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ARTEMISIA ANNUA (QINGHAO): A PHARMACOLOGICAL REVIEW

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ABSTRACT

Artemisia annua L., also known as sweet wormwood, sweet annie, sweet sagewort and annual wormwood (Chinese: qngho), is a common type of wormwood that is native to temperate Asia, but naturalized throughout the world, and that belongs to the family of the Asteraceae. Currently, *Artemisia annua* is the source for the production of artemisinin and semi-synthetic artemisinin derivatives (including dihydroartemisinin, artesunate, artemether and arteether) that are used for the production of combination therapies for treatment of malaria (ACTs = Artemisinin-based Combination Therapy). Animal studies suggested that artemisinin and related compounds inhibit tumor growth and metastasis. However, there is no reliable evidence from clinical trials at the moment that effects from animal studies translate into benefits for cancer patients. Experiences from malaria treatment indicate a good tolerability of artemisinin-based drugs. However, there are two case reports with severe adverse effects if artemisinin-based drugs were used at higher doses.

INTRODUCTION: *Artemisia annua* is an annual herb native in Asia, especially in China. The name of the plant is Qinghao. It has become naturalized in many countries all over the world, like Argentina, Bulgaria, France, Hungary, Italy, Romania, Spain and USA [1, 2].

Artemisia annua L., also known as sweet wormwood, sweet annie, sweet sagewort and annual wormwood and belongs to the family of the Asteraceae with great therapeutic and economic importance. It is well recognized wind pollinated cosmopolitan genus, chiefly spread in temperate areas of mid to high latitudes of the northern hemisphere, settled in arid and semiarid environments landscape and has only few representatives in the southern hemisphere [3]. *A. annua* is well-known medicinal plant for being as a source of antimalarial compound artemisinin (Qinghaosu), which is a cadinane-type sesquiterpene lactone with an endoperoxide bridge that presently is the most potent and efficacious compound against chloroquine and quinine-resistant *Plasmodium falciparum* and other malaria-causing parasites [1, 4].

Beside antimalarial effects, *A. annua* has biological activities such as antibacterial, anti-inflammatory, angiotensin converting enzyme inhibitory, cytokinin-like and antitumor effects [5].

Plant description: It is the annual herb native to Asia, most probably China. Occurs naturally as part of steppe vegetation in the northern parts of Chahar and Suiyuan provinces in China, at 1000 to 1500 m above sea level. Now naturalized in many countries including the United States [6, 7].

A. annua is a large shrub often reaching more than 2.0 m in height, usually single-stemmed withalternate branches. The aromatic leaves are deeply dissected and range from 2.5 to 5 cm inlength. Leaves and flowers contain both 10-celled biseriate trichomes and 5 cell filamentous trichomes [7, 8]. *Artemisia annua* is a potent antimalarial plant and used in folks, Homeopathic system and in Ayurvedic system of medicine. According to the literatures, in China, aqueous preparation of the dried herb was applied against fever, malaria, skin diseases, jaundice and haemorrhoids [5, 9, 10].

Literature survey also reveals that this plant other than parasiticidal and antimalarial, it was also active with the patients suffering from malarial infections with *Plasmodium falciparum* and *Plasmodium vivax*, mainly such one with the chloroquine resistant strains. World Health Organization shows high interest with the active constituent Artemisinin and its chemical derivatives. They are used worldwide as an Antimalarial drug [8].

Artemisia annua is a popular plant used in treating various ailments and used as one of the important ingredient in several Ayurvedic formulations, very little efforts have also been made to verify its efficacy through scientific screening in animal models and clinical trials. The present review highlights the Phytochemical and Pharmacological studies conducted on *Artemisia annua* [11].

Pharmacognostical studies: Leaves of *Artemisia annua* are widely used for the treatment of malaria and as anti-inflammatory in most part of the world and in most of herbal drug market, leaves are being sold along with the aerial parts as Qinghao[12]. Therefore, macroscopic and microscopic characters of the aerial parts are described below:

1. **Macroscopic Characteristics:** An aromatic annual herb 0.9 to 1.95 m in height with deeply grooved branches. Variation generally present in the leaves and aerial parts. The leaves margins are not entire but the base is asymmetrical. The leaves are light green to dark green in color and strongly aromatic in smell and slight bitter in taste[13]. The lamina is completely divided into two separate segments called leaflets. The leaflets are arranged in pairs. The leaves are arranged in pinnately as well as shapes of the leaves are lanceolate to oblong plus several deeply cut segments are present. The both outer and inner surfaces are glabrous along with a thin brittle texture. The leaves are dorsiventral histologicallly. The leaves contain anomocytic stomata with numerous glandular and non-glandular trichomes on both the surfaces with little stalk. Spongy parenchyma contains 4-6 layers of loosely arranged cells. Reticulate xylems are lignified and present in the ventral surface of the leaf [14].

