The Therapeutic Effect of Artemisinin and Its Derivatives in Kidney Disease

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Artemisinin (ARS) and its derivatives (ARSs) are recommended as the first-line antimalarial drugs for the treatment of malaria. Besides antimalarial function, its potent anti-inflammatory and immunoregulatory properties, as well as the ability to regulate oxidative stress have brought them to a prominent position. As researchers around the world are continually exploring the unknown biological activities of ARS derivatives, experimental studies have shown much progress in renal therapy. This review aims to give a brief overview of the current research on ARSs applications for kidney treatment with the evaluation of therapeutic properties and potential molecular mechanisms.

Keywords: artemisinin derivatives (artemisinins), kidney disease, inflammation, immunity, oxidative stress

INTRODUCTION

The imbalance between the molecular mechanisms that govern oxidative stress, inflammation, immunity, and cell death are important causes of acute kidney injury (AKI) and chronic kidney diseases (CKD) (Sureshbabu et al., 2015). Both AKI and CKD can lead to diminished kidney function and are associated with high mortality and morbidity. Accumulated evidence demonstrated that natural products are alternative sources for treating renal diseases on account of the conventional experience and multi-target characteristics (Chen et al., 2018).

Artemisinin (ARS) is an effective constituent with a molecular weight of 282 originally extracted from traditional Chinese medicine Artemisia annua L, which was first discovered by Chinese scientists in 1972. Its chemical structure-sesquiterpene lactone with a peroxide bridge has been demonstrated to exert an excellent antimalarial effect (White et al., 2015; Chang, 2016). In the presence of heme or free iron, the production of reactive oxygen species and carbon-centered free radicals generated by the cleavage of the endoperoxide bridge can directly poison the parasites (Vennerstrom et al., 2004). ARS selectively kills plasmodium-infected red blood cells without destroying healthy cells, making it the recommended drug for the treatment of malaria (Lalloo et al., 2016) and more clinically effective than other antimalarial drugs such as hydroxychloroquine (HCQ) and chloroquine (CQ) (Golenser et al., 2006; Efferth and Kaina, 2010). ARS has a rapid onset of action and can be rapidly absorbed by the gastrointestinal tract after oral administration, with half-live ranging from 2 to 5 h. It is mainly distributed in the liver, kidney, and bile, and approximately 80% of the drug was excreted through the urine and feces within 24 h of administration (German and Aweeka, 2008; Li, 2012). Currently, a series of ARS derivatives (ARSs) with improved pharmacological features are used in clinical treatment including artemether (ARM), artesunate (ART), β-aminooctether maleate (SM934), and dihydroartemisinin (DHA) (chemical structures were shown in Figure 1). The half-lives of ARM (2–4 h), ART (< 1 h), DHA (~1 h) are...
shorter (Krishna et al., 2004; German and Aweeka, 2008) and oral intake represents a relatively safe route in the clinic.

In addition to decades of remarkable progress against malaria, studies have demonstrated a variety of other pharmacological effects beyond antimalarial, such as anti-virus, anti-neoplastic, anti-inflammation as well as immunosuppressive effects (An J. et al., 2017). The properties of ARSs have been intensively reviewed in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, etc (Shi et al., 2015; Mu and Wang, 2018), while the treatment of kidney disease has not been summarized. This review will focus on the proposed therapeutic properties and mechanisms of ARSs in kidney disease, and discuss the potential application of ARSs as novel agents for future treatment.

SEARCH STRATEGY

Comprehensive literature searches for candidate studies were undertaken in two English and three Chinese biomedical databases from inception through February 2020. These databases included PubMed, Springer, Chinese National Knowledge Infrastructure, WanFang Med Online, and Chinese Biomedical Databases. Searches were limited to studies in English and Chinese. The following terms were used in the search: “artemisinin,” “artemisinins,” “artesunate,” “dihydroartemisinin,” “artemether,” “SM934,” “β-aminoartether maleate,” “kidney,” “renal,” “nephro,” “nephritis,” “nephropathy.”

