

## Annual Wormwood (*Artemisia annua* L.)

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### Common Names

**English:** annual wormwood, sweet annie, sweet wormwood

**Chinese:** qinghao, huag hua hao

### Scientific Names

**Species:** *Artemisia annua* L.

**Family:** Asteraceae (Compositae)

### Uses

#### Traditional and Artisanal

Used traditionally in China to treat fevers and hemorrhoids. Used in the crafting of aromatic wreaths, as a flavoring for spirits such as vermouth, and as a source of essential oils for the perfume industry.

## **Human (pharmacological and antioxidant activities)**

Mainly as the source of artemisinin (qinghaosu), an important natural sesquiterpene lactone with antimalarial effect against susceptible and multi-drug resistant *Plasmodium* spp. Current research also shows that artemisinin drugs are effective against cancer, Leishmania (Yang and Liew, 1993; Sen et al., 2007), Trypanosoma (Mishina et al., 2007), and some viruses (Khan et al., 1991; Li et al., 2005). In addition, *A. annua* has a high content of flavonoid compounds which are responsible for its high antioxidant activity. There are potential uses of the *Artemisia annua* plant extracts for humans and livestock based on the synergistic effects of flavonoids, artemisinin precursors, etc., including antimalarial effects reported for the *A. annua* traditional tea (Mueller et al., 2004; Blanke et al., 2008). Despite the use of traditional tea preparations not being recommended as a replacement for the WHO's recommendation use of artemisinin-based combination therapies (ACT) it deserves further investigation on its combined use with other non-artemisinin drugs commonly used in ACTs. In addition, *A. annua* leaves (Zheng and Wang, 2001) and crude extracts have been reported to be a good source of antioxidants (Cai et al., 2004), being among the four medicinal plants with the highest ORAC (oxygen radical absorbance capacity) level among other medicinals (Zheng and Wang, 2001). This high antioxidant capacity is probably due to the high content (Bilia et al., 2006) and diversity of its leaf flavonoids, including the newly-reported C-glycosyl flavonoids as a possible component of the antioxidant and antiviral activity (Han et al., 2008). Flavonoids have been reported to be responsible for more of the antioxidant activity of leafy vegetables and herbs than vitamin E, C, or glutathione (Cao et al., 1996).

## **Livestock (anti-parasitic and nutritional potential)**

*Artemisia annua* and artemisinin uses for the livestock industry are currently in expansion based on current reports of its anti-protozoal, anti-bacterial and antioxidant activities of the plant, its extracts, and its essential oil. Some examples include *Babesia* (Kumar et al., 2003), *Eimeria* or coccidiosis (Allen et al., 1997; Arab et al., 2006; Brisibe et al., 2008), and the trematodal blood fluke *Schistosoma* spp (Xiao and Catto, 1989; Xiao et al., 2000; Lescano et al., 2004), bacteria (Juteau et al., 2002). Recently, different tissues of the plant have been analyzed for its potential use in animal feed and scored high values for antioxidant capacity (ORAC and total phenolics) and as source of aminoacids, with negligible amounts of anti-nutritive components such as phytates and oxalates

## **Agriculture**

Artemisinin has been also shown to be an effective non-selective herbicide such as glyphosate (Duke et al., 1987), but its mode of action has not been established. The plant has also been used to impair the growth and development of insects that attack stored grains (Tripathi et al., 2000; Tripathi et al., 2001).

## Origin

Annual herb native to Asia, most probably China. Occurs naturally as part of a 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 (Ferreira et al., 1997).

## Crop Status

An annual crop cultivated in China and Vietnam as a source of artemisinin. Cultivated in Romania as a source of essential oils. Cultivated on small scale in the United States as a source of aromatic wreaths. Cultivation has greatly expanded in China and Africa, mainly Kenya, Tanzania, and Nigeria to support new processing plants on the production of the antimalaria artemisinin. Cultivation of *A. annua* in Africa has started after the World Health Organization recommended Artemisinin Combination Therapies (ACT) as a replacement of artemisinin monotherapy in the fight against multi-drug resistant *Plasmodium falciparum* malaria (Ferreira et al., 2005).

## Toxicity

Artemisinin has no reported toxicity if taken in recommended doses for short periods in the treatment of malaria (Meshnick, 2002). The pollen is extremely allergenic and a cause of hay fever as its cousin ragweed (*Ambrosia artemisiifolia*). In animal studies, artemisinin has been used in high oral doses in dogs and rabbits (Zhao and Song, 1990) and at 200-300 mg/kg BW in mice (Shuhua and Catto, 1989) without toxicity. In humans, artemisinin has been effective against *Plasmodium* in doses of about 30 mg/kg BW, but it has poor bioavailability and a short half-life being quickly eliminated from the body (Titulaer et al., 1990; Navaratman et al., 1995). Artemisinin derivatives (dihydroartemisinin, artesunate, artemether, arteether) present better bioavailability and antimalarial activity than artemisinin, but have different safety margins than artemisinin. The bioavailability and half-lives also vary with the delivery system (intra-muscular, intra-venous, intra-peritoneal, oral).

