Herbal Treatments for Age-Related Macular Degeneration: A Literature Review

Leva Hajatdoost

RAFT Publications Editorial Board Member at International Research Journal of Ophthalmology, Iran

*Corresponding Author: Leva Hajatdoost, RAFT Publications Editorial Board Member at International Research Journal of Ophthalmology, Iran, Email: leva.hajatdoost@bihe.org

Received Date: Jan 15, 2020 / Accepted Date: Jan 27, 2020 / Published Date: Jan 29, 2020

Abstract

**Background and aim:** Age-related macular degeneration (AMD) is one of the major causes of blindness and it has risk factors such as obesity, hypertension, smoking, or genetic characteristics. There is no certain cure for AMD till now, so it is very important to design new therapeutic agents or strategies for treatment of AMD. This literature review assessed the effects of different plants or herbal extracts on the retinal diseases such as AMD either for treatment or prevention of disease.

**Materials and methods:** Fifteen studies were included in this literature review and assessed possible herbal treatments or preventions of AMD or its related diseases and risk factors.

**Results:** From a wide range of medicinal plants, *Artemisia annua* contained artemisinin, *Lycium barbarum*, *Fructus barbarum* rich in carotenoids like zeaxanthin, *Scutellaria baicalensis* contained wogonin, saffron, rosemary contained carnosic acid, and *Melissa officinalis* are of the most important and beneficial medicinal plants that can be used for production and design of new drugs and therapeutics for AMD. They act via different mechanisms such as anti-oxidation, anti-VEGF, or anti-inflammatory actions. There are several other important herbal effective compounds for AMD, such as fisetin and luteolin that are polyphenols. Also, there are other herbal compounds such as HESA-A, Traditional Chinese Medicine (TCM), Guibi-tang (GBT), Samul-tang (SMT), and Sipjeondaebotang (SDT) that are contained in several different beneficial medicinal plants and their extracts for AMD.

**Conclusion:** There is a need for more investigations on these medicinal plants and their benefits on AMD, but they can be beneficial in lowering the risk of AMD or several other retinal diseases and prevention of them. For each mechanism included in AMD pathogenesis, one or more medicinal plant is introduced in this review.

Cite this article as: Leva Hajatdoost. 2020. Herbal Treatments for Age-Related Macular Degeneration: A Literature Review. Int Res J Ophtha. 2: 01-13.

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. Copyright © 2020; Leva Hajatdoost

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible sight loss in the elderly. There are several risk factors such as genetic characteristics, aging, obesity, smoking, and hypertension [1]. AMD is a chronic age-related degenerative eye disorder

www.raftpubs.com
and one of the major causes of blindness globally which has two main distinct types, dry or atrophic (nonneovascular) and wet or exudative (neovascular). The most common form of AMD is dry form which visual loss is usually gradual and irreversible and causes permanent scars in the retina. A common characterization of wet AMD is development of new blood vessels or neovascularization. Wet form of AMD damages the central eye very badly and patients with this form lose their visual tendency, rapidly. One of the most important causes of AMD is the abnormal levels of reactive oxygen species (ROS) in the retinal pigment epithelium (RPE) which will exert oxidative stress to the eyes and will damage to the DNA and mitochondria which will affect the cellular functions and morphological changes of RPE. Age-related degeneration of RPE causes loss of central vision via the death of photoreceptor cells in the eyes [2]. Retinal neovascularization or pathological growth of new blood vessels, is a cause of many diseases such as neovascular macular degeneration. Vascular endothelial growth factor (VEGF) plays a role in physiological and pathological angiogenesis and collaborates with other angiogenic factors such as fibroblast growth factor 2 (FGF2) and insulin-like growth factor-1 (IGF-1) to stimulate retinal neovascularization [3]. The development and progression of AMD are the results of a complex interaction between genetic and environmental risk factors. Oxidative stress and chronic inflammation are important in pathogenesis of AMD [4].

There is no certain cure for AMD till now and current treatments for wet AMD are restricted to photodynamic therapy, anti-angiogenesis/permeability agents, and thermal laser very rarely. Several anti VEGF drugs have been approved by FDA and are used at clinics to cure choroidal neovascularization (CNV) in wet AMD, such as ranibizumab, pegaptanib, VEGF-trap (Eyelea), and avastin (off-lable) which has price advantage than other VEGF antagonists. Only 30-40% of patients experience vision improvement after treatment of wet AMD with anti-VEGF agents [5]. So, it is very important to search new therapeutic agents or strategies for treatment of AMD. One of these strategies could be herbal therapy. The aim of this literature review is to assess the effects of different plants or their extracts on the retinal diseases such as AMD either for treatment or prevention of disease.

Methods

This review was conducted in accordance with PRISMA guidelines. Bibliographic searches were carried out in PubMed for all studies and trials published between 1987 and 2019. The search comprised the terms macular degeneration herbal treatment, macular degeneration plant derived treatment, and macular degeneration and herbal extracts. We considered in all these searches and studies, both macular degeneration and other eye diseases related to this disease as its causes or results. Studies about diseases other than macular degeneration or related eye diseases, and studies that investigated any therapy other than herbal therapy were excluded.

