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 is 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 artemisifolia*). In animal studies, artemisinin has been used in high oral doses in dogs an drabits (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 acrtivity 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 form 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% artemisin 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 incommercial production.

Germplasm

Various specialty herb seed sources sell *A. annua* seed for the wreath market. (See S. Facciola, l990. 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.

Key References

(Arab et al., 2006)
Delabays, N., A. Benakis, and G. Collet. l993. Selections and breeding for high artemisinin (qinghaosu) yielding strains of *Artemisin annua*. Acta Hort. 330:203–207.
(Duke and Paul, 1993)
(Efferth, 2007)
(Efferth et al., 2008)
Ferreira, Jorge F.S., James E. Simon, and Jules Janick. 1997. *Artemisia annua*: Botany, horticulture, pharmacology. Horticulture Reviews 18.
(Ferreira and Janick, 1995)
(Ferreira and Janick, 2002)
(Ferreira et al., 2005)
(Hsu, 2006)
(Keiser and Utzinger, 2007)
Laughlin, J. C. l994. Agricultural production of artemisinin: A review. Trans. Royal Soc. Trop. Med. Hyg. 88(Suppl.1):21–22.
(Mueller et al., 2004)

(Ro et al., 2006)
Simon, J.E., D. Charles, E. Cebert, L. Grant, J. Janick, and A. Whipkey. 1990. *Artemisia annua* L.: A promising aromatic and medicinal. p. 522–526. In: J. Janick and J.E. Simon (eds.), Advances in New Crops. Timber Press, Portland, Oregon.
(World Health Organization, 2001)
Woerdenbag, H.J., N. Pras, W. Van Uden. T.E. Wallaart, A.C. Beekman, and C.B. Lugt. 1994. Progress in the research of artemisinin-related antimalarials: An update. Pharm. World Sci. 16:169–180.

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Allen, P.C., Lydon, J., Danforth, H.D., 1997. Effects of components of *Artemisia annua* on coccidia infections in chickens. Poult Sci 76:1156–1163.

Arab, H.A., Rahbari, S., Rassouli, A., Moslemi, M.H., Khosravirad, F., 2006. Determination of artemisinin in Artemisia sieberi and anticoccidial effects of the plant extract in broiler chickens. Tropical Animal Health and Production 38:497–503.

Bilia, A.R., Melillo de Malgalhães, P., Bergonzi, M.C., Vincieria, F.F., 2006. Simultaneous analysis of artemisinin and flavonoids of several extracts of *Artemisia annua* L. obtained from a commercial sample and a selected cultivar. Phytomedicine 13:487–493.

Blanke, C.H., Naisabha, G.B., Balema, M.B., Mbaruku, G.M., Heide, L., Muller, M.S., 2008. Herba Artemisiae annuae tea preparation compared to sulfadoxine-pyrimethamine in the treatment of uncomplicated falciparum malaria in adults: a randomized double-blind clinical trial. Trop Doct 38:113–116.

Brisibe, E.A., Umoren, U.E., Owai, P.U., Brisibe, F., 2008. Dietary inclusion of dried *Artemisia annua* leaves for management of cocidiosis and growth enhancement in chickens. African Journal of Biotechnology 7:4083–4092.

Cai, Y., Luo, Q., Sun, M., Corke, H., 2004. Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. Life Sciences 74:2157–2184.

Cao, G., Sofic, E., Prior, R.L., 1996. Antioxidant Capacity of Tea and Common Vegetables. Journal of Agricultural and Food Chemistry 44:3426–3431.

Duke, S., Paul, R.N., 1993. Development and fine structure of the glandular trichomes of *Artemisia annua* L. International Journal of Plant Sciences 154:107–118.

Duke, S.O., Vaughn, K.C., Croom, E.M.J., Elsohly, H.N., 1987. Artemisinin, a constituent of annual wormwood (*Artemisia annua*), is a selective phytotoxin. Weed Science 35:499–505.

Efferth, T., 2007. Antiplasmodial and antitumor activity of artemisinin—from bench to bedside. Planta Medica 73:299-309.

Efferth, T., Romero, M.R., Wolf, D.G., Stamminger, T., Marin, J.J.G., Marschall, M., 2008. The Antiviral Activities of Artemisinin and Artesunate. Clinical Infectious Diseases 47:804–811.

Ferreira, J.F.S., Janick, J., 1995. Floral morphology of *Artemisia annua* with special reference to trichomes. International Journal of Plant Sciences 156:807–815.

Ferreira, J.F.S., Simon, J.E., Janick, J., 1997. *Artemisia annua*: botany, horticulture, pharmacology (A Review). Horticultural Reviews 19:319–371.

Ferreira, J.F.S., Janick, J., 2002. Production of Artemisinin from in vitro cultures of *Artemisia annua* L., Biotechnology in Agriculture and Forestry Vol. 51, Springer-Verlag, Berlin, Germany, p. 1–12.

Ferreira, J.F.S., Laughlin, J.C., Delabays, N., Magalhaes, P.M.d., 2005. Cultivation and genetics of *Artemisia annua* for increased production of the anti-malarial artemisinin. Plant Gen Resourc 3:206–229.

Han, J., Ye, M., Qiao, X., Xu, M., Wang, B.-r., Guo, D.-A., 2008. Characterization of phenolic compounds in the Chinese herbal drug Artemisia annua by liquid chromatography coupled to electrospray ionization mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis 47:516–525.

