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A review on pharmacological properties of *Artemisia annua*

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Abstract
The genus *Artemisia* includes the largest genus of family Asteraceae. It has several medicinal uses in human and plant diseases ailments. *Artemisia* species grow in temperate climates of both hemispheres, usually in dry or semi-arid habitats. Due to presence of terpenoids and sesquiterpene lactones, most of the species possess strong aromas and bitter tastes, which discourage herbivory, and may have had a selective advantage. There are several species of *Artemisia* that have been investigated as antimicrobial, antioxidant, cytotoxic, insecticidal, repellent and anticonvulsant agents. Artemisinin is isolated from the plant *Artemisia annua*, sweet wormwood, a herb employed in Chinese traditional medicine. Treatments containing an artemisinin derivative are now standard treatment worldwide for *Plasmodium falciparum* malaria. The present review comprises information of traditional uses, phytochemistry and pharmacology of *Artemisia*sps providing preliminary information and gives a direction for the basic and clinical research on *Artemisia annua.*

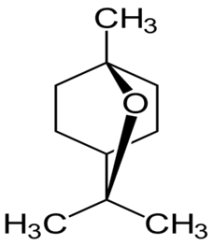
Keywords: *Artemisia annua*, terpenoids and sesquiterpene lactones

Introduction
Artemisia is the largest genus belonging to the daisy family Asteraceae. It comprising of about 400 species widely distributed in South Africa and South America. Common names for various species in the genus include mugwort, wormwood, and sagebrush. This genus is named in honor of *Artemis* "the Greek goddess of chastity". The word 'Artemisia' comes from the ancient Greek word: '*Artemis*'=The Goddess (the Greek Queen Artemisia). The word 'Wormwood' is influenced by the traditional use as a cure for intestinal worms. Most of the *Artemisia* species are perennial, biannual, annual herbaceous ornamental, medicinal and aromatic plant or shrubs. The members of this genus are silver green, dark green or blue-green in colour, heavily scented and bitter taste due to presence of terpenoids and sesquiterpene lactones [1].

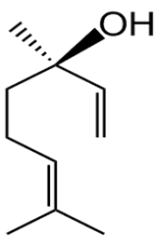
Because of their pungent smell and bitter taste they are unattractive for browsing animals but are useful for their essential phytochemical constituents and oils. Some species of *Artemisia* are *Artemisia abrotanum* L., *A. afra*, *A. annua* L., *A. arborescens*, *A. arenicola*, *A. maritima*, *A. capillaris*, *A. dracunculus*, *A. stricta*, *A. laciniata*, *A. wallichiana*, *A. Japonica and A. siversiana* [2].

It has been found that plants have the ability to generate a lot of secondary metabolites which occurs naturally, and may be important in pharmacologically. *A. annua* has been known for its antimalarial component, artemisinin [3]. Other derivatives of artemisinin include artesunate, artemether, artemether, dihydroartemisinin, and artemotil [4].

The analysis of *Artemisia annua* by GC/MS led to the identification of 81 constituents, forming 91–97.1% of the essential oil composition. The major constituents were camphor (22.8–42.6%), 1,8-cineole, linalool, β-caryophyllene, alpha-thujone, (E)-β-farnese, germacrene D and 1-epi-cubenol. However, the essential oil content was found to vary from 0.3% to 0.7% at different stages of growth [5].



1, 8-cineole



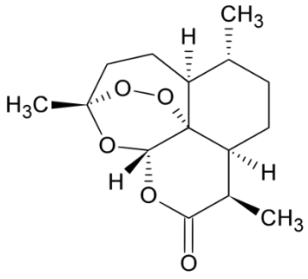
Linalool

Plant profile
Kingdom: Plantae
Division: Angiosperms
Class: Eudicots
Order: Asterales
Family: Asteraceae
Genus: Artemisia

Description
Artemisia is grown for their silvery-green foliage and for their aromatic, culinary, and medicinal properties. *Artemisia annua* (qinghao in Chinese), native to China and is a short-day, cross-pollinated medicinal plant. But now it has been spread to most parts of the world and known for its medicinal properties [6]. It is an annual, biennial, or perennial weed reaching about 2 m in height with alternate branches. Leaves are deeply dissected, with an aromatic odour, 2.5 to 5 cm in length, 1 to 3 cm in width [7]. Sourav Das Flowers are tiny nodding (capitula) only 2 or 3 mm across, greenish or yellowish, enclosed by numerous, imbricated bracts, displayed in lose panicles, bisexual central (disc) florets containing little nectar and pistillate marginal (ray) florets. It flowers from August to September with mature seeds produced in September and October. In the tropics, flowering is induced when the plants are very small. The scented flowers are pollinated by insects and wind action [8].

