Artemisia annua (Asteraceae)

English: Sweet wormwood, Chinese wormwood, Sweet Annie
French: Absinthe chinoise, armoise annuelle
Chinese: Qinghao (pronounced ching how), Cao hao, Cao Qinghao, Cao
Haozi, Chou Qinghao, Haoz, Kuhao, Xianghao, Xiang Qinghao, Xihehao
Japanese: Kusoninijin   Vietnamese: Than hao, Than cao hoa vang
Korean: Chui ho, Hwang-hwa-ho, Gae-tong-sok
German: Chinesischer Beifuß
Pharmaceutical definitions: Herb: Artemisiae herba, Root: Artemisiae radix
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Extract: Artemisiae extractum
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Description of the plant
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.
A.annua is an annual weed reaching about 2 m in height with alternate branches. Leaves are deeply dissected, with an aromatic odor, 2.5 to 5 cm in length, 1 to 3 cm in width. Flowers are tiny and yellow, in lose panicles with capitula 2 to 3 mm across. There are central and marginal florets. The seed vessels consist of one achaene, faintly nerved and 1 mm long. Naturally the plant is pollinated by insects and by the wind (11, 12).

Plant parts used
The dried aerial parts collected before the flowers are in full bloom without the lignified stem, not the roots

Constituents
Artemisia annua contains sesquiterpene lactones, flavonoids and essential oils.
In the **green parts** of Artemisia annua the bitter sesquiterpenlacton-peroxid artemisinin is the main natural constituent. It is called quinghaosu. From the chemical view it has a 1, 2, 4-trioxane structure with a special endo-peroxide bridge, but lacking a nitrogen-containing ring system. The peroxide moiety appears to be indispensable for the chemotherapeutic activity. In the roots artemisin is not present.

Artemisinin: $C_{15}H_{22}O_5$, MG 282,35, mp 157 ^{0} C, white crystals or white crystalline powder solubility in water: 0.113 mg/ml (37^0C), 0.084 mg/ml (25^0 C)

In the plant genus Artemisia only Artemisia annua, A. apiacea and A. lancea have artemisinin.
Its highest content in Artemisia annua wild plants is 0.01-0.5 % per dry weight before flowering (19). Other authors report about a content of 0.01-0.8 % (1). Yields from 0.01 to 0.6 % have been found in China (46). A hybrid form cultivated in Central Africa contained 0.63-0.70 % artemisinin from which 40 % could be extracted by simple tea preparation (16).
The production of 1 kg artemisinin requires 1200 kg of dried leaves on three acres (1.2 ha) of land. Because Artemisia annua plants harvested from various sources showed no sufficient yields, companies cultivate hybrids with higher contents, therefore (11). In Vietnam

farmers obtain a net yield of 20 kg/ha (58).

Plants are the only valid source, while chemical synthesis is too complicated. The chemical synthesis of artemisinin cannot be performed with any economic standard, therefore (46).

The low yield is a serious limitation for the commercialization of the drug. As the yearly demand of the whole world 114 tons of artemisinin are postulated.

The fresh or air-dried plant material is extracted by mixtures of solvents which are not published anywhere.

Semisynthetic derivatives of artemisinin are artemether (methylether), arteether (ß-ethylether; and artesunate (12alpha succinate). They are produced commercially. They are used in form of tablets for oral ingestion and for intramuscular, rectal and intravenous application (41). They are applied instead of artemisinin because of its poor solubility in water. They are often dissolved in oil for intramuscu1ar injections and for suppositories. Oily suspensions given subcutaneously are more effective (30).

Accompanying substances of artemisinin are dihydroartemisinin (dihydroqinghaosu), artemisinic acid, a potential precursor of artemisinin, and arteannuin A and B (2).

Artemisinin treated with sodiumborohydrid yields dihydroartemisinin (dihydroqinghaosu, artenimol). It brings an enhanced antimalarial activity and was approved by the Ministry of Health in China as an antimalarial remedy (47). It is regarded as the main metabolic substance of all artemisinin related compounds.

