• Review Article •

# Therapeutic potential of artesunate in retinal diseases: from mechanism to clinical applications

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## Abstract

• Artesunate is a derivative of artemisinin, and due to its high solubility, and it has a broader application in clinical settings. Extensive research has confirmed that artemisinin-based drugs show significant activities in anti-inflammatory, anti-tumor, anti-viral, and anti-angiogenesis aspects, suggesting that artesunate might have potential in treating retinal diseases. Currently, the etiology of most retinal diseases is not fully understood, and there is a lack of effective treatment methods. This paper summarized the research progress of artesunate in the treatment of retinal diseases, including retinoblastoma, choroidal melanoma, diabetic retinopathy, central retinal vein occlusion, proliferative retinopathy, and ocular neovascularization. In addition, the potential applications and future research directions of artesunate in the treatment of retinal diseases were also discussed.

• **KEYWORDS:** artesunate; diabetic retinopathy; retinoblastoma; choroidal melanoma; proliferative vitreoretinopathy; retinal vein occlusion; ocular neovascularization
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## INTRODUCTION

In the 1950s, Chinese scientist Tu Youyou *et al*[1] discovered and extracted artemisinin, which rapidly gained global recognition for its effectiveness against malaria. In recent years, artemisinin-based drugs have attracted renewed attention due to their various pharmacological activities, including anti-inflammatory, anti-tumor, anti-viral, anti-parasitic, and anti-angiogenic properties. These pharmacological activities extend beyond the treatment of malaria[2-5]. Of course, there are many artemisinin-based drugs, and various derivatives of artemisinin have emerged with ongoing research, including dihydroartemisinin, artesunate, artemether, arteether, and artesunic acid. Compared to artemisinin itself, its derivatives are faster-acting, more efficient, better tolerated, and exhibit relatively slower development of parasite resistance[6], making them of greater clinical value.

It is worth noting that artemisinin is not soluble in water. However, artesunate, as one of the most important semi-synthetic derivatives of artemisinin, is significantly more soluble in water than artemisinin, dihydroartemisinin, and artemether. This characteristic is beneficial for the development of formulations and clinical applications of the drug[7]. The World Health Organization's (WHO) malaria treatment guidelines state that a single intravenous dose of artesunate within the range of 1.75–4 mg/kg has not been observed to cause toxicity. In addition, artesunate has the advantages of low cost and easy availability. Therefore, artesunate is considered the most promising of all artemisinin derivatives and is the only water-soluble derivative with clinical applications[4].

The ability of artesunate to maintain a high concentration in the brain, along with its lower neurotoxicity, suggests that this drug may have unique advantages in treating neurological diseases[8]. This finding provides a new perspective for the application of artesunate in the treatment of retinal diseases, indicating its potential for a broader range of therapeutic applications in clinical practice.

## APPLICATION OF ARTESUNATE IN RETINAL DISEASES

### Intraocular Tumors

**Choroidal melanoma** Choroidal melanoma is the most

common primary malignant intraocular tumor in adults, and currently, there are no effective targeted therapeutic drugs available. Angiogenesis and vasculogenic mimicry play a key role in the proliferation and metastasis of choroidal melanoma, ensuring the tumor receives sufficient blood supply[9-10]. Geng *et al*[11] found that artesunate might inhibit the angiogenesis and vasculogenic mimicry of choroidal melanoma through mechanisms associated with the inhibition of the Wnt/CaMKII signaling pathway. This further leads to the degradation of hypoxia inducible factor (HIF)-1α[12], thereby reducing the expression levels of vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor A (VEGFA), VE-cadherin, and Ephrin type-A receptor 2 (EphA2), successfully inhibiting tumor cell proliferation, invasion, and migration.

