India, belongs to family *Simaroubaceae* is widely used in Ayurveda and evidence based phytotherapy. The tribal population uses the plant for antifertility, anthelmintic and rejuvenating purpose. Alkaloids, flavonoids, triterpenoids and bitter principles like quassinoids are reported in this plant. Several quassinoids from *Simaroubaceae* are designated as potent antimalarial especially against the chloroquine-resistant *Plasmodium falciparum*. The roots of this plant also serve as substitute for *Oroxylum indicum,* one of the constituents of an ayurvedic formulation *Dasmularista*. In the present review an attempt has been made to explore different aspects of *Ailanthus excelsa*.

KEY WORDS

Ailanthus excelsa, Quassinoids, Anticancer, *Simaroubaceae*, Canthin alkaloids, Antimalarial.

INTRODUCTION

During the past decade, the traditional systems have gained importance in the field of medicine. In many developing countries, a large proportion of the population relies heavily on traditional practitioners, who are dependent on medicinal plants to meet the primary health care needs. Although, modern medicines are available, herbal medicines have often retained popularity for historical and cultural reasons. Since the usage of these herbal medicines has increased, the issues regarding their safety, quality, and efficacy in industrialized and developing countries are cropped up (1). Growing interest has also prompted researcher to screen scientifically various claims regarding properties and uses of medicinal plant materials. Presently, both, common consumers and health-care professionals seek updated, authoritative information towards safety and efficacy of any recommended medicinal plant as drug prior to its use. The present attempt is to review and compile updated information on various aspects of *Ailanthus excelsa* a plant used in Indian system of medicine for variety of purposes. *Ailanthus* is a genus of tall, lofty trees, distributed in Indo-Malaya, China, Japan and Australia (2). The genus is noted for its antidiarrhoel and antidysenteric properties (3). Different species of the genus are *Ailanthus glandulosa* in Malay Peninsula and China, (leaflets very coarsely toothed at the base and filaments several times exceeding the anther), *Ailanthus excelsa* in India (leaflets coarsely toothed and filaments shorter than anthers) and *Ailanthus malbarica* in Indo-china (leaflets entire and filaments larger than anthers) (2). *Ailanthus excelsa* Roxb (Simaroubaceae) is commonly known as "Mahanimba" due to its resemblance with neem tree (*Azadirachta indica*). The term *Ailanthus* is from ailanto which means *Tree of Heaven* and is the name for one of the species in the Moluccas, while in Latin *excelsa* means tall. The plant is known by different names like, *tree of heaven* in English, *ardusi*, *aralavo* in Gujarati, *maruk, ghoda karanj, aakashneem, arlu* in Hindi, *peruvagai* in Tamil and *peddamanu* in Telgu (2). It is a fast growing tree extensively cultivated in many parts of India towards the vicinity of villages. The tree is indigenous to central and southern India and is distributed in Madhya Pradesh, Gujarat, some costal districts of Andhra Pradesh, Ganjam and Puri districts of Orissa (4). The plant is known for its high commercial and economic importance (5).

Botanical description

It is a large deciduous tree of upto 24 m height with a straight cylindrical bole. Bark is light grey and smooth in young trees with large leaf-scars, rough, granular and grayish brown in older trees. Leaves are pinnately compound, upto 90 cm long with 8-14 pairs of leaflets. Flowers small, yellowish in panicles and fruits are single seeded samara **(Fig. 1 and 2)** (2)**.** The leaves are reported to be used as an adulterant for *Adhatoda zeylanica*. It is cultivated as an avenue tree for its deep shade and can be used for anti-erosion purposes. It thrives best on porous loamy soil. The tree can be raised from both seeds and stumps. Its quick growth and absolute immunity to grazing gives the species first choice among the soft woods (6).

