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Review article

Therapeutic applications of artemisinin in ophthalmic diseases

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ABSTRACT

Artemisinin is a sesquiterpene lactone extracted from the chrysanthemum plant, *Artemisia annua*. It is known for its curative effects in the treatment of pulmonary hypertension, leukemia, diabetes, malaria, and other diseases, owing to its abundant biological activity. In recent years, with the development of plant secondary metabolite research, other potential pharmacological effects of artemisinin-based drugs have received increasing attention; in particular, reports of their application for the potential treatment of ophthalmology-related diseases have gradually increased. Recently, studies confirmed that artemisinin plays therapeutic roles in eye diseases through regulation of signaling pathways, such asNrf2/HO-1/Keap1, TLR/MyD88/NF-κb, PI3K/AKT/mTOR, and FASN/Kmal-mTOR/SREBP1, and biological factors, such as protein kinase B, AMP-activated protein kinase, tumor necrosis factor alpha, nod-like receptor protein 3, vascular endothelial growth factor, malonyl-coenzyme A and cytochrome C. However, since ocular diseases are often caused by various factors, how artemisinin can play a good disease prevention role by modulating these factors needs to be further verified, and most of the current studies focus on *in vitro* and animal experiments, lacking sufficient information on clinical trial studies. To better explore and perfect the mechanism of action of artemisinin in ophthalmic diseases, and to better promote the clinical application of artemisinin, this study reviews the latest progress of artemisinin treatment for uveitis, uveal melanoma, age-related macular degeneration, diabetic retinopathy, ocular neovascularization, and dry eye, and it will provide theoretical support for the large-scale application of artemisinin in ophthalmic diseases in the future.

1. Introduction

Artemisinin, a sesquiterpene lactone, is one of the main active components in *Artemisia annua*. It has various pharmacological activities, including antitumor [1], antiviral [2], anti-inflammatory [3,4], antifibrosis [5], antischistosomiasis [6,7], and

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antineovascularization effects [8]. Before Tu Youyou's groundbreaking work, people did not know the specific compound artemisinin. Tu Youyou's discovery of artemisinin's anti malaria properties completely changed the treatment of malaria worldwide and earned her the 2015 Nobel Prize in Medicine for this. This greatly increases the research interest of researchers in artemisinin research and further expands its application scope. To achieve higher clinical efficacy and reduce side effects, representative drugs of artemisinin derivatives, such as artesunate, dihydroartemisinin, and β-aminoartemisinin maleate, have also been widely studied [10].

Recently, artemisinin showed good prevention and treatment effects on ophthalmic diseases, which has been constantly explored in uveitis, uveal melanoma (UM), age-related macular degeneration, diabetic retinopathy (DR), ocular neovascularization, and dry eye diseases (DEDs) [11]. However, systematic evaluation of artemisinin application in ophthalmology is scarce, and pharmacological studies lack detailed investigations. We summarized the research progress of artemisinin in ophthalmic diseases over the past decade by reviewing the relevant literature at home and abroad. Furthermore, we reviewed the physicochemical properties, biological activities, and pharmacological mechanisms of action of artemisinin in the treatment of ophthalmic diseases, as well as the research on its clinical applications. Our objective was to establish a theoretical foundation for the rational application of artemisinin in ophthalmology and drug development.

2. Physicochemical property of artemisinin

Artemisinin is a sesquiterpene lactone compound, with the function of an endoperoxide, colorless needle crystal, molecular formula for $C_{15}H_{22}O_5$, and relative molecular mass of 282.34; owing to its chemical structure, artemisinin is insoluble in water but easily soluble in chloroform, acetone, ethyl acetate, benzene, and other organic solvents [12–15]. Numerous artemisinin derivatives have been developed to achieve higher clinical efficacy and reduce side effects [16] (Fig. 1). The lower water solubility of artemisinin results in slow release and absorption of intramuscularly injected drugs, whereas oral artemisinin tablets have poor absorption, low bioavailability (only 30 %), poor efficacy, and a short *in vivo* half-life, which results in poor disease treatment [17–20]. For ocular surface drug administration, drug availability is low because of factors such as tear dilution, blood-water, and the blood-retina barrier [21–23]. Intravitreal injection of artemisinin increases the local concentration of the drug but is also associated with complications such as cataracts, fundopathy, hemorrhage, and retinal detachment [24]. Recently, new drug delivery methods, such as artemisinin nanoparticles biological preparation and self-emulsification systems have significantly improved drug bioavailability and safety, providing possibilities for expanding their clinical applications [25–27].

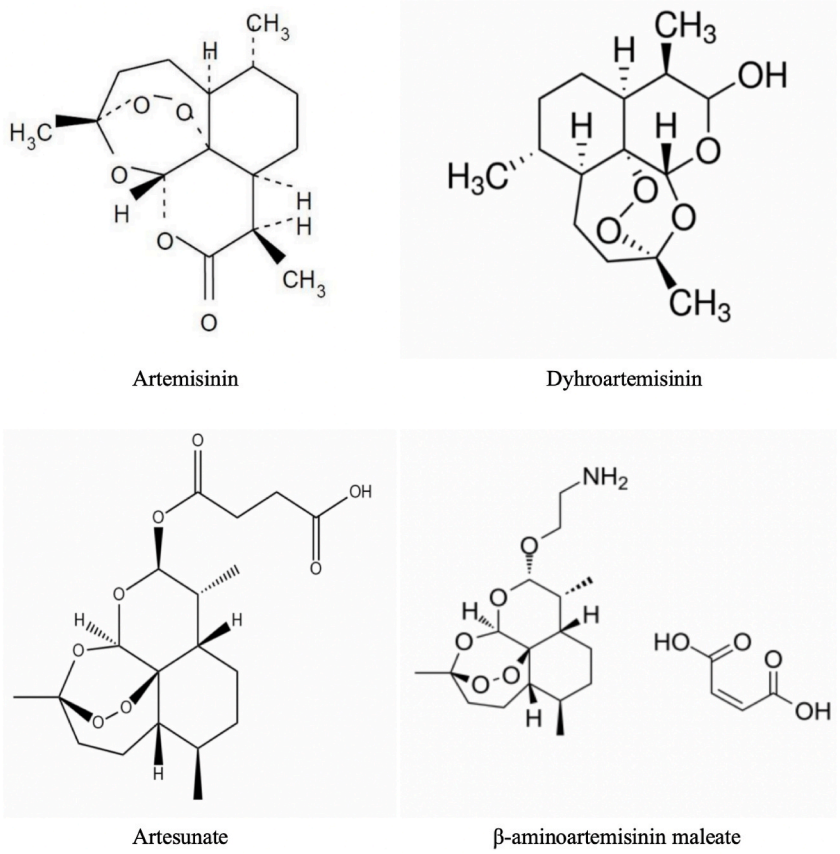

Fig. 1. Chemical structures of artemisinin and its derivatives.

3. Bioactivity of artemisinin

Artemisinin has a wide range of biological activities [28,29], such as antitumor [1] anti-inflammatory [3,4], anti-neovascularization [8] and antioxidant [30], and can play biological roles by signal pathways including Nrf2/HO-1/Keap1, TLR/MyD88/NF-κb, PI3K/AKT/mTOR, FASN/Kmal-mTOR SREBP1 and physiological processes, such as protein kinase B, AMP-activated protein kinase (AMPK), tumor necrosis factor α (TNF-α), vascular endothelial growth factor (VEGF), and cytochrome C.