OVERVIEW OF RESEARCHES ON ARSs IN RENAL DISEASE

The effects of ARSs were mainly studied on animal models and cells, with two clinical studies targeting lupus nephritis (LN). In a randomized, 5-year follow-up clinical trial for LN (Lu, 2002), the treatment group (ARS 0.6 g/d and cordyceps 3–4 g/d) was reported to improve 24 h urine protein, creatinine clearance rate, level of C3, and was more effective than the control group (tripterygium wilfordii polyglycosides tablets 1 mg/kg, three times a day and/or prednisone 0.5 mg/kg/d). However, these two studies were not blinded and placebo-controlled, which may result in information bias, and observations of larger samples are still lacking.

Table 1 summarized the characteristics of animal studies with ARSs treatment, covering LN, adriamycin nephropathy (AN), subtotal nephrectomy (SNx), IgA nephropathy (IgAN), diabetic nephropathy (DN), AKI, unilateral ureteral obstruction (UUO), pristine or lipopolysaccharide (LPS)-induced nephritis, nephrotic syndrome (NS), and Heymann nephritis (HN). In vitro cell models and in vivo animal models investigations for ARSs efficacy on kidney disease involve various aspects including oxidative stress, inflammation action, and immune response, we will describe the effects of ARSs in sections below.

MECHANISM OF ARSs IN KIDNEY

Oxidative Stress Regulation of Artemisinins

Oxidative stress is an important mediator in the development and progression of CKD and AKI and its complications due to increased production of reactive oxygen species (ROS) and diminished antioxidant capacity (Ruiz et al., 2013). In the condition of a surplus of ROS, ARSs were reported to exhibit an antioxidant effect (Kim et al., 2014; Yang et al., 2018; Liu et al., 2019). In addition, according to the characteristics of ARSs, tumor cells are more vulnerable due to higher levels of iron (Robert et al., 2005) and more susceptible to further ROS insults induced by ARSs (Hamacher-Brady et al., 2011; Efferth, 2017). Accordingly, ARSs have the potential to treat kidney cancer, and the emergence of new technologies such as ARS-based smart nanomedicine offers more possibilities (Luo et al., 2019).

In Vitro

Receptor-interacting protein kinase 1 (RIP1) is verified to modulate mitochondrial ROS production via excessive generation of
TABLE 1 | Study characteristics of animal experiments in kidney disease.

