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Review Article

Exploring *Artemisia annua* L., artemisinin and its derivatives, from traditional Chinese wonder medicinal science

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Abstract

Artemisia annua L. (Chinese wormwood herb, Asteraceae) synthesizes artemisinin, which is known as qinghaosu, considers as a unique sesquiterpene endoperoxide lactone. In traditional Chinese medicine, it has been used for the treatment of fevers and haemorrhoides. More researches on *Artemisia annua* L. and its derivatives, especially artemisinin and other metabolites will help to increase the knowledge and value of *A. annua* and its constituents. Phenolics from *Artemisia annua* consists of coumarins, flavones, flavonols, phenolic acids, and miscellaneous. Artemisinin has attracted much attention from scientists due to its potent antimalarial properties as secondary metabolites. Moreover, more attentions are focusing on the roles of artemisinin and its derivatives in treating obesity and metabolic diseases. They also have anti-bacterial, anti-inflammatory, anti-tumor, anti-protozoa, anti-helminthic, anti-fungal, anti-angiogenic and antiproliferation properties. The most important derivatives of *Artemisia annua* L. are arteether, artemether, artemiside, artemisinin, artemisone, artesunate, and dihydroartemisinin. Artemisinin also use against some cancers such as liver cancer, brain glioma, leukemia, nasopharyngeal cancer, gallbladder cancer, gastric cancer, cervical cancer, lung cancer, breast cancer and colon cancer. This important gift from ancient Chinese traditional medicine can guarantee health of people all around the world. Further researches should be done on the new advances and development of artemisinin and its derivatives as potential natural medicine in the global fight against so many diseases, malaria included.

Keywords: artemisia; artemisinin; cancer; Chinese medicine; malaria

Introduction

For thousand years, the most commonly treatment which has been widely used in different parts of the world, especially Asia was traditional herbal medicines (Shahrajabian *et al.*, 2020a, b; Sun *et al.*, 2020a, b), because of containing various ranges of chemical contents with different pharmacological applications. They are used by people because of effectiveness, frequently inadequate provision of modern medicine, cultural beliefs and preferences (Sun *et al.*, 2019a, b; Shahrajabian *et al.*, 2020c, d). *Artemisia annua* L., Asteraceae, has diverse biological actions from anticancer to anti-malarial activities (Beekman *et al.*, 1998) with high

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antioxidant activities from its leaves because of the high content of flavonoids (Zheng and Wang, 2001; Bilia *et al.*, 2006). The goal of this manuscript is review of *Artemisia annua* and its derivatives with considering tremendous health benefits.

Artemisia annua L. an ancient herb in traditional Chinese medicine to modern drug

One of the most important branches of traditional medicine is traditional Chinese medicine with more than 3500 years medical practices (Shahrajabian *et al.*, 2019a, b, c, d). Malaria affects more than 200 million people in many African and Asian countries (NaB and Efferth, 2019). Artemisia is the largest genus in the tribe Anthemideae of the Asteraceae family consisting of more than 500 species (Lim *et al.*, 2018; Li *et al.*, 2020; Lu *et al.*, 2020). The most important species of *Artemisia* are *A. absinthium*, *A. abrotanum*, *A. afra*, *A annua*, *A. arborescens*, *A. asiatica*, *A. capillaries*, *A. campestris*, *A. douglasiana*, *A. dracunculus*, *A. judaica*, *A. maritime*, *A. mogoltavica*, *A. monospermal*, *A. nilagirica*, *A. scoparia*, *A. tripartite*, *A. verlotorum*, *A. vestita*, and *A. vulgaris* (Bora and Sharma, 2011). The content of *Artemisia annua* L. is artemisinin, which is a member of the Artemisia family which has been used in traditional Chinese medicine for thousand years (Njuguna *et al.*, 2012; Tu, 2016). It is a typical short-day photoperiod (Lv *et al.*, 2018). It has appeared in many ancient Chinese medical manuscripts, which describe its uses to include treatment of wounds, alleviating intermittent fevers, as well as enhancing the brightness of eyes and even improving longevity (Liu *et al.*, 2013). In traditional Chinese medicine, it used to treat fever, chill and an ancient Chinese herbal remedy for pyrexia (Abba *et al.*, 2018). It is called sweet wormwood, Chinese wormwood, Sweet Annie in English; Absinthe chinoise, armoise annuelle in French; Qinghao, Cao hao, Cao Qinghao, Cao Haozi, Chou Qinghao, Haoz, Kuhao, Xianghao, Xiang Qinghao and Xihehao in Chinese; Kusoninijin in Japanese, Than Hao and Than Cao Hoa Vang in Vietnamese, Chui Ho, Hwang-Hwa-Ho and Gae-Tong-Sok in Korean. The growing period of *Artemisia annua* from seedling until harvest is 190-240 days, depending on the climate and altitude of the production area. Artemisinin also known as Qinghaosu, and of over 2000 types of traditional Chinese herbs that were investigated, *Artemisia annua* (Sweet Annie, or Sweet Wormwood) exhibited significant inhibitory properties against malaria parasites (Lu *et al.*, 2019). *Artemisia* L. is a genus of small herbs and shrubs, belonging to an important family Asteraceae (Salehi *et al.*, 2018), which are mainly found in Asia, North America and Europe (Bora and Sharma, 2011).Its molecular formula is C15H22O5 and molecular mass 282.332 g/mol. El-Naggar *et al.* (2013) reported that Qinghao (*Artemisia annua* L.) is among the top 10 pharmaceutical crops which are receiving intensive worldwide scientific attention as it is currently only source for pharmaceutical production of artemisinin. The most important provinces under cultivation of *A. annua* L. in China are Chongqing, Hunan, Hubei and Guizhou (Huang *et al.*, 2010).

