THE PHARMACOLOGICAL IMPORTANCE OF *AILANTHUS ALTISSIMA- A REVIEW*

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ABSTRACT

Ailanthus altissima contained proteins, flavonoids, alkaloids, quassinoids, terpenylated coumarins, tetracyclic triterpenoids, fatty acids, volatile oils and many other active compounds. It exerted antibacterial, antiviral, antioxidant, cytotoxic, antidiarrheal, anti-inflammatory, antipyretic, analgesic, antihistaminic, antiparasitic, insect repellent, anti-progestogenic and many other pharmacological effects. This paper will highlight the chemical constituents and pharmacological effects of *Ailanthus altissima*.

Key words: *Ailanthus altissima*, Constituents, Pharmacology.

INTRODUCTION

Since the dawn of civilization, man utilized plants for their medicinal and edible value. By trial and error, and before the introduction of chemical medicines, man distinguished between the beneficial and poisonous plants. Each population in the world developed its own traditional medical knowledge and experiences. World health organization estimates that about 80% of the world populations rely almost exclusively on traditional medicine for their primary healthcare needs. *Ailanthus altissima* contained proteins, flavonoids, alkaloids, quassinoids, terpenylated coumarins, tetracyclic triterpenoids, fatty acids, volatile oils and many other active compounds. It exerted antibacterial, antiviral, antioxidant, cytotoxic, antidiarrheal, anti-inflammatory, antipyretic, analgesic, antihistaminic, antiparasitic, insect repellent, anti-progestogenic and many other pharmacological effects. This paper will highlight the chemical constituents and pharmacological effects of *Ailanthus altissima.*

Synonyms

Ailanthus glandulosa Desf; *Toxicodendron altissimum* Mill [1-3].

Taxonomic classification
Kingdom: Plantae
Phylum:Spermatophyta
Subphylum: Angiospermae

Class: Dicotyledonae
Order: Rutales
Family: Simaroubaceae
Genus: Ailanthus
Species: *Ailanthus altissima* [4].

Common names

Arabic: shajarat el- sama; Chinese: bai chun, chou chun, chun shu; English: tree of heaven, ailanthus, Chinese sumac, stinking shumac; Germany: Götterbaum; French: ailante, ailante glanduleux, arbre des dieux, arbre du ciel, faux vernis du Japon; Italy: ailanto, albero del paradiso; Russian: ajlant vysočajšij; South Africa: hemelboom; Sweden: gudatraed, himmelstraed [5].

Traditional uses

Ailanthus altissima was used in traditional medicine for treatment of dysentery, gonorrhea, hemorrhoids and a remedy for cough, gastric and intestinal upsets. The bark is prescribed to treat anemia, diarrhea, hemorrhage and spermatorrhea. It is also used as antispasmodic, antiasthmatic, cardiac depressant, astringent and for treatment of epilepsy [6-7].

Distribution

Tree of heaven (*Ailanthus altissima* (Mill.) is a fast-growing deciduous tree which is native to Asia. It was introduced into Europe (1751) and to the United States

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(1784), into Eastern states by a Philadelphian gardener and into Western States by Chinese immigrants who used it for medicinal purposes [8]. However, the tree was originally indigenous to China, but today it grows in the wild and is cultivated in tropical and subtropical eastern Asia, Northern Europe and North America [9].

