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Chapter 5

# Retinal Ischemia: MMP-9; Its Relation to Resveratrol, Baicalein, S-allyl L-cysteine and Chi Ju Di Huang Wan

Hsiao-Ming Chao, Wen-Jin Chao and Ing-Ling Chen

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**Abstract**

Ischemia has been reported to be related to matrix metalloproteinase-9 (MMP-9) level upregulation. Neovascular glaucoma (NVG) (in proliferative diabetic retinopathy and central/branch retinal vein occlusion) and age-related macular degeneration are known vision-threatening retinal ischemic disorders. In this review, an extensive discussion has been made into how MMP-9 is related to retinal ischemia and what the underlying mechanisms of various traditional Chinese medicine (TCM) compounds and combinations are. High intraocular pressure-induced retinal ischemic changes were characterized by decreased electroretinogram (ERG) b-wave amplitudes, a loss of choline acetyltransferase (ChAT) immunopositive amacrine neurons/processes, increased Müller's vimentin immunoreactivity, and profound retinal ganglion cell (RGC) death. It has also been observed hypoxia inducible factor-1$\alpha$ (HIF-1$\alpha$), MMP-9 and vascular endothelium growth factor (VEGF) upregulation at the protein/mRNA levels. After ischemia, both the p38 mitogen-activated protein kinases (MAPKs)-stimulated MMP-9 upregulation and HIF-1$\alpha$-triggered VEGF overexpression might result in neovascularization. Conclusively, baicalein seems to have neuroprotection via antioxidation, antiapoptosis, HO-1 upregulation and HIF-1$\alpha$, VEGF, and/or MMP-9 downregulation. Furthermore, baicalein inhibition on retinal ischemia-induced MMP-9 upregulation seems to be "partly" associated with its antioxidation. Additionally, retinal ischemia, oxidative stress, and/or kainate excitotoxicity could be protected by resveratrol: "via MMP-9 and inducible nitric oxide synthetase (iNOS) downregulation, and heme oxygenase-1 (HO-1) upregulation," S-allyl L-cysteine (SAC): "through iNOS, HIF-1$\alpha$, VEGF inhibition and/or MMP-9 downregulation, and antiapoptosis," Chi Ju Di Huang Wan: "by means of antiapoptosis, antioxidation, MMP-9 downregulation and p38 MAPK inhibition."

**Keywords:** matrix metalloproteinase-9, retinal ischemia, traditional Chinese medicine, hypoxia inducible factor-1$\alpha$, vascular endothelium growth factor, p38 mitogen-activated protein kinase, baicalein, resveratrol, inducible nitric oxide synthetase, heme oxygenase-1, S-allyl L-cysteine, Chi–Ju–Di–Huang–Wan

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## 1. Introduction

Central retinal artery occlusion (CRAO) [16], primary open angle glaucoma (in urban areas) [24], diabetic retinopathy (type 2 diabetes) [21], and age-related macular degeneration (AMD; age ≥40 of years [17]) is related to retinal ischemia with the incidences of 0.0018, 4, 2.9, and 0.36%, respectively.

Central/branch retinal vein occlusion (CRVO/BRVO) are also associated with retinal ischemia. Retinal or choroidal ischemia can lead to angiogenesis, associated with subretinal fluid and bleeding. Fifteen percent of AMD patients experience profound central vision loss owing to choroidal neovascularization (CNV), namely neovascular AMD (nvAMD) [11]. This explains why nvAMD becomes a leading cause of blindness in the elderly. Vision deterioration further puts patients at a greater danger of falls and possibility of being in need of residential nursing care. There is an eminent necessity for new agents that trigger the self-protective mechanisms and avoid harmful neovascularization.

Oxidative stress in the human retinal pigment epithelium (hRPE) leads to the upregulation of matrix metalloproteinase-9 (MMP-9). Upregulation of MMP-9 can adversely degrade the extracellular matrix and induce irreversible retinal ganglion cell (RGC) death [9]. Brain ischemia has been reported to trigger MMP-9 upregulation [8]. In AMD, plasma MMP-2 and MMP-9 levels have been also indicated to be upregulated [6]. As a consequence, ischemia or oxidative stress may be related to MMP-9 level upregulation. In AMD, plasma MMP-9 concentrations promote neovascularization throughout the early phases of CNV [6]. Previous results have supported that increases in MMP-9, hypoxia inducible factor-1$\alpha$ (HIF-1$\alpha$), and vascular endothelium growth factor (VEGF) levels in the retina/RGCs directly have a relation with ischemia [5, 13].