Studies have shown that in primary choroidal melanoma, the expression levels of Wnt5a and one of its downstream effectors, β-catenin, are increased and are somewhat correlated with patient survival rates[13-14]. Research shows that artesunate reduces the protein levels of β-catenin and its downstream targets (c-Myc, cyclin D1) by inhibiting the phosphorylation of GSK3β at S9[15], inhibits the tumor promoting effect of choroidal melanoma *via* downregulating EphrinA3[16], meantime, artesunate induces melanoma cell ferroptosis and augments antitumor immunity through targeting Ido1[17]. All of these demonstrate potential therapeutic effects on choroidal melanoma. The efficacy of artesunate in increasing the apoptosis rate of C918 cells is associated with the MALAT1/YAP signaling pathway, and combined use with verteporfin can enhance the above targeting effects[18].

In summary, artesunate may inhibit the angiogenesis and vasculogenic mimicry of choroidal melanoma by inhibiting the Wnt/CaMKII signaling pathway, thereby suppressing tumor cell proliferation. Additionally, artesunate shows targeted therapeutic effects by regulating the expression levels of Wnt5a and its downstream effector β-catenin, the MALAT1/YAP signaling pathway, *etc*. Current research focuses more on the mechanism of action of artesunate and experiments at the cellular level, with a lack of extensive clinical trial support. The specific mechanisms and effects of the combined use of artesunate with other drugs (such as verteporfin) require further study. Future clinical trials could validate the efficacy and safety of artesunate in actual treatment, explore the combined therapeutic effects of artesunate with other potential drugs, and further study the effectiveness of artesunate on different types and stages of choroidal melanoma, as well as its impact on disease progression.

**Retinoblastoma** Retinoblastoma is a common malignant ocular tumor in infants and young children. In recent years, significant progress has been made in the treatment of retinoblastoma, but eye enucleation still remains the most advanced treatment to date. It was revealed that artesunate alone showed antitumor effects on head and neck squamous cell carcinoma cell lines[19], while its toxicity to normal retinal cells is relatively low, also demonstrating the good safety profile of artesunate[20]. In addition, the combination of cisplatin and iron enhanced the antitumor effect of artesunate and cisplatin compared with that of each agent alone[19]. When used alone, artesunate acts on multiple molecular targets, regulates immune activity and cell metabolism, inhibits tumor cell proliferation, migration, and invasion, and induces tumor cell cycle arrest, autophagy, apoptosis, ferroptosis, and necrosis[21]. When used in combination with other chemotherapy drugs, it also has sensitizing and synergistic therapeutic effects[21]. Zhang *et al*[20] found in a small-scale clinical study that artesunate is a drug with good safety and certain therapeutic effects on retinoblastoma. However, its mechanism of action is not yet clear, and its clinical efficacy lacks large-scale research. Whether the multiple pharmacological activities of artesunate can provide new therapeutic targets, and whether there are differences in efficacy between its sole use and combination therapy, remain key areas of interest.

**Diabetic Retinopathy** Diabetic retinopathy (DR) is one of the most common complications of diabetes, a chronic, progressive microvascular disease of the retina, posing a potential threat to vision. In addition to microvascular changes, inflammation, oxidative stress, and retinal neurodegeneration can also lead to early diabetic retinal damage[22-23].

Currently, clinical treatment of DR primarily focuses on anti-retinal neovascularization, with methods including laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs, and steroids. Although anti-VEGF treatment as a first-line method has a significant effect against neovascularization, a considerable proportion of patients are not sensitive to such treatments[24]. Therefore, there is an urgent need to find other less harmful and long-lasting therapeutic drugs, and the in-depth study of the pathogenesis of DR provides more potential targets for action.

In DR, autophagy plays a key role in regulating oxidative stress and inflammation[25-26]. In related studies on DR rats, it was found that artesunate might alleviate the oxidative stress and pro-inflammatory factor release in rat retinal pigment epithelial (RPE) cells under high glucose conditions by inducing autophagy through the AMP-activated protein kinase/silent information regulator of transcription 1 (AMPK/SIRT1) pathway. This mechanism effectively reversed the inflammation and increased retinal thickness in DR rat retinal tissue[27-28]. Additionally, artesunate can inhibit the expression of matrix metalloproteinase-9 in DR, reduce the levels of

VEGF and angiopoietin (ANG) in the retinas of diabetic rats, thereby inhibiting neovascularization[29-30], thus demonstrating a therapeutic effect on DR. It also promotes the expression of anti-apoptotic factor Bcl-2 and cell protective factor Hsp27 in the retinas of diabetic rats, showing the potential to improve and protect retinal cell damage[31].

