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Review

Artemisinin and its derivatives in treating protozoan infections beyond malaria

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ABSTRACT

Parasitic protozoan diseases continue to rank among the world's greatest global health problems, which are also common among poor populations. Currently available drugs for treatment present drawbacks, urging the need for more effective, safer, and cheaper drugs. Artemisinin (ART) and its derivatives are some of the most important classes of antimalarial agents originally derived from *Artemisia annua* L. However, besides the outstanding antimalarial and antischistosomal activities, ART and its derivatives also possess activities against other parasitic protozoa. In this paper we review the activities of ART and its derivatives against protozoan parasites in vitro and in vivo, including *Leishmania* spp., *Trypanosoma* spp., *Toxoplasma gondii*, *Neospora caninum*, *Eimeria tenella*, *Acanthamoeba castellanii*, *Naegleria fowleri*, *Cryptosporidium parvum*, *Giardia lamblia*, and *Babesia* spp. We conclude that ART and its derivatives may be good alternatives for treating other non-malarial protozoan infections in developing countries, although more studies are necessary before they can be applied clinically.

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Abbreviations: ART, artemisinin; b.i.d., two times per day; CH_2CL_2, dichloromethane; CI, cell index; DART, dehydroartemisinin; Deoxy-ATS, deoxygenated artesunate; Deoxy-DHA, deoxydihydroartemisinin; DHA, dihydroartemisinin; DMSO, dimethyl sulphoxide; HFF, human foreskin fibroblast; IC_{50}, concentration that causes 50% inhibition of growth; IC_{90}, concentration that causes 90% inhibition of growth; i.g., intragastric administration; i.m., intramuscular injection; i.p., intraperitoneal injection; iTRAQ, isobaric tags for relative and absolute quantitation; i.v., intravenous injection; Luc value, luciferase value; MeOH, methanol; NO, nitric oxide; PCV, packed cell volume; PGDH, phosphoglycerate dehydrogenase; p.i., post-infection; PI staining, propidium iodide staining; p.o., oral administration; PSAT, phosphoserine aminotransferase; q.d., one time per day; q.i.d., four times per day; RBC, red blood cell; s.c., subcutaneous injection; SEM, scanning electron micrograph; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; SI, selectivity index; TD_{50}, median cytotoxic dose; TI, therapeutic index; TEM, transmission electron micrograph; t.i.d., three times per day; t.p., topical administration.

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1. Introduction

The World Health Organization recognizes 17 major parasitic and related infections as neglected tropical diseases (NTDs) that affect many countries in Africa, Asia, and Latin America. However, the lack of commercial interest in developing new pharmaceutical compounds for combating these diseases has impaired efforts to eliminate them [1,2]. Discovery of new, safe, effective, and affordable active drugs is thus urgently needed. Artemisinin (ART) and its derivatives are one of the most important classes of antimalarial drugs. Like many other natural sesquiterpenes, ART displays a range of different biological and pharmacological properties. Except for its antimalarial and antischistosomal activities, ART has also been shown to possess antimicrobial [3] and antiviral activities [4]. In addition, the antiparasitic function of ART against non-malarial parasites cannot be ignored. Here we screened the literature through extensive searches of PubMed, ResearchGate, Elsevier ScienceDirect, Wiley Online Library, and the Springer-Link Journals database using the search term "artemisinin" for publications in English with no date limits as well as through manual review of some related journals. We outline the use of ART and its derivatives in treating parasitic diseases or parasitic infections caused by protozoan parasites including *Leishmania* spp., *Trypanosoma* spp., *Toxoplasma gondii*, *Neospora caninum*, *Eimeria tenella*, *Acanthamoeba castellanii*, *Naegleria fowleri*, *Cryptosporidium parvum*, *Giardia lamblia*, and *Babesia* spp.; only drugs with activities against these protozoan parasites are reported. Studies have demonstrated good efficacies of ART and its derivatives in vivo and in vitro towards some of the parasitic protozoan infections. Clinical trials using different semisynthetic and synthetic ART derivatives should be undertaken to develop treatments for these parasitic diseases.

