Chin J Integr Med 2019 Apr;25(4):316-320

Chinese Journal of Integrative Medicine

Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Review

Chinese Medicines in Diabetic Retinopathy Therapies

SONG Wei and ZHU Yong-wei

ABSTRACT Diabetic retinopathy (DR), a chronic microvascular retinal disorder leading to retinal nonperfusion and ischemia, is one of the leading causes of blindness among individuals of working age. Inflammation and neovascularization play important roles in the development of DR, especially proliferative DR (PDR). Therapies with Chinese medicines (CMs) that improve microcirculation complementary to conventional treatments increase the chances of delaying PDR development and improving visual acuity in diabetes patients. This review aimed to introduce promising CMs targeting DR patients in clinical practice, together with their underlying molecular mechanisms.

KEYWORDS diabetic retinopathy, Chinese medicine, inflammation, neovascularization

Diabetic retinopathy (DR) is one of the leading causes of blindness among the working-age population, with around 93 million cases reported globally in 2012.[1] As a chronic microvascular retinal disorder, DR is characterized by progressive occlusion of capillaries, resulting in retinal nonperfusion and ischemia.[2] DR can be further classified into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The symptoms of NPDR include microaneurysms, intraretinal hemorrhages, cotton wool spots and intraretinal microvascular abnormalities. Compared to NPDR, the distinctive feature of PDR is the vascular endothelial growth factor (VEGF)-mediated pathological intraocular neovascularization.[3]

In current clinical practice, only close monitoring is required for NPDR patients without pronounced macular edema. However, clinically significant macular edema often involves focal laser therapy. In addition, intravitreal injections of triamcinolone or anti-VEGF agents including ranibizumab are also effective in improving the visual acuity. For PDR patients, pan-retinal laser photocoagulation is the preferable treatment to induce new vessel regression and prevent severe visual loss.

Since the pathophysiological feature of DR is the occlusion of retinal ischemia and intraocular neovascularization, Chinese medicines (CMs) known to improve microcirculation within the retina have their unique advantages in the DR treatment. Therapies combining CMs with conventional surgical and medical treatments show great promise in delaying PDR development and improving the visual acuity in these diabetes patients. In this review, we aimed to summarize the mechanisms of CMs in treating DR and highlighting promising CMs that may be beneficial for DR patients.

Mechanisms of CMs in Treating DR

Recent studies revealed that inflammation plays an important role in the development of DR.[4] In diabetes patients, hyperglycemia leads to inflammation and vascular dysfunction through several molecular signaling pathways.[5] Consequently, retinal leukostasis will develop in the retinas and correlates with the increased expression of retinal intercellular adhesion molecule-1 and CD18.[6] The development of retinal leukostasis might contribute to retinal vascular permeability and capillary nonperfusion. In addition to retinal inflammation, neovascularization is another key mechanism in the development of DR, especially in PDR cases. Ocular neovascularization may lead to severe complications like neovascular glaucoma and vitreous hemorrhage.

Based on these findings, multiple research groups have demonstrated the anti-inflammation and anti-neovascularization effects of CMs on DR both *in vitro* and in diabetic animal models.

Department of Ophthalmology, Jiaxing Traditional Chinese Medicine Hospital Affiliated to Zhejiang Chinese Medical University, Jiaxing, Zhejiang Province (314000), China
Correspondence to: Prof. ZHU Yong-wei, Tel: 86-573-82055510, E-mail: zywei3950@sina.com

DOI: https://doi.org/10.1007/s11655-017-2911-0

Puerarin

Puerarin is the active constituent of a *Radix puerariae*. In a study by Zhu, et al,[7] cultured retinal capillary endothelial TR-iBRB2 cells were treated with interleukin (IL)-1 β , a key proinflammatory factor in the development of DR, to induce leukostasis, validated by the elevated expression of leukocyte endothelial adhesion process. Strikingly, the treatment of puerarin was capable to inhibit the IL-1 β -induced leukostasis by inhibiting the involved upstream and downstream signaling pathways, suggesting the potential anti-inflammation effect of puerarin in the retina.