Description

Tree-of-heaven is deciduous. It may reach 60 to 70 feet (18-21 m) in height, 80 feet (24 m) in crown width, and 20 feet (6 m) in trunk diameter at maturity. Tree-of-heaven may be shrubby when suppressed beneath the canopy or pruned regularly. It has smooth, thin bark and a straight bole. Branches are brittle and self-pruning. There are 2 branch types: long and short shoots. Long shoots are sterile and may extend 18 feet (5 m), while short shoots bear flowers and rarely reach more than 18 inches (46 cm) long. The large, malodorous leaves are pinnately compound, with prominent glands on the back of each leaflet. Leaflets range from 15 to 41 in number, and total leaf length may reach 3 feet (1 m). Leaf stipules have nectaries that excrete sugars. Most flowers are unisexual, but some trees may have perfect flowers. The inflorescence is a 4- to 7-inch (10-20 cm) long panicle with 6- to 8-mm long flowers. Staminate flowers have a strong odor that is objectionable to humans. Fruits are one-seeded, dry schizocarps with wings. They are 1 to 2 inches (2.5-5 cm) long and propeller-shaped, resembling maple (Acer spp.) fruits. The fruits grow in clusters; a fruit cluster may contain hundreds of seeds. Seeds average 0.2 × 1.0 inch (0.6 × 0.25 cm) in area and 27 mg in mass. Roots are shallow and wide-spread. Young trees have a taproot and several large lateral roots, although the taproot may diminish with age. In dry, rocky soil or beneath pavement, tree-of-heaven grows long, horizontal roots that do not branch until reaching a more favorable substrate. Roots near the trunk thicken with age, serving as storage organs. Deep roots send out smaller roots that grow near the soil surface; stem shoots generally sprout from these shallow roots. Most roots occur in the upper 18 inches (46 cm) of soil [10-20].

Part used: Dried trunk and root bark [9].

Chemical constituents

The seed contained 27.5–27.6g/100g protein, 55.5–59.1g fat/100g, 6α-tigloyloxy chaparrinone, ailanthone and quassiin. The different parts of the plant contained many quassinoids: ailantinols A-G, shinjulactone A-O and altissinol A-H [21-34].

Three neolignan glycosides were extracted from the ethanolic extract of the root bark of *Ailanthus altissima* (7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-O-4'-neolignan-4-O-β-D-glucopyranoside, sonchifolignan B and citrusin B) [35].

Many terpenylated coumarins were isolated from the stem bark of *Ailanthus altissima*, including (2'R,3'R)-7-(2',3'-dihydroxy-3',7'-dimethylocta-6'-nyloxy)-6,8-dimethoxy coumarin, 6,8-dimethoxy-7-(3',7'-dimethylocta-2',6'-dienyloxy)coumarin, (2'R,3'R,6'R)-7-

(2',3'-dihydroxy-6',7'-epoxy-3',7'-dimethyloctaoxy)-6,8-dimethoxy coumarin, and (2'R,3'R,4'S,5'S)-6,8-dimethoxy-7-(3',7'-dimethyl-4',5'-epoxy-2'-hydroxyocta-6'-enyloxy)coumarin [36].

Tetracyclic triterpenoids (altissimanins A-E,) and a terpenylated coumarin (altissima coumarin G), were isolated from the bark of *Ailanthus altissima* [37].

A new seco-neolignan glycoside, seco-dehydrodiconiferyl alcohol-4-O-β-D-glucopyranoside were obtained from the ethanolic extract of the root bark of *Ailanthus altissima* [35].

Cerebroside and three cycloartan triterpenes were also isolated from fruits of *Ailanthus altissima* Swingle. Their structures were identified as 1-O-beta-D-glucopyranosyl-(2S, 3R, 4E, 9E)-2-(2'R-hydroxyhexadecenoy)-4, 9-octadecadiene-1, 3-diol ; 9, 19-cyclolanost-23 (Z)-ene-3beta, 25-diol; cycloart-25-ene-3beta, 24R-diol; and cycloart-25-ene-3beta, 24S-diol [38].

Alkaloidal glycosides, canthin-6-one, 1-methoxycanthin-6-one canthin-6-one-5-o-beta-D-xylopyranosyl- (1→6)-beta-D-glucopyranoside and canthin-6-one-1-o-beta-D-xylopyranosyl- (1→6)-beta-D-glucopyranoside named ailantcanthinosides A and B, were isolated from the root bark of *Ailanthus altissima* [39-40].

The leaves contain 12% tannin, quercetin, as well as isoquercetin, and the alkaloid linuthine [41-43]. The methanolic extracts from leaves contained the highest level of total phenolic content, while those from the hydrodistilled residues showed the highest total flavonoid content. The most frequent phenolic compounds identified by HPLC-DAD–MS were gallic acid, chlorogenic acid, HHDP-galloylglucose, epicatechin, rutin, hyperoside and quercetin-3-galloyl hexoside [44]. The amount of total phenolic compounds in ethanolic extract fraction was (12.25%), represented the highest compared with other extract or fractions [45-46]. However, Low *et al*., isolated eight compounds from the flowers of the plant including, brevifolin, brevifolin carboxylic acid, methyl brevifolin carboxylate, ellagic acid, diethyl-2,2',3,3',4,4'-hexahydroxybiphenyl-6,6'-dicarboxylate, rutin, gallic acid, ethyl gallate [47].

