Traditional Chinese Medicine (TCM) for the treatment of Age-related Macular Degeneration--Evaluation of WO2012079419

Shusheng Wang[1,2] and **Khrishen Cunnusamy**[3]

[1]Department of Cell and Molecular Biology, Tulane University, LA, USA

[2]Department of Ophthalmology, Tulane University, LA, USA

[3]Department of Pathology, University of Texas Southwestern Medical Center, TX, USA

Abstract

A pharmaceutical composition composed of several traditional Chinese medicines is claimed to treat Age-related Macular Degeneration (AMD). This represents a novel and alternative therapeutic solution for wet AMD, with the potential advantage of treating both the symptoms and the underlying causes of this devastating degenerative retinal disease.

Keywords

Age-related Macular Degeneration (AMD); Traditional Chinese Medicine (TCM); Choroidal Neovascularization (CNV)

1. Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness among the elderly in the industrialized world, affecting more than 30 million individuals globally. In USA alone, about 1.8 million individuals are afflicted by this disease and the number is projected to increase to an epidemic level of approximately 3 million by 2020. It is estimated that the global direct health care cost due to AMD is US$255 billion. This represents a huge socio-economic burden to the society.

AMD is a chronic and progressive disease of the macula (central portion of retina responsible for fine vision acuity) that blurs, distorts and weakens central vision required for daily visual tasks. Early AMD is characterized by yellow drusen deposits and hypo- or hyper-pigmentation in the choroid/retinal pigment epithelium (RPE) layers in the macula. Late AMD has 'dry' and 'wet' forms. Geographic atrophy (GA), the advanced form of dry AMD, is characterized by extensive loss of the RPE, as well as its neighboring photoreceptors and choriocapillaris. Choroidal neovascularization (CNV), which involves abnormal growth of blood vessels from the choroid into the retina, is a hallmark of wet (or neovascular) AMD. Although its etiology remains unclear, AMD is generally believed to be a multifactorial disease. A combination of predisposing genetic and environmental factors, aging, oxidative stress and chronic inflammation contributes to AMD pathogenesis.

To date, there is no cure for AMD, and current therapeutic approaches for wet AMD are restricted to anti-angiogenesis/permeability agents, photodynamic therapy and, in rare cases,

Correspondence to: Shusheng Wang.

Author for correspondence: swang1@tulane.edu.

thermal lasers. Several agents against vascular endothelial growth factors (VEGF) have been approved by FDA and are currently used at clinics to treat CNV in wet AMD. These reagents include Macugen (pegaptanib) developed by Eyetech and Pfizer, Lucentis (ranibizumab) developed by Genentech, and Eylea (VEGF-trap) developed by Regeneron Pharmaceuticals and Bayer HealthCare. Avastin, another anti-VEGF cancer drug from Genentech, is also used off-label clinically largely due to its price advantage. Although anti-VEGF agents can markedly improve the clinic outcome of wet AMD, they have been unable to induce complete regression of the choroidal neovascular membranes, and only 30-40% of individuals experienced vision improvement after treatment. Nevertheless, major breakthroughs have taken place in the last decade in understanding the pathogenesis of AMD, and next-generation therapeutic solutions for AMD are on the horizon (1).

2. Pharmaceutical Composition for AMD

The current report evaluates a novel alternative therapeutic composition for wet AMD devised by Jin *et al* (WO2012079419). The pharmaceutical composition can enhance and stabilize the vision of an AMD patient, promote absorption of hemorrhage, as well as reduce macular area CNV leakage and CNV area. The pharmaceutical composition consists of several traditional Chinese medicine (TCM) components, including Astragalus membranaceus bunge, Angelica sinensis, Poria cocos wolf, Fritillaria thunbergii, Panax pseudo-ginseng, charred Radix et Rhizoma Rhei, Pollen Typhae and *Curcuma aromatica Salisb*. The pharmaceutical composition can be prepared into various pharmaceutically acceptable formulations including decoction, tablet, capsule, bolus, oral liquid preparation, and injection.