In earlier times the name for all these compounds together was quinghaosu. In older literature there was confusion and often it is complicated to differentiate their pharmacological effects. In Chemical Abstracts the term artemisinin is settled for quinghaosu, now (Chem. Abstr. No 63 968-64-9).

Artemisinin and its semi-synthetic derivatives act essentially as blood schizonticides against the malaria parasites.

The flavonoids of Artemisia annua are artemetin, chrysosplenetin, eupatorin and casticin, special flavonoids with methy1ated character. They contribute to the pharmacological efficacy of artemisinin (10,35).

The **essential oil** up to 3 % of the leave weight is stored in the glandular trichomes of the leaf epidermis. Analyzed by GC-MS it contains camphor (44 %), germacrene D (16 %), trans-pinocarveol (11 %), beta-selinen (9 %), beta caryophyllene (9 %), Artemisia ketone (3 %) and around further 20 substances of which the content is less than 1 % (15).

Further investigations with GC and NMR about the oil of A. vestita revealed the presence of around 15 compounds like alpha terpinene, ß-phellandrene, 1,4-cineole, beta-thujone, nerol, alpha-phenanthrene, 1,8-cineole, citral, chamazulene and citronellal. These compounds are responsible for the characteristic odor and for the antibacterial activity (53).

Extraction and measuring of artemisinin

Between all solvent extraction processes the most modern method is the supercritical fluid extraction with CO_2. Optimal operating conditions are: Supercritical CO_2 with 3 % methanol, 50 ^{0} C, pressure 15 mPa, flow rate 2 ml/min. These conditions avoid degradation of the analyte and give clean extracts ready for being analysed (20). Generally ethylacetate (best solubility) and n-hexane (best selectivity) are used for extraction, but combinations of these and other solvents are possible (58).

Artemisinin and its related substances can be quantified by many analytical methods, such ones like TlC, GC, HPLC, enzyme-linked assay and radioimmunoassay.

HPLC conditions: Column reversed phase 5µ, solvent 0.01M Na_2HPO_4/NaH_2PO_4,
   H_2O /MeOH, 55+45 v/v , injection volume 10µl, l = 260 nm, time 20 min (50).

TlC conditions for field use preferently: HPTlC plates (UV), solvent toluene,

diethylamin, methanol 8/1/1, application 25 µl, Eppendorf pipettes (3).

Traditional uses

In the traditional Chinese medicine Artemisia annua was used for over two millenia. Aqueous preparations of the dried herb were applied against fever, malaria, skin diseases, jaundice and haemorrhoids. A. annua is included in the official Pharmacopoeia of China, its name is qinghao and in the drug directories of India, Japan and Vietnam it can be found. Using this knowledge, modern Chinese scientists extracted the plant and discovered the active principle artemisinin, so called "qinghaosu". Besides a lot of other parasiticidal and antimalarial effects it was active with patients suffering from malaria infections with Plasmodium falciparum and P. vivax, especially such ones with chloroquine-resistant strains (19). Artemisinin and its chemical derivatives attracted the high interest of the WHO. They are used worldwide as drugs against malaria.
Artemisinin is now available commercially in China and in Vietnam as an antimalarial drug efficacious against drug-resistant strains of Plasmodium falciparum and Plasmodium vivax.
A semisynthetic drug based on artemether has been registered as "Paluther" (Rhone Poulence) in Africa.

Results of experimental studies

Phytotoxicity
Artemisinin exhibits phytotoxic properties by inhibiting germination and reducing the growth of many weeds and crop plants. It can be used as a selective phytotoxin.

Antimicrobial activity
In antibacterial screenings artemisinin did not show any inhibiting activity neither towards Gram-positive nor Gram-negative bacteria. A yeast strain with a defective mitosis regulating BUB 3 gene showed increased sensitivity against artesunate (19).

Coccidia infection in chickens
Chickens were infected with different parasitic Eimeria species and fed by artemisinin and leaf preparations over 4 weeks at levels of 2.0, 8.5 and 17.0 ppm. The oocyst output of 2 coccidia species was reduced depending on the time of exposition. Dried leaf preparations were not sufficient because of the lack of artemisinin. Therefore such preparations can not be used for bioprotection (2).