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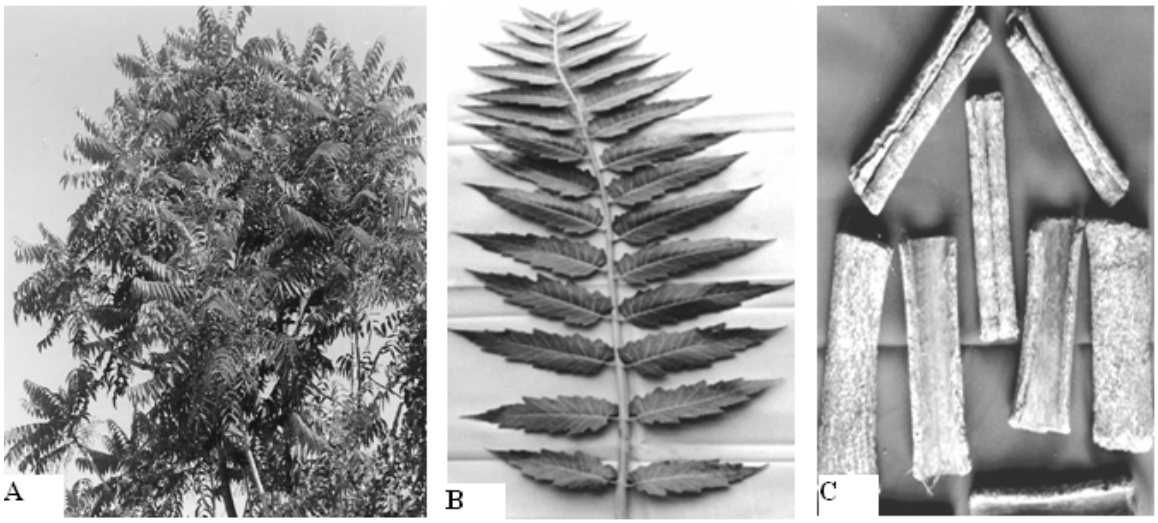

Fig. 1. **(A)** ***Ailanthus excelsa*** **tree, (B) Leaves, (C) Stem bark**

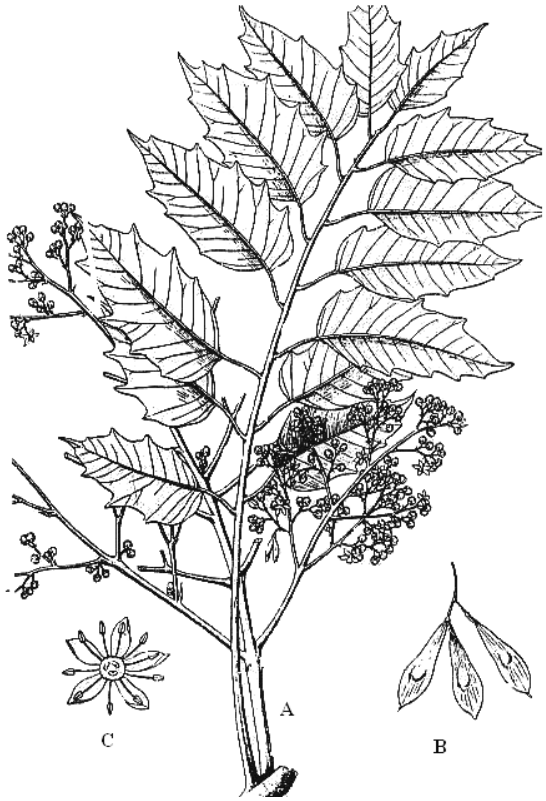

Fig. 2. Ailanthus excelsa **(A) - A flowering twig, (B) - fruits, (C) - flower.** (Ref. 8)

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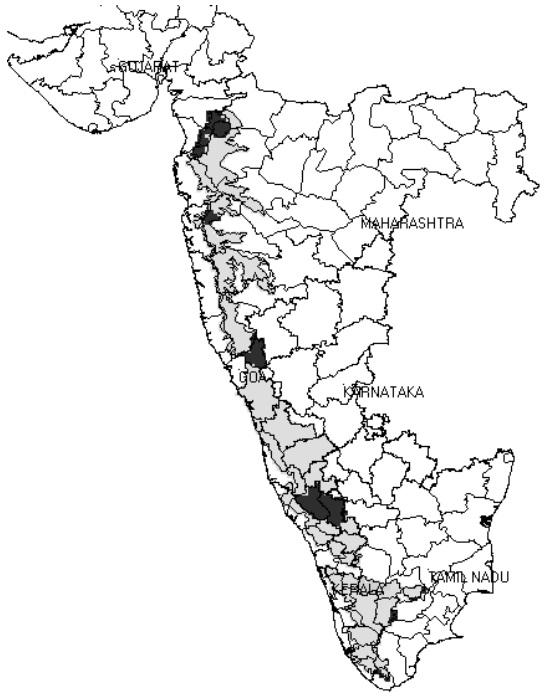


***Fig. 3*. Distribution of *Ailanthus excelsa* in western ghat region.**

The leaves are rated as highly palatable and nutritious fodder for sheep and goats and an average tree yields about 500-700 kg of green leaves twice a year. The wood is sainty, yellowish white and well suited for cabinet making (7).