Data extraction

The titles and abstracts of articles were assessed to determine study inclusion. Information from the full texts using a predefined data extraction sheet was extracted. Extracted study details were study characteristics (first author, year of publication, study design), and treatment (plants, herbal extracts, effective components of a plant).

Data synthesis

Studies were arranged and the data was synthesized based on direct treatment or prevention of age-related macular degeneration or its risk factors and related diseases by herbal medicine or plant-derived therapies.
Results

The initial search of the literature using keywords according to the inclusion criteria retrieved 46 records. Three duplicate studies were removed and 43 potentially relevant studies were identified. After screening these 43 studies more carefully based on their titles and abstracts, 23 articles were excluded and remaining 20 full-text articles were assessed for eligibility; irrelevant articles, reviews, and studies that investigated any therapy other than herbal therapy, were excluded. Finally, 15 articles fulfilled the inclusion criteria which the language of all was English. Figure 1 shows the flow diagram for study selection. The studies are categorized based on the plants or herbal effective components that were assessed in the articles.

**Artemisinin from Artemisia annua**

Based on the study of Shuai Li et al. [2], Artemisinin is a herbal natural product extracted from *Artemisia annua* (sweet wormwood), a Chinese medicinal plant which is an anti-malarial and anti-fever compound.
also with anti-tumor, anti-viral, anti-allergic, anti-inflammatory, anti-helminth, and antiprotozoan activities. More recently, Shuai Li et al. have found that clinical relevant dosages of artemisinin promote PC12 and cortical neuron cells survival against nitric oxide-induced toxicity and human retinal pigmented cells (D407) from hydrogen peroxide-induced cell damage. The results of this study with evidence on the protective activity of artemisinin in D407 cells and primary cultured RPE cells against H2O2-induced injury mediated by the activation of AMP-activated protein kinase (AMPK), indicate that H2O2 resulted in death of RPE cells, while pretreatment with artemisinin protected cells from H2O2-induced oxidative damage correlated with activation of AMPK. Artemisinin protection against H2O2-induced cell damage involves various mechanistic routes such as reduction of intracellular ROS generation and inhibition of oxidative stress, decreasing lactate dehydrogenase (LDH) release and loss of mitochondrial membrane potential and changing the cell morphology. Therefore, artemisinin could be a potential therapeutic agent for treatment of AMD [2].

**Polysaccharides of Wolfberry from *Lycium barbarum***

Feng-Chi Hsieh et al. assessed wolfberry which is the fruit of *Lycium barbarum* (LB), a traditional Chinese herbal medicine that has several pharmacological effects such as antioxidation, neuroprotection, antiaging, immunomodulation and cytoprotection, which are resulted from polysaccharides extracted from fruit of *L. Barbarum* called LBP. The antioxidation effect of LBP causes its protective effect against oxidative injury in cells. Crude polysaccharide extracts have stronger antioxidant activity than purified polysaccharide extracts, because other antioxidants such as ascorbic acid, riboflavin, carotenoids, thiamine, and nicotinic acid are more abundant in crude extracts. Environmental chronic photooxidative stress could cause increased ROS, integrity of the membrane, DNA damage and cell death of RPE and this could be involved in pathogenesis of AMD. Antioxidants could prevent from the oxidative stress. The primary active ingredient isolated from the aqueous extracts of *L. Barbarum*, LBA, could exert protective effects on hepatocytes and neurons of the eye. Both aqueous and ethanol extracts of *L. Barbarum* are potent antioxidants and could protect eyes from UVB-induced DNA damage and apoptosis of human retinal pigment epithelial (ARPE-19) cells and ethanol extracts have stronger antioxidant effects than aqueous extracts. More investigations are needed but it seems that extracts of *L. Barbarum* especially ethanol extracts could be effective in prevention of retinal degenerative-associated diseases such as AMD [6].

**Zeaxanthin from *Fructus barbarum L***

Dietary intake of zeaxanthin, an oxygenated carotenoid (xanthophyll), is negatively associated with the incidence of several cancers such as colorectal and lung cancer, progression of the early atherosclerosis, and ischemic stroke. Also, this compound has photo protective effect in the eye and the skin and can be concentrated in the central area of the macula, yellow spot of the eye, based on the study of Iris F. F. Benzie et al. [7]. Thinning of the macular pigment is associated with aging, and irretrievable loss of central vision that is known as AMD. Increased intake of foods and beverages rich in carotenoids can be a successful strategy in lowering the AMD risk. *Fructus barbarum L.* which is a small red berry and known as Gou Qi Zi, Kei Tze (Cantonese), and wolfberry is one of the richest plant sources of zeaxanthin. The zeaxanthin bioavailability in a natural product, wolfberry, can be increased three-fold via homogenisation of the berries in hot skimmed milk. This strategy for enhancement of the bioavailability of zeaxanthin is important because increased dietary intake of zeaxanthin can help maintaining the macular pigment which lowers
the risk of AMD which is a cause of visual disability [7].

