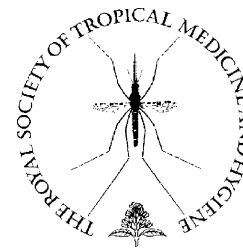




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# The history of *qing hao* 青蒿 in the Chinese *materia medica*

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**Summary** Artemisinin is currently used for treating drug-resistant malaria. It is found in *Artemisia annua* and also in *A. apiacea* and *A. lancea*. *Artemisia annua* and *A. apiacea* were known to the Chinese in antiquity and, since they were easily confused with each other, both provided plant material for the herbal drug *qing hao* (blue-green *hao*). This article shows, however, that since at least the eleventh century Chinese scholars recognized the difference between the two species, and advocated the use of *A. apiacea*, rather than *A. annua* for 'treating lingering heat in joints and bones' and 'exhaustion due to heat/fevers'. The article furthermore provides a literal translation of the method of preparing *qing hao* for treating intermittent fever episodes, as advocated by the eminent physician Ge Hong in the fourth century CE. His recommendation was to soak the fresh plant in cold water, wring it out and ingest the expressed juice in its raw state. Both findings may have important practical implications for current traditional usage of the plant as an antimalarial: rather than using the dried leaves of *A. annua* in warm infusions, it suggests that fresh juice extraction from *A. apiacea* may improve efficacy.

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## 1. Introduction

Artemisinin and its derivatives are now widely promoted as part of artemisinin combination therapies for treating drug-resistant malaria (Duffy and Mutabingwa, 2004; Woodrow et al., 2005), 30 years after their discovery in the People's Republic of China in the early 1970s. Furthermore, they produce rapid parasite clearance, which is significantly faster than that of any other antimalarial (Sriram et al., 2004); this

is clinically important, particularly in cases of cerebral and severe malaria.

Artemisinin, which is poorly soluble in both oil and water, is found in three species of the genus *Artemisia*, most importantly in *A. annua* L. and in minor quantities in *A. apiacea* Hance and *A. lancea* Vaniot. It is certainly the most important antimalarial substance in those plants, which contain other substances with antimalarial properties (Willcox et al., 2004). In spite of extraction problems, Chinese physicians have used *A. annua* and *A. apiacea* for producing drugs with antimalarial and other apparently therapeutic properties since at least the second century BCE (before common era). However, while the literature on the chemistry of artemisinin and clinical trials reporting its effects is vast,

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research into the history of the Chinese medical drug *qing hao* 青蒿 is scarce, or even non-existent (Hsu, *in press*).

Here I outline three themes that arise from research into the history of the Chinese medical drug *qing hao*. The first concerns the Linnaean identification of the plant *qing hao*; the second, methods recommended in antiquity for extracting the plant's pharmacologically active substances; and the third, a wide range of therapeutic applications recorded in the Chinese *materia medica* (*ben cao* 本草).

## 2. *Qing hao* is *Artemisia apiacea* and *huang hua hao* is *A. annua*

The name *qing hao* sometimes refers to the 'drug' (*yao* 藥), and sometimes to the 'kind' of plant from which the drug is derived (*zhong* 種). In the history of *qing hao*, *A. annua* and *A. apiacea* were not always kept apart. The drugs derived from both species were known by the names of *cao hao* 草蒿 (herbaceous *hao*; first century CE), *qing hao* (blue-green *hao*; first mentioned in second century BCE), and several other names (*Shen nong ben cao jing*). By the third century CE, their ecological habitat was recorded as 'wastelands' (*ze* 澤); the plant *cao hao* was said to grow everywhere as a ruderal (i.e. a plant growing in rubble and wastelands). By the tenth century, physicians were paying more attention to the appearance of the plants whence they derived drugs. One tenth century work distinguished between *qing hao* (blue-green *hao*) and *chou hao* 臭蒿 (stinking *hao*), and this distinction became definitive in the work of the famous physician and natural historian Li Shizhen 李時珍 (1518–1593), whose encyclopaedic *Classified Materia Medica* was published posthumously in 1596 and represents a landmark in the history of the Chinese *materia medica*. Li Shizhen did away with the main term *cao hao*, probably because he considered it too general and vague, and instead differentiated between two kinds, *qing hao* (blue-green *hao*) and *huang hua hao* 黃花蒿 (yellow blossom *hao*). Modern botanists have identified the former as *A. apiacea*, the latter as *A. annua*.

