Traditional Medicinal Uses of Yingzhao

Subjects: Pharmacology & Pharmacy

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The medicinal plant *Artabotrys hexapetalus* (synonyms: *A.uncinatus* and *A. odoratissimus*) is known as yingzhao in Chinese. Extracts of the plant have long been used in Asian folk medicine to treat various symptoms and diseases, including fevers, microbial infections, ulcers, hepatic disorders and other health problems. In particular, extracts from the roots and fruits of the plant are used for treating malaria. Numerous bioactive natural products have been isolated from the plant, mainly aporphine (artabonatines, artacinatine) and benzylisoquinoline (hexapetalines) alkaloids, terpenoids (artaboterpenoids), flavonoids (artabotrysides), butanolides (uncinine, artapetalins) and a small series of endoperoxides known as yingzhaosu A-to-D. These natural products confer antioxidant, anti-inflammatory and antiproliferative properties to the plant extracts. The lead compound yingzhaosu A displays marked activities against the malaria parasites *Plasmodium falciparum* and *P. berghei*.

Artabotrys hexapetalus | endoperoxide | malaria | natural products | yingzhaosu

1. Introduction

Despite new treatment modalities, malaria remains a major public health threat worldwide, causing more than 400,000 deaths per year, predominantly in children in sub-Saharan Africa and tropical regions [1]. Recently, the malaria vaccine RTS,S (Mosquirix™) has received regulatory approval for the prevention of malaria infection. The launch of this vaccine represents a major achievement in limiting the transmission of the parasite, but it shows a modest efficacy against malaria illness [2]. New treatments are still needed to combat the disease, notably the drug-resistant forms, which develop rapidly. There is a significant need for efficient, affordable and well-tolerated antimalarial drugs [3].

The first-line treatment of *Plasmodium falciparum* mild malaria generally relies on combination therapy, including artemisinin (ART) and/or chloroquine, whereas intravenous artesunate is often preferred in cases of severe malaria, at least in developed countries [4]. The combination of artesunate and pyronaridine (Pyramax®) is also approved to treat uncomplicated malaria [5][6]. ART and derivatives have been extensively studied as antimalarial drugs. The discovery of artemisinin was largely based on traditional Chinese medicine (TCM), as recognized by Dr. Youyou Tu, who was awarded the Nobel Prize in Physiology and Medicine in 2015 for her discovery of ART and its therapeutic effects on malaria [7]. Herbs of the *Artemisia* family (qinghao in Chinese) have been extensively studied for their pharmacological properties and phytochemical content.

In contrast, the plant yingzhao (*Artabotrys unciatus* (L.) Meer.) has been considerably less investigated. Moreover, the main phytochemical compounds found in yingzhao, known as yingzhaosu, have been essentially neglected, at

least from a pharmacological viewpoint (**Figure 1**).

