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Safety Assessment of Artemisinin and Its Derivatives

Shuyao Xie

Guanghua Qidi College, Shanghai, China
shuyaoariel@outlook.com

Abstract. Artemisinin and derivatives, which are the main drugs used to prevent and control malaria in the world, have greatly minimized the morbidity and mortality caused by malaria since they were discovered by a research team led by Tu Youyou. With an established efficacy, concerns relating to safety have been building up with increased and widespread clinical use. In particular, organ-specific toxicities that could be brought about by long-term or high dosage, such as hepatotoxicity, cardiotoxicity, and neuroretinal toxicity, are yet to be systematically assessed. The current research advancement in this area is observed in this paper beginning with the safety of artemisinin, its extracts, and most of the key derivatives such as artesunate and dihydroartemisinin. This paper discusses their toxic manifestations and determining factors on the cell, animal, and clinical levels and examines the safety and pharmacokinetic properties of artemisinin-hydroxychloroquine combination therapy. The evidence of the research is that the drugs based on artemisinin have dose-dependent toxicity and species differentiation, where a significant organ damage in the animal model was frequently observed and responded mildly or resolved in humans. However, there are still some clinical risks including neurotoxicity and ocular adverse events. The future work should develop a safety monitoring system that incorporates real-world and species-specific pharmacokinetics along with genetic biomarkers to an optimal use of drugs without compromising the efficacy to help achieve sustainable development of the global malaria eradication programs.

Keywords: artemisinin, artesunate, hepatotoxicity, cardiotoxicity.

1. Introduction

In the 1970s, a group of researchers led by Professor Tu Youyou discovered a group of Artemisinin that is a sesquiterpene lactone extracted in the artemisinin that was a Chinese traditional herb, Artemisia annua [1]. This accomplishment revolutionized the control of malaria, which is an infectious disease that has a long-term association to the world, especially in tropical and sub-tropical parts. Professor Tu became the first Nobel Prize laureate in the field of Physiology or Medicine in 2015, and the major part of her discovery was honored.

The artemisinin and its analogues have acquired the position of first-line treatment in global malaria control since they are rapid parasiticidal agent and they are also highly effective [1]. The compounds are commonly administered in sub-Saharan Africa and the Southeast Asian regions where they are now popular. They have contributed immensely to the government population health

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both internationally and nationally through key contributions to malaria related morbidity and mortality, saving millions of lives, and significantly reducing the global burden of disease and mortality.

Antimalarial effect of artemisinin is a result of endoperoxide bridge structure in the molecular structure. In erythrocytes infected by Plasmodium, intraparasitic iron promotes the breaking of this bridge and thus results in the generation of reactive oxygen species and carbon-centered free radicals. These include molecules that lead to oxidative stress on essential cellular biomolecules including proteins, lipids, and nucleic acids alternative, completely affecting fundamental cellular activities and ultimately leading to the death of the parasites [2].

Although the therapeutic effect of artemisinin-based agents has been proved, the broad clinical usage and pharmacological studies pending have caused concerns about their safety. A number of serious doubts still exist about any potential adverse reactions with the use that could not be ruled out due to the long-term or high-dose use. Organ-specific toxicities, including hepatotoxicity, cardiotoxicity, and neuroretinal toxicity, and drug-drug interactions are poorly understood and not thoroughly and comprehensively examined. Hence, there is a need to undertake further research on the safety of artemisinin and its analogs. Not only does it support the safety of patients in practice, but it also serves to optimize treatment regimens and to promote the long-term objectives of malaria eradication on a worldwide scale. This paper reviews the recent studies on the safety of artemisinin based compounds to inform the provision of evidence based, rational and safe clinical prescription [3].

2. The safety evaluation progress of artemisinin and its derivatives

2.1. Artemisinin, Artemisia annua extract

Artemisinin and its source extract, Artemisia annua, display comprehensive, multi-dimensional toxicological profiles at the cellular, animal, and clinical formulation levels, which are closely linked to their mechanisms of action and treatment regimens.