Zeaxanthin is a structural isomer of lutein which is located primarily in the central area of the macula, but lutein is found more peripherally; however, both compounds are concentrated in the yellow spot of the eye. These two compounds have antioxidant properties and also can absorb blue light; so, they can protect the retina against photodamaging damage and reduce light scatter in the eye and therefore they maintain visual acuity. Increased dietary intake of carotenoids like zeaxanthin and lutein to enhance macular pigment is a suggested strategy to prevent AMD or delay in it and promote visual function. Studies of Chung Yuen Cheng et al. have shown that 6 weeks supplementation of monkeys with a wolfberry extract enhanced their plasma and macular zeaxanthin [8]. A controlled food-based supplementation trial showed that short term supplementation with 15 mg of whole wolfberries that is a modest daily dose of them, increased zeaxanthin in fasting plasma of healthy subjects. Wolfberry offers an inexpensive, safe and effective whole food dietary strategy to increase plasma concentration of zeaxanthin [8].

Wogonin from *Scutellaria baicalensis*

One of the most important pathological markers of dry AMD is the presence of age-dependent degenerative damage to the RPE which is a common barrier for solutes and fluids from the choroidal vasculature that must access the inner retina. The liquid is not able to penetrate the blood-retinal barrier (BRB) because of well-developed tight junctions Zonula Occludens-1 (ZO-1) and Claudin-1. Increased BRB permeability results in the activation of Toll-like receptor 4 (TLR4) and TLR4-mediated signalling pathways will activate nuclear transcription factor-kB (NF-kB). The activation of NF-kB is a cause of ocular inflammatory diseases such as AMD. Based on the study of Chen Chen et al., wogonin (5,7-dihydroxy-8-methoxylavone) is a naturally-derived ingredient isolated from the roots of *Scutellaria baicalensis* (Huang-Qin) and it has been used to treat inflammatory diseases, allergies, and tumors in traditional Chinese medicine [1]. It has been revealed that wogonin could inhibit the activation of NF-kB. Wogonin inhibits inflammation in LPS-stimulated ARPE-19 cells and results in the protection of the tight junction proteins ZO-1 and Claudin-1. Also, wogonin reduces the LPS-induced inflammatory response by inhibition of IL-6, IL-8, IL1 beta, iNOS, TNF alpha, and COX-2 gene expression. The activation of the TLR4/NF-kB pathway is associated with the inflammatory response and wogonin inhibits this pathway. Therefore, according to this study, wogonin can be effective in treatment of AMD [1].

**Guibi-Tang**

Retinal neovascularization is a cause of neovascular macular degeneration. VEGF plays a role in physiological and pathological angiogenesis and collaborates with other angiogenic factors such as FGF2 and IGF-1 to stimulate retinal neovascularization. In studies and experiments of Yun Mi Lee et al. in cultured bovine endothelial cells, VEGF and FGF2 induced production of uPA and plasminogen activator inhibitor 1 (PAI-1) [3]. Loss or inhibition of PAI-1 downregulates overall retinal angiogenesis and can be a potential therapeutic target for retinal neovascularization. Guibi-tang (GBT) is a mixture of 12 herbs for treatment of anorexia, amnesia, fatigue, palpitation, insomnia, poor memory or forgetfulness, and neurosis and has specific bioactivities such as anti stress effects, antioxidant effects, immune regulation, and protective effect on the gastric mucosa. Also, GBT is a Chinese patent formula for wet maculopathy. One of the major ingredients in GBT is a coumarin called decursin which inhibited retinal neovascularization in a mouse model of retinopathy of prematurity. GBT could reduce VEGF, FGF2, and PAI-1 expression in oxygen-
induced retinopathy (OIR) mice model. Another ingredient in GBT is a flavonoid called glycyrrhizin which is antiangiogenic and selective inhibitor of high mobility group box-1, so reduced retinal neovascularization in OIR mice. Other ingredients also could suppress several factors like VEGF, FGF2 or PAI-1 and can be effective in reduction of retinal neovascularization, but it is still unclear which compound in the GBT is the most important one. Yun Mi Lee et al. have demonstrated in their experiments that GBT inhibited ischemic retinopathy-induced retinal pathogenic angiogenesis in OIR mice and reduced overexpression of VEGF, FGF2, and PAI-1 significantly [3].