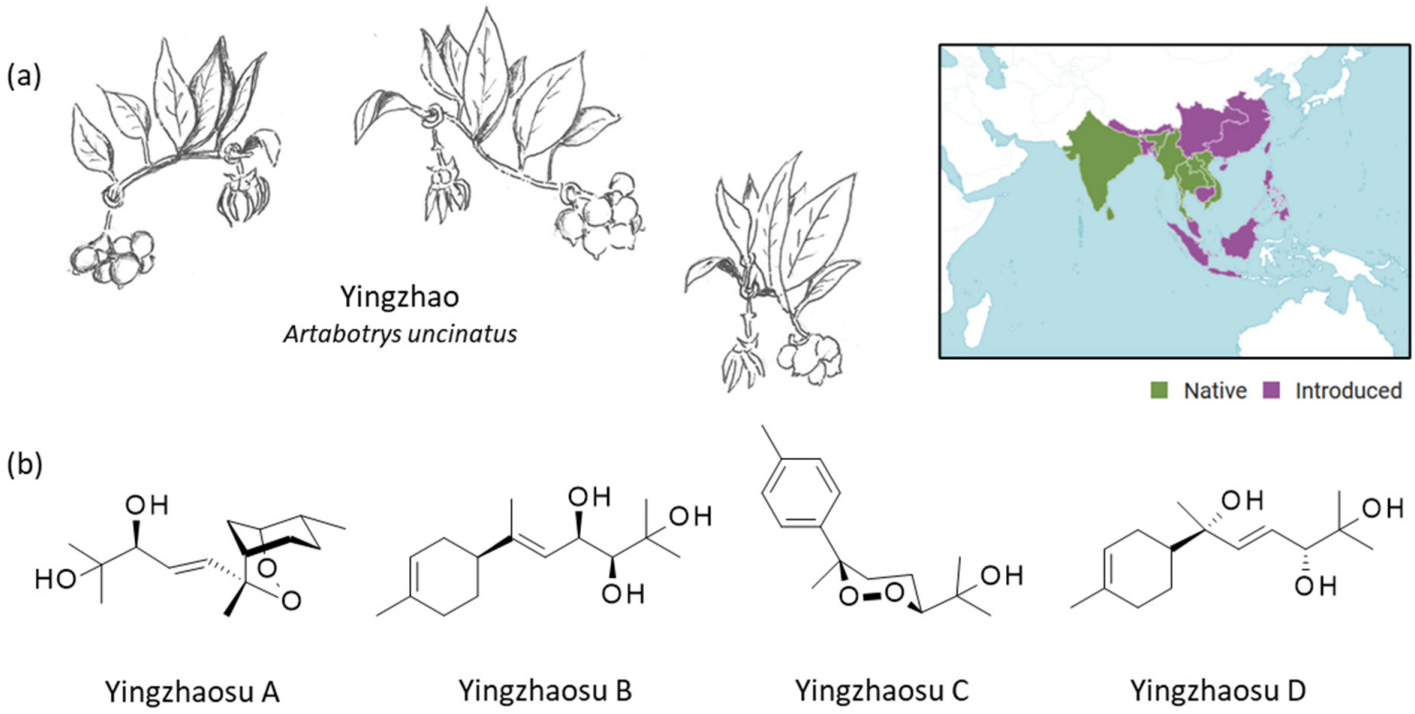


Figure 1. Yingzhao plant and yingzhaosu compounds. (**a**) The plant yingzhao (*Artabotrys uncinatus* (L.) Meer.) with a view of the young fruits, the leaves and the flower (drawing: Prof. J.-P. Hénichart). The plant is largely distributed in Southeast Asia. The plant is native to countries such as India, Thailand, Vietnam, and Sri Lanka (and other counties in green) and has been introduced in Indonesoia, China, Japan (and other countries in purple) (https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:72395-1, accessed on 14 September 2022). (**b**) Structure of the four yingzhaosu compounds, all isolated from yingzhao.

2. The Plant Yingzhao

The Chinese medicine yingzhao is usually associated with the plant name *Artabotrys uncinatus* (L.) Meer. (Annonaceae), from which yingzhaosu compounds have been isolated, as discussed above (**Figure 1**). However, and in fact, *A. unciatus* is one of the synonyms for the plant *Artabotrys hexapetalus* (L.f.) Bhandari, which is the accepted botanical name [8]. Other synonyms are used, such as *A. odoratissimus* R.Brown. (**Table 1**). This plant, commonly called tail grape or climbing ylang-ylang, can be found in China, India, Malaysia, Indonesia, Vietnam and other countries of Southeast Asia. It is native to Sri Lanka and Southern India and can be grown in many places [9]. For example, two established plants of *A. hexapetalus* (L.f.) Bhand. growing at the Fairchild Tropical Garden in Miami (US) have been used to study plant architecture during growth [10]. It can also be found in some tropical African countries, like Tanzania [11].

Table 1. The plant yingzhao, accepted botanical names and synonyms.