At the cellular level, the toxicity of artemisinin to HepG2 hepatocellular carcinoma cells primarily results from the cleavage of its endoperoxide bridge, forming carbon-centered free radicals and reactive oxygen species (ROS). These reactive molecules target intracellular protein networks, damage DNA sequences, and impair mitochondrial function. Experiments have demonstrated that artemisinin inhibits mitochondrial ATPase activity, disrupts membrane potential, and ultimately induces cell cycle arrest and apoptosis. Notably, artemisinin interacts with intracellular iron ions, enhancing oxidative stress through the Fenton reaction and thereby increasing cytotoxicity [4].

Animal studies have shown that Artemisia annua extracts induce organ-specific subchronic toxicity in SD rats. Wang Na et al. conducted a systematic study on the subchronic toxicity of Artemisia annua extract to evaluate the safety of long-term administration and identify target organs. Using SD rats as models, the study established four gavage dose groups (3.0, 3.9, 5.1, and 6.8 g/kg) and a soybean oil blank control group. Administration occurred once daily for 28 consecutive days, with monitoring of rat behavior, hematological and physiological-biochemical indicators, organ coefficients, and histopathological changes. Study results revealed that male rats in the 5.1 and 6.8 g/kg dose groups exhibited reduced hearing after 5 consecutive days of administration. Hematological analysis indicated that white blood cell and lymphocyte counts in male rats of the 3.9, 5.1, and 6.8 g/kg groups were significantly higher than those in the control group, while red blood cell counts in male rats of all administration groups were lower than those in the control group. In addition, serum creatinine levels of rats in all dose groups were decreased compared with

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the control group. Pathological examinations further showed that liver organ coefficients of rats in the high-dose groups (5.1 and 6.8 g/kg) were significantly increased, with liver tissue displaying structural disorganization, and small intestines presenting lesions such as serosal shedding and reduced intestinal villi. This study is the first to systematically report the toxicity profile of Artemisia annua extract under subchronic exposure, clarifying its toxic damage to the nervous system (auditory function), hematopoietic system (effects on red and white blood cells), liver, and digestive tract at high doses (≥5.1 g/kg), and establishing 3.0 g/kg as a safe dose without obvious toxic reactions under the experimental conditions. It provides key experimental data support for the safety evaluation of Artemisia annua extract [5].

These toxic effects are dose dependent. The higher the dosage to the therapeutic dose, the higher the rate and intensity of the organ damage. Mild hematological toxicity including reduced red blood cell counts has also proven to occur. Notably, artemisinin effects on toxicity have species-specific variations. Severe organ toxicity in animal models usually translates into the mild or reversible toxicity in humans, perhaps because of the accelerated turnover of artemisinin in humans [6].

There are plans to reduce toxicity by use of the proposals such as change of route of administration to minimize accumulation of the drug and use of solvents that are water soluble to reduce local irritation [7]. The new formulations of artemisinin like artemisinin nanoparticles and emulsions show better bioavailability and less cytotoxicity [7]. The methods provide potential opportunities of safe application of artemisinin and Artemisia annua extracts.

2.2. Artesunate

Artesunate is a prominent water-soluble congener of artemisinin, and is known to possess a quick-effect and is still part of the core malaria control efforts in the world [1]. As its clinical use continues to grow, and new therapeutic uses are investigated, the in-depth analysis of the safety profile of the drug, especially the retina and heart, has become an essential topic of toxicological studies.

The antimalarial effect of artemisinin products, such as artesunate, is mainly performed through the endoperoxide bridge in their chemical structure [2]. In target cells, intracellular iron breaks this bridge to produce cytotoxic radicals that are carbon centered and reactive oxygen species (ROS). Although this mechanism will specifically attack Plasmodium parasites, it equally has a potential of causing harm to the mammalian cells that experience a lot of iron turnover or are prone to oxidative stress.

It is upon this basis that artesunate exhibits organ-specific toxicities as observed. Research has discovered that the medication is potentially toxic to the retinal cells in dosage effect, and this can result in neuroretinal damage. Likewise, there is toxicological research evidence concerning artesunate that it can cause cardiotoxic effects which is probably due to processes associated with oxidative stress and loss of cellular iron homeostasis which has effects on the functionality and survival of the cardiac tissues [3].