In our previous publications, there were active components of traditional Chinese medicine (TCM) that were proved to be antioxidants such as ferulic acid from Chuang Xiong [1, 2]. These include baicalein from Huángqín (*Scutellaria baicalensis*) [13, 3] and S-allyl L-cysteine (SAC) from old garlic [5]. SAC could also act as a kainate antagonist [4]. In addition, Chi Ju Di Huang Wan (CJDHW), a "vision preserved" TCM combination, was demonstrated to protect against retinal ischemia through the attenuation of apoptosis, increase of antioxidative activity, downregulation of MMP-9, and inhibition of p38 mitogen-activated protein kinase (MAPK) [7]. Besides, efficient components of beverages, such as epigallocatechin-3-gallate [18] in green tea and resveratrol [15] in red wine, were also reported to possess protective effect on retinal ganglion cells injured after optic nerve axotomy and retinal ischemia, respectively. This review aimed at evaluating the effects of the following compounds or TCM combinations on retinal ischemia and their relations to MMPs.

Resveratrol has shown to possess strong antioxidant properties. Resveratrol has also been confirmed to provide neuroprotective effects during cerebral ischemia plus reperfusion (I/R), [19], mice retinal I/R [12], and *in vitro* experimental optic neuropathy [14]. However, the effects of resveratrol are not completely highlighted. Therefore, it has been investigated whether and how resveratrol protects against retinal I/R [15].

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one) is a natural flavonoid from *Scutellaria baicalensis*. It has been studied whether baicalein can alleviate retinal ischemia using electroretinogram (ERG), immunohistochemistry [vimentin/glial fibrillary acidic protein (GFAP), choline acetyltransferase (ChAT)], TdT-mediated dUTP-digoxigenin Nick and Labeling (TUNEL), and real time PCR (rtPCR) to detect mRNA levels of HIF-1$\alpha$, VEGF, MMP-9, and/or heme oxygenase-1 (HO-1). In brain ischemia, baicalein inhibited MMP-9 expression. It has also been examined whether and how baicalein can suppress MMP-9 upregulation induced by retinal I/R [3].

Within macrophages and endotheliums, SAC, an organosulfur compound in aged garlic extracts, serves as an antioxidant [10]. It has been investigated whether and how SAC can protect against retinal ischemia. Changes in Thy-1, HIF-1$\alpha$, VEGF, or MMP-9 levels were also intensively observed [4, 5].

Traditional CJDHW includes *Fructus lycii* (Gou qi zi), *Chrysanthemi flos* (Ju hua), Chi-Ju-Di-Huang-Wan (CJDHW) is a classic herbal formula, traditionally used to stabilize tear film and decrease abnormalities of the corneal epithelium in dry eye patients. *Liu Wei Di Huang Wan, Rehmanniae Radix Preparata* (Shu di huang), *Corni fructus* (Shan zhu yu), *Rhizoma Dioscoreae* (Shan yao), *Poria* (Fu ling), *Cortex Moutan radicis* (Mu dan pi), and *Alismatis Rhizoma* (Ze xie). The active compounds of CJDHW known to have antioxidant properties include Zeaxanthin and Lutein from F. Lycii and C. Flos and Trehalose from R. Radix preparata. It has been evaluated regarding the protective effects and underlying mechanisms of CJDHW against retinal ischemia [7].

## 2. Body-research methods

*In vivo* rat retinal ischemia was induced by high intraocular pressure (HIOP) of up to 120 mmHg for 60 min. The mechanism and management were evaluated by ERG b-wave amplitude measurement, immunohistochemistry, and rtPCR.

*Resveratrol related to MMP and others*: Drug administration (single intravitreous injection of 5 μL) involved either preischemic (15 min before retinal ischemia) or postischemic administration (15 min after retinal ischemia) of resveratrol (0.05, 0.5 nmol) or vehicle (ethanol; control).

*Baicalein related to MMP and others: In vitro*, an oxidative stress was also established by incubating dissociated retinal cells with 100-μM ascorbate and 5-μM $FeSO_4$ (iron) for 1 h. The rats or the dissociated cells were 15 min pretreated with baicalein [(5 μL invitreous injection (i.v.i.) preischemia: 0.05 or 0.5 nmol; *in vitro* preoxidation: 100 μM)], vehicle (1% ethanol), or trolox (i.v.i.: 5 nmol; *in vitro*: 100 μM or 1 mM). These treatment effects were also evaluated by TUNEL, Western blotting, or *in vitro* dichlorofluorescein assay. In addition, the rtPCR assessed the retinal mRNA expression of HIF-1$\alpha$, MMP-9, VEGF, and HO-1. The other *in vitro* methods for hRPE subjected to $H_2O_2$ (500 μM)-induced oxidative stress included lactate dehydrogenase or enzyme-linked immunosorbent assay to measure cell viability or the levels of VEGF/MMP-9, respectively.

