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REVIEW ARTICLE

The pharmacological activities and mechanisms of artemisinin and its derivatives: a systematic review

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Abstract Artemisinin and its derivatives have now become essential antimalarial drugs for increasingly widespread drug-resistant malaria strains. Although artemisinin was first used for the treatment of malarial ailments, lots of subsequent studies have demonstrated it possesses other multiple pharmacological functions such as antitumor, antiarrhythmic, anti-fibrosis, as well as the activity against schistosomiasis. A wide array of the molecular mechanisms based on above-mentioned functions of artemisinin and its derivatives have also been explored. Experimental evidences suggest that artemisinin compounds may exert its functions via mechanisms like regulating key factors such as apoptosis-related BAX, FASL and caspase-3, multi-drug resistence genes, cytokines such as CD4+ and CD8+, inflammation-related NF-κB and COX2, telomerase, oxidative stress molecules, and so on. In this article, the proposed mechanisms of action of artemisinins are reviewed with the hope of gaining more insight into the multiple actions of these potent drugs and how they work.

Keywords Artemisinin · Pharmacological effect · Antimalaria · Antitumor

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Abbreviations

ART (page 1, line 1)	artemisinin
DHA (page 2, line 10)	dihydroartemisinin
ATS (page 2, line 11)	artesunate
NF-Kb (page 1, line 11)	nuclear factor kappa-light-chain-enhancer of activated B cells
COX-2 (page 1, line 11)	cyclooxygenase-2
SM934 (page 2, line 9)	2-aminoarteether (β)maleate
SM905 (page 2, line 9)	1-(12-β-dihydroartemisinoxy) -2-hydroxy-3-tert-butylaminopropane maleate
SM735 (page 2, line 10)	3-(12-β-artemisininoxy) phenoxyl succinic acid
Da (page 3, line 4)	Dalton
TNF-α9 (page 4, line 36)	tumor necrosis factor α
Hgb (page 5, line 7)	hemoglobin
G0/G1 (page 8, line 1)	resting phase or Gap 1 phase (cell cycle)
VEGF (page 13, line 5)	vascular endothelial growth factor
Erα (page 13, line 15)	estrogen receptor α
PGE2 (page 13, line 22)	prostaglandin E2
COX-2 (page 13, line 23)	cyclooxygenase-2
CDC25A (page 14, line 18)	cell division cycle 25 homolog A gene
ConA (page 15, line 6)	concanavalin A
LPS (page 15, line 6)	lipopolysaccharides
TLR4/IRF/IFN (page 16, line 21)	Toll-like receptor 4/Interferon regulatory factors/ Interferons
TGF-β1 (page 17, line 8)	transforming growth factor beta 1
CNS (page 17, line 10)	central nervous system
HHV-6 (page 17, line 18)	human herpes virus 6

HBV (page 17, line 27)	hepatitis B virus
HCV (page 18, line 3)	hepatitis C virus
HIV-1 (page 18, line 7)	human immunodeficiency virus-1
TLR9 (page 18, line 26)	Toll-like receptor 9
I_{Na}(page 19, line 14)	the "rapid" delayed rectifier current that conducts sodium (Na^+) ions out of the muscle cells of the heart
I_{Ca} (page 19, line 14)	the "rapid" delayed rectifier current that conducts calcium (Ca^+) ions out of the muscle cells of the heart
I_{Kr} (page 19, line 16)	the "rapid" delayed rectifier current that conducts potassium (K^+) ions out of the muscle cells of the heart

Introduction

Artemisinin was first isolated from the plant *Artemisia annua*, *sweet wormwood*, an herb employed in traditional Chinese medicine. Its structure belongs to the category of sesquiterpene lactone containing an unusual endoperoxide bridge, which is generally thought to be the key player of biological activity. The endoperoxide bond could be activated by reduced heme or ferrous iron [20], leading to the production of cytotoxic carbon-centered radicals, which are highly potent alkylating agents (Meshnick et al. 1991). Radicals may target essential parasite macromolecules that causes parasite's death. However, the precise mechanism of action and primary target of artemisinin (ART) remain unclear (Olliaro et al. 2001). Up to date, a series of active ART derivatives including dihydroartemisinin(DHA), artemether, arteether, and artesunate(ATS) were synthesized, universally with endoperoxide bridge as the key framework (Zhang et al. 2014). The strategy of ART reduction by potassium borohydride was used to produce DHA. Futhermore, artemether and arteether were made by the catalytic action of BF_3-EtO_2 on ART. And ATS was easily obtained by using the reduction reaction of acid anhydride on ART, which was dissolved in pyridine (Mei et al. 2008). Both SM934 and SM905 were synthesized on the basis of the structure modification of arteether, SM905 as well. And SM735 was synthesized from artemether (Hou and He 2009) (Fig. 1).

ART was discovered by the Chinese professor Youyou Tu in 1972, who was awarded the 2011 Lasker-DeBakey Clinical Medical Research Award and the 2015 Nobel Prize in Physiology or Medicine, respectively. ART is a colorless, crystalline substance with a molecular weight of 282 Da, a molecular formula of $C_{15}H_{22}O_5$, and a melting point of 156–157 °C. Compared with other antimalarial drugs, ART and its derivatives have the most rapid action on malaria. Currently, ART-combination therapies have become the antimalarial standard treatment all over the world. Because of the effectiveness, low toxicity, and minimal side effects, ART and its derivatives are increasingly being used in Plasmodium vivax malaria. In addition to its certainly well antimalarial properties, compelling evidence had supported that ART-related compounds have potent biological activities in a variety of other human diseases, especially for cancers (Fig. 2).