| Animal model | Drug and dose | Application mode | Targets | Reference |
|--------------|---------------|------------------|---------|-----------|
| LN mice      | ARS (150 mg/kg/d) | p.o. for 8 weeks | ↓TNF-α, IL-6 in serum; ↓NF-kB, iNOS p65, ↑TGF-β1 in renal tissue | Wu X. et al., 2010 |
| LN mice      | ARS (150 mg/kg/d) + prednisolone (3.225 mg/kg/d) | p.o. for 8 weeks | ↓GRα, ↑GRβ in PBMC; ↑P000/CPB in renal tissue | Wu X. L. et al., 2011 |
| LN mice      | ARS (5.55 mg/kg/d) + HCO (16.6 mg/kg/d) | p.o. for 8 weeks | ↓Anti-dsDNA, ↓ANA, ↓IgG, ↓IFN-γ, ↓TNF-α, ↑TGF-β1 in serum; ↑HLF15, ↓NF-xB in renal tissue | Lian et al., 2018 |
| LN mice      | ART (125 mg/kg/d) | p.o. for 16 weeks | ↓Anti dsDNA, ↓ANA, ↓MCP-1 in serum; ↓VEGF in renal tissue | Jin et al., 2007; Jin et al., 2009; Wang et al., 2010; Hou et al., 2011 |
| LN mice      | ART (50 mg/kg/d) | p.o. for 16 weeks | ↓COMA-1 in renal tissue | Jia et al., 2007 |
| LN mice      | SM934 (10 mg/kg/d) | p.o. for 4 weeks | ↓IL-2, ↓IL-17, ↓IFN-γ, ↓Anti-dsDNA IgG in serum; ↓STAT-1, ↓STAT-3, ↓STAT5, ↓CD3+CD8+CD4-CD8-T cells, ↑Th1, Th17, ↑Treg in splenocytes | Lin et al., 2016 |
| LN mice      | SM934 (2.5, 5, 10 mg/kg/d) | p.o. for 8 weeks | ↑Fratactin, ↓INF-β, ↓NF-xB p65 in renal tissue | You et al., 2014 |
| LN mice      | DHA (5, 25, 125 mg/kg/d) | p.o. for 10 d | ↓NF-κB, ↓NF-xB p65 in renal tissue | Dong et al., 2003 |
| LN mice      | DHA (5, 25, 125 mg/kg/d) | p.o. for 10 d | ↓INF-κB, ↓INF-xB p65, ↓INF-xB α in renal tissue | Li et al., 2006 |
| LN mice      | DHA (60 mg/kg/d); DHA (60 mg/kg/d) + Prednisolone (9 mg/kg/d) | p.o. for 8 weeks | ↓Fractakin, ↓INF-β, ↓NF-xB p65 in renal tissue | You et al., 2014 |
| AKI mice     | DHA (25, 50, 100 mg/kg/d) | p.o. for 12 weeks | ↓SIGIR, ↓TLR4/INF-xB in renal tissue | Huang et al., 2015 |
| AKI mice     | DHA (20, 40, 80 mg/kg/d) | p.o. for 10 d (pretreated) | ↓MDA, ↓GSH, ↑SOD activity in renal tissue | An Y. et al., 2017 |
| AKI mice     | DHA (50 mg/kg/d) | p.o. for 1 d | ↑Occludin, ↓INF-xB α in renal tissue | Cheng et al., 2018 |
| AKI mice     | DHA (20 mg/kg/d) | p.o. for 3 d (pretreated) | ↓Apat-1, ↓cleaved-caspase-3, ↓IL-1β, ↓IL-5, ↓IL-6, ↓IL-17α, ↓IFN-γ, ↓INF-xB, ↓OCXCL1, ↓MCP-1, ↓MIP-2 in serum; ↓NF-κB p65, ↓IMDA, ↓NO, ↑GSH, ↑CAT, ↑SOD activity in renal tissue | Liu et al., 2019 |
| DN rats      | ARS (300 mg/kg/d) | i.p. for 3, 6 weeks | ↓PDGF-B, ↓TIMP-2, ↓MMP-2, ↓PKC activation in renal tissue | Zhang et al., 2014a; Zhang et al., 2014b; Zhang et al., 2014c; Zhou et al., 2014a; Zhou et al., 2014b; Zhou et al., 2014c |