Anticancer activity
Artesunate, a semisynthetic derivate of artemisinin tested in 55 cell lines of the National Cancer Institute, USA was most active against leukemia and colon cancer cell lines with mean GI 50 values 1.11+/-0, 56 µM and 2.13+/-0, 74 µM, respectively. Compared with established antitumour drugs artesunate ranges in the same area (9).
Artesunate inhibits the angiogenesis and VEGF production in chronic myeloid leukemia (CML) K 562 cells in vitro. It decreased the VEGF level in CM at 2µM/L. In vivo the angiogenic effect was evaluated in chicken choriallantoic membran neovascularization model. Artesunate decreased the angiogenic activity in a dose-dependant manner of 3 –12 µM/L. Authors suggest artesunate to be a potential antileucemic substance (13, 52).
Rats treated with a single dose of 50 mg/kg of 7,12-dimethylbenz(a)anthracene develop breast cancer. Immediately after this treatment rats were provided with a rat chow containing 0.02 % artemisinin. After 40 weeks the rats were monitored for breast cancer. Oral artemisinin significantly delayed (p <0.02) and in some animals prevented breast cancer development, 57 % of artemisinin-fed versus 96 % of the controls. Breast tumors in artemisinin rats were fewer (p <0.02) and smaller in size (p < 0.05) when compared with controls. Authors believe artemisinin to be a potent cancer chemoprevention agent (22).

An enriched sesquiterpene fraction of an ethanolic extract from Artemisia annual aerial parts showed antiulcerogenic activity when administered orally to rats with indometacin induced ulcers. Out of the column chromatography of the sesquiterpene fraction three fractions were yielded with different polarity. Between these the medium fraction maintained the antiulcerogenic activity and it produced adherent mucus in the gastric mucosa (7).

Hepatocarcinoma cells (SMMC-7721) were treated with essential oil of A.annua 100 µg/ml for 24h. By this treatment apoptosis was induced, verified by light and electronic microscopy and Giemsa stain. The apoptosis was observed by condensated cytoplasm, fragmentation of nuclear chromatin and apoptosis bodies, morphologically (23).

Artemisinin and the flavonoid quercetagetin 6, 7, 3`,4`-tetramethyl ether showed significant cytotoxicity against P-388, A-549, HT-29, MCF-7, and other human KB tumour cells (51).

Antiviral activity

The antiviral activity of artemisinin was investigated in vitro using a model of bovine epithelial cells infected with a cytopathic strain of bovine viral diarrhea. Antiviral activity was estimated by the degree of protection against the cytopathic effect on host cells and by the reduction of the viral DNA release to the culture medium. Treatment of infected cells with artemisinin reduced the cell death markedly. The combination of artemisinin with other drugs like IFN-alpha or Ribavirin produced an additive protective effect. Artemisinin induced no toxicity in host cells. According to the authors artemisinin is useful in combination with current pharmacological therapy for the treatment of human and veterinary infections by flaviviruses (34).

Activity on immune responses

Artemisinin, dihydroartemisinin and arteether in doses of 400 and 600 mg/kg body weight suppressed humoral responses of sheep, as measured by the hemolytic plaque assay. Arteether was the most effective drug. When tested on carrageenan-induced edema all three agents did not possess any anti-inflammatory activity. In contrast to sodium artesunate they did not exhibit any immuno-stimulating effect (39).

The water-soluble sodium-hemisuccinate of artemisinin suppressed markedly the in vitro 3HTdR incorporation in mitogen-stimulated mouse spleen cells, in human peripheral lymphocytes and in blood cells from some leukemia patients (38).

Choleretic activity

In Wistar rats the administered water extract of spikes and leaves from different Artemisia plants increased bile flow. Both extracts of A. annua increased bile flow 30 min after administration. 120 - 150 min after administration the flow decreased, but remained at a higher level than before (48).

Effect on enzymes

Cytochromoxidase being located in the membran and mitochondria of Plasmodium berghei trophocytes was inhibited completely by sodium artesunate, in vitro at 1 mMol and in vivo at 100 mg/kg iv. This enzyme seems to be a target for antimalarial action of artesunate and qinghaosu.