Scientific classification
Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Asterales
Family: Asteraceae
Genus: *Artemisia*
Species: *A. annua*

There are now many large *A. annua* L. plantations, which produce about 80% of Chinese artemisinin, in Chongqing, Southwest China (Zeng *et al.*, 2018). The malaria drug artemisinin is an example of doing researches for many years on *A. annua*, a Chinese medicinal plant (Qinghao), which is known as sweet worm (Ikram and Simonsen, 2017). It is believed to have been first described by the Chinese during the Jin dynasty around 317-420 AD due to its medicinal properties specifically for reducing fever (Konstat-Korzenny *et al.*, 2018). The artemisinin content of wild *A. annua* L. has been described to vary between 0.02% and 1.1% of the dry weight, depending on plant source and cultivation conditions (Delabays *et al.*, 2001). Atremisinin isolated from the traditional Chinese herb *Artemisia annua* serves as a precursor to today's most effective antimalarial

drugs against strains of *Plasmodium falciparum* parasites (Meshnick *et al.*, 1996). Wild or cultivated *A. annua* L. is a major source for artemisinin because chemical and biological synthesis of artemisinin is still under development due to poor yields (Huang *et al.*, 2010). Tu was awarded her Nobel Prize in Physiology or Medicine in 2015 for the discovery of this important antimalarial compound as a head of a scientific group in 1967-1969 (Salehi *et al.*, 2018). Artemisinins are a family of sesquiterpene trioxane lactone bearing an endoperoxide bridge, and used artemisinins includes artemisinin (ART), artesunate (AS), artemether (AM), arteether (AE) and dihydro-artemisinin (DHA) (Asano and Iwahashi, 2017; Shi *et al.*, 2018). Artemisinin and its derivatives are powerful and important medicine because of their ability to swiftly reduce the number of Plasmodium parasites in the blood of patients affected by malaria (Negi *et al.*, 2018; Lv *et al.*, 2019). However, Phyo *et al.*, (2018) noted that reliable efficacy of artesunate for the treatment of severe malaria may no longer be assured in areas where artemisinin resistance has emerged. Rath *et al.* (2004) stated that one liter of an aqueous preparation of nine grams of *Artemisia annua* contained 94.5 milligrams of artemisinin, which is approximately 19% of the usually recommended daily dose. It can grow easily in the humid tropics though the artemisinin yield appears to be affected significantly by several factors such as seed origin, planting season, soil moisture availability and cultivation methods (Brisibe *et al.*, 2012). Moderate salt stress has been proved to increase the artemisinin synthesis by the plant (Correa-Ferreira *et al.*, 2019).

Phenolic constituents of Artemisia annua L. and Artemisinin biosynthetic pathways in A. annua

Flavonoids, coumaris, steroids, phenolics, purines, lipids, aliphatic compounds, monoterpenoids, triterpenoids and sesquiterpenoids such as artemisnin have been isolated from the leaves and flower of *A. annua* (Bhakuni *et al.*, 2001). Phenolics from *Artemisia annua* consists of coumarins, flavones, flavonols, phenolic acids, and miscellaneous. Coumarins included coumarin, aesculetin, iso-fraxidin, scopoletin, scopolin and tomentin. Flavones consiss of apigenin, luteolin, luteolin-7-methyl ether, acacetin, chrysoeriol, chrysin, cirsilineol, cirsiliol, cynaroside, eupatorin, cirsimaritin. Flavonols consist of artemetin, chrysosplenol C, chrysosplenol D, mikanin, astragalin, axillarin, casticin, eupatin, kaempferol, kaempferol-6-methoxy glucoside, tamarixetin, myricetin, gossypetin-3,-dimethyl ether, laricitrin, mearnsetin, quercetin, quercetin-3-glucoside, quercetin-3-methyl ether, quercimeritin, retusin, rhamnetin, isorhamnetin, rutin, mearnsetin-glucoside, chrysosplenetin, 3,5-Dihydroxy-3′,4′,6,7, tetra-methoxyflavone, Syringetin, Isokaempferide and Quercetagetin 3,4′-dimethyl-ether. Phenolic acids are chlorogenic acid, quinic acid and coumaric acid. Miscellaneous consist of 2,4-Dihydroxy-6 methoxy-acetophenone, 5-Nonadecy-3-O methyl ether- recorcinol, 2,2,6-trihydroxy chromene and 2,2-didhyroxy-6- methoxy-chromene (Hethelyi *et al.*, 1995; Shatar *et al.*, 2003; Rao *et al.*, 2014; Lohani *et al.*, 2016). Artemisia ketone, 1, 8-cineole and camphor are major essential oil composition of *A. annua* L. (Jain *et al.*, 2002; Mukhtar *et al.*, 2007; Goel *et al.*, 2008; Liu *et al.*, 2019). Other major chemical composition of the volatile oil from its seeds are *Trans*-3(10)-caren-4-ol, and δ-selinene (Malik *et al.*, 2009; Habibi *et al.*, 2013). Libbey and Sturtz (1989) reported that the major components of the essential oil of *A. annua L.* was Artemisia ketone (35.7%), 1,8-cineole (31.5%), alpha-pinene (11.2%), Artemisia alcohol (5.2%) and myrcene (4.6%). Charles *et al.* (1991) reported that the major components of the oil in leaves are Artemisia ketone (35.6%), and 1,8-cineole (28.1%) at the early summer harvested plants, artemisia ketone (26.8%) and camphor (20.5%) in leaves of fall harvested plants, and artemisia ketone (56%), and camphor (10.5%) in flowers of fall harvested plants. Ma *et al.* (2007) reported that terpene compounds are the main components of *Artemisia annua* L. Kazemi (2015) observed α-pinene (7.33%), camphene (5.68%), sabinene (4.78%), β-myrcene (22.41%), 1,8-cineole (17.17%) and camphor (20.41%) as major constituents of *Artemisia annua* L. in Iran. Molecular structures of several common artemisinin monomers are shown in Figure 1.