Hsu, E., 2006. The history of *qing hao* in the Chinese *materia medica*. Transactions of the Royal Society of Tropical Medicine and Hygiene 100:505–508.

Juteau, F., Masotti, V., Bessiere, J.M., Dherbomez, M., Viano, J., 2002. Antibacterial and antioxidant activities of *Artemisia annua* essential oil. Fitoterapia 73:532–535.

Keiser, J., Utzinger, J., 2007. Food-borne trematodiasis: current chemotherapy and advances with artemisinins and synthetic trioxolanes. TRENDS in Parasitology 23:555–562.

Khan, M.M.A.A., Jain, D.C., Bhakuni, R.S., Zaim, M., Thakur, R.S., 1991. Occurrence of some antiviral sterols in *Artemisia annua*. Plant Science 75:161–165.

Kumar, S., Gupta, A.K., Pal, Y., Dwivedi, S.K., 2003. *In-vivo* therapeutic efficacy trial with artemisinin derivative, Buparvaquone and Imidocarb Dipropionate against *Babesia equi* infection in donkeys. J Vet Med Sci 65:1171–1177.

Lescano, S.Z., Chieffi, P.P., Canhassi, R.R., Boulos, M., Neto, V.A., 2004. Antischistosomal activity of artemether in experimental Schistosomiasis mansoni. Revista de Saude Publica 38:71–75.

Li, S., Chen, C., Zhang, H., Guo, H., Wang, H., Wang, L., Zhang, X., Hua, S., Yu, J., Xiao, P., Li, R., Tan, X., 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Research 67:18–23.

Meshnick, S.R., 2002. Artemisinin: mechanisms of action, resistance and toxicity. International Journal for Parasitology 32:1655–1660.

Mishina, Y.V., Krishna, S., Haynes, R.K., Meade, J.C., 2007. Artemisinins Inhibit *Trypanosoma cruzi* and *Trypanosoma brucei rhodesiense* In Vitro Growth. Antimicrob. Agents Chemother. 51:1852–1854.

Mueller, M.S., Runyambo, N., Wagner, I., Borrmann, S., Dietz, K., Heide, L., 2004. Randomized controlled trial of a traditional preparation of *Artemisia annua* L. (Annual Wormwood) in the treatment of malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 98:318–321.

Navaratman, V., Mansor, S.M., Chin, L.K., Mordi, M.N., Asokan, M., Nair, N.K., 1995. Determination of artemether and dihydroartemisinin in blood plasma by high-performance liquid chromatography for application in clinical pharmacological studies. J.Chrom. 669:289–294.

Ro, D.-K., Paradise, E.M., Ouellet, M., Fisher, K.J., Newman, K.L., Ndungu, J.M., Ho, K.A., Eachus, R.A., Ham, T.S., Kirby, J., Chang, M.C.Y., Withers, S.T., Shiba, Y., Sarpong, R., Keasling, J.D., 2006. Production of the antimalarial drug precursor artemisinic acid in engineered yeast. Nature 440:940–943.

Sen, R., Bandyopadhyay, S., Dutta, A., Mandal, G., Ganguly, S., Saha, P., Chatterjee, M., 2007. Artemisinin triggers induction of cell-cycle arrest and apoptosis in *Leishmania donovani* promastigotes. J Med Microbiol 56:1213–1218.

Shuhua, X., Catto, B.A., 1989. In vitro and in vivo studies of the effect of artemether on *Schistosoma mansoni*. Antimicrobial Agents and Chemotherapy 33:1557–1562.

Titulaer, H.A.C., Zuidema, J., Kager, P.A., Wetsteyn, J.C.F.M., Lugt, C.B., Merkus, F.W.H.M., 1990. The pharmacokinetics of artemisinin after oral, intramuscular and rectal administration to volunteers. J. Pharm. Pharmacol. 42:810–813.

Tripathi, A.K., Prajapati, V., Aggarwal, K.K., Khanuja, S.P., Kumar, S., 2000. Repellency and toxicity of oil from *Artemisia annua* to certain stored-product beetles. Ecotoxicology 93:43–47.

Tripathi, A.K., Prajapati, V., Aggarwal, K.K., Kumar, S., 2001. Toxicity, feeding deterrence, and effect of Activity of 1,8-cineole from *Artemisia annua* on progeny production of *Tribolium castanaeum* (Coleoptera: Tenebrionidae). Journal of Economic Entomology: 94:979–983

World Health Organization, W., 2001. Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation. In: WHO/CDS/RBM (Ed). Geneva, Switzerland, p. 4–5 April 2001. 2036 pgs.

Xiao, S.H., Catto, B.A., 1989. In vitro and in vivo studies of the effect of artemether on Schistosoma mansoni. Antimicrob. Agents Chemother. 33:1557–1562.

Xiao, S.H., Booth, M., Tanner, M., 2000. The prophylactic effects of artemether against *Schistosoma japonicum* infections. Parasitology Today 16:122–126.

Yang, D.M., Liew, F.Y., 1993. Effects of qinghaosu (artemisinin) and its derivatives on experimental cutaneous leishmaniasis. Parasitology 106:7–11.

Zhao, K., Song, Z., 1990. The pharmacokinetics of dihydroqinghaosu given orally to rabits and dogs (chinese). Acta Pharmaceutica Sinica 25:161–163.

Zheng, W., Wang, Y., 2001. Antioxidant activity and phenolic compounds in selected herbs. Journal of Agricultural and Food Chemistry 49:5165–5170.