Ethno medical information
A. annua is a member of the Asteraceae, the largest family of flowering plants, which comprises more than 23, 000 species, including many with considerable medicinal, ornamental, and economic importance [9]. The plant has been known for its antpyretic, antiseptic, antispasmodic, carminative, tonic [10], antimalarial, anti-inflammatory, antioxidant and allelopathic [11], antibacterial and antinoceptive [12], anti-cancerous [13] actions. In some studies it has benn founded that *A. annua*, along with *Moringa oleifera* leaf powder can be used as a supportive treatment in HIV/AIDS patients. The Artemisinin found in *A. annua* has some antiviral activity against HIV and other viruses like cytomegalovirus and herpes virises [14].

Pharmacological properties of plant



Antimalarial activity
Artemisinins are found in extracts of *A. annua* and are well known for their action against *P. falciparum* malaria including highly drug resistant strains [15]. Artemisinins are classified as sesquiterpene lactones whose antimalarial activity is linked to an endoperoxidetrioxane moiety. Artemisinin does not dissolve in oil or water and so can only be given by the enteral route. Although its derivatives have been derived after modification in its structure like artesunate, artemether, arteether, dihydroartemisinin, and artelinic acid which can be given by oral, rectal, or parenteral administration [16]. Artemisinin-based combination therapy (ACT) is considered as the first line of treatment for uncomplicated *P. falciparum* malaria. ACT includes co-administration of artemisinin derivative along with longer acting partner drug [17]. World Health Organization (WHO) has recommended ACT as a principal treatment for malaria initiated by *Plasmodium falciparum*. They act against young ring form of malarial parasites and preventing their development to the more mature pathogenic stages [18]. They might act by interfering with digestion of hemoglobin in the food vacuole of parasite or may attack the mitochondria of the parasite [19]. Artemisin produces cytotoxic radicals by reacting with either heme groups or intracellular iron. Artemisinin accumulates in the lysosomes and cause lysosomal acidification and protein degradation, hence cell death [20].

Antimicrobial activity
A. annua L., a medicinal herb, produces secondary metabolites with antimicrobial property. The essential oil of Artemisia annua aerial parts, consisting of monoterpenes, ketones, camphor, 1,8-cineole, sesquiterpene hydrocarbons, germacrene and β-caryophyllene found to be responsible for its antimicrobial properties[21]. The phytoconstituents present in the extracts may be responsible for the antimicrobial activity. Antimicrobial activity of the extracts was tested against *Staphylococcus aureus, Bacillus subtilis, Bacillus thuringenesis, E. Coli and Salmonella* using the disc diffusion method and MIC assay. Different extracts of plant were found to be effective against all of these bacteria with maximum activity against *S.aureus*[22]. Out of different extracts the methanol extracts has exhibited the strongest activity against *S. aureus* [23].
Artemisinin and its derivatives like artesunate has shown the antiviral activities against human cytomegalovirus, Epstein-Barr virus, herpes simplex virus 1, and human herpes virus 6A, hepatitis B and C virus and HIV-1 virus [24].
The antiviral constituents from *Artemisia* species were limited to plant sterols and acetylenes. Furthermore, a few flavonoids like fisetin and quercetin were found to be inhibitors of HIV replication in H9 cells. Many *Artemisia* plants are being used for the treatment of the virus-related disease such as influenza indicating that more antiviral *Artemisia* constituents are to be characterized [25].

Antidiabetic activity
The extract of *A. annua* is abundant with many flavonoids such as afroside, cirsimartin, chrysoplenol and cirsiliol. In a study, diabetic rats when treated with aqueous Extract of *A. annua*, exhibited significant anti-hyperglycemic and anti-hypoinsulinemia activities in diabetic animals as compared to untreated diabetic rats [26]. Artemether, a derivative of artemisinin, has been found to increase sensitivity of mice cells to insulin, improved insulin resistance, prevent development of hepatic fibrosis and reduce lipid accumulation

and inflammation in the liver with reduced food intake and body weight increase rate. Moreover, artemether shows its antidiabetic effect by reducing the apoptosis of pancreatic beta cells and increasing insulin secretion [27].

Antipyretic activity

The study on antipyretic activity of ethanol and aqueous exract have shown positive results in mice. The extracts has time dependent activity against yeast induced pyrexia in mice which may be due to presence of flavonoids as phytochemical constituents in plant decreases the synthesis of prostaglandins and other mediators along with inhibition of enzymes responsible for prostaglandins synthesis [28].

Hypolipidemic activity

The combination of artesunate and ursolic acid has been found to have synergistic lowering effect on the lipid levels in plasma and liver. High dose of the combination resulted in lowering of plasma cholesterol and LDL and liver cholesterol and triglycerides in rats [29].

Flavonoids and polyphenols may also contribute to the hypolipidemic activity by increasing the cholesterol metabolism and by modulating the enzymes involved in cholesterol metabolism, such as HMG-CoA reductase, lecithin cholesterol acyl transferase, cholesterol 7α-hydroxylase and acyl-CoA: cholesterol acyl transferase [30].

Anti-inflammatory activity

The major active anti-inflammatory components of *Artemisia annua*are artemisinin and scopoletin, which have been reported to have anti-inflammatory effects. The crude extracts of leaves and twigs of *A. annua* effectively inhibited the production of NO in macrophages without effecting viability of the cells [31].