These side effects are not very common when administering the standard doses of antimalarials and within a short period of treatment, but with an increase in doses or the length of treatment, this risk may escalate. Thus, retinal and cardiac safety of artesunate need to be comprehensively understood and constantly monitored to be further used safely in clinical practice, as in malaria or when this medication is considered in the perspective of its repeated application [3].

Chen Lulu et al. integrated network toxicology prediction and serum untargeted metabolomics analysis to systematically reveal potential therapeutic targets and metabolic disorder mechanisms underlying artesunate-induced cardiotoxicity [8]. First, the study predicted and screened 326 potential targets of artesunate through multiple database platforms including PharmMapper,

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STITCH, and SwissTargetPrediction. Meanwhile, 756 cardiotoxicity-related targets were obtained from disease databases such as DiGSeE and GeneCards. Finally, 64 common targets were identified through Venn diagram analysis. Further, the STRING database was used to construct a protein-protein interaction network, and topological analysis was performed via Cytoscape software. Results showed that the top four key targets in terms of Degree value were AKT1, EGFR, CASP3, and VEGFA. In the animal experiment section, C57BL/6J mice were divided into a blank control group, a low-dose (400 $mg \cdot kg^{-1}$) artesunate gavage group, and a high-dose (600 $mg \cdot kg^{-1}$) artesunate gavage group, with continuous administration for 7-10 days for observation. Major results indicated that mice in the high-dose group died on the 7th day of administration. Additionally, serum levels of myocardial injury markers creatine kinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH) in the high-dose group were significantly higher than those in the control group, showing a dose-dependent pattern. Moreover, HE staining of cardiac histopathological sections revealed that cardiomyocytes in the administration groups exhibited injuries such as vacuolar degeneration, edema, and coagulative necrosis, with injury scores increasing significantly with dose elevation. For mechanism exploration, untargeted metabolomics analysis of serum from administered mice was conducted using UPLC-Q-TOF/MS, identifying differential metabolites including various lysophosphatidylcholines (e.g., LysoPC(16:0/0:0), LysoPC(18:2/0:0)) and indoleacetaldehyde. Further pathway enrichment analysis showed that these differential metabolites were significantly enriched in glycerophospholipid metabolism and tryptophan metabolism pathways. This study combined computational prediction, in vivo experimental validation, and systems biology analysis. It not only predicted key signaling pathways potentially mediating cardiotoxicity such as PI3K-Akt, FoxO, and HIF-1 but also revealed a novel mechanism by which artesunate interferes with lipid and amino acid metabolic networks at the endogenous metabolite level. Such findings provide a multi-dimensional perspective beyond traditional toxicity evaluation methods for understanding the complex biological processes of artesunate-induced cardiotoxicity [8].

2.3. Dihydroartemisinin

Dihydroartemisinin (DHA), a semi-synthetic derivative of artemisinin, is widely used in clinical practice due to its potent antimalarial and anti-tumor pharmacological activities [7]. In-depth investigations into its toxicological properties have highlighted embryotoxicity as a major risk. In SD rats, oral administration of DHA at 11 $mg \cdot kg^{-1} \cdot d^{-1}$ for 10 consecutive days induced adverse developmental outcomes such as embryonic death and skeletal malformations [9]. Toxicokinetic studies show that the manifestation of DHA toxicity is closely related to dosage and administration route, with potential cumulative effects during long-term treatment [10]. Despite these preclinical findings, DHA-based combinations remain effective in clinical settings. For example, dihydroartemisinin-piperaquine tablets demonstrated excellent therapeutic effects against Plasmodium falciparum in Laiza, Myanmar [11]. Clinically, adverse reactions to DHA and its combinations are mostly manageable, primarily involving mild gastrointestinal symptoms, although high doses may lead to toxicity in the liver, kidneys, and hematopoietic system [11]. Clark et al.'s study on cynomolgus monkeys confirmed the developmental toxicity of artemisinin derivatives and recommended caution when using them during early pregnancy [12].