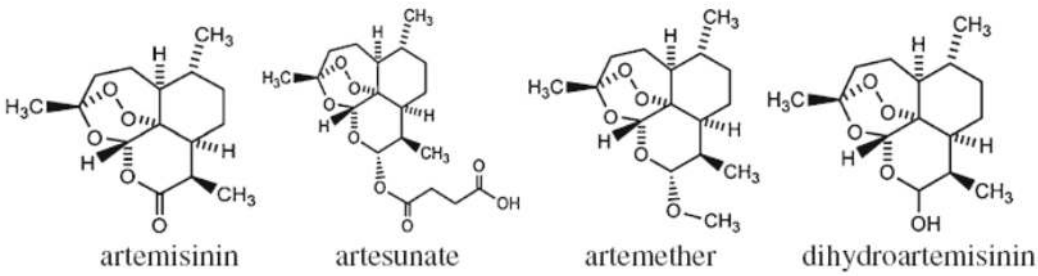

Figure 1. Molecular structures of several common artemisinin monomers (Lai *et al.*, 2013)

Artemisinin and its derivatives

Artemisinin is a sesquiterpene lactone, an antimalarial substance, is obtained on large scale from dried leaves of *Artemisia annua* L. (Usuda *et al.*, 2000; Widmer *et al.*, 2007; Sulsen *et al.*, 2011; Kumar *et al.*, 2013). The biosynthesis of artemisinin was reported in the shoot cultures and genetically modified roots (hairy roots) of *A. annua* (Ram *et al.*, 2014). Its derivatives such as artesunate, dihydroartemisinin and artemether are the most potential antimalarials available, rapidly killing all asexual stages of the parasite *Plasmodium flaciparum* (O' Neill, 2005). Fu *et al.* (2016) concluded that both plant height and stem bottom diameter had the most important positive impact on artemisinin content of the leaves and herb yield. Artemether is the methylated derivatives of artemisinin.

Artemether showed anti-parasitic properties toward many protozoan parasites such as *Leishmania*, *Toxoplasma gondii* and *Trypansoma* spp. (Mishina *et al.*, 2007), and also a promising drug in control of *schistosomiasis mansoni* due to its reductive impact on worm burden and its role in improvement of hepatic granulomatous lesions (Madbouly *et al.*, 2015). Production of artemisinin in genetically modified microorganisms is an attractive way to enable sufficient supply of the effective antimalarial agent (Zeng *et al.*, 2012). It can be extracted using ultrasound-assisted extraction (UAE) and then detected via HPLC (Widmer *et al.*, 2007; Wang and Liu, 2012; Zhang *et al.*, 2014). The biosynthetic pathway of artemisinin belongs to the isoprenoid pathway and its production pathway was divided in two stages: in the first step Acetyl-CoA make isopentenyl diphosphate (IPP) and its isomer, dimethylallyl diphosphate; in the next step IPP produces artemisinin (Mirzaee *et al.*, 2016). There are four enzymes, namely ADS, CYP71AV1, DBR2 and ALDH1 in artemisinin biosynthetic pathway, and the artemisinin content was determined by the chemo-type of CYP71AV1 (Lv *et al.*, 2017), and the highly active CYP71AV1 is decided by an amino acid residue (Ser479) (Komori *et al.*, 2013). Artemisinin derivatives are effective against other parasites such as *Toxoplasma gondii* (De Oliveira *et al.*, 2009), *Trypanosoma cruzi* (Sulsen *et al.*, 2008), Schistosoma japonicum, *Schistosoma mansoni, Fasciola hepatica*, and *Clonorchis sinensis* (Fathy, 2011), and *Acanthamoeba* spp. (Derda *et al.* 2016). Lai *et al.* (2005) discovered that artemisinin and artemisinin-tagged iron-carrying compounds could be developed into powerful anticancer drugs. Njuguna *et al.* (2012) stated that artemisinin and its derivatives have revealed its potential use in treating other infectious and noninfectious diseases. Ivanescu *et al.* (2011) found artemisinin content in Romanian *A. annua* wild plants varies between 0.17 and 0.21% dry weight basis. Artemisinin, artesunate and artemether are well-tolerated in both children and adults, with no evidence of serious clinical toxicity (Price, 2000). Artemether-lumefantrine is the most widely used artemisinin-based combination therapy for malaria (Christian *et al.*, 2017). Wojtkowiak-Giera *et al.* (2018) observed that *A. annua* extract is a natural substance which is well tolerated in animals and may be considered as a combination therapy in treatment of acanthamoebiasis. Artesunate is the most versatile derivative of artemisinin, because it is easily soluble in water, which has facilitated the development of oral and rectal formulas (Angus *et al.*, 2002); it is an antimalarial agent and acts cytotoxically on tumor cells (Aquino *et al.*, 2011; Kannan *et al.*, 2019). Artseunate is not only an effective drug for treating tumor, but also it has been used for curing malaria, improving inflammation and protecting nerves (Noubiap, 2014; Bigoniya *et al.*, 2015; Zhao *et al.*, 2017; Gugliandolo *et al.*, 2018; Wen *et al.*, 2018). Kong *et al.* (2019) demonstrated that artesunate targeted activating

