Review Article

The Potential Therapeutic Effects of Artesunate on Stroke and Other Central Nervous System Diseases

Shilun Zuo,[1] Qiang Li,[1,2] Xin Liu,[1] Hua Feng,[1] and Yujie Chen[1]

[1]*Department of Neurosurgery, Southwest Hospital, Third Military Medical University, Chongqing, China*
[2]*Department of Neurobiology, College of Basic Medical Sciences, Third Military Medical University, Chongqing, China*

Correspondence should be addressed to Hua Feng; fenghua8888@vip.163.com and Yujie Chen; yujiechen6886@foxmail.com

Artesunate is an important agent for cerebral malaria and all kinds of other severe malaria because it is highly efficient, lowly toxic, and well-tolerated. Loads of research pointed out that it had widespread pharmacological activities such as antiparasites, antitumor, anti-inflammation, antimicrobes activities. As we know, the occurrence and development of neurological disorders usually refer to intricate pathophysiologic mechanisms and multiple etiopathogenesis. Recent progress has also demonstrated that drugs with single mechanism and serious side-effects are not likely the candidates for treatment of the neurological disorders. Therefore, the pluripotent action of artesunate may result in it playing an important role in the prevention and treatment of these neurological disorders. This review provides an overview of primary pharmacological mechanism of artesunate and its potential therapeutic effects on neurological disorders. Meanwhile, we also briefly summarize the primary mechanisms of artemisinin and its derivatives. We hope that, with the evidence presented in this review, the effect of artesunate in prevention and curing for neurological disorders can be further explored and studied in the foreseeable future.

1. Introduction

Malaria has been a life-threatening disease for thousands of years in human history. With a variety of pharmacological activities, artemisinin has been widely considered as an essential antimalaria drug derived from a Chinese herb Qinghao. By the development of treating malaria, artemisinin overcame its alternatives by high efficiency and few side-effects [1]. Millions of patients who suffered from malaria were saved by artemisinin-based combination therapies (ACTs) every year [2]. In recognition of this great achievement, Youyou Tu won 2015 Nobel Prize in Physiology or Medicine, as one of the three contributing scientists to discovering artemisinin. Moreover, research has found that artemisinin not only possessed the antiparasite effect, but it also could have antitumor, anti-inflammation, and antimicrobes, and so forth effects. This therefore leads us to draw a conclusion that artemisinin is a pluripotent agent. Thus, to exploit its advantages, a large number of artemisinin derivatives have been synthesized according to different purposes. As one of

the syntheses, artesunate was proved to be great promotion in the treatment of clinical disease.

Artesunate, the water-soluble semisynthetic derivative of artemisinin, has been a standard treatment for cerebral malaria and all kinds of other severe malaria [3]. The antimalarial effect of artesunate is commonly recognized as highly efficient, generally safe, and well-tolerated. In addition, numerous studies also pointed out that artesunate had widespread pharmacological activities, such as antiparasite, antitumor, antimicrobial, anti-inflammatory, antioxidant, impeding angiogenesis, protecting the BBB, and immunoregulatory effect. And, more importantly, artesunate could be maintained as a higher concentration in brain [4], so that artesunate could be beneficial for treating diseases with rather intricate pathophysiologic mechanisms and multiple etiopathogenesis, such as neurological disorders.

As is known, the nervous system is one of the most complex and crucial systems in human body, resulting in considerable complicated neurological disorders. There are intricate pathophysiologic mechanisms and multiple etiopathogenesis

involved in the occurrence and development of these disorders, whose clinic treatments are less effective by drugs with single mechanism and serious side-effects. In that case, importance should be attached to the pluripotent action of artesunate in study of the prevention and treatment of neurological disorders.

In this review, we initially depict the primary mechanisms of artemisinin and its derivatives in brief, followed by a thorough elaboration of the primary mechanisms of artesunate and its potential therapeutic effects on neurological disorders. Thereafter, we comment on past and current relevant basic studies and clinical trials. Moreover, we discuss possible research areas for further studying in future.

2. Main Effects of Artemisinin and Its Derivatives

2.1. Main Effects of Artemisinin. Since it was discovered back in 1972, researchers worldwide have carried out a large number of extensive and in-depth researches on artemisinin. The main efficacy of artemisinin they found was antiparasites, antitumor, anti-inflammation, antimicrobes, and so forth efficacy. In terms of antiparasites, artemisinin not only has a good effect on killing *Plasmodium falciparum* but also has promising antibabesial, antieimerial, antileishmanial, anticoccidian, antischistosomal, antitoxoplasmal, antitrypanosomal, and so forth activity. We are very surprised that artemisinin has such a wide range of antiparasites effects but even more amazed at its antitumor action. As early as the 1990s, artemisinin was found to have anticancer activity [5, 6]. A large number of studies have pointed out that artemisinin played the antitumor role in nervous system, respiratory system, digestive system, urinary system, reproductive system, blood system, and so forth. On the other hand, in the face of such powerful antitumor effect, we should note that these studies are mostly carried out in vitro and thus need to be confirmed in vivo. Another aspect that we need to be concerned about is the anti-inflammation action of artemisinin. Lu first reported *Cordyceps* and artemisinin could be used to prevent the recurrence of lupus nephritis and protect kidney function in 2002 [7]. Nonetheless, it has not attracted the attention of researchers until recent studies showed that artemisinin was very effective on autoimmune and allergic diseases. But we should also be aware that the anti-inflammatory effect of artemisinin still requires further confirmation due to the fact that studies are quite insufficient currently. Antimicrobial effect is another vital action of artemisinin. Some studies demonstrated that artemisinin worked well on eliminating some kinds of viruses, bacteria, and fungi. But these studies were also mostly conducted in vitro and need to be affirmed in vivo. There are other functions of artemisinin, containing the induction of neurite outgrowth, inhibiting vascular smooth muscle cells proliferation, and inducing apoptosis. Studies on these functions are mostly fragmented and need to be further verified. In general, the clinical application of artemisinin could be extensively broad, so that this domain is worth exploring.