3. Artemisinin-hydroxychloroquine combination therapy

Preclinical research on the safety and pharmacokinetics of artemisinin-hydroxychloroquine sulfate tablets (AH) provides essential data for clinical translation. Acute oral toxicity studies in beagle dogs

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determined an approximate lethal dose range of 790–1180 mg/kg. Pre-death symptoms included gait instability, limb weakness, lethargy, tachypnea, and convulsions [13]. In 14-day subacute toxicity tests, administration of AH at 126 mg/kg to dogs induced vomiting, soft feces, anorexia, splenic red pulp vacuolation, and prolonged QTc interval. The no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) were established at 84 mg/kg and 126 mg/kg, respectively [13]. Pharmacokinetic and toxicokinetic studies in rats and dogs revealed distinct metabolic profiles. Artemisinin was rapidly absorbed and eliminated in rats, showing clear gender differences. In contrast, hydroxychloroquine exhibited slow absorption and elimination with a linear dose-AUC relationship and no gender-related bias. Repeated 14-day dosing led to hydroxychloroquine accumulation in both species. However, in female rats, autoinductive metabolism reduced systemic exposure to artemisinin, consistent with dose-time-dependent toxic reactions. These findings indicate that the toxicity of the combination is manageable within therapeutic ranges and support dose optimization for clinical use.

4. Conclusion

This study systematically reviews the research progress on the oral safety of artemisinin and its derivatives. Focusing on organ-specific injuries such as hepatotoxicity, cardiotoxicity, and neuroretinal toxicity that may occur during long-term or high-dose use, the key achievements obtained are summarized from major sections including artemisinin and its extracts, artesunate, dihydroartemisinin, and the artemisinin-hydroxychloroquine combination therapy. At the level of toxicity mechanisms, studies have confirmed that the toxicity of artemisinin-based drugs is closely associated with the production of reactive oxygen species (ROS) from their endoperoxide bridge structure via iron ion-catalyzed reactions in cells. This mechanism has been validated in cellular and animal models, and the characteristics of dose dependence and species differences have been revealed. For artemisinin extracts, subchronic toxicity studies have initially defined the safe dose range and systematically described the toxicity profile on the nervous system, hematopoietic system, and liver at high doses, providing a dose reference for clinical applications. Regarding artesunate, the integration of emerging technologies such as network toxicology and metabolomics has not only predicted potential key targets and signaling pathways of its cardiotoxicity but also revealed a novel mechanism by which the drug disrupts lipid and amino acid metabolic networks in animal models, offering a multi-dimensional perspective beyond traditional methods for an in-depth understanding of its toxicity. For dihydroartemisinin, studies have focused on its embryotoxicity, clarified its risk characteristics, and provided a basis for warnings regarding clinical medication during pregnancy. For the artemisinin-hydroxychloroquine combination therapy, systematic preclinical toxicological and pharmacokinetic studies have determined the dose levels without obvious toxic reactions, revealed the metabolic and accumulation characteristics of different components in the combination, and supported the controllable safety within the therapeutic window. These achievements collectively complement the understanding of the safety of artemisinin-based drugs, initially establishing an evaluation framework from molecular mechanisms to overall toxicity, and providing key scientific data and theoretical support for addressing safety pain points in clinical applications caused by insufficient toxicity cognition, lack of monitoring, and individualized regimens. Looking forward, the development of technologies to solve the safety pain points of artemisinin-based drugs will show an overall trend of systematization, precision, and intelligence. On one hand, safety research will more deeply integrate multi-omics technologies, organoid models, and real-time dynamic biomarker monitoring to construct a cross-species and cross-lifespan systematic safety evaluation system, enabling early warning of toxicity risks and clarification of mechanisms. On the

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other hand, precision medicine strategies based on pharmacogenomics and individualized pharmacokinetic models will become a focus, maximizing the reduction of toxicity risks by identifying susceptible populations and optimizing dosage regimens. Meanwhile, the development of novel drug delivery systems such as nanoformulations and target-modified derivatives will continue to advance, aiming to improve therapeutic targeting, reduce non-specific distribution, and thus enhance efficacy while expanding the safety window. In addition, the use of real-world big data and artificial intelligence for active mining of drug safety signals and risk prediction will promote the formation of a dynamic and forward-looking paradigm for drug safety monitoring and management, ultimately achieving the safe and sustainable application of artemisinin-based drugs while ensuring global antimalarial efficacy.

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