Antiparasitism effect

Antimalaria

ART is the earliest found having antimalarial effect of all the ART compounds. Thereafter a series of ART derivatives were synthesized, including DHA, artemether, arteether, ATS, and so on. These derivatives all showstrong antimalarial actions to different degrees, even for the drug-resistant malaria. Interestingly, the potent anticancer action of ART can also be attributed to the endoperoxide bond. However, Lack of the endoperoxide moiety does not completely abrogate anticancer activity (Galal et al. 2002). Residual anticancer activity may be related to an alternative peroxide-independent mechanism (Beekman et al. 1998). Recent researches indicated that ART could effectively inhibit heme polymerization mediated by *Plasmodium falciparum* histidine-rich protein II and *Plasmodium yoelii* lysates. Furthermore, the interaction between ART and the purified malarial hemozoin could lead to malaria pigment concentration-dependent breakdown in vitro (Pandey et al. 1999).

Physiologically malaria pigment is stored in the food cavity of insect body. Chloroquine has a strong affinity for hemoglobin so that it exerts antimalarial action, but ART take effect via inhibiting the internalization of hemoglobin to block the parasite to use iron and protein (Hoppe et al. 2004). Ponmee et al. (2007) also found that heme and heme-containing proteins in the erythrocyte could notably reduce ART's effectiveness, and may make for resistance of *Plasmodium falciparum* infected with α-thalassemic erythrocytes found in vitro. The antimalarial effect of ART could be increased by the extracellular hemin as a result of improving oxidative effect of hemin(Tangnitipong et al. 2012). Gupta et al. (2002) had done a study in the interactions of ART and mefloquine, quinine, and atovaquone respectively in three *Plasmodium falciparum* strains (K-1, FCR-3, and F-32)and the experimental results showed that

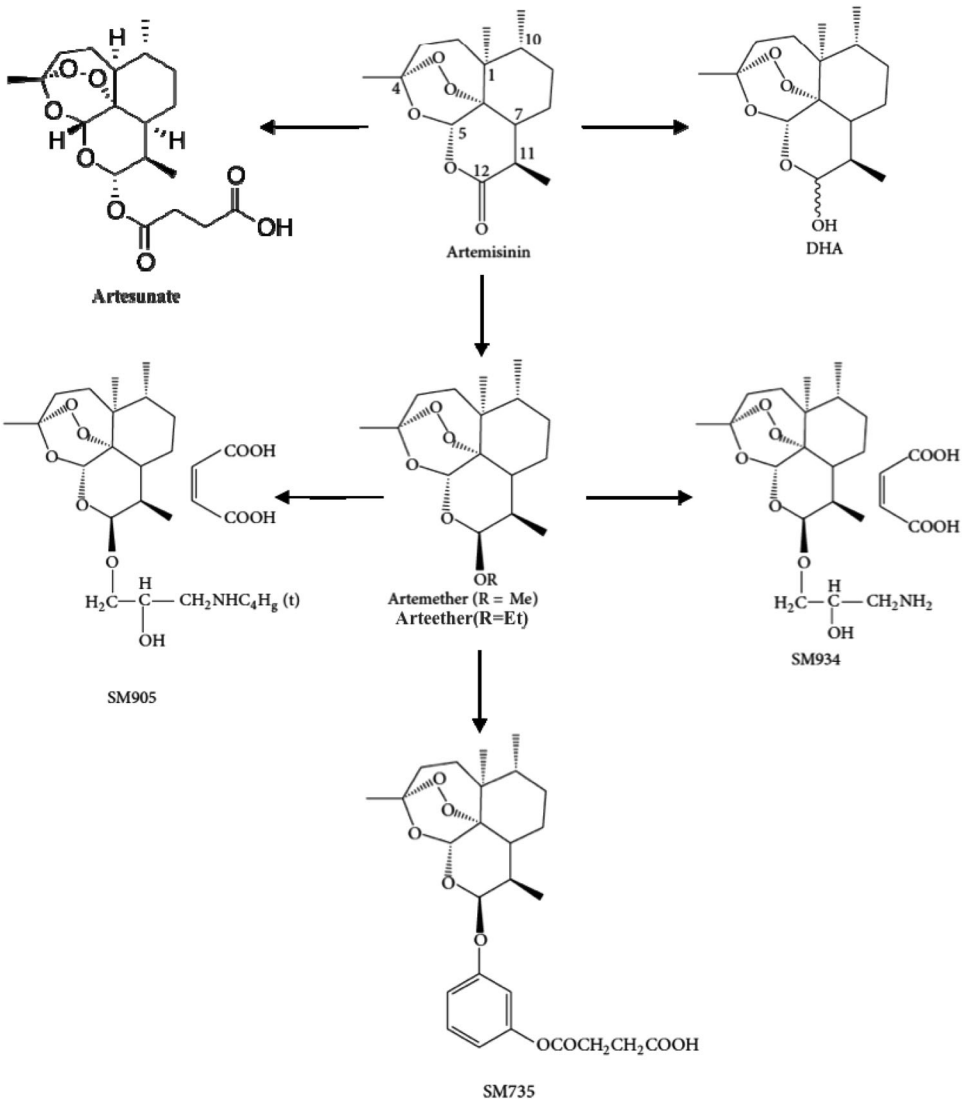

Fig. 1 Synthetic routes of artemisinin compounds

the interaction of ART and quinine is most effective against malaria.

In addition, Conyers et al. (2014) tested eight new ART-derived trioxane dimer esters in mice infected with *Plasmodium falciparum*. With a single oral dose of 6 mg/kg combined with 18 mg/kg of mefloquine, five new ART derivatives had been shown to have a better effect than artemether. It is noteworthy that artecyclopentyl mether (CPM-1, a novel ART derivative) possesses a dose-dependent efficacy in mice infected with *Plasmodium yoelii nigeriensis*. In another study, CPM-1 had proved to have a potential antimalarial activity against asexual stages of the parasite (Agarwal et al. 2011).

To our knowledge, the death of *Plasmodium* may be the result of changes in a series of biochemical and physiological functions. Although lots of studies regarding various mechanisms of ART and/or ART derivertives have been conducted, their antimalarial mechanisms have not yet been elucidated completely.