Besides of anti-inflammation effects, Teng, et al[8] demonstrated its anti-neovascularization effect in streptozotocin (STZ)-induced diabetic rats. Systemic administration of puerarin significantly reduced DR progression indicated by morphological changes of inner nuclear layer and outer nuclear layer within retina. Additionally, they performed reverse transcription-polymerase chain reaction (RT-PCR) to compare the VEGF expression levels between the treated and untreated groups. Consistently, the ocular expression of VEGF in puerarin-treated group was significantly decreased. Similarly, Song, et al[9] observed systemic puerarin treatment was able to block the initiation of DR in STZ-induced Wistar rats, indicated by slightly changed retinal structure, including inner nuclear layer and outer nuclear layer.[10] Therefore, the *in vivo* experiments demonstrated that puerarin may be a promising candidate in treating DR patients by regulating angiogenesis factors expression.

Dendrobium Chrysotoxum Lindl

Dendrobium chrysotoxum Lindl (DC) has been reported to exhibit antioxidant, immunomodulatory, anticancer, and antisenescence activities.[11] Yu, et al[12] tested ethanol extract of DC to investigate its effects on DR in STZ-induced diabetic rats. The anti-inflammation effects of DC were confirmed by reduced retinal expression of inflammatory factors, including IL-1 β , IL-6 and tumor necrosis factor (TNF)- α , within the retina of diabetic rats. Additionally, the increased serum levels of these factors were also attenuated.[12,13] DC treatment also restored the increased retinal mRNA expressions of VEGF and VEGF receptor 2 (VEGFR2), together with the elevated serum VEGF level in diabetic rats. As a result, the retinal vessel density was decreased in DC-treated diabetic rats.[13,14] Similar anti-neovascularization effects were also observed in STZ-induced diabetic mice by another Chinese group.[15] Further observation showed that DC suppressed high-glucose-induced VEGF expression and VEGFR2 activation through VEGFR2-cRaf-MEK1/2-ERK1/2 and PI3K-AKT signaling pathways.[14] Based on these *in vitro* and *in vivo* experiments, Yu, et al[12] confirmed the therapeutic effects of DC in DR through both anti-inflammation and anti-angiogenesis mechanisms.

Andrographolide

Andrographolide (Andro) is the main chemical compound derived from *Andrographis paniculat*..[16] Yu, et al[17] also tested the therapeutic effects of Andro in the retinas of STZ-induced DR mice. Resembling DC, Andro was able to reduce the elevated serum and retinal mRNA expression of inflammatory factors in NPDR rats. As a result, the breakdown of blood-retina barrier by inflammatory factors, a critical step in DR development, was effectively blocked. As expected, Andro significantly blocked the increase in VEGF in serum and vitreous cavity, and the increase in retinal mRNA expressions of VEGF and its receptors in PDR rats. Therefore, the newly formed retinal vessels were effectively suppressed during the development from NPDR to PDR.

Stephania tetrandra S. Moore

Stephania tetrandra S. Moore (STSM) is used traditionally to remove fluid and to eliminate "wind and damp" from the body and has been used for centuries in China for the treatment of edema and arthritis. Two major chemical components, tetrandrine and fangchinoline, can be isolated from STSM.

