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Non-neglectable therapeutic options for age-related macular degeneration: a promising perspective from traditional Chinese medicine

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Abstract

Ethnopharmacological relevance: Age-related macular degeneration (AMD) is a chronic neurodegenerative disease which causes irreversible central vision loss among the elderly population. Traditional Chinese Medicine (TCM), including formulas, acupuncture and herbs, has been used in the treatment of AMD for thousands of years and is currently used by many AMD patients around the world.

Aim of the review: A comprehensive, in-depth literature review examining the use of TCM in the treatment of AMD has yet to be compiled. This review will improve current knowledge relating to the use of TCM and will open new avenues of exploration in developing new drugs for the treatment of AMD.

Methods: A literature search of the PubMed database, Web of Science, Google Scholar and China National Knowledge Infrastructure (CNKI) was performed using relevant terms and keywords related to TCM in the treatment of AMD. Related books, PhD and master's theses were also researched.

Results: The TCM-based interpretation of AMD has been used to establish a theoretical foundation for understanding the effect of TCM formulas and acupuncture on AMD. The possible mechanism of action of common Chinese herbs has also been discussed in detail.

Conclusion: TCM is a promising treatment option of AMD patients. However, lack of rigorous scientific evidence has limited the impact and uptake of TCM therapy. Future research should focus on improving understanding of the mechanism of action and bioactive components of TCM therapies.

Key words age-related macular degeneration; pathogenesis; therapy; Traditional Chinese Medicine

Abbreviations

AMD age-related macular degeneration; Aβ Amyloid β-protein; AKT Protein kinase B; p-Akt phosphorylated Akt; APS astragalus polysaccharides; ARMS2 age-related maculopathy susceptibility 2; AS-IV astragaloside IV; ASIV-LNC AS-IV lipid nanocapsules; ARE antioxidant response element; Bcl-2 B-cell lymphoma -2; Bax Bcl-2 associated X protein; CAT catalase; CNV choroidal neovascularization; CRP C-reactive protein; CCR3 chemokine receptor 3; CFH complement factor H; COX-2 cyclooxygenase-2; Caspase-3 cysteine aspartic acid protease-3; ECM extracellular matrix; EDV end-diastolic flow; ER endoplasmic reticulum; ERK extracellular signal-regulated kinase; GSH glutathione peroxidase; GSH-Px glutathione peroxidase-px; GFAP glial fibrillary acidic protein; H_2O_2 hydrogen peroxides; HO-1 heme oxygenase-1; HRECs human retinal vascular endothelial cells; HIF hypoxia inducible factor; IL interleukin; ICAM-1 intercellular adhesion molecule-1; IgG Immunoglobulin G; INF-α interferon-α; Keap-1 Kelch Like ECH Associated Protein 1; LPS lipopolysaccharide; LBP *Lycium barbarum* polysaccharides; MMPs matrix metalloproteinase; mTOR mammalian target of rapamycin; MDA malondialdehyde; NF-κB nuclear factor-kappa B; NFE2L2 nuclear factor erythroid 2-related factor 2; NO nitric oxide; NQO1 NAD(P)H quinone oxidoreductase-1; Nrf2 nuclear factor erythroid 2-related factor 2; NLRP3 NLR family pyrin domain containing 3; OS oxidative stress; ox-LDL oxidized low-density lipoprotein; PARP1 poly (ADP-ribose) polymerase-1; PCP *Poria cocos (Schw.)*

Wolf polysaccharide; PSV peak systolic short-velocity; PECCL pigment epithelium and choroid capillary composite layer; PGE prostaglandin E; PI3K phosphatidylinositol 3-kinase; RPE retinal pigment epithelium; RI resistance index; RGCs retinal ganglion cells; RNL retinal neuroepithelial layer; ROS reactive oxygen species; SIRT1 silent information regulator 1; SOD superoxide dismutase; TCM traditional Chinese medicine; TNF-α tumor necrosis factor-α; TIMPs tissue inhibitors of metalloproteinases; VEGF vascular endothelial growth factor; VEGFR VEGF receptor.

1. Introduction

Age-related macular degeneration (AMD) is an eye disorder that is characterized by a progressive degeneration of the neurosensory retina, retinal pigment epithelium (RPE) and choriocapillaris in the macular area of the retina. The incidence of AMD increases with age and despite some treatment options now being available, is the main cause of visual impairment in the elderly in developed countries (Owen et al. 2003; Klein et al. 2007; Ashraf, Souka, and Adelman 2018). Projections suggest that approximately 200 million people globally were affected by AMD in 2020, with around 300 million expected to be affected by 2040 (Wong et al. 2014). There are two types of AMD, the exudative or “wet” form, with choroidal neovascularization, and the more prevalent atrophic or “dry” form, with geographic atrophy of the photoreceptors and RPE. Both types of AMD result in partial or complete loss of central vision, which impacts many visual tasks including reading and facial recognition (Kokotas, Grigoriadou, and Petersen 2011).

Currently there is no ideal treatment available for the dry form of AMD; although anti-VEGF (vascular endothelial growth factor) treatment often helps to stabilise disease progression and to improve visual function in wet AMD patients. However, some patients do not respond well to anti-VEGF treatment (Mettu et al., 2021) and the administration mode of intravitreal injection can cause adverse complications, such as retinal detachment and intraocular inflammation (Falavarjani and Nguyen, 2013). Improving our understanding of the pathogenesis of AMD will help in the development of more treatments which can prevent or slow the

visual impairment of patients with dry or wet AMD.

Many clinicians have reported that therapies based on traditional Chinese medicine (TCM) are effective in treating AMD, with no obvious side effects. This has stimulated the interest of medical researchers around the world but a lack of high quality research outputs in the form of randomized controlled trials and systematic review has limited the impact of TCM in this field. Given that the various approaches adopted by modern medicine have had limited success to date, TCM represents a novel approach to help to identify drugs with the potential to improve AMD treatment. Here, we review the current research relating to the use of TCM in the treatment of AMD and based on this knowledge, provide suggestions for developing the role of TCM in future AMD treatment strategies.

2 Risk factors of AMD

AMD is a multifactorial disease with numerous risk factors thought to play a role in its development. Associated non-modifiable risk factors include increased age, gender, genetic factors, Caucasian race and light iris color. Modifiable risk factors include smoking, increased body mass index, alcohol intake and diet (Thomas, Mirza, and Gill 2021; Chapman, Jacobs, and Braakhuis 2019; Ristau et al. 2014; Hyman and Neborsky 2002). Multiple genetic risk factors are also associated with AMD. Genome wide association studies have reported that 52 genetic variants in 34 genetic loci are associated with AMD. The complement factor H (*CFH*) gene at chromosome 1q31 and the age-related maculopathy susceptibility 2 (*ARMS2*) gene at chromosome 10q26 are the major susceptibility genes for AMD, affecting for more than 50% of cases. Genetic variants in other genetic loci also make a small contribution to AMD risk (Handa et al., 2019; Hazdziahmetovic and Malek, 2021).

3 Pathophysiology and therapeutic strategies of AMD

The outer segments of photoreceptors are renewed on a daily basis; the shed outer segments are phagocytized and digested by the RPE cells, thus maintaining photoreceptor function and normal vision. With

increasing age, the ability of RPE cells to remove metabolites from photoreceptor cells decreases. As a result, metabolites accumulate in the inner layer of Bruch's membrane located between the RPE and the choroidal capillaries, resulting in thickening of Bruch's membrane and the formation of drusen. In severe cases of AMD, irregular RPE and choroidal capillary atrophy appear in the posterior pole. This so-called geographic atrophy is characterized by scattered or confluent areas of degeneration of RPE cells and the overlying light-sensing retinal photoreceptors, which rely on the RPE for trophic support (Nasim et al. 2019; Ambati and Fowler 2012). As the disease progresses, the associated photoreceptor cells and choroidal capillaries are destroyed, resulting in damage and atrophy of adjacent tissues which, in turn, aggravates the atrophy of RPE. In addition, thickening of collagen and rupture of the posterior elastic layer in Bruch's membrane occurs, resulting in choroidal capillaries entering the sub-retina, via fissures in Bruch's membrane, to form choroidal neovascularization (CNV). The unstable structural characteristics of neovascularization cause leakage and hemorrhage, resulting in formation of wet AMD. Wet AMD is generally characterized by CNV accompanied by liquid and lipid exudation, whereas dry AMD is associated with the formation of retinal drusen. More than 90% of the vision loss in AMD results from abnormal choroidal circulation (Gopinath et al. 2017).

Although the complex nature of AMD pathology is not fully understood, there is convincing evidence to support the involvement of drusen formation (Magnusson et al. 2006), oxidative damage (Cai et al. 2000), immune inflammatory reaction (Xu, Chen, and Forrester 2009), lipofuscin deposition (Jarrett and Boulton 2012), photoreceptor dysfunction (Petrukhin 2013) and, in the case of wet AMD, CNV (Li et al. 2020). Drusen is composed of extracellular material deposited between the basement membrane of RPE and Bruch's membrane (Magnusson et al. 2006), mainly containing enriched lipid, C-reactive protein (CRP), complement inhibitors and immunoglobulin light chains (Cao 2016). Angiogenesis is the normal response of the body to trauma or inflammation. The intraocular inflammation in AMD patients is associated with elevated CNV activity (Arnett et al. 2020). All of this suggests that immune inflammatory reaction plays a vital role in the

pathogenesis of AMD. There are abundant antioxidant enzymes in the body, which means that the oxidative damage response is not apparent at a young age. However, with the process of aging, the activity of retinal mitochondria changes, decreasing antioxidant capacity and creating an imbalance of the oxidative-antioxidant system. This produces a gradual change in retinal function and optic cell apoptosis, which act as markers for early AMD (He et al. 2010). Overall this highlights the complex nature of the AMD disease mechanisms which involve multiple signalling pathways (Handa et al., 2019).

Based on the pathobiology of AMD, anti-oxidative damage and anti-inflammation are considered to be effective strategies for treating dry AMD. Evidence suggests that antioxidant supplement in diets decreases AMD progression (Handa et al., 2019) and the effectiveness of targeting-components (e.g. CD59 and C5) of the complement system is being examined in clinical trials (Kumar-Singh, 2019). Other potential treatments include cell therapy using human embryonic stem cell derived RPE for dry AMD (Hazdziahmetovic and Malek, 2021). For wet AMD, the most effective treatment is limiting VEGF function via anti-VEGF therapy. There are currently four anti-VEGF drugs available. Bevacizumab is an off-label drug for treating AMD and the other three are approved by the United States Food and Drug Administration. Bevacizumab is a full-length anti-VEGF-A humanized monoclonal antibody, ranibizumab is a humanized monoclonal antibody fragment targeting VEGF-A and brolucizumab is a single chain fragment of humanized anti-VEGF-A antibody. Aflibercept is a soluble protein targeting VEGF receptor (VEGFR). All four drugs have shown protective effects in wet AMD patients (Hazdziahmetovic and Malek, 2021). Recent studies demonstrate brolucizumab has better safety and efficacy than that of aflibercept; possibly due to brobucizumab's ability to cross retinal layers leading to higher exposure in the retina and RPE/choroid (Dugel et al., 2020, 2021).