Activity against pneumocystis *carinii* pneumonia

Li et al. (2001) tested the effect of DHA on apoptosis of alveolar macrophages (AMs) in *pneumocystis carinii pneumonia* (PCP)—infected mice, and the result showed that DHA therapy could decrease the apoptosis of AMs in PCP rats. It also showed that DHA therapy decreases the apoptosis in spleen cells of PCP rats (Li et al. 2003). AMs of PCP rats produce a high level of TNF-α, but the level of TNF-α is decreased after DHA therapy (Li et al. 2001). DHA could also alleviate inflammatory responses and kill Pc trophozoites and cysts in the lung tissues in PCP infected mice (Li et al. 2004). Previously, it had been reported that DHA and sodium ATS have therapeutic

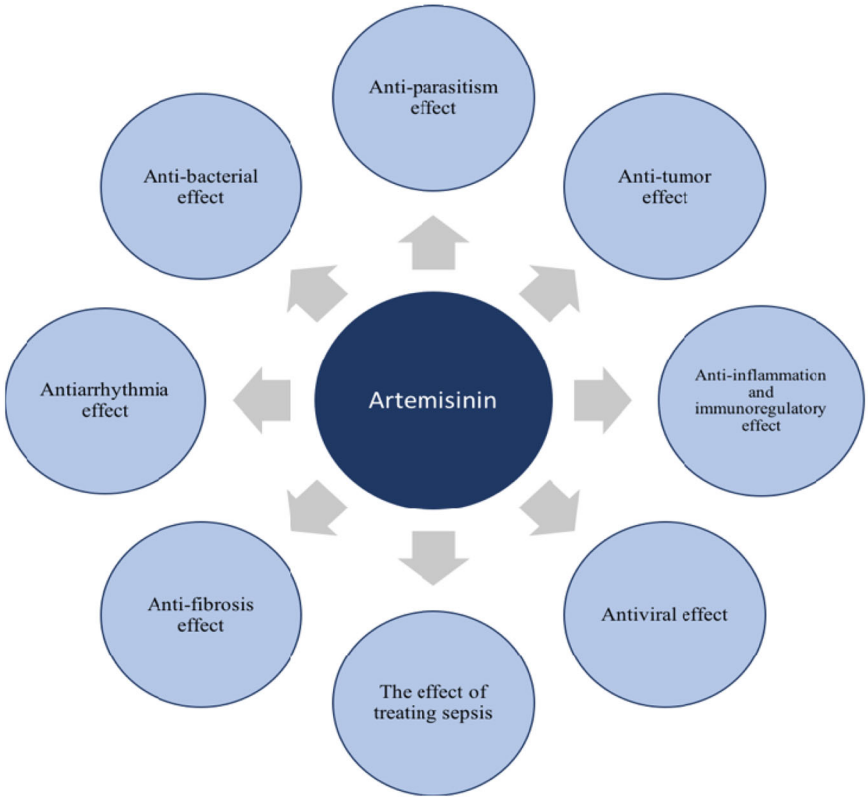

Fig. 2 Pharmacological activities of artemisinin compounds

effects in treating *Pneumocystis carinii pneumonia* (Ye et al. 2001).

Anti-schistosoma

Tu et al. (2005) explored the therapeutic effect of ATS and artemether in *Schistosoma mansoni*—infected adult mice. The data showed that the efficacy of therapy with artemether and ATS on the mice were excellent and human Hgb could be degraded by the hemoglobinase of *S.japoncium*. Gong et al. (1997) reported that artemether had an inhibitory effect on hemoglobinase of *S.japonicum*. Moreover, it was also demonstrated that artemether had remarkably schistosomicidal effects on juvenile stages of *S. mansoni* Egyptian strain in vivo, thus preventing disease progression and morbidity (El-Beshbishi et al. 2013). In line with previous reports, recent studies have shown that artemether could be expected to protect the host from schistosomal infection or reduce the intensity of infection by using artemether in the early stage after infection (Xiao et al. 1994). Liu (2001) studied the therapeutic effect of DHA on experimental rats infected with *Pneumocystis carinii*. As a result, the survival rate increased and lung inflammation was alleviated. Thus it was concluded that DHA is one of the useful drugs to treat Pneumocystis carinii pneumonia. Xiao et al. (1995) also proved that artemether possesses an effect for prevention of schistosomiasis by reducing the infection rate and intensity of infection, as well as controlling acute schistosomiasis. Consistent with DHA, ATS also has significant anti-schistosoma action, it can kill schistosomula and reduce the fecundity of females effectively (Lu et al. 2004). No severe side effect was seen in animals treated with ATS (Le et al. 1983). As expected, arteether has a dramatic therapeutic effect on NIH mice infected with *Schistosoma japonicum cercariae* (Xiao et al. 1992). There is now a general consensus that ART-based combination therapies have beneficial actions against schistosomiasis.

Anti-leishmania

Want et al. (2015) tested ART-loaded poly lactic co-glycolic acid (ALPLGA) nanoparticles on mice with established visceral leishmaniasis infection. After in vitro treatment, ALPLGA nanoparticle can escalates lgG2a levels, increases lymphoproliferation, as well as enhances proinflammatory cytokines (IL-2 and IFN-γ) with effective inhibition of Th2 cytokines (IL-4v and IL-10) compared with ART treatment. Ghaffarifar et al. (2014) had also tested ART on leishmania both in vitro and in BALB/c mice. All of the results suggested that ART exerts an anti-

leishmania effect in vivo and in vitro via apoptosis-related mechanism.

Anti-toxoplasma

Schultz et al. (2001) tested two thiazole derivatives of ART in *Toxoplasma gondii* (*T. gondii*) infected mice. Both derivatives showed moderate efficacy in a mouse model of acute toxoplasmosis, and one derivative CPH4-136 modestly but significantly decreased mouse brain cyst burden in a chronic *T. gondii* infected mouse model. These results suggest that ART derivatives have some action in treating *Toxoplasma gondii*. El Zawawy (2008) also tested ATS on *T. gondii* in vitro and in vivo. In vivo tests revealed that infected mice treated with ATS induced a remarkable reduction in the mortality rate and increased the survival time. Moreover, in vitro tests demonstrated a remarkable decrease in infectivity and viability of tachyzoites exposed to ATS compared with untreated controls. It is thus concluded that ATS would be a novel anti-toxoplasma drug in the future.