### 2.1. Shen Gua's distinction between the fragrant *hao* and the common *hao* in 1086 CE

This leads to the first finding worth stressing: strictly speaking, *A. annua* is *huang hua hao* and not, as is commonly assumed, *qing hao*. Chinese researchers are well aware of this, although few know that the difference between the two species can be traced to a botanical observation of 1086 known to Li Shizhen. It was that of the great scholar Shen Gua 沈括 (1031–1095):

The categories (*lei* 類) of *hao* 蒿 are very numerous. For the category *qing hao*, there are two kinds, one is yellow and one is blue-green. There is the kind that the entire *materia medica* literature calls *qing hao*, yet I fear there is another that can be distinguished from it. In Shaanxi, between Sui and Yin, there are *qing hao* in midst of clumps of *hao*, sometimes there are one or two stocks that are markedly blue-green in colour, the local people call them 'fragrant *hao*' 香蒿 (*xiang hao*). The stalks and leaves are the same as those of the 'common *hao*' 常蒿 (*chang hao*), but while the common *hao*'s colour is light green (*lü* 綠), this *hao*'s colour is blue-green and emerald (*qing cui* 青翠), just like the

colour of pine and juniper. In the depth of autumn, when the other *hao* are yellow, this type alone is blue-green; its smell (*qi* 氣) is quite aromatic. I suggest that this is the type that the ancients used; they considered it as the preferred variety (*Meng xi bi tan*, p. 873)

The plant with the markedly blue-green colour, called 'blue-green *hao*' (*qing hao*) or 'fragrant *hao*' 香蒿 (*xiang hao*), is today identified as *A. apiacea*. In Shen Gua's view it was the one used by the ancients, and was also recommended by Li Shizhen for the treatment of fevers. Li Shizhen's recommendation thus directly contradicts modern research, for the antimalarial substance artemisinin is found in larger quantities in *A. annua* than *A. apiacea*.

One could dismiss Li Shizhen downright, and perhaps one should do so. However, if one were inclined to grant him possible accuracy, one would have to take seriously the problem of the extraction of artemisinin and its derivatives. Perhaps, the traditional recipes recommended methods that made possible the extraction of more substantial quantities of the *Artemisia* sesquiterpenes from *A. apiacea* than from *A. annua*. Furthermore, possible synergistic effects of various constituents in *A. apiacea* versus *A. annua* may have played a role. I suggest these possibilities, without having done any laboratory research.

### 3. The preparation of the drug: soak the fresh plant in water and wring it out

This leads to the second theme, which concerns the preparation of the Chinese medical drug *qing hao*. Ge Hong 葛洪, in the fourth century CE, described an ingenious method of preparing *qing hao*, although it was not until 1596 that, due to Li Shizhen, his method was recorded within the genre of the Chinese *materia medica*. Unfortunately, no one has published this method in a Western language, although it may have important practical implications for future antimalarial applications of the fresh plant.

Ge Hong's method consisted of soaking the fresh plant in water, and then wringing out the whole plant and ingesting its juice in its entirety. The soaking of the entire fresh plant in water and its subsequent wringing out must have resulted in an emulsion of water, flavonoids and other etherical oils contained in stem and leaves (as mentioned above, one of the names of the plant was 'fragrant *hao*'), which may have facilitated the extraction of the *Artemisia* sesquiterpenes. It was this emulsion of the plant's expressed juice (*zhi* 汁) that should be ingested. Ge Hong's text reads as follows:

Another recipe: take a bunch of *qing hao* and two *sheng* 升 ( $2 \times 0.2$  l) of water for soaking it, wring it out to obtain the juice and ingest it in its entirety (*Emergency Prescriptions kept in one's Sleeve*, chapter 3.16; (N.B. one *sheng* amounted to 0.2 l at the time).