*S-allyl L-cysteine related to MMP and others: In vivo* excitotoxicity or *in vitro* oxidative stress was also induced by 100 μM kainate injected into a Wistar rat's vitreous for 1 day or 24 h $H_2O_2$ (500 μM) incubation of RGC-5 cell line. The management and mechanisms of 100 μM SAC (5 μL intravitreous injection or incubation) and/or the kainate receptor antagonist 100 μM CNQX (5 μL intravitreous injection or incubation) applied 15 min preexcitotoxocity/preischemia/preoxidative stress were evaluated by histopathology (TUNEL, fluorogold retrograde labeled RGCs), and various biochemical approaches [inducible nitric oxide synthetase (iNOS), HIF-1$\alpha$, VEGF and/or MMP-9 mRNA/protein levels].

*Chi Ju Di Huang Wan related to MMP and others*: The effects of CJDHW were studied by (i) rtPCR for retinal Thy-1 and MMP-9 mRNA levels; (ii) Western blotting for retinal B-cell lymphoma 2 (Bcl-2), HO-1, P-p38 MAPK and MMP-9 protein levels; (iii) Hematoxylin and haematoxylin and eosin (HE) staining; (iv) fluorogold retrograde labeling; and (v) TUNEL apoptosis assay.

A daily oral intake of 3 mL of water (vehicle; Group 2) or CJDHW (2.8 or 4.2 g/kg/day; CJDHW2.8 or CJDHW4.2; Group 3 or 4) was given for 7 consecutive days preischemia or postischemia. In Group 5, 4 μL of 0.5 mM SB203580 (p38 MAPK inhibitor) was intravitreously injected to the ischemic eye (15 min preischemia). The control rats received a sham procedure (Group 1).

## 3. Conclusion: key results

The role of MMP-9 in a TCM compound or the TCM combination: An invention of a new small-molecule medicine will run through considerable tedious and prolonged processes. These include the selection of a single compound, animal safety study, investigational new drug, preclinical trial, clinical trials, and new drug application. Launching a new medicine might take 10–15 years and cost billions of US dollars. The institutional review board would be somehow strict to the investigators or the pharmaceutical companies when they were involved in implementing their clinical trials.

Artemisinin, one effective compound against malaria, was first isolated from the TCM, Qinghao, and tested in the 1970s in China [22]. Thrillingly, the discovery of artemisinin that awarded Professor Youyou Tu, the first Chinese Nobel Winner of Medicine in 2016 has pushed the era of traditional medicine come around [23]. There are many intractable disorders, such as the ischemia-related vision-threatening eye diseases, namely nvAMD, branch retinal artery occlusion (BRAO)/BRVO, CRAO/CRVO, proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), NVG, or choroidal melanoma as described previously. It is clear that the traditional medicine could be an alternative way, which might be able to be complementary to the modern medicine. With the evidence described above and discussion as follows (**Figure 1**), we hopefully could find a way out to manage with the defined retinal ischemia-associated vision-threatening ocular disorders.

The HIOP-induced retinal ischemic changes were characterized by a decrease in ERG b-wave amplitudes, a loss of choline acetyltransferase immunopositive amacrine cell bodies/neuronal