3.1. Antioxidant activity

Artemisinin is an antioxidant that can exert antioxidant effects through the Nrf2/HO-1/Keap1 antioxidant stress pathway, which leads to an increase in Nrf2 nuclear translocation and transcription of Nrf2 target genes, thereby protecting cells from oxidative stress [31–34]. Furthermore, artemisinin regulates the expression of caspase-3, PARP, and Bcl-2, improves the activity of intracellular SOD, and increases the levels of intracellular antioxidants [35,36]. Huang et al. [37] used hydrogen peroxide to construct an retinal pigment epithelium (RPE) cell model damaged by oxidative stress. After intervention with artemisinin at different concentrations, they observed nuclear morphology and used a JC-1 probe experiment to determine whether artemisinin could reduce the loss of mitochondrial membrane potential of the Adult Retinal Pigment Epithelial cell line-19 (ARPE-19) caused by hydrogen peroxide. Western blot analysis revealed that artemisinin promoted the proliferation of ARPE-19 cells by promoting Protein Kinase B (PKB) phosphorylation. Artemisinin reduced the apoptosis in ARPE-19 cells induced via hydrogen peroxide by regulating the expression of Caspase-3, PARP, and Bcl-2. During oxidative stress induced by hydrogen peroxide in RPE cells, the expression of Keap1 increased, and the expression of Nrf2 and HO-1 decreased. Thus, artemisinin activates Nrf2 through the Nrf2/HO-1 Keap1 pathway to improve the antioxidant stress ability of cells [38,39]. This may also explain the damage to mitochondrial DNA in RPE cells and the loss of the cell membrane potential transport chain during macular degeneration. The anti-oxidative stress effects of artemisinin provide a new basis for clinical studies on oxidative stress injury.

3.2. Anti-tumor activity

Studies have confirmed that artemisinin reduces the migration and invasion abilities of tumor cells through the PI3K/AKT/mTOR pathway, thereby playing an antitumor role. Artemisinin substantially reduces the phosphorylation of PI3K, AKT, and mTOR in tumor cells [40,41]. Farhan et al. [42] found that artemisinin reduced the migration and invasion of UM cells in a concentration-dependent manner. Further studies have shown that artemisinin significantly reduced the phosphorylation of PI3K, AKT, and mTOR in UM cells. This pathway was further inhibited by selective phosphatidylinositol 3-kinase inhibitors (ly294002) or mammalian target of rapamycin (mTOR) inhibitors, which blocked the ability of UM cells with effects similar to those of artemisinin. In this study, the AKT activator (Sc79) and mTOR activator (MHY1485) were used to successfully weaken the inhibitory effect of artemisinin on the migration and invasion abilities of UM cells, further confirming that the anticancer effect of artemisinin may be mediated by inhibition of the PI3K/AKT/mTOR pathway [43]. Phosphorylated retinoblastoma (RB) protein can serve as an intermediate of the E2F transcription factor and cyclin-dependent kinases (CDKs). These proteins ablate the cell cycle as they transition from the G1 to S phase, induce G1 cell cycle arrest, inhibit cell division, and exert antitumor effects [44–47]. Additionally, it has been confirmed that [48] artesunate, an artemisinin-based drug, inhibited tumor growth, multiplication, and metastasis of choroidal melanoma *in vitro* by downregulating the expression of EFNA3 via the Stat3/Akt signaling pathway.

3.3. Anti-inflammation activity

Artemisinin can exert anti-inflammatory effects by inhibiting the TLR/MyD88/NF-κB signal pathway, resulting in aberrant expression of TLR4, reducing B cell activation and plasma cell formation. Additionally, β-aminoartemisinin maleate (SM934), a water-soluble artemisinin derivative, can inhibit the expression of IL-6, TNF-α, and IL-1β, promote the secretion of IL-10 by macrophages and impede T-cell activation and proliferation, thus producing anti-inflammatory effects [49–52]. Yang et al. [53] developed models of dry eye with insufficient tears and hyperevaporative dry eye through subcutaneous injection of scopolamine hydrobromide and benzamide chloride. It was found that the expression levels of TLR4, MyD88, NF-KB, and Nod-like receptor protein 3 (NLRP3) in the artemisinin derivative SM934 group were decreased. The volume of tear secretion and number of goblet cells increased significantly. Lee et al. [54] believed that artemisinin derivative SM934 could comprehensively regulate the abnormal expression of TLR4 and inhibit the activation of B cells and formation of plasma cells by inhibiting the inflammatory pathway of TLR/MyD88/NF-κB both *in vivo* and *in vitro*, to recover the secretion of tears, tear film integrity, keratoconjunctivitis, and other symptoms caused by dry eye.

3.4. Inhibiting neovascularization

Artemisinin plays an anti-neovascularization role by inhibiting vascular endothelial growth factor [55,56]. Artemisinin ester can downregulate VEGF-A expression by blocking VEGFR2 and PDGFR activation and inhibiting vascular permeability, vascular endothelial cell migration, and angiogenesis [57]. Dihydroartemisinin can reduce mTOR acylation on lysine 1218 (K1218) attenuate the activation of mTOR complex 1 (mTORC1) by decreasing fatty acid synthase (FASN) levels in cells, and inhibit of FASN decreasing the expression of cholesterol regulatory element-binding protein 1, which inhibits the proliferation of human retinal microvascular endothelial cells and neovascularization [58]. In addition, artemisinin inhibits VEGF-induced corneal neovascularization via the AKT

and ERK1/2 pathways [59].

4. Applications in ophthalmic diseases

Artemisinin possesses a wide range of benefits for the treatment of senile macular degeneration, DED, DR, UM, RB, uveitis, and other diseases and has great application prospects in clinical ophthalmology (Table 1 and Fig. 2).

4.1. Senile macular degeneration (SMD)

Senile macular degeneration, also known as age-related macular degeneration, is a chronic and progressive neurodegeneration of retinal photoreceptors, retinal pigment epithelium, and Bruch's membrane in the macula [65,66]. SMD are usually divided into two lesion types: dry (non-exudative) and wet (neovascular). Although the wet type accounts for only 20 % of all SMD cases, 80–90 % of wet SMD cause severe visual impairment [67]. In wet SMD, fluid leakage due to abnormal retinal neovascularization leads to submacular hemorrhage and severe loss of central vision. Elevated intracellular iron levels in the retina promote oxidative stress and exacerbate SMD [68]. Studies have confirmed that oxidative stress is a key factor in the pathogenesis of SMD. Oxidative stress induces the accumulation of reactive oxygen species (ROS) in the retinal pigment epithelium (RPE), leading to retinal dysfunction and structural disorders. The accumulation of ROS and obstruction of clearance in RPE cells aggravates oxidative damage and forms a vicious cycle [69]. Currently, the mainstay of treatment for wet SMD is resistance to oxidative stress within retinal cells and inhibition of neoangiogenesis. Previous studies have confirmed that artemisinin has considerable inhibitory effects on oxidative stress, increases superoxide dismutase (SOD) activity, improves antioxidant capacity, inhibits neovascularization, and protects RPE cells from oxidative stress damage [70,71]. It was found that artemisinin significantly reduced the potential damage to the mitochondrial membrane of human RPE cells (ARPE-19) by interfering with the oxidative stress response induced by hydrogen peroxide [37]. Additionally, artemisinin regulates the proliferation of ARPE-19 cells by promoting the phosphorylation of protein kinase B. Other studies have shown that artemisinin reduces hydrogen peroxide-induced apoptosis in ARPE-19 cells via the Nrf2/HO-1/Keap1 signaling pathway. Artemisinin increases the expression of Keap1, decreases the expression of Nrf2 and HO-1, protects the mitochondrial DNA of RPE cells from damage, and prevents loss of the cell membrane potential transport chain in macular degeneration. AMPK plays a crucial role in regulating cell survival under stress conditions [72]. Artemisinin, an activation mediator between AMPK and RPE cells, can activate AMPK and increase Nrf2 phosphorylation, leading to Nrf2 nuclear translocation and increased transcription of target genes, which can protect RPE cells from oxidative damage induced by hydrogen peroxide [73]. Artemisinin has poor water solubility owing to its physicochemical properties, and the development of nanoparticle drug delivery systems [74] has greatly improved water solubility and corneal permeability, prolonged drug release time, and effectively broadened the ocular utilization of artemisinin. Thus, the conditions were created for artemisinin to become a candidate drug for the treatment of SMD.

4.2. Dry eye disease (DED)

DED is a chronic multifactorial disease of the tears and ocular surface that typically causes eye discomfort and visual impairment

Table 1
Studies related to artemisinin treatment of ocular diseases.