Ge Hong was the first in medical history to recommend the drug *qing hao* for the treatment of 'intermittent fevers' (*nüe* 瘧). The term 'intermittent fevers' designated many different morbid conditions, and in all likelihood, also referred to intermittent fevers due to malaria. It is possible that his method of extraction, which is likely to have yielded artemisinin in larger quantities than other methods recorded in the Chinese *materia medica*, was directly linked

to his recommendation of treating acute episodes of intermittent fever.

One such other method consisted of soaking the entire plant in urine rather than water. It is given in a manuscript unearthed from a tomb near Mawangdui in Hunan province that was closed in 168 BCE and it occurs repeatedly in the medical genre of formularies (*fang ji shu* 方劑書) of the Tang Dynasty (618–907), which from the Song Dynasty (960–1279) onwards started to be quoted in the *materia medica*. Probably the use of urine was imbued with symbolic meanings, although it is difficult to know what meanings exactly; a toddler's urine makes all the difference to the taste of sorghum beer in the film *Red Sorghum* (*Honggaoliang* 紅高粱) by Zhang Yimou 張藝謀 released in the 1980s. But there may also have been practical reasons that prompted doctors to use urine. For instance, if the fresh juice from the raw plant was thereafter ingested, as recommended by Chen Jiamo 陳嘉謨 in 1565, the use of urine rather than water may have had two advantages. First, urine is generally not contaminated with as harmful microbes as water can be (e.g. *Salmonella* Typhi, *Vibrio cholerae*), and second, use of urine may have optimized the process of extracting *Artemisia* sesquiterpenes and other pharmaceutically active substances from the plant.

#### 4. The therapeutic usage of *qing hao* according to the Chinese *materia medica*

Intrinsically related to the methods of drug preparation are its applications, the third theme of this article. In the *materia medica* from the Han through to the Tang Dynasty, *qing hao*'s prime indication were haemorrhoids, lice, wounds, boils and sores of various kinds, sometimes treated by external application of the crushed fresh plant. It was also recommended for treating 'lingering heat in joints and bones' (*liu re zai gu jie jian* 留熱在骨節間), which is a term reminiscent of 'bone breaker', commonly used for designating malaria today, and for 'exhaustion due to heat/fevers' (*re lao* 熱勞), which may have been caused by the anaemia that arises after recurrent episodes of malaria. Furthermore, it was valued as a food supplement and was considered to have longevity-enhancing properties (for instance, it 'brightened the eyes' (*ming mu* 明目) or 'caused growth of head hair' (*zhang fa* 長髮), which may have been an indirect consequence of its antimalarial effects, since chronic malaria debilitates and eventually causes anaemia. By the late Tang dynasty, when the drug was commonly prepared by first soaking the plant in urine, *qing hao* was also recommended for treating disorders with acute convulsions, which in China were related to pollution through contact with the dead and possession by demons (*shi zhu* 尸注, *gui qi* 鬼氣, *fu lian* 伏連). There certainly were other possible causes, but some of these convulsions may have been symptomatic of cerebral malaria.

Although in the genre of formularies, Ge Hong recommended *qing hao* for treating intermittent fevers as early as the fourth century, it is only in the twelfth century that 'eliminating bone steaming and heat/fevers arising from exhaustion' (*mie gu zheng lao re* 滅骨蒸勞熱) is given as the prime indication of *qing hao* in the *materia medica*. The Song Dynasty is well known for its innovative agricultural technol-

ogy, particularly in the domain of wet rice cultivation, which on the one hand provided the necessary nutritional basis that led to a significant increase in population (and also population density), and on the other to an increased incidence of malaria and other epidemics. Accordingly, many governmental measures addressed this public health problem, not least through the compilation of government sponsored *materia medica*.