Activity against *Clonorchis sinensis* (*C. sinensis*)

Xiao et al. (2008) proved that artemether, artesunate, tribendimidine and praziquantel are active against *C. sinensis*, and these drugs combination possesses synergy. In addition, ATS, tribendimidine and praziquantel are also effective against *Clonorchis sinensis*, but ATS is only efficacious against adult worms (Xue et al. 2009). Previously, it had been reported that both artemether and tribendimidine rapidly destroy the tegument and the suckers of adult *C. sinensis*. However, the activity mechanisms of these drugs against *C. sinensis* have not to be fully defined (Xiao et al. 2009).

Activity against *Trichomonas vaginalis*

Tang et al. (2007) tested the efficacy of DHA on the ultrastructure of *Trichomonas vaginalis* trophozoites in vitro, and found DHA could result in decomposition and necrosis of the parasite via destroying membrane structure and organelles of *Trichomonas vaginalis* trophozoites.

Activity against *Acanthamoeba spp*

ATS can inhibit the growth of *acanthamoeba* trophozoites at a rate of 93.2% when treated with 100 μg/ml (after 2 days), and application at 500–700 μg/ml concentration can lead to an inhibition on the first day. These data showed that ATS was amebastatic rather than amebicidal in an axenic culture with trophozoites at the highest concentration of 100 μg/ml (Nacapunchai et al. 2002).

Anti-eimeria

Pop et al. (2015) used ART on *Eimeria acervulina, E. tenella,* and *E. maxima* in battery trials infected broiler chickens. The experimental results suggest that ART has little effect in single eimerian infections but could be used as a replacement for mixed coccidiosis.

Activity against gastrointestinal nematodes

Haemonchus contortus (*H. contortus*) is the leading pathogenic nematodes, a kind of parasites in abomasum, accidentally found in small intestine. This disease can result in digestive disorders, gastrointestinal tract inflammation, diarrhea, and angular. Serious cases will occur in mandibular interstitial edema. Temperature increases in a few cases, and breathing, pulse frequency and heart sounds are subdued, which eventually can lead to death due to the body extreme failure. Cala et al. (2014) studied the anthelmintic activity of *A. annua* crude extracts in vitro and compared the most valid extract with ART in *H. contortus* infected sheep. The data showed ART and *A. annua* extract had certain therapeutic effect on *H. contortus.* However, further studies are needed to determine the interactions of ART with commercial anthelmintics in infected animals.

Activity against giardia lamblia

To directly study the effect of DHA on *Giardia lambia* (*G. lamblia*) in vitro, Tian et al. had cultivated the trophozoites of *G. lamblia* with modified TYI-S-33 medium that contains DHA. The results conclusively indicated that DHA possesses a strong impairment on the plasma membrane and cytoskeleton of *G. lamblia* (Tian et al. 2005).

Anti-heterophyid

Fathy (2011) has tested the therapeutic effect of ATS in heterophyid infected mice. The results indicated that ATS has a notably action in treating experimental heterophyidiasis. Furthermore, surface tegumental damages of the adult worm was found in the form of bleb formation, disruption, erosion, and peeling. This drug would be a novel alternative therapy to treat human heterophyidiasis.

Antitumor

Although ART was first used against malaria, a wide range of research was later conducted indicating that ART and its derivatives have anticancer properties as well. Most of these agents exert their anticancer function via mechanisms like

apoptosis, arrest of cell cycle at G_0/G_1, and so on. (Fig. 3 and Table 1)

Induce apoptosis of tumor cells

As an active death process involved in the specified procedures, apoptosis occurs after cells are induced by some kinds of signal molecules, characterized by a series of distinct genetic and biochemical and morphological changes. Induction of apoptosis currently becomes one of the most important strategy to treat cancer. Sheng et al. (2009) observed the action of ATS on tumor in murine transplanted hepatocarcinoma 22 (H22). As a result, daily intraperitoneal injection of ATS (15–60 mg/kg/day) caused a significant decrease of FasL expression in tumors. ATS can also enhance the radiosensitivity of HeLa cells. And its mechanism may be concerned with upregulation of cyclin B1 expression and downregulation of Weel expression (Gong et al. 2009). Zeng et al. (2009) examined the efficacy of ATS on the proliferation of Jurkat cells, Raji cells and acute lymphoblastic leukemia (ALL) primary cells. These were found that apoptosis occurred in Jurkat cells and Raji cells after exposure to ATS, and mitochondria transmembrane potential collapses and caspase-3 activities were increased in Jurkat, Raji, and ALL primary cells. In addition, ATS could induce apoptosis and suppress proliferation in K562 cells by activating caspase-3 and delivery of cyt-c (Xie et al. 2008; Lee et al. 2012) . Furthermore, Huang et al. (2012) treated HCT-8 human colon cancer cells with ATS at 10 ~ 30 μmol/L for 10 h, and found 41.4% of the cancer cells showed apoptosis when the concentration of ATS reached 30 μmol/L. Furthermore, ATS could inhibit the growth of HCT-8 cells and induce apoptosis of HCT-8 cells via regulating the expression of Bax genes. Dong et al. (2002) also demonstrated that ART can suppress the proliferation of HeLa cells and induce its apoptosis. It was also found that ATS may inhibit the growth of human liver cancer cell line (Bel-7402) via inducting cell apoptosis (Zhang et al. 1998) (daily oral administration of 100–324 mg/kg). The cytotoxic activity of artemether is correlated with its apoptosis induction (Guo et al. 2007). Fox et al. (2016) examined the ART-derived trioxane diphenylphosphate dimer 838 (ART-838) on 23 acute leukemia cell line. As a result, the cell proliferation and clonogenicity were decreased but the intracellular levels of reactive oxygen species were increased. Recently, Ooko et al. (2015) found that ART and its derivatives can induce iron-dependent apoptosis in cancer cells. This new form of apoptosis is called ferroptosis. ART's powerful anticancer effect correlated with Fe^{2+}-mediated cleavage of the endoperoxide bridge. Therefore, Chen et al. (2015) had also tried to replace Fe^{2+} with Mn^{2+} to react with ART, and the results suggest this way can produce better antitumor efficiency but more toxic products.