Accepted Name	Synonyms *	Common Names **
Artabotrys hexapetalus (L.f.) Bhandari	*Annona hexapetala* L.f.	Tail grape (English); Hari champa, Kath champa, Madanmast (Hindi); Manoranidam (Tamil); Kothali-champa (Assamese); kenanga tanduk (Indonesian). Ylang-Ylang grimpant (French); Cay Móng rồng (Vietnamese); karawek (Thailand); iraniran noki, tsuru iraniran (Japanese); lanalana (Hawaiian); kathali champa, kaanthaali chaanpaa (Bengali).
	Annona uncinata Lam.	
	Artabotrys hamatus (Dunal) Blume	
	Artabotrys intermedius Hassk.	
	Artabotrys odoratissimus R.Br.	
	Artabotrys odoratissimus Wight & Arn.	
	Artabotrys uncata (Lour.) Baill.	
	Artabotrys uncatus (Lour.) Baill.	
	Artabotrys uncinatus (Lam.)	

Accepted Name	Synonyms *	Common Names **
	Merr.	
	Unona uncata (Lour.) Dunal	
	Unona uncinata (Lam.) Dunal	
	Uvaria esculenta Roxb. ex Rottler	
	Uvaria odoratissima Roxb.	
	Uvaria uncata Lour.	

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Yingzhao behaves as a woody climber, possibly growing up to 10 m in height. It should not be confused with *Cananga odorata* (ylang-ylang) used in perfumery. *A. hexapetalus* is a woody scandent climbing shrub. The leaves are oblong to broadly lanceolate in shape and the flowers are fragrant, with yellow petals (**Figure 1**). The plant is recognizable from the flower stalks, which are shaped like hooks. With beautiful and aromatic flowers, it is an ornamental plant now cultivated and also used in the perfume industry. The seeds are used for propagation, but the germination process is complex and long, taking as long as 238 days [12]. The plant is appreciated for its pleasant-smelling yellow flowers, from which a delicate essential oil, rich in sesquiterpenoids (such as β-caryophyllene and caryophyllene oxide), can be prepared [13]. Essential oils can also be obtained from the stem bark or leaves of the plant to be used as a mosquito repellent [11].

3. Traditional Medicinal Uses of Yingzhao

For a long time, yingzhao-based preparations have been used to treat human diseases. Different parts of the plant have been used. The symptoms and pathologies treated with plant extracts vary from one country to another. In Malaysia, leaf decoctions were given for curing cholera, whereas the roots and fruits have been used for the treatment of malaria and scrofula (tuberculous lymphadenitis). There is also mention of the use of the plant to treat fever, diarrhea, dysentery, cuts, sprains, ulcers, and asthma.

Recently, Kousalya and Doss [14] have inventoried the diverse ethnomedicinal uses of *A. hexapetalus* extracts. These can range from antibacterial and antifungal effects to hepato-protective and anti-ulcer activities (**Table 2**). In

general, the pharmacological effects were obtained with organic extracts prepared from the plant's leaves, bark, or roots. For example, methanolic leave extracts were found to display antifungal and antibacterial effects [15][16][17]. The essential oil of *A. odoratissimus* R.Br. (synonym) has shown a broad-spectrum activity against 14 different storage fungi, and interestingly, it was reported to arrest aflatoxin B1 secretion by a toxic strain of *Aspergillus flavus* [18]. Flower extracts of *A. hexapetalus* also revealed antifungal effects [19].

Table 2. Pharmacological properties of *A. hexapetalus* extracts.

Pharmacological Activities	Comments	References
Antiparasitic	Extracts of the roots and fruits are used to treat malaria (*Plasmodium falciparum* infection) and leishmania (*Leishmania donovani infection).* Numerous antimalarial compounds characterized, principally the yingzhaosu.	[20][21][22][23]
Antibacterial	Activities against *Salmonella, Staphylococcus, Pseudomonas* and other bacteria reported with hydroalcoholic extracts of the flowers and leaves. Bactericidal effect of silver nanoparticles made with an aqueous extract of *A. hexapetalus*.	[24][25]
Antifungal	Activities against *Candida albicans*, *Aspergillus niger* and other fungi reported with a methanolic extract.	[16][19]
Antifertility	Reduction of sperm count and fertility with a hydroalcoholic leave extract, and modulation of the oestrus cycle. Regulation of steroidal hormone levels.	[26][27][28][29][30]
Anticancer	A fruit extract of *A. odoratissimus* reduced proliferation of MIA PaCa-2 pancreatic cancer cells and induced their apoptotic cell death.	[31]
Anti-ulcer and hepatoprotection	Protection against liver injuries and oxidative stress with a hydroalcoholic extract. Anti-inflammatory activity of an ethanolic extract of aerial parts. Cytoprotection conferred by antioxidant flavonoids and alkaloids.	[32][33][34][35]