Active ingredient	Models	Patient type	Result	Refs
Artemisinin	HRPE cell lines D407 and RGC-5	UM	inhibits the migration and invasion in UM via the PI3K/AKT/mTOR signaling pathway	[42]
SM934	SD rats and C57/BL6 mice	DED	Administration of SM934 significantly ameliorated SCOP and BAC-induced DED in rodent models	[53]
Dihydroartemisinin	C57BL/6J mice	DR	ameliorates retinal vascular dysfunction in diabetes mellitus via FASN/Kmal-mTOR/SREBP1 feedback loop	[58]
Artesunate	Long-Evans rats	Uveitis	Dose-dependent decreases of infiltrating cells, protein concentration, TNF-D, PGE2, NO, and MCP-1 in the aqueous humor by artesunate treatment after LPS injection indicate that artesunate can suppress the inflammation of EIU by inhibiting the production of inflammatory mediators	[60]
Artemisinin	HRPE cell line (D407)	SMD	Artemisinin is able to reduce H2O2-induced oxidative stress in D407 retinal pigment epithelial cells through the regulation of multiple mechanisms including (1) inhibiting the generation of intracellular ROS; (2) modulating $\triangle\psi m$ and caspase 3/7 dependent pathway; (3) activating ERK1/2 signaling pathway	[61]
Artesunate	ARPE-19 and CM cell	CM	Artesunate attenuates the tumorigenesis of choroidal melanoma via inhibiting EFNA3 through Stat3/Akt signaling pathway	[62]
Artesunate	SD rats	RB	induces mitochondria-mediated apoptosis of human retinoblastoma cells by upregulating Kruppel-like factor 6	[63]
Artesunate	RB-Y79 and HRPE cell line	RB	exerts specific cytotoxicity in retinoblastoma cells via CD71	[64]

CM, choroidal melanoma; DED, dry eye disease; DR, diabetic retinopathy; EIU, endotoxin-induced uveitis; HRPE: Human retinal pigment epithelium; LPS, lipopolysaccharide; RB, retinoblastoma; SMD, senile macular degeneration; UM: Uveal melanoma.

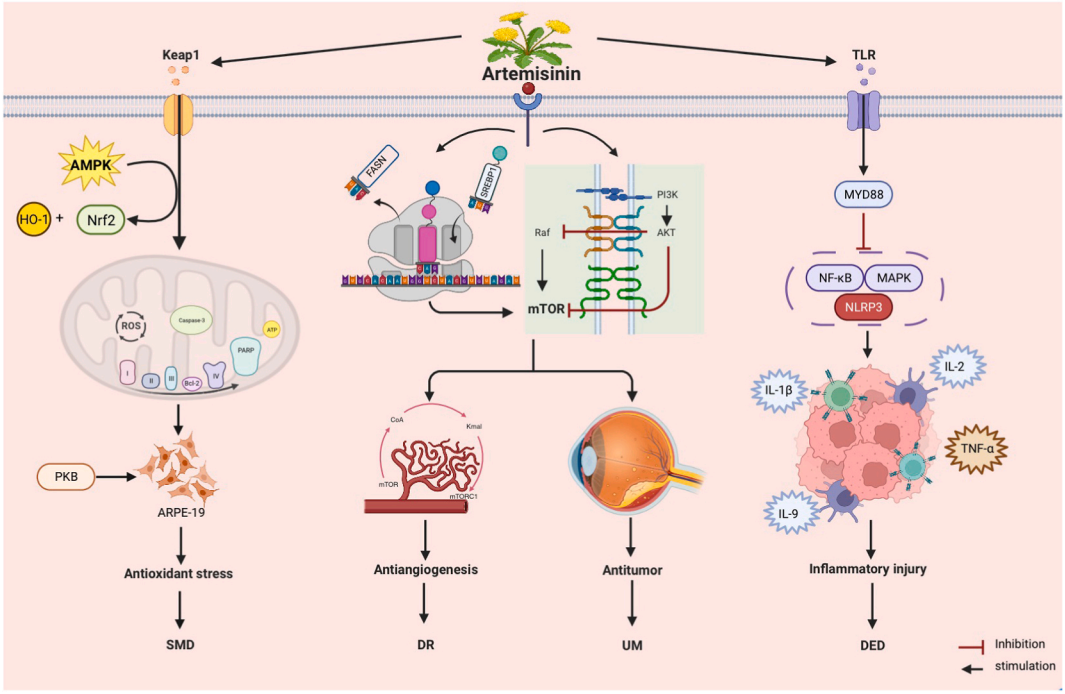

Fig. 2. Signaling pathways of artemisinin treating eye diseases.

and substantially affects the quality of life [75]. Although its pathogenesis has not been fully elucidated, several studies have shown that the inflammatory response plays a crucial role in the pathogenesis of DED [76]. When the ocular surface barrier function is disrupted, the expression of TLRs is considerably increased, and the secretion of inflammatory factors, such as IL-1β, IL-2, IL-9, and TNF-α is induced through myeloiddifferentiationfactor88 (MyD88)-dependent activation of nuclear factor κB and mitogen-activated protein kinase (MAPK) cascade, which stimulates immune cells and promotes inflammatory cell infiltration [77]. Fortunately, anti-inflammatory treatments for moderate and severe DEDs can help break the vicious cycle of ocular surface damage caused by inflammation. Artificial tears continue to be used as the first-line treatment for dry eye. However, because their clinical effectiveness is limited to supportive adjuvant therapy, they are unable to target inflammation or other causes of dry eye [78]. Artemisinin has attracted the attention of researchers owing to its significant anti-inflammatory effects and has been found to play an increasingly important role in the treatment of DEDs. Lee et al. [54] confirmed that artemisinin derivative, SM934 topical eye spotting can regulate TLR4 expression *in vivo* and *in vitro* by inhibiting the TLR/MyD88/NF-κB inflammatory pathway, inhibit B cell activation, and plasma cell formation, which can improve symptoms, such as insufficient tear secretion, tear film integrity destruction, keratitis, and conjunctivitis. Yang et al. [53] used 0.5 % artemisinin-derived SM934 topical eye-spotting to treat DED and found that the expression of TLR4, MyD88, NF-κB, and nod-like receptor protein 3 decreased, whereas tear secretion and goblet cell number increased considerably. Moreover, SM934 can promote the secretion of IL-10 by macrophages, inhibit the response of Th1 and Th17 cells, and induce the differentiation and proliferation of regulatory T cells (Treg). Additionally, it can inhibit the expression of TNF-α, IL-6, MCP-1, MPO in conjunctiva, and TNF-α and IL-1β mRNA in the cornea, then improves the symptoms of DED. SM934 plays an important role in various inflammatory and autoimmune diseases [79,80], and in addition to its pharmacological effects, its stability and high solubility further ensure the potential of SM934 as an ophthalmic therapeutic agent for DED. This finding has important clinical implications for the treatment of DED.

4.3. Diabetic retinopathy (DR)

DR is a major ocular complication of diabetes, affecting the quality of life in 30–40 % of patients with diabetes [81]. Abnormal lipid metabolism is a potential risk factor for vascular dysfunction in DR, and dyslipidemia can increase mitochondrial damage in retinal endothelial cells induced by glucose toxicity, leading to the senescence of RPE cells [82–84]. Furthermore, FASN plays a key role in the progression of insulin-resistant disease in type 2 diabetes, and the inhibition of mTOR in FASN-related signaling pathways can control ocular pathological angiogenesis [85–88]. Currently, anti-VEGF drugs such as ranibizumab and bevacizumab are widely used in the treatment of diabetic retinopathy. However, the short half-life, high molecular weight, and resistance to these drugs have led to a significant increase in the recurrence rate of anti-VEGF therapy, and frequent intravitreal injections further increase the risk of endophthalmitis infection [89]. Studies have shown that dihydroartemisinin can reduce the level of FASN, decrease mTOR acylation on lysine, and activate mTORC1, thereby inhibiting the proliferation of retinal microvascular endothelial cells and formation of new blood vessels [58]. Additionally, it has been shown that artesunate attenuates diabetic retinopathy by activating autophagy through

regulating the AMPK/SIRT1 pathway [90]. Artesunate interferes with the activation of VEGFR2 and PDGF, thereby inhibiting neovascularization, and its inhibitory effect is stronger and longer-lasting than that of the anti-vascular endothelial growth factor drug bevacizumab [91,92]. Moreover, Li et al. [93] found that a single intravitreal injection of 20 μg dose of artesunate in rabbit and monkey models can reverse retinal and iris neovascularization, vasodilatation and tortuosity, macular edema, and fluorescein leakage after six months. An intravitreal injection of 80 μg of artesunate in a patient with retinal neovascularization at a follow up of 52 weeks revealed substantial improvement in retinal neovascularization, optic disc edema, and high IOP. Compared to traditional anti-VEGF drugs, artemisinin analogs have the advantages of low molecular weight, high safety, low toxicity, and multiple targets. Artemisinin, a new type of anti-angiogenic drug, especially when administered as eye drops or intravitreal injections for the treatment of fundus neovascularization, has several advantages worthy of further exploration.