Kobayashi, et al[18] tested the anti-angiogenesis effects of tetrandrine both *in vitro* and *in vivo*. Tetrandrine potently inhibited choroidal angiogenesis in cultured choroids in STZ-induced diabetic Wistar rats. Such inhibition were also observed in air-pouch granuloma angiogenesis in diabetic mice. After establishing a retinal capillary in STZ-induced diabetic rats in culture, the researchers tested the efficacy of the root extract of STSM in suppressing neovascularization. The results showed that administration of STSM significantly inhibited neovascularization of both retinal capillary and choroidal capillary in culture in a dose-dependent manner. Furthermore, tetrandrine was able to protect both the retinal and choroidal capillary from neovascularization development in the same way. Thus, it was concluded that STSM may delay the progression of retinopathy in diabetic patients through

Chin J Integr Med 2019 Apr;25(4):316-320

the biological activity of tetrandrine.[19]

Other Potential Compounds

Lonicerae Japonicae Flos (FL) is another traditional Chinese drug used to clear away "heat" and toxic material.[20,21] In STZ-induced diabetic mice, Zhou, et al[22] observed the inhibitory effects of aqueous extract of FL on new vessel formation. Retinal histopathological observation showed that FL effectively reduced the elevated number of newly formed blood vessels in the retina. For the underlying molecular mechanism, FL was also shown to reduce the increased serum VEGF content and VEGF-induced choroid-retinal endothelial RF/6A cells proliferation in a dose-dependent manner. Therefore, FL may be beneficial for retinal angiogenesis inhibition in DR patients.

Tauroursodeoxycholic acid (TUDCA) derived from bear gall shows pharmacological effects in treating various diseases.[23] Wang, et al[24] conducted *in vivo* experiments in STZ-induced diabetic rats and found that TUDCA administration was able to decrease the VEGF expression in the retina. Meanwhile, the serum content of nitric oxide (NO) was also lowered. Since NO is a causative factor to retinal microvascular endothelial cells dysfunction in DR patients, TUDCA may be another potential agent in inhibiting neovascularization in DR patients.

The compound rhodiola cretini is able to clear away free radical in human beings.[25] In the STZ-induced diabetic rats, daily rhodiola cretinii administration by gastric perfusion significantly lowered VEGF expression levels, indicated by both immunochemistry staining and RT-PCR.[26]

Chinese Classic Herbal Formulae

Different from individual herbs, Chinese classic herbal formulae as part of Chinese herbology combine multiple herbs for greater efficiency. Danggui Buxue Decoction (DBD, 当归补血汤) is the aqueous extract of *Radix Astragal* and *Radix Angelica sinensis*. Intragastrically administration of DBD (3.6 g/kg) in STZ-induced diabetic rats for 8 weeks restored the elevated serum and vitreous levels of VEGF.[27] With the additional ingredient *Panax notoginseng* (RRP), the modified DBD reported by Gao, et al[28] successfully abolished the leukostasis in retinal vasculature in STZ-induced diabetic rats. Moreover, they found that RRP decreased the expression of key inflammatory factors in the retina. Thus, they inferred that RRP had a potent effect in preventing the progression of DR by inhibiting the inflammation of diabetic retina.

Shiquan Dabu Decoction (十全大补汤, SDD, Sipjeondaebo-tang in Korean), is a widely used traditional herbal formula to treat patients with fatigue, loss of appetite, anemia, atopic dermatitis and rheumatoid arthritis.[29] In oxygen-induced retinopathy (OIR) mice, Lee, et al[30] found that systemic administration of SDD by intraperitoneal injection significantly reduced retinal neovascularization by suppressing the expression of platelet derived growth factor, a angiogenesis factor in PDR development.[30]

Guipi Decoction (归脾汤, GPD, Guibi-tang in Korean), also named Guipi Decoction in Chinese, is another oriental herbal formula widely used in East Asia.[31] Lee, et al[32] reported GBD's function in depressing neovascularization in OIR mice. They measured several angiogenesis-related factors reflecting the retinal neovascularization process in the animal model. Intraperitoneally administration of GBD daily effectively decreased the VEGF expression compared to the control group. Lee, et al[33] also observed the inhibitory function of Siwu Decoction (四物汤, SWD, Samul-tang in Korean) in DR neovascularization. Similar results obtained from *in vivo* experiments also indicated that it is a potential herbal formula for DR treatment.