Ethnopharmacology

In Chinese system of medicine bark of *A. excelsa* is used to treat diarrhea and dysentery, especially when there is a blood in stool (3, 9). The bark has been used in Asian and Australian medicine to counteract worms, excessive vaginal discharge, malaria and asthma (2, 10). It has marked antispasmodic and cardiac depressant properties (4). The root bark is used to cure epilepsy and heart troubles. In Africa the plant is used to treat cramps, gonorrhea epilepsy, tape warm infestation and high blood pressure (11-12). Alcoholic extract of the leaf and stem bark shows anti-implantation and early abortificient activity (13). Traditionally the mattress made of leaves is used as bed for children suffering from fever (2). In Bombay the bark and leaves are of great repute as a tonic especially in debility after child birth. They are used in dyspepsia, bronchitis and asthma (2, 4). In Konkan the juice of the leaves is usually administered in *khir*, or the juice of the fresh bark is given with coconut juice and treacle or with aromatics or honey to stop after pains (2, 4, 14). It is also used to cure wounds and skin eruptions (2). The plant is used as natural antifertility agent by the Irula women in Mavanahalla region of the Nilgiri district in Tamil Nadu (15). The fresh juice of stem bark mixed with either honey or sugar is given to pregnant woman during evening for three consecutive days to induce permanent sterility (6). In Kanakpura taluka in Karnataka, the pest of stem barks along with goat milk and neem oil is used for curing the nose rope wound in ox. The bark is used as bitter, refrigerant, astringent, appetizer, anthelmintic, febrifuge, in dysentery, earache, skin disease, troubles of the rectum, fever due to *tridosha* and allay thirst (2, 6, 16). It is also used in gout and rheumatism (17). In Ayurveda it is used to remove the bad taste of mouth (2). The bark is a good substitute for kurchi, *Holarrhena antidysenterica* (6). *A. excelsa* along with *Arjuna myrobalans* strengthen the body's natural rejuvenative processes. Fruits are used in diarrhea, polyurea, piles and fever (18). Leaves along with twigs are found to be suitable fodder for cattle, sheep and goats (19-20). The tree yields an inferior quality of bassora or hog gum. The plant serves as one of the host for silk worms. In France the tree is cultivated for its leaves, on which the caterpillar of the silk spinning *Ailanthus* moth (*Bombyx cynthia*) is fed yielding a silk of more durable and cheaper than mulberry silk. The wood is short fibered, admixture with long fiber pulp, such as bamboo pulp, used in the manufacture of paper (6). It is also used for the preparation of pencils (21).

Preparations

Ailanthus is an important ingredient in most of the ayurvedic preparations like, *Pusyanuga churna, Brahat Gangadhara churna and Aralu putpaka*, used in the management of atisara, krimi, arsa, sannipatajwara, brama, tvakroga, chardi, kustha, pravahika, grahani, prameha, gulma, swasa, musaka and visaja roga (22). *Dasmularista,* a highly prized ayurvedic formulation for fatigue, is actually a mixture of ten different herbs out of which one is Shyonak/Sonapatha. It aids in cellular regeneration to hasten removal of dead or weak cells and replace them with fresh, vital ones (23). In ayurvedic literature there happens to be a controversy between the common name used for both *Ailanthus excelsa* and *Oroxylum indicum* mentioned as *Shyonak* (24). In the Bhavprakashnighantu also *Ailanthus excelsa*, is described under the name of 'Aralu' and Sonapatha/Shyonak is mentioned as its synonym (25-26). In Amarkosh *aralu*, *shyonak* and *tintuk* are the names given to the same plant (27). In the title "Some controversial drugs in Indian medicine" the Nighantu writers have confounded it with *Oroxylum indicum* (Bignoniaceae) (24). As per the Adarsha Rajniguntakar Nighantu, the description under Shyonakyugal mentioned that in case of two *Shyonakas*, one should be *aralu* and other is *tintuk*, whereas European practitioners consider both *Ailanthus excelsa* and *Oroxylum indicum* as totally different plants; however *Ailanthus excelsa* is said to be a substitute for Shyonak (28).