Eight different proteins were isolated (16.6 – 66.1 kDa) from *Ailanthus altissima* leaves and nine proteins from *Ailanthus altissima* stems (16.6-83.2 kDa) [46].

Chemical analysis showed that the leaf volatile oils were a complex mixture, mainly composed of non-terpenic compounds (tetradecanol, heneicosane, tricosane and docosane) and sesquiterpene hydrocarbons (α-curcumene and α-gurjunene) [44].

The essential oils of different plant parts of *Ailanthus altissima* (Mill.) Swingle cultivated in Tunisia, viz., roots, stems, leaves, flowers, and samaras (ripe fruits), were evaluated by hydrodistillation. In total, 69 compounds, representing 91.0-97.2% of the whole oil composition, were identified in these oils by GC-FID and GC/MS analyses. The root essential oil was clearly distinguishable for its high content in aldehydes (hexadecanal; 22.6%), while those obtained from flowers and leaves were dominated by oxygenated sesquiterpenes (74.8 and 42.1%, respectively), with caryophyllene oxide

as the major component (42.5 and 22.7%, respectively). The samara oil was rich in the apocarotenoid derivative hexahydrofarnesyl acetone (58.0%), and the oil obtained from stems was characterized by sesquiterpene hydrocarbons (54.1%), mainly β-caryophyllene (18.9%) [48].

However, the content and chemical composition of the volatile compounds of ailanthus were evaluated. The yields of volatile compounds in fresh leaves were 210.5 mg/kg for the young plant and 120.6 mg/kg for the old plant. After drying, the yields were several times smaller, 51.3 mg/kg for the young and 60.2 mg/kg for the old plant. The ailanthus volatiles are characterised by a high content of oxygenated aliphatic compounds (alcohols, aldehydes, ketones, acids and esters), especially C6-compounds. From young plants, the contents of aliphatic volatile compounds were 58.5% for fresh and 59.7% for dried leaves. The main aliphatic compounds were: (Z)-3-hexen-1-ol, (E)-2-hexenal, (Z)-3- hexen-1-ol esters (butanoate, acetate and hexanoate) and hexadecanoic acid for fresh young plant material; while, the main aliphatic compounds in the dried young plant material were (E)-2-hexenal, 6-methyl-5-hepten-2-on, esters of (Z)-3-hexen-1-ol (butanoate and methylbutanoate), nonanal and hexadecanoic acid. However, the main aliphatic compounds in the dried old plant were (Z)-3-hexen-1-ol, (Z)-3-hexen-1-yl acetate, 1-hexadecanol and tetradecanal, octadecanal; while, (E)-2-hexenal, 6-metil-5-hepten-2-on, hexadecanoic, dodecanoic and tetradecanoic acid. The highest contents of (Z)-3-hexen-1-ol, and its esters (acetate, butanoate and hexanoate) were found in the fresh material of young plants. (Z)-3-hexen-1-yl acetate was not identified in dried (young and old) materials. On the other hand, dried plant materials contained several times higher amounts of (E)-2-hexenal and 6-methyl-5-hepten-2-one than the fresh ones. Hexadecanoic, dodecanoic, tetradecanoic and 9-octadecenoic acids were most abundant in the fresh leaves of young plants. Furthermore, twelve sesquiterpene compounds were identified, representing the second significant group of ailanthus volatiles. Among them, γ-cadinene, β-caryophyllene, α-humulene and calarene were the main components. Sesquiterpene hydrocarbons were many times higher in fresh plant materials than in the dried ones. The smaller part of sesquiterpene compounds were oxygenated sesquiterpenes, such as α-sinesal, (E,E)-farnesal and farnesol. Oxygenated monoterpenes represented the third group of ailanthus volatile compounds. Seven oxygenated monoterpenes were identified, linalool and β-cyclocitral being the most representative. However, unlike most aromatic plants, monoterpene hydrocarbons were not identified among the ailanthus volatile compounds [49].

