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A combination of the main constituents of Fufang Xueshuantong Capsules shows protective effects against streptozotocin-induced retinal lesions in rats

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Abstract

Ethnopharmacological relevance

Fufang Xueshuantong Capsule, an herbal formula licensed for clinical use in China, which is composed of *Panax notoginseng* (Burkill) F.H. Chen, *Salvia miltiorrhiza* Bunge, *Astragalus membranaceus* (Fisch.) Bunge, and *Scrophularia ningpoensis* HemsI, has proven effective for the treatment of diabetic retinopathy. However, its bioactive constituents are still ambiguous. In this study, the therapeutic effects of a combination of the main constituents of Fufang Xueshuantong Capsule (cFXT) were evaluated in streptozotocin (STZ)-induced retinal lesions to identify the bioactive constituents.

Methods

Sprague-Dawley rats, except for those in the control group (vehicle+vehicle), were administered a single injection of 60 mg/kg STZ. One-week later, STZ-treated rats were randomly divided into three groups—one STZ group (STZ+vehicle) and two cFXT treatment groups (STZ+cFXT). The rats in the latter two groups received cFXT 44.8 mg/kg or cFXT 22.4 mg/kg by intragastric gavage once per day, for 24 consecutive weeks. The rats in the control and STZ groups received the vehicle in the same way. Body weights and fasting blood glucose levels were recorded every four weeks. After treatment, hemorheological tests were performed to record the erythrocyte aggregation indexes, blood viscosity, and plasma viscosity. The trypsin digestion method was used to observe pericyte and acellular capillary the trypsin in the retina. Ultraviolet spectrophotometry was utilized to measure the activity of aldose reductase (AR) by measuring the nicotinamide adenine dinucleotide phosphate (NADPH) consumption at 340 nm. An immunohistochemical assay was used to observe the expressions of vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) in the retina. The expression levels of intercellular adhesion molecule-1 (ICAM-1), endothelin-1 (ET-1), and occludin in the retina were tested by the western blot assay.