| DN rats      | ARS (300 mg/kg/d) | i.p. for 4 weeks | ↓DNA binding activity of NF-κB, ↓c-fos, ↓c-jun, ↓DNA binding activity of AP-1 in renal tissue | Wang et al., 2014a; Wang et al., 2014b |
| DN rats      | ARS (300 mg/kg/d) | p.o. for 4 weeks | Differentially gene expression profile | Xiong et al., 2014 |
| DN rats      | ART (10, 30 mg/kg/d) | p.o. for 12 weeks | ↓TLR4, ↓IL-8 in renal tissue | Nie et al., 2015 |
| DN rats      | ARM (670 mg/kg/d) | p.o. for 12 weeks | ↓IL-6, ↓TPCQ-1a in serum and urine; ↓mitochondrial MIP content in renal tissue | Han et al., 2019 |
| IgAN rats    | ARS (16.7 mg/kg/d) + HCO (16.7 mg/kg/d); ARS (8.3 mg/kg/d) + HCO (25 mg/kg/d) | p.o. for 90 d | ↓Deposition of IgA immune complexes and C3 in renal tissue | Lin et al., 2016 |
| IgAN rats    | ARS (33.3 mg/kg/d) + HCO (33.3 mg/kg/d); AH (16.65 mg/kg/d); AH (33.3 mg/kg/d); 66.66 mg/kg/d; ARS: HCO=1:1:1:3 | p.o. for 4 weeks | ↓IL-4, ↓IL-17, ↓IFN-γ, ↓Th2, ↓Th17, ↓Th1, ↓Treg proportion in peripheral blood and spleen; ↓Deposition of IgA immune complexes and C3 in renal tissue | Bai et al., 2019 |
| IgAN rats    | ARS (25, 50 mg/kg/d) | p.o. for 4 weeks | ↓MCP-1 in renal tissue | Mi et al., 2009 |
| IgAN rats    | ART (25, 50 mg/kg/d) | p.o. for 4 weeks | ↓IL-2, ↓IL-6 in serum | Ma et al., 2009 |
| UUO mice     | ART (25, 50 mg/kg/d) | p.o. for 3, 7, 14, 21 d | ↓α-SMA, ↓CTGF in renal tissue | Mi et al., 2007 |
| UUO mice     | ART (25, 50 mg/kg/d) | p.o. for 3, 7, 14, 21 d | ↓NF-κB p65, ↓NF-κB-α, ↓Smad7 in renal tissue | Ma et al., 2010 |
| UUO mice     | ART (15, 30, 60 mg/kg/d) | p.o. for 14 d | ↓α Fibronectin, ↓collagen I, ↓α-SMA, ↓E-cadherin, ↓USAG-1, ↓EMP-7 in renal tissue | Cao et al., 2016 |
| UUO mice     | DHA (40 mg/kg/d) | p.o. for 14 d | ↓Collagen I, ↓collagen III, ↓Fibronectin, ↓TGF-β1, ↓PCNA, ↓α-SMA, ↓P13k/akt in renal tissue | Zhang et al., 2019 |
| NS rats      | ART (5 mg/kg/d) | i.p. for 28 d | ↓Triglyceride, ↓albumin in serum; ↓polymorphonuclear cells infiltration in renal tissue | Raza et al., 2008 |
| Nephritis mice | DHA (20 mg/kg/d) | i.p. for 48 h | ↓TNF-α, ↓IL-6 in serum | Wu P. et al., 2011 |
| Nephritis mice | ART (28.8 mg/kg/d) | p.o. for 6 weeks | ↓TNF-α, ↓IL-6 in serum; ↓α-SMA, ↓TLR4, ↓MyD88, ↓NF-κB p65, ↓TGF-β1, ↓Ip3-caspase-3 in renal tissue | Wang and Li, 2017 |
| AN rats      | ARS (150 mg/kg/d) | p.o. for 4 weeks | ↓Nephrin, ↓podocin in renal tissue | Wu et al., 2014 |
| HN rats      | ARS (100 mg/kg/d) | p.o. for 4 weeks | ↓Podocyte, ↓nephrin, ↓podocin in urine | Liu et al., 2017 |