hepatic stellate cells ferroptosis, and its effect was associated with activation of ferritinophagy. Phenolics compounds from *Artemisia annua* is shown in Table 1.

Table 1. Phenolics from *Artemisia annua* (Ferreira *et al.*, 2010)

Coumarins	1-	Coumarin
	2-	Aesculetin
	3-	Iso-Fraxidin
	4-	Scopoletin
	5-	Scopolin
	6-	Tomentin
Flavones	7-	Apigenin
	8-	Luteolin
	9-	Luteolin-7-methyl ether
	10-	Acacetin
	11-	Chrysoeriol
	12-	Chrysin
	13-	Cirsilineol
	14-	Cirsiliol
	15-	Cynaroside
	16-	Eupatorin
	17-	Cirsimaritin
Flavonols	18-	Artemetin
	19-	Chrysosplenol C
	20-	Chrysosplenol D
	21-	Mikanin
	22-	Astragalin
	23-	Axillarin
	24-	Casticin
	25-	Eupatin
	26-	Kaempferol
	27-	Kaempferol-6-methoxy glucoside
	28-	Tamarixetin
	29-	Myricetin
	30-	Gossypetin-3,-dimethyl ether
	31-	Laricitrin
	32-	Mearnsetin
	33-	Quercetin
	34-	Quercetin-3-glucoside
	35-	Quercetin-3-methyl ether
	36-	Quercimeritrin
	37-	Retusin
	38-	Rhamnetin
	39-	Isorhamnetin
	40-	Rutin
	41-	Mearnsetin-glucoside
	42-	Chrysosplenetin
	43-	3,5-Dihydroxy-3′,4′,6,7, tetra-methoxyflavone
	44-	Syringetin
	45-	Isokaempferide

	46-	Quercetagetin 3,4′-dimethyl-ether
Phenolic acids	47-	Chlorogenic acid
	48-	Quinic acid
	49-	Coumaric acid
Miscellaneous	50-	2,4-Dihydroxy-6 methoxy-acetophenone
	51-	5-Nonadecy-3-O methyl ether- recorcinol
	52-	2,2,6-trihydroxy chromene
	53-	2,2-didhyroxy-6- methoxy-chromene

From plant to medicine, the most important pharmacological properties of artemisinin and its derivatives