2. Chemical characteristics of ART and its derivatives

In 1967, under the instructions of Chairman Mao and Premier Zhou, a secret project called "Project 523" was launched to develop a new drug to combat drug-resistant malarial parasites [5,6]. In 1971, Youyou Tu and her team isolated a new anti-malarial drug, called Qinghaosu (or ART), from *Artemisia annua* L. (Qinghao), which was shown to inhibit proliferation of *Plasmodium* parasites [6].

ART and its derivatives share a common structural feature called endoperoxide linkage [7]. In general, ART has poor solubility in both water and oil. However, by reducing the C-10 carbonyl group of ART, a more water-soluble derivative dihydroartemisinin (DHA) can be obtained [5,8]. Artesunate is the water-soluble hemisuccinate ester of DHA [9]. According to Chaturvedi et al., by adding a methyl or ethyl ethers at the same carbonyl group, higher oil soluble compounds like artemether and arteether were obtained [7]. Artemisone was obtained by replacing the same carbonyl with amines in the ART molecule, which showed improved water solubility, better toxicity profile, and a longer half-life [8]. Due to the short in vivo half-lives and low bioavailability of ART derivatives, arterolane and artefenomel (1, 2, 4-trioxolane analogues) were created to achieve more favourable pharmacokinetics. They were synthesized by coupling symmetrical O-methyl 2-adamantanone oxime with cyclohexanones by the Griesbaum co-ozonolysis [10]. Arterolane and artefenomel have longer half-lives compared to DHA, higher bioavailability than artemether, and are comparable to artesunate [11]. However, trioxolane-like arterolane has relatively low in vivo stability [8]; that is why 1, 2, 4, 5-tetraoxanes with similar peroxide bridges, better stability, and more potent anti-malarial activity such as RKA 216 and RKA182 were developed [12]. In addition, deoxygenated artesunate (Deoxy-ATS), artemiside, synthetic trioxolanes (LC50, LC67, and LC95), and fluoro-artemisinin derivatives (BB200, BB201, BB241, and BB242) are proven to have anti-protozoal effects. The structures of ART and its derivatives included in this publication are shown in Fig. 1.

3. ART and its derivatives on *Leishmania* spp.

Leishmaniasis affects approximately 350 million people in 98 countries around the world [13]. The disease manifests primarily as three forms, namely cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis, with the last being fatal if left untreated [14]. Current anti-leishmanial drugs include pentavalent antimony, amphotericin B, paromomycin, pentamidine, and miltefosine, with toxic effects to the liver, heart, and kidney, as well as anemia, fever, and hypokalemia. Therefore, usage is limited by their toxicity and adverse reactions [15,16]. Miltefosine and paromomycin are two drugs that have been introduced more recently for the treatment of leishmaniasis [16]. However, long-term therapy with miltefosine's long half-life (about 152 h) can promote early onset of drug resistance, and potential teratogenic and abortifacient effects limit its prescription during pregnancy [17,18]. Paromomycin is an aminoglycoside antibiotic that has shown promising results in the treatment of leishmaniasis, mainly for treating its cutaneous form [16]. However, in vitro tests have led to the emergence of paromomycin-resistant [19], miltefosine-resistant [19], meglumine antimoniate-resistant [20], and pentamidine-resistant [21] parasites; therefore the therapy of visceral leishmaniasis is limited by resistance, toxicity, and decreased bioavailability of the existing anti-leishmanial agents [22]. The effects of ART and its derivatives on *Leishmania* parasites have been studied in mice and in vitro. They are efficient in inhibiting the parasite metabolism, while showing limited adverse effects on the host, indicating a higher safety index of the drugs [23,24]. A large number of in vitro and in vivo studies have now shown that ART and its derivatives have activities in controlling *Leishmania* parasites; the drugs shown effective against the protozoan are selected and summarized in Table 1.