2.2. Main Effects of Artemisinin Derivatives. As research develops, the deficiencies of artemisinin were gradually revealed. In order to overcome its shortcomings or to enhance some of its effect, a good many artemisinin derivatives have been synthesized according to different purposes, as in the case of dihydroartemisinin (DHA), artesunate, artemether, arteether, artelinic acid, artemiside, artemisone, artemisinic acid, artemisitene, artefenomel, arterolane, arteanuin B, SM735, SM905, SM933, SM934, SM1044, and so forth. Most of them have equivalent or even better antimalaria effect as artemisinin, such as DHA, artesunate, artelinic acid, artemether, arteether, arterolane, and so forth. Among them, artesunate and artelinic acid are water-soluble; SM735, SM905, SM933, and SM934 have shown strong immune regulatory functions. At present, DHA, artesunate, artemether, and arteether are used more widely in clinical practice. Their action is summarized accordingly in Table 1.

3. Main Function and Advantage of Artesunate

3.1. Advantage of Artesunate. As is known to us, artemisinin is not soluble in water; thereby it cannot be used for intramuscular or intravenous injection, which seriously restrains its effect in severe malaria. To overcome this shortcoming, artelinic acid and artesunate have been synthesized. Research reported that both of them could effectively kill *Plasmodium falciparum*, while, comparing with artesunate, artelinic acid had more embryotoxicity, neurotoxicity, nephrotoxicity, reticulocytopenia, vascular irritation, and anemia, and so forth. Artesunate was also defective owing to its ability of exterminating ring-stage parasites too rapidly which would result in delayed haemolysis [3]. Delayed haemolysis was frequent in patients (about 20%) with severe malaria treated with intravenous artesunate [8, 9]. Fortunately, the resulting anemia remained mild in 85% of cases [8]. And World Health Organization (WHO) guideline for treating malaria also indicated that, in individual parenteral artesunate doses between 1.75 and 4 mg/kg, no toxicity has been observed [3]. Besides, the price is cheap relatively. Consequently, artesunate was deemed to be the most striking in all the artemisinin derivatives and also the only clinical application of water-soluble derivatives of artemisinin. WHO has strongly recommended intramuscular or intravenous artesunate as the first-line treatment for cerebral malaria and all kinds of other severe malaria [3].

Another noteworthy advantage is that artesunate could be maintained as a higher concentration in brain. It is suggested even if the drug levels of artesunate dropped significantly in all tissues at 1 h, the proportion in brain, fat, intestine, and serum is still high and with very slight neurotoxicity [4]. This implied that artesunate might have superb advantages in the treatment of nervous system diseases.

3.2. Main Function of Artesunate. Artesunate is prepared from DHA by reacting it with succinic acid anhydride in basic medium. The same as artemisinin, it has four main functions: antiparasites, antitumor, anti-inflammation, antimicrobes functions. Of these four, antiparasitic function plays the most classic and important role for artesunate,

TABLE 1: The main effects of artemisinin derivatives.

Name	Main functions		Mechanism	Adverse events
Arteether	Antiparasites	Plasmodium	Inducing iron-dependent free radicals' generation	Anorexia Cardiovascular symptom Embryotoxicity Immunosuppressive activity neurotoxicity
		Schistosoma	Reducing glycogen content and alkaline phosphatase activity	
		Toxoplasma gondii	Unknown	
	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	
	Antifungi	Cryptococcus neoformans	Unknown	
Artelinic acid	Antiparasites	Plasmodium	Unknown	Anemia Embryotoxicity Neurotoxicity Nephrotoxicity Reticulocytopenia Vascular irritation
Artemether	Antiparasites	Plasmodium	Increasing production of reactive oxygen intermediates and reactive nitrogen intermediates	Anemia Clastogenic potential Distal tubular ectasia Emesis Endocrine disruption Fetal growth retardation Flattened epithelium in the kidney Haemolytic anemia Hemolysis Hepatocellular hypertrophy Hepatotoxicity High liver weight Immunosuppressive activity Increases in hemoglobin levels Meningeal inflammation Neurotoxicity Prolonged QT interval Reduction in fetal body weight Reduced oxytocin-induced contraction of uterine tissues Slight damage to the proprius layer lamina of intestinal villi Suppression of humoral responses Transient focal vesicle degeneration of the liver
		Acanthamoeba castellanii	Be used as a hosphoglycerate dehydrogenase inhibitor	
		Schistosoma	(1) Affecting both carbohydrate and protein metabolism of schistosomes; (2) By inhibition of GST and SOD enzymes, leading to increased schistosome susceptibility to oxidant attacks	
		Toxoplasma gondii	By affecting the glucose-6-phosphatase of T. gondii, resulting in the energy metabolism of the parasite	
		Pituitary macroadenoma	Unknown	
	Anticancer	Glioma	Inhibiting the migration, invasiveness, expression of MMP-2/MMP-9 and p-Akt significantly while also promoting the apoptosis of tumor cells	
	Anti-inflammation	Neuroinflammation	Inducing Nrf2 expression which results in the anti-inflammatory effect	
	Antivirus	Cytomegalovirus	Unknown	

TABLE 1: Continued.