Effect on malaria vectors

The petrolether extract of A. annua has remarkable effect on metamorphosis of the malaria vector Anopheles stephensi Liston. It induces developmental deformities with an LC 50 after 24 h administering of 16.85 ppm and after 48 hr administering of 11.45 ppm. The phytoextract is recommended as an effective biocontrol agent against malaria vectors (42).

Activity on rodent malaria

Malaria in rodents (rats, mice, rabbits) and different other animals is caused by the parasites Plasmodium berghei and P.yoelii. An oily suspension of artemisinin given subcutaneously acted rapidly against blood schizontocides of P.berghei and P.yoelii. A number of more soluble derivatives worked in the same way. But they all had no prophylactic action against gametocytes or sporocytes (30).

When dihydroartemisin was given orally in tablet form to rabbits at doses of 10, 20, and 30 mg/kg

peak serum levels of 0.03, 0.05 and 0.13 µg/ml were obtained in 1 to 2 h. The corresponding $T_{1/2}$ values were 1.19, 1.0, and 1.10 h, respectively. When dogs were given dihydroartemisinin tablets with a dose of 20 mg/kg the peak serum concentration was 0.13 mg/ml in about 2 h and $T_{1/2}$ was 3.04 h. However, dogs given tablets with 70 mg/kg had no drug in the blood serum (48).

With a normal susceptible strain of P.berghei marked synergism was found with mefloquine, tetracycline and spiramycin. With a primaquine resistant strain a high potentiation was shown between artemisinin and primaquine, like the combination with mefloquine in a mefloquine-resistant strain (4).

Activity of the essential oil

Sixteen essential oils from tropical plants were tested for their fungitoxicity. Five of them showed a strong activity against Trichophytum rubrum, Microsporum gypseum and other eight dermatophytes. An ointment made with Artemisia oil was the most active to cure experimental ringworm infection of guinea pigs within 7 to 12 days (18).

The essential oil of A.annua was tested for its repellent and inhibitory activity against two stored product insects, Tribolium castaneum and Callosobruchus maculates. Adult beetles of
T. castaneum were repelled significantly by 1 % oil v/v of A.annua. An increase in dose caused decrease in larval, pupal survival and emergence of adults. The effective concentration EC50 to reduce F 1 progeny by 50 % was calculated to be 2.6 and 4.1 µM/ml for both insect species, respectively (40).

The essential oil of A.annua obtained by hydrodestillation was tested in animals in a psychopharmacological screening. The doses increased the latency time to convulsions induced by picrotoxin and pilocarpine, prevented the onset of pentylenotetrazol and strychnine induced seizures and caused marked inhibition in the Rota-rod assay. In addition, the essential oil has a high acute toxicity and a possible cholinergic reaction.

The following values were found

For the essential oil: ED50 470 mg/kg   LD50 790 mg/kg

For the ethanolic extract from fresh leaves: ED50 450 mg/kg   LD50 >2g/kg (29)

Antiparasitic activity

A study against Neospora canum, a protozoal parasite infecting a wide range of mammals and causing abortion in cattle was performed. 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 (17).

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 did not 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 – 82.0 % compared to the non-treated controls. The animals subjected to various schedules of repeated treatment resulted in 97.2 – 100 %. Almost complete protection was reached in further experiments (54).

The chemotherapy of leishmaniosis is handicapped by drug resistance, especially that of sodium antimony gluconate. Artemisinin showed anti-leishmanial activity in both promastigotes and amastigotes with IC50 values of 160 and 22 µM, with a high safety index (>22-fold), respectively.

This activity was mediated via apoptosis, damages of mitochondrial membrane and cell-cycle arrest at the G(0)/G(1) phase (36).