4. TCM-based interpretation of AMD

The Five Wheel Theory is an ancient doctrine of ophthalmology in TCM. The theory originates from the Huang Di Nei Jing which is one of the most important ancient Chinese medicine books. From a holistic point

of view on TCM, the anatomy, physiology and pathology of the eyes are organically related to the function of the viscera, which provides a practically theoretical basis for syndrome differentiation and the treatment of ophthalmic diseases. The central concept of the Five Wheel Theory is to divide the eye from outside to inside into five specific parts: meat wheel, blood wheel, gas wheel, wind wheel, and water wheel. The eyelids belong to the spleen (the meat wheel); the blood collaterals in the canthus are associated with the heart (the blood wheel); the Baijing, which includes the bulbar conjunctiva and the sclera, is at the disposal of the lung (the gas wheel); the Heijing, which is equivalent to cornea, is linked to the liver (the wind wheel); and the Tongren is closely connected with the kidney (the water wheel). Tongren also encapsulates the concept of pupil God. Constrained by the primitive ophthalmic examination technology, ancient physicians were unable to observe the ocular tissues posterior to the lens meaning that the broad concept of “pupil God” refers to various tissues inside the eyeball including the retina. Hence, the macula is considered to be part of pupil God (Hu, Wei, and Sun 2019).

The original "Five Wheel Theory" is simplistic and has been unable to systematically explain some complex ophthalmic diseases so many practitioners have been prompted to advocate the alternative theory that inner eye tissue is closely associated with meridians, the distribution network for the fundamental substances of qi, blood and body fluids throughout the body. The macula is yellowish on the unshaded fundus or eyeball, and so is considered to belong to the Foot Taiyin Spleen Channel (Ou, Zhou, and Peng 2020). Among the twelve meridians, only the liver meridian is directly connected to the eye; consequently, the liver meridian plays a significant role in linking the eye with the liver, as well as running qi and blood. In this system, the liver is the main reservoir of blood and the eyes need to be nourished by blood. In addition, liver-qi is also closely related to the function of the eye. Only when the liver-qi is comfortable the eye can perform optimally. Therefore, TCM holds that the disease origins of AMD are mainly in the kidney, spleen and liver. Many specialists also treat AMD via these three visceras, yielding favourable results (Qin et al. 2021; Qiu,

Liu, and Jin 2020; Li, Kang, et al. 2020)

Ancient medical practitioners failed to explore AMD in depth due to limitations in diagnostic skills at the time and as a result archaic medical books did not record the Chinese medicine disease name corresponding to AMD. Modern Chinese medicine practitioners mainly attribute AMD to one of the following categories of "Shizhan Hunmiao", an ophthalmic disease characterized by decreased eyesight and blurred vision; "Yunwu Yijing" is defined as presence of cloudiness in the vitreous humor; “Shizhan Youse" describes a colored shade before eye; " Shizhi Ruqu" refers to an eye disorder in which the view of a straight object is curved and "Baomang" is characterized by a dramatic decline in eye vision or even blindness in TCM based on clinical manifestations. In some way all these characteristics are related to the type of visual symptoms experienced by patients with AMD. For example, if maculopathy affects the pigment epithelium and neuroepithelium causing retinal neuroepithelial detachment, it will produce a degree of vision loss and visual deformation, which falls into the category of "Shizhan Hunmiao". If a small amount of blood penetrates into the vitreous, it will cause a vitreous opacity, as in "Yunwu Yijing". Substantial vitreous hemorrhage leading to a sudden reduction in visual acuity is classified in the "Baomang" range (Meng and Jin 2020). With the accumulation of experience in treating AMD, a comprehensive understanding of the etiology, pathogenesis and syndrome differentiation has been gradually formed. AMD is regarded as a disease that is secondary to a weakness of visceral function; and as a result early stage AMD is characterized by a deficiency of visceral essence and blood. As mentioned above, AMD patients have local symptoms such as fundus drusen, edema, exudation and hemorrhage. Furthermore, modern studies have found that fundus degeneration involves manifestations of blood stasis. To sum up, early stage AMD is primarily characterized by the deficiency of essence and blood whereas pathological products such as phlegm and blood stasis gradually appear in the mid and late stages, forming the characteristics of complex pathogenesis and difficult recovery.

5. Impact of TCM formulas on AMD

5.1 Impact of TCM formulas on Dry AMD

AMD can be grouped into several categories on the basis of histopathological features. Geographic atrophy and early and intermediate AMD are normally regarded as dry AMD that, from the perspective of TCM, originates from old age and physical deficiency. In this context, the disease location is in the fundus of the pupil God that belongs to the kidney storing essence. The eyes are the orifices of the liver that store blood. Meanwhile, the liver and kidney are homologous; that is to say, the essence and blood are homologous. The various pathological changes of dry AMD lie in the continuous attenuation of essence and blood with aging, so the age-related deficiency of essence and blood is the basic pathogenesis of dry AMD. Clinical studies have confirmed the effectiveness of tonifying essence and blood in dry AMD, using treatments with TCM such as Ziyin Mingmu pills (Fu and Hui 2019), Ziyin Bushen tablets (Su and Liu 2017), Shenling Baizhu storm (Liu 2009), Fuming capsule (Zhao, Yan, and Jiao 2013), Bushen Yijing Fang (Hou 2017) and Qihuang granule (Zhang et al. 2017; Zhong 2015). All of these treatments have been reported to alleviate symptoms of AMD, including reducing central visual field loss and improving vision-related quality of life in dry AMD patients. Using *Radix Rehmanniae*, *Polygonatum sibiricum* Red. and *Lycium barbarum* L.as key constituents, Ziyin Mingmu pills can effectively improve the symptoms of liver and kidney Yin deficiency, visual acuity and the visual field of patients, while not increasing the rate of adverse drug reactions (Fu and Hui 2019). Used in the treatment of dry AMD, both Fuming capsule (Zhao, Yan, and Jiao 2013) and Qihuang granules (Zhong 2015) can improve vision and the quality of life, while Qihuang granules markedly reduce the area of drusen that is measured by fundus examination and the serum concentration of the membrane attack complex, as well as inhibit the complement activation to protect RPE cells from attack.

Dry AMD belongs to the category of retinal degenerative disease and its pathological basis lies in irreversible damage to retinal neuronal cells. In recent years, with the development of regenerative medicine, stem cell transplantation has brought potential hope for the treatment of dry AMD. Stem cells are a population

of cells with self-replicative ability and multi-lineage differentiation potential in the growth of biological individuals. The "essence" in TCM theory is similar to stem cells in connotation and function (Zhang et al. 2004), and implies some efficacies for "tonifying kidney essence" treatment for dry AMD. Recent studies have found that bone marrow stem cells (BMSCs) can be stimulated to repair tissue damage in a safer and easier manner than the traditional bone marrow stem cell transplantation method (He et al. 2014; Tuekprakhon et al. 2021; Weiss and Levy 2018). Based on the above observations, a study (Hou 2017) has found that “Bushen Yijing Fang” can significantly improve electroretinogram (ERG) parameters and slow the loss of photoreceptor cells in mice with dry AMD. The data suggested mechanism is the promotion of mobilization of bone marrow cells (BMCs) in the early stage and of chemotaxis and adhesion, and homing of BMCs in the middle and late stages. In addition, the secretion of neurotrophic factors such as basic fibroblast growth factor, brain-derived neurotrophic factor and ciliary neurotrophic factor, plays a role in inhibiting the occurrence and development of photoreceptor injury and ultimately delaying the development of AMD.

5.2 Impact of TCM formulas on wet AMD

AMD patients typically develop the dry form initially, with wet AMD occurring against a background of dry AMD. This means that dry AMD can be considered a risk factor or even precursor state for wet AMD (Ambati and Fowler 2012). As mentioned previously CNV is characterized by the formation of new blood vessels, leading to leakage, hemorrhages and sudden loss of vision. Fundus neovascularization is similar to the pathological factor of blood stasis from the perspective of local syndrome differentiation in TCM, but its essence lies in the deficiency of qi, blood and Yin. Therefore, both tonifying viscera and eliminating pathogenic factors are often considered when TCM is used to treat wet AMD. *In vivo* animal studies (Tao et al. 2020; Tian et al. 2013) have found that the modified Zhujing decoction, possessing the effects of invigorating the kidney, tonifying qi, promoting blood circulation and removing blood stasis, could inhibit the growth and leakage of CNV as well as the expression of VEGF induced by krypton laser. A subsequent *in*

vitro experimental study (Gao et al. 2014) revealed that this decoction medicated serum suppressed the proliferation of ARPE-19 cells and the expression of VEGF in a hypoxic environment. This was likely to be achieved by improving blood circulation, ischemia and hypoxia, as well as repressing the secretion of cytokines.

The majority of clinical TCM prescriptions for treating wet AMD are a combination of tonifying viscera and eliminating pathogenic factors, such as Liangxue huayu decoction (Hu, Qi, and Chen 2013), Yiqi Yangyin Sanjie Tongluo decoction (Yang, Wang, et al. 2020), Bushen Lishui decoction (Zhang et al. 2020), modified Wendan decoction (Zhang, Lu, et al. 2019), Chailing decoction (Liao et al. 2013), Sanxue Mingmu tablets (Jiang et al. 2020) and Gushi decoction (Zhang 2017). In one study, 65 patients with wet AMD were divided into two groups randomly: 34 cases (39 eyes) in the treatment group and 31 cases (35 eyes) in the control group. The treatment group was treated with Yiqi Yangyin Sanjie Tongluo decoction, while the control group received esculin and digitalisglycosides eye drops via eye dripping and Hexue Mingmu tablets via oral administration. The results showed that the total effective rate of the treatment group, that is the ratio of cases with improved vision, reduced macular degeneration and enhanced visual field after treatment to the total cases, was higher than that of the control group (76.92% vs 62.86%). Macular retinal thickness after treatment was also thinner than the control group, suggesting Yiqi Yangyin Sanjie Tongluo decoction promotes the absorption of macular hemorrhage and exudation, reduces scar formation, and improves systemic symptoms of wet AMD patients (Yang, Wang, et al. 2020). Other studies have observed the effect of adjuvant treatment of wet AMD with TCM. For example, the Sanxue Mingmu tablet together with Combercept ophthalmic injection promoted the absorption of retinal exudation and improved the best corrected visual acuity of wet AMD patients (Jiang et al. 2020). Bushen Lishui decoction combined with intravitreal injection of Lucentis had enhancing effects on vision and reduced macular fovea retina thickness, making it more effective for the treatment of wet AMD than intravitreal injection of Lucentis alone (Zhang et al. 2020). It has also been

reported that the effectiveness of intravitreal injection of Lucentis in conjunction with the Chinese medicine Gushi decoction is improved, in comparison with anti-VEGF treatment alone, resulting in the interval between intravitreal injection of drugs being extended. This leads to a reduction in the frequency of anti-VEGF therapy, which reduces the economic burden of patients and health systems and reduces the amount of physical pain experienced by intravitreal injection (Zhang 2017). The impact of various TCM formulas on AMD is summarized in **Table 1**.