Pilex, the most popularly used ointments for piles contains bark of *Ailanthus excelsa* and is indicated in hemorrhoids, anal fissures, fistulae, proctitis, venous stasis, varicose veins, thrombophlebitis, varicocele and varicosity (29). Lukol tablets used in leucorrhoea contains Loh Bhasma, along with extracts of *Withania somnifera*, *Saraca indica, Woodfordia floribundi, Symplocos racemosa, Ailanthus excelsa, Leptadenia reticulata* and *Asparagus racemosus* which acts synergistically as uterine tonics, nervine sedatives and have a stimulating action on the endometrium and ovarian tissues (30-33). Sports

massage oil prepared from the bark of A. *excelsa* is used to keep muscles relaxed. "Rain tree's Simarouba extract" the preparation of *Simarouba amara*, contain quassinoids like ailanthinone and glaucarubinone as the main active constituents, which are also present in *Ailanthus excelsa*, and are considered to be the main therapeutic constituents for dysentery (amebic and bacterial) and diarrhea; intestinal worms and internal parasites; malaria; as an astringent to stop internal bleeding (stomach ulcers, hemorrhages) and externally for wounds and in viral infections (34).

EARLY PHYTOCHEMICAL STUDIES

Quassinoids: Plants from *Simaroubaceae* are known to contain compounds with highly oxygenated triterpenens and bitter taste called as quassinoids (35). Initially the compounds of such chemical nature were known by the term "quassin" after the physician "Quassi" who used the bark of plants from this family for the treatment of fever. Studies on quassinoids have shown their promising role as therapeutic agents as an antitumor, antiviral (36-37), anti-inflammatory, antiamoebic (38-49) antimalarial (40-41), insecticidal, antitubercular (42), anticancer (43), amoebicidal (36), antiulcer (44), herbicidal and antifeedent, etc (45). Stem bark of *A. excelsa* contains quassinoids like excelsin, 1,4-dihydroexcelsin (46-47), 2,4-dihydroexcelsin, 3,4-dihydroexcelsin (48), 13,18-dehydroexcelsin, glaucarubin (49), glaucarubol (50), ailanthinone, 1,12-deoxy-13-formyl ailanthiol, ailanex A, ailanex B, polyandrol and glaucarubolone (51-52) while the root bark is reported to contain ailanthinone, glaucarubinone and mixture of glaucarubin -15 - isovalerate, 13, 18-dehydroglaucarubol 15-isovalerate (53). Ailanthone is toxic to some fungi and may therefore acts to protect plants against fungal pathogens and is associated with the observed toxicity of this species (54-55). A total control on *Chenopodium album* and *Amaranthus retroflexus,* the two weeds associated with soybean was observed with excelsin (50). Quassinoids from *Simarouba amara* were tested in vitro against a multi drug resistant strain of *Plasmodium falciparum* and in vivo against *Plasmodium berghei* in mice. Although the in vitro studies indicated activity in the region of 23-52 times greater than that for chloroquine, the toxicity was found to be very high (56). Few quassinoids isolated from *Simana cedron* showed good activity against chloroquine-resistant and chloroquine sensitive strains of *Plasmodium falciparum* and *Plasmodium vinckei petteri* in mice. (57) Quassinoids also play an important role in treating Epstein- Barr virus infection (58), HIV infection (59-61), and neoplasms (62) possibly by depolarization of mitochondrial membranes (63). **(Fig. 4)**

2, 6-dimethoxy benzoquinone and malanthin: An yellowish green viscous oil was obtained by percolation of air dried powder of trunk bark from an old tree of *A. excelsa*. This oil after refrigeration in minimum amount of benzene and light petroleum gives colorless crystalline malanthin. Saponification of the mother liquor left after malanthin crystallization gives 10% saponifiable matter and 90% unsaponifiable material. The unsaponifiable material upon column chromatography on alumina gives 2, 6 dimethoxy benzoquinone and β –sitosterol (64-67).