(Continued)
SNx rats ARS (100 mg/kg/d) p.o. for 16 weeks

↓

inhibit rok knock down of RIP1 reverted ART-induced human renal carcinoma cells, while pretreatment with RIP1 ART was reported to induce ROS production and cell death in mice by restoring malonyl dialdehyde (MDA), nitric oxide (NO), mitochondrial superoxide and depletion of GSH (Zhou et al., 2017). ART was reported to induce ROS production and cell death in human renal carcinoma cells, while pretreatment with RIP1 inhibitor or knockdown of RIP1 reverted ART-induced cytotoxicity (Chauhan et al., 2017).

In Vivo

Pretreated DHA or ARS could ameliorate oxidative stress in AKI mice by restoring malonyl dialdehyde (MDA), nitric oxide (NO), glutathione peroxidase (GSH), catalase (CAT), and superoxide dismutase (SOD) activity in the kidney (An Y. et al., 2017; Liu et al., 2019). In addition, ARM was shown to reduce the serum H2O2 level and elevated renal cortical PGC-1α expression, but it did not exert obvious effects on CAT and SOD expression in the renal cortex in DN (Han et al., 2019). In normal rats without oxidative stress, orally taken artemether-lumefantrine (1.14/6.86 mg/kg/d, twice a day) or artesunate-amodiaquine (2.86/5.8 mg/kg/d, twice a day) for 7 d did not apparently alter renal antioxidant status compared with the control. Although there was no significant alteration in kidney, liver, lung, and brain weights, the artesunate-amodiaquine group showed cardiotoxicity (decreased heart weight by 27.2% compared with control) (Otteuchere et al., 2012).

To date, ARSs could trigger cell death by inducing oxidative stress, and could also resist oxidation to reduce cell damage. Detailed understanding of the molecular mechanisms and the events by which ARSs regulate oxidative stress to control cellular processes in different cells remain to be explored.

Anti-Inflammation Effect of ARSs

Inflammation plays a pivotal role in the pathophysiological processes of kidney diseases and associated with renal injury (Ernandez and Mayadas, 2016). The anti-inflammatory effects of ARS have been widely recognized, including repression of nuclear factor-κB (NF-κB), toll-like receptors (TLRs), signal transducer and activator of transcription (STAT), and phosphatidylidyinositol-3-kinase (PI3K)/protein kinase B (AKT) activity (Aldieri et al., 2003; Ho et al., 2014; Shi et al., 2015), which are key factors mediating immune-inflammatory response and are associated with kidney disease progression (Ruiz-Andres et al., 2016).

In Vivo

ART ameliorated high glucose-induced injury by suppressing TLR4/NF-κB/nod-like receptor protein 3 (NLRP3) inflammasome pathway in rat glomerular mesangial cell (Sun et al., 2018).

In Vivo

For LN mice, it has been reported that treatment with ARSs could decrease interferon-γ (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) in serum, and blocked intercellular adhesion molecule-1 (ICAM-1), fractalkine, NF-κB signaling pathway in renal (Dong et al., 2003; Li et al., 2006; Wang et al., 2010; Wu X. et al., 2011; Wan and Li, 2017; Liu et al., 2019). Also, ARSs were proved to alleviate the tubule-interstitial inflammation and fibrosis by inhibiting NF-κB and mothers against decapentaplegic homolog 2-3-7, significance of 0.1 and 0.05 is at the 0.05 level.

These data indicate that ARSs act as anti-inflammatory drugs at multiple components of inflammation signals and have a potential therapeutic effect on disease activity.

Immunoregulatory Effect of ARSs

Under physiological conditions, the kidney contributes to immune homeostasis, assist in the removal of metabolic wastes and toxins, and maintain peripheral tolerance. The disruption of immune homeostasis an autoimmune response, such as the occurrence of LN and IgAN, resulting in the loss of renal
function (Tecklenborg et al., 2018). T cells, B cells, and macrophages, as well as cytokines, are involved in immune regulation and are activated to varying degrees depending on disease pattern. The activated pathogenic cells are more likely to lead the breakdown of the peroxide bridge structure of ARS (Shi et al., 2015).

**In Vitro**
Chemokine ligand 2 (CCL2) and single immunoglobulin IL-1-related receptor (SIGIRR) are involved in the inflammatory pathogenesis of LN, DHA was reported to inhibit CCL2 secretion and increase SIGIRR expression and protect LPS-pathogenesis of LN, DHA was reported to inhibit CCL2.