**Samul-Tang**

The activation of VEGF increases the migration and proliferation of endothelial cells and the formation of new blood vessels; therefore, VEGF plays a central pathogenic role in retinal neovascularization which is caused by hypoxia-induced retinal damage. The antagonists of VEGF can inhibit the angiogenesis, but such therapies can achieve only partial clinical success because they need repeated injections of expensive antagonists of VEGF. Also, this treatment has effects on the HIF pathway-mediated expression of other pro-angiogenic factors, such as platelet-derived growth factor-B (PDGF), stromal cell-derived factor 1 (SDF-1), erythropoietin, IGF-1, and etc. SDF-1 is one of the most important chemokines induced by ischemia. CXCR4 is a known receptor for SDF-1. SDF-1 and CXCR4 regulate specific steps in formation of new vessels, proliferation and angiogenesis. VEGF upregulates CXCR4 which is selectively expressed in vascular endothelial cells. Samul-tang (SMT), Shimotsu-to in Japanese and Si-Wu decoction in Chinese, consists of four herbs, *A. gigas*, *C. officinale*, *P. lactiflora*, and *R. glutinosa*. SMT has been a traditional treatment for promoting blood circulation, relieving pain, and improving gynecological diseases, blood deficiencies, and chronic inflammation, for hundreds of years in Eastern Asia. It has recently been reported by Yun Mi Lee et al. that SMT has several other pharmacologic activities such as anti-cancer, anti-inflammatory and anti-pruritic effects [9]. Yun Mi Lee et al. showed that this herbal prescription has an inhibitory effect on the expression of VEGF, SDF-1, CXCR4, and HIF-1 alpha in OIR mice. The findings of this study indicate that SMT has anti-angiogenic activity in pathological retinal neovascularization. The observations on all four components of SMT suggest that the prevention of retinal neovascularization by SMT may occur due to a combination of the effects of all these four herbs. By the way, SMT inhibits the retinal pathogenic angiogenesis induced by ischemic retinopathy in OIR mice and also inhibits the overexpression of SDF-1, HIF-1 alpha, VEGF, and CXCR-4. Therefore, SMT could be a useful herbal medicine for treatment of ischemic retinopathy which is related to AMD and several other retinal diseases [9].

**Sipjeondaebotang**

Platelet-derived growth factor (PDGF) family consists of five dimeric ligands, PDGF-AA, -BB, -AB, -CC, and -DD. These dimers bind to two membrane receptor tyrosine kinases, PDGF receptor alpha (PDGFR alpha) and PDGF receptor beta (PDGFR beta) and activate them. One of the most important regulators of angiogenesis is PDGF-BB which is released from platelets, endothelial cells, inflammatory cells, and vascular smooth muscle cells at sites of angiogenesis and it binds to PDGFR beta and leads to activation of downstream signalling pathways. Therefore PDGF-BB is important in retinal pathogenic angiogenesis. Sipjeondaebotang (SDT), Shi-Quan-Da-Bu-Tang in Chinese and Juzen-taiho-to in Japanese, is an important traditional herbal medicine for treatment of patients with lose of appetite, fatigue, anaemia, rheumatoid arthritis and atopic dermatitis in Korea, China and Japan. This herbal formula has 12 crude medicinal herbs and has several pharmacological activities such as antimicrobial, antioxidative, stimulation of
immune cells, and anti-tumor effects; also, SDT has an anti-angiogenic effect in malignant glioma. Studies on SDT by Yun Mi Lee et al. have shown that this formula could prevent retinal neovascularization and inhibit the expression of PDGF-BB and VEGF in OIR mice [10]. These studies also showed that SDT inhibited the binding of PDGF-BB to PDGFR beta which is its receptor. Based on these findings, SDT has anti-angiogenic effects on retinal neovascularization. It has found that SDT inhibited the interaction between PDGF-BB and its receptor PDGFR beta in vitro and blocked retinal neovascularization via down-regulation of PDGF-BB and VEGF in vivo. It is very important that SDT has anti-angiogenic effect in ischemic retinopathy. The daily dose of SDT in human is almost 175.5 mg/kg/day and is clinically useful as herbal medicine for human ischemic retinopathy. The oral route is the most appropriate route of administration, but in these studies on SDT, this drug was administered intraperitoneally [10].

**HESA-A**

HESA-A is a recently developed natural drug in Iran and contains elements such as P2O5, CaO, Na2O, SO3, MgO, SiO2, Fe2O3, K2O, and Al2O3 as well as Ag, As, Zn, Cu, Ti, Ti, Sr, Mn, Br, Se, Ca, Cd, Te, Cs, Er, Lu, and other elements at very low quantities. Some of these elements have anti-tumor properties, so HESA-A has anti cancer effects as well as hepatoprotective effect. Antiangiogenic drugs or anti-VEGF therapies like pegaptanib and ranibizumab have some disadvantages that are the need for repeated intravitreal injections, high cost and the need for long term treatment for several years. HESA-A has herbal-marine origin. In a study of Amrollah Ahmadi et al., after 4 weeks of treatment with HESA-A there was no need for retreatment in patients up to 5 months [11]. The advantages of this drug are its efficacy, simple oral usage and short treatment course. Therefore, based on the investigations on this drug, treatment of AMD with HESA-A for 4 weeks improved visual acuity. This effect was obvious up to 5 months after treatment [11].