2. **Microscopic Characteristics:** *Artemisia annua* leaf includes stomatal number of upper epidermis (32-47) and lower epidermis (62-66); stomatal index of upper epidermis (0.05-0.08) and lower epidermis (4-9); palisade ratio (35.5-5.75); Vein islet number (3-5) and Vein termination number (6-8). The average values of moisture content (9.2w/w), total ash (8.3w/w); acid insoluble ash (0.91) as well as alcohol (6.2w/w) and water (3.8) soluble extractives of *Artemisia annua* leaves were determined [13].

3. **Chemical constituents:** The chemical composition of *Artemisia annua* consists of volatile and non-volatile constituents. The volatile components are mainly attributable to essential oils with the content of the latter being 0.2–0.25%. The main compounds, which account for about 70% of the essential oils, appear to be camphene, β-camphene, isoartemisia ketone, 1-camphor, β-caryophyllene and β-pinene. In addition, other minor ingredients, such as artemisia ketone, 1, 8-cineole, camphene hydrate, and cuminal are also found in the volatile parts of *Artemisia annua* [17].

   The main non-volatile ingredients include sesquiterpenoids, flavonoids and coumarins, together with proteins (such as β-galactosidase, β-glucosidase), steroids (e.g. B-sitosterol and stigmasterol). The main chemical constituents of *Artemisia annua* are sesquiterpenoids, including artemisinin, artemisinin I, artemisinin II, artemisinin III, artemisinin IV, artemisinin V, artemisic acid, artemisilactone, artemisinol and epoxyarteannuinic acid [18].

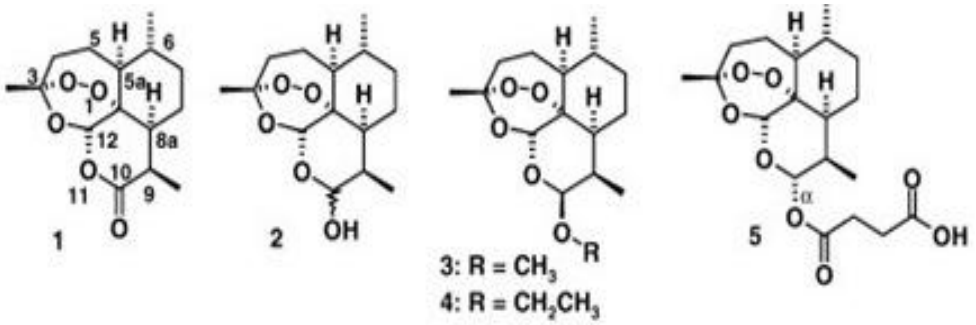

Figure 1: Qing hao su or artemisinin (1) and derivatives dihydroartemisinin (2), artemether (3), arteether (4), andartesunate (5). The numbering scheme is that by chemical abstracts. Artemisinin is a sesquiterpene, a natural product containing 15 carbon atoms, which like all terpenes, is biosynthesized in Artemisia annua from mevalonic acid via dimethylallyl and isopentenyl pyrophosphates.

General Pharmacological Activities: Following the folk and traditional uses of the plant, it has been investigated scientifically to validate the potential of plant in cure of variety of ailments.

1. **Antihypertensive activity:** It was found according to the literature that, feeding diabetic rats and rabbits with 100-390 mg kg^{-1} of the aqueous extract of the aerial parts of some species of Artemisia for 2-4 weeks could cause a significant reduction in blood level. This action prevents elevation of glycosylated hemoglobin level and possesses a hypoliposis effect, in addition to the protective effect against body weight loss of diabetic animals. It has been also determined that the sub chronic administration of 100 and 200 mg kg-1aqueous Artemisia annua extract significantly inhibited the phenylephrine-induced contraction and potentiated the endothelium-dependent relaxation of rat aortic rings in Krebs solution[2].

2. **Antimicrobial activity:** The essential oils obtained from *Artemisia annua* shows significant activity in the experiments. The essential oil shows antimicrobial activity against all the tested microorganisms, excepted *Pseudomonas aeruginosa*. Study also reveals that maximum activity against fungal microorganisms Saccharomyces cerevisiae (MIC = 2 mg/ml) and *Candida albicans* (MIC = 2mg/ml) [10]. Moderate inhibitory activity of the oil against *Staphylococcus aureus* and *Escherichia coli* was found with MIC value of 32mg/ml and 64 mg/ml respectively. No activity was observed against *Pseudomonas aeruginosa* [12].

3. **Anti-inflammatory activity:** The aqueous methanolic extract of *Artemisia annua* possesses anti-inflammatory activity when studied using carrageenan and egg albumin induced rat paw edema in acute, and cotton pellets and grass pith induced chronic inflammation models. The extract at a dose of 200gm/kg has been found to possess significant anti-inflammatory activity on the tested experimental models. The extract exhibited maximum anti-inflammatory effect, that is 55.44 and 53.16% at the end of 5h with carrageenan and egg albumin induced rat paw edema, respectively.

   In chronic model the extract at a dose of 200mg/kg showed 60% reduction in granuloma weight. The effect produced by the extract was comparable to that of Diclofenac Sodium, a non-steroidal anti-inflammatory agent. Phytochemical results also suggest that the triterpenoids, flavonoid, polyphenols and coumarin present in the plant extract inhibit the development of maximum edema response in acute and chronic models[8].