Pharmacological Activities	Comments	References
Mosquito repellent [35]	Essential oils made from leaves and stem bark extracts obtained by hydro-distillation have revealed mosquito repellency activity, attributed to the presence of β-caryophyllene oxide.	[11]

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The hydroalcoholic leave extracts of *A. hexapetalus* have been found to reduce sperm count and mobility in rats, reducing the diameter of seminiferous tubules. The extract lowered the testosterone level and significantly reduced fertility in rats [28]. The observation was consistent with the reported antifertility activity of various leaf extracts of *A. odoratissimus* Roxb. (synonym). In this case, the extracts (obtained with benzene, ethanol and water) were found to disturb the oestrus cycle and reduce implantation and thus fertility [26]. Antifertility activity has been confirmed in a recent study performed with extracts from the leaves and stem of *A. odoratissimus* Roxb. in female rats. The extracts altered the level of cholesterol and steroidal hormones (estradiol and progesterone) and caused polycystic ovaries in rats [28][29]. In India, antifertility activity of *A. odoratissimus* plant extracts is known for several decades [36][37] and remains considered today for the regulation of fertility [30].

The main bioactivity of *A. hexapetalus* refers to antiparasitic effects. For a long time, yingzhao (roots and fruits) has been used to combat parasites such as *Plasmodium falciparum* and *Leishmania donovani*. A petroleum ether extract of *A. hexapetalus* was shown to moderately reduce the growth of the promastigote forms of cultured *L. donovani*. The effect was attributed to the presence of flavonoids such as quercetin and apigenin [23]. Notwithstanding, there are many other flavonoids in the plant extracts, such as taxifolin, apigenin glycosides, glucoluteolin, arabotrysides A and B (**Figure 2**), and the flavonol glycosides called arapetalosides A and B [38][39]. Hydroalcoholic leaf extracts of *A. hexapetalus* display activities against *Plasmodium* and *Leishmania*, but not against the African earthworm *Eudrilus eugeniae* (African nightcrawler) [22][23]. It should be noted that there is not many published information about the antiplasmodial activity of *A. hexapetalus*. Solid data have been reported with other species, such as *A. crassifolius* [40], but not for yingzhao extracts despite the traditional use.