3. Functional Mechanism-the Biology Behind

Wet AMD is characterized by the presence of exudate, bleeding, edema, pigment changes and CNV in the fundus. Chinese medicine attributes the pathological changes in AMD to defects in 'Qi or Vital Energy', 'Blood stasis' and 'Phlegm'. The pharmaceutical composition of the present invention is based on the concept that TCM can treat both the symptoms and the causes of the disease. It contains a combination of raw materials from herbs that can nourish vital energy, promote blood stasis and prevent bleeding, clear and/or soften phlegm, promote the absorption of macular exudate, edema and hemorrhage, reduce CNV lesion, and thereby improving visual acuity. From the contemporary biology point of view, the compounds in the pharmaceutical composition can, surprisingly but consistently, target hallmarks of AMD, which include: (A) oxidative stress and RPE cytotoxicity; (B) inflammation and; (C) vascular edema.

Astragalus membranaceus extracts have been shown to possess potent immunomodulatory and antioxidant properties (2, 3). However, in the ischemic injured heart, *Astragalus membranaceus* extract exerted cardiac protective effects and promoted neovascularization through activation of AKT pathways and elevation of VEGF expression (4).

Angelica sinensis can reduce oxidative stress and inflammation. Specifically, *Angelica sinensis* was shown to reduce NF-κB activation and inflammatory gene expression in endotoxin-induced uveitis (5). Polysaccharide fractions of *Angelica sinensis* can protect against macrophage-mediated damage by inhibiting the release of excess nitrogen oxide (NO) and reactive oxygen species (ROS) (6). The extracts of *Angelica sinensis* can be pro-angiogenic or anti-angiogenic depending on the formulations (7, 8).

Panax notoginseng extract was shown to inhibit inflammatory gene expression and inflammation in a collagen-induced arthritis model (9, 10). It also exerts anti-oxidation effects by suppressing xanthine oxidase activity (11).

Poria cocos wolf has been shown anti-inflammatory properties in a clinical study of contact dermatitis (12). Polysaccharide from the mycelia of *Poria cocos wolf* also showed antitumor effects (13). Amyloid β has been implicated in the pathogenesis of AMD (14). In this context, *Poria cocos wolf* might also be beneficial in dry AMD since a combination of *Poria cocos wolf* and *Angelica gigas Nakai* has been shown to protect against β-amyloid plaque deposition and Alzheimer's disease-like pathology in mice (15).

Fritillaria ussuriensis was shown to possess anti-inflammatory properties in an animal model of passive cutaneous anaphylaxis (16). A derivative from *Charred Radix et Rhizoma Rhei* also showed anti-inflammatory properties and could alleviate pancreatic and pulmonary damage in rats (17).

Pollen Typhae selectively targets vascular edema as a rapid hemostyptic (18). Using a mouse tail bleeding model, *Pollen Typhae* significantly decreased tail bleeding and reduced prothrombin time.

Curcuma aromatica Salisb was shown to protect retinal cells from light- and oxidant stress-induced cell death by inhibition of NF-κB activation and down-regulation of inflammatory genes (19). Additionally, Curcumin from the roots of *Curcuma aromatica Salisb* also suppressed the inflammatory response in human umbilical vein endothelial cells through an antioxidant mechanism (20).

4. Evaluation and Expert Opinion

The claim by *Jin et al.* to use TCM-based pharmaceutical composition as therapeutic agents for wet AMD is intriguing, and may represent an alternative treatment option for wet AMD.

Using a laser-induced CNV rat model, Jin and colleagues compared the effect of the TCM, Avastin and saline-treated control on fluorescein leakage and CNV area. The TCM treatment was administered orally by gavage twice daily for 4 weeks post laser injury whereas the Avastin treatment group received a single intravitreal injection of anti-VEGF agent Avastin at 7 days post injury in addition to saline gavage. By fluorescein angiography, the authors found that the TCM group was comparable to the Avastin group, and had significantly less vascular leakage compared to the saline controls (Table. 1). Histopathological and electron microscopy analyses showed a similar decrease in retinal and choroidal capillary damage, decreased CNV and limited proliferation and migration of RPE cells, fibroblast and collagen fibers in both the TCM and Avastin-treated groups compared to the saline control group.