4. **Nutritional characteristics and Antioxidant activity:** According to the research articles antioxidant potential experimental models demonstrated that the leaves and inflorescences had the highest percentage of protein, crude fat and *in vitro* digestible fractions but the lowest levels of detergent fibers. These tissues also had the highest composition of the major elements as well as manganese and copper [20]. Their relatively high amino acid and vitamin profiles equally reflect a desirable nutritional balance adding to their high antioxidant capacities.

Collectively, these high levels of the different nutritional constituents and antioxidant activities coupled with the very low and often negligible levels of inherent anti-nutritive factors, especially in the leaves, which are far below recommended toxic levels, establishes *Artemisia annua* as a good reservoir of nutrients and antioxidants that might favors its use as a potential herbal tonic by humans or an important supplementary feed additive for livestock production systems [9].

5. **Immunosuppressive activity:** *Artemisia annua* has been widely used to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in traditional Chinese medicine. Ethanolic extract of *Artemisia annua* significantly suppressed concanavalin A (Con A) and lipopolysaccharide (LPS)- stimulated splenocyte proliferation *in vitro* in a concentration-dependent manner. The ethanol extract of *Artemisia annua* could suppress the cellular and humoral response. *Artemisia annua* has immunosuppressive activity for treatment of some autoimmune diseases [20].

6. **Amelioration of collagen induced arthritis:** Researchers have found out that the water soluble artemisnin derivative SM905 (obtained from *Artemisia annua*) improves collagen induced arthritis by the suppression of inflammatory and Th17 responses [21]. Experimental approaches were made by inducing collagen induced arthritis (CIA) by type II bovine collagen (CII) in DBA/1 mice. SM905 was given orally either before (continuously 1 day before booster immunization) or after disease onset (continuously 14 days after booster immunization).

   Disease incidence and severity were monitored, mRNA expression of pro-inflammatory mediators was determined by real-time PCR, purified T cell proliferation was assessed using [3H]-thymidine incorporated assay, and T helper (Th) 17/Th1/Th2 type cytokine production was examined by ELISA [15]. Oral treatment with SM905 delayed disease onset, reduced arthritis incidence and severity, and suppressed the enhanced expression of pro-inflammatory cytokines, chemokines and chemokine receptors in draining lymph nodes.

7. **Antimalarial activity:** Artemisinin and its derivatives exert their effect by interfering with theplasmodial hemoglobin catabolic pathway and inhibition of heme polymerization. *In-vitro* experiment shows inhibition of digestive vacuole proteolyticactivity of malarial parasite by artemisinin [23]. *Ex vivo* experiments has also shown accumulation of hemoglobin in the parasites treated with artemisinin, suggesting inhibition of hemoglobin degradation. Artemisinin has found to be a potent inhibitor of heme polymerization activity mediated by *Plasmodium yoelii* lysates as well as *Plasmodium falciparum* histidine-rich protein II [24].

8. **Antiparasitic activity:** A study against *Neospora canum*, a protozoal parasite infecting a wide range of mammals and causing abortion in cattle was performed [13]. The cultured host cells (Vero cells or mouse peritoneal macrophages) were infected with N. caninum tachyzoites and supplemented with concentrations of 20, 10, 1, 0.1 and 0.01 µg/ml artemisinin. At 20 or 10 µg/ml for 11 days artemisinin eliminated all microscopic foci of N. caninum completely. At 1 µg/ml for 14 days there was the same result. In shorter times 0.1 µg/ml artemisinin reduced the intracellular multiplication of N.caninum tachyzoites ($p < 0.05$).

   Pretreatment of host cells had no effect on this multiplication. There was no apparent toxicity to host cells in long-term studies. The effect of artemether was tested against the larval stages of *Schistosoma mansoni* covering the time from skin penetration to the early adult liver stage in mice and hamsters. The animals didn't develop schistosomiasis if treated with artemether during the first month after infection. The parasite was especially susceptible during the third and fourth week after infection, resulting in worm reduction of 75.3 ñ 82.0 % compared to the non-treated controls.

   The animals subjected to various schedules of repeated treatment resulted in 97.2 ñ 100 %. The chemotherapy of leishmaniosis is handicapped by drug resistance, especially that of sodium antimony gluconate.

Artemisinin showed antileishmanial activity in both promastigotes and amastigotes with IC50 values of 160 and 22 µM, with a high safety index (>22-fold), respectively [1, 20, 23].

DISCUSSION AND CONCLUSION: In the recent years, the traditional uses of the natural compounds especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. These are necessary classical approaches in search of new lead compounds for management of various diseases. HIV/AIDS is now becoming a very common and lethal disease through the world and a lot of new drugs are being synthesized for the same.

Artemiisia annua has an important place among the HIV/AIDS procuring medicinal plants. The mechanisms of action of the active ingredients artemisin and their derivatives for procurement of HIV/AIDS are still unknown. Furthermore, in future study, the isolated principles from Quinghao needs to be evaluated in scientific manner using various innovative experimental models and clinical trials to understand its mechanism of action, in search of other active constituents, so that its other therapeutic uses can be widely explored.

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