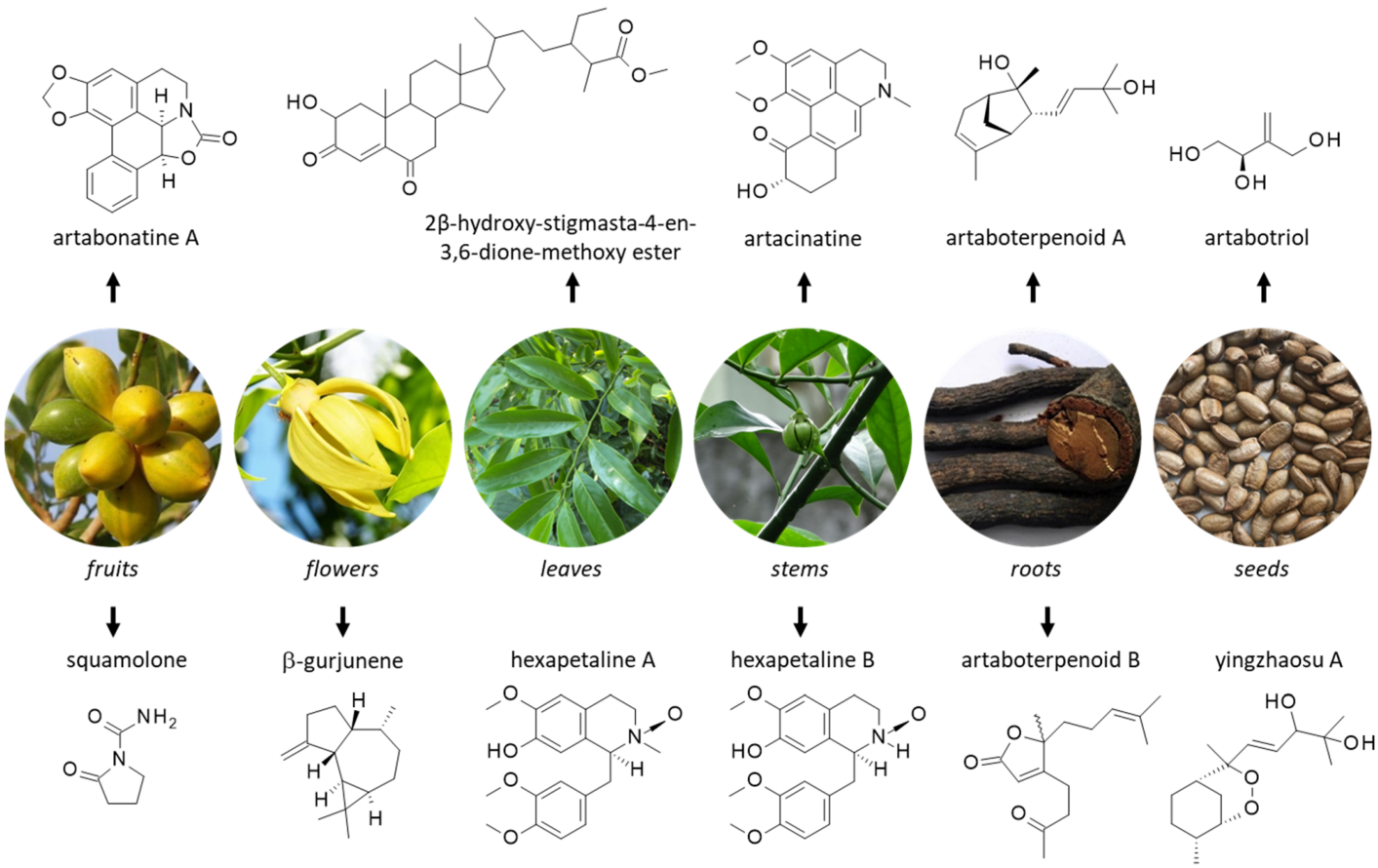


Figure 2. Structure of selected natural products isolated from different parts of yingzhao. Detailed botanical information on yingzhao can be found at http://www.instituteofayurveda.org/plants/plants_detail.php?i=75&s=Local_name (accessed on 14 September 2022).

Occasionally, other pharmacological effects have been reported. For example, a recent study underlined the antiproliferative activity of *A. odoratissimus* fruit extract against MIA PaCa-2 pancreatic cancer cells. The organic (ethyl acetate) extract reduced cell growth, revealed an antioxidant effect, and induced apoptotic cell death associated with DNA damage [31]. The phytochemicals at the origin of the anticancer action were not specified, but it could be linked to the presence of cytotoxic alkaloids. More than 25 alkaloids have been isolated from *A. uncinatus* (synonym), including cytotoxic oxoaporphines and other alkaloids endowed with cytotoxic effects such as atherospermidine and squamolone (**Figure 3**) [41][42].