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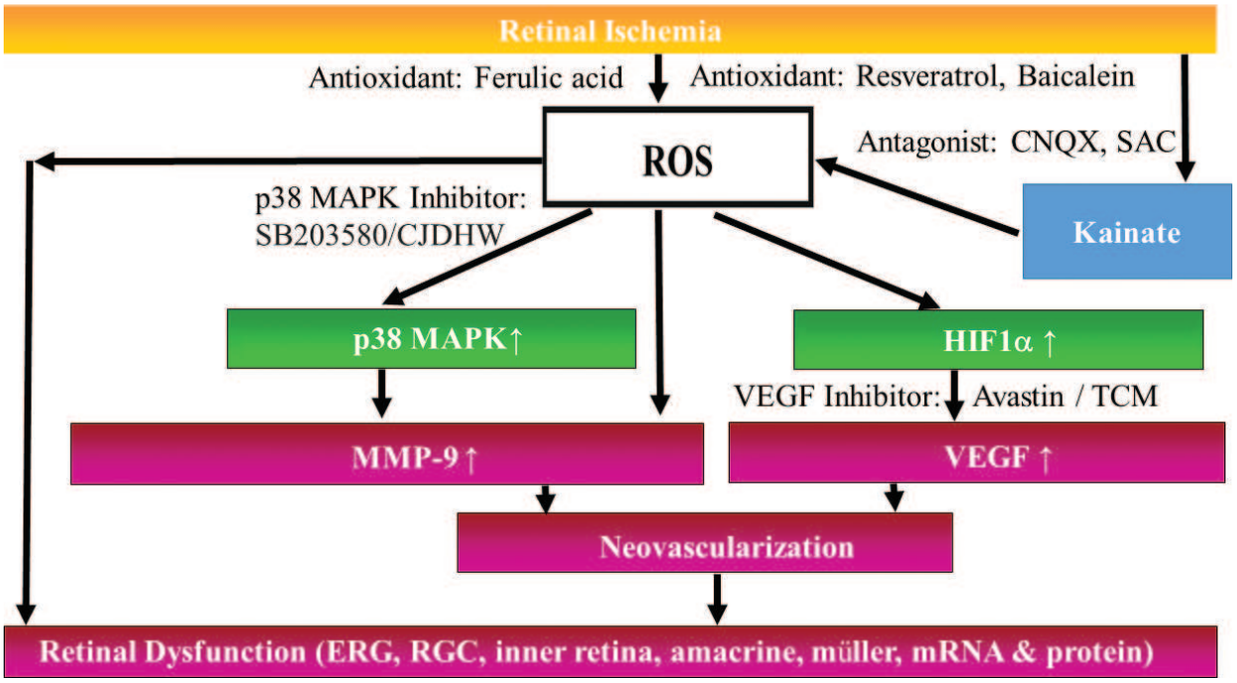


**Figure 1.** MMP-9 has been reported to play an important role in the retinal ischemia/excitotoxicity/oxidative stress [9, 11–15, 17]. Excitotoxicity and reactive oxygen species (ROS), such as $\cdot O_2$-, $H_2O_2$ and $\cdot OH$, are widely accepted to be provided through the Fenton reaction in alive cells. The HIOP-induced retinal ischemic changes were characterized by a decrease in ERG b-wave amplitudes, a loss of choline acetyltransferase immunopositive amacrine cell bodies/neuronal processes, an increase in vimentin immunoreactivity, a Müller cell marker and tremendous death of retinal ganglion cells. It has been also observed the upregulation of HIF-1$\alpha$, MMP-9 and VEGF at the protein/mRNA levels. Both the p38 MAPK-stimulated MMP-9 upregulation and HIF-1$\alpha$-triggered VEGF overexpression would result in neovascularization. Neovascular glaucoma (in PDR, CRVO/BRVO) and nvAMD are known to be troublesome vision-threatening retinal ischemia-realted ocular disorders. A combination of single compounds or TCM combinations [24] might produce combined drug effects to the commercial agents due to their different treatment mechanisms with less complications. As described previously [9, 11–15, 17], baicalein seems to have protective effect via antioxidation, antiapoptosis, HO-1upregulation and downregulation of HIF-1$\alpha$, VEGF, and/or MMP-9. Furthermore, the underlying mechanism of the baicalein inhibition on retinal ischemia-induced upregulated MMP-9 level seems to be only ''in part'' associated with its anti-oxidative effect [13]. In addition, retinal ischemia, oxidative stress and/or kainate excitotoxicity could be protected by resveratrol: "via downregulation of MMP-9 and iNOS as well as upregulation of HO-1"; SAC: "through an inhibition of iNOS, HIF-1$\alpha$, VEGF and/or MMP-9 upregulation as well as apoptosis"; CJDHW: "by means of anti-apoptosis, anti-oxidation, MMP-9 downregulation and p38 MAPK inhibition". Abbreviations: proliferative diabetic retinopathy, PDR; central/branch retinal vein occlusion, CRVO/BRVO; neovascular age related macular degeneration, nvAMD; traditional Chinese medicine, TCM; hypoxia inducible factor-1$\alpha$, HIF-1$\alpha$; vascular endothelium factor, VEGF; matrix metalloproteinase-9, MMP-9; inducible nitric oxide synthetase, iNOS; heme oxygenase-1, HO-1; S-allyl L-cysteine, SAC; Chi Ju Di Huang Wan, CJDHW; mitogen-activated protein kinase, MAPK.

processes, and an increase in vimentin immunoreactivity, a Müller cell marker. It has also been observed the upregulation of MMP-9 at the protein/mRNA level.