Table 1 Impact of traditional Chinese medicine formulas on age-related macular degeneration

Subjects	Formulas	Experimental group	Control group	Outcomes	Ref.
Dry AMD patients	**Ziyin Mingmu Pills** consist of *Radix Rehmanniae*, *Polygonatum sibiricum* Red., *Fructus Lycii*, *Cuscuta australis* R. Br., *Cornus officinalis* Sieb. et Zucc, *Dioscorea opposita* Thunb., *Poria*, *Broussonetia papyrifera* (L.) Vent., *Paeonia suffruticosa* Andr., *Panax notoginseng* (Burk.) F. H. Chen., *Radix Salviae liguliobae*, *Achyranthes bidentata* Bl., *Radix Angelicae sinensis*, *Haliotis diversicolor* Reeve., *Radix chuanxiong*, *Notopterygium incisum* Ting ex H. T. Chang., *Acorus tatarinowii* Schott. in the ratio of 3：3：3：2：2：2：2：2：2：1：1：1：1：1：1：1：1.	Vitamins B, C, E and adenosine disodium triphosphate tablets + Ziyin Mingmu Pills	Vitamins B, C, E and adenosine disodium triphosphate tablets	Efficiency of vision and visual field improvement ↑; TCM symptom score ↓; No serious adverse drug reactions	(Fu and Hui 2019)
Dry AMD patients	**Rougan Jianpi, Ziyin Mingmu Decoction** consist of *Bupleurum chinense* DC., *Radix Angelicae sinensis*, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch. *Atractylodes macrocephala* Koidz., *Citrus reticulata* Blanco,	Rougan Jianpi, Ziyin Mingmu Decoction	Qiju Dihuang Pill and Xiaoyao Pill	Total effective rate was 73.3%; Distant vision and central scotoma distribution ↑; TCM symptom score ↓.	(Lu et al. 2012)

	Dipsacus asper Wall. ex Henry, *Radix Rehmanniae*, *Fructus Lycii*, *Polygonatum sibiricum* Red., *Polygonum multiflorum* Thunb., *Curcuma longa* L., *Ligustrum lucidum* Ait., *Psoralea corylifolia* L., *Pueraria lobata* (Willd.) Ohwi in the ratio of 2:4:4:2:3:3:4:4:4:4:4:4:4:4:4.				
Dry AMD patients	**Ziyin Bushen Tablets** consist of *Radix Rehmanniae*, *Polygonum multiflorum* Thunb., *Ligustrum lucidum* Ait., *Morus alba* L., *Paeonia lactiflora* Pall., *Dioscorea opposita* Thunb., *Alisma orientale* (Sam.) Juzep, *Ophiopogon japonicus* (L. f) Ker-Gawl., *Schisandra chinensis* (Turcz.) Baill.	Ziyin Bushen Tablets	——♦	Visual related quality of life ↑.	(Su and Liu 2017)
Dry AMD patients	**Shenling Baizhu storm** consist of *Poria*, *Panax ginseng* C. A. Mey., *Glycyrrhiza uralensis* Fisch, *Atractylodes macrocephala* Koidz., *Dioscorea opposita* Thunb., *Nelumbo nucifera* Gaertn., *Coix lacryma-jobi* L. var. mayuen (Roman.) Stapf, *Amomum villosum* Lour., *Platycodon grandiflorum* (Jacq.) A.DC., *Dolichos lablab* L. in the ratio of 3:2:2:3:3:4:6:2:2:2.	Shenling Baizhu storm	Vitamins C, E and inosine tablets	Efficacy of TCM syndrome and quality of life ↑.	(Liu 2009)
AMD* patients	**Yiqi Yangyin Mingmu Decoction** consist of *Radix Rehmanniae*, *Codonopsis pilosula* (Franch.) Nannf., *Ligustrum lucidum* Ait., *Polygonum multiflorum* Thunb., *Cornus officinalis* Sieb. et Zucc, *Dioscorea opposita* Thunb., *Poria*, *Paeonia suffruticosa* Andr., *Citrus reticulata* Blanco, *Leonurus japonicus* Houtt.,	Photodynamic therapy + Yiqi Yangyin Mingmu Decoction	Photodynamic therapy	Effective rate of vision treatment was 88.10%; Effective rate of fundus treatment was 90.48% Vision ↑; Fundus hemorrhage and exudation area, retinal thickness, TCM syndrome score ↓.	(Li, Shao, and Yan 2019)

	Alisma orientale (Sam.) Juzep, *Glycyrrhiza uralensis* Fisch. in the ratio of 8:8:5:5:4:4:3:3:3:3:3:2.				
AMD* patients	**Yiqi Fuming Decoction** consist of *Radix Astragali*, *Codonopsis pilosula* (Franch.) Nannf., *Poria*, *Pueraria lobata* (Willd.) Ohwi, *Leonurus japonicus* Houtt., *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., *Panax notoginseng* (Burk.) F. H. Chen. in the ratio of 30:20:20:15:15:12:10:3.	Photodynamic therapy + Yiqi Fuming Decoction	Photodynamic therapy	Effective rate of treatment was 95.35%; Catalase, glutathione peroxidase-px (GSH-Px), regulatory T cells ↑; reactive oxygen species (ROS), malondialdehyde (MDA), interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), Th17 ↓.	(Wang et al. 2019)
Dry AMD patients	**Fuming Capsule** consist of *Cornus officinalis* Sieb. et Zucc, *Dendrobium nobile* Lindl., *Fructus Lycii*, etc.	Fuming Capsule	Mingmu Dihuang pills	Total effective rate was 71.87%; Visual acuity and central scotoma distribution improved; Area of drusen and TCM syndrome score ↓.	(Zhao, Yan, and Jiao 2013)
AMD* patients	**Qiju Dihuang Pills** consist of *Poria*, *Radix Rehmanniae*, *Cornus officinalis* Sieb. et Zucc, *Alisma orientale* (Sam.) Juzep, *Fructus Lycii*, *Chrysanthemum morifolium* Ramat., *Paeonia suffruticosa* Andr., *Dioscorea opposita* Thunb..	VitaminsA, C, E and compound anisodine injection + Qiju Dihuang Pills	VitaminsA, C, E and compound anisodine injection	Total effective rate was 90.91%; Levels of packed cell volume ↑; Levels of serum C-reactive protein (CRP) level and chemokine receptor 3 (CCR3) on the surface of T lymphocytes and eosinophils in peripheral blood, erythrocyte sedimentation rate ↓.	(Wang and Gao 2016)
AMD* patients	**Modified Danggui Shaoyao powder** consist of *Radix Angelicae sinensis*, *Paeonia lactiflora* Pall., *Radix*	Esculin and digitalisglycosides eye drops +	Vitamins C, E combined with Esculin and	Visual acuity, total effective rate, complement C3, complement C4 ↑; CRP,	(Cao 2016)

	chuanxiong, Atractylodes macrocephala Koidz., *Poria, Alisma orientale* (Sam.) Juzep., *Pinellia ternata* (Thunb.) Breit., *Citrus reticulata* Blanco., *Eclipta prostrata* L., *Ginkgo biloba* L., *Lycopus lucidus* Turcz. var. *hirtus* Regel., *Whitmania pigra* Whitman, *Fritillaria thunbergii* Miq., *Oroxylum indicum* (L.) Vent.	Modified Danggui Shaoyao powder	digitalisglycosides eye drops	hs- CRP, Immunoglobulin G (IgG) of anti-cardiolipin antibody ↓.	
Dry AMD mouse model induced by sodium iodate	**Bushen Yijing Fang** consist of *Polygonum multiflorum* Thunb., *Polygonatum sibiricum* Red., *Cuscuta australis* R. Br., *Fructus Lycii, Radix Astragali, Radix Angelicae sinensis*	Bushen Yijing Fang	Distilled water	ERG index ↑; Promote the mobilization of bone marrow cells (BMCs) in the early stage, and chemotaxis, adhesion and homing of BMCs in the middle and late stage, and secrete neurotrophic factors.	(Hou 2017)
Dry AMD patients	**Qihuang particles** consist of *Radix Salviae liguliobae, Fructus Lycii, Broussonetia papyrifera* (L.) Vent., *Leonurus japonicus* Houtt., etc.	Qihuang particles	Vitamins C	Vision ↑; TCM syndrome score ↓.	(Zhang et al. 2017)
Dry AMD patients	**Qihuang granule** consist of *Radix Salviae liguliobae, Fructus Lycii, Broussonetia papyrifera* (L.) Vent., *Leonurus japonicus* Houtt., etc.	Qihuang particles	Vitamins C	Vision, total effective rate ↑; TCM syndrome score, drusen area, complement C5b-9 complex level ↓.	(Zhong 2015)
Wet AMD patients	**Liangxue huayu decoction** consist of *Typha angustifolia* L., *Curcuma longa* L., *Eclipta prostrata* L., *Ligustrum lucidum* Ait., *Radix Angelicae sinensis, Radix*	Liangxue huayu decoction	——♦	Visual acuity improvement rate was 78.95%; CCR3 on T lymphocytes and/or eosinophil peripheral blood cell surface ↓.	(Hu, Qi, and Chen 2013)

	chuanxiong, Radix Salviae liguliobae, Fructus Lycii, Cuscuta australis R. Br., *Radix Astragali, Pinellia ternata* (Thunb.) Breit., *Fritillaria thunbergii* Miq..				
AMD* patients	**Jianpi Huayu Decoction** consist of *Radix Astragali, Pueraria lobata* (Willd.) Ohwi, *Radix Rehmanniae, Poria, Radix Salviae liguliobae, Fructus Lycii, Atractylodes macrocephala* Koidz., *Sargassum pallidum* (Turn.) C. Ag., *Laminaria japonica* ***Aresch.***, *Radix Angelicae sinensis, Cuscuta australis* R. Br., *Schisandra chinensis* (Turcz.) Baill. in the ratio of 30:30:20:20:20:20:15:15:15:10:10:6.	Jianpi Huayu Decoction	Vitamins E, C and zinc sulfate tablets	Vision, visual acuity, SOD, peak systolic short-velocity (PSV), end-diastolic flow (EDV) ↑; Clinical symptom score, MDA, resistance index (RI) ↓.	(Wu, Yang, and Shang 2018)
Wet AMD patients	**Yiqi Yangyin Sanjie Tongluo Decoction** consist of *Ostrea gigas* Thunberg, *Area subcrenata Lischke, Radix Rehmanniae, Radix Astragali, Atractylodes macrocephala* Koidz., *Poria, Cornus officinalis* Sieb. et Zucc, *Taxillus chinensis* (DC.) Danser, *Ligustrum lucidum* Ait., *Eclipta prostrata* L., *Leonurus japonicus* Houtt., *Prunella vulgaris* L., *Pheretima aspergillum* (E. Perrier), *Glycyrrhiza uralensis* Fisch., *Whitmania pigra* Whitman in the ratio of 30:30:15:10:10:10:10:10:10:10:10:10:10:3.	Yiqi Yangyin Sanjie Tongluo Decoction	Esculin and digitalisglycosides eye drops combined with Hexue Mingmu tablets	Total effective rate was 76.92%; Visual acuity, 30°visual field ↑; Macular retinal thickness, TCM syndrome score ↓.	(Yang, Wang, et al. 2020)