4.4. Uveal melanoma (UM)

UM is the most common primary intraocular cancer in adulthood and is mainly confined to the choroid [94]. Studies have confirmed that the PI3K/AKT/mTOR pathway is important for mammalian tumor immunity and plays an extremely important role in the evolution of various malignant tumors [95]. In UM cells, activation of the PI3K/AKT pathway contributes to their growth and metastasis, and elevated levels of threonine protein kinase B (Applied Komatsu Technology) phosphorylation contribute to a poor prognosis [96–98]. The anticancer effect of artemisinin has been a hot topic in academic research, and relevant studies have shown that artemisinin has a strong inhibitory effect on uveal melanoma [99]. Research confirms that artemisinin (100 μmol^{-1}) considerably reduced the phosphorylation levels of PI3K, AKT, and mTOR in UM cells and attenuated the migration and invasive abilities of UM cells in a concentration-dependent manner, which was comparable to the effects of a selective phosphatidylinositol 3-kinase inhibitor (lys 294002) or an mTOR inhibitor [42,100]. Additionally, studies utilizing AKT (Sc79) and mTOR (MHY1485) activators to attenuate the ability of artemisinin to inhibit the migration and invasion of UM cells reverse-validated that artemisinin exerts its anti-cancer effects by the inhibition of the PI3K/AKT/mTOR pathway. Furthermore, artemisinin induces the loss of mitochondrial membrane potential and apoptosis in UM cells via this pathway [42]. The results showed that artesunate (80 μmol^{-1}) could inhibit the Wnt/β-catenin pathway, regulate the biological function of tumor stem cells, interfere with tumor progression, and substantially reduce the percentage of aldehyde dehydrogenase cells in UM. This reduces the ability of cells to form continuous melanin balls, thereby inhibiting UM cell growth [101]. Compared to traditional chemotherapeutic drugs, artemisinin has the advantages of low toxicity, multiple targets, fewer side effects, and suitability for long-term use. Thus, artemisinin is a potential drug candidate for the treatment of UM. However, more *in vivo* experiments are needed to explore the optimal dosage and higher therapeutic efficacy of the drug so that it can be better applied to the clinical treatment of UM.

4.5. Retinoblastoma (RB)

RB is the most common intraocular malignancy in infants and the second most common pediatric malignancy [102]. Some studies have confirmed that the induction of apoptosis plays an important role in RB treatment, which is expected to cure RB [103,104]. In recent years, artemisinin has been shown to exert inhibitory effects on various types of cancer [105]. Relevant studies have shown that artemisinin can trigger apoptosis and play an active therapeutic role in cancer [106,107]. Willoughby et al. [44] demonstrated that 300 μmol-1 artemisinin blocks prostate cancer growth and cell cycle progression by disrupting Sp1 interactions with the cyclin-dependent kinase-4 (CDK4) promoter and inhibiting CDK4 gene expression. Zhao et al. [64] explored the 200 μmol^{-1} antitumor activity of artesunate in RB and found that artemisinin exhibited low toxicity in normal retinal cells and high cytotoxicity in RB cells in a dose-dependent manner. It can block the G1-phase cellular process of RB cells at low doses and induce the apoptosis of RB cells at high doses. Artemisinin also has potential applications in the induction of growth arrest at different stages of cell division. Several clinical studies have confirmed the antitumor effects of artemisinin. Yang et al. [63] injected 80 μg/ml artesunate into the vitreous cavity of a mouse RB xenotransplantation model and found that artesunate upregulated the expression of KLF6, induced RB cell apoptosis, and inhibited the growth of RB tumors in time- and dose-dependent manners. In addition, no significant retinal functional damage or structural disturbances were observed on fundus photography, fundus fluorescein angiography, optical coherence tomography, electrophysiology, or other ophthalmological examinations. Artesunate was also found to be effective in advanced RB, with a favorable safety profile and no adverse reactions such as allergies [108]. Compared to traditional chemotherapeutic drugs, which have numerous side effects, high toxicity, and other shortcomings, artemisinin is more suitable for long-term treatment with fewer side effects. Therefore, artemisinin is a promising agent for the treatment of RB. However, further studies are required to determine the optimal therapeutic dose and efficacy to provide better insights.

4.6. Uveitis

Uveitis is the most common intraocular inflammatory disease and is an important cause of visual impairment worldwide [109]. During acute episodes of uveitis, the iris and ciliary body are infiltrated by numerous inflammatory cells and release numerous chemokines and inflammatory mediators, such as TNF-α, MCP-1, and IL-6, which further stimulate cellular inflammatory responses and exudate inflammatory cells into the anterior chamber [110]. TNF-α is a cytokine involved in systemic inflammation, apoptosis, cell death, and immune cell regulation, which plays an important role in stimulating the acute response to inflammation [111]. The anti-inflammatory effects of artemisinin have been well-established over the past few decades [112]. Wang et al. [46] utilized endotoxin-induced uveitis as an experimental model for human uveitis to investigate the anti-inflammatory effects of artesunate.

Artesunate (10 mg kg^{-1} and 100 mg kg^{-1}) can inhibit the release of TNF-α, reduce the concentration of infiltrating cells and proteins in aqueous humor, and inhibit the inflammatory response in uveitis rats. However, artemisinin treatment of uveitis has not been well studied, and more research is needed in the future to clarify the specific cellular mechanisms of its treatment and provide theoretical support for the use of artemisinin in modifying the ocular inflammatory response.

The strong anti-inflammatory, antioxidant, antitumor, antineovascular, and other biological activities of artemisinin and some of its derivatives have demonstrated their potential in the prevention and treatment of various ocular diseases, such as diabetic retinopathy, age-related macular degeneration, retinoblastoma, uveal melanoma, uveitis, and dry eye. Artemisinin monomer is insoluble in water and only soluble in organic solvents, and its bioavailability is low. Consequently, the current research on the subject is limited to cell and animal experiments, and the clinical promotion and application continue to encounter major challenges. With the development of artemisinin nanoparticle drug delivery system, artemisinin self-emulsifying systems, the new dosage form of artemisinin, and structural modification of artemisinin, its physicochemical properties have been improved, bioavailability has been greatly increased, the medicinal value of artemisinin has been continuously explored, and the potential for clinical application is vast. This is anticipated to provide a novel perspective on clinical research. Ocular diseases result from a combination of these factors. For example, diabetic retinopathy and age-related macular degeneration may be caused by inflammation, oxidative stress, or apoptosis. In addition, excessive ROS production can lead to oxidative stress damage and may also lead to mitochondrial dysfunction, thus promoting apoptosis and inflammatory responses. The therapeutic role of artemisinin in the complex pathogenesis of ophthalmic diseases needs to be studied to provide a better basis for the treatment of clinical diseases.

5. Conclusions and perspectives

Artemisinin plays an important role in DED, age-related macular degeneration, RB, UM, DR, and other eye diseases because of its strong anti-inflammatory, antioxidant, anti-cancer, immunomodulatory, vascular-protective, and other biological activities. Therefore, it is expected to become a potentially effective treatment option for ophthalmic diseases. However, owing to its poor water solubility and low bioavailability, most studies have focused on *in vitro* and animal experiments, and there is a lack of sufficient information regarding human studies. Based on a series of technological innovations, such as artemisinin nanoparticle drug delivery systems, artemisinin self-emulsifying systems, new dosage forms of artemisinin, and structural modifications of artemisinin, the physicochemical properties of artemisinin have improved and its bioavailability has greatly increased. In the future, we need to develop new, safe and effective forms of drug delivery to improve the physicochemical properties of artemisinin to expand its clinical use in ophthalmology.