**In Vivo**
ARS combined with prednisone was reported to increase the sensitivity of glucocorticoid compared to the group administrated glucocorticoid only in LN (Wu X.L et al., 2011), which may offer a possibility of alleviating the common side effects of existing glucocorticoids or immunosuppressants. SM934 was shown to protect LN mice by inhibiting both Th1 cells and Th17 cells responses (Hou et al., 2011) and reduce the number of activated B cells by inhibiting the expression of TLR7/9 (Gui et al., 2019). SIGIRR, as an inhibitor of TLR signal transduction, could be elevated by DHA. This might be a negative immune-modulating way for DHA to slow the progression of LN (Huang et al., 2015). In addition, ARS combined with HCQ was shown to improve IgAN rats immunity (Lin et al., 2016), possibly via inhibiting the differentiation of Th2 and Th17 cells while promoting Th1 and Treg cells differential (Bai et al., 2019).

All these studies suggest that ARS family drugs are able to perform immunosuppressive functions primarily through suppressing the activation of pathogenic immune cells and have a regulatory effect on autoimmune diseases.

**Other Effects**

**Anti-Fibrosis**
Myofibroblasts can be differentiated by the epithelial-mesenchymal transformation (EMT) process, and are primarily responsible for excessive extracellular matrix production. TGF-β1, smooth muscle actin (α-SMA) and connective tissue growth factor (CTGF), metalloprotease (MMP), bone morphogenetic protein (BMP) are all considered to be major regulators of EMT and renal fibrosis (Liu et al., 2018). For UUO, both in vitro and in vivo study showed anti-fibrosis effect of ARSs related to the inhibition of EMT, fibroblast proliferation, and collagen synthesis (Zhang et al., 2017). And upregulating BMP-7 and downregulating BMP antagonist-uterine sensitization-associated gene-1 (USAG-1) (Cao et al., 2016), or mitigating CTGF, α-SMA (Mi et al., 2007), or PI3K/AKT pathway (Zhang et al., 2019) are all possible mechanisms.

**Anti-Proliferation**
Glomerular mesangial cell proliferation is a common pathological change of glomerular disease, effective control of mesangial cell proliferation is of great clinical significance. ARSs were reported to exert an inhibitory effect on the proliferation of rat mesangial cells (MA et al., 2007a; Ma et al., 2007b), possibly by inducing apoptosis and downregulating inflammatory cytokines TNF-α and IL-6 (Wang et al., 2016) or enhance caspase-3 activity (Wu X.L. et al., 2010). Our team recently demonstrated that DHA could inhibit the proliferation of αlgA1-induced human mesangial cells through the mTOR signaling pathway in vitro (Xia et al., 2020). In addition, ARSs were found to inhibit renal carcinoma cell proliferation by inhibiting the expression of fascin (Zhang et al., 2018), meanwhile inhibiting colony formation, migration, invasion, and tumorigenesis (Yu et al., 2019).

**Regulate Glomerular Filtration**
Glomerular permeability is regulated by the glomerular filtration barrier (GFB), which composed of glomerular endothelium, the glomerular basement membrane, and the podocyte layer. The dysfunction of intercellular adhesion and connection will result in the loss of the structural and functional integrity of GFB and the occurrence of proteinuria (Mehta and Malik, 2006). ART was proved to reduce glomerular permeability and improve proteinuria in LN mice by inhibiting vascular endothelial growth factor (VEGF) (Jin et al., 2007). Studies also showed that DHA ameliorated the hyperpermeability of GFB by inhibiting TNF-α and maintaining occludin expression (Cheng et al., 2018) or elevation of vascular endothelial (VE)-cadherin expression in endothelial cells (Li et al., 2018). In addition, ARS was observed to attenuate podocyte effacement and fusion via nephrin and podocin regulation in adriamycin-induced nephropathy (Wu et al., 2014), and reduce the shedding of podocyte and excretion of nephrin and podocin in Heymann nephritis (Liu et al., 2017).