	Bushen Lishui Decoction consist of *Radix Rehmanniae*, *Plantago asiatica* L., *Pueraria lobata* (Willd.) Ohwi, *Fructus Lycii*, *Broussonetia papyrifera* (L.) Vent., *Cuscuta australis* R. Br., *Cinnamomum cassia* Presl, *Polyporus umbellatus* (Pers.) Fries, *Poria*, *Prunella vulgaris* L., *Ostrea gigas* Thunberg, *Radix Salviae liguliobae*, *Radix chuanxiong* in the ratio of 20:15:15:12:12:12:10:10:10:10:10:9:9.				
Wet AMD patients		Intravitreal injection of Lucentis + Bushen Lishui Decoction	Intravitreal injection of Lucentis	Best corrected visual acuity (BCVA) ↑; Macular retinal thickness, TCM syndrome score ↓.	(Zhang et al. 2020)
	Modified Wendan Decoction consist of *Citrus reticulata* Blanco, *Pinellia ternata* (Thunb.) Breit, *Poria*, *Atractylodes macrocephala* Koidz., *Citrus aurantium* L., *Bambusa tuldoides* Munro, *Glycyrrhiza uralensis* Fisch., *Leonurus japonicus* Houtt., *Typha angustifolia* L.in the ratio of 10:10:15:15:12:15:3:15:10.				
Wet AMD patients		Vitamins E and Mecobalamin capsules + Modified Wendan Decoction	Vitamins E and Mecobalamin capsules	BCVA↑; Macular choroidal thickness, incidence of neovascular leakage ↓.	(Zhang, Lu, et al. 2019)
	Chailing Decoction consist of *Bupleurum chinense* DC., *Pinellia ternata* (Thunb.) Breit, *Alisma orientale* (Sam.) Juzep, *Poria*, *Polyporus umbellatus* (Pers.) Fries, *Atractylodes macrocephala* Koidz., *Scutellaria baicalensis* Georgi, *Panax ginseng* C. A. Mey., *Glycyrrhiza uralensis* Fisch., *Cinnamomum cassia* Presl, *Zingiber officinale* Rosc. in the ratio of 15:9:10:10:15:20:10:10:5:10:5, Jujubae Fructus 3 pieces.				
Wet AMD patients		Photodynamic therapy + Chailing Decoction	Photodynamic therapy	Choroidal neovascularization (CNV) leakage area, CNV complex thickness ↓.	(Liao et al. 2013)
	Sanxue Mingmu Tablets consist of *Panax notoginseng* (Burk.) F. H. Chen, *Typha angustifolia* L., *Imperata cylindrica* Beauv. var. *major* (Nees) C. E. Hubb., *Stephania tetrandra* S. Moore, *Leonurus japonicus* Houtt., *Rheum palmatum* L., *Equisetum hyemale* L., *Pheretima aspergillum* (E. Perrier), *Alisma*				
Wet AMD patients		Intravitreal injection of conbercept + Sanxue Mingmu Tablets	Intravitreal injection of conbercept	BCVA, PSV, EDV ↑; RI, macular foveal thickness (CMT), recurrence rate ↓.	(Jiang et al. 2020)

	orientale (Sam.) Juzep, *Polyporus umbellatus* (Pers.) Fries, *Crataegus pinnatifida* Bge. in the ratio of 3:20:30:15:20:10:15:10:15:20:10.				
AMD* patients	**Qiming Pills** consist of *Radix Rehmanniae*, *Cornus officinalis* Sieb. et Zucc, *Dioscorea opposita* Thunb., *Fructus Lycii*, *Chrysanthemum morifolium* Ramat., *Radix Astragali*, *Codonopsis pilosula* (Franch.) Nannf., *Alisma orientale* (Sam.) Juzep, *Poria*, *Paeonia suffruticosa* Andr., *Haliotis diversicolor* Reeve, *Cryptotympana pustulata* Fabricius, *Equisetum hyemale* L., etc.	Vitamins B_6, C, E and ethamsylate, Xuesaitong + Qiming Pills	Vitamins B_6, C, E and ethamsylate, Xuesaitong	Effective rate of treatment was 78.84%; visual evoked potential improved, Plasma homocysteine levels ↓.	(Zhuo and Peng 2013)
Wet AMD patients	**Gushi Decoction** consist of *Radix Astragali*., *Codonopsis pilosula* (Franch.) Nannf., *Atractylodes macrocephala* Koidz., *Poria*, *Alisma orientale* (Sam.) Juzep, *Fructus Lycii*, *Ligustrum lucidum* Ait., *Polygonum multiflorum* Thunb., *Pinellia ternata* (Thunb.) Breit, *Bambusa tuldoides* Munro, *Fritillaria thunbergii* Miq., *Citrus reticulata* Blanco, *Radix chuanxiong*, *Prunus persica* (L.) Batsch, *Buthus martensii* Karsch, *Carthamus tinctorius* L., *Pheretima aspergillum* (E. Perrier), *Panax notoginseng* (Burk.) F. H. Chen. in the ratio of 20:15:12:12:15:15:15:15:15:15:12:12 :12:12:12:6:10:12:6.	Intravitreal injection of Lucentis + Gushi Decoction	Intravitreal injection of Lucentis	BCVA, CNV closed situation ↑; CMT, injection frequency of anti-VEGF drugs ↓.	(Zhang 2017)

Note: *Not acquired AMD type. ♦Self-control research method was adopted. ↑ Indicates upregulated. ↓ Indicates downregulated.

6. Possible functions of TCM compounds used in AMD treatment

Based on the TCM inheritance platform, researchers analyzed 196 prescriptions for treating AMD (including 168 herbs) and found that the herbs used most frequently were *Poria cocos* (Schw.) Wolf, *Radix*

Angelicae sinensis, *Radix Rehmanniae*, *Fructus Lycii*, *Radix Salviae liguliobae*., *Radix Astragali*., *Radix chuanxiong*. Extracts and compounds from these herbs provide new insights into the future direction of Chinese medicine drug development in the treatment of AMD (Qin 2017).

6. 1 *Poria*

Poria, the dried sclerotia of *Poria cocos (*Schw.) Wolf, is an edible medicinal fungus known as “Fuling” in Chinese, which has been used in TCM for more than two thousand years. Reported effects include promoting diuresis and resolving dampness, strengthening the spleen and calming the mind. *Poria cocos* (Schw.) Wolf polysaccharide (PCP) is one of the most important active substances in *Poria cocos* (Schw.) Wolf, accounting for 84% of all components in dried sclerotia and possessing anti-inflammatory and anti-oxidative properties. PCP significantly attenuates oxidized low-density lipoprotein (ox-LDL) induced oxidative stress (OS), as evidenced by decreased reactive oxygen species (ROS) and malondialdehyde (MDA) levels, and increased SOD activity. At the same time, PCP suppresses the induction effect of ox-LDL on inflammatory cytokines and inflammatory mediators. Mechanistically, PCP activates the extracellular signal-regulated kinase (ERK)1/2 signaling pathway, increasing nuclear factor erythroid 2-related factor 2 (Nrf2) translocation from the cytoplasm to the nucleus and heme oxygenase-1 (HO-1) expression. In summary, these results demonstrate that PCP exerts its protective effects against OS and inflammation via the ERK/Nrf2/HO-1 signaling pathway (Zhao et al. 2020). PCP has a strong scavenging effect on free radicals and participates in the regulation of antioxidant enzymes, which may be the main pharmacodynamic mechanism by which *Poria* exerts its anti-oxidative effects (Guo et al. 2018). The carboxymethyl polysaccharide CMP33, also isolated from edible and pharmaceutical mushroom *Poria*, can reduce nitric oxide (NO) release and cytokine secretion (interleukine (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α)), and also inhibit lipopolysaccharide (LPS)-stimulated overproduction of NO, IL-6, TNF-α and IL-1β in RAW264.7 cells, which suggests that CMP33 possesses anti-inflammation and immune-stimulation activities (Liu et al. 2019).

Researchers isolated six triterpenoids from the ethanol extract of *Poria* sclerotia, including poricoic acid A, 3-O-acetyl-16α-hydroxydehydrotrametenolic acid, polyporic acid C, 3β-hydroxylmonili-7, 9(11), 24-trien-21-oic acid, trametenolic acid and dehydroeburictrametoic acid, which inhibit LPS-stimulated NO production and NO lyase expression in Raw264.7 cells. Among the above, poricoic acid A exerts the highest inhibitory activity and reduces prostaglandin E (PGE) levels by downregulating cyclooxygenase-2 (COX-2) protein expression (Lee et al. 2017). It has been speculated that it targets macrophage-mediated inflammatory response via the nuclear factor-κB (NF-κB) signaling pathway (Jeong et al. 2014).

Although there are not many studies on the effectiveness of single *Poria* in the treatment of AMD, a large dose of *Poria* combined with Jiangtang Huoxue Recipe has been shown to reduce exudation area, the number of microhemangiomas in retinopathy patients, and the serum VEGF level. As a result, the researchers suggest that *Poria* inhibits retinal vascular endothelial cell proliferation and reduces the number and permeability of microhemangiomas by decreasing the serum VEGF level (Liu and Chen 2018).

6.2 *Radix Angelicae sinensis*

Radix Angelicae sinensis **(**Danggui in Chinese), the dried root of *Angelica sinensis (Oliv.) Diels*, is a crude drug widely used in the alleviation of various disease syndromes in TCM for more than two thousand years. Investigations at a cellular level suggest that *Radix Angelicae sinensis* extract could significantly enhance the mitochondrial membrane potentials and fluctuate the excitability of adult retinal nerve cells (Shen, Wang, and Li 2013). This has certain protective effect on adult retinal nerve cells and as a result has been proposed as a new adjuvant treatment drug for preventing and treating retinal diseases.

Angelica polysaccharide, principally composed of glucose and galactose, is the main pharmacological component of *Radix Angelicae sinensis*. Recent pharmacological studies (Oh et al. 2019; Zhang, Xue, et al. 2019) have shown that Angelica polysaccharide is able to enhance the immune function, scavenging active oxygen free radicals with strong antioxidant capacity. Additionally, it was found to have a neuroprotective

effect on the retina (Qi et al. 2018), with the main mechanisms being reduction of MDA and NO levels, increased SOD activity, suppression of cysteine aspartic acid protease-3 (Caspase-3) mRNA and protein expression in retinal tissue.