PHARMACOLOGICAL EFFECTS
Antimicrobial effects

Metanolic extracts from leaves and hydrodistilled residues were efficient against gram-positive bacteria [44]. A new naturally occurring sterol and six known stigmasterols isolated from fruits of *Ailanthus altissima* showed potent activity against many bacterial isolates.

However, two compounds exhibited moderate activity [50].

The antibacterial effects of methanolic extracts of *Ailanthus altissima* leaves were evaluated by agar disk diffusion method against 11 (six gram-positive and five gram-negative) foodborne bacteria. The methanol extract and its different polar subfractions inhibited significantly the growth of all six gram-positive bacteria: [*Listeria monocytogenes* (ATCC 19116, ATCC 19118 and ATCC 19166), *Staphylococcus aureus* (ATCC 6538 and KCTC 1916) and *Bacillus subtilis* ATCC 6633] and two gram-negative bacteria: [*Pseudomonas aeruginosa* KCTC 2004 and *Escherichia coli* ATCC 8739]. The zones of inhibition of methanol extract and its derived different polar subfractions against the tested bacteria were found in the 12.1–23.2 mm range and the minimum inhibitory concentration values were recorded between 62.5 and 500 mg/ml [46]. Anti-tuberculosis activity was conducted for quassinoids isolated from *Ailanthus altissima*, although the activities were low, the resulting data provided a picture of structure-activity relationships [51].

Antiviral effect

Three neolignan glycosides extracted from the ethanolic extract of the root bark of *Ailanthus altissima* (7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-O-4'-neolignan-4-O-β-D-glucopyranoside, sonchifolignan B and citrusin B) exhibited moderate *in vitro* inhibitory effect on tobacco mosaic virus replication with IC_{50} values 0.30, 0.35 and 0.26 mmol/l, respectively [35].

The methanolic stem bark extract of *Ailanthus altissima* showed potent anti-HIV activity (74.9 ± 4.4%) at a concentration of 100 microg/ml (applied to a syncytia formation inhibition assay, which is based on the interaction between the HIV-1 envelope glycoprotein gp120/41 and the cellular membrane protein CD4 of T lymphocytes) [52].

Ailantinol E, ailantinol F, and ailantinol G, and related compounds isolated from *Ailanthus altissima* grown in Taiwan, were evaluated for its antitumor promoting effects against Epstein-Barr virus early antigen activation introduced by 12-O-tetradecanoylphorbol-13-acetate in Raji cells. Quassinoids were found to show potent activity [31].

Antiparasitic and Repellent effects

The chloroform extract of *Ailanthus altissima* stem bark was tested for their antischistosomal and hepatoprotective effects. The effect of schistosomal infection and treatment with extracts on the activities of aspartate and alanine aminotransferases, acid phosphatase, 5'nucleotidase, glucose-6-phosphatase, lactate dehydrogenase, alkaline phosphatase and succinate dehydrogenase were estimated, the effect on free radical production in the form of lipid peroxides and on the levels of certain antioxidants namely, catalase, glutathione, vitamins C and E were also evaluated. In addition, the efficiency of the tested extracts on reducing the worm burden and ova counts in the infected mice was studied. The results revealed that infection with *S. mansoni*

increased lipid peroxides and decreased all antioxidant levels. On the other hand, the activities of acid phosphatase and 5`nucleotidase were higher while those of glucose-6-phosphatase, lactate dehydrogenase, alkaline phosphatase and succinate dehydrogenase were lower with respect to control. However, treatment with *Ailanthus altissima* ameliorated the disturbed lipid peroxides, antioxidants and enzymes' levels to nearly the control values [53].

Extracts and isolated compounds from seedlings of *Ailanthus altissima*, were assessed for antiplasmodial activity *in vitro*. Two quassinoids, ailanthone and 6 alpha-tigloyloxychaparrinone, isolated from the active extracts showed activity against both chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium falciparum in vitro* [54].