#### 5. Conclusion

To summarize, the history of *qing hao* in the Chinese *materia medica* has shown that, first, the plant material whence the drug *qing hao* was produced may have been predominantly *A. apiacea* rather than *A. annua*. Second, it reveals an ingenious method of extracting the pharmacologically active substances for treating acute intermittent fever attacks, which consisted of soaking the whole plant in water, then wringing out the plant, thereby creating an emulsion that may have enhanced extraction of the *Artemisia* sesquiterpenes, known to be neither easily water-soluble nor oil-soluble, and, finally, ingesting the juice of the fresh plant in its entirety (rather than making a herbal tea with its dried leaves). Third, the range of therapeutic applications of *qing hao* was very wide indeed, although many of its indications may have been indirectly related to its antimalarial effects.

This work has important implications for current research on the use of traditional preparations of *Artemisia annua*. Several organizations are now promoting the local cultivation and use of this plant as an antimalarial in areas where modern drugs are not easily accessible (mentioned in Willcox et al., 2004). The plant distributed is *A. annua* rather than *A. apiacea*, and the preparation is a warm water infusion or boiling water decoction rather than the cold juice wrung out of the plant. This preparation has reasonable clinical efficacy, but there is still a relatively high recrudescence rate (Mueller et al., 2004). It could be that a fresh juice extraction, using *A. apiacea*, would improve the efficacy.

#### Conflicts of interest statement

The author has no conflicts of interest concerning the work reported in this paper.

#### References

- Duffy, P.E., Mutabingwa, T.K., 2004. Drug combinations for malaria: time to ACT? *Lancet* 363, 3–4.
- Hsu, E., (in collaboration with F. Obringer), in press. *Qing hao* 青蒿 (*Herba Artemisiae annuae*) in the Chinese *materia medica*, in: E. Hsu, S. Harris (Eds), *Plants, Health, and Healing: on the Interface of Medical Anthropology and Ethnobotany*. Berghahn, Oxford.
- 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. *Trans. R. Soc. Trop. Med. Hyg.* 98, 318–321.
- Sriram, D., Rao, V.S., Chandrasekhara, K.V., Yogeewari, P., 2004. Progress in the research of artemisinin and its analogues as anti-malarials: an update. *Nat. Prod. Res.* 18, 503–527.
- Willcox, M., Bodeker, G., Rasoanaivo, P., 2004. *Artemisia annua* as a traditional herbal antimalarial, in: Willcox, M., Bodeker, G.,

Rasoanaivo, P. (Eds.), *Traditional Medicinal Plants and Malaria*. CRC Press, Boca Raton, pp. 43–59.

Woodrow, C.W., Haynes, R.K., Krishna, S., 2005. Artemisinins. *Postgrad. Med. J.* 81, 71–78.

#### Premodern sources

*Ben cao gang mu* 本草綱目 (Classified Materia Medica). Ming, 1596. Li Shizhen 李時珍. 4 vols. Renmin weisheng chubanshe, Beijing, 1977–1981.

*Meng xi bi tan* 夢溪筆談 (Dream Pool Essays). Song, 1086. Shen Gua 沈括. Cited from *Mengxi bitan jiazheng* 夢溪筆談校證, annotated by Hu Daojing 胡道靜. 2 vols. Shanghai guji chubanshe, Shanghai, 1987.

*Shen nong ben cao jing* 神農本草經 (Shennong's Canon on *materia medica*). Han, 1st c. CE. Anon. References to *Shennong bencaojing jizhu* 神農本草經輯注. Annotated by Ma Jixing 馬繼興. Renmin weisheng chubanshe, Beijing, 1995. English translation by Shouzhong Yang, 1997. *The Divine Farmer's Materia Medica: a translation of the Shen Nong Ben Cao Jing*. Blue Poppy Press, Boulder, CO.

*Zhou hou bei ji fang* 肘後備急方 (Emergency Prescriptions kept in one's Sleeve). Jin, 4th century CE, Ge Hong 葛洪 (284–363). *Si ku quan shu* 四庫全書 (Collection of the Works from the Four Storehouses). References to *Wen yuan ge Si ku quan shu* 文淵閣四庫全書. Shangwu yinshuguan, Taipei, 1983.