Name	Main functions		Mechanism	Adverse events
Artemisinin	Antiparasites	Plasmodium	Generating highly reactive carbon-centered radicals via endoperoxide cleavage	Anemia
		Schistosoma	Unknown	Anorexia
		Toxoplasma gondii	(1) Inhibiting the intracellular growth of T. gondii in vitro by imposing oxidative stress within the cells (2) Perturbing calcium homeostasis in T. gondii	Cholestatic liver injury
		Trypanosoma	Inhibiting calcium-dependent ATPase activity in T. cruzi membranes	Genital system injury
	Anticancer	Brain tumor	(1) Bringing about reactive oxygen species-mediated action (2) Inducing iron-dependent cell death	Hepatitis
	Anti-inflammation	Alzheimer's disease	Suppressing NF-κB activity and NALP3 inflammasome activation	Immunosuppressive activity
	Antifungi	C. neoformans	Unknown	Neurotoxicity
		C. albicans	Unknown	Ptyalism
	Antivirus	Cytomegalovirus	Modulating cell cycle through CDKs and pRb	
		Herpes virus	Unknown	
	Schizophrenia		Reducing levels of antibodies to gliadin	
	Others	Neurite outgrowth	Activating ERK and p38 MAPK signaling pathways	
		Vascular	(1) Inhibiting VSMC migration through down-regulation of ERK1/2 and MMP9 phosphorylation (2) Inhibiting the inflammation of VSMCs induced by TNF-α through ROS-mediated NF-κB signal pathway	

TABLE 1: Continued.

Name	Main functions		Mechanism	Adverse events
Artesunate	Antiparasites	Plasmodium	(1) Inhibiting the activity of the cytochrome oxidase (2) Increasing oxidant stress on the infected red cells	Anaphylaxis Anemia Cardiovascular system Contragestational action Haemolysis Immunosuppressive activity Neurotoxicity
		Echinococcus	Unknown	
		Heterophyid	Unknown	
		Schistosoma	Reducing expression of schistosome thioredoxin glutathione reductase and cytochrome c peroxidase	
		Toxoplasma gondii	Distorting in tachyzoites' shape, peeling, erosions and discontinuity in areas of surface membrane	
		Trypanosoma	Unknown	
	Anticancer	Glioma	Inducing oxidative DNA lesions and DNA double-strand breaks	
		Neuroblastoma	Inducing apoptosis and reactive oxygen species in neuroblastoma cells	
		Schwannoma	Inducing cell death dependent on necroptosis	
		Neurofibromatosis	Binding to and degrading translationally controlled tumor protein	
		Growth hormone adenoma	Inhibiting proliferation and inducing apoptosis by caspase-dependent pathways	
	Anti-inflammation	Neuroinflammatory	Influencing NF-kB, p38 MAPK and Nrf2/ARE-dependent signal pathway	
	Antivirus	Cytomegalovirus	Interfering with the NF-κB pathway by targeting RelA/p65	
		Ebola virus	Unknown	
		Epstein-Barr virus	Blocking viral immediate early protein synthesis	
		Herpes virus	Unknown	
		Polyomavirus	Leading to cytostatic effects on the host cell	
	Others	Subarachnoid hemorrhage	Protecting BBB via S1P1/PI3K pathway after subarachnoid hemorrhage	
		Vascular	(1) Inhibiting VSMCs proliferation by disturbing DNA replication, inducing cell apoptosis and blocking cell cycle in G0/G1 phase (2) Inducing apoptosis of endothelial cells via an iron/ROS-dependent p38 MAPK-mitochondrial pathway (3) Inhibiting NF-κB nuclear translocation and the subsequent expression of ICAM-1	

TABLE 1: Continued.

Name	Main functions		Mechanism	Adverse events
	Antiparasites	Plasmodium	(1) Generating highly reactive carbon-centered radicals via endoperoxide cleavage (2) Causing the pigment of P. berghei to clump	Contragestational effects Embryotoxicity Erythroid cell differentiation Hemolysis Immunosuppressive activity Neurotoxicity Suppression of humoral responses
		Naegleria fowleri	Unknown	
		Schistosoma	Causing damage to the genital system of worms	
		Toxoplasma gondii	Unknown	
Dihydroartemisinin	Anticancer	Neuroblastoma	Damaging mitochondrial cristae and endoplasmic reticulum	
		Glioma	(1) Inhibiting the Raf/ERK/MEK, ADAM17, PI3K/AKT pathways and activating caspase-3 (2) Increasing the reactive oxygen species and inhibiting hypoxia inducible factor-1α activation	
	Others	Neurite outgrowth	Activating ERK and p38 MAPK signaling pathways	
		Vascular	(1) Inhibiting VEGF-induced EC migration via a p38 MAPK-independent pathway (2) Repressing the NF-κB pathway	
Artemiside	Antiparasites	Plasmodium	Unknown	Unknown
		Toxoplasma gondii	Unknown	
Artemisitene	Antiparasites	Plasmodium	Unknown	Unknown
		Trypanosoma	Unknown	
	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	
Artemisone	Antiparasites	Plasmodium	Resulting in antimalarial activities by the Fe2+-mediated decomposition, PfATP6 binding	Embryotoxicity Cardiac ventricular septal defects Vascular variation
		Toxoplasma gondii	Unknown	
Artefenomel (OZ439)	Antiparasites	Plasmodium	Activating hemoglobin degradation	Unknown
Arterolane (OZ277)	Antiparasites	Plasmodium	Activating hemoglobin degradation	Embryotoxicity
		Schistosoma	Unknown	

TABLE 1: Continued.

Name	Main functions		Mechanism	Adverse events
Arteanuin B	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	Unknown
	Others	Vascular	Inhibiting immune mediators of angiogenesis	Unknown
SM735	Anti-inflammation	Immunosuppressive activity	Inhibiting the proliferation of splenocytes, proinflammatory cytokine production, T cell-mediated delayed-type hypersensitivity (DTH) and B-cell-mediated QHS reactions	Unknown
SM905	Anti-inflammation	Immunosuppressive activity	Inhibiting T cell activation, NO and proinflammatory cytokine production by suppressing and Ras activation, MAPK and NF-kappaB pathways	Unknown
SM933	Anti-inflammation	Autoimmune encephalomyelitis	Involving the NF-kB and the Rig-G/JAB1 signaling pathways	Unknown
SM934	Anti-inflammation	Autoimmune encephalomyelitis Immunosuppressive activity	Inducing Treg differentiation and expansion Inhibiting T cell activation	Unknown
Artemisinin dimer 1	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	Unknown
Artemisinin dimer 2	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	Unknown
Artemisinin dimer hemisuccinate	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	Unknown
Artesunate derivative	Anticancer	Tumor of the central nervous system	Inducing iron-dependent cell death	Unknown
CPM-1	Antiparasites	*Plasmodium*	Unknown	Unknown
11-Azaartemisinins	Antiparasites	*Plasmodium*	Unknown	Unknown
10-Aminoethylether derivatives of artemisinin	Antiparasites	*Plasmodium*	Unknown	Unknown
Artefanilide	Antivirus	*Cytomegalovirus*	Unknown	Unknown