CRediT authorship contribution statement

Hao Sun: Formal analysis, Data curation, Conceptualization. **Ping Zhao:** Software, Resources, Project administration, Methodology. **Lianghui Zhao:** Writing – original draft, Visualization, Validation, Supervision. **Zhizhong Zhao:** Writing – review & editing, Writing – original draft, Conceptualization. **Haoyu Chen:** Visualization, Validation, Resources. **Cong Ren:** Project administration, Methodology, Investigation, Funding acquisition. **Bin Guo:** Visualization, Validation, Supervision, Software.

Consent for publication

Not applicable.

Availability of data and material

The authors have provided all the main data in the form of tables and figures.

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Declaration of competing interest

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

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References

[1] H.C. Lai, N.P. Singh, T. Sasaki, Development of artemisinin compounds for cancer treatment, Invest. N. Drugs 31 (2013) 230–246.
[2] T. Efferth, Beyond malaria: the inhibition of viruses by artemisinin-type compounds, Biotechnol. Adv. 36 (2018) 1730–1737.
[3] X. Wang, B. Zheng, U. Ashraf, H. Zhang, C. Cao, Q. Li, Z. Chen, M. Imran, H. Chen, S. Cao, J. Ye, Artemisinin inhibits the replication of flaviviruses by promoting the type I interferon production, Antivir. Res. 179 (2020) 104810.
[4] F. Qiu, J. Liu, X. Mo, H. Liu, Y. Chen, Z. Dai, Immunoregulation by artemisinin and its derivatives: a new role for old antimalarial drugs, Front. Immunol. 12 (2021) 751772.
[5] D. Dolivo, P. Weathers, T. Dominko, Artemisinin and artemisinin derivatives as anti-fibrotic therapeutics, Acta Pharm. Sin. B 11 (2021) 322–339.
[6] S.A.P. Correa, R.N. de Oliveira, T.M.F. Mendes, K.R. Dos Santos, J.r.S. Boaventura, V.L. Garcia, V.L.S. Jeraldo, S.M. Allegretti, In vitro and in vivo evaluation of six artemisinin derivatives against Schistosoma mansoni, Parasitol. Res. 118 (2019) 505–516.
[7] N.F. Abd El-Aal, R.S. Hamza, M. Magdy, Anti-angiogenic and anti-lymphangiogenic role of praziquantel and artemether in experimental mansoniasis, Acta Parasitol. 62 (2019) 708–716.
[8] X. Lu, M. Elbadawi, S. Blatt, M.E.M. Saeed, X. Xiao, X. Ma, E. Fleischer, P.W. Kämmerer, T. Efferth, Artemisinin derivative FO-ARS-123 as a novel VEGFR2 inhibitor suppresses angiogenesis, cell migration, and invasion, Chem. Biol. Interact. 365 (2022) 110062.
[10] L. Nahar, M. Guo, S.D. Sarker, A review on the latest advances in extraction and analysis of artemisinin, Phytochem. Anal. 31 (2020) 5–14.
[11] B.W. Lu, L.K. Xie, Potential applications of artemisinins in ocular diseases, Int. J. Ophthalmol. 12 (2019) 1793–1800.
[12] T. Fröhlich, A. Çapcı Karagöz, C. Reiter, S.B. Tsogoeva, Artemisinin-derived dimers: potent antimalarial and anticancer agents, J. Med. Chem. 59 (2016) 7360–7388.
[13] X. Feng, S. Cao, F. Qiu, B. Zhang, Traditional application and modern pharmacological research of Artemisia annua L, Pharmacol. Ther. 216 (2020) 107650.
[14] A. Capci, L. Herrmann, H.M. Sampath Kumar, T. Frohlich, S.B. Tsogoeva, Artemisinin-derived dimers from a chemical perspective, Med. Res. Rev. 41 (2021) 2927–2970.
[15] N. Ma, Z. Zhang, F. Liao, T. Jiang, Y. Tu, The birth of artemisinin, Pharmacol. Ther. 216 (2020) 107658.
[16] B.H. Kiani, W.K. Kayani, A.U. Khayam, E. Dilshad, H. Ismail, B. Mirza, Artemisinin and its derivatives: a promising cancer therapy, Mol. Biol. Rep. 47 (2020) 6321–6336.
[17] A. Hussain, Recent trends on production sources, biosynthesis pathways and antiviral efficacies of artemisinin: a candidate phytomedicine against SARS-CoV-2, Curr. Pharmaceut. Biotechnol. 24 (2023) 1859–1880.
[18] D.H.J. Cheong, D.W.S. Tan, F.W.S. Wong, T. Tran, Anti-malarial drug, artemisinin and its derivatives for the treatment of respiratory diseases, Pharmacol. Res. 158 (2020) 104901.
[19] J.B. Gerard Yameogo, R. Mazet, D. Wouessidjewe, L. Choisnard, D. Godin-Ribuot, J.L. Putaux, R. Semde, A. Geze, Pharmacokinetic study of intravenously administered artemisinin-loaded surface-decorated amphiphilic gamma-cyclodextrin nanoparticles, Mater. Sci. Eng., C 106 (2020) 110281.
[20] V. Agrahari, A. Mandal, V. Agrahari, H.M. Trinh, M. Joseph, A. Ray, H. Hadji, R. Mitra, D. Pal, A.K. Mitra, A comprehensive insight on ocular pharmacokinetics, Drug Deliv Transl Res 6 (2016) 735–754.
[21] S. Sapino, D. Chirio, E. Peira, E. Abellan Rubio, V. Brunella, S.A. Jadhav, G. Chindamo, M. Gallarate, Ocular drug delivery: a special focus on the thermosensitive approach, Nanomaterials 9 (2019) 1–19.
[22] V. Gote, S. Sikder, J. Sicotte, D. Pal, Ocular drug delivery: present innovations and future challenges, J. Pharmacol. Exp. Therapeut. 370 (2019) 602–624.
[23] S. Swetledge, J.P. Jung, R. Carter, C. Sabliov, Distribution of polymeric nanoparticles in the eye: implications in ocular disease therapy, J. Nanobiotechnol. 19 (2021) 10–30.
[24] L. Li, J. Chen, Y. Zhou, J. Zhang, L. Chen, Artesunate alleviates diabetic retinopathy by activating autophagy via the regulation of AMPK/SIRT1 pathway, Arch. Physiol. Biochem. 129 (2023) 943–950.
[25] C. Ponnusamy, A. Sugumaran, V. Krishnaswami, R. Palanichamy, R. Velayutham, S. Natesan, Development and evaluation of polyvinylpyrrolidone K90 and poloxamer 407 self-assembled nanomicelles: enhanced topical ocular delivery of artemisinin, Polymers 13 (2021) 1–17.
[26] R. Varela-Fernandez, V. Diaz-Tome, A. Luaces-Rodriguez, A. Conde-Penedo, X. Garcia-Otero, A. Luzardo-Alvarez, A. Fernandez-Ferreiro, F.J. Otero-Espinar, Drug delivery to the posterior segment of the eye: biopharmaceutic and pharmacokinetic considerations, Pharmaceutics 12 (2020) 269–299.
[27] X. Zhou, F. Suo, K. Haslinger, W.J. Quax, Artemisinin-type drugs in tumor cell death: mechanisms, combination treatment with biologics and nanoparticle delivery, Pharmaceutics 14 (2022) 395.
[28] L. Guan, H. Wang, X. Xu, H. Fan, Therapeutical utilization and repurposing of artemisinin and its derivatives: a narrative review, Adv Biol (Weinh). 7 (2023) e2300086.
[29] F. Gao, Z. Sun, F. Kong, J. Xiao, Artemisinin-derived hybrids and their anticancer activity, Eur. J. Med. Chem. 15188 (2020) 112044. Feb.
[30] C. Shi, H. Li, Y. Yang, L. Hou, Anti-inflammatory and immunoregulatory functions of artemisinin and its derivatives, Mediat. Inflamm. (2015) 435713.
[31] R. Varshney, S. Gupta, P. Roy, Cytoprotective effect of kaempferol against palmitic acid-induced pancreatic beta-cell death through modulation of autophagy via AMPK/mTOR signaling pathway, Mol. Cell. Endocrinol. 448 (2017) 1–20.
[32] C. Mo, L. Wang, J. Zhang, S. Numazawa, H. Tang, X. Tang, X. Han, J. Li, M. Yang, Z. Wang, D. Wei, H. Xiao, The crosstalk between Nrf2 and AMPK signal pathways is important for the anti-inflammatory effect of berberine in LPS-stimulated macrophages and endotoxin-shocked mice, Antioxidants Redox Signal. 20 (2014) 574–588.
[33] X.Y. Lei, R.Z. Tan, J. Jia, S.L. Wu, C.L. Wen, X. Lin, H. Wang, Z.J. Shi, B. Li, Y. Kang, L. Wang, Artesunate relieves acute kidney injury through inhibiting macrophagic mincle-mediated necroptosis and inflammation to tubular epithelial cell, J. Cell Mol. Med. 25 (2021) 8775–8788.
[34] Y. Yokoyama, K. Maruyama, K. Yamamoto, K. Omodaka, M. Yasuda, N. Himori, M. Ryu, K.M. Nishiguchi, T. Nakazawa, The role of calpain in an in vivo model of oxidative stress-induced retinal ganglion cell damage, Biochem. Biophys. Res. Commun. 451 (2014) 510–515.
[35] M. Barman, D. Dandasena, A. Suresh, V. Bhandari, S. Kamble, S. Singh, M. Subudhi, P. Sharma, Artemisinin derivatives induce oxidative stress leading to DNA damage and caspase-mediated apoptosis in Theileria annulata-transformed cells, Cell Commun. Signal. 17 (2023) 21–78.
[36] L. Xiao, C. Xu, P. Lin, L. Mu, X. Yang, Novel dihydroartemisinin derivative Mito-DHA$_5$ induces apoptosis associated with mitochondrial pathway in bladder cancer cells, BMC Pharmacol Toxicol 20 (2022) 23, 10.
[37] H. Xiao-Xu, S. Rong-Jian, L. Hua, Inhibition of artemisinin on oxidative stress injury induced by hydrogen peroxide in human retinal pigment epithelium cells, Rec Adv Ophthalmol 39 (2019) 306–311.
[38] D. Matsunaga, P.G. Sreekumar, K. Ishikawa, H. Terasaki, E. Barron, P. Cohen, R. Kannan, D.R. Hinton, Humanin protects RPE cells from endoplasmic reticulum stress-induced apoptosis by upregulation of mitochondrial glutathione, PLoS One 11 (2016) e0165150.
[39] N. Pineda-Ramirez, G.F. Gutierrez Aguilar, M. Espinoza-Rojo, P. Aguilera, Current evidence for AMPK activation involvement on resveratrol-induced neuroprotection in cerebral ischemia, Nutr. Neurosci. 21 (2018) 229–247.
[40] J. Luo, H. Li, J. Xiu, J. Zeng, Z. Feng, H. Zhao, Y. Li, W. Wei, Elevated ZNF704 expression is associated with poor prognosis of uveal melanoma and promotes cancer cell growth by regulating AKT/mTOR signaling, Biomark. Res. 10 (11) (2023), 38.
[41] Y. Peng, Y. Wang, C. Zhou, W. Mei, C. Zeng, PI3K/Akt/mTOR pathway and its role in cancer therapeutics: are we making headway? Front. Oncol. 24 (2022) 819128.
[42] M. Farhan, M. Silva, X. Xingan, Z. Zhou, W. Zheng, Artemisinin inhibits the migration and invasion in uveal melanoma via inhibition of the PI3K/AKT/mTOR signaling pathway, Oxid. Med. Cell. Longev. (2021) 9911537.
[43] X. Zhang, Z. Liang, Y. Zhou, F. Wang, S. Wei, B. Tan, Y. Guo, Artesunate inhibits apoptosis and promotes survival in schwann cells via the PI3K/AKT/mTOR axis in diabetic peripheral neuropathy, Biol. Pharm. Bull. 46 (2023) 764–772.
[44] J.A.Sr. Willoughby, S.N. Sundar, M. Cheung, A.S. Tin, J. Modiano, G.L. Firestone, Artemisinin blocks prostate cancer growth and cell cycle progression by disrupting Sp1 interactions with the cyclin-dependent kinase-4 (CDK4) promoter and inhibiting CDK4 gene expression, J. Biol. Chem. 284 (2009) 2203–2213.