**Saffron**

Dario Marangoni et al. Said that the development and progression of AMD are the results of a complex interaction between genetic and environmental risk factors [4]. Oxidative stress and chronic inflammation are important in pathogenesis of AMD. The polymorphism of Y402H in the complement factor H (CFH) gene is one of the strongest genetic factors in AMD susceptibility. CFH is the major inhibitor of the alternative complement pathway and a reduction in its function causes inadequate control of complement driven inflammation and development of a retinal chronic inflammatory response in AMD, also in early stages. On the other hand, CFH could act as a protective factor against retinal oxidative stress [4]. A randomized clinical trial by Falsini B et al. has shown that dietary supplementation with saffron can improve significantly the focal electroretinogram (fERG) estimated retinal flicker sensitivity in early AMD patients [12]. Saffron has a neuroprotective effect on dysfunctional fERG generators, namely photoreceptors or bipolar cells. A daily oral administration of saffron is effective in ameliorating the macular function of patients with early AMD over a one-year period. Saffron can protect photoreceptors from retinal stress and it can preserve morphology and function via its antioxidant and anti-inflammatory properties and is a regulator of programmed cell death. Saffron treatment exerts a long-term efficacy in all genotypes. The improvement of macular function observed after three months of supplementation with saffron, remained stable in the 12 months follow up in all patients with different genotypes [4].

ATP is a source of energy for the cell and extracellular ATP is also a neurotransmitter in the nervous system. The purinergic system can
Herbal Treatments for Age-Related Macular Degeneration: A Literature Review

DOI: https://doi.org/10.36811/irjo.2020.110005
IRJO: January-2020: Page No: 01-13

www.raftpubs.com

trigger cell death in the central nervous system (CNS). According to the study of Lucia Corso et al., purines in the retina are involved in signalling between the different cell types and high levels of extracellular ATP cause retinal neurodegeneration [14]. In various retinal cell types like retinal ganglion cells, photoreceptors, Muller cells, and bipolar cells, both P2X and P2Y purinoceptors are expressed. P2X7 receptor (P2X7R) exists in immune cells and in the CNS including the retina. This receptor has two states of permeability inducing a Ca2+ enhancement. The stigmas of saffron contain many volatile and non-volatile components such as minerals, sugars, vitamins, different carotenes, crocins, and carotenoids like zeaxanthin and crocetin. Studies of Lucia Corso et al. have shown that saffron is protective in a rat model of light-induced retinal degeneration [14]. A clinical trial has shown that saffron has the potential of treatment in neurodegenerative diseases such as AMD [12],[13]. The activation of degenerative proteases like calpains causes elevations in Ca2+ and induces photoreceptor apoptosis. Saffron directly reduces the Ca2+ response caused by purinergic P2X7R stimulation and thus has protective role in neurodegeneration. Also, it can be protective against light-induced photoreceptor degeneration and AMD [14].

Traditional Chinese Medicine

Shusheng Wang and khrishen Cunnusamy assessed a pharmaceutical composition which consists of several traditional Chinese medicine (TCM) components, such as Angelica sinensis, Astragalus membranaceus bunge, Poria cocos wolf, Panax pseudo-ginseng, Fritillaria thunbergii, charred Radix et Rhizoma Rhei, Curcuma aromatica Salisb, and Pollen Typhae, which can be prepared into various pharmaceutical formulations like tablet, capsule, decoction, bolus, injection, and oral liquid preparation [5]. This pharmaceutical composition can promote and stabilize the vision of a patient with AMD, enhance absorption of haemorrhage, and reduce macular area CNV leakage and CNV area. This TCM can treat both the symptoms and the causes of AMD. The herbs in this formula can promote blood stasis and prevent bleeding, nourish vital energy, clear or soften phlegm, reduce CNV lesion, promote the absorption of edema, haemorrhage and macular exudate, and totally improving visual acuity. This pharmaceutical composition targets hallmarks of AMD such as inflammation, vascular edema, oxidative stress and RPE cytotoxicity [5].

Carnosic Acid from Rosemary

Those protection strategies which activate endogenous antioxidant proteins in RPE cells and photoreceptors, can attenuate progression of AMD. Also, a study on age-related eye diseases by Tayebeh Rezaie et al. has shown that daily intake of vitamins C and E, zinc, copper, and beta-carotene reduced the progression of human's late AMD up to about 25% [15]. Sulforaphane and curcumin are two natural compounds that protect photoreceptor and RPE cells via induction of phase 2 genes by activation of the Nrf2 transcriptional pathway against light-induced oxidative damage. Carnosic acid (CA) is a pro-electrophilic compound in rosemary and it crosses the blood-brain barrier. At the site of redox stress, CA undergoes oxidation which converts the compound from a prodrug to its active electrophilic form. This electrophilic form of compound upregulates a potent endogenous antioxidant enzyme system, causes activation of the Nrf2 transcriptional pathway. In this study, Tayebeh Rezaie et al. have found that CA activated phase 2 antioxidant genes and protected cells of the outer retina in vitro and in vivo. Thus, CA can be a useful therapeutic agent for diseases progressing with oxidative stress like AMD [15].