Steroidal compounds: The petrol extract of stem bark on column chromatography over silica gel gives β –sitosterol and Stigmasta-4, 22-diene-3-one with hexane- ethyl acetate (9:1) (66). **(Fig. 5)**

Triterpine: Root bark showed the presence of a new triterpene alcohol, 3S, 24S, 25-trihydroxytirucall-7-ene (47, 67-68) **(Fig. 5)**

Triacontane and Hexatriacontane: Stem Bark showed the presence of triacontane and hexatriacontane (69).

Alkaloids: Methanol extract from root bark after solvent extraction with chloroform gave four alkaloids viz., canthin-6-one, 1-methoxy canthin -6-one, 5-methoxy canthin -6-one and 8-hydroxy canthin-6-one (70-72). These alkaloids were studied for nasopharynx carcinoma in Eagles but none of the compounds were sufficiently active to meet the required criteria. On the other hand these alkaloids have shown significant cytotoxicity against 12-O-tetradecanoylphorbol-13-acetate induced Epstein-Barr virus early antigen (EBV-EA). Canthin-6-one and 4-methoxy canthin-6-one showed potent antiulcerogenic activity in gastric lesions induced animals, as well as significant antinociceptive activity in mice (73-74). **(Fig. 6)**

Proteins: Leaves contain considerable amount of proteins where, cytoplasmic protein fraction can be used for human consumption; while the unfractionated and chloroplastic fractions could be utilized as a nutritious feed for ruminants and nonruminants. Proximate analysis of various fractions of fresh leaves showed 62.71% crude protein in cytoplasmic protein fraction, while whole leaf showed 20.86% protein. The unfractionated and fractions from chloroplastic protein contained more crude fat than the whole leaf and pressed cake. Compared to whole leaf and pressed cake, protein fractions were low in crude fiber content. The amino acid compositions of protein sample, showed an excellent balance of essential amino acids. The leaf protein fractions were nutritionally superior to the whole leaf, pressed cake as well as soyabean protein (75-76) **(Table-1)**.

Flavonoids: From a pharmaceutical perspective flavonoids possess a remarkable spectrum of biochemical and pharmacological activities. The leaves were reported to contain different flavonoids like kaempferol (5, 4', 5, 7-Tetrahydroxy flavone), luteolin (3', 4', 5, 7-tetrahydroxy flavone), apigenin (4'.5, 7-trihydroxy flavone) while fruits contains quercetin (77-78). These flavonoids were reported to possess many biological activities such as antibacterial, anti-inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, anti-thrombotic and vasodilatory properties. The flavon-C-glycosides like vitexin show antioxidant, analgesic and antithyroid activities (79-81), where as quercetin inhibits the growth of leukemic cells, ehrlich ascites tumor cells, and other ascites tumor cells (82-85). It potentates the cytotoxicity of DNA-damaging anticancer drugs, such as cis-platin (86-89). **(Fig. 7)**

Ailantic acid: Bark contains wax like, reddish brown, water soluble bitter principle, known as ailantic acid. It is given as a tonic and alterative in dyspepsia and constipation (4).

PHARMACOLOGICAL PROPERTIES

Antifertility activity: The alcoholic extract of the leaf and

Table.1 Amino acid composition of the fractionated leaf protein concentrate (grams per 16 gram of nitrogen) (75-76).

S.NO	Amino acid	Unfractionated LPC*	Chloroplastic LPC	Cytoplasmic LPC	Soyabean Protein
1	Lysine	6.17	5.99	7.75	6.40
2	Threonine	4.72	4.69	4.85	4.10
3	Serine	4.87	4.71	4.38	5.60
4	Glutamic acid	12.27	12.26	12.53	19.10
5	Glysine	6.57	7.19	6.89	4.20
6	Alanine	6.67	6.645	6.79	4.30
7	Valine	7.20	7.08	7.20	5.00
8	Isoleucine	6.18	6.09	6.16	4.00
9	Leucine	10.75	11.27	10.10	7.80
10	Tyrosine	5.98	5.90	6.01	3.80
11	Phenylalanine	7.87	8.25	7.65	5.20
12	Methionine	1.79	1.65	2.11	1.40
13	Cystine	1.00	0.96	1.58	1.80
14	Aspartic acid	10.80	10.80	11.13	11.60
15	Arginine	6.37	6.21	8.01	7.70
16	Histidine	2.43	2.41	2.98	2.80

*LPC- Leaf proteins concentrate.