[45] B.W. Lu, L.K. Xie, Potential applications of artemisinins in ocular diseases, Int. J. Ophthalmol. 12 (2019) 1793–1800.
[46] H. Okamoto, K. Yoshikawa, A. Shimada, R. Sano, D. Inukai, S. Yamanaka, S. Suzuki, R. Ueda, H. Ueda, Y. Fujimoto, T. Ogawa, Artesunate and cisplatin synergistically inhibit HNSCC cell growth and promote apoptosis with artesunate-induced decreases in Rb and phosphorylated Rb levels, Oncol. Rep. 50 (2023) 154.
[47] E. Im, C. Yeo, H.J. Lee, E.O. Lee, Dihydroartemisinin induced caspase-dependent apoptosis through inhibiting the specificity protein 1 pathway in hepatocellular carcinoma SK-Hep-1 cells, Life Sci. 192 (2018) 286–292.
[48] N. Yao, Q. Ma, W. Yi, Y. Zhu, Y. Liu, X. Gao, Q. Zhang, W. Luo, Artesunate attenuates the tumorigenesis of choroidal melanoma via inhibiting EFNA3 through Stat3/Akt signaling pathway, J. Cancer Res. Clin. Oncol. 150 (2024) 202.
[49] R.J. Wan, Y.H. Li, Effects of artesunate prevent nephritis via the Toll-like receptor 4/nuclear factor-κB signaling pathway in rats, Mol. Med. Rep. 16 (2017) 6389–6395.
[50] W. Qiang, W. Cai, Q. Yang, L. Yang, Y. Dai, Z. Zhao, J. Yin, Y. Li, Q. Li, Y. Wang, X. Weng, D. Zhang, Y. Chen, X. Zhu, Artemisinin B improves learning and memory impairment in AD dementia mice by suppressing neuroinflammation, Neuroscience 395 (2018) 1–12.
[51] X. Li, T.T. Lin, X.H. Zhang, L.F. Hou, X.Q. Yang, F.H. Zhu, W. Tang, J.P. Zuo, Artemisinin analogue SM934 ameliorates murine experimental autoimmune encephalomyelitis through enhancing the expansion and functions of regulatory T cell, PLoS One 8 (2013) e74108.
[52] Y. Wu, S. He, B. Bai, L. Zhang, L. Xue, Z. Lin, X. Yang, F. Zhu, P. He, W. Tang, J. Zuo, Therapeutic effects of the artemisinin analog SM934 on lupus-prone MRL/lpr mice via inhibition of TLR-triggered B-cell activation and plasma cell formation, Cell. Mol. Immunol. 13 (2016) 379–390.
[53] F.M. Yang, D. Fan, X.Q. Yang, F.H. Zhu, M.J. Shao, Q. Li, Y.T. Liu, Z.M. Lin, S.Q. Cao, W. Tang, S.J. He, J.P. Zuo, The artemisinin analog SM934 alleviates dry eye disease in rodent models by regulating TLR4/NF-kappaB/NLRP3 signaling, Acta Pharmacol. Sin. 42 (2021) 593–603.
[54] H.S. Lee, T. Hattori, E.Y. Park, W. Stevenson, S.K. Chauhan, R. Dana, Expression of toll-like receptor 4 contributes to corneal inflammation in experimental dry eye disease, Invest. Ophthalmol. Vis. Sci. 53 (2012) 5632–5640.
[55] J. Mesquita, J.P. Castro-de-Sousa, S. Vaz-Pereira, A. Neves, L.A. Passarinha, C.T. Tomaz, Vascular endothelial growth factors and placenta growth factor in retinal vasculopathies: current research and future perspectives, Cytokine Growth Factor Rev. 39 (2018) 102–115.
[56] X. Lu, S. Blatt, M. Dawood, S.M. Klauck, E. Fleischer, P.W. Kämmerer, T. Efferth, Novel artemisinin derivative FO8643 with anti-angiogenic activity inhibits growth and migration of cancer cells via VEGFR2 signaling, Eur. J. Pharmacol. 930 (2022) 175158.
[57] Y. Zong, Y. Yuan, X. Qian, Z. Huang, W. Yang, L. Lin, Q. Zheng, Y. Li, H. He, Q. Gao, Small molecular-sized artesunate attenuates ocular neovascularization via VEGFR2, PKCα, and PDGFR Targets, Sci. Rep. 6 (2016) 30843.
[58] C. Gu, X. She, C. Zhou, T. Su, S. He, C. Meng, Q. Gu, D. Luo, Z. Zheng, Q. Qiu, Dihydroartemisinin ameliorates retinal vascular dysfunction in diabetes mellitus via the FASN/Kmal-mTOR/SREBP1 feedback loop, Pharmacol. Res. 174 (2021) 105871.
[59] W. Ding, Y. Su, J. Mo, D. Sun, C. Cao, X. Zhang, Y. Wang, Novel artemisinin derivative P31 inhibits VEGF-induced corneal neovascularization through AKT and ERK1/2 pathways, Heliyon 10 (2024) e29984.
[60] X.Q. Wang, H.L. Liu, G.B. Wang, P.F. Wu, T. Yan, J. Xie, Y. Tang, L.K. Sun, C. Li, Effect of artesunate on endotoxin-induced uveitis in rats, Invest. Ophthalmol. Vis. Sci. 52 (2011) 916–919.
[61] C.M. Chong, W. Zheng, Artemisinin protects human retinal pigment epithelial cells from hydrogen peroxide-induced oxidative damage through activation of ERK/CREB signaling, Redox Biol. 9 (2016) 50–56.
[62] N. Yao, Q. Ma, W. Yi, Y. Zhu, Y. Liu, X. Gao, Q. Zhang, W. Luo, Artesunate attenuates the tumorigenesis of choroidal melanoma via inhibiting EFNA3 through Stat3/Akt signaling pathway, J. Cancer Res. Clin. Oncol. 150 (2024) 202.
[63] Y. Yang, N. Wu, Y. Wu, H. Chen, J. Qiu, X. Qian, J. Zeng, K. Chiu, Q. Gao, J. Zhuang, Artesunate induces mitochondria-mediated apoptosis of human retinoblastoma cells by upregulating Kruppel-like factor 6, Cell Death Dis. 10 (2019) 862.
[64] F. Zhao, H. Wang, P. Kunda, X. Chen, Q.L. Liu, T. Liu, Artesunate exerts specific cytotoxicity in retinoblastoma cells via CD71, Oncol. Rep. 30 (2013) 1473–1482.