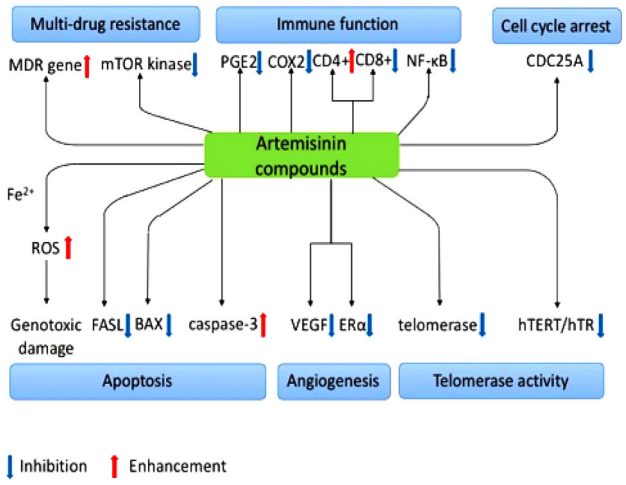

Fig. 3 Anticancer mechanism of artemisinin compounds

Prevent cancer invasion and metastasis

The basic characteristics of a malignant tumor include invasion and metastasis, which is a main cause of tumor treatment failure. It has been noted that about 30% of the patients with tumor at the time of diagnosis is metastasis stage. Therefore, how to find a drug that has an effective inhibition on invasion and metastasis of cancer is of great significance. Michaelsen et al. (2015) had also examined short-term bicalitumide combined with long-term treatment with *A. annua* capsules therapy that lead to important regression of advanced metastasized prostate cancer.

Inhibit tumor angiogenesis

Primary tumors have the capability of inducing new angiogenesis and metastasis process. Tumor angiogenesis process is controlled by many positive and negative factors and inhibition of tumor angiogenesis has become a novel antitumor treatment strategy. Wang et al. (2012) proved that DHA can induce the apoptosis of prostate cancer cell line PC-3M and the expression of VEGF mRNA and protein is decreased in a concentration-dependent way. DHA's inhibitory effects on tumor angiogenesis were further confirmed by the experimental results that the growth of PC-3M cells was suppressed, together with the decreased expression of VEGF mRNA and protein. Wu et al. (2009) explored the antitumor effect of artemether in the growth of glioma and angiogenesis in brain cancer SD rats. The results showed artemether can remarkably inhibits the growth of brain glioma by penetrating the blood-brain barrier and inhibiting angiogenesis. Mondal and Chatterji (2015) studied the antitumor action of ART in HPV-39-infected human

Table 1 Both in vivo and in vitro studies of ART and its derivatives on cancer growth

Compound	Tumor	Treatments	In vivo /in vitro	Results	Refs
ATS	Hepatoma	H22 hepatoma mouse xenograft; started immediately after cancer implantation, artesunate (15, 30, 45, 60 mg/kg/day, i.p. for 15 days)	In vivo	32, 57, 65, and 50 % inhibition for artesunate at 15, 30 ,45 ,60 mg/kg.	(Sheng et al. 2009)
ART		H22 hepatoma cells; started after cancer cells 12 h trained, artemisinin (50 µl, 50,100,150,200 µmol/L, 16 h)	In vitro	Inhibited cancer cells growth in a dose-dependent manner; at 200 µmol/L, cancer cells on 16 h was 71% of control.	(Deng et al. 2007)
ATS		H22 hepatoma mouse xenograft; started after cancer implantation 1 day, artesunate (15, 30, 45, 60 mg/kg/day, i.p. for 14 days)	In vivo	32, 44, 65 and 38 % inhibition for artesunate at 15, 30 ,45 ,60 mg/kg/day.	(Sheng et al. 2008)
ATS		HEPG-2 human hepatoma cells; artesunate (50,100,200 µg/ml, 24,48,72 h)	In vitro	Inhibited cancer cells growth in a dose-dependent manner; at 200 µg/ml, 56.1 ± 3.4, 68.9 ± 5.7 and 79.6 ± 5.2 inhibition of cancer cells growth on 24,48 and 72 h.	(Li et al. 2008)
ATS		Bel-7402 human hepatoma mouse xenograft; started when tumors at 3 ~ 4 mm diameter, sodium artesunate (100,180,324 mg/kg/day p.o. for 15 days).	In vivo	Inhibited tumor growth in a dose-dependent manner; at 324 mg/kg, tumor volume on day 15 was 71% of control.	(Zhang et al. 1998)
ATS		H22 human hepatoma mouse xenograft; started after cancer implantation 1 day, artesunate(180 and 300 mg/kg/day, p.o. for 7 days)	In vivo	Artesunate inhibited cancer growth (maximum inhibition rate 49 % in the 300 mg/kg group)	(Qin et al. 2001)
ATS	Esophageal cancer	Eca109 human esophageal cancer cells; started when tumors reached 0.4 mm^3, artesunate (100,200 and 300 mg/kg/day, i.p. for 14 days)	In vivo	34,72 and 39 % inhibition for artesunate at 100,200 and 300 mg/kg.	(Liu et al. 2008)
ATS		Eca 109 esophageal cancer mouse xenograft; started immediately after cancer implantation, artesunate (100,200 and 300 mg/kg/day, i.p. for 14 days)	In vivo	The tumor inhibition effect of artimisinin at 200 mg/kg is best.	(Wang et al. 2007a)
ATS	Sarcocarcinoma	Implanted S180 Sarcocarcinoma in rats; started immediately after cancer implantation, artesunate (150,300 and 600 mg/kg/day, i.g. for 14 days)	In vivo	Inhibited tumor growth in a dose-dependent manner; at 600 mg/kg/day, tumor on day 14 was 42.2% of control.	(Wu and Zhang 2008)
ATS	Leukemia	Raji lymphoma and Jurkat leukemia cells; artesunate (12.5,6.25,3.125,1.5625 µg/ml, 72 h) ALL leukemia cells; artesunate (12.5,6.25,3.125,1.5625 µg/ml, 48 h)	In vitro	Inhibited cancer cells growth in a dose-dependent manner; Raji cells- artimisinin 12.5 µg/ml-90.16 ± 1.78% inhibition; Jurkat cells-artimisinin 12.5 µg/ml-82.68 ± 2.32% inhibition; ALL cells- artimisinin 12.5 µg/ml-45.79 ± 3.24% inhibition.	(Zeng et al. 2009)
ART		Molt-4 leukemia cells; started after cancer cells 6 h, with artemisinin (200 µM, 8 h)	In vitro	Artemisinin have potent anti-leukemia effect.	(Ohgami et al. 2010)
DHA	Lung adenocarcinoma	A549 human lung adenocarcinoma mouse xenograft; started when tumors was formed, dihydroartemisinin (100 mg/kg/day, i.g. for 4 weeks)	In vivo	Tumor volume on day 28 was 54.3 % of control.	(Chen et al. 2005)
ATM		A549 lung adenocarcinoma cells; started after cancer cells 2 h trained, artemether (0.2,1,5,10,20,40,80,160 mg/L, 4 h)	In vitro	Inhibited cancer cells growth in a dose-dependent manner; at 160 mg/L, cancer cells on 4 h was 95% of control	(Guo et al. 2007)
ART	Cervical carcinoma	HeLa cervical carcinoma cells; started after cancer cells 12 h trained, artemisinin(50 µl, 5,10,20,40,80 µmol/L, 48 h)	In vitro	Induced apoptosis of cancer cells in a dose-dependent manner; at 80 µmol/L, cancer cells on 48 h was 48% of apoptosis.	(Dong et al. 2002)
ART	Glioblastoma	U87MG and A172 glioblastoma cells; started after cancer cells 24 h trained, artemisinin (50 µl, 50 µmol/L, 144 h)	In vitro	U87MG cells-artemisinin 50 µmol/L-44% died;A172 cells- artemisinin 50 µmol/L-36% died.	(Karpelmassler et al. 2014)
ATS	Colon cancer	HCT-8 human colon cancer cells; artesunate (10,20,30 µmol/L, 10 h)	In vitro	Induced apoptosis of cancer cells in a dose-dependent manner; at 30 µmol/L, cancer cells on 10 h was 41.4% of apoptosis.	(Huang et al. 2012)
ATS	Pancreatic cancer	MiaPaCa-2 and BxPC-3 Pancreatic cancer cells; started after cancer cells 3 h trained, artesunate (100 µl, 10,25,50,100 µM, 48 h)	In vitro	Induced apoptosis of cancer cells in a dose-dependent manner; MiaPaCa-2 cells—artesunate 100 µM-11.5% died (relative to control);BxPC-3 cells- artesunate 100 µM-2.4% died (relative to control).	(Youns et al. 2009)