Extracts *of Ailanthus altissima* (Mill.) Swingle have been tested for activity against *Plasmodium falciparum in vitro* and against *P. berghei* infections in mice. The activity of the chloroformic extract *in vitro* (IC_{50} 5 µg/m) and *in vivo* (ED_{50} 82.94 mg kg/d after oral administration), the activity was due, principally to the presence of the quassinoid ailanthone (IC_{50} *in vitro*: 0.015µg/ ml, ED_{50} *in vivo*: 0.76 mg kg/d) [55].

The potential acaricidal properties of an *Ailanthus altissima* bark extract were assessed against two common species of animal ectoparasitic mites, *Psoroptes cuniculi* and *Sarcoptes scabiei var. cuniculi*, *in vitro*. *Ailanthus altissima* bark extract was obtained by ethanol thermal circumfluence and tested at four concentrations (1.0, 0.5, 0.25 and 0.125 g/ml) on mites collected from rabbits. Compared to the fenvalerate treatment group, the *Ailanthus altissima* bark exhibited significant acaricidal properties for both mite species. The extract at concentrations of 1.0, 0.5 and 0.25 g/ml killed all tested *S. scabiei* within 7 h, however, only 1.0 and 0.5 g/ml of extract killed all the treated *P. cuniculi*. The median lethal time (LT_{50}) values at 1, 0.5 and 0.25 g/ml were 0.60, 0.78, 1.48 h for *S. scabiei* and 0.74, 1.29, 3.33 h for *P. cuniculi*. The median lethal concentration (LC_{50}) for *P. cuniculi* was approximately 1.6 times that for *S. scabiei var. cuniculi* at 4 h. The extract showed stronger toxicity against *S. scabiei* than against *P. cuniculi*. Mortality rates increased with increasing concentration of extract administered and with increasing time post-treatment, indicating that the acaricidal activity of *Ailanthus altissima* bark extract is both time- and dose-dependent [56].

The essential oil of *Ailanthus altissima* bark repelled *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionidae), *Oryzaephilus surinamensis* (Linnaeus) (Coleoptera: Silvanidae), *Sitophilus oryzae* (Linnaeus) (Coleoptera: Curculionidae) and *Liposcelis paeta* Pearman (Psocoptera: Liposcelididae) adults, with the repellency value reaching IV grade or stronger during the whole exposure period. *Ailanthus altissima* bark oil also possessed strong contact toxicity on *S. oryzae* adults which gradually enhanced with increased exposure time and the corrected percentage mortality reached 76.5% after 72h treatment. Furthermore, *Ailanthus altissima* bark oil had high fumigant activity against *O. surinamensis* and *S.*

oryzae adults with the corrected percentage mortality 99.3 and 81.9% within 24 h, respectively [57].

Methanol extracts of various plant parts of *Ailanthus altissima* were tested against the root knot nematode *Meloidogyne javanica*. Extracts of bark (ABE), wood (AWE), roots (ARE), and leaves (ALE) from *Ailanthus altissima* were investigated against freshly hatched second-stage juveniles (J2). AWE was the most active extract, with EC_{50}/3d) of 58.9 mg/l, while ALE, ARE, and ABE did not show nematicidal activity. The chemical composition of the extracts of *Ailanthus altissima* was determined by gas chromatography-mass spectrometry, and (E,E)-2,4-decadienal, (E)-2-undecenal, (E)-2-decenal, hexanal, nonanal, and furfural were the most prominent constituents. (E,E)-2,4-Decadienal, (E)-2-decenal, and furfural showed the highest nematicidal activity against *M. javanica*, with EC_{50}/1d: 11.7, 20.43, and 21.79 mg/l, respectively, while the other compounds were inactive at the tested concentrations [58].

The mollusicidal effects of *Ailanthus altissima* cultivated in the hilly and mountainous areas, on Oncomelania hupensis against *O. hupensis* snails was studied.

The LC50 of *Ailanthus altissima* in 24, 48, and 120h reached the middle noxious level against *O. hupensis* snails [59].

Antidiarrhoeal effects
The methanolic extract of root bark of *Ailanthus altissima* (MEA) was investigated for anti-diarrhoeal activity in castor oil induced diarrhoea and small intestine transit method on mice. The methanolic extract of root bark of *Ailanthus altissima* 200 mg/kg reduced the total weight of the faeces [60].