Another study onLPS-treatedRAW264.7cellline have shown that *A. annua* extracts have inhibitory effects on, IL-1β, IL-6 and IL-10 production, all of the pro-inflammatory cytokines [32].

A. annua extract also had significant inhibitory activity against TNF-α and PGE2 production by activated neutrophils in a dose-dependent manner. Complete inhibition by the extract was found at 50 μg/mL and above [33].

Anticancer activity

Artemisinins show promising anti-cancer activities when tested *in vitro* and *in vivo*. Artemisinins contain an endoperoxide group that is essential for their antimalarial and anticancer activities. Artemisinin derivatives induce programmed cell death of cancer cells by activating the intrinsic or the cytochrome C-mediated pathway for apoptosis. The generation of free radicals originating from the reaction of artemisinin with molecular iron is one of the main mechanism for its anticancer activity [34].

A study conducted on artemisinin and hydroethanolic extract of *Artemisia annua* has shown to have significantly toxic effect on Canine Osteosarcoma cell line. It has been reported that artemisinins induce apoptosis and ferroptosis, reduce cell proliferation through cell cycle arrest, and inhibit angiogenesis and tissue invasion of the tumor, as well as cancer metastasis [35].

Artesunate, a derivative of artemisinin found to inhibit proliferation of cells and especially endothelial cell proliferation by Vascular endothelial growth factor inhibition thus inhibiting angiogenesis in tumourous cells. When artesunate is given with captopril, it has been reported to show synergistic action against tumourous cells suggesting their combination to treat cancerous cells [36].

Anthelmintic activity

A. annua produces monoterpenes and sesquiterpenes, including the well-known sesquiterpene lactone artemisinin which is the main compound responsible for the anthelmintic activity of *A. annua*. The mechanisms of action attributed to this metabolite include interference with parasite transport proteins, disruption of parasite mitochondrial function, modulation of host immune function and inhibition of angiogenesis [37].

Researches have shown that artemisinin drugs are effective against *Leishmania, Trypanosoma, Eimeria (coccidia), Fasciola, Trichostrongylus, Babesia, Giardia* and *Haemonchus* [38] mainly.

A. annua extracts have also shown to possess pest control activity by effecting the digestive enzymes activities in a study the plant extracts were fed to a pest *Eurygaster integriceps* which results in decrease activity of α-amylase, α- and β-glucosidases, protease and lipase enzymes. It causes significant reduction in the velocity of enzyme substrate reaction by decreasing the affinity of enzyme for substrate and hence interferring in the breakdown of enzyme substrate complex in the digestive tract of pest [39].

Antiasthmatic activity

The chloroform extract of *A. annua* possesses smooth muscle relaxing effect, mediated possibly through the combination of anticholinergic and Ca2+ antagonist mechanisms by blocking calcium influx by inhibition of voltage dependent calcium current and also inhibit the high K+-induced contraction in a dose-dependent manner on mouse tracheal rings [40] which provides sound mechanistic background for its application in traditional medical system for the hyperactive gut and airways disorders, such as abdominal colic, diarrhea and asthma.

Antiallergic effect

A study conducted in rats by demonstrated that the systemic anaphylactic shock, histamine release, scratching behavior and vascular permeability induced by compound 48/80 were found to be reduced when rats were pretreated with *A. annua* extract [41].

Other effects

According to a study the feeding of *A. annua* to laying hens results in decreased FCR, increase in yolk colour intensity and shell thickness and decrease in yolk cholesterol. The findings of the present study indicated that the dietary treatments decreased the FCR of laying hens [42]. *A. annua* leaves has essential amino acid profile and high mineral content mainly Ca, Mg, and P which are necessary for shell formation [43].

It can be supplemented as feed additive as it has antioxidant properties and gut pH reduction effects [44]. The high protein, energy, essential fatty acids, amino acids, mineral and vitamin content of *A. annua* meal makes it a plant protein source with essential oils and high antioxidant potential that could be used in formulating poultry diet.

Conclusion

In the plant kingdom, family Asteraceae is endowed with essential oil-yielding plants, and among these plants, the genus *Artemisia* occupies top position for its bio-prospection. Aromatic and medicinal plants are important sources of secondary metabolites, which have a wide range of

applications in control of plant and human diseases, cosmetics, as well as in the pharmaceutical industry. Extensive investigations on essential oil composition, antimicrobial, insecticidal and antioxidant studies have been conducted for *A. annua* species of this genus. Till now main focus has been given over artemisinin obtained from this plant and other constituents are not studied deeply. This plant has wide and varied applications in plants and human disease control and in the pharmaceutical industry. Thus proper scientific techniques should be employed to extract out all the medicinal uses of *A. annua* for advancement in its use as a pharmaceutical agent. Preclinical and clinical research needs to be done on the use of these plants and further in depth investigations are urgently necessary to study all bioactive compounds and their biomolecular mechanisms at the cellular and tissue levels.

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