cervical cancer Me-180 cells, and the result indicated that ART can notably inhibit the expression of VEGF and ERα. In addition, ART can reduce the expression of the HPV-39 viral E6 and E7 components. All in all, to achieve an inhibitory effect on tumors via controlling angiogenesis becomes an important aspect of actions for artimisinin derivatives.

Regulate the body's immune function

Killing tumor cells by regulating the body's immune function has become one of the essential mechanisms of the therapy for cancer. ART was found to inhibit the growth of orthotopic tumor, which was related to a decrease in the percentage of immune T cells and the level of PGE2 in mice with cervical carcinoma. In addition, ART can decrease the expression of COX-2 and production of PEG2 in HeLa and CaSki cells. Thus, ART will be a potential drug for immunotherapy of cervical carcinoma (Zhang et al. 2014). Cui et al. (2006) tested ATS on mouse colon-rectal carcinoma cell line colon 26. The results showed that the ATS can suppress the colon 26 cells growth. In the supernatant fluid, ATS increased the expression of CD4+ T cells and reduced the expression of CD8+ T cells. It is thus concluded that ATS can inhibit colon 26 cells by regulating the cellular immune function. Additionally, recent researches showed that the concomitant immunosuppression cannot decrease the cytostatic and apoptotic effects of ATS (Ramacher et al. 2009). Wang et al. (2010) pointed out that gemcitabine-induced growth inhibition and apoptosis in BxPC-3 and PANC-1 cell lines is increased by DHA in vitro. It's also demonstrated that gemcitabine can dramatically increase the anticancer effect of DHA, as manifested by remarkably increased apoptosis, as well as decreased NF-κB activity, Ki-67 index and its related gene products, accompanied by decreased cancer volume.

Inhibit telomerase activity

Telomerase, composed of RNA and protein body, belongs to a specific reverse transcriptase relying on its own RNA as a template, to make up the loss of telomere DNA due to cell division, making the cells immortalized. Tumor tissue can proliferate infinitely bacause of the increased telomerase. Thus inhibition of telomerase activity has been one of the elementary ways to treat tumor. Ai (2007) found that artesiminin can suppress the human HeLa cells growth, and reduce the telomerase activity. In Me-180 cervical cancer cells, the antiproliferative activity of ART was further confirmed by decreasing telomerase activity and reducing expression of hTERT and hTR subunits, and inducing apoptosis by nuclear chromatin condensation, FACS, and annexin V staining (Mondal and Chatterji 2015).