Artemisinin family drugs regulate innate immune cells, regulate adaptive immune cells, and it has efficacy in treating autoimmune diseases (Hou and Huang, 2016; Shen *et al.*, 2018). Daddy *et al.* (2017) suggested the use of *Artemisia annua* dried leaf tablets to treat resistant malaria in which the synergic role of other components with artemisinin is claimed to tackle plasmodium resistance. The most important pharmacological effects of artemisinins consist of anti-virus, anti-cancer, anti-inflammatory and anti-oxidant (Ho *et al.*, 2014; Shi *et al.*, 2015). Lam *et al.* (2018) found that Artemisinin (ART) and its derivatives are potentially effective drugs for treating various helminthic diseases of public health significance. It has been reported that ART derivatives and synthetic peroxides such as ozonides and trioxolanes maybe used as alternative or complementary drugs against schistosomes (Keiser *et al.*, 2012; Xiao *et al.*, 2012). Moreover, ART and its derivatives also have activities against nematodes and cestodes (Kuster *et al.*, 2014; Abou Rayia *et al.*, 2017). Magoulas *et al.* (2017) suggested that artemisinin dimmers are good candidates for the development of effective anticancer agents. Shi *et al.* (2018) suggested that artemisinins are capable to treat neuroinflammation-related central nerve system (CNS) diseases in both direct and indirect manners. Qiang *et al.* (2018) provides direct evidence for the potential application of artemisinin B in the treatment of neuroinflammatory diseases. Wu *et al.* (2016) described the novel artemisinin derivatives in the treatment of autoimmune diseases. Lai *et al.* (2013) reported that artemisinin dimmers and trimers, artemisinin hybrid compounds, and tagging of aretemisnin compounds are involved in the intracellular iron-delivery mechanism, and all these compounds are promising potent anticancer compounds which may produce significantly less side effect than traditional chemotherapeutic agents. Zhao *et al.* (2017) noted that artemisinin enhances the stability of liver cell membrane, and reduce the damage of liver cell membrane and liver cell; it also showed a protective effect against chronic alcohol poisoning and incredible clinical potential to treat the liver injury induced by alcohol. Abba *et al.* (2018) also indicated that artemisinin-type drugs may be safely applied to prevent carcinogenesis and cancer metastasis in human beings. It has been reported that artemisinins possess immunoregulatory properties and modulate components of the immune system (Yao *et al.*, 2016). Abou Rayia *et al.* (2017) revealed that artemisinin has the potential to be an alternative drug against trichinellosis. Yuan *et al.* (2019) found that ART ameliorated rosacea-like dermatitis by regulating immune reponse and angiogenesis, indicating that it could represent an effective therapeutic option for patients with rosacea. The mechanism for the antimalarial activity of artemisinin has been examined using artemisinin and its model compounds 1,2,4,5-tetraoxane and 1,2,4-trioxolane derivatives (Garah *et al.*, 2011). Chen *et al.* (2018) suggested that artemisinin had significant anti-tumor activities on C6 cells both *in vitro* and *in vivo*, and artemisinin might be exploited as a promising clinical anti-cancer drug in future. Leng *et al.* (2019) declared that an extract of an artemisinin-deficient *Artemisia annua* herbal preparation exhibits potent anticancer activity against triple negative human breast cancer. Yao *et al.* (2018) also concluded that artemisinin derivatives are potential therapeutic agents for the treatment of breast cancer. Konstat-Korzenny *et al.* (2018) found that both *in vitro* and *in vivo* clinical trials have shown promising activity of the artemisinin drug derivatives in treating certain types of cancer. Although, the artemisinin-based combination therapies have become more popular in the fight against malaria,

resistance to artemisinin has begun to emerge (Shen *et al.*, 2016). Lang *et al.* (2019) announced that an extract of an artemisinin-deficient *Artemisia annua* herbal preparation exhibits potent anti-cancer activity against triple negative human breast cancer. Li *et al.* (2018) indicated that artemisinin exhibited anti-allergic effect by inhibiting ERK activation and increasing Treg cell proportion, which subsequently decreased the expressions of allergic mediators. They have also found that artemisinin combined with neurectomy of pterygoid showed better efficacy than artemisinin alone. Artemisinin also use against liver cancer, brain glioma, leukemia, nasopharyngeal cancer, gallbladder cancer, gastric cancer, cervical cancer, lung cancer, breast cancer and colon cancer through reducing cell proliferation, inducing cell cycle arrest, promoting cell apoptosis, blocking tumor cell invasion, chaning the tumor microenvironment and reducing angiogenesis (Aderibigbe, 2017; Zhang *et al.*, 2018). Munyangi *et al.* (2018) reported the effective treatment of schistosomiasis by using *A. annua*. Phytochemical constituents of aqueous extract are tannins, anthraquinones, cardic glycosides, saponins, phenolic compounds, flavonoids, alkaloids, terpenoids and steroids, and phytochemical constituents of hexane extract are cardic glycosides, flavonoids, alkaloids, terpenoids and steroids (Abubakar *et al.*, 2018). The major influences of artemisinin and its derivatives are direct manner such are regulating neuroinflammatory processes, anti-oxidative stress, neuroprotection, preventive Aβ accumulation and neurotoxicity, and the main indirect impacts are maintaining BBB integrity, suppression systemic inflammatory and alleviating intestinal inflammation (Shi *et al.*, 2018). Sarder and Pkharel (2018) reported artemisinin and its derivatives such as artesunate, dihydroartemisinin, anhydrodihydroartemisinin, 10-dihydroartemisinyl acetate, 10-dihydroartemisinyl butyrate, 10-(2'-butyloxy) dihydroartemisinin, 10-dihydroartemisinyl 2'-propylpentanoate, 10-dihydroartemisinyl 2',2'-dimethylpropionate, 10-dihydroartemisinyl dimethylcarbamate, 10-dihydroartemisinyl dimethylcarbamate, artemether and arteether. Anti-malarial drugs that have been used in artemisinin combination are chloroquine, piperaquine, amodiaquine, dihydroartemisinin, artesunate, artemether, mefloquine, halofantrine, lumefantrine, pyrimethamine, chlorproguanil, atovaquone, sulfadoxine and dapsone (Nosten and White, 2007).