Z-ligustilide (3-butylidene-4,5-dihydrophthalide), one of the most essential volatile oils from the Chinese herb *Radix Angelicae sinensis*, can protect retinal function and morphology from damage and alleviate retinal cell apoptosis by increasing the expression of B-cell lymphoma-2 (Bcl-2) and suppressing the expression of Bcl-2 related X protein (Bax) and cleaved-Caspase-3. Moreover, Z-ligustilide may combat inflammation by regulating expression of IL-1β, TNF-α and VEGF-A (Yang, Ma, and Liu 2020). Another study demonstrated the potent neuroprotective effects of Z-ligustilide on the LPS-induced pro-inflammatory response in primary rat microglia, which is mediated at least partially by its effects on the NF-κB signaling pathway, providing valuable information about the mechanisms underlying the neuroprotective effects of Z-ligustilide (Wang et al. 2010).

6.3 *Radix Rehmanniae*

Radix Rehmanniae (Dihuang in Chinese) is the fresh or dry root of *Rehmannia glutinosa* Libosch. which belongs to the family of Scrophulariaceae. Catalpol, an important component of *Radix Rehmanniae*, has been found to repress hydrogen peroxide (H_2O_2)-induced apoptosis by preventing cytochrome c release and inactivating the asparaginase cascade (Jiang et al. 2004). Other functions include enhancing the activity of antioxidant enzymes (SOD, glutashione peroxidase (GSH-Px), catalase (CAT)) and decreasing the level of MDA in order to restore the balance between oxidase and antioxidant enzymes (Zhu, Wang, et al. 2016).

Polysaccharides from *Radix Rehmanniae*, are able to suppress the expression of pro-apoptotic gene *egl-1* (Li et al. 2016) and activate the antioxidant enzyme system to delay aging, which is connected with the regulation of antioxidant gene and the *DAF-16* gene expression in the insulin/IGF-1 signaling pathway (Yuan et al. 2019). A previous study (Hesp, Smant, and Kammenga 2015) has found that the mammalian *DAF-16*

gene is involved in growth control, apoptosis, DNA repair and OS.

6.4 *Fructus Lycii*

Fructus Lycii (Gouqizi in Chinese), the dried and ripe fruit of *Lycium bararum* L, is an important ingredient in promoting health and longevity as well as a food supplement in Western countries. Recent investigations of *Fructus Lycii* have focused on some of its particularly valuable components, the *Lycium bararum* L polysaccharides (LBP), which constitute more than 40% of the fruit extract (Yang et al. 2012) and have inhibitory effects on OS and inflammatory the response. The research demonstrated a neuroprotective effect of LBP on retinal ganglion cells (RGCs) in glaucoma (Chang and So 2008; Li et al. 2011), mechanistically, LBP can protect RGCs from apoptosis by inhibiting the generation of ROS and the reduction of mitochondrial membrane potential (Liu et al. 2020). Further study is needed to determine the mechanism of the protective effect of LBP on RGCs *in vitro*. Lipofuscin is a non-degradable pigment with fluorescence and is sensitive to blue light. Under aerobic environment, blue light stimulates the retina to initiate photooxidation, which triggers cellular oxidative damage and disrupts the normal redox response of cells, resulting in RPE cell injury or even necrosis. However, LBP is able to reduce the blue light-induced oxidative damage in ARPE-19 cells by inhibiting excessive production of lipofuscin (Anderson et al. 2018). This protective effect on photoreceptor cells has received increasing attention. Recently, another important finding (Zhu, Zhao, et al. 2016) has demonstrated that LBP can inhibit N-methyl-N-nitrosourea-induced apoptosis of rat photoreceptor cells and protect retinal structure by regulating the expression of poly (ADP-ribose) polymerase and caspase.

Multiple inflammatory factors are closely associated with AMD progression. LBP has an inhibitory effect on the levels of serum inflammatory factors (including IL-2, IL-6, TNF-α, interferon-α (INF-α), intercellular adhesion molecule-1 (ICAM-1)). In addition, serum SOD and GSH-PX activities are significantly increased after LBP intervention, which is related to the antioxidant and anti-inflammatory activities mediated by NF-κB (Du et al. 2016). Amyloid β (Aβ) is a widespread physiological peptide in the human body $A\beta_{1\text{-}40}$ may in

fact be one of the main components of drusen (Wang et al. 2017). Studies (Gao et al. 2015) have shown that $A\beta_{1\text{-}40}$ promotes the increase of IL-1β, IL-8, IL-6 and TNF-α levels in the retinal nerve fiber layer, RPE and choroidal tissue of rats, as well as activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome that is considered to be an important cause of RPE dysfunction and degeneration. LBP effectively protects ARPE-19 cells against $A\beta_{1\text{-}40}$ oligomer-induced damage via its anti-$A\beta_{1\text{-}40}$ oligomer and anti-pyrogenic effects (Yang, So, et al. 2020).

VEGF, a key regulator of angiogenesis, promotes cell proliferation and induces neovascularization by binding to receptors on endothelial cell membranes. It has previously been demonstrated that the receptors related to retinal neovascularization include VEGF receptor (VEGFR)1, 2, and 3, among which VEGFR1 is more expressed in retinal microvasculature, while VEGFR2 and VEGFR3 are more expressed in leaky microvasculature (Ruszkowska-Ciastek et al. 2014). *In vivo*, LBP significantly reduces the levels of VEGFR1, VEGFR2 and VEGFR3 in the retina of mice, suggesting that it has the potential to inhibit retinal angiogenesis, OS and inflammation (Zhang et al. 2016).

Drusen are abnormal extracellular matrix (ECM) deposits characteristic of AMD. Matrix metalloproteinase (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are the main regulators of ECM renewal, and also the main factors that maintain the balance of ECM degradation and synthesis (Leu et al. 2002). An *in vitro* study (Huang et al. 2013) showed that in ARPE-19 cells both MMP-2 and TIMP-2 were up-regulated under OS, while the intervention of *Fructus Lycii* extract, lutein and zeaxanthin, decreased the high expression of MMP-2 and TIMP-2, suggesting that lutein and zeaxanthin play a vital role in AMD.

6.5 *Radix Salviae liguliobae*

*Radix Salviae liguliobae (*Danshen in Chinese), also known as purple salvia and red roots, is the dried root of *Salvia miltiorrhiza* Bge., which mainly contains fat-soluble diterpenoids and water-soluble phenolic acids. Recently, some researchers (Quan, Qin, and Quan 2020) found that *Radix Salviae liguliobae*. extract

inhibited high glucose-induced apoptosis of human retinal vascular endothelial cells (HRECs), and its mechanism may be by inhibiting the activation of the NF-κB signaling pathway, up-regulating the expression of Bcl-2 protein, down-regulating Caspase-3 and Bax levels, as well as decreasing the secretion of inflammatory cytokines. In brief, *Radix Salviae liguliobae* extract protects HRECs from high-glucose-induced damage by inhibiting the NF-κB signaling pathway to suppress inflammation and reduce apoptosis.

Tanshinone is the active ingredient of *Radix Salviae liguliobae* contains more than 50 compounds such as liposoluble compound tanshinone I, tanshinone IIA and tanshinone IIB, of which tanshinone IIA inhibits proliferation, migration and angiogenesis of HRECs, which is related to down-regulation of VEGF and ICAM-1 expression (Fan et al. 2017). Further study (Han et al. 2018) found that sodium tanshinone IIA sulfonate a water-soluble compound derived from the sulfonation of tanshinone activated the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway, inhibited autophagy of ARPE-19 cells under OS, and reduced the expression of autophagy proteins, so demonstrating a protective effect on ARPE-19 cells in conditions of OS and offering a promising strategy for AMD treatment.

6.6 *Radix Astragali*

Radix Astragali, known as Huangqi in China, is the dried root of *Astragalus membranaceus* (Fisch.) Bge. and has been shown to contain mainly astragalus polysaccharides (APS) and astragaloside IV(AS-IV). RPE cells are of central importance in the eye, supporting the nutrition and metabolism of photoreceptor cells. Hence, RPE cell damage may cause the degeneration of photoreceptor cells (Organisciak and Vaughan 2010). A study has shown that the survival rate of ARPE-19 cells was increased and apoptosis was decreased after the intervention of APS, which was due to a decrease in Caspase-3 expression (Si 2015). In addition, APS antioxidant potential was also connected with increased SOD and GSH-PX activities, as well as decreased ROS and MDA levels (Li et al. 2016).

Another study (Zhou et al. 2017) found that AS–IV markedly inhibited the decrease of ARPE-19 cell

viability induced by methyl glyoxal. On one hand, the mechanism is related to regulating the expression of the Bcl-2 family and Caspase family proteins in the mitochondrial pathway and so playing an anti-apoptosis role; on the other hand, AS-IV intervention can reduce the level of ROS and MDA, increase the activity of SOD, and thus enhance the antioxidant capacity of cells. The exploration of the application of Chinese herbal monomer AS-IV in ophthalmology has been substantial. Researchers modified AS-IV eye drops into nanoemulsion gel with a long ocular residence time and strong permeability, and found that the gel inhibited retinal cell apoptosis and repaired mitochondrial DNA damage in experimental dry AMD rats, an effect that was connected with the regulation of Kelch Like ECH Associated Protein 1(Keap-1)-Nrf2/antioxidant response element (ARE) signaling pathway (Xu 2018). Recently, researchers incorporated AS-IV into phospholipid complexes and loaded them into three different sizes (20nm, 50nm and 90nm) of AS-IV lipid nanocapsule (ASIV-LNC). They found that ASIV-LNCS-20 effectively inhibited the production of ROS in dry AMD mouse model and decreased the apoptosis rate of retinal cells from 5.12% to 0.533%, indicating a substantial protective effect on the morphology and function of the retina (Sun et al. 2020) .

6.7 *Radix chuanxiong*

Radix chuanxiong is derived from the rhizome of Ligusticum chuanxiong Hort. and grows primarily in Southwestern China and is usually used to promote blood flow and alleviate pain (Yuan et al. 2020). Hypoxia inducible factor (HIF)-1 is closely associated with VEGF and together promotes the development of AMD. Ligustrazine is an alkaloid isolated from *Radix chuanxiong*, which can dilate blood vessels, promote microcirculation and improve tissue ischemia and hypoxia. A study (Wang, Xu, and Li 2015) shows that the mechanism of ligustrazine in treating retinopathy is possibly related to down-regulation of HIF-1 and VEGF expression. Fortunately, two main mechanisms of neuroprotection of *Radix chuanxiong*. extract have been confirmed (Wang et al. 2020). First, it promotes the production of neural differentiation factors; second, it inhibits expression of IL-1β, TNF-α and glial fibrillary acidic protein (GFAP), thus exerting an anti-

neuroinflammatory effect. Mechanisms and targets of active ingredients of herbs used in the treatment of AMD are shown in **Table 2**.