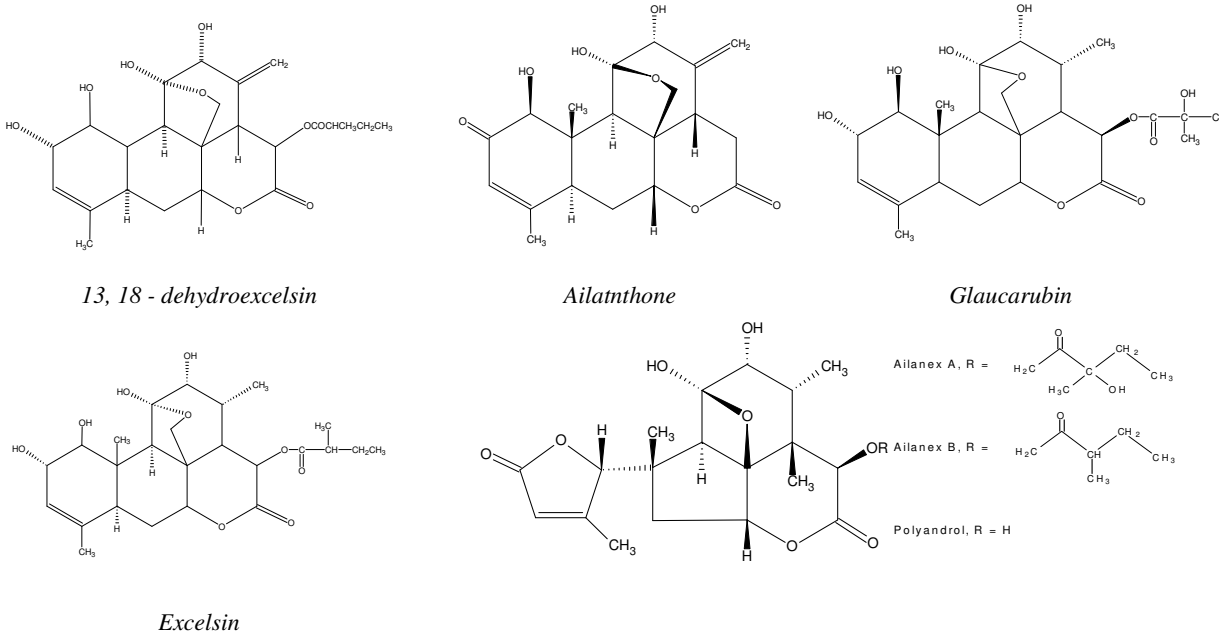
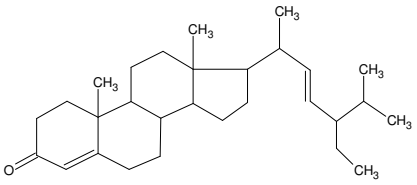
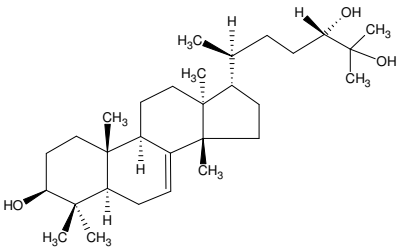


Fig. 4. Structures of quassinoids from Ailanthus excelsa

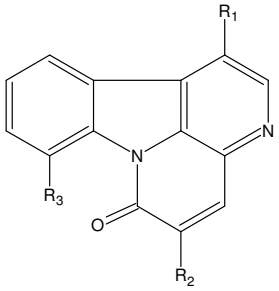


Stigmasta -4, 22-diene-3-one



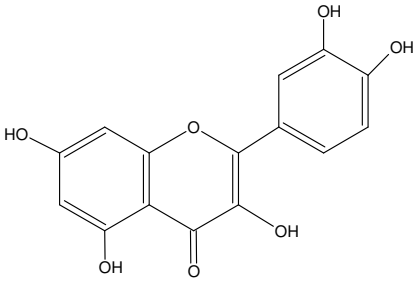
3S, 24S, 25 - trihydroxytirucall-7-ene

Fig. 5. Structures of Steroid and Triterpenoid from Ailanthus excelsa.