Anti inflammatory, analgesic, antipyretic and antihistaminic effects
Ailanthus altissima stem bark of Egyptian origin were evaluated for their analgesic, antipyretic and antiulcer activities. Analgesic and antipyretic activities were evaluated by hot plate test at doses of 50 mg/ kg and 100 mg/kg of the extracts. The extracts have similar analgesic activity and the ether extract showed good analgesic activity at 30min. Also extracts showed a decrease on rectal temperature that means an hypothermic activity of the plant extracts with longer effect for the ether extract. Ether extracts showed a gastric ulcer protection activity and cytoprotection activity in a doses of 100 mg/kg as well as 50 mg/kg in ethanol induced ulcer in mice [61].

Luteolin-7-O-glucoside (L7G), isolated from *Ailanthus altissima*, inhibited 5-lipoxygenase (5-LOX)-dependent leukotriene C_4 (LTC_4) production in bone marrow-derived mast cells (BMMCs) in a concentration-dependent manner with an IC_{50} of 3.0 µM. To determine the action mechanism of L7G, immunoblotting for cytosolic phospholipase A2 (cPLA2) and mitogen-activated protein kinases (MAPKs) following c-kit ligand (KL)-induced activation of BMMCs with or without L7G were performed. Inhibition of LTC_4 production by L7G

was accompanied by a decrease in cPLA2 phosphorylation, which occurred via the extracellular signal-regulated protein kinase-1/2 (ERK1/2) and p38 and c-Jun N-terminal kinase (JNK) pathways. In addition, L7G also attenuated mast cell degranulation in a dose-dependent manner (IC$_{50}$, 22.8 µM) through inhibition of phospholipase Cγ1 (PLCγ1) phosphorylation. Accordingly, the authors suggested that the anti-asthmatic activity of L7G may be mediated in part via the inhibition of LTC4 generation and mast cell degranulation [62].

The Antiinflammatory effect of an ethanol extract from the parts of *Ailanthus altissima* was evaluated by both *in vitro* and in *in vivo* system. The ethanol extract of *Ailanthus altissima* (EAa) inhibited generation of the cyclooxygenase-2 (COX-2) dependent phases of prostaglandin D2 in bone marrow-derived mast cells (BMMC) in a concentration-dependent manner with an IC$_{50}$ value of 214.6 microg/ml. However, this compound did not inhibit COX-2 protein expression up to a concentration of 400 microg/ml in the BMMC, indicating that EAa directly inhibits COX-2 activity. In addition, EAa inhibited leukotriene C4 production with an IC$_{50}$ value of 25.7 microg/ml. Furthermore, this compound inhibited degranulation reaction in a dose dependent manner, with an IC$_{50}$ value of 27.3 microg/ml. When ovalbumin (OVA)-sensitized mice were orally pretreated with EAa before aerosol challenges. EAa reduced the eosinophil infiltration into the airway and the eotaxin, IL-4, and IL-13 mRNA expression levels [63].

The ethanol extract of *Ailanthus altissima* showed antiinflammatory activity in an ovalbumin (OVA)-sensitized murine asthmatic model. To determine the anti-inflammatory compounds in the plant, luteolin-7-O-glucoside (L7G) was isolated and its antiasthmatic activity was evaluated in an *in vivo* murine asthmatic model. L7G (10 to 100 mg/kg, po) reduced the amount of eosinophil infiltration in bronchoalveolar lavage (BAL) fluid in a dose-dependent manner. L7G inhibited both the prostaglandin E2 (PGE2) and serum immunoglobulin E level in BAL fluid in a dose-dependent manner. In addition, L7G inhibited the transcript profiles of interleukin IL4, IL5, and IL13 mRNA expression levels in the murine asthma model [64].