[65] I. Bellezza, Oxidative Stress in Age-Related macular degeneration: Nrf2 as therapeutic target, Front. Pharmacol. 9 (2018) 1280.
[66] A. Lipecz, L. Miller, I. Kovacs, C. Czako, T. Csipo, J. Baffi, A. Csiszar, S. Tarantini, Z. Ungvari, A. Yabluchanskiy, S. Conley, Microvascular contributions to age-related macular degeneration (AMD): from mechanisms of choriocapillaris aging to novel interventions, Geroscience 40 (2019) 813–845.
[67] M. Fleckenstein, S. Schmitz-Valckenberg, U. Chakravarthy, Age-related macular degeneration: a review, JAMA 331 (2024) 147–157.
[68] C. Papaioannou, Advancements in the treatment of age-related macular degeneration: a comprehensive review, Postgrad Med J 100 (2024) 445–450.
[69] M. Lopez-Luppo, J. Catita, D. Ramos, M. Navarro, A. Carretero, L. Mendes-Jorge, P. Munoz-Canoves, A. Rodriguez-Baeza, V. Nacher, J. Ruberte, Cellular senescence is associated with human retinal microaneurysm formation during aging, Invest. Ophthalmol. Vis. Sci. 58 (2017) 2832–2842.
[70] F. Yan, H. Wang, Y. Gao, J. Xu, W. Zheng, Artemisinin protects retinal neuronal cells against oxidative stress and restores rat retinal physiological function from light exposed damage, ACS Chem. Neurosci. 16 (8) (2017) 1713–1723.
[71] Y. Pang, G. Qin, L. Wu, X. Wang, T. Chen, Artesunate induces ROS-dependent apoptosis via a Bax-mediated intrinsic pathway in Huh-7 and Hep3B cells, Exp. Cell Res. 347 (2016) 251–260.
[72] M.M. Mihaylova, R.J. Shaw, The AMPK signalling pathway coordinates cell growth, autophagy and metabolism, Nat. Cell Biol. 13 (2011) 1016–1023.
[73] S. Li, S.C. Chaudhary, X. Zhao, U. Gaur, J. Fang, F. Yan, W. Zheng, Artemisinin protects human retinal pigmented epithelial cells against hydrogen peroxide-induced oxidative damage by enhancing the activation of AMP-active protein kinase, Int. J. Biol. Sci. 15 (2019) 2016–2028.
[74] C. Ponnusamy, A. Sugumaran, V. Krishnaswami, R. Kandasamy, S. Natesan, Design and development of artemisinin and dexamethasone loaded topical nanodispersion for the effective treatment of age-related macular degeneration, IET Nanobiotechnol. 13 (2019) 868–874.
[75] V.L. Perez, F.S. Mah, M. Willcox, S. Pflugfelder, Anti-inflammatories in the treatment of dry eye disease: a review, J Ocul Pharmacol Ther 39 (2023) 89–101.
[76] M. Safir, G. Twig, M. Mimouni, Dry eye disease management, BMJ 25 (2024) e077344, 384.
[77] L.M. Periman, V.L. Perez, D.R. Saban, M.C. Lin, P. Neri, The immunological basis of dry eye disease and current topical treatment options, J Ocul Pharmacol Ther 36 (2020) 137–146.
[78] R.Y. Reins, C. Lema, J. Courson, C.M.E. Kunnen, R.L. Redfern, MyD88 deficiency protects against dry eye-induced damage, Invest. Ophthalmol. Vis. Sci. 59 (2018) 2967–2976.
[79] Z.M. Lin, X.Q. Yang, F.H. Zhu, S.J. He, W. Tang, J.P. Zuo, Artemisinin analogue SM934 attenuate collagen-induced arthritis by suppressing T follicular helper cells and T helper 17 cells, Sci. Rep. 6 (2016) 38115.
[80] Y.X. Yan, M.J. Shao, Q. Qi, Y.S. Xu, X.Q. Yang, F.H. Zhu, S.J. He, P.L. He, C.L. Feng, Y.W. Wu, H. Li, W. Tang, J.P. Zuo, Artemisinin analogue SM934 ameliorates DSS-induced mouse ulcerative colitis via suppressing neutrophils and macrophages, Acta Pharmacol. Sin. 39 (2018) 1633–1644.
[81] T.E. Tan, T.Y. Wong, Diabetic retinopathy: looking forward to 2030, Front. Endocrinol. 13 (2022) 1077669.
[82] J.V. Busik, Lipid metabolism dysregulation in diabetic retinopathy, J. Lipid Res. 62 (2021) 100017.
[83] Y. Gong, Z. Fu, R. Liegl, J. Chen, A. Hellstrom, L.E. Smith, Omega-3 and omega-6 long-chain PUFAs and their enzymatic metabolites in neovascular eye diseases, Am. J. Clin. Nutr. 106 (2017) 16–26.
[84] Q. Chen, L. Tang, G. Xin, S. Li, L. Ma, Y. Xu, M. Zhuang, Q. Xiong, Z. Wei, Z. Xing, H. Niu, W. Huang, Oxidative stress mediated by lipid metabolism contributes to high glucose-induced senescence in retinal pigment epithelium, Free Radic. Biol. Med. 130 (2019) 48–58.
[85] B. Bathish, H. Robertson, J.F. Dillon, A.T. Dinkova-Kostova, J.D. Hayes, Nonalcoholic steatohepatitis and mechanisms by which it is ameliorated by activation of the CNC-bZIP transcription factor Nrf2, Free Radic. Biol. Med. 188 (2022) 221–261.
[86] T. Nakahara, A. Morita, R. Yagasaki, A. Mori, K. Sakamoto, Mammalian target of rapamycin (mTOR) as a potential therapeutic target in pathological ocular angiogenesis, Biol. Pharm. Bull. 40 (12) (2017) 2045–2049.
[87] Y.S. Kim, M. Kim, M.Y. Choi, D.H. Lee, G.S. Roh, H.J. Kim, S.S. Kang, G.J. Cho, K.H. Park, S.J. Kim, J.M. Yoo, W.S. Choi, Aralia elata (Miq) seem extract decreases O-GlcNAc transferase expression and retinal cell death in diabetic mice, J. Med. Food 20 (2017) 989–1001.