**Anti-Virus**
ARS was shown to be effective in inhibiting polyomavirus BK replication in primary human kidney cells (Sharma et al., 2014).

**Renal-Protective.**
ART was reported to ameliorate proteinuria and suppress the progression of NS (Razavi et al., 2007). Studies also showed that ARS could relieve renal lesions in DN rats, through inhibiting platelet-derived growth factor-B (PDGF-B) expression (Zhang et al., 2014a), metalloproteinase tissue inhibitor-2 (TIMP-2) (Zhang et al., 2014b), spatiotemporal dynamics activation of protein kinase c (PKC) (Zhang et al., 2014c) and its downstream c-fos and c-jun (Zhou et al., 2014b), and their heterodimer activator protein (AP-1) (Zhou et al., 2014c). The results from the high-throughput sequence from DN rats treated with ARS may identifying promising targets for future treatment (Xiang et al., 2019). In addition, kidney function was found to be improved in cases of malarial nephropathy after treatment with ARSs (Ezzedine et al., 2007; Calitri et al., 2014; Gleeson et al., 2019).

**INTERACTION, SAFETY, AND SIDE EFFECTS**
The toxicity of ARSs in cell culture, animals (mice, rats, rabbits, dogs, monkeys), and human clinical trials were well described (Efferth and Kaina, 2010). Large clinical studies and meta-
analyses did not show serious side effects, despite mild and self-limited effects including mild nausea, vomiting, and diarrhea (Mssusa et al., 2016). Individual patients may appear transient transaminase elevated and mild rash. Non-hematological side effects include mild hepatitis, neurological, renal, cutaneous, and cardiac manifestations were uncommon (Roussel et al., 2017). Rare severe adverse events include prolongation of the QTc interval and cardiac arrhythmias (in LiverTox, 2012).

In addition, animal studies showed that artesunate can reduce glomerular filtration rate, increase renal blood flow, and has certain organ toxicity (Campos et al., 2001; Otuechere et al., 2012), while in a clinical study, liver function, kidney function, and routine blood tests remained normal in most patients treated with artesunate (von Hagens et al., 2017). A systematic review and routine blood tests remained normal in most patients treated in the 2nd or 3rd trimester was relatively safe (Kovacs et al., 2012), while in a clinical study, liver function, kidney function, and routine blood tests remained normal in most patients treated with artesunate (von Hagens et al., 2017). A systematic review and routine blood tests remained normal in most patients treated in the 2nd or 3rd trimester was relatively safe (Kovacs et al., 2016). The drug interactions of ARSs are relatively unknown, more rigorous and comprehensive studies of interaction mechanisms are needed, as well as monitoring the safety of ARSs, especially concerning the genotoxicity and embryotoxicity (Amorim et al., 2013).

**CONCLUSION AND FUTURE DIRECTIONS**

Much knowledge has been gained about the antimalarial drugs in recent years, and more attention has been paid to ARSs application for renal damages. Many years of laboratory applications and research proved that ARSs have excellent anti-inflammatory and immunoregulatory functions. It is also a good regulator of the balance between oxidation and oxidation resistance. The regulation of the glomerular barrier highlights a unique aspect of the use of ARSs in kidney disease.

Despite accumulating evidence on the use of ARSs, the literature on its potential as a treatment for renal disease is still insufficient due to the lack of randomized controlled clinical trials. The additive effects of ARSs in combined administration with immunosuppressants and the structure-activity relationship need to be further clarified. Investigation of the improved properties of ARSs analogs also facilitates the discovery of novel drug targets for kidney disease (Santos et al., 2015; Zuma et al., 2016; de Lange et al., 2018).

**AUTHOR CONTRIBUTIONS**

MX provided direction, collected related literature, and drafted the manuscript. DL and YL made significant revisions to the manuscript and directed the review to be more focused. HL gave the final approval for the article to be published. All authors have read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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