Neurotoxicity in dogs

Beagle dogs treated with arteether were investigated for neurotoxicity. In a first study two groups of dogs were given 20 mg/kg/day for 5 and 30 days. Only from day 23 on clinical signs of neurotoxicity were noted in some individuals, one dog had to be sacrificed pre-timely. The signs were movement disturbances and neuropathic changes in the hindbrain of intramuscularly treated dogs. Haematological findings indicated a hypochromic microcytic anaemia, neuronal and secondary axonal damage, most prominent in the cerebellar roof, pontine and vestibular nuclei as examined by microscopic investigation after 30 days, but not after 5 days. In a second experiment artemisinin was administered to two groups of 4 male and 4 female dogs at 8 daily doses of 0, 20, 40, and 80 mg/kg intramuscularly or in contrast 0, 50, 150, and 600 mg/kg per os. Neurological signs were seen only at high intramuscular doses. In most animals the signs were inspicuous and consisted in reduced activity with convulsions in single dogs before death. Minimal effects occurred at 20 mg/kg in 5 from 8 dogs. Neuronal damages occurred in all animals at 40 and 80 mg/kg following intramuscular treatment.

No comparable lesions were observed after oral administration. Both i.m. and p.o exposures at high doses were associated with a prolongation of mean QT interval of ECG (6).

Mode of action studies

The definite mode of action is not yet known.

Tests about uptake of radio-labeled substances like hypoxanthin in infected cells suggest that artemisinin diminishes the nucleic acid synthesis and that protein synthesis is one of its prime targets. In concentrations equivalent to therapeutic levels artemisinin alters polyamine metabolism of Plasmodium falciparum in vivo. Assays conducted in cultured endothelial cells indicated that artemisinin has little or no effect in preventing or reversing parasite adherence to endothelial cells. Artemisinin does not cause malaria parasite haemin to clump, but it inhibits clumping caused by subsequent exposure to chloroquine. Membrane changes may be associated with a decrease of cytochrome-oxidase activity.

Dihydroartemisinin in human erythrozoites infected with P.falciparum rapidly raised to the 300 fold concentration compared to uninfected cells which had only a duplication of the supplied substance. The steady state had been reached after 30 min. Dihydroartemisinin was concentrated mainly in the region of the parasite membrane.

Some authors conclude that dihydroartemisinin is the main metabolic form of artemisinin (45). Interaction between artemisinin with its analogues and haemin was investigated with high sensible physico-chemical methods. Molecular docking simulations generated bioactive conformations between artemisinin derivatives and haemin. The experimental results correlated well with the calculated binding energies. The interaction of the drugs with haemin seems feasible, therefore (5).

Antimalarial activity

Malaria, along with HIV/AIDS and tuberculosis is a main disease in tropical countries. Worldwide each year 500 million people are infected, 1 million people die. The economic costs of malaria in Africa are estimated 12 billion US dollar.

But malaria is a curable disease Artemisinin and its semisynthetic relatives, artemether, artesunate and artenimol held out hope for millions of people.

Tea preparations

In poor countries where synthetic antimalarial drugs often are unavailable tea preparations with

locally grown Artemisia plants seem to offer an alternative.

In Central Africa a study with tea made from Artemisia annua herb grown up there (0.63 0.70% artemisinin) was performed. In all patients symptoms showed a marked improvement. In five patients the parasitaemia disappeared within 2 - 4 days, and in 42 from 44 patients (= 92 %) the parasitaemia disappeared within four days (26).

Randomized trial of tea preparations in the treatment of malaria

In an open, randomized, controlled pilot trial the efficacy and safety of traditional tea preparations from Artemisia annua herb was investigated for the treatment of uncomplicated malaria. The treatment resulted in a quick resolution of parasitaemia and clinical symptoms. After 7 days of medication, cure rates were on average 74% for the Artemisia preparations compared with 91 % of quinine, respectively. However**, recrudescence rates** were high in the Artemisia groups. As alternative to modern antimalarials, monotherapy with Artemisia annua cannot be recommended (25).

Pharmacokinetic study of tea preparations with human volunteers

Aqueous tea preparations of dried Artemisia annua were used. One liter tea made from 9 g herb was given to 14 healthy male volunteers. Blood samples were taken and artemisinin content was detected by HPLC. One liter of the aqueous herb preparation contained 94.6 mg artemisinin, approximately 19 % of the usually recommended daily dose. The mean +/- SD maximum plasma concentration of artemisinin was 240+/-75 ng/ml and the mean +/- SD area under the plasma concentration-time curve was 336 +/-71 ng/ml x h. Artemisinin was absorbed faster from herbal tea preparations than from oral solid dosage forms, but bioavailability was similar. Artemisinin plasma concentrations after intake of this herb as tea are sufficient for clinical effects, but insufficient to recommend such preparations as equivalent substitutes for modern artemisinin drugs in malaria therapy (32).