Through various pathways, artesunate can exert autophagy induction, anti-inflammatory, antioxidant, anti-neovascularization, anti-apoptosis, and cell protective effects, which hold significant potential in combating DR. However, current research is primarily based on animal models, and clinical application data are limited. The long-term efficacy and safety have not been fully verified in diabetic patients. Future clinical trials could be conducted to validate the efficacy and safety of artesunate in human diabetic patients. Additionally, exploring the combined treatment of artesunate with existing therapies (such as anti-VEGF treatment) could be a promising research direction.

**Retinal Vein Occlusion** Retinal vein occlusion (RVO) is a common retinal vascular disease, second only to DR, and its secondary macular edema (ME) is the main cause of impaired vision or even blindness in patients. The pathogenesis of RVO is related to various factors, including endothelial damage within blood vessels, changes in hemorheology and hemodynamics, as well as intraocular pressure and local ocular compression. It is also closely related to risk factors such as age, cardiovascular and cerebrovascular diseases, arteriosclerosis, hypertension, and diabetes. This suggests that prevention and treatment of RVO can be approached through these pathways. Current treatment methods mainly involve intravitreal injections of long-acting steroids or anti-VEGF drugs, but their resistance, benefits, and sustainability are limited[32].

Lu *et al*[33] established an experimental branch retinal vein occlusion (BRVO) model in rats using a photochemical method and evaluated the inhibitory effect of different concentrations of artesunate on rat BRVO through intravitreal injection. The results suggest that artesunate may alleviate retinal damage in BRVO rats by reducing the activity of the HIF-1α/VEGF signaling pathway[34]. Research on artesunate in the treatment of RVO is currently mainly based on animal experiments, and its effects and safety in humans need further study. Future research should focus on the mechanism of action of artesunate, develop cellular models (such as human retinal microvascular endothelial cells), explore its potential applications in humans, and assess its synergistic effects with existing treatment methods.

**Proliferative Vitreoretinopathy** Proliferative vitreoretinopathy (PVR) is the most common cause of failure in the repair of rhegmatogenous retinal detachment, primarily due to the formation of extensive fibroproliferative membranes in the vitreous on the retinal surface, causing tractional retinal detachment. Although the mechanism of PVR development is not yet fully understood, it has been established that epithelial-mesenchymal transitions (EMTs) of the retinal pigment epithelium (RPE) play a key role in the formation and contraction of PVR membranes[35-37].

In cell studies, Wang *et al*[38] treated adult retinal pigment epithel cell line-19 (ARPE-19) cells that underwent EMT with artesunate to simulate the role of artesunate in PVR. The results suggest that artesunate may inhibit the proliferation, contraction, and autocrine actions of ARPE-19 cells post-EMT through the Smad signaling pathway. The study also found that artesunate could inhibit the proliferation, migration, and EMT of ARPE-19 cells by reducing the expression of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway[39]. In animal experiments, Wu *et al*[40] found that artesunate could slow down the EMT process in a rabbit model of traumatic PVR, and Chen *et al*[41] further discovered that the combined use of luteolin and artesunate was more effective than artesunate alone, further proving artesunate's potential in preventing and treating traumatic prolifertive vitreoretinopathy.

Regarding the research on artesunate in PVR, current studies are mainly based on cellular models and animal experiments, lacking human clinical data. Artesunate has been found to potentially inhibit the EMT process by affecting the Smad and PI3K/Akt signaling pathways, slowing the progression of PVR. However, research on its long-term efficacy and safety remains insufficient. Future research needs to further validate the effects of artesunate on a clinical level and explore its potential for combined therapy with other drugs.