Block cell cycles

ART and its derivatives can block the cell cycle to exert anti-cancer action. ATS can inhibit the proliferation of tumor via making the cancer cells blocked at G0-G1 stage and reducing the CDC25A expression in esophageal cancer cells (Liu et al. 2008). Chen et al. (2005) treated rats with DHA at 100 mg/kg/day for 4 weeks and found the tumor volume in the treated rats on day 28 was about 54.3% of that of the controls. These data showed that DHA has dramatically antitumor activity on A549 human lung adenocarcinoma cell both in vitro and in vivo, and the inhibition in vitro may be associated to blockade of G0-G1 phases. Wang et al. (2007a) also showed that ATS can inhibit the mRNA, as well as protein expression of CDC25A in the Eca109 human esophageal carcinoma cells, and most of Eca 109 cells were arrested at the G2/M phase. Reichert et al. (2012) examined the radiation sensitizing properties of ATS on LN229 and U87MG cells. Glioma cells treated with ATS and irradiation led to an increased apoptosis rate, pronounced G2/M arrest and raised DNA damage as demonstrated by an elevated amount of γ-H2AX foci/nucleus. Incubation with ATS lowered survivin expression in a time and dose-dependent manner, but the expressions of XIAP, CIAP1, and CIAP2 were not affected. Li et al. (2009) also proved that ATS can increase the proportion of SP2/0 myeloma cells in G0/G1 phase and reduce the proportion of cells in S or G2/M phase.

Anti-inflammation and immunoregulation

Immunosuppressive activity

Zhou et al. (2005) investigated the inhibitory effect of SM 735 in the proliferation of splenocytes induced by ConA, MLR or LPS. The results showed SM 735 has a remarkable immunosuppressive action on both T-cell-mediated delayed-type hypersensitivity and B-cell-mediated QHS reactions in a dose-dependent manner. Combined with the previous in vitro experimental results, it is reasonable to think of SM 735 as a potential immunosuppressive agent. Aside from SM 735, it has been noted that SM 905 also suppressed T cell activation by inhibiting MAP kinases and Ras activation (Wang et al. 2007c). Recent researches also showed SM 905 inhibited NO and pro-inflammatory cytokine production in LPS-stimulated RAW 264.7 cells and the mechanism may relate to its inhibition on the MAPK and NF-κB signaling pathways (Wang et al. 2009). Consistent with SM 735 and SM 905, SM 934 also exerted significant immunosuppressive actions both in vitro and in vivo (Wang et al. 2007b). Artemether was also found to possess immunosuppressive action on T cells both in vivo and

in vitro by lowering the activation of the Ras-Raf1-ERK1/2 protein kinase cascade in T cells (Wang et al. 2007b). In 2010, Ye et al. (2010) also reported DHA has an immunosuppressive effect on the proliferation of murine T-lymphocytes.

Rheumatoid arthritis (RA)

RA is a kind of chronic systemic inflammatory disease with unknown etiology that can lead to joint deformity and loss of function. In 2007, Smith et al. (2007) reported that ATS exerts a therapeutic effect for RA via inhibiting the inflammatory responses in RA fibroblast-like synoviocytes. In 2009, another study (He et al. 2011) found that ATS can down-regulate angiogenic factor expression in RA fibroblast-like synoviocytes. In addition, Wang et al. (2008) also found ATS has anti-inflammatory effect in collagen-induced arthritis rats by inhibiting inflammatory factors. As with ATS, a novel aretmisinin derivative SM905 is also capable of decreasing the inflammatory and pathogenic Th17 responses in collagen-induced arthritisin DBA/1 mice (Wang et al. 2008). In order to ascertain the anti-inflammatory mechanism of ART and its derivatives, Li et al. (2010) compared the effects of different concentrations of ATS and methotrexate on the apoptosis and proliferation of fibroblast-like synoviocytes (FLS). The results indicated that the anti-inflammatory mechanism is inhibiting FLS proliferation and advancing FLS apoptosis.

Systemic lupus erythematosus (SLE)

ART and its derivatives have a significant therapeutic effect in SLE in addition to their roles in treating malaria and cancer. SLE is a systemic autoimmune disease that may affect many internal tissues and/or organs such as heart, lungs, joints, skin, blood vessels, liver, kidneys, and nervous system in the body. Wu et al. (2015) showed SM 934 (a chemosynthetic ART derivative) is able to significantly prolong the life-span of MRL/lpr rats, improve the lymph adenopathy symptoms and reduce the levels of serum antinuclear antibodies as well as the pathogenic cytokines IL-6, IL-10, and IL-21. Additionally, SM 934 treatment can restore the B cell compartment in the spleen of MRL/lpr mice. It was also found that SM 934 has inhibitory effects on plasma cell formation and B-cell activation in MRL/lpr mice. Huang et al. (2014) also demonstrated that DHA can suppress LPS-induced cell activation by blocking the TLR4/IRF/IFN pathway in spleen cells of MRL/lpr mice. Moreover, Hou et al. (2011) showed that ART analog SM 934 can remarkably prolong the life-span and relieve the symptoms of glomerulonephritis in the lupus-prone female MRL/lpr mice by down-regulating both Th1 cell and Th17 cell responses. Ouyang et al. (2009) also examined the immunomodulatory property of ATS in systemic lupus erythematosus by using a MRL/lpr murine model. The results indicated that ATS can reduce monocyte chemotactic protein-1(MCP-1), a major pro-inflammationary cytokine, in serum, urine and kidney. Moreover, the expression of B cell activating factor was reduced in MRL/lpr mice treated with ATS. It was thought that the therapeutic effect of ATS on MRL/lpr nephritis mice is related to its inhibition on ICAM-1 expression (Wang et al. 2010). ART has an anti-inflammatory effect in lupus nephritis mice by regulating the expression of the mRNA of GR alpha and GR beta in peripheral blood mononuclear cells and the transcriptional coactivator P300/CBP protein in renal tissue (Wu et al. 2012). Wu et al. (2010) found that ART can remarkably reduce the serum levels of TNF-α and IL-6 and reduce the expression of the NF-κB p65 protein, and NF-κB and TGF-β1 mRNA in renal tissue.

Treating neuroinflammation

Neuroinflammation in the central nervous system is often generated after the prompt response of the CNS by activating resident immune cells (especially microglia cells) to infection, trauma and stroke, and many other stimuli. It is noteworthy that uncontrolled neuroinflammation may lead to various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis. Professor Okorji (2015) investigated the effects of ART and its derivatives in LPS-activated BV2 microglia. The results indicated that ART, artemether and ATS could suppress neuroinflammation in LPS-activated BV2 microglia via interfering with NF-κB and p38MAPK signaling.