due to the effect of killing *Plasmodium falciparum*. Malaria remains an important cause of illness and death in children and adults in countries in which it is endemic. And its control requires an integrated approach, including prevention and prompt treatment with effective antimalarial agents. The third edition of guidelines for the treatment of malaria especially emphasized that treating adults and children with severe malaria (including infants, pregnant women in all trimesters, and lactating women) with intravenous or intramuscular artesunate was a recommended treatment, which fully illustrated its importance on antimalaria. The antimalarial mechanism of artesunate works primarily by means of completely inhibiting the activity of the cytochrome oxidase in the *Plasmodium* and promoting the generation of active oxygen species in erythrocytes [10, 11]. Likewise, schistosomiasis is considered by WHO as the second most socioeconomically devastating parasitic disease (after malaria). More than 61.6 million people have been reported for being treated for schistosomiasis in 2014 (721, 722). Massive studies both in vivo and in vitro confirmed that artesunate is credibly effective on *S. japonicum* and *S. mansoni*. These findings allow us to have a new choice in the treatment of schistosomiasis. Artesunate is also effective on other parasites, like *Fasciola hepatica, Clonorchis sinensis, Babesia, Leishmaniasis* and *Toxoplasma gondii*, and so forth (Table 1), which fully illustrated that artesunate had broad antiparasitic effects.

Cancer is one of the leading causes of death in the world. Research indicated that artesunate could inhibit or even kill as many as 32 kinds of tumor cells, for instance, glioblastoma, esophageal cancer, breast cancer, lung cancer, hepatocellular carcinoma, prostate cancer, ovarian cancer, leukemia and myeloma (Table 1). As for why artesunate has such wide and highly effective antitumor capabilities, recent studies suggested artesunate could induce ROS response in tumor cells, specifically the oxidative DNA lesions and double-strand breaks [12, 13]; and it could increase the apoptosis of tumor cells by downregulation of the expression of PCNA and Bcl-2 genes and upregulation of the expression of Bax gene as well [14]; what is more, it also could enhance the radiosensitivity by reducing the expression of the inhibitor of apoptosis protein surviving [15] and so forth. In addition, recent research has shown that artesunate could induce ferroptosis in tumor cells by increasing the expression of iron-related genes [16]. This finding represented an attractive strategy for cancer therapy in the future. In spite of how exciting these findings are, we should note that these achievements, mainly derived from in vitro experiments, need to be confirmed further in vivo.

Anti-inflammation is the third main effect of artesunate. Evidence showed that it had a good effect on autoimmune and allergic diseases, such as allergic asthma, arthritis, dermatitis, hepatic fibrosis, pulmonary fibrosis, and myasthenia gravis (Table 1). Current thinking suggested that the anti-inflammatory mechanism of artesunate was mainly to inhibit the production of autoantibodies, proinflammatory cytokines and inflammatory cytokines, and so forth. Nevertheless, despite the successful application in many inflammatory disease models, study on anti-inflammatory efficacy of artesunate is quite limited and further research is still required.

The last but not least major role of artesunate is antimicrobes role. At present, the drug resistance of microorganisms is becoming more and more severe. To solve this problem, we need to find synergistic effect between antibiotics and nonantibiotic drugs. In that case, we are delighted with the capability of artesunate of providing synergistic effects with some antibiotics. Research reported artesunate could enhance the anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activity of oxacillin [17]. Additionally, it also could kill *Saccharomyces cerevisiae* [18] and inhibit the replication of some kind of virus, such as *Cytomegalovirus*, Ebola virus, Epstein-Barr virus, polyomavirus, hepatitis B virus, and herpes virus (Table 1). And the effect of inhibiting the replication of *Cytomegalovirus* has been confirmed in clinical trials. As for other kinds of virus, this needs to be further studied.

Artesunate also has effect on other diseases, such as cardiovascular disease, hyperlipidemia, diabetes, lung injury, and hypertrophic scar (Table 1). These studies, however, are not sufficient and need to be further confirmed. To sum up, artesunate has widespread pharmacological activities, requiring further exploration and study.

4. Effect of Artesunate on Central Nervous System Diseases

4.1. Central Nervous System Infections. For years, a number of efficient antibiotics have been widely used in clinical practice, until the issue of drug resistance arises. Consequently, the antimicrobes function of artesunate got back to our sight. Antimicrobes role is one of the primary roles of artesunate; many pathogens that cause the infection of the CNS are in the range of its actions. For instance, *Staphylococcus aureus* is the pathogen of epidural abscess, subdural abscess, purulent meningitis, brain abscess and intraspinal abscess, and so forth. Research reported artesunate could enhance the anti-MRSA activity of oxacillin [17]; when combined with ampicillin sodium-sulbactam sodium, it could further increase survival rate of mice challenged with *S. aureus* [19]. Virus is another important cause of infection in CNS. *Cytomegalovirus*, herpes simplex virus, and Epstein-Barr (EB) virus can lead to the occurrence of viral encephalitis. And the human JC polyomavirus is a leading cause of the fatal demyelinating disease progressive multifocal leukoencephalopathy (PML). Studies have shown that artesunate could obviously inhibit the replication of the *Cytomegalovirus*, herpes simplex virus, polyoma virus, and EB virus in vitro (Table 1). Furthermore, animal experiments confirmed that artesunate combined with valacyclovir had a good effect on mice with herpes simplex virus encephalitis [20]. Fungal infections of the CNS are rare, and the main pathogenic fungi were *Candida*, *Cryptococcus*, *Mucor,* and *Actinomycetes*. There are few studies on fungicidal efficacy of artesunate, conveying artesunate has distinctly killing effect on *Saccharomyces cerevisiae*, while artemisinin has a good killing effect on *Aspergillus fumigatus*, *C. neoformans,* and *C. albicans* in vitro (Table 1). Whether artesunate has a similar effect needs further study to be confirmed.