Outlook and Conclusion

Multiple studies have been performed in DR models to investigate the effects of CMs in DR treatment (Table 1). Their common molecular mechanism was through the inhibition of retinal vascular endothelial inflammation or neovascularization.

To date, only a few clinical trials using CMs to prevent PDR development in diabetes patients have been conducted. Luo, et al[34] used retinal arterio-venous circulation time as an indicator of blood flow and reported that Qiming Granule (杞明颗粒) may increase retinal blood flow and improve blood circulation. Another clinical study by Lian, et al[35] demonstrated that *Salvia miltiorrhiza* was also beneficial for DR patients. Lin, et al[36] tested the therapeutic effects of modified DBD with photocoagulation in treating PDR.

Although the effects of several CMs have been tested in DR patients, the number of enrolled subjects

Table 1. Potential Chinese Medicines in Treating DR

Mechanism	Chinese medicines	Biological effects in experimental DR
Inhibit retinal vascular endothelial inflammation	Puerarin	Inhibit leukostasis of TR-iBRB2 cells induced by IL-1 β
	Modified DBD with RRP	Inhibit leukostasis and decrease expression of inflammatory factors in DR rats
	DC	Reduce increased retinal expression and serum levels of inflammatory factors in DR rats
	Andrographolide	Reduce increased retinal expression and serum levels of inflammatory factors in DR rats
Inhibit retinal neovascularization	STSM	Inhibit neovascularization of both retinal capillary and choroidal capillary in DR rats in culture
	Puerarin	Reduce DR progression in inner nuclear layer and outer nuclear layer within retina, decrease ocular VEGF expression
	Rhodiola cretinii	Decrease ocular VEGF expression in DR rats
	DC	Decrease ocular VEGF and VEGFR2 expression in DR rats
	Andrographolide	Decrease ocular VEGF and VEGFR2 expression in DR mice
	FL	Decrease ocular VEGF expression in DR mice
	TUDCA	Decrease ocular VEGF expression and serum content of NO in DR rats
	SDD	Decrease expression of PDGF in oxygen-induced retinopathy mice
	GBD	Decrease ocular VEGF expression in oxygen-induced retinopathy mice
	SMD	Decrease ocular VEGF expression in oxygen-induced retinopathy mice

Notes: DBT: Danggui Buxue Decoction; DC: *Dendrobium Chrysotoxum* Lindl; STSM: *Stephania tetrandra* S. Moore; FL: *Lonicerae Japonicae* Flos; TUDCA: tauroursodeoxycholic acid; SDD: Shiquan Dabu Decoction; Guipi Decoction; SWD: Siwu Decoction.

was insufficient. Therefore, further clinical trials, especially randomized controlled trials, are necessary to confirm the safety and utility of CMs. At the same time, exploring other novel traditional herbal formulae based on the above-mentioned mechanisms may potentially increase the cure rate of DR.

Conflict of Interest

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

Author Contributions

Conception: Zhu YW; article drafting and final approval: Song W and Zhu YW.

Acknowledgement

We are grateful to Ms. Julie Qiaojin Lin (Department of Physiology, Development and Neuroscience, University of Cambridge) for editing the manuscript.