Antiviral activity

Currently, the treatment to HHV-6 infection still remains unsatisfactory so new effective drugs are urgently needed. Romero et al. (2005) proved that treatment of HHV-6-infected cells with ATS notably decreased viral protein synthesis at both early and late stages without apparent necrotic cytotoxicity or drug-induced apoptosis, and HHV-6A genome replication was remarkably reduced as well. Furthermore, ATS also possesses unique activity against human cytomegalovirus (Chou et al. 2011). Compared with ART monomers, ART-derived dimers had a better anti-cytomegalovirus activity (Arav-Boger et al. 2010). It was previously reported that several natural products including ATS derived from medicinal herbs used in traditional Chinese medicine possess anti-HBV effect. It was also found that HBV DNA release was suppressed when treated with ATS with an IC_{50} of 0.5 mM and a synergistic action

was generated when used together with lamivudine (Romero et al. 2005). Previous studies had indicated that ART and its analogs may possibly have anti-HCV effect by the induction of reactive oxygen species (Obeid et al. 2013). In addition, hemin can potentiate anti-HCV activity of ART (Paeshuyse et al. 2006). Further, 12-n-butyldeoxoART, an ART-related trioxane, has been shown to have a great antiviral activity against HIV-1 in a recent study (Jung and Schinazi 1994). In general, ART and its derivatives can inhibit a variety of viruses, such as human cytomegalovirus, hepatitis B virus, hepatitis C virus, and HIV-1. Further study of the complete profile of the pharmacological activities and molecular modes of action of ART and its derivatives as well as their performance in clinical trials will helpful to reveal the full antiviral potential of these versatile pharmacological tools.

Treating sepsis

Sepsis is a systematic inflammatory response syndrome with high mortality and no specifically effective drug on the market today. Endotoxin is one of main pathogenic molecules that induce sepsis. It was early reported that ART drugs antagonized the inflammation induced by endotoxin. Zhang et al. (2005) studied the effects of ATS on free calcium ion concentration in peritoneal macrophages of endotoxemia mouse induced by hyperthermia and found that ATS can remarkably decrease the level of intracellular free calcium. A study conducted by Liang et al. (2002) proved that ATS can dramatically inhibit endotoxin-induced production of inflammatory mediators from macrophages both in vivo and in vitro, indicating that ATS can inhibit the inflammatory responses caused by endotoxin. Li et al. (2008) also tested the effect of ATS in sepsis mouse model and the result showed that ATS can protect rats against a lethal challenge with heat-killed *E. Coli* in a dose-dependent manner by decreasing the expression of NF-κB and TLR4, TLR9 mRNA. Cao et al. (2007) observed the therapeutic action of ART on lung injury in septic mice, and demonstrated that ART might reduce the concentration of LPS, and suppress the expression and the releasing of proinflammatory cytokines in lung tissues, alleviating the pathological lung injury in septic mice as a result.

Anti-fibrosis

Fibrosis which occurs in a variety of organs is a serious threat to human health and life. Xu et al. (2009) reported that ATS could decrease the expression of TGF-β1 and TNF-α in pulmonary fibrosis mice, significantly reducing the degree of pulmonary fibrosis similar to the therapeutic effect of methylprednisolone. Lai et al. (2015) found that ART can relieve hepatic fibrosis induced by various pathogenic factors and inflammation via inhibiting LPS/TLR4/NF-κB signaling pathway in mice. Li et al. (2009) proved the inhibition effect of ATS on mastocyte in a rabbit ear hypertrophic scar model. The results showed ATS can suppress fibroblast proliferation by reducing mastocyte and collagen synthesis. In addition, ATS also has a notably inhibitory activity on the liver fibrosis. A recent study showed it can suppress the activated proliferation of hepatic stellate cells by increasing the expression of apoptosis genes, leading to the rebalance of apoptosis and proliferation and finally the hepatic fibrosis is reduced (Yang and Liu 2009).

Antiarrhythmia

ART was shown to has an obvious inhibitory action on arrhythmia in rat and guinea pig models induced by aconitine and uabain. Studies have proven that aconitine-induced arrhythmia in rats is associated to its promotion to I_{Na}, I_{Ca} and prolongation of action potential duration, while uabain-induced arrhythmia in guinea pigs mainly involves the regulation on I_{Ca}, I_{Kr} and shortening of the action potential duration. These results suggest ART may have the potential to be further developed as a anti-arrhythmic agent in the future (Du and Liu 2003).

Antibacterial action

The anti-bacterial effect of ART had been studied in a wide range of bacteria, such as *Escherichia coli* (Sack 1975), *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Mycobacterium intracellulare* (Slade et al. 2009). Combination-therapy research was also performed. It was found that ATS could increase the antibacterial effect of various *β*-lactam antibiotics against *E. coli*, which might be related to the inhibition of a major multidrug efflux pump system, AcrAB-TolC (Li et al. 2011). Interestingly, Appalasamy et al. (2014) demonstrated that ART and a precursor had an inhibitory effect on the growth of Gram-positive and Gram-negative bacteria but not *Candida albicans*. Their antibacterial activity was similar to that of antibiotic streptomycin.

Concluding remarks

More than 40 years has passed since artermisinin' discovery by professor Tu Youyou in China in 1972. Artermisinin currently saves millions of patients suffering from malignant malaria worldwide annually. Cancer is another life-

threatening disease and current cancer therapeutic strategies have been reported to cause many serious side effects in patients. Tumor heterogeneity further devaluates the effectiveness of a given therapeutic strategy. There is, thus, a strong demand for therapeutic agents that are efficacious against a specific cancer type and yet have a minimal to no side effects. Besides the therapeutic effect against malaria, cancer therapy has been proved to be the most potentially clinically applied action of ART and its derivatives among all their biological functions. ART is an already approved antimalarial drug in humans and therefore uncovering its anticancer properties and underlying mechanisms will be critical to determine which cancer phenotype can best be treated with this phytochemical ingredient or its derivatives. This is the precondition for the realization of accurate treatment of ART compounds to malignant tumors.

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Competing financial interests

Conflict of interest The authors declare that they have no conflict of interest.

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