The CNS parasitic disease, caused by parasites invading the CNS, is part of systemic parasitic disease. The main pathogens of the CNS parasitic diseases are cysticercus cellulosae, *Paragonimus westermani, Schistosoma, Echinococcus* and *Toxoplasma gondii*, and so forth. As the disease is part of systemic parasitosis, the researches for the CNS parasitic infection are few. Research indicated that artesunate had evident inhibitory effect on *Toxoplasma gondii* in vitro and in vivo [21]. Moreover, artesunate-DHA combination could substantially reduce the size of the cerebral cysts of *Toxoplasma gondii* in mice after only 5 days of treatment [22]. In 1983, Le et al. first reported that artesunate was demonstrated to exert antischistosomal effect in experimental animals infected with *Schistosoma japonicum* and had no severe side-effects [23]. Subsequently, the antischistosomiasis effect of artesunate was further confirmed in different animal models, such as mice, rabbits, dogs, and even human. Present study suggests that the antischistosomiasis effect of combining artesunate-praziquantel is superior to each of them alone [24]. Unfortunately, there is no research report on nervous system of schistosomiasis. Echinococcosis, also called hydatid disease, is a parasitic disease of tapeworms of the *Echinococcus* type. The disease is widely distributed around the world and causes great loss of life and property every year. Cerebral echinococcosis and intraspinal hydatid disease are rare but seriously affect the human health. One piece of research pointed out that artesunate could effectively kill *Echinococcus multilocularis* and *Echinococcus granulosus* in vitro but had no effect in vivo [25]. Cysticercus cellulosae and *Paragonimus westermani* are important pathogens in the CNS parasitic diseases; however, no study mentioned the effects of artemisinin and its derivatives on both of them.

In short, the effects of artesunate for treatment of the CNS infections and parasites are affirmative and worthy of being studied deeply.

4.2. Vascular Diseases of the Brain and Spinal Cord. Vascular diseases of brain and spinal cord mainly include subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), ischemic cerebrovascular disease (ICD), intracranial aneurysm, intracranial vascular malformation, carotid-cavernous fistula, moyamoya disease, and spinal vascular malformation. Establishment of animal models of SAH, ICH, and ischemic cerebrovascular disease is much easier than other diseases; therefore, numerous studies have mostly concentrated on these three diseases at present.

4.2.1. Subarachnoid Hemorrhage. SAH is a devastating cerebrovascular disease with complex mechanisms, closely linked with high morbidity and fatality rate at relatively young age and leading to a great loss of the economy and society. Artesunate has wide impact on animal body system, one of which is protecting BBB after SAH. Our study demonstrated that artesunate could preserve blood-brain barrier (BBB) integrity and improve neurological outcome after SAH, possibly through activating $S1P_1$, enhancing PI3K activation, stabilizing β-catenin via GSK-3β inhibition, and then effectively raising the expression of Claudin 3 and Claudin 5 [26].

In addition, artesunate could attenuate the generation of pro-inflammatory mediators in BV2 microglial cells by influencing NF-kappaB, p38 MAPK, and Nrf2/ARE-dependent signal pathway [27, 28]. As is well known, microglial cells play an important role in the pathogenesis of SAH. Inhibition of microglia activation could alleviate the early brain injury (EBI) after SAH. Furthermore, recent research demonstrated that intraparenchymal activation of accumulated resident microglia, between days 4 and 28 after SAH, was accountable for neuronal cell death [29]. Therefore, artesunate probably has a protective effect on secondary brain injury after SAH. Another noticeable therapeutic effect is that artesunate could inhibit vascular smooth muscle cells (VSMC) proliferation by disturbing DNA replication, blocking cell cycle in G0/G1 phase, and inducing cell apoptosis [30]. Early studies had shown that VSMC proliferation and subsequent vessel wall thickening contributed to the syndrome of delayed cerebral vasospasm after SAH [31]. Thus, we have reason to believe that artesunate could prevent damage from delayed brain injury (DBI). Mounting evidence indicates that the leukocyte exerts a crucial effect in the pathophysiology of SAH. Elevated leukocyte count has been reported to increase the risk of experiencing symptoms of vasospasm, and it was closely associated with a 90% rate of poor outcomes [32]. Leukocytes adherence and accumulation in brain vessel, an important feature of the late-stage of cerebral malaria, could be rapidly decreased by artesunate [33]. Such studies said that artesunate could not only regulate the function of leukocyte but also destroy it [34–36]. So, the effect of artesunate on leukocytes after SAH is worthy of further study. Adhesion molecule, an important mediator of inflammation after stroke, mediates endothelial capture, adhesion, extravasation of leukocytes, and recruitment to the site of injury [32]. Intercellular adhesion molecule-1 (ICAM-1), an important adhesion molecule, could help leukocytes binding to endothelial cells and then transmigrating into brain tissue [37]. During the early and late period after SAH, the level of ICAM-1 was significantly elevated in the serum of patients [38]. Monoclonal antibodies against ICAM-1 could attenuate cerebral vasospasm by 22% after SAH in rabbits [39]. As anti-ICAM-1 antibody, artesunate could inhibit the expression of ICAM-1 in order to resist the *P. berghei*-induced inflammatory response [40]. It implied that artesunate probably also had the effect of inhibiting the expression of ICAM-1 after SAH. Aside from neurological injuries, SAH has been associated with nonneurologic medical complications, and pulmonary complications are one of them. Pulmonary complications are the most frequent extracerebral cause of death after SAH [41, 42], which include pneumonia, aspiration, and neurogenic pulmonary edema [43]. Pulmonary complications in SAH patients occurred under a few mechanisms, and one of them is SAH induced expression of the proinflammatory mediators in the lung [44]. We know that artesunate possesses anti-inflammatory and antioxidative properties. Relevant research indicated that artesunate, through controlling the expression of both proinflammatory mediators and prooxidants, could significantly prevent the lung injury of rodents induced by ovalbumin, cigarette smoke, and paraquat [45–47]. This

research implied that artesunate might have therapeutic potential for treating pulmonary complications after SAH.

