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Artemisinins: Pharmacological actions beyond anti-malarial

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ABSTRACT

Artemisinins are a family of sesquiterpene trioxane lactone anti-malarial agents originally derived from *Artemisia annua* L. The anti-malarial action of artemisinins involves the formation of free radicals via cleavage of the endoperoxide bond in its structure, which mediate eradication of the *Plasmodium* species. With its established safety record in millions of malarial patients, artemisinins are also being investigated in diseases like infections, cancers and inflammation. Artemisinins have been reported to possess robust inhibitory effects against viruses (e.g. *Human cytomegalovirus*), protozoa (e.g. *Toxoplasma gondii*), helminths (e.g. *Schistosoma species* and *Fasciola hepatica*) and fungi (e.g. *Cryptococcus neoformans*). Artemisinins have demonstrated cytotoxic effects against a variety of cancer cells by inducing cell cycle arrest, promoting apoptosis, preventing angiogenesis, and abrogating cancer invasion and metastasis. Artemisinins have been evaluated in animal models of autoimmune diseases, allergic disorders and septic inflammation. The anti-inflammatory effects of artemisinins have been attributed to the inhibition of Toll-like receptors, Syk tyrosine kinase, phospholipase Cγ, PI3K/Akt, MAPK, STAT-1/3/5, NF-κB, Sp1 and Nrf2/ARE signaling pathways. This review provides a comprehensive update on non-malarial use of artemisinins, modes of action of artemisinins in different disease conditions, and drug development of artemisinins beyond anti-malarial. With the concerted efforts in the novel synthesis of artemisinin analogs and clinical pharmacology of artemisinins, it is likely that artemisinin drugs will become a major armamentarium combating a variety of human diseases beyond malaria.

Contents

Abbreviations: Bcl-2, B-cell lymphoma 2; CMV, cytomegalovirus; CDK, cyclin-dependent kinase; DHA, dihydroartemisinin; dsDNA, double-stranded DNA; HBV, hepatitis B virus; HIF-1α, hypoxia-inducible factor 1α; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; MRSA, methicillin-resistant *Staphylococcus aureus*; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Nrf-2, Nuclear factor (erythroid-derived 2)-like 2; PI3K, phosphatidylinositide 3-kinase; PZQ, praziquantel; ROS, reactive oxygen species; SERCA, sarcoplasmic, endoplasmic reticulum PfATPase6 calcium pump; SLE, systemic lupus erythematosus; Syk, spleen tyrosine kinase; TfR, transferrin receptor; TIMP, tissue inhibitor of metalloproteinase; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

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1. Introduction

Artemisinins are a family of sesquiterpene trioxane lactone anti-malarial agents, derived from the sweet woodworm *Artemisia annua*, a medicinal herb which has long been used in traditional Chinese medicine to treat fevers. This series of potent anti-malarial derivatives was developed from artemisinin, which is the parent compound isolated in a Chinese drug discovery screen for traditional herbal extracts against *Plasmodium* parasite species in the 1970s (van Agtmael et al., 1999; Li, 2012). There are recent comprehensive reviews on the anti-malarial mechanisms of action of artemisinins (Krishna et al., 2008; Krishna et al., 2010; Ding et al., 2011). The strength of artemisinins in anti-malarial therapy lies in their unique chemical structures which differ much from the standard quinoline (Kremsner & Krishna, 2004), and a significantly rapid clearance of malaria parasites from the blood than other available anti-malarial agents. Artesunate, artemether and arteether are the more widely used derivatives of artemisinin for malaria (Fig. 1), and are universally converted to the active metabolite, dihydroartemisinin (DHA), upon administration into the body (Zhu et al., 1983; Melendez et al., 1991). Among the family of artemisinins, artesunate is the most studied analog due to the addition of a hemisuccinate group which confers substantial water-solubility and high oral bioavailability, resulting in a more favorable pharmacological profile (Newton et al., 2000). Multiple anti-malarial mechanisms of action by artemisinins have been proposed and are generally involved in the formation of free radicals of artemisinin, due to the cleavage of the endoperoxide bond by heme iron in its structure. These free radicals of artemisinin can mediate eradication of *Plasmodium* species by altering biochemical pathways within the parasites (Meshnick et al., 1991; Posner et al., 1995; Jefford et al., 1996), including (1) alkylation of heme molecules and interference with the heme detoxification pathway, (2) inactivation of the sarcoplasmic, endoplasmic reticulum PfATPase6 calcium pump (SERCA), (3) alkylation of cytosolic proteins, such as PfTCTP, a potential tumor protein possibly related to parasite replication, and (4) disruption of mitochondrial functions, as summarized by a recent review (Ding et al., 2011).