Table 2 The mechanisms and targets of the active ingredients of herbs used in traditional Chinese medicine treatment of age-related macular degeneration

Formation	Experiment type	Experiment subject	Mechanisms and targets	Ref
Poria cocos (Schw.) Wolf polysaccharide	*In vitro*	Vascular smooth muscle cells	Regulate ERK/Nrf2/HO-1 signaling pathway.	(Zhao et al. 2020; Guo et al. 2018)
	In vitro	RAW264.7 cells	Inhibit IL-6, TNF-α, and IL-1β overproduction.	(Liu et al. 2019)
Triterpenoids from *Poria*	*In vitro*	Raw264.7 cells	Down-regulate COX-2 protein expression and decrease PGE levels.	(Lee et al. 2017)
	In vitro	RAW264.7 macrophages	Inhibit LPS-induced DNA-binding activity of NF-κB and nuclear translocation of NF-κB p65.	(Jeong et al. 2014)
Angelica polysaccharide	*In vivo*	SD rats	①Reduce MDA and NO levels and increase SOD activity. ②Decrease the expression of Caspase-3mRNA and protein.	(Qi et al. 2018)
Z-ligustilide	*In vivo*	Rats	①Increase the expression of Bcl-2 and suppress the expression of Bax and cleaved-Caspase-3.②Down-regulate expression of IL-1, TNF-α and VEGF-α.	(Yang, Ma, and Liu 2020)
	In vitro	Rat microglia	Regulate NF-κB signaling pathway.	(Wang et al. 2010)
Radix Rehmanniae Polysaccharides	*In vitro*	Nematodes	Decrease the proapoptotic gene egl-1 expression.	(Li et al. 2016)
	In vitro	Nematodes	Activate the antioxidant enzyme system, stimulate the antioxidant genes expression, and regulate the DAF-16 gene expression on insulin/IGF-1 signaling pathway.	(Yuan et al. 2019)
Catalpol	*In vivo*	Rats	Enhance the antioxidant enzymes activity (SOD, GSH-PX, CAT), and reduce MDA level.	(Zhu, Wang, et al.

				2016)
	In vitro	Rat pheochromocytoma cell line	Prevent cytochrome c release, inactivate asparaginase cascade, and inhibit hydrogen peroxide-induced apoptosis.	(Jiang et al. 2004)
Lycium barbarum polysaccharides	*In vitro*	Retinal ganglion cells	Inhibit ROS generation and reduce mitochondrial membrane potential.	(Liu et al. 2020)
	In vivo	SD rats	Inhibit the levels of inflammatory factors and increase the activities of SOD and GSH-PX.	(Du et al. 2016)
	In vitro	ARPE-19	Anti-A β 1-40 oligomer and anti-pyroptosis.	(Yang, So, et al. 2020)
	In vivo	Mice	Reduce the levels of VEGFR1, VEGFR2 and VEGFR3	(Zhang et al. 2016)
Lutein and zeaxanthin	*In vivo*	AMD model mice	Regulate the balance of MMP/TIMP system.	(Huang et al. 2013)
Radix Salviae liguliobae extract	*In vitro*	Human retinal vascular endothelial cells	Inhibit the activation of NF- κ B signaling pathway.	(Quan, Qin, and Quan 2020)
Tanshinone	*In vitro*	Human retinal endothelial cells	Down-regulate VEGF and ICAM-1 expression.	(Fan et al. 2017)
	In vitro	ARPE-19	Activate PI3K/AKT/mTOR pathway, inhibit autophagy of ARPE-19 cells, and reduce the expression of autophagy proteins.	(Han et al. 2018)
Astragalus polysaccharides	*In vitro*	Nematodes	Increase SOD and GSH-PX activities, as well as reduce ROS and MDA levels.	(Li et al. 2016)
	In vitro	ARPE-19	Decrease Caspase-3 expression.	(Si 2015)
Astragaloside IV	*In vitro*	ARPE-19	①Reduce ROS and MDA level, and increase the activity of SOD. ②Regulate Bcl-2 family and Caspase family proteins expression in the mitochondrial pathway.	(Zhou et al. 2017)
	In vivo	Dry AMD rats model	Regulate Keap1-Nrf2/ARE signaling pathway.	(Xu 2018)
	In vivo	Dry AMD mice model	Decrease ROS production and reduce the apoptosis rate.	(Sun et al. 2020)
Ligustrazine	*In vivo*	Patients with	Down-regulated HIF-1 and VEGF expression	(Wang,

		retinopathy		Xu, and Li 2015)
Radix chuanxiong extract	*In vivo*	Wister rats	Promote production of neural differentiation factor and inhibit the expression of IL-1β, TNF-α and GFAP.	(Wang et al. 2020)

6.8 Other pure compounds as a source of treatment for AMD

In addition to the above active ingredients of herbs, some pure compounds from other herbs also have potential to treat AMD. The mechanisms of action of numerous flavonoids have been evaluated in the AMD-related models. Flavonoids are a group of natural chemical compounds found mainly in fruits, vegetables and Chinese herbs. Kaempferol is a natural flavonoid widely distributed in many traditional medicines such as *Paeoniae Radix Alba*, *Herba Patriniae*, *Ardisiae Japonicae Herba*, and has been reported to possess antioxidant, anti-inflammatory, anticancer and antimicrobial activities. Degenerative and progressive conditions of RPE cells are the key pathogenic mechanisms in AMD (van Lookeren Campagne et al. 2014). One study indicates that kaempferol protects human RPE cells (ARPE-19) from H_2O_2-induced oxidative cell damage and apoptosis through regulating the Bax/Bcl-2 and caspase-3 molecules expression. Kaempferol also downregulates VEGF mRNA expression in ARPE-19 cells and affects the balance between oxidation and antioxidation through regulating the activities of ROS and SOD (Du, An, He, Zhang, He, et al. 2018). Another study shows that the kaempferol protects RPE cell from H_2O_2-induced damage via the poly (ADP-ribose) polymerase-1 (PARP1)/silent information regulator 1 (SIRT1) signaling pathway (Al Sabaani 2020). Quercetin is a ubiquitous flavonoid compound, which is widely distributed in *Ardisiae Japonicae Herba*, *Folium Artemisiae Argyi*, and *Anisi Stellati Fructus*. The ROS accumulation was reduced, and expression of Nrf2 and NAD(P)H quinone oxidoreductase-1 (NQO1) was induced in ARPE-19 cells following pretreatment with quercetin (Weng et al. 2017). Myricetin derivatives, isolated from leaf extract of *Syzygium malaccense*, protected the ARPE-19 cells against glucose oxidase-H_2O_2-induced oxidative stress by the activation of Nrf2/nuclear factor erythroid 2-related factor 2 (NFE2L2) and antioxidant enzyme (*SOD2*), as well as

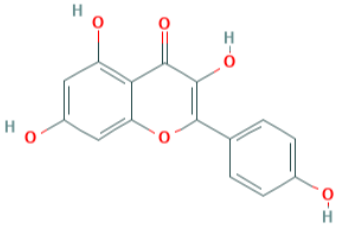
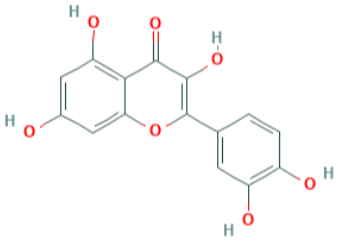
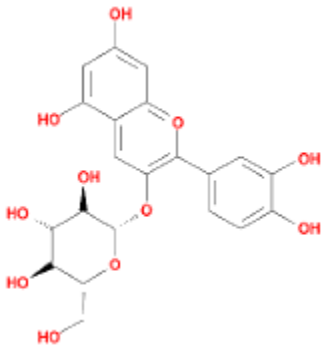
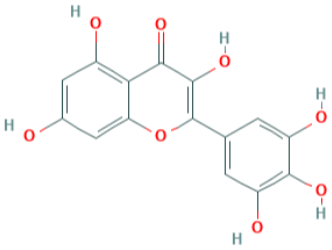
downregulation of nitric oxide producer (*NOS2*) (Arumugam et al. 2019). Hesperidin is a citrus flavonoid that has been demonstrated to possess numerous biological properties, particularly antioxidant and anti-inflammatory capacity. Studies have found that hesperetin, the aglycone of hesperidin, effectively protected ARPE-19 cells against H_2O_2-induced oxidative damage by inhibiting cell apoptosis, ROS overproduction and MDA formation as well as increasing the SOD and glutathione peroxidase (GSH) levels, which may be related to the activation of the Keap1-Nrf2/HO-1 signal pathway (Zhu et al. 2017). Nobiletin, a dietary polymethoxylated flavonoid maninly found in *Citrus Reticulata*, *Aurantii Fructus* and *Citri Reticulatae Pericarpium Viride*, has been reported to inhibit H_2O_2-induced ROS production and caspase-3/7 activity in ARPE-19 cells. Furthermore, nobiletin significantly increased AKT phosphorylation in ARPE-19 cells exposed to H_2O_2. Wogonin is a naturally flavonoid isolated from the root of *Scutellaria baicalensis Georgi*. A study showed that wogonin pre-treatment improved the RPE cell viability and reduced cell death rate in a dose-dependent manner, further, wogonin could reduce the level of phosphorylated Akt (p-Akt) significantly, which might be the mechanism of it (Yan, Bi, and Wang 2014).

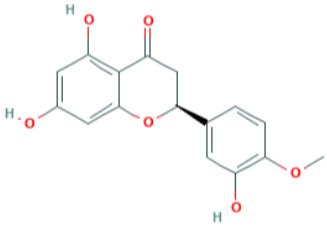
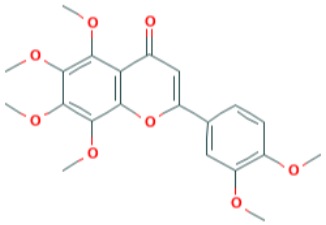
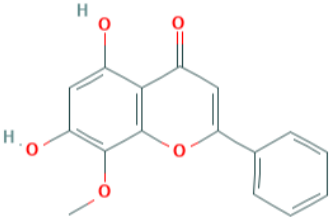
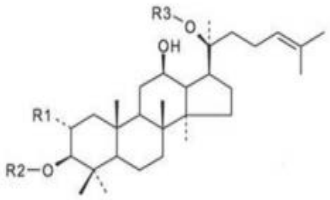
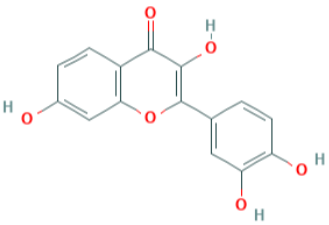
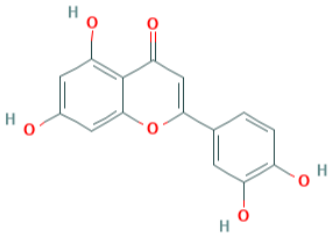
Two polyphenols, fisetin and luteolin, have been reported increasing the survival of RPE cells suffering from oxidative stress and decreasing inflammation. A model of nonoxidative DNA damage-induced cell death in human RPE cells was used to analyze the effects of fisetin and luteolin on inflammation. The result showed that the fisetin and luteolin treatment was able to reduce the release of two proinflammatory cytokines, IL-6 and IL-8, as well as augment the etoposide-induced acetylation of p53 and decrease SIRT1 levels (Hytti et al. 2017).