Melissa officinalis L. Extract

Oxidative stress from H2O2 causes preferential damage to mitochondrial DNA of RPE cells and leads to death of RPE cells. Antioxidants
have protective effects on progression of AMD and studies have shown that daily oral supplementation with antioxidant vitamins and minerals can reduce the risk of developing advanced AMD up to 25% during five years. The leaves of *Melissa officinalis* L., lemon balm, have been used as a traditional medicine for their anti spasmodic, tonic, carminative, anxiolytic, mood altering, memory enhancing, and sedative effects. It has also antitumoral, antiviral, neuroprotective, and antiangiogenic effects. Cheul Jeung et al. said that the extract of *M. officinalis* L. effectively protects human RPE cells from oxidative stress induced by H2O2 by its antiapoptotic and antioxidant properties [17]. High dietary intake of polyphenols can decrease the risk of developing various chronic diseases such as several cancers, cardiovascular diseases, osteoporosis, diabetes, and neurodegenerative diseases. The *M. officinalis* L. extract can scavenge a wide range of synthetic and naturally occurring free radicals. This plant has a lot of polyphenolic compounds such as phenolic acid with derivatives of hydroxycinnamic acid, coumaric acid, flavonoid with caffeic acid, naringin, eriodictyol-7-O-glucoside, hesperidin, naringenin, rosmarinic acid, and hesperetin. The AREDS and AREDS2 formula used to prevent the progression of dry AMD consist of antioxidants such as zinc, copper, vitamins C and E, lutein, b-carotene, and zeaxanthin. Also, flavonoids and hydroxycinnamic acid derivatives in *M. officinalis* L. are scavengers of ROS. An animal study by Lee EK et al. has shown that systemic administration of the *M. officinalis* L. extract inhibited formation of choroidal neovascularization via suppressing the expression of VEGF and matrix metalloproteinase-9 because of its antioxidant activity [16]. In clinical experiments, these activities can prevent the development of dry AMD and prevent conversion of dry into wet AMD. Therefore, this plant and its extract can act as potential natural treatment for dry AMD or can prevent it [17].

### Plant-Derived Polyphenols

Plant-derived polyphenols can possess anti inflammatory and antioxidant effects and have potential benefits for treating chronic diseases associated with prolonged inflammation and excessive oxidative stress such as AMD. Fisetin and luteolin are two polyphenols which can increase the survival of RPE cells suffering from oxidative stress and decrease inflammation, based on the study of Maria Hytti et al [18].

### Discussion and Conclusion

This literature review investigated all types of studies and trials between 1987 and 2019 that assessed herbal treatments for AMD. All 15 included studies assessed plant-derived therapies for AMD. Reviewing the trends of the use of herbal agents or natural products in these articles can reveal new therapeutic targets or formulations for future AMD treatments or researches.

There are different mechanisms included in AMD pathogenesis. Oxidative stress and chronic inflammation are important in pathogenesis of AMD [4]. Abnormal levels of ROS in the RPE will exert oxidative stress to the eyes and will damage to the DNA and mitochondria which will lead to loss of central vision via the death of photoreceptor cells in the eyes [2]. VEGF plays a role in physiological and pathological angiogenesis and collaborates with other angiogenic factors such as FGF2 and IGF-1 to stimulate retinal neovascularization [3]. The activation of NF-kB also is a cause of ocular inflammatory diseases such as AMD [1]. There is no certain cure for AMD till now and just several anti VEGF drugs have been approved by FDA and are used at clinics to cure CNV in wet AMD [5]. It is very important to search new therapeutic agents or strategies for treatment of AMD such as herbal therapy. This study has investigated the effects of plant-derived components and herbal extracts on AMD or its related retinal diseases. Different
plants in this review has effects on AMD via different mechanisms.

Artemisinin from *Artemisia annua* protected cells from H2O2-induced oxidative damage correlated with activation of AMPK via reduction of intracellular ROS generation and inhibition of oxidative stress, decreasing LDH release and loss of mitochondrial membrane potential and changing the cell morphology. Therefore, artemisinin could be a potential therapeutic agent for treatment of AMD [2]. Aqueous and ethanol extracts of *L. Barbarum* are potent antioxidants and could protect eyes from UVB-induced DNA damage and apoptosis of ARPE-19 cells, however ethanol extracts have stronger antioxidant effects. It seems that extracts of *L. Barbarum* especially ethanol extracts could be effective in prevention of diseases such as AMD [6].

*Fructus barbarum* L. and wolfberry are of the richest plant sources of zeaxanthin, a carotenoid that has photo protective effect in the eye and the skin and can be concentrated in the central area of the macula, yellow spot of the eye. The zeaxanthin bioavailability in a natural product, wolfberry, can be increased three-fold via homogenisation of the berries in hot skimmed milk. Dietary intake of zeaxanthin can help maintaining the macular pigment which lowers the risk of AMD which is a cause of visual disability [7]. Increased dietary intake of carotenoids like zeaxanthin and lutein to enhance macular pigment is a suggested strategy to prevent AMD or delay in it and promote visual function [8].