The authors then carried out a clinical study on 70 AMD individuals (85 eyes) from the Beijing Sino-Japan Friendship Hospital to investigate the effectiveness of the drug. The individuals with a mean of 58.21 ± 7.21 years old had typical choroidal neovascularization as demonstrated by fluorescein angiography. The duration of decoction treatment for the individuals ranged from 0.5 months to 40 months, with an average of 8.63 ± 7.24 months. The efficacy of the drug was determined by performing eye examination before and after treatment using the following outcome measures: 1) intraocular pressure; 2) direct ophthalmoscope fundus examination; 3) Amsler table; 4) fluorescein angiography neovascularization leakage area; 5) optical coherence tomography (OCT); 6) macular volume. The results from the clinical trial showed that 68.24% of the 85 treated eyes experienced an increase in visual acuity (from 4.23 ± 0.39 to 4.87 ± 0.55, less than 5 letters in US standard) (Table 2 and 3). Similarly, 65.53% of eyes experienced decreased visual distortion and central scotoma as shown by numbers from the Amsler table (from 65.23 ± 30.32 to 44.87 ± 28.35). Fluorescence angiography analyses revealed a 71.43% effectiveness of the TCM in decreasing CNV leakage. Consistently, 85% of the treated eyes

also experienced a significant decrease in CNV area (from 0.88 ± 0.31 to 0.24 ± 0.27). By OCT, the treated eyes also demonstrated a significant decline in the macular volume (from 341.37 ± 66.13 m^3 to 204.14 ± 45.80 m^3). Based on the results of the drug treatment in the animal model of the disease and in the clinical trial, the TCM treatment shows significant enhancement in visual acuity and prevents progression of macular degeneration.

Overall, the TCM-based pharmaceutical composition is effective in treating wet AMD. Based on the animal model, its efficacy seems to be comparable to anti-VEGF agent Avastin. The clinical trial results appear to be exciting, although a large scale clinical trial with Lucentis (or Avastin) as control is warranted to validate its effect in AMD individuals. Excitingly, some individual components of the TCM-based pharmaceutical composition have been shown to suppress oxidative stress, inflammation and vascular edema, which are hallmarks of AMD. In this context, it would be interesting to see its long term effect of the drug on AMD progression, especially on dry AMD. If TCM treatment does indeed inhibit dry AMD, this will support the concept that TCM-based medicine can treat both the symptoms and the causes of AMD; making it an appealing therapeutic agent to AMD individuals.

References

1. Cunnusamy K, Ufret-Vincenty R, Wang S. Next-generation therapeutic solutions for age-related macular degeneration. Pharmaceutical Patent Analyst. 2012; 1(2):193–206.

2. Ko JK, Chik CW. The protective action of radix Astragalus membranaceus against hapten-induced colitis through modulation of cytokines. Cytokine. 2009; 47(2):85–90. [PubMed: 19539495]

3. Yang WJ, et al. Synergistic antioxidant activities of eight traditional Chinese herb pairs. Biological & pharmaceutical bulletin. 2009; 32(6):1021–1026. [PubMed: 19483308]

4. Zhang L, Yang Y, Wang Y, Gao X. Astragalus membranaceus extract promotes neovascularisation by VEGF pathway in rat model of ischemic injury. Die Pharmazie. 2011; 66(2):144–150. [PubMed: 21434579]

5. Han C, Guo J. Antibacterial and anti-inflammatory activity of traditional Chinese herb pairs, Angelica sinensis and Sophora flavescens. Inflammation. 2012; 35(3):913–919. [PubMed: 21976127]

6. Yang X, et al. Component and antioxidant properties of polysaccharide fractions isolated from Angelica sinensis (OLIV.) DIELS. Biological & pharmaceutical bulletin. 2007; 30(10):1884–1890. [PubMed: 17917256]

7. Lam HW, et al. The angiogenic effects of Angelica sinensis extract on HUVEC in vitro and zebrafish in vivo. Journal of cellular biochemistry. 2008; 103(1):195–211. [PubMed: 17497682]

8. Yeh JC, et al. The natural compound n-butylidenephthalide derived from the volatile oil of Radix Angelica sinensis inhibits angiogenesis in vitro and in vivo. Angiogenesis. 2011; 14(2):187–197. [PubMed: 21327473]

9. Chang SH, et al. Anti-inflammatory effects of BT-201, an n-butanol extract of Panax notoginseng, observed in vitro and in a collagen-induced arthritis model. Clin Nutr. 2007; 26(6):785–791. [PubMed: 17933436]