Shortly, artesunate has significant therapeutic effects on animal model of SAH, and the studies on the mechanisms have achieved some progress, but there are still many problems that need to be deeply investigated.

4.2.2. Intracerebral Hemorrhage. ICH is a stroke subtype closely linked with high mortality (about 40.4% at 1 month), and even the surviving patients frequently have serious neurological damage [48]. More than primary brain injury, secondary injury after ICH needs drug treatment. Secondary injury could be caused by a cascade of events initiated by the primary injury, such as thrombin, inflammation, complement, hemoglobin, iron, cell-death pathways, endogenous defence mechanisms, and free radicals [49]. The effects of artesunate for treating the ICH have not been reported at present. However, numerous studies of artesunate have reminded us that it might play an important role in the secondary injury after ICH. For instance, inflammatory reaction was the basic factor causing the secondary injury after ICH, which was mainly concerned with activation of resident microglia, an influx of leucocytes into the brain, and production of inflammatory mediators, and so forth [49]. One of the main functions of artesunate is anti-inflammation. Mentioned in the preceding paragraphs, artesunate could attenuate the generation of proinflammatory mediators in BV2 microglial cells and prevent leukocytes from transmigrating into brain tissue through inhibiting the expression of ICAM-1 on endothelial cells. In addition, another important factor causing the secondary injury after ICH was that endogenous defence mechanisms were barely strong enough to resist the oxidative stress. Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that responds to oxidative stress, might be a key regulatory factor of endogenous defence mechanisms after ICH [50]. Studies found that artesunate was a potential activator of the Nrf2/ARE-dependent signal pathway, which could attenuate LPS-induced inflammatory responses in microglial BV2 cells [28]; and it significantly enhanced the expression of Nrf2 in lung tissues from ovalbumin-challenged mice and in TNF-alpha-stimulated human bronchial epithelial cells [46]. Autophagy is another contributing factor to the secondary injury after ICH. Research indicated that many substances could activate autophagy which caused secondary injury in the brain after ICH [51–53]. We are glad to see that the suppressed autophagy effect of artesunate has been confirmed in in vitro experiment [54]. In a word, there are reasons to believe that artesunate would exert effect in the secondary injury after ICH.

Confusingly, artesunate also could enhance the formation of reactive oxygen species and then induce DNA double-strand breaks in *P. falciparum* and killing cancer cells [55, 56]. About autophagy, other researches proposed that artesunate, through upregulating the expression of Beclin1 and stimulating the aggregation of LC3, induced autophagy in tumor cells and then exerted the antitumor effects [57]. Many contradictions about the effects of artesunate exist. Therefore, it needs further experimental studies to confirm the effect in the secondary injury after ICH.

4.2.3. Ischemic Cerebrovascular Disease. Ischemic cerebrovascular disease (ICD), the most common and frequent cerebrovascular disease, is one of the main causes of morbidity and mortality all over the world. So far, no research on the effects of artesunate for treatment of the ICD has been reported. We suspect that artesunate would exert effect in the ICD because it has a wide spectrum of pharmacological effects. For example, cerebral ischemic injury, an important clinical appearance of ICD, is a condition of complex pathology that includes several inflammatory events, such as aggregation of inflammatory cells, activation of immune cell responses, and upregulation of cytokines [58]. Artesunate, as mentioned earlier, could inhibit the aggregation of inflammatory cells and upregulation of cytokines. Toll-like receptors (TLRs), as an important mediator of cerebral ischemic injury, have played an important role in the initial activation of immune cell responses. Studies found that artesunate could significantly reduce the expressions of TLR4 and myeloid differentiation factor 88 (MyD88) in lipopolysaccharide-stimulated proinflammatory responses and experimental hepatic fibrosis, which serves as the underline mechanism for the anti-inflammation effect of artesunate [59–61]. So, artesunate probably has the effect of inhibiting the activation of immune cell responses in cerebral ischemic injury. In addition, ischemia/reperfusion injury is most likely to occur after intravenous thrombolysis which is the standard of care for patients with acute ischemic stroke. Previous studies found that antioxidation and scavenging free radicals could alleviate the ischemia/reperfusion injury in rats [62]. As noted above, artesunate has the effect of antioxidation and scavenging free radicals in microglial BV2 cells. Therefore, artesunate probably has the therapeutical effect of the cerebral ischemia/reperfusion injury after ICD. Hemorrhagic transformation (HT) is a frequent asymptomatic event after ICD, especially in the reperfusion after acute ischemic stroke [63]. Hamann and his colleagues suggested that compromised microvascular basal lamina integrity might be a potential precursor of HT [64]. The activation of proteolytic enzymes, especially matrix metalloproteinases 9 (MMP-9), was thought to further be contributed to dysfunction of the basal lamina [65]. Artesunate could antagonize the expression of MMP-9 in the haemozoin-induced human monocytic cells and the hepatic tissue of cirrhotic rats induced by bovine serum albumin [66, 67]. Accordingly, artesunate may prevent the occurrence of HT after acute ischemic stroke. Diabetes and ICD often arise simultaneously. Patients with diabetes have more than double the risk of ICD after correction for other risk factors, relative to individuals without diabetes [68]. Yu et al. newly found that artesunate could elicit a protective effect on pancreatic beta-cells exposed to IL-1β by stimulating SIRT1 expression, which resulted in the decrease of NF-kB activity, iNOS expression, and NO production [69]. Hence, ART might be an effective drug for diabetes after ICD. Intracranial atherosclerosis, one of the leading causes of ICD, is associated with an increased risk for recurrent ICD [70]. Hypercholesterolemia was an independent risk factor for intracranial atherosclerosis. One finding was that artesunate (25 mg/kg) could significantly decrease the plasma

cholesterol and triglyceride in rabbits [71]. This implied the preventative effect of artesunate to ICD.