Neither artemisinin nor its derivatives like artemether, artesunate and dihydroartemisinin can be used in monotherapy because of the high rate of recrudescence.

In all clinical applications they are applied only in combination with synthetic antimalarials. So in seven years a combination of artesunate and mefloquine remained satisfactory in Thailand (56).

Undesired effects and cautions

There is a high danger of recrudescence: The malaria parasites cannot be eradicated totally by tea preparations! The Artemisia derived tea can be applied only in combination with other antimalarial substances.
A monotherapy with tea or with artemisinin or its derivatives never brings a total cure. Every times there will be the danger of recrudescence.

Pharmacokinetics of dihydroartemisinin (dihydroqinghasu) in humans

Dihydroartemisinin in tablet form was given to human volunteers at doses of 1.2 – 2.2 mg/kg. In 1.33 h peak serum levels of 0.13 – 0.71 µg/ml were obtained. When artemisinin tablets at the dose of 15 mg/kg were given the peak serum level found in 1.5 h was only 0.09 µg/ml. Therefore the bioavailability of dihydroartemisinin seems higher than that of artemisinin (48).

Results of clinical studies

In the Hospital of the Department of Clinical Tropical Medicine, Mahidol University at Bangkok, **Thailand,** 111 patients with uncomplicated falciparum malaria were submitted a sequential treatment regimen over two or three days. All patients received artesunate (Group I 2x 400 mg, total 8oo mg, Group II 4x 200 mg, total 800 mg), followed by a gift of 750 mg and 500 mg (total 1250 mg)

mefloquine after 12 h. All patients were admitted to the hospital for 28 d in order to preclude reinfection. 96 patients completed the study. The results indicated that the sequential treatment with artesunate, followed by mefloquine is effective and well tolerated in patients with an acute, uncomplicated falciparum malaria. This sequential treatment seems suitable as an alternative for the multidrug-resistant falciparum malaria, too (24).

The clinical data obtained in **China** with formulations of artemisinin, artemether and sodium artesunate indicated that optimum results with all three drugs were obtained following the admini stration of daily doses for three days. Even the best formulations did not cure more than 90 % of the cases of falciparum malaria. In other clinical reports recrudescence rate was more than 40 %. Recrudescence is the main problem of monotherapeutic treatment.

In **Vietnam** 638 patients suffering either from Plasmodium falciparum or P.vivax malaria were treated with artemisinin (quinghaosu) given as tablets or capsules. The treatment resulted in a rapid clearance of parasitaemia and fever. Recrudescence rates (50 %) were highest in groups receiving treatment for five or less days, but were between 10 % and 23 % in groups receiving treatment for 5 – 10 days. A low recrudescence rate (9.5%) was found when patients were treated with a combination of artemisinin for three days and tetracycline for five days (27).

Furthermore, in **Vietnam** an open randomized trial with 120 patients was performed for falciparum malaria. Artesunate was given for three days combined with either 2 or 3 days of mefloquine coadministration. The cure rates of two groups were 100 and 99 %. Simultaneous, rather than sequential treatment with the two drugs artesunate and mefloquine, was the most effective treatment for multidrug-resistant Plasmodium falciparum malaria, at this time (55).