## Botany

### Taxonomy

*Artemisia* belongs to the tribe Anthemideae of the Asteroideae, a subfamily of the Asteraceae. Various taxonomic treatments subdivide genus *Artemisia* into various subgeneric sections; *A. annua* has been considered in the subsection *Absinthium* (Hall and Clements 1923) or in a combined subsection *Artemisia* (*Absinthium* + *Abrotanum*). (Poljakov 1961, Yeou-ruenn 1994).

### Morphology and Floral Biology

*A. annua* is a large shrub often reaching more than 2.0 m in height, usually single-stemmed with alternate branches. The aromatic leaves are deeply dissected and range from 2.5 to 5 cm in

length. Leaves and flowers contain both 10-celled biseriate trichomes and 5 cell filamentous (T) trichomes.

The nodding flowers (capitula), only 2 to 3 mm in diameter, are greenish-yellow enclosed by numerous, imbricated bracts. Capitula are displayed in loose panicles containing numerous central bisexual florets and marginal pistillate florets, the latter extruding stigmas prior to the central flowers. Both flowers have synpetalous tubular corolla with the top split into five lobes in the hermaphroditic florets and 2–3 lobes in the pistillate florets. The receptacle is glabrous, not chaffy, and triangular in shape. Both florets and receptacle bear abundant 10-celled biseriate trichomes; T-trichomes (filamentous) occur at the pedicel and bracts. The biseriate glandular trichomes sequester artemisinin as well as highly aromatic volatile oils (essential oils).

### **Ecology**

*A. annua* is a determinate short-day plant. Non-juvenile plants are very responsive to photoperiodic stimulus and flower about two weeks after induction. The critical photoperiod seems to be about 13.5 hours, but there are likely to be photoperiod × temperature interactions. In Lafayette Indiana, USA (40°21'N) plants flower in early September with mature seeds produced in October. Brazilian and Swiss cultivars are being slowly adapted to the tropics for the production of artemisinin.

### **Secondary Metabolites**

Biseriate glandular trichomes are the source of highly aromatic volatile oils, mainly artemisia ketone, 1.8-cineole camphor; germacrene D, camphene hydrate, and alpha-pinene; beta-caryophyllene, myrcene, and artemisia alcohol. Nonvolatile sesquiterpenes can be recovered from the plant by solvent extraction, some of which show high antimalarial activity. There are at least 20 known sesquiterpenes including artemisinin (arteannuin A), arteannuin B, artemisitene, and artemisinin acid.

### **Crop Culture (Horticulture)**

Most collections of artemisia derive from natural stands with highly variable artemisinin content, some as low of 0.01%. Currently-used selections from Chinese, Swiss, and Brazilian origin vary from 0.3 to 1.5%. Swiss researcher N. Delabays reported a clonal selection derived from Chinese material which produces 1.1% artemisinin and is very late flowering; proprietary hybrids (although not from homozygous parents) have been obtained in Brazil (Unicamp-CPQBA) and in Switzerland (Mediplant) that have established well in latitudes closer to the equator, benefiting the crop establishment in tropical Africa.

### **Horticulture**

#### **In vitro Production**

*A. annua* is easily propagated in vitro by standard protocols. Cytokinins increase shoot proliferation but decrease rooting and increase vitrification. *A. annua* can be grown and

propagated by microcuttings in a hormone-free medium. Artemisinin is produced in shoots in vitro and is enhanced by the presence of roots. None or trace levels of artemisinin are found in roots, callus, cells, or cell free medium. There is no evidence that in vitro production of artemisinin in tissue culture will ever be commercially feasible. However, researchers have succeeded in producing artemisinic acid (a precursor) in yeast cultures and artemisinin production, through its precursor, in bioreactors might be a future avenue to explore.

## **Field Production**

Field production of *A. annua* is presently the only commercially viable method to produce artemisinin because the synthesis of the complex molecule is uneconomic. Currently used selections reach the peak in artemisinin before flowering and at the end of vegetative growth, allowing maximal biomass accumulation of artemisinin before harvest. The most important management problems involve planting, the achievement of uniform stands, weed control, and post-harvest drying of the crop. The plant is extremely vigorous and essentially disease and pest free. Most researchers transplant seedlings but direct seeding and mechanical transplanters have been used in commercial production.

## **Germplasm**

Various specialty herb seed sources sell *A. annua* seed for the wreath market. (See S. Facciola, 1990. *Cornucopia: A source book of edible plants* Kampong Publications. Vista, California)

Large amounts of seed can be purchased from CPQBA (Unicamp, Brazil) or from Mediplant (Conthey, Switzerland) with price varying upon availability. Wild type *Artemisia* seeds purchased from general seed catalogs are not recommended for artemisinin production, but can be used for wreaths and for their essential oils.

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