**Age-Related Macular Degeneration** Age-related macular degeneration (AMD) includes dry AMD (atrophic AMD) and wet AMD (neovascular AMD). Currently, intravitreal injections of anti-VEGF therapy for wet AMD are considered relatively safe and effective in clinical practice[42]. However, studies have shown that in the treatment of wet AMD with anti-VEGF, there is an expansion of macular atrophy areas, leading to long-term decline in visual function in patients. The anti-VEGF treatment for wet AMD eyes may itself be correlated to some extent with the degree of macular atrophy[43]. Therefore, finding safer and more effective treatment options is an important research direction. The pathogenesis of AMD involves retinal aging damage characterized by the accumulation of vitreous drusen, changes in Bruch's membrane and the extracellular matrix composition, vascular inflammation and dysregulation, mitochondrial dysfunction and accumulation of reactive oxygen species, and RPE aging[44]. Thus, treating AMD can also start from the perspective of preventing and treating retinal damage.

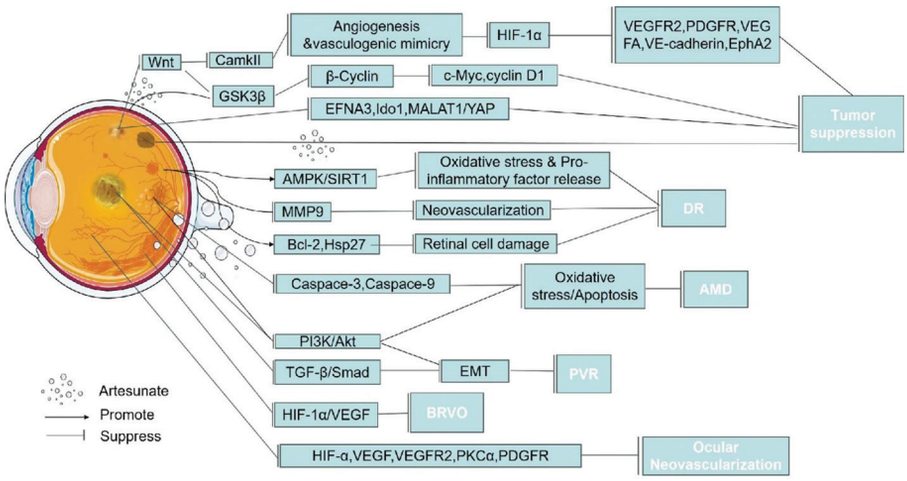


**Figure 1 Progress in the therapeutic use of artesunate in fundus diseases** DR: Diabetic retinopathy; AMD: Age-related macular degeneration; PVR: Proliferative vitreoretinopathy; BRVO: Branch retinal vein occlusion; EMT: Epithelial-mesenchymal transition; VEGF: Vascular endothelial growth factor; VEGFR2: Vascular endothelial growth factor receptor 2; PDGFR: Platelet-derived growth factor receptor; VEGFA: Vascular endothelial growth factor A; AMPK/SIRT1: AMP-activated protein kinase/silent information regulator of transcription 1; TGF-β: Transforming growth factor-β; VE-cadherin: Vascular endothelial-cadherin; EphA2: Ephrin type-A receptor 2; PI3K/Akt: Phosphoinositide 3-kinase/protein kinase B.

Artesunate can reduce oxidative stress in rats by inhibiting the expression of Caspase-3 and Caspase-9, and suppressing the expression of apoptosis-related proteins[45], thereby protecting retinal morphology. At the same time, artesunate may reduce oxidative stress damage to retinal ganglion cells induced by $H_2O_2$ by activating the PI3K/Akt signaling pathway[46]. Additionally, recent studies have found that transforming growth factor-β (TGF-β) mediates the involvement of RPE and/or choroidal endothelial cells in the development of AMD through EMT and endothelium-mesenchymal transition (EndMT) respectively[47]. Artesunate can inhibit the proliferation, migration, and TGF-β2-mediated EMT of ARPE-19 cells by reducing the expression of the PI3K/Akt pathway[39], which may suggest that artesunate can fight AMD by inhibiting EMT and EndMT, but further research is still needed.