The plant extract of *A. annua* has a modulatory impact on components of the immune system such as TLR2 and TLR4 (Wojtkowiak-Giera *et al.*, 2019). Dihydroartemisinin showed colon cancer growth by inducing apoptosis and increase the expression of PPARγ, which has made it a promising natural compound for the treatment of colon cancer (Lu *et al.*, 2018). Artemisinin and its derivatives for the treatment of various diseases are shown in Table 2.

Table 2. Artemisinin and its derivatives for the treatment of different diseases (Rahman *et al.*, 2019).

Therapeutics	Drugs	Diseases/pathogens
Anticancer	Artemisinin	Prostate cancer
	Artemisinin	Kidney cancer
	Artemisinin	Hepatocellular carcinoma
	Artemisinin	Ovary cancer
	Artemisinin	Colon cancer
	Artesunate	Cervical cancer
	Artesunate	Kaposi's sarcoma
	Artesunate	Colorectal carcinoma
	Artesunate	Melanoma
	Artesunate	Ovarian cancer
	Dihydroartemisinin	Breast cancer
	Dihydroartemisinin	Glioma
	Dihydroartemisinin	Gastric cancer
	Dihydroartemisinin	Lung carcinoma
	Dihydroartemisinin	Leukemia
	Dihydroartemisinin	Osteosarcoma
Antiviral	Artemisinin	Hepatitis C virus

	Artemisinin	Bovine
	Artesunate	Viral diarrhea virus (BVDV)
	Artesunate	Herpes virus
	Artesunate	Hepatitis B virus
	Artesunate	Human cytomegalovirus (HCMV)
	Artesunate	HCMV
Antischistosomiasis	Artesunate	*Schistosoma haematobium*
	Artesunate	*Schistosoma mansoni*
	Praziquantel	*Schistosoma japonicum*
	Praziquantel	*Schistosoma mansoni*
	Praziquantel	*Schistosoma mekongi*
Antituberculosis	Artemisinin	Tuberculosis
	Artesunate	Tuberculosis
Autoimmune diseases	Artemisinin	Endometriosis
	Artemisinin	Lupus nephritis
	Artemisinin	Alzheimer, s Disease
	Artesunate	Rheumatoid arthritis
	Artesunate	Systemic lupus erythematosus (SLE)
	Artesunate	Asthma
	Artesunate	Uveitis
	Artesunate	Inflammatory bowel disease (IBD)
	Artemether	Rheumatoid arthritis
	Dihydroartemisinin	SLE
	Dihydroartemisinin	Experimental autoimmune encephalomyelitis (EAE)
Antimalarial	Artemether	Vivax malaria
	Arteether	Cerebral malaria
	Artesunate	Vivax malaria
	Dihydroartemisinin	Vivax malaria

The most important pharmacological properties of artemisinin are anti-malarial activity, antiviral, antibacterial, antihelminthis, antiprotozoa, antifungal, anti-inflammatory and anti-tumor properties (Zyad *et al.*, 2017; Qiu *et al.*, 2018). Phenolics enhance artemisinin water solubility and extraction efficiency as phenolics, mainly chlorogenic acids, are highly present in teas from *A. annua* (Carbonara *et al.*, 2012). Higher artemisinin concentrations when multiplied by total leaf dry matter at the higher boron application rates may increase in total artemisinin production per plant (Davies *et al.*, 2011). Wu *et al.* (2017) reported that antioxidant activity of volatile oils in the flowering and post-flowering stages were stronger than that in pre-flowering and initial flowering stages. Fu *et al.* (2020) found that geographic content differences of the components in *A. annua* indicate the potential differences in the health-promoting effects of its clinical application. Its essential oil extracts have a good antioxidant capacity, especially as antiradical scavengers (Gouveia and Castilho, 2013). Artesunate can compromise the repair of DNA double-strand breaks (DSBs) in ovarian cancer cells which shows its ability as a sensitizing agent in chemotherapy (Wang *et al.*, 2015). Artesunate has anti-proliferative properties in colorectal cancer (CRC) and is generally well tolerated (Krishna *et al.*, 2015). The most important pharmaceutical benefits of Artemisia are shown in Table 3. The most important natural components and pharmaceutical benefits of *Artemisia annua* L is shown in Figure 2.