Wogonin from *Scutellaria baicalensis* could inhibit the activation of NF-kB and inflammation in LPS-stimulated ARPE-19 cells and results in the protection of the tight junction proteins ZO-1 and Claudin-1. Wogonin reduces the LPS-induced inflammatory response and inhibits the TLR4/NF-kB pathway. Therefore, wogonin can be effective in treatment of AMD [1]. GBT is a Chinese patent formula for wet macular degeneration. One of the major ingredients in GBT is a coumarin called decursin and another one is a flavonoid called glycyrrhizin which both could inhibit or reduce retinal neovascularization in mouse models. GBT could reduce VEGF, FGF2, and PAI-1 expression in OIR mice model. Other ingredients also could suppress several factors like VEGF, FGF2 or PAI-1 and can be effective in reduction of retinal neovascularization. Therefore, GBT can be effective in prevention or treatment of AMD [3].

SMT inhibits the retinal pathogenic angiogenesis induced by ischemic retinopathy in OIR mice and also inhibits the overexpression of SDF-1, HIF-1 alpha, VEGF, and CXCR-4. Therefore, SMT could be a useful herbal medicine for treatment of ischemic retinopathy which is related to AMD [9]. SDT could prevent retinal neovascularization and inhibit the expression of PDGF-BB and VEGF in OIR mice. SDT has anti-angiogenic effects on retinal neovascularization. The daily dose of SDT in human is almost 175.5 mg/kg/day and the oral route is the most appropriate route of administration [10]. Treatment of AMD with HESA-A for 4 weeks can improve visual acuity. This effect was obvious up to 5 months after treatment. The advantages of this drug are its efficacy, simple oral usage and short treatment course [11]. Saffron can protect photoreceptors from retinal stress and it can preserve morphology and function via its antioxidant and anti-inflammatory properties and regulates the programmed cell death. A daily oral administration of saffron can ameliorate the macular function of patients with early AMD over a one-year period. The improvement of macular function observed after three months of supplementation with saffron, remained stable in the 12 months follow up in all patients with different genotypes [4]. The activation of degenerative proteases like calpains causes elevations in Ca2+ and induces photoreceptor apoptosis. Saffron directly reduces the Ca2+ response caused by purinergic P2X7R stimulation and thus has protective role in neurodegeneration.
and light-induced photoreceptor degeneration and AMD [14].

The electrophilic form of CA of rosemary at the site of redox stress, upregulates a potent endogenous antioxidant enzyme system, causes activation of the Nrf2 transcriptional pathway. CA activates phase 2 antioxidant genes and protects cells of the outer retina in vitro and in vivo. Thus, CA can be a useful therapeutic agent for diseases progressing with oxidative stress like AMD [15]. The *M. officinalis* L. extract can scavenge a wide range of synthetic and naturally occurring free radicals. Flavonoids and hydroxycinnamic acid derivatives in *M. officinalis* L. are scavengers of ROS. Systemic administration of the *M. officinalis* L. extract can inhibit formation of choroidal neovascularization via suppressing the expression of VEGF and matrix metalloproteinase-9 because of its antioxidant activity. These activities can prevent the development of dry AMD and prevent conversion of dry into wet AMD. Therefore, this plant and its extract can act as potential natural treatment for dry AMD or can prevent it [17]. Fisetin and luteolin are two polyphenols which can increase the survival of RPE cells suffering from oxidative stress and decrease inflammation. Plant-derived polyphenols can possess anti inflammatory and antioxidant effects and have potential benefits for diseases like AMD [18].

TCM consists of *Angelica sinensis*, *Astragalus membranaceus bunge*, *Poria cocos* wolf, *Panax pseudo-ginseng*, *Fritillaria thunbergii*, charred *Radix et Rhizoma Rhei*, *Curcuma aromatica Salisb*, and *Pollen Typhae*, can promote and stabilize the vision of a patient with AMD and reduce macular area CNV leakage. This TCM can treat both the symptoms and the causes of AMD. The herbs in this formula totally improve visual acuity. This pharmaceutical composition targets hallmarks of AMD such as inflammation, vascular edema, oxidative stress and RPE cytotoxicity [5]. Overall, this literature review is showing there are different plants and herbal extracts that could be beneficial in prevention or treatment of AMD and scientists should consider them for designing new formulations. There are different mechanisms included in AMD pathogenesis and for each mechanism, one or more medicinal plant is introduced in this review. However, there is a need for more investigations on these medicinal plants and their benefits on AMD, but they can be beneficial in lowering the risk of AMD or several other retinal diseases and prevention of them.