Gypenosides are the main ingredient of the Chinese medicine, *Gynostemma pentaphyllum*. Gypenosides significantly counteract the reduction of the GSH level, SOD and catalase activities, NRF2 expression and antioxidant genes, as well as the increase in ROS, MDA and proinflammatory cytokines in ARPE-19 cells exposed to H_2O_2 (Alhasani et al., 2018). Another study demonstrated that cholesterol efflux to high-density

lipoprotein and human serum, as well as the expression of cholesterol metabolism and trafficking genes were markedly increased in Gypenosides-treated RPE cells, which provide pharmacological evidence that Gypenosides have the potential to treat patients with early onset AMD (Biswas et al. 2020). Collectively, all these TCM pure compounds can inhibit the development or progression of AMD. These compounds may lead to a new strategy to combat AMD in the future. Details of these TCM compounds from other herbs are shown in **Table 3**.

Table 3 Traditional Chinese medicine compounds with potential therapeutic effects in age-related macular degeneration

Compound name	Chemical structure	Mechanism of action	Ref
Kaempferol		• Decreased the Bax and caspase-3 expression; • Increased the Bcl-2 expression; • Downregulated the VEGF expression; • Stimulated the SIRT1 and PARP1 signaling pathway.	(Du, An, He, Zhang, and He 2018; Al Sabaani 2020)
Quercetin		• Reduced ROS accumulation; • Enhanced the total expression levels of Nrf2 and NQO1; • Inhibited endoplasmic reticulum (ER) stress; • Upregulated Bcl-2 expression; • Downregulated Bax expression.	(Weng et al. 2017)
Cyanidin-3-glucoside		•Inhibited the formation of photooxidized-A2E species; • Protected glutathione from reaction with photooxidized A2E.	(Wang, Kim, and Sparrow 2017)
Myricetin		• Upregulated Nrf2/ NFE2L2 and antioxidant enzyme (*SOD2*); • Attenuated intracellular ROS; • Deactivated the nitric oxide producer (*NOS2*); • Controlling proapoptotic factors and inflammatory markers.	(Arumugam et al. 2019)

Hesperetin		• Decreased ROS generation; • Enhanced the SOD and GSH levels; • Activated the Keap1-Nrf2/HO-1 signal pathway.	(Zhu et al. 2017)
Nobiletin		• Inhibited ROS production and caspase-3/7 activity; • Increased AKT phosphorylation.	(Liu and Wu 2018)
Wogonin		• Modulated PI3K/AKT pathway.	(Yan, Bi, and Wang 2014)
Gypenosides		• Suppressed ROS, MDA production and inflammation genes; • Increased the SOD, GSH and catalase activities ; • Upregulated NRF2 expression and antioxidant gene expression; • Promoted cellular cholesterol removal from RPE cells.	(Alhasani et al. 2018; Biswas et al. 2020)
Fisetin		• Reduced IL-6 and IL-8 release; • Increased the acetylation of p53; • Decreased SIRT1 levels.	(Hytti et al. 2017).
Luteolin			

6 Effect of Acupuncture on AMD

Acupuncture, an adjuvant therapy that complements conventional medicine, has been widely implemented in Asia and the West. Traditional manual acupuncture is the act of inserting a needle into the acupuncture point, sometimes twisting the needle following insertion. As a well-known medical treatment, acupuncture supplemental therapy has been used to treat AMD in clinical practice, a procedure that is safe and

has no obvious side effects. At present, the selection of acupoints for treating AMD is mainly around the eyes, applying the acupuncture treatment principle that acupoints are taken at the proximal end of the disease site (Details of acupoint location are shown in Supplementary Materials **Table S1** and **Figure S1**). Acupuncture stimulates meridian acupoints corresponding to energy flow in the body, which may have an anti-inflammatory effect by inhibiting the reflex center of the innate immune system (Chan and Ng 2020). Moreover, acupuncture adjuvant treatment of AMD also has the advantages of avoiding the stimulation and first-pass effect of oral drugs on the gastrointestinal tract, which is of significant benefit. Nomenclature and location of each acupuncture point mentioned in this paper mainly refers to the standards proposed by the World Health Organization (Luo and Wu 2008; Committee 2016; Huang 2010).

Zheng et al. (2015) treated 37 cases (67 eyes) of wet AMD with body acupuncture, acupoint injection, plum-blossom needle percussion and auricular point sticking simultaneously by adopting self-control method, and found that acupuncture supplemental therapy could significantly improve visual function assessed by standard logarithmic visual acuity chart and Amsler grid chart and the quality of patients' life.The treatment is more effective in patients who are younger or have shorter course of disease (Zheng et al. 2015). Jiao (2011) randomly divided 84 AMD patients (90 affected eyes) into two groups. The acupuncture group (56 cases, 60 eyes) was treated with acupuncture, taking Guangming (GB37), Jingming (BL1), Cuanzhu (BL2), Taiyang (EX-HN5), Sibai (ST2), Yangbai (GB14), Tongziliao (GB1), Fengchi (GB20), Ganshu (BL18), Shenshu (BL23) and Fenglong (ST40) acupoints. However, the control group (28 cases, 30 eyes) was treated with conventional Western medicine, such as oral vitamin C and vitamin E, and intramuscular injection of Antuoiodine. The results showed that the ratio of cases with improved visual acuity, relieved or disappeared symptoms of visual distortion and fundus hemorrhage after treatment to the total cases in the acupuncture group was 88.3%, which was significantly better than that of Western medicine group (60.0%), indicating that acupuncture has better clinical efficacy for AMD patients (Jiao 2011).

Unfortunately, there is currently no specific Western medical therapy for dry AMD. Although taking high doses of antioxidants can significantly delay the progression of dry AMD, it does not cure the disease, nor restore or improve the vision that has been lost. In one study, 328 dry AMD patients were treated with acupuncture for 2 weeks (5 days a week). In the first week, the acupoints selected for treatment were Yintang (EX-HN3), Yuyao (EX-HN4), Cuanzhu (BL2), Cervical vertebrae (AH_{13}), Zhongzhu (TE3), and Hegu (LI4), in the second week, the treatment acupoints were Zhiyin (BL67), Kunlun (BL60), Zusanli (ST36), Taichong (LR3) and Gan auricular. Treatment was conducted twice a day, at a treatment interval of at least 60 minutes. After the first and second weeks, the baseline visual acuity was evaluated by distance (3 m) and near (40 cm) standard reading tests. The results showed that, during the first week, the median vision of AMD patients at both distances was significantly improved. Further improvement was observed at the second week. From the baseline examination to the end of the trial, 145 patients (44.2%) had a change in visual acuity at a distance of 3m, and 290 patients (88.4%) at a distance of 40cm with no side effects or complications. Therefore, acupuncture can reverse the vision loss of AMD patients (Krenn 2008). In another study, 47 dry AMD patients were randomly divided into three groups: the acupuncture group (22 cases, 44 eyes), the Western medicine group (15 cases, 30 eyes) and control group (10 cases, 20 eyes). The acupuncture group was given acupuncture, with slight lifting, inserting and twisting maneuvers at periocular acupoints, until severe pain and expansion behind the eyeball occurred. Then, the needle was retained for 30 mins and administered two times per week for two months. The Western medicine group was treated with vitamin C and E, while the control group received no treatment except for outpatient follow-up. The results demonstrated that acupuncture significantly alleviated the symptoms, such as blurred vision, sharply decreased and distorted visual acuity, central scotoma, asthenopia and dry eye. Visual function is closely related to viscera and meridians. The study also observed other systemic symptoms accompanying macular degeneration, such as headache, dizziness, poor memory, poor appetite, dry mouth, dry stool, frequent urination, waist and knee pain/weakness, all of which were

greatly alleviated after acupuncture treatment, suggesting that the overall effect of acupuncture therapy on dry AMD is consequential (Xia et al. 2013).

Acupuncture manipulation is also significant to the effectiveness of acupuncture. One study compared the clinical efficacy of "Ema Yaoling" acupuncture manipulation and conventional manipulation in the treatment of early AMD (Li, Shao, and Yin 2017). They randomly divided 110 AMD patients into observation group (55 cases, 73 eyes) and control group (55 cases, 76 eyes). In the observation group, acupuncture was performed at Cuanzhu (BL2) and Yiming (EX-HN13) points for 30 mins; then Ganshu (BL18), Pishu (BL20), and Shenshu (BL23) were taken without retaining the needle. The acupuncture manipulation of the observation group was the "Ema Yaoling" method, with the specific operations as follows: needle was twisted with the right thumb and index finger, then twisted back and forth, the force and twist amplitude being greater when the thumb was forward, and lesser when the thumb was backward. The entire operation process needs to be slow and gentle, in the manner of a "hungry horse ringing the bell", the phrase, from which comes the name "Ema Yaoling". In the control group, the acupoints and needle retention time were the same as those in the observation group, but conventional acupuncture manipulation was performed. The results showed that the improvement of visual acuity in the observation group was higher than that in the control group, and the optical coherence tomography (OCT) showed that the thickness levels of macular nerve fiber layer (MNFL), retinal neuroepithelial layer (RNL) and pigment epithelium and choroid capillary composite layer (PECCL) in the observation group were lower than those in the control group after treatment and during follow-up. This study confirmed the value of the “Ema Yaoling” acupuncture technique, which not only offers a new approach for acupuncture treatment of AMD, but also furnishes data support for acupuncture manipulation research. The effects of acupuncture on AMD are shown in **Table 4**.