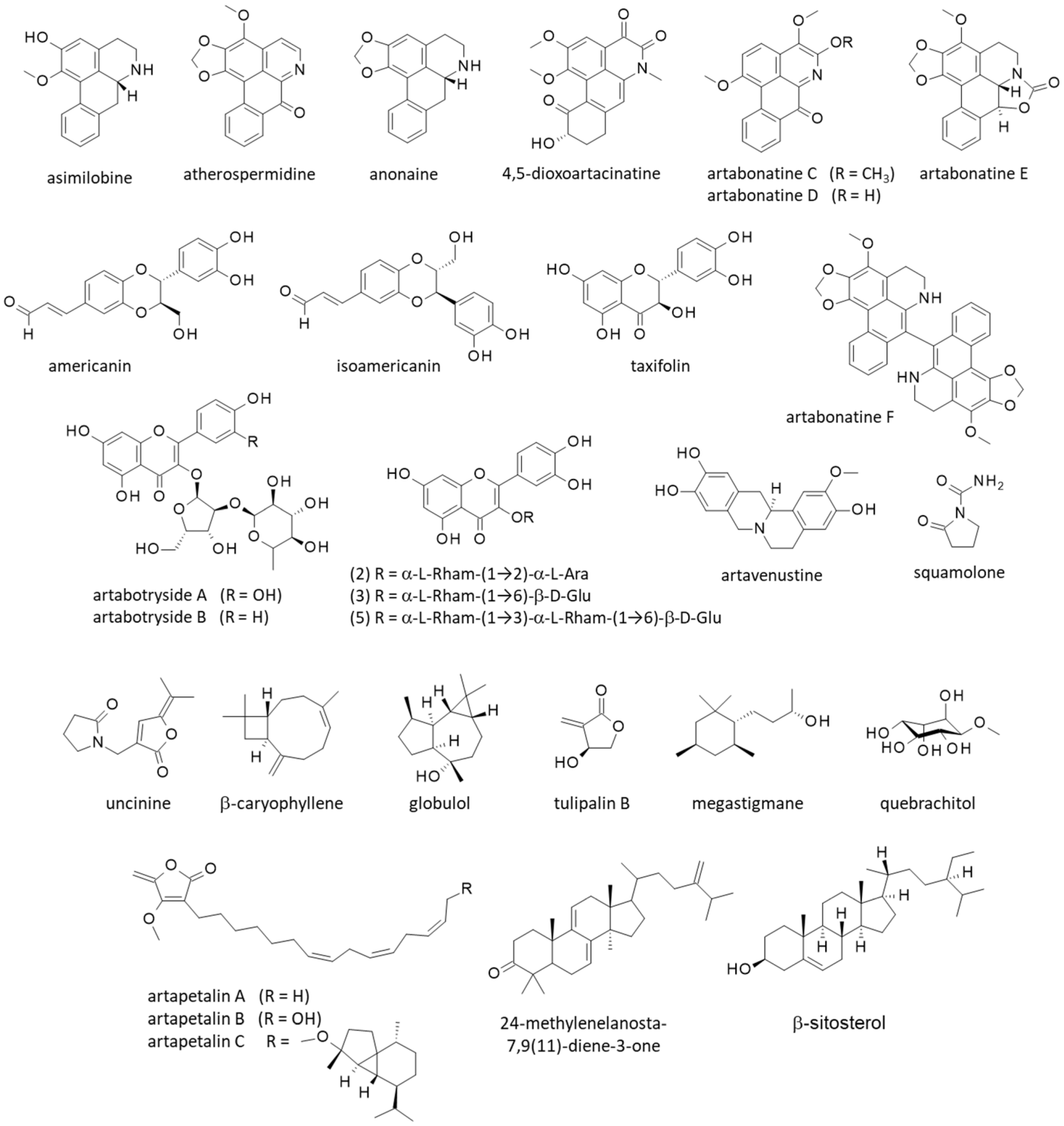


Figure 3. Structure of other natural products isolated from yingzhao.

The multiple bioactive properties evidenced by extracts of the plants stimulate research and the elaboration of novel bioinspired products. For example, silver nanoparticles have been made using an aqueous extract of *A. hexapetalus* with the objective to propose new bactericide products [25]. There are also non-medicinal usages of the plant extracts. For example, the plant leaf extract has shown anticorrosion activity. It could be used as an eco-friendly green inhibitor for acidic-induced corrosion of mild steel [43][44].

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