[88] M. Nalini, B.V. Raghavulu, A. Annapurna, P. Avinash, V. Chandi, N. Wasim, Correlation of various serum biomarkers with the severity of diabetic retinopathy, Diabetes Metabol. Syndr. 11 (2017) S451–S454.
[89] J. Mesquita, J.P. Castro-de-Sousa, S. Vaz-Pereira, A. Neves, L.A. Passarinha, C.T. Tomaz, Evaluation of the growth factors VEGF-a and VEGF-B in the vitreous and serum of patients with macular and retinal vascular diseases, Growth Factors 36 (2018) 48–57.
[90] L. Li, J. Chen, Y. Zhou, J. Zhang, LChen, Artesunate alleviates diabetic retinopathy by activating autophagy via the regulation of AMPK/SIRT1 pathway, Arch. Physiol. Biochem. 129 (2023) 943–950.
[91] M. Moreno, P.Y. Pow, T.S.T. Tabitha, S. Nirmal, A. Larsson, K. Radhakrishnan, J. Nirmal, S.T. Quah, S. Geifman Shochat, R. Agrawal, S. Venkatraman, Modulating release of ranibizumab and aflibercept from thiolated chitosan-based hydrogels for potential treatment of ocular neovascularization, Expet Opin. Drug Deliv. 14 (2017) 913–925.
[92] A.G. Marneros, Increased VEGF-A promotes multiple distinct aging diseases of the eye through shared pathomechanisms, EMBO Mol. Med. 6 (2016) 208–231.
[93] C. Li, X. Feng, X. Wen, Y. Li, B. Liu, J. Hu, L. Lu, Y. Zhuo, Y. Fu, X. Qian, W. Shao, Q. Zheng, L. Lin, Y. Yang, H. Zheng, X. Lin, Q. Gao, A pilot clinical study of intravitreal injection of artesunate for ocular neovascularization, J Ocul Pharmacol Ther 35 (2019) 283–290.
[94] H. Bai, J.J. Bosch, L.M. Heindl, Current management of uveal melanoma: a review, Clin. Exp. Ophthalmol. 51 (2023) 484–494.
[95] L.Y. Tian, D.J. Smit, M. Jücker, The role of PI3K/AKT/mTOR signaling in hepatocellular carcinoma metabolism, Int. J. Mol. Sci. 24 (2023) 3.
[96] F. Janku, T.A. Yap, F. Meric-Bernstam, Targeting the PI3K pathway in cancer: are we making headway? Nat. Rev. Clin. Oncol. 15 (2018) 273–291.
[97] H. Populo, P. Soares, A.S. Rocha, P. Silva, J.M. Lopes, Evaluation of the mTOR pathway in ocular (uvea and conjunctiva) melanoma, Melanoma Res. 20 (2010) 107–117.
[98] P.S. Ong, L.Z. Wang, X. Dai, S.H. Tseng, S.J. Loo, G. Sethi, Judicious toggling of mTOR activity to combat insulin resistance and cancer: current evidence and perspectives, Front. Pharmacol. 7 (2016) 395.
[99] L. Zheng, J. Pan, The anti-malarial drug artesunate blocks wnt/β-catenin pathway and inhibits growth, migration and invasion of uveal melanoma cells, Curr. Cancer Drug Targets 18 (2018) 988–998.
[100] N. Babchia, A. Calipel, F. Mouriaux, A.M. Faussat, F. Mascarelli, The PI3K/Akt and mTOR/P70S6K signaling pathways in human uveal melanoma cells: interaction with B-Raf/ERK, Invest. Ophthalmol. Vis. Sci. 51 (2010) 421–429.
[101] L. Zheng, J. Pan, The anti-malarial drug artesunate blocks Wnt/beta-catenin pathway and inhibits growth, migration and invasion of uveal melanoma cells, Curr. Cancer Drug Targets 18 (2018) 988–998.
[102] C.L. Shields, Z. Bas, A. Laiton, A.M.V. Silva, A. Sheikh, S.E. Lally, J.A. Shields, Retinoblastoma: emerging concepts in genetics, global disease burden, chemotherapy outcomes, and psychological impact, Eye 37 (2023) 815–822.
[103] R.B. Thomas, S. Joy, M.S. Ajayan, C.S. Paulose, Neuroprotective potential of bacopa monnieri and bacoside a against dopamine receptor dysfunction in the cerebral cortex of neonatal hypoglycaemic rats, Cell. Mol. Neurobiol. 33 (2013) 1065–1074.
[104] G. Global Retinoblastoma Study, I.D. Fabian, E. Abdallah, S.U. Abdullahi, R.A. Abdulqader, et al., Global retinoblastoma presentation and analysis by national income level, JAMA Oncol. 6 (2020) 685–695.
[105] T. Efferth, Willmar Schwabe Award 2006: antiplasmodial and antitumor activity of artemisinin–from bench to bedside, Planta Med. 73 (2007) 299–309.
[106] Y. Meng, N. Ma, H. Lyu, Y.K. Wong, X. Zhang, Y. Zhu, P. Gao, P. Sun, Y. Song, L. Lin, J. Wang, Recent pharmacological advances in the repurposing of artemisinin drugs, Med. Res. Rev. 41 (2021) 3156–3181.
[107] S. Gunjan, T. Sharma, K. Yadav, B.S. Chauhan, S.K. Singh, M.I. Siddiqi, R. Tripathi, Artemisinin derivatives and synthetic trioxane trigger apoptotic cell death in asexual stages of plasmodium, Front. Cell. Infect. Microbiol. 8 (2018) 256–265.
[108] H. Okamoto, K. Yoshikawa, A. Shimada, R. Sano, D. Inukai, S. Yamanaka, S. Suzuki, R. Ueda, H. Ueda, Y. Fujimoto, T. Ogawa, Artesunate and cisplatin synergistically inhibit HNSCC cell growth and promote apoptosis with artesunate-induced decreases in Rb and phosphorylated Rb levels, Oncol. Rep. 50 (2023) 154.
[109] X.F. Huang, M.A. Brown, Progress in the genetics of uveitis, Gene Immun. 23 (2022) 57–65.
[110] C.E. Egwuagu, S.A. Alhakeem, E.C. Mbanefo, Uveitis: molecular pathogenesis and emerging therapies, Front. Immunol. 30 (12) (2021) 623725.
[111] K. Aquilano, V. Ceci, A. Gismondi, S. De Stefano, F. Iacovelli, R. Faraonio, G. Di Marco, N. Poerio, A. Minutolo, G. Minopoli, A. Marcone, M. Fraziano, F. Tortolici, S. Sennato, S. Casciardi, M. Potesta, R. Bernardini, M. Mattei, M. Falconi, C. Montesano, S. Rufini, A. Canini, D. Lettieri-Barbato, Adipocyte metabolism is improved by TNF receptor-targeting small RNAs identified from dried nuts, Commun. Biol. 2 (2019) 317.
[112] N. Stübiger, K. Ruprecht, U. Pleyer, Uveitis und multiple Sklerose : Klinik, Diagnostik, Management und Therapie [Uveitis and multiple sclerosis : Clinical aspects, diagnostics, management and treatment], Ophthalmologie 121 (2024) 665–678.