10. Jang YJ, Kim ME, Ko SY. n-Butanol extracts of Panax notoginseng suppress LPS-induced MMP-2 expression in periodontal ligament fibroblasts and inhibit osteoclastogenesis by suppressing MAPK in LPS-activated RAW264.7 cells. Archives of oral biology. 2011; 56(11):1319–1327. [PubMed: 21703595]

11. Choi RC, et al. Anti-oxidative effects of the biennial flower of Panax notoginseng against H2O2-induced cytotoxicity in cultured PC12 cells. Chinese medicine. 2010; 5:38. [PubMed: 21029415]

12. Fuchs SM, et al. Assessment of anti-inflammatory activity of Poria cocos in sodium lauryl sulphate-induced irritant contact dermatitis. Skin Res Technol. 2006; 12(4):223–227. [PubMed: 17026651]

13. Kanayama H, Adachi N, Togami M. A new antitumor polysaccharide from the mycelia of Poria cocos wolf. Chemical & pharmaceutical bulletin. 1983; 31(3):1115–1118.

14. Ding JD, et al. Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108(28):E279–287. [PubMed: 21690377]

15. Seo JS, et al. A modified preparation (LMK03) of the oriental medicine Jangwonhwan reduces Abeta(1-42) level in the brain of Tg-APPswe/PS1dE9 mouse model of Alzheimer disease. Journal of ethnopharmacology. 2010; 130(3):578–585. [PubMed: 20669372]

16. Cho IH, et al. Fritillaria ussuriensis extract inhibits the production of inflammatory cytokine and MAPKs in mast cells. Bioscience, biotechnology, and biochemistry. 2011; 75(8):1440–1445.

17. Li Z, et al. Up-regulation of Toll-like receptor 4 was suppressed by emodin and baicalin in the setting of acute pancreatitis. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2009; 63(2):120–128.

18. Ohkura N, Tauchi C, Nakayama A, Atsumi G. Pollen Typhae is a rapid hemostyptic. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2012; 23(3): 254–255.

19. Mandal MN, et al. Curcumin protects retinal cells from light-and oxidant stress-induced cell death. Free radical biology & medicine. 2009; 46(5):672–679. [PubMed: 19121385]

20. Lee HS, et al. Curcumin inhibits TNFalpha-induced lectin-like oxidised LDL receptor-1 (LOX-1) expression and suppresses the inflammatory response in human umbilical vein endothelial cells (HUVECs) by an antioxidant mechanism. Journal of enzyme inhibition and medicinal chemistry. 2010; 25(5):720–729. [PubMed: 20163327]

Table 1

Effect of TCM, Avastin on vascular leakage and CNV in BN rats.

	Untreated	Avastin-treated	Chinese-Medicine treated
Fluorescein leakage (OD) - 7 days	78.83 ± 2.29	77.36 ± 2.17	68.81 ± 4.29
Fluorescein leakage (OD) - 14 days	105.78 ± 8.55	88.73 ± 5.55	90.38 ± 7.55
Fluorescein leakage (OD) - 21 days	123.25 ± 8.44	93.25 ± 8.44	95.85 ± 7.22
CNV central thickness (μm)	63.59 ± 4.08	40.36 ± 3.55	39.65 ± 4.24
CNV area ($10^3 \times \mu m^2$, x ± s)	2.539 ± 0.528	1.513 ± 0.421	1.423 ± 0.547

Table 2

Vision efficacy and CNV severity in wet AMD individuals before and after TCM treatment.

Visual Acutity (± s)		Amsler Table Number		CNV Area		Total Macular Volume (± s, m³)	
Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
4.23 ± 0.39	4.87 ± 0.55	65.23 ± 30.32	44.87 ± 28.35	0.88 ± 0.31	0.24 ± 0.27	341.37 ± 66.13	204.14 ± 45.80

Table 3

Response rate in wet AMD individuals with TCM treatment.

	Visual acuity	Amsler Table Number	CNV Area	CNV leakage
No. of Eyes	85	85	60	70
Markedly Effective	30.55% (26)	28.24% (24)	31.67% (19)	45.71% (32)
Effective	37.65% (32)	35.29% (30)	53.33% (32)	25.71% (18)
Stable	22.35% (19)	22.53% (20)	11.67% (7)	25.71% (18)
Not effective	9.41% (8)	12.94% (11)	3.33% (2)	2.86% (2)
Total response rate	68.24% (58/85)	65.53% (54/85)	85.00% (51/60)	71.43% (50/70)