*Resveratrol related to MMP and others:* It has also been demonstrated the upregulation of HO-1, and iNOS, as well as the downregulation of Thy-1, at the protein/mRNA level. The ischemic detrimental effects were concentration-dependent (weaker effect at 0.05 nmol) and/or significantly (at 0.5 nmol) altered when resveratrol was applied 15 min before or after retina ischemia. Conclusively, this study supports the hypothesis that resveratrol may be able to protect the retina against ischemia by downregulating MMP-9 and iNOS, and upregulating HO-1.

*Baicalein related to MMP and others:* The retinal ischemic changes also included Bcl-2 protein linked to an increased apoptotic cells, and changes in the HIF-1$\alpha$, VEGF, and HO-1 mRNA levels; in hRPEs, $H_2O_2$ (500 μM) induced oxidative stress was associated with the upregulated VEGF and MMP-9 protein levels. Notably, the ischemic or oxidative injures were concentration-dependent and/or significantly (0.05 nmol and/or 0.5 nmol; 25 and/or 50 μM) altered when baicalein was applied 15 min before retinal ischemia or $H_2O_2$ (500 μM). In retinal cells or hRPEs subjected to ascorbate/iron or $H_2O_2$ (500 μM), there was an increased ROS, which was significantly attenuated by 100-μM baicalein and trolox (100 μM or 1mM) or 50/25 μM baicalein which downregulated the VEGF and MMP-9 protein overexpression. Furthermore, the underlying mechanism of the baicalein inhibition on retinal ischemia-induced upregulated MMP-9 level seems to be only "in part" associated with its antioxidative effect [9].

*SAC related to MMP and others*: Retinal excitotoxic/ischemic changes were also identified by fluorogold retrograde labeled RGCs, and increases in RGC layer apoptotic cells. Upregulated mRNA levels of iNOS, HIF-1$\alpha$, and/or VEGF were also detected in the retina subjected to kainate excitoxicity or HIOP. The increased HIF-1$\alpha$ and VEGF protein levels were also seen in RGC-5 cells subjected to defined oxidative stress. Importantly, the excitotoxicity/ischemia/oxidative stress-induced alterations were significantly blunted when kainate receptor antagonist 100 μM CNQX and/or SAC (5 μL intravitreous injection or incubation) was applied 15 minutes before ischemia, oxidative stress or excitotoxicity. Conclusively, SAC would seem to protect against retinal ischemia/oxidative stress/kainate excitotoxicity via an inhibition of iNOS, HIF-1$\alpha$, VEGF and/or MMP-9 upregulation as well as a modulation of glial activation and apoptosis.

*CJDHW related to MMP and others:* The ischemia-induced changes (Group 2) were significantly modulated by preischemic treatment with CJDHW (Group 4) on I/R day 7. These modulations included (Group 2 *vs*. 4) increased ERG b-wave amplitudes, inner retinal thickness, ChAT immunolabeling amscrines, and RGCs. They also showed decreased vimentin/GFAP immunolabeling Müllers and RGC layer apoptotic cells. Moreover, increased Thy-1 and decreased MMP-9 mRNA (mean: 4.44 *vs*. 1.13) levels were found, respectively. Furthermore, the Bcl-2 protein level increased while the HO-1, P-p38 MAPK (mean: 1.12 *vs*. 0.57) and MMP-9 levels (mean: 0.70 *vs*. 0.39) were decreased. The ischemia-associated increases in P-p38 and MMP-9 protein levels (mean) were also attenuated by 0.5 mM SB203580 (P-p38 MAPK: 1.12 *vs*. 0.18; MMP-9: 0.70 *vs*. 0.21). This was also the case with the MMP-9 enzyme activity (Group 2 *vs*. 4 *vs*. 5: 5.03 *vs*. 1.59 *vs*. 1.35). Conclusively, CJDHW prevented retinal ischemia through antiapoptosis, antioxidation, MMP-9 downregulation, and p38 MAPK inhibition.

A combination of single compounds or TCM combinations [20] might create synergistic pharmaceutical effects to the modern medicine owing to their various therapeutic mechanisms with less unwanted drug effects. Whether the traditional medicine is ready to be complementary to the modern medicine, it is will be clear if the era of Ethnopharmacology would be ready, is not it.

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