Table 3. The most important health benefits of Artemisia

Pharmaceutical benefits	Mechanisms and impacts	References
Anti-malarial	a. Artemisinin is the key anti-malarial compound of *A annua* L. b. The efficacy of artemisinin against malaria has promoted its use as a tea drink in endemic communities. c. Artemisia appeared to break the cycle of malaria by eliminating gametocytes. d. Artemether is co-administered with lumefantrine as part of a fixed-dose combination therapy for malaria in both adult and pediatric patients.	Mueller *et al.* (2004) Atemnken *et al.* (2009) Ghafoori *et al.* (2013) Abolaji *et al.* (2014) Weathers *et al.* (2014) Lin *et al.* (2016) Xiao *et al.* (2016) Baldino *et al.* (2017) Munyangi *et al.* (2019)
Anti-microbial	a. The extracts of Artemisia are novel natural source of antimicrobial agents for the treatment of microbial infections.	Viljoen *et al.* (2006) Cavar *et al.* (2012) Kazemi *et al.* (2012) Ashraf *et al.* (2017) Li *et al.* (2017) Mohamed *et al.* (2017) Allam *et al.* (2019)
Anti-cancer	a. The inhibition of immune mediators of angiogenesis by sesquiterpene lactones and flavonoids may be of the mechanisms of anticancer activity of *Artemisia annua* L. b. The cellular response of artemisinin and its derivatives such as dihydroartemisinin, artesunate, artemether, and arteether towards cancer cells include oxidative stress response by reactive oxygen species and nitric oxide, DNA damage and repair, various cell death modes, inhibition of angiogenesis and tumor-related signal transduction pathways and signal transducers. c. Some trioxane dimmers have selective and very potent anticancer activity even at low nanomolar concentrations. d. An extract of an artemisinin-deficient *Artemisia annua* herbal preparation exhibits potent anticancer activity against triple negative human breast cancer. e. Its dried leaf has high efficacy against non-small cell lung cancer.	Posner *et al.* (2006) Crespo-Ortiz and Wei (2012) Zhu *et al.* (2013) Zhang *et al.* (2015) Efferth (2017) Koul *et al.* (2017) Lang *et al.* (2019) Omar *et al.* (2019) Rassias *et al.* (2019)
Anti-fungal	a. Artemisia oil possess anti-fungal, insecticidal and larvicidal activity. b. Coumarins and lignans from *A. annua* have antifungal activities.	Behravan *et al.* (2006) Saleh *et al.* (2006) Suresh *et al.* (2011) Li *et al.* (2019)

Anti-bacterial activity	a. Essential oil Artemisia species inhibit inhibitory activity against certain human pathogens. b. Artemisia species have antibacterial activity against multi-drug resistance extended-spectrum β-lactamse (ESBL) positive *Escherichiacoli*. c. Its essential oil may exhibit good antibacterial activity against *Staphylococcus aureus*, *Bacillussubtilis*, *Staphylococcusepidermidis*, Salmonella typhimurium and *Streptococcus mutans*. d. Its extract showed cytotoxicity against oral gingival carcinoma cell.	Lima *et al.* (2008) Asili *et al.* (2015) Donato *et al.* (2015) Goswami *et al.* (2016) Lee (2016) Rafika *et al.* (2018)
Anti-oxidant activity	a. Administration of its extract ameliorate blood glucose, total cholesterol, triglycerides, and malondialdehyde. b. Essential oil showed antioxidant activity comparable with thymol.	Ahuja *et al.* (2011) Bora and Sharma (2011) Cavar *et al.* (2012) Gouveia and Castilho (2013) Bourgou *et al.* (2016) Mohammadi *et al.* (2017) Seiko *et al.* (2019) Zhigzhitzhapova *et al.* (2019) Messaili *et al.* (2020) Ranjbar *et al.* (2020)
Anti-complement	a. The solvent chloroform extracts of Artemisia plants showed inhibitory activity against complement system with 50% inhibitory concentrations.	Moon *et al.* (2012)
Hepatoprotective activity	a. It high hepatoprotective activity is connected to hydroxycinnamoyl quinic acids and flavonoids	El-Askary *et al.* (2019)
Anti-inflammatory	a. The flavonoids casticin and chrysosplenol D from *A. annua* L. may inhibit inflammation *in vitro* and *in vivo*. b. α-bisabolol which is a famous anti-inflammatory extract found in essential oil. c. Artemisinin may protect the aortas from atherosclerotic lesions by suppression of inflammatory reaction via AMPK/NF-κB/NLRP3 inflammasomes signaling in macrophages.	Ashok and Upadhyaya (2013) Li *et al.* (2015) Vasylievna *et al.* (2015) Jiang *et al.* (2020)
Anti-mutagenic		Taherkhani (2015)
Anti-inflammatory	a. Its essential oil possesses biologically active constituents which have significant activity against acute inflammation and have central and peripheral antinociceptive effects. b. Artemisinin may be a potential	Magenta *et al.* (2014) Li *et al.* (2015) Song *et al.* (2017) Wang *et al.* (2017) Tadayoni *et al.* (2018)

	useful therapeutic agent for inflammatory-related diseases. c. The beneficial clinical effects of artemisinins for the treatment of malaria include the apparent ability to attenuate the inflammatory response. d. The flavonoids casticin and chrysosplenol D from *A. annua* L. inhibited inflammation *in vitro* and *in vivo*. e. The enzymatically treated *Artemisiaannua* (EA) supplementation could alleviate the intestinal inflammatory response, and improve the intestinal barrier function in broilers during the heat stress period.	
Anti-tumor	a. Water-soluble polysaccharide inhibits HepG2 cell growth via inducing caspase-dependent mitochondrial apoptosis and inhibition of NF-κB p65. b. Its supplementation may alleviate the intestinal inflammatory response, and improve the intestinal barrier function in broilers during the heat stress period.	Song *et al.* (2017) Yan *et al.* (2019)
Anti-complement activities	a. The high contents of galacturonic acid are important for anti-complement activities of the polysaccharides from *A. annua*.	Huo *et al.* (2020)
Anti-HIV	a. The *A. annua* tea infusion was found to be highly active with IC50 values as low as 2.0 μg/mL, and it provides the *in vitro* evidence of anti-HIV activity of *A. annua* tea infusion.	Lubbe *et al.* (2012)
Anti-plasmodial	a. Arteannuin B (AB) is one of the main contributors in *A. annua* leading to enhanced antiplasmodial potency of QHS via regulation of its metabolism.	Cai *et al.* (2017)