REFERENCES

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-564.
2. Hendrick AM, Gibson MV, Kulshreshtha A. Diabetic retinopathy. Primary Care 2015;42:451-464.
3. Zhang X, Bao S, Lai D, Rapkins RW, Gillies MC. Intravitreal triamcinolone acetonide inhibits breakdown of the blood-retinal barrier through differential regulation of VEGF-A and its receptors in early diabetic rat retinas. Diabetes 2008;57:1026-1033.
4. Liou GI. Diabetic retinopathy: role of inflammation and potential therapies for anti-inflammation. World J Diabetes 2010;1:12-18.
5. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res 2011;30:343-358.
6. Joussen AM, Poulaki V, Le ML, Koizumi K, Esser C, Janicki H, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. FASEB J 2004;18:1450-1452.
7. Zhu X, Xie M, Wang K, Zhang K, Gao Y, Zhu L, et al. The effect of puerarin against IL-1beta-mediated leukostasis and apoptosis in retinal capillary endothelial cells (TR-iBRB2). Mol Vis 2014;20:1815-1823.
8. Teng Y, Cui H, Yang M, Song H, Zhang Q, Su Y, et al. Protective effect of puerarin on diabetic retinopathy in rats. Mol Biol Rep 2009;36:1129-1133.
9. Song H, Teng Y, Yang MM, Ma QS. Protection effect of puerarin to rats' diabetic retinopathy. Heilongjiang Med J (Chin) 2014;2:113-114.
10. Yu Y, Yang M, Zhang QS, Liu YW, Liu HF, Yao P, et al. Effects of puerarin on diabetic retinopathy. Heilongjiang Med Pharm (Chin) 2009;2:1-2.
11. Zhao Y, Son YO, Kim SS, Jang YS, Lee JC. Antioxidant and anti-hyperglycemic activity of polysaccharide isolated from *Dendrobium chrysotoxum* Lindl. J Biochem Mol Biol 2007;40:670-677.