References

1. Chen Chen, Danni Guo, Guohua Lu. 2017. Wogonin protects human retinal pigment epithelium cells from LPS-induced barrier dysfunction and inflammatory responses by regulating the TLR4/NF-κB signaling pathway. *Mol Med Rep.* 15: 2289-2295. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/282600

2. Shuai Li, Shubhash Chandra Chaudhary, Xia Zhao, et al. 2019. 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: 2016-2028. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/31523201

3. Yun Mi Lee, Yu-Ri Lee, Chan-Sik Kim, et al. 2015. Effect of Guibi-Tang, a Traditional Herbal Formula, on Retinal Neovascularization in a Mouse Model of Proliferative Retinopathy. *Int J Mol Sci.* 16: 29900-29910. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/26694358

4. Dario Marangoni, Benedetto Falsini, Marco Piccardi, et al. 2013. Functional effect of Saffron supplementation and risk genotypes in early age-related macular degeneration: a preliminary report. *J Transl Med.* 11: 228. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/24067115
5. Shusheng Wang, Khrishen Cunnusamy. 2013. Traditional Chinese Medicine (TCM) for the treatment of Age-related Macular Degeneration—Evaluation of WO2012079419. Expert Opin Ther Pat. 23: 269-272. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/23215532

6. Feng-Chi Hsieh, Chun-Tzu Hung, Kai-Chun Cheng, et al. 2018. Protective Effects of Lycium barbarum Extracts on UVB-Induced Damage in Human Retinal Pigment Epithelial Cells Accompanied by Attenuating ROS and DNA Damage. Oxid Med Cell Longev. 2018: 4814928. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/30524656

7. Iris FF Benzie, Wai Y Chung, Junkuan Wang, et al. 2006. Enhanced bioavailability of zeaxanthin in a milk-based formulation of wolfberry (Gou Qi Zi; Fructus barbarum L.). Br J Nutr. 96: 154-160. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/1687004

8. Chung Yuen Cheng, Wai Yuen Chung, Yam Tong Szeto, et al. 2005. Fasting plasma zeaxanthin response to Fructus barbarum L. (wolfberry; Kei Tze) in a food-based human supplementation trial. Br J Nutr. 93: 123-130. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/15705234

9. Yun Mi Lee, Chan-Sik Kim, Kyuhyung Jo, et al. 2015. Inhibitory effect of Samul-tang on retinal neovascularization in oxygen-induced retinopathy. BMC Complement Altern Med. 15: 271. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/26264147

10. Yun Mi Lee, Chan-Sik Kim, Eunjin Sohn, et al. 2014. Sipjeondaeb-Tang, a Traditional Herbal Formula, Inhibits Retinal Neovascularization in a Mouse Model of Oxygen-Induced Retinopathy. Tohoku J Exp Med. 234: 229-236. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/25365937

11. Amrollah Ahmadi, Heshmatollah Ghanbari, Masoud Soheilian, et al. 2009. The Effect of HESA-A (Natural Drug) on Visual Acuity in Age Related Macular Degeneration: A Randomized Double Blind Controlled Clinical Trial. Afr J Tradit Complement Altern Med. 6: 549-553. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/20606776

12. Falsini B, Piccardi M, Minnella A, et al. 2010. Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration. Invest Ophthalmol Vis Sci. 51: 6118-6124. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/20688744

13. Piccardi M, Marangoni D, Minnella AM, et al. 2012. A longitudinal follow-up study of saffron supplementation in early age-related macular degeneration: sustained benefits to central retinal function. Evid Based Complement Alternat Med. 2012: 429124. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/22852021

14. Lucia Corso, Anna Cavallero, Debora Baroni, et al. 2016. Saffron reduces ATP-induced retinal cytotoxicity by targeting P2X7 receptors. Purinergic Signalling. 12: 161-174. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/26739703

15. Tayebeh Rezaie, Scott R Mckercher, Kunio Kosaka, et al. 2012. Protective Effect of Carnosic Acid, a Pro-Electrophilic Compound, in Models of Oxidative Stress and LightInduced Retinal Degeneration. Invest Ophthalmol Vis Sci. 53: 7847-7854. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/23081978

16. Lee EK, Kim YJ, Kim JY, et al. 2014. Melissa officinalis Extract Inhibits Laser-Induced Choroidal Neovascularization in a Rat Model. PLoS One. 9: 110109. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/25314292

17. In Cheul Jeung, Donghyun Jee, Chang-Rae Rho, et al. 2016. Melissa Officinalis L. Extracts
Protect Human Retinal Pigment Epithelial Cells against Oxidative Stress-Induced Apoptosis. Int J Med Sci. 13: 139-146. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/26941573

18. Maria Hytti, Dora Szabo, Niina Piippo, et al. 2017. Two dietary polyphenols, fisetin and luteolin, reduce inflammation but augment DNA damage-induced toxicity in human RPE cells. J Nutr Biochem. 42: 37-42. Ref.: https://www.ncbi.nlm.nih.gov/pubmed/28113103