In general, artesunate probably has effect on prevention and treatment of ICD. But the roles in some aspects that artesunate play require further confirmation. For instance, as mentioned above, 25 mg/kg artesunate on hypercholesterolemia was effective in rabbits [71]. Meanwhile some other researches on artesunate pointed out 50 mg/kg had no effect on the levels of cholesterol in rats [72]. Moreover, artesunate was not very efficient on inhibition of the expression of MMP-9. The study found that artesunate could only reduce the expression of MMP-9 in the haemozoin-induced human monocytic cells by 25%, while DHA could reduce that by 50% [67]. Thus, it is needed to validate the effect of artesunate on prevention and treatment of ICD with experimental data.

4.3. Nervous Tissue Tumors. The nervous tissue tumors can be categorized as primary or metastatic. The incidence and prevalence of primary nervous tissue tumors outweigh metastatic nervous tissue tumors by 1 : 4 [73].

4.3.1. Primary Nervous Tissue Tumors. The primary nervous tissue tumors include central nervous system tumors and peripheral nervous system tumors, most of whose underlying causes remain unclear. Currently, treatments for the nervous tissue tumors could be separated into three categories: blasting it with radiation, surgically removing a tumor, and using drugs to kill the cancerous cells. The toxicity and various side-effects of the drugs and the uncertain outcome of chemotherapy in brain tumors put this treatment further down the line of treatment options with surgery and radiation therapy preferred. But treating tumor with chemotherapeutic drugs is always the hot topic of research. In addition to high potential and low toxicity, artesunate could also pass through the blood-brain barrier and be maintained as higher concentration in the nervous system [4]. These characteristics of artesunate were paid attention to by oncology researchers and lots of researches were carried out. Glioblastoma is the most common and aggressive cancer that starts within the brain. Research suggested that artesunate could induce oxidative DNA lesions and sustain double-strand breaks and finally lead to human glioblastoma cells death [12]. Moreover, several studies have pointed out that a combination of artesunate and temozolomide or OSI-774 might result in increased cytotoxicity in glioblastoma cells [74–76]. What is more significant is that artesunate could selectively decline survivin that contributes to radiosensitization of glioblastoma cells by an increased induction of apoptosis, cell cycle arrest, and a hampered DNA damage response [15]. Neuroblastoma is a type of pediatric tumor of neural crest origin with heterogeneous phenotypes [77]. Currently, there is no adequate therapy for refractory neuroblastoma and the mechanisms underlying its chemoresistance are poorly understood. As early as 2010, Michaelis et al. pointed out that neuroblastoma represented an artesunate-sensitive cancer entity and that artesunate was also effective in chemoresistant neuroblastoma cells [78]. The growth hormone (GH) adenoma could secrete excessive GH which causes acromegaly. Not only could artesunate inhibit proliferation and induce

apoptosis in GH3 cells by caspase-dependent pathways, but it could also restrain GH synthesis and secretion [79]. In conclusion, artesunate has apparent therapeutic effects on some central nervous system tumors.

Schwannoma is a benign nerve sheath tumor composed of Schwann cells and the most common tumor of peripheral nerves. Study indicated that artesunate effectively induced cell death in RT4 schwannoma cells and human primary schwannoma cells by suppressing autophagy and promoting necroptosis [80]. Neurofibromatosis type 1 (NF1) is an autosomal dominant disease that predisposes individuals to develop benign neurofibromas and malignant peripheral nerve sheath tumors (MPNSTs). The research suggested that a positive feedback loop between TCTP and mTOR contributed to NF1-associated tumor formation [81]. Artesunate, which binds to and degrades TCTP, significantly suppressed the viability of MPNST cells but not normal Schwann cells [81]. Moreover, combinational usage of artesunate and rapamycin enhances the cytotoxic effect on MPNST cells [81]. This demonstrates that artesunate has remarkable therapeutic effect against peripheral nerve sheath tumor.

4.3.2. Metastatic Nervous Tissue Tumors. Lung and breast carcinoma make up the majority of metastatic tumors. There are a large number of studies on the role of artesunate in the treatment of lung cancer. For example, research demonstrated that artesunate could induce Bak-mediated caspase-independent intrinsic apoptosis in both ASTC-a-1 and A549 lung adenocarcinoma cell lines [82]. And artesunate combined with NP (a chemotherapy regimen of vinorelbine and cisplatin) could elevate the short-term survival rate and prolong the time to progression of patients with advanced non-small cell lung cancer without extra side-effects [83]. These findings suggested that artesunate had potent therapeutic effect for lung cancer. Notably, artesunate could also significantly impair matrigel invasion of A549 cells through inhibiting urokinase-type plasminogen activator (u-PA) activity and the expression of u-PA, ICAM-1, MMP-2, MMP-7 and MMP-9, and so forth [84, 85]. This reminds us that artesunate possibly could stop the brain metastases of lung cancer. Artesunate could also inhibit the proliferation and differentiation of breast carcinoma through activating programmed cell death in vivo and in vitro [55, 86, 87]. When used in combination with lenalidomide or camptothecin, artesunate could induce higher apoptosis rates in breast carcinoma cells [88, 89]. These researches imply that artesunate may have curative effect for the brain metastases of breast carcinoma.

To sum it up, artesunate has obvious curative effects for some primary and metastatic nervous tissue tumors with various mechanisms. However, we must note that the effect of artesunate against nervous tissue tumors mainly come from in vitro experiments, which needs to be certified further in vivo.