There are continuous effort and increasing interest in developing newer derivatives of artemisinins with higher efficacy for anti-malarial treatment, and more efficacious artemisinin-based combination therapies to overcome potential drug resistance (Guo et al., 2012; Singh et al., 2012). In the meantime, with the established record of safety in millions of patients with malaria infection (Efferth & Kaina, 2010; Jelinek, 2013), artemisinins are being investigated in disease conditions beyond malaria, ranging from cancers, inflammatory diseases, to viral and other parasite-related infections. Indeed, this is reflected by the steady growth in publications of artemisinins in non-malarial research

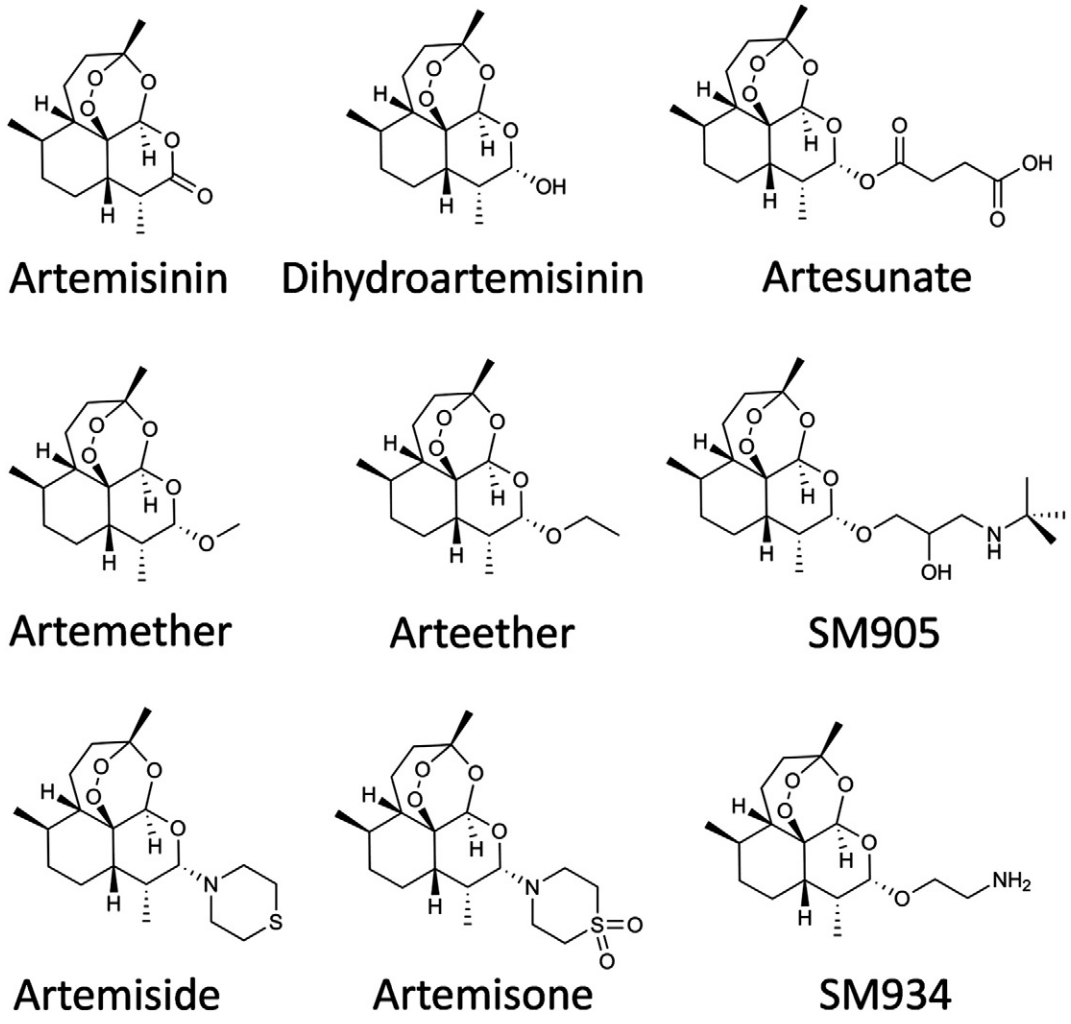

Fig. 1. Chemical structures of artemisinin and its derivatives. Artemisinin (parent drug), dihydroartemisinin (DHA, active metabolite), arteether and artemether (lipid-based derivatives), artesunate (polar derivative), SM905 (1-(12β-dihydroartemisinoxy)-2-hydroxy-3-tert-butylaminopropane maleate, new water-soluble derivative), SM934 (β-aminoarteether maleate, new water-soluble derivative), artemiside (a 10-alkylamino sulfide derivative, lipophilic with limited water-solubility) and artemisone (new 10-alkylamino sulfone derivative with enhanced water-solubility and reduced toxicity) are shown. Most derivatives of artemisinins are semi-synthesized from the parent compound or DHA and are universally metabolized into DHA upon administration into the body.