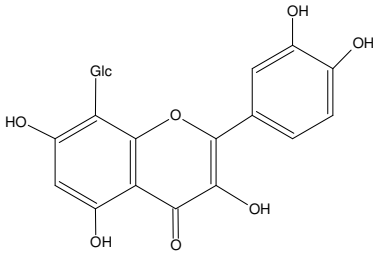


	R_1	R_2	R_3
Canthin-6-one	*H*	*H*	*H*
1-methoxy canthin-6-one	OCH_3	*H*	*H*
5-methoxy canthin-6-one	*H*	OCH_3	*H*
8-hydroxy canthin-6-one	*H*	*H*	*OH*

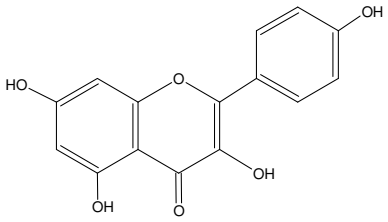
Fig.6. Structure of Alkaloids from Ailanthus excelsa



Quercetin



Vitexin (5,7,4'- trihydroxyflavone-8-glucoside)



Kaempferol

Fig. 7. Structures of phenolics from Ailanthus excelsa

stem bark at a dose of 250mg mg/kg body weight exhibited a remarkable antimplantation and early abortificient activity in female albino rats (13).

Antifungal activity: Chloroform fraction of the methanol extract of stem bark showed significant fungistatic and fungicidal activity against *Aspergillus fumigatus*, *Penicillium frequentence*, *Aspergillus niger*, *Penicillium notatum* and *Botrytis cinerea* (90).

Antimalarial activity: It has been considered as a great discovery that several quassinoids possess potent antimalarial activity especially against the chloroquine-resistant *Plasmodium falciparum* (91-96). Excelsin was found to inhibit the growth of malarial parasites even at a concentration of 0.2μM (51). Glaucarubinone is much more potent than that of chloroquine and acts by inhibiting the protein synthesis in mammalian cells as well as in malaria parasites. It has been suggested that this effect also accounts for their amoebicidal activity (97-98). However, their antimalarial action is

different from that of cytotoxicity, as some quassinoids have shown greater selectivity against *P. falciparum* than against KB cells (99-100). The cytotoxicity of glaucarubinone against KB cells is 285 times of its activity against *P. Falciparum* (101). All quassinoids inhibits protein synthesis more rapidly than nucleic acid synthesis in the *P. falciparum* infected human erythrocytes which is mainly due to its effects upon ribosome rather than upon nucleic acid metabolism. Inhibition of nucleic acid synthesis was observed following the failure of protein synthesis. As chloroquine does not affect protein synthesis so the chance of cross-resistance of malaria between quassinoids and chloroquine is less (97).

Antibacterial activity: Ethyl acetate fraction of dried stem bark inhibited the growth of *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* (MIC: 6mg/disc). Three active principles, excelsin, 13, 18-dihydroexcelsin and 1, 12-deoxy-13-formylailanthinol, isolated from bark are said to be responsible for this activity. The antibacterial activity of all three compounds was more pronounced than the antifungal potency (102-104).

Hypoglycemic activity: A single administration of leaves or stem bark extracts of *A. excelsa* lowered the blood glucose of normal rats in a glucose tolerance test. Administration of each extract for 60 days produced a significant hypoglycemic effect on STZ-induced diabetic rats, with improved renal parameters which suggest of its potential use in the treatment of diabetes (105).

Insect feedent-deterrent: Bioassay directed fraction of the methanol extract of the stem bark led to the isolation and identification of antifeedent constituent excelsin. A leaf disc method of bioassay showed the potency of excelsin to prevent feeding was 75.94% at a concentration of 1000 ppm against *Spilosoma oblique*. This insect is a destructive lepidopterous pest in the northern parts of India, attacking a wide range of crops. The ED_{50} of excelsin was found to be 0.563% (46). Structure activity correlation indicates that cytotoxicity might be involved in the mode of action of these compounds. Ailanthone acts as a feeding deterrent to herbivores because of its extremely bitter taste (106-110).