Table 4 Effect of Acupuncture on age-related macular degeneration

Subjiect	Control group	Experimental group	Changes after treatment	Ref.
Wet	——•	Body acupuncture (acupoints select Xinming	Visual acuity, quality of life scale	(Zheng

AMD patients		1, Sizhukong (TE23), Tongziliao (GB1), Shangjingming, Chengqi (ST1), Shangming, Qiuhou (EX-HN7), Xinming 2, Taiyang (EX-HN5), Fengchi (GB20), Shangtianzhu). Acupoint injection was performed on the Qiuhou and Taiyang after acupuncture. Zhengguang 1 and Zhengguang 2 were stabbed by plum-blossom needle. Auricular acupressure (acupoints: Eye (LO_5), Anterior Intertragic Notch (TG_{21}), Posterior Intertragicus (AT_{11}), Ear center (HX_1), Liver (CO_{12}), Kidney (CO_{10}) and Shenmen (TF_4)).	score, and Amsler square table examination of the suffering eye were significantly improved, with an overall response rate of 77.6%.	et al. 2015)
AMD* patients	Oral vitamin C and vitamin E, and intramuscular injection of prolonium iodide injection.	Acupoints select Guangming (GB37), Jingming (BL1), Cuanzhu (BL2), Taiyang (EX-HN5), Sibai (ST2), Yangbai (GB14), Tongziliao (GB1), Fengchi (GB20), Ganshu (BL18), Shenshu (BL23), Fenglong (ST40).	Effective rate of acupuncture (88.3%) was significantly higher than that of the control group (60.0%).	(Jiao 2011)
AMD * patients	Oral compound Xuesaitong capsules and vitamin E capsules	Chinese medicine decoction combined with acupuncture therapy, and acupoints select Jingming(BL1), Taiyang (EX-HN5), Baihui (DU20), Chengqi (ST1), QiuHou (EX-HN7), Fengchi (GB20), Cuanzhu (BL2), Ganshu (BL18), Shenshu (BL23), Zusanli (ST36) and Sanyinjiao (SP6).	Improvement of vision and TCM syndrome is better than that of the control group.	(Zhu and Zou 2015)
Dry AMD patients	——♦	The first week of treatment acupoints were Yintang (EX-HN3), Yuyao (EX-HN4), Cuanzhu (BL2), Cervical vertebrae (AH13), Zhongzhu (TE3), and Hegu (LI4). The second week were Zhiyin (BL67), Kunlun (BL60), Zusanli (ST36), Taichong (LR3), and Gan auricular point.	Visual acuity was improved significantly.	(Krenn 2008)
Dry AMD patients	Control group 1 ： Oral vitamin C and vitamin E. Control group 2: No treatment was given except for outpatient follow-up	Carry out acupuncture at Jingming (BL1), Shangming, Neitongziliao, Jianming, Chengqi (ST1), Qiuhou (EX-HN7), Taichong (LR3).	The symptoms of blurred vision, sharp decrease in visual acuity, visual distortion, central scotoma, asthenopia, dry eye, and systemic symptoms related to macular degeneration were significantly improved in the observation group.	(Xia et al. 2013)
AMD* patients	The acupoints and needle retention time taken from the control group were the same as those in the observation	Firstly, taking acupuncture at Cuanzhu (BL2) and Yiming (EX-HN13), retain the needle for 30 minutes, then taking Ganshu (BL18), Pishu (BL20), and Shenshu (BL23), without leaving the needle. Most importantly, the acupuncture manipulation is "Ema Yaoling"	The improvement of visual acuity in the observation group was higher than that in the control group, and the levels of MNFL, RNL, and PECCL were lower than those in the control group	(Li, Shao, and Yin 2017)

	group, but conventional acupuncture manipulation was performed.			after treatment and during follow-up

Note: *Not acquired AMD type. ♦ Self-control research method was adopted. Nomenclature and location of each acupuncture point mentioned in **Table 2** mainly refers to standards proposed by the World Health Organization. Specific acupoint locations are shown in the Supplementary Materials **Table S1** and **Figure S1**.

7. Conclusion and perspective

TCM has been practiced for thousands of years and has performed an important role in maintaining the health of Chinese people. Despite recent advances, AMD remains difficult to treat and is the main cause of severe visual impairment and blindness in the elderly population. This review summarizes the possible underlying mechanisms whereby TCM (formula, Chinese herbal medicine and acupuncture included) can inhibit factors which play a role in the development and progression of AMD such as oxidative stress, inflammation, apoptosis and angiogenesis (**Figure 1**). While high level evidence in support of TCM treatment is limited there are a number of potential clinical advantages including fewer side effects, better compliance, low recurrence rate and cost, multi-target effects and better clinical prognosis which make TCM worthy of further investigation. In addition, TCM also has potential to be used in combination with conventional treatment.

Despite the progress made in improving the knowledge base of TCM treatment or adjuvant treatment of AMD, there remain some limitations. Firstly, the theoretical research on TCM treatment of AMD is not comprehensive, systematic and in-depth, especially on the regulation of the pathological progression of AMD. At present, studies on the TCM mechanisms in the treatment of AMD are largely limited. The multi-target, multi-pathway, holistic and systematic nature of TCM makes full understanding of the therapeutic response difficult. It is necessary to use a system biology approach (e.g. transcriptomics, metabolomics, proteomics and

microbiome), combined with pharmacology and retinal pathology, to improve understanding of the underlying mechanisms of TCM treatment in AMD animal models and patients. Furthermore the function of isolated compounds in TCM formulas need to be fully understood before clinical trials in AMD patients can be developed. At present most of the clinical studies are limited to the efficacy observation of small samples, and there are few standardized prospective, multicenter, large-sample, randomized controlled studies, resulting in a shortage of robust evidence related to the clinical efficacy evaluation of TCM therapies. Therefore, more rigorous controlled clinical trials need to be developed and funded to provide more reliable scientific evidence for treating AMD with TCM. Thirdly, the classification of TCM syndromes of AMD has no universally accepted standard. In the treatment of AMD, macroscopic diagnosis methods with strong subjectivity are generally adopted, which are inconsistent with the specificity of modern medical diagnostic standards. The use of diagnostic markers (e.g. electroretinogram and optical coherence tomography) will help in providing evidence of any beneficial effect of TCM in AMD treatment.

A remaining major challenge is to overcome the language barrier in order to improve understanding and dissemination of TCM knowledge. This review suggests that TCM could be a useful adjunct in the treatment on AMD, but the different thinking modes between Chinese and Western medicine limit the recognition of TCM overseas, and difficulties in the translation of TCM terms also reduce TCM uptake. For example, the Five Wheel Theory is a profound theory guiding AMD's TCM treatment from ancient times up to the present day. However, many Western clinicians fail to take in its true connotation, making it unlikely that they will use TCM to influence their clinical decision making.

A TCM knowledge dissemination platform which could improve understanding of the exact curative effects of TCM on AMD would be a useful first step in helping to improve the knowledge base. Strengthening collaborations in the use of TCM among international organizations, and promoting the exchange of TCM experience in the treatment of AMD would build prominence. The development of open policies to attract

foreign ophthalmologists to further study in China would also strengthen cooperation and collaboration with international scientific research institutions and improve the research and application of TCM. Furthermore, experts in the fields of ophthalmology, translation and education of TCM should be organized to improve core textbooks of TCM to make them easy to understand and accepted by the international community.

In conclusion, it is hoped that this review will bring to the fore the potential importance of TCM as an affordable disease-modifying agent in treating AMD and help more academics and clinicians to investigate novel approaches for the future treatment of AMD.

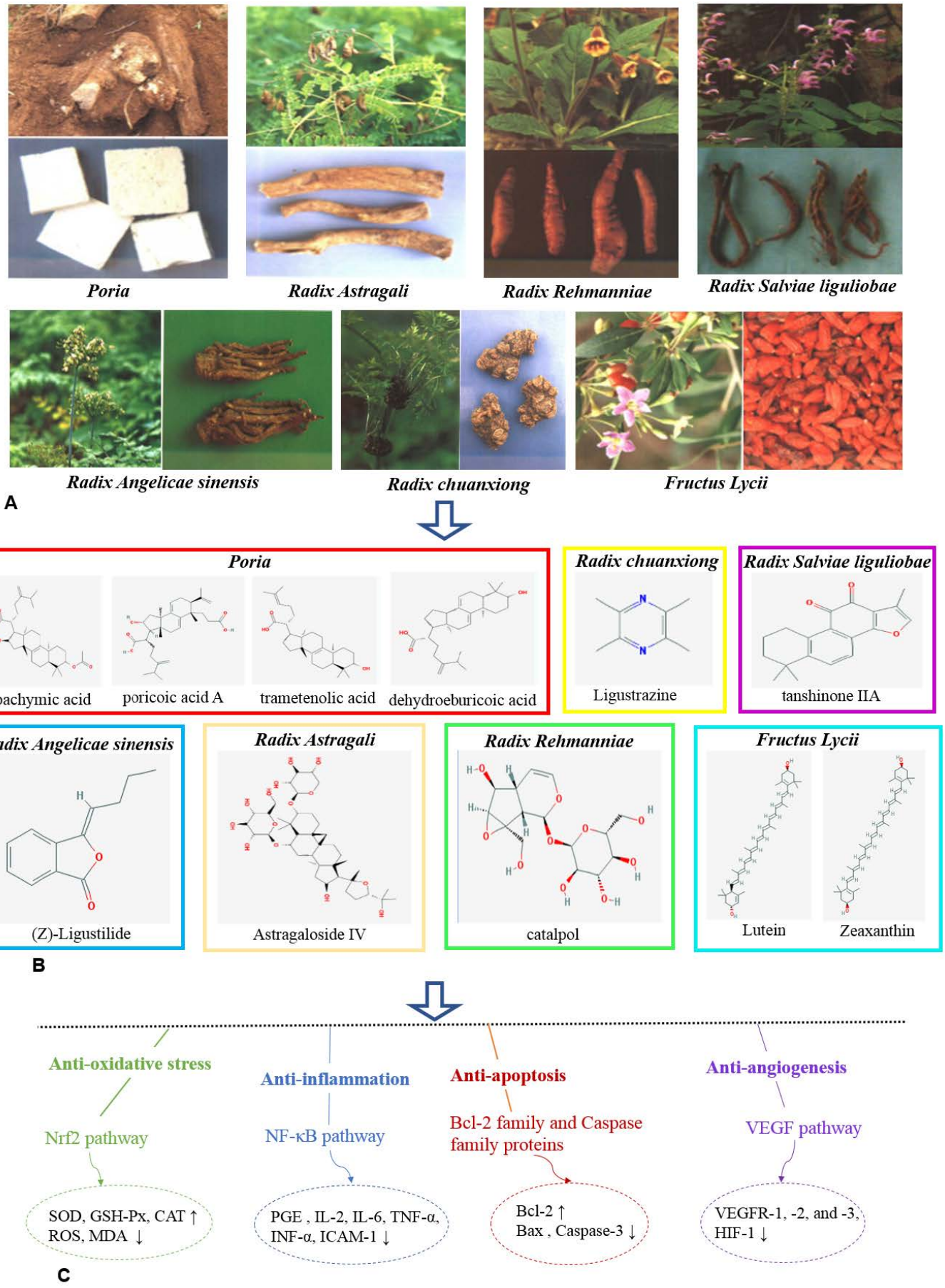


Figure 1. Effects and associated functional pathways of active ingredients of commonly used herbs on age

related macular degeneration.

Note: A represents commonly used traditional Chinese herbal medicines for the treatment of age related macular degeneration treatment. B represents the active ingredients isolated from A. (Z)-Ligustilide is isolated from *Radix Angelicae sinensis*. Catalpol is isolated from *Radix Rehmanniae*. Lutein and zeaxanthin are isolated from *Fructus Lycii*. Tanshinone IIA is isolated from *Radix Salviae liguliobae*. Astragaloside Ⅳ is isolated from *Radix Astragali*. Ligustrazine is isolated from *Radix chuanxiong*. Pachymic acid, poricoic acid A, trametenolic acid and dehydroeburicoic acid are isolated from *Poria*. C represents functional pathways of active ingredients of commonly used herbs on age related macular degeneration.

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

Availability of data and material Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions X.S. conceived the project. Y.L. searched the literatures and drafted the primary version of manuscript. Z.Z. and X.L. adjusted the main structure of the manuscript. N.S., X.S. and Z.T. revised the final draft. All authors read and approved the final manuscript. The decision to submit the manuscript for publication was made by all the authors.

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