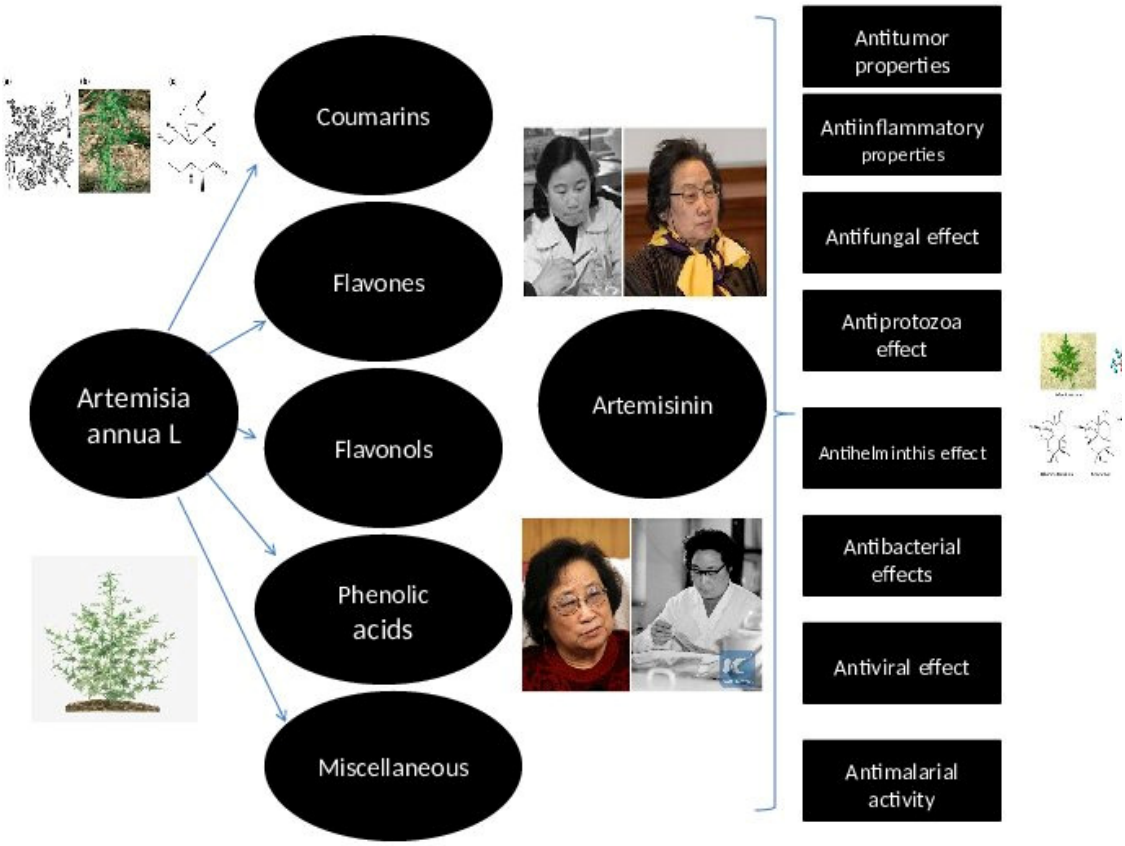

Figure 2. The most important natural components and pharmaceutical benefits of *Artemisia annua* L.

Conclusions

Traditional Chinese medicine is a medical system based on theory, pathology, diagnosis, treatment and herbal pharmacology principles. *Artemisia annua* L. is a Chinese medicinal herb, which has significant efficacy against malaria with low toxicity. Artemisinin discovered and isolated by Chinese scientists in the early 1970s, as a natural peroxide drug for the treatment of malarial. Artemisinin combination therapies are used worldwide as the appropriate treatment against *Plasmodium falciparum* malaria. This important drug has been developed from the Chinese traditional herbal medicine and is known as Qinghaosu. Artemisinin demonstrates prominent biological activities and attracts great attention nowadays. Artemisinin and its derivatives, namely artemiside, artesunate, artemisone, arteether, artemether, and dihydroartemisinin have significant anti-malaria, anti-viral, anti-fungal, anti-cancer and anti-inflammatory properties. The artemisinin content is highly dependent on plant ecotypes, ecological interactions, seasonal and geographical variations. The discovery of artemisinin has been presented as the important example of the face of adversity, social commitment to the good of humanity, genuine esteem for past and traditional wisdom and of course a heartfelt belief in the value of science. More researchers of relationship of artemisinin and its derivatives are necessary to develop and optimize new therapeutics with significant impacts. On the basis of traditional Chinese medicine, the metabolic properties of artemisinin and its derivatives bring more hope to treat malaria, obesity and some other metabolic diseases.

Authors' Contributions

All authors read and approved the final manuscript.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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