These research findings indicate that artesunate may protect the retina by reducing oxidative stress responses and the expression of apoptosis-related proteins, activate the PI3K/Akt pathway to mitigate oxidative damage, and fight AMD by inhibiting the EMT and EndMT processes. As a new anti-angiogenic drug, artesunate has several advantages over anti-VEGF, including being a small molecule, low toxicity, and multiple targets. Future research should focus on evaluating the efficacy and safety of artesunate in clinical settings and exploring its potential mechanisms of action in the treatment of AMD.

**Ocular Neovascularization** Ocular neovascularization plays a key role in the tissue development and pathological progression of various retinal diseases, such as the previously mentioned choroiditis, ocular tumors, RVO, DR, and PVR. In normal adult mammals, the vascular system is quiescent, and the formation of new blood vessels primarily occurs through VEGF signal transduction driving new capillaries to sprout from existing vessels. Therefore, VEGF has been identified as a key factor in angiogenesis, making the VEGF/VEGFR2 axis an important therapeutic target[48].

However, the limitations of anti-VEGF treatment, which is currently the main drug for treating ocular neovascularization, have raised concerns. Studies suggest that long-term anti-VEGF treatment might affect the vitality and function of RPE cells[49], cause chronic high intraocular pressure[50], and after a period of continuous anti-VEGFR2 monotherapy, tumors may rebound, and the adaptive immune response of tumors limits the efficacy of VEGF/VEGFR inhibitors[48]. Additionally, despite the low amount of drugs for ocular indications delivered locally to the eye, anti-VEGF treatment may still increase the risk of cardiovascular diseases such as hypertension and arterial thrombosis in the elderly and/or diabetic patients[51]. These limitations mean that single anti-VEGF treatment can no longer meet current treatment needs, making it necessary to find other safe and effective drugs against neovascularization.

Li *et al*[52] established an experimental choroidal neovascularization animal model using a 532 nm laser and demonstrated through oral administration that artesunate can inhibit angiogenesis by downregulating the expression of HIF-1α and VEGF in the early formation of experimental choroidal neovascularization, thereby suppressing its formation and development. Additionally, by downregulating the expression of VEGFR2, PKCα, and PDGFR[53], inhibiting mononuclear phagocyte recruitment[54], artesunate significantly inhibited choroidal neovascularization and the accompanying fibrotic scar. Studies have proven that intravitreal injection of artesunate can effectively reduce the formation of choroidal

and retinal neovascularization[55]. Furthermore, animal experiments have shown that artesunate can significantly inhibit retinal neovascularization in rabbits, with stronger anterior chamber permeability and longer-lasting effects than bevacizumab[53]. Compared to anti-VEGF treatment, artesunate has more targets, broader therapeutic pathways, and more durable effects. These results suggest that as a potential long-lasting small molecule drug, artesunate, with its multi-target treatment of ocular neovascularization, could become a new alternative to current anti-VEGF drugs used to inhibit ocular neovascularization and improve visual function.

## DISCUSSION AND OUTLOOK

Artesunate, a semi-synthetic compound derived from artemisinin, has shown promising potential in the treatment of retinal diseases due to its multi-target therapeutic action and low toxicity. In this review, we summarized the research progress of artesunate in retinal diseases (Figure 1). Artesunate has been proven to inhibit neovascularization, tumor cell proliferation, oxidative stress, and EMT in related studies of retinal diseases, and has shown significant effects in the treatment of choroidal melanoma, retinoblastoma, DR, RVO, and PVR. Particularly in inhibiting the formation of ocular neovascularization, artesunate demonstrates strong therapeutic potential and may serve as an effective alternative to anti-VEGF therapy. However, most of these studies are limited to the laboratory environment and lack extensive clinical data support. Further exploration of the efficacy, safety, and specific mechanisms of artesunate in human clinical trials is necessary. Future research should focus on verifying its effects in actual clinical applications and exploring the potential of combined use with existing treatment methods.

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