In Southern **Papua** an open-label randomized comparison between two widely available fixed-dose artemisinin combinations was performed, basing on the 2003 WHO in-vivo antimalarial drug sensitivity protocol. The study was approved by three ethic committees in Jakarta (Indonesia), Darwin (Australia) and Oxford (UK), registered with clinical trials (Gov. Number NCT 00157833). 774 patients with slide confirmed malaria received either artemether-lumefantrin (Coartem, Novartis Pharma Basel, Switzerland) or dihydroartemisinin-piperaquine (Artekin, Holleykin Pharmaceuticals Guangzhou, China) .Of the 754 evaluable patients 466 had infections with Plasmodium falciparum, 175 with P. vivax and 113 with a mixture of both. Patients were followed up for 42 days, with a standard clinical record form for drug efficacy. Both combinations were suitable. Finally both were safe and effective for the treatment of multi-drug resistant uncomplicated malaria. But both combinations affect only the asexual forms in the blood, but not the hypnozoites in the liver. Here primaquine must be administered. But post-treatment prophylaxis should not be ignored in order to reduce recurrence and reinfections. However dihydroartemisinin-piperaquine needed a grater post-treatment prophylaxis than artemether-lumefantrin in order to reduce P. falciparum reinfection and P. vivax recurrency (33).

Dosage

Herba Artemisiae: 1.5 g   Radix Artemisiae: 1.9 g   Extractum Artemisiae: 0.2 g
No information about maximum values   (59)

Toxicity

Artemisinin (Qinghaosu)
LD50 in mice: 4228 mg/kg per os   3840 mg/kg i.m.   1558 mg/kg i.p.
LD 50 in rats: 5576 mg/kg per os,   2571 mg/kg i.m. (57)

Essential oil
LD 50 in mice: >790 mg/kg (29)

Ethanolic extract from fresh leaves:
  LD50 in mice: > 2g/kg (29)

Crude drug
  LD 50 in mice: 162.5 +/- 10.1 mg/kg
  ED 50 in mice, infected with Plasmodium berghei: 11.9 +/- 2.4 mg/kg

ACT-Therapy

Artemisinin is a highly effective antimalarial plant extract.
But if it is used alone the malaria parasite cannot be eradicated totally, leading to the development of resistance against artemisinin. This has already happened to three previous antimalarial therapies such ones as sulfadoxine - pyrimethamine (fansidar), chloroquine and andatovaquone (introduced 1997) treatments, which use the addition of another antimalarial drug in order to kill any parasites that survive this treatment.
As a response to the antimalarial drug resistance situation with monotherapy WHO recommends

Artemisinin-based combination therapy: ACT Therapy

The following therapeutic options are currently recommended:
  Artemether + lumefantrine (Coartem^R Novartis)
  Artesunate + amodiaquine
  Artesunate + sulfadoxine+pyrimethamine
  Artesunate + mefloquine

These combinations are produced worldwide and are approved in most tropical countries. Since 2002 WHO warns pharmaceutical companies from producing "single-drug artemisinin malaria medicines".

Evaluation

Artemisinin, the natural product of the plant Artemisia annua became a well established antimalarial drug. Together with its derivatives it is a totally new class of antimalarials.
The clinical efficacy of these drugs is characterized by an almost immediate onset and by a rapid reduction of parasitaemia, especially in countries with a rampant multidrug resistance of different Plasmodium strains. The Artemisia drugs show a very low toxicity. Serious side effects are nearly not known. But a monotherapy with artemisinin or its analogues does not bring a total cure because of recrudescence. Therefore combinations of artemisinin and its relatives with another antimalarial drug are recommended urgently by WHO.
All over the world there is a strong demand for artemisinin. The supply does not meet the demand. Estimations run up to 114 tons artemisin each year. But the only source of artemisinin is the plant Artemisia annua. The relative low yield of artemisinin is a serious limitation for the commercialization. A lot of efforts are done to raise the yield by agriculture, tissue cell culture and genetic engineering (8).
Furthermore artemisinin and its analogues possess an antiparasitic efficacy against Schistosoma japonicum and Clonorchis sinensis, immunmodulating and antitumour activity. The toxicity is very low. In therapeutic ranges there are nearly no side effects (14).
Green parts of the plant can only be used for tea.

Warning

According to the findings about tea preparations and earlier clinical results the monotherapy with tea from Artemisia annua or Artemisia derived drugs cannot be recommended. Here it must be advised against.

WHO recommends ACT cure: Artemisin – based combination therapy

Artemisia annua

for tea preparations in combination with other antimalarials	
only as an adjuvant	*******
for tea preparations exclusively	**- - -**
monotherapy with Artemisia derived drugs	**- - -**

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