The effect of *Ailanthus altissima* Swingle (ailanthic cortex, AAS) on the mast-cell-mediated allergic and inflammatory reaction were studied using *in vivo* and *in vitro* models with elucidation of its molecular mechanisms. AAS significantly inhibited compound 48/48-induced edema and systemic anaphylaxis. AAS significantly inhibited passive cutaneous anaphylaxis. AAS inhibited histamine release from rat peritoneal mast cells (RPMCs) in a dose-dependent manner. Moreover, AAS significantly inhibited production of inflammatory cytokines, tumor necrosis factor (TNF), interleukin (IL)-6, and IL-8 on the phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-stimulated human mast cell line, HMC-1 cells. AAS inhibited the IgE or stem cell factor-induced TNF production on RPMCs. In activated HMC-1 cells, the level of NF-kappaB/Rel A in the nucleus was decreased by AAS treatment. In addition, AAS inhibited the PMACI-induced IkappaBalpha degradation [65].

Cytotoxicity effects

The cytotoxic activities of quassinoids were evaluated on the tumor cell lines HeLa, MCF-7, MDA-MB-231, HepG2 and A549 cells, as well as the normal HUVEC line *in vitro*. They exhibited different levels of inhibitory activity against tumor cell lines [33,66]. However, MTT assay was carried out to investigate the cytotoxic effect of *Ailanthus altissima* extract on PAE cells. It didn't exert significant toxic effect on PAE cells at 40-100 µg/ml compared to control [67].

The cytotoxicities of canthin-6-one, 1-methoxycanthin-6-one, 5-methoxycanthin-6-one, and canthin-6-one-3-N-oxide to guinea pig ear keratinocytes were studied, they showed cytotoxicity with IC$_{50}$ values range from 1.11 to 5.76 micrograms/ml. There is no significant difference in activity among these four cytotoxic alkaloids [40].

The anti-tumor constituents of fruits of *Ailanthus altissima* (Mill) Swingle were also investigated. Four compounds were isolated and identified as shinjulactone A, shinjuglycoside B, 5-hydroxymethylfuraldehyde and protocatechuic acid. The anti-tumor activities of two of them and the extracts of the fruits of *Ailanthus altissima* (Mill) Swingle were evaluated by MTT. The anti-tumor results demonstrate that shinjulactone A, shinjuglycoside B, 5-hydroxy methyl furaldehyde, together with extracts I (the extract with water of fruits of *Ailanthus altissima* chromatographed on HPD-100 resin and eluted 60% ethanol) and II (the EtOAc extract of ethanolic extract of fruits of *Ailanthus altissima*), exhibit moderate antiproliferative activity [68].

Ailantinol E, ailantinol F, and ailantinol G, and related compounds isolated from *Ailanthus altissima* grown in Taiwan, were evaluated for its antitumor promoting effects against Epstein-Barr virus early antigen activation introduced by 12-O-tetradecanoylphorbol-13-acetate in Raji cells. Quassinoids were found to show potent activity [31]. Short-term *in vitro* assays for tumor promoters and antitumor promoters (Epstein-Barr virus activation test) were carried out for 14 quassinoids isolated from *Ailanthus altissima*. Some quassinoids, including ailantinol B, ailantinol C, ailanthone, and shinjulactone A, showed moderate activity at a molar ratio of 1:100 [69].

The cytotoxic potential of the extracted quassinoids, altissinol A and B, together with 12 known quassinoids were evaluated *in vitro* against three human hepatoma cell lines. Seven quassinoids displayed potent cytotoxic activities against human hepatoma Hep3B and HepG2 cell lines. Three compounds exhibited cytotoxic activity against multidrug resistance HepG2/ADM cell line with IC50 value 4.3-fold more sensitive to Doxorubicin [70].

Ailanthus altissima Swingle was evaluated for its cytotoxic and antiproliferative activities by a bioassay-oriented study. Cytotoxicity observed in HeLa cells was time-dependent; the treatment with 10 microg/ml of the root chloroform extract reduced cell viability by 56% at

24h and 29% at 48 h of exposure. Significant effects were observed also for chromatographic fractions and the pure isolated alkaloid 1-methoxy-canthin-6-one. After 72h of incubation cell viability was less than 10% for all treatments. A possible apoptotic effect was evaluated by monitoring the presence of hypodiploid elements in HeLa cells as well as in SAOS, U87MG and U-937 tumor cell lines. The cells incubated for different times with the active extract. Fractions and pure alkaloid isolated from *Ailanthus altissima* showed a remarkable increase in the apoptosis [66,71].