4.4. Neurological Autoimmune Diseases and Neurodegenerative Disorders. Autoimmune diseases stemming from an abnormal immune response of the body resist substances and tissues normally present in the body. Neurological

autoimmune diseases are part of the autoimmune diseases. Artesunate exhibited potent immunosuppressive activity in several autoimmune disease models. For example, the research indicated that artesunate could prevent arthritis development in young K/BxN mice by inhibiting germinal center formation and production of autoantibodies [90]. And, also, artesunate could inhibit the progression of disease and reverse the pathologic lesion of lupus nephritis in MRL/lpr mice through decreasing the level of MCP-1 and BAFF [91]. However, it is surprising that, during the treatment of neurological autoimmune diseases, artesunate has not been reported. Notably, a case indicated that a woman that suffered from mixed malaria infection, while recovering by artesunate and doxycycline therapy, ended up with developing acute disseminated encephalomyelitis (ADEM) [92]. Does this mean artesunate has no effect on ADEM and even neurological autoimmune diseases? This is the issue worth exploring and studying in the future.

Neurodegenerative disorders, mainly including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease, occur as a result of neurodegenerative processes. There has been no report about the therapeutic effect of artesunate on neurodegenerative disorders. However, study clearly demonstrated that artemisinin had protective effects on Alzheimer's disease pathology through suppressing NF-κB activity and NALP3 inflammasome activation in APPswe/PS1dE9 transgenic mice [93]. As the water-soluble derivatives of artemisinin, the protective effects of artesunate on Alzheimer's disease or even neurodegenerative disorders merit in-depth studies.

4.5. Epilepsy. Epilepsy is a common disease in nervous system. Epilepsy is also an important sign of severe malaria, particularly in children. For instance, study showed that epilepsy was present at 25.6% of 261 malaria patients from 3 tropical clinics in South Sudan [94]. Artesunate could effectively inhibit seizure caused by severe malaria. Research suggested that prevalence of seizure in African children with severe malaria after 6 hours of admission was 10.1% in the quinine group and 8.3% in the artesunate group ($p = 0.0199$) [95]. However, the cause of most patients of epilepsy was unclear, although some developed epilepsy as a result of traumatic brain injury, brain tumors, stroke, intracranial infections, birth defects, and so forth. Whether antiepileptic effect of artesunate is the optimal therapy for other origins of epilepsy requires further confirmation. Another issue that we need to be concerned about is that animal experiments could not completely simulate human epilepsy, such as the antiepileptic properties of quinine which only worked in animals, not in human [96]. So, a discreet selection of animal models is needed to confirm the antiepileptic effect of artesunate.

4.6. Traumatic Brain Injury and Spinal Cord Injury. Traumatic brain injury (TBI), which occurs when an external force traumatically injures the brain, is a leading cause of mortality and is a major public health issue in children and young adults. No research has investigated the treatment effect of artesunate on TBI so far. Various findings suggested indirectly that artesunate probably played a role in treatment of TBI. For example, one of the primary concerns was controlling raised intracranial pressure (ICP) after TBI, since high ICP could reduce the level of blood-oxygen in brain and cause deadly brain herniation [97]. As stated above, artesunate could preserve BBB integrity, reduce brain water content, and then improve neurological outcome after SAH. Thus, the role of artesunate played may contribute to the reduction of ICP after TBI. In addition, artesunate could also inhibit the expression of ICAM-1 on endothelial cells, attenuate the generation of proinflammatory mediators, and activate the Nrf2/ARE-dependent signal pathway in microglia. These studies reminded us that artesunate might play an important role in the secondary injury after TBI. To summarize, there is reason for optimism, but we must confirm the therapeutic effect of artesunate on TBI by experiment.

Spinal cord injury (SCI) is the damage to the spinal cord that causes partial or total loss of muscle function, sensation, and autonomic nerve function below the level of the lesion, either temporary or permanent. So far, we have found no report about artesunate on SCI. As described above, artesunate has a powerful anti-inflammatory and antioxidant effect, so we have reason to believe that it has a certain therapeutic effect on SCI.

5. Perspective and Conclusion

As is widely known, the occurrence and development of neurological disorders can be extremely complicated. A number of pathogenic mechanisms are involved in different pathological progress of neurological disorders. Several pathogenic mechanisms would interact with each other even at the same period of one neurological disorder, which is becoming a huge obstacle during treatment of diseases. Agents with more than one protective effect are attractive as potential therapeutic drugs of neurological disorders. Artesunate has a powerful protective effect, such as antineuroinflammatory, antiparasite, antitumor, antimicrobial, antioxidant, protecting the BBB, and immunoregulatory effect. Therefore, we have reasons to believe that it also has certain therapeutic effects on other neurological disorders. Moreover, artesunate not only could dissolve in water and be maintained as a high concentration in the CNS but also has fewer side-effects and can be fairly cheap. So if any therapeutic effect of artesunate on other neurological disorders can be discovered, it will be of benefit both socially and economically. In a word, artesunate is worthy of further study in neurological disorders.

A single medication only has limited therapeutic effects; therefore, combined medicine has more advantages for preventing or reversing occurrence and development of diseases. A large number of studies implied that when combined with other drugs, artesunate could enhance therapeutic effects on parasites, microbes, tumors, and so forth. Thus, we should actively explore the combined therapeutic effect of artesunate on neurological disorders.

Biochemical targets of artesunate are another subject that deserves greater attention. There is no consensus on biochemical targets of artesunate at present. Excitedly, recent research has shown that DHA could specifically target

PfPI3K [98]. However, whether the PfPI3K is also the biochemical target of artesunate remains unknown and requires further research. Elsewhere, the mechanisms of artesunate on some signal pathway need to be further elucidated. For instance, our evidences showed that artesunate could activate the PI3K/Akt pathway, but some research found the opposite [99, 100].

In conclusion, artesunate, as a pluripotent agent, needs to be further explored and studied on the effect of prevention and treatment of neurological disorders.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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