Antipyretic activity: Ethanol extract of *A. excelsa*, showed moderate to significant degree of antipyretic activity against yeast suspension induced hyperthermia in an experimental rat model (111).

Leishmanicidal: A genus of parasitic flagellate protozoans causes leishmania. In man it invades the cells of the lymphatic system, spleen, and bone (kala-azar). Canthin-6-one alkaloid from *Ailanthus* was found to be active against these protozoans (112).

Antitumor and cytotoxicity: Aqueous extracts of roots when screened by the brine shrimp lethality assay it showed significant toxicity to the brine shrimp (<60 µg/ml) (113). The quassinoids like Ailanthione, glaucarubinone and a mixture of glaucarubol 15-isovalerate have shown substantial antitumor and cytotoxic activities against the P 388 lymphocytic leukemia and KB test system respectively (6, 99, 114). The observed antitumor activity is by inhibiting the protein synthesis of ribosomal peptidyl transferase leading to the termination of chain elongation (115).

Hepatoprotective activity: Ethanol extract of leaves showed protective effects against CCL_4 induced liver injury as evidenced by a significant reduction in the CCL_4 induced elevated enzyme levels of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase and serum alkaline phosphatase. The presence of phenolics might be the responsible factor for the above activity (116-117).

Toxicity: Large dosage of drug are said to lead queasiness, dizziness, headache, tingling in limbs and diarrhea, myocarditis associated with fever, chills, epigastric pain, substernal chest pressure, and shortness of breath which may likely due to exposure to quassinoids present in tree sap (118).

SUMMARY AND CONCLUSION

In the present review we have made an attempt to congregate the botanical, phytochemical, nutritional, ethnopharmacological, pharmacological and toxicological information on *Ailanthus excelsa,* a medicinal herb used in the Indian system of medicine. Survey of literature revealed the presence of quassinoids, alkaloids, proteins, triterpenoids, flavonoids and steroids in different parts of this plant. Research on quassinoids has gained a special attention in recent times as several of them have shown promising activities like antitumor, antiviral, antimalarial, antileukemic, antifeedent, etc. The antitumor activity of quassinoids is definite, but most of the compounds are too toxic to be clinically used. Investigating the new sources of natural products to isolate more potent and less toxic quassinoids and structurally modifying the known compounds to retain activity and lower toxicity are still the best possible ways to develop safe and effective anticancer drugs of this class. Malaria claims several million deaths every year on a global basis which is mainly due to increased resistance to chloroquine and quinine. In spite of the fact that two of the clinically used antimalarials, quinine and artemisinin, were originally derived from plants, further search for isolation and identification of new antimalarial lead structures from natural sources are extremely limited. The ethnopharmacological approach used in the search for new antimalarial compounds from such plants appears to be helpful compared to the random screening approach. However, a promising approach is needed to use these agents as templates for designing new derivatives with improved properties. Quassinoids have demonstrated a potent antimalarial activity against the chloroquine-resistant *P. falciparum* and the chances of cross-resistance of malaria between quassinoids and chloroquine is less, as quassinoids inhibits bacterial protein synthesis while chloroquine does not affect protein synthesis. Therefore, these triterpenoids offer a promising source for the development of new antimalarial agents. Few drugs of plant origin have been screened for antifertility but with only limited efficacy, where as *Ailanthus excelsa* would be worthwhile in serving as a tool, in birth control. Due to contraversy in ayurvedic literature between *Ailanthus excelsa* and *Oroxylum indicum* for the common name, today also few practitioners are using *A. excelsa* roots in *Dasmularista* under the name *Shyonak,* but as these roots are reported to contain canthin group of alkaloids and the bitter quassinoids, one

must keep in mind the toxicity of these compounds while using them in such a rejuvenating preparation. This review will definitely help for the researchers as well as practitioners, dealing with this plant, to know its nature proper usage. *A. excelsa* be treated as highly palatable and nutritious fodder for sheep and goats, where the cytoplasmic protein fraction can be used for human consumption; and the other two fractions could be utilized as a nutritious feed for ruminants and nonruminants (119). The extract and purified fractions of *A. excelsa* were strong plant growth inhibitors, therefore could be considered as potent, effective and environmentally safe agricultural pesticides (120).

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