The effect of 1-methoxy-canthin-6-one, isolated from *Ailanthus altissima* Swingle was studied on apoptosis in human leukemia (Jurkat), thyroid carcinoma (ARO and NPA), and hepatocellular carcinoma (HuH7) cell lines. Cultures incubated with the compound showed >50% of sub-G1 (hypodiploid) elements in flow cytometry analysis; the apoptosis-inducing activity was evident at <10 micromol/l and half-maximal at about 40 micromol/l 1-methoxy-canthin-6-one. The appearance of hypodiploid elements was preceded by mitochondrial membrane depolarization, mitochondrial release of cytochrome c, and Smac/DIABLO and procaspase-3 cleavage. The effect of 1-methoxy-canthin-6-one was investigated in combination with human recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in the four cell lines. Suboptimal concentrations (10 micromol/l 1-methoxy-canthin-6-one and 0.25 ng/m TRAIL, respectively) of the two agents, unable to elicit apoptosis when used alone, induced mitochondrial depolarization, activation of caspase-3, and 45% to 85% of sub-G1 elements when added together to the cells. The synergism seemed to rely partly on the enhanced expression of TRAIL receptor 1 (TRAIL-R1; DR4), by 1-methoxy-canthin-6-one. Cell incubation with 1-methoxy-canthin-6-one resulted in activating c-Jun NH2-terminal kinase (JNK), as revealed by Western blotting; induction of apoptosis and TRAIL-R1 up-regulation by 1-methoxy-canthin-6-one were >80% prevented by the addition of the JNK inhibitor (JNKI) SP600125JNKI, indicating that both effects were almost completely mediated by JNK activity. On the other hand, synergism with TRAIL was reduced by about 50%, suggesting that besides up-regulating TRAIL-R1, 1-methoxy-canthin-6-one could influence other factor(s) that participated in TRAIL-induced apoptosis [72].

Antioxidant effect

The free radical scavenging activity of ethyl acetate (EtOAc) fraction of *Ailanthus altissima* was superior to all other fractions (IC_{50} = 16.45 mg/ml) and was higher potent than synthetic antioxidant butylated hydroxyanisole [46]. Evaluation of the antioxidant activities by using four complementary tests (DPPH, ABTS, 2-deoxyribose and FRAP) showed that the methanolic extracts from leaves and hydrodistilled residues exhibited strong concentration-dependent antioxidant activities [44].

Effect on age-related disorders

Four terpenylated coumarins isolated from the stem bark of *Ailanthus altissima* were strongly enhanced SIRT1 activity in an *in vitro* SIRT1-NAD/NADH assay and an *in vivo* SIRT1-p53 luciferase assay. These compounds also increased the NAD-to-NADH ratio in HEK293 cells. Accordingly, terpenylated coumarins from *Ailanthus altissima* have a direct stimulatory effect on SIRT1 deacetylation activity and may serve as lead molecules for the treatment of some age-related disorders [73].

Anti-progestogenic effects

Ailanthus altissima was evaluated for progestogenic and anti-progestogenic properties. Extracts of the plant were analysed by using progesterone response element-driven luciferase reporter gene bioassay. *Ailanthus altissima* was recognized to have anti-progestogenic like activities. It inhibited the 314.46 ng/ml progesterone activity in a dose-response manner [67].

Precautions and adverse reactions

A tree surgeon presented to hospital with multiple blackening, non-blanching regions of skin on both forearms, following exposure to sap from the tree of heaven (*Ailanthus altissima*). A referral to plastic surgery was made to consider debridement. Following input from the national poisons centre and dermatology, conservative management with emollient was undertaken. The lesions blistered and exfoliated and were treated with topical steroid and oral antihistamines. Furthermore, two previous cases of contact dermatitis were reported in the literature [74]. However, large doses of the drug are said to lead to queasiness, dizziness, headache, tingling in the limbs and diarrhea. Fatal poisonings have been observed in animal experiments. Treatment of poisonings should be conducted symptomatically, following stomach and intestinal emptying [9].

Dosage

Ailanthus altissima is still being researched as a drug, the prescribed daily dose: 6 to 9 gm of drug [9].

CONCLUSION

The paper reviewed *Ailanthus altissima* as promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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