12. Yu Z, Gong C, Lu B, Yang L, Sheng Y, Ji L, et al. *Dendrobium chrysotoxum* Lindl. alleviates diabetic retinopathy by preventing retinal inflammation and tight junction protein decrease. J Diabetes Res 2015;2015:518317.
13. Gong CY, Yu ZY, Lu B, Yang L, Sheng YC, Fan YM, et al. Ethanol extract of *Dendrobium chrysotoxum* Lindl ameliorates diabetic retinopathy and its mechanism. Vascul Pharmacol 2014;62:134-142.
14. Yu Z, Zhang T, Gong C, Sheng Y, Lu B, Zhou L, et al. Erianin inhibits high glucose-induced retinal angiogenesis via blocking ERK1/2-regulated HIF-1alpha-VEGF/VEGFR2 signaling pathway. Sci Rep 2016;6:34306.
15. Yu ZY, Lu B, Ji LL, Wang ZT. Ethanol extract of *Dendrobium chrysotoxum* Lindl. on the amelioration of diabetic retinopathy and its engaged mechanism. J Int Pharm Res 2016;2:301-306.
16. Lim JC, Chan TK, Ng DS, Sagineedu SR, Stanslas J, Wong WS. Andrographolide and its analogues: versatile bioactive molecules for combating inflammation and cancer. Clin Exp Pharmacol Physiol 2012;39:300-310.
17. Yu Z, Lu B, Sheng Y, Zhou L, Ji L, Wang Z. Andrographolide ameliorates diabetic retinopathy by inhibiting retinal angiogenesis and inflammation. Biochim Biophys Acta 2015;1850:824-831.
18. Kobayashi S, Kimura I, Fukuta M, Kontani H, Inaba K, Niwa M, et al. Inhibitory effects of tetrandrine and related synthetic compounds on angiogenesis in streptozotocin-diabetic rodents. Biol Pharm Bull 1999;22:360-365.
19. Liang XC, Hagino N, Guo SS, Tsutsumi T, Kobayashi S. Therapeutic efficacy of *Stephania tetrandra S*. Moore for treatment of neovascularization of retinal capillary (retinopathy) in diabetes—*in vitro* study. Phytomedicine 2002;9:377-384.
20. Jiang M, Han YQ, Zhou MG, Zhao HZ, Xiao X, Hou YY, et al. The screening research of anti-inflammatory bioactive markers from different flowering phases of *Flos Lonicerae Japonicae*. PLoS One 2014;9:e96214.
21. Shang X, Pan H, Li M, Miao X, Ding H. *Lonicera japonica* Thunb.: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine. J Ethnopharmacol 2011;138:1-21.
22. Zhou L, Zhang T, Lu B, Yu Z, Mei X, Abulizi P, et al. *Lonicerae Japonicae Flos* attenuates diabetic retinopathy by inhibiting retinal angiogenesis. J Ethnopharmacol 2016;189:117-125.
23. Xu K, Zheng S, Zhai Y, Guo L, Tang P, Yan J, et al. Two solid forms of tauroursodeoxycholic acid and the effects of milling and storage temperature on solid-state transformations. Int J Pharm 2015;486:185-194.
24. Wang CF, Yuan JR, Qin D, Gu JF, Zhao BJ, Zhang L, et al. Protection of tauroursodeoxycholic acid on high glucose-induced human retinal microvascular endothelial cells dysfunction and streptozotocin-induced diabetic retinopathy rats. J Ethnopharmacol 2016;185:162-170.
25. Chen YM, Chen H, Mao GM, Fu JY, Xu CJ, Meng J. Study on anti-hypoxia effect of *Rhodiola sachalinensis A*. Bor. Chin J Health Lab Technol (Chin) 2007;8:1494-1495.
26. Zhao HS, Wei WB. Effect of compound rhodiola cretinii on VEGF expression in retina of rats with diabetes mellitus. Chin Ophthalmic Res (Chin) 2010;6:513-518.
27. Qian ZG, Ke M, Zhang YW. Effects of *Angelicae sinensis* Decoction on vitreous and serum vescular endothelial growth factor level in diabetes mellitus rats. Chin J Exp Ophthalmol (Chin) 2011;8:734-737.
28. Gao D, Guo Y, Li X, Li X, Li Z, Xue M, et al. An aqueous extract of *Radix Astragali*, *Angelica sinensis*, and *Panax notoginseng* is effective in preventing diabetic retinopathy. Evid Based Complement Altern Med 2013;2013:578165.
29. Kogure T, Hoshino A, Ito K, Sato H, Tatsumi T, Ohyama Y, et al. Beneficial effect of complementary alternative medicine on lymphedema with rheumatoid arthritis. Mod Rheumatol 2005;15:445-449.
30. Lee YM, Kim CS, Sohn E, Jo K, Lim HR, Kim SK, et al. Sipjeondaebo-tang, a traditional herbal formula, inhibits retinal neovascularization in a mouse model of oxygen-induced retinopathy. Tohoku J Exp Med 2014;234:229-236.
31. Kim JH, Kim JH, Lee YM, Ahn EM, Kim KW, Yu YS. Decursin inhibits retinal neovascularization via suppression of VEGFR-2 activation. Mol Vis 2009;15:1868-1875.
32. Lee YM, Lee YR, Kim CS, Jo K, Sohn E, Kim JS, et al. Effect of Guibi-Tang, a traditional herbal formula, on retinal neovascularization in a mouse model of proliferative retinopathy. Int J Mol Sci 2015;16:29900-29910.
33. Lee YM, Kim CS, Jo K, Sohn EJ, Kim JS, Kim J. Inhibitory effect of Samul-tang on retinal neovascularization in oxygen-induced retinopathy. BMC Complement Altern Med 2015;15:271.
34. Luo XX, Duan JG, Liao PZ, Wu L, Yu YG, Qiu B, et al. Effect of Qiming Granule on retinal blood circulation of diabetic retinopathy: a multicenter clinical trial. Chin J Integr Med 2009;15:384-388.
35. Lian F, Wu L, Tian J, Jin M, Zhou S, Zhao M, et al. The effectiveness and safety of a Danshen-containing Chinese herbal medicine for diabetic retinopathy: a randomized, double-blind, placebo-controlled multicenter clinical trial. J Ethnopharmacol 2015;164:71-77.
36. Lin T, Shi YL, Zhang S, Su SJ, Yang SY, Zhuang JY. Therapeutic effect of Modified Danggui Buxue Decoction on proliferative diabetic retinopathy with photocoagulation treatment. Chin Foreign Med Res (Chin) 2017;14:3-6.

(Received August 16, 2017; First Online September 28, 2018)
Edited by WANG Wei-xia