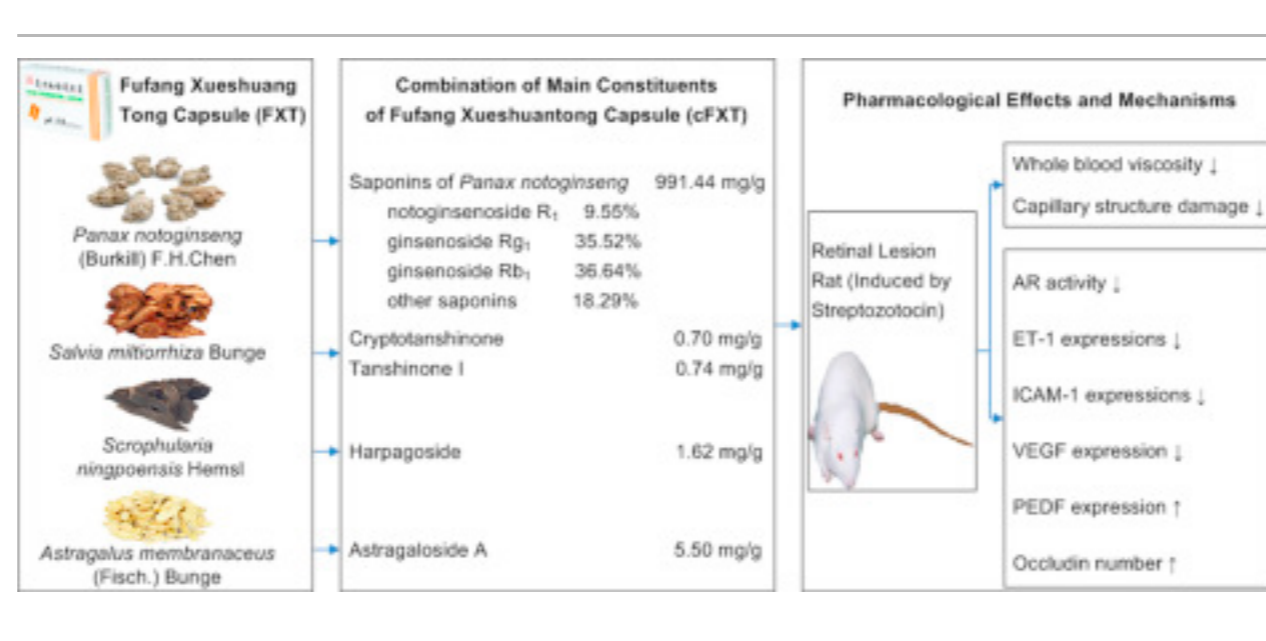
Results

cFXT is composed of 991.44 mg/g saponins of *Panax notoginseng*, 1.62 mg/g harpagoside, 0.70 mg/g cryptotanshinone, 0.74 mg/g tanshinone I, and 5.50 mg/g astragaloside A. Although it showed no effects on the increased body weight and blood glucose levels induced by STZ in rats. However, it showed a tendency to attenuate the increase in erythrocyte aggregation, plasma viscosity, and acellular vessel and pericyte loss, paralleled with a reversal of the hyper-activation of AR, the hyper-expression of VEGF, ICAM-1, and ET-1, and the hypo-expression of PEDF and occludin in the retinas of STZ-treated rats.

Conclusion

The saponins of *Panax notoginseng*, harpagoside, cryptotanshinone, tanshinone I, and astragaloside A are the main bioactive constituents of Fufang Xueshuantong Capsule and contribute to the attenuation of STZ-induced retinal lesions in rats. These constituents can be used as the base to optimize a new drug for the treatment of diabetic retinopathy, and can be selected for quality control of Fufang Xueshuantong Capsules.

Graphical abstract



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Introduction

Diabetic retinopathy (DR) is a disease induced by diabetes that involves the retinal capillaries, arterioles, and venules and is accompanied by leakage or occlusion of the small vessels (Nentwich and Ullbig, 2015). Phaneros lesions are observed with the progression of DR, such as microaneurysms, hemorrhages, vessel abnormalities, fibrous proliferation, and angiogenesis (Bandello et al., 2013). Studies have demonstrated that down-regulation of the factors involved in the pathogenesis of DR, such as hyper-activation of aldose reductase (AR) (Hattori et al., 2010), over expression of vascular endothelial growth factor (VEGF) (Matsuda et al., 2014) and intercellular adhesion molecule-1 (ICAM-1), and up-regulation of pigment epithelium-derived factor (PEDF) (Bucolo et al., 2012, Bucolo et al., 2009, Miyamoto et al., 2000, Ogata et al., 2002) are effective strategies for the treatment of DR.

Fufang Xueshuantong Capsule (FXT, also called Compound Xueshuantong) is a Chinese herbal formula composed of *Panax notoginseng* (Burkill) F.H. Chen (Araliaceae), *Salvia miltiorrhiza* Bunge (Lamiaceae), *Astragalus membranaceus* (Fisch.) Bunge (Leguminosae), and *Scrophularia ningpoensis* HemsI (Scrophulariaceae) (Sheng et al., 2014). It has been clinically used to treat DR (Cheng, 2013). Our previous research in a model of streptozotocin (STZ)-induced rat diabetes showed that FXT could normalize abnormal whole blood viscosity (WBV), plasma viscosity (PV), and erythrocyte aggregation indexes (HXBJJ). In addition, FXT attenuated the development of microvessel lesions in the retina by decreasing pericyte loss and reducing acellular capillaries. This was in parallel to down-regulation of AR hyper-activity and over expression of VEGF and ICAM-1, and up-regulation of the hypo-expression of PEDF and occludin. FXT thus showed protective effects against STZ-induced retinal lesions in rats (Duan et al., 2013).

By reviewing the literature, we found that the characteristic constituents of the four herbs might be related to the pharmacological effects of FXT. Ginsenoside Rb₁ from *Panax notoginseng* showed inhibitory effects on endothelial proliferation with increased production of superoxide anion (Ohashi et al., 2006). Ginsenoside Rb₁, ginsenoside Rg₁, and notoginsenoside R₁ were effective in treating microcirculatory disturbances induced by lipopolysaccharide (Sun et al., 2007). Cryptotanshinone and tanshinone I from *Salvia miltiorrhiza* showed inhibitory effects on ICAM-1 and endothelin-1 (ET-1) expression in human umbilical vein endothelial cells (Jin et al., 2009, Onitsuka et al., 1983, Zhou et al., 2006). Harpagoside from *Scrophularia ningpoensis* showed protective effects against human vascular endothelial cell injury induced by hydrogen peroxide (Kim et al., 2002). Astragaloside A from *Astragalus membranaceus* reduced retinal ganglion cell apoptosis and down-regulated AR activity to prevent DR (Ding et al., 2014). In this study, the afore mentioned bioactive constituents of FXT were selected to form a constituent combination (cFXT). The quantity of the selected constituents in cFXT was in accordance with that in FXT as had been determined previously (Yu et al., 2014). The therapeutic effects of cFXT on STZ-induced retinal lesions in rats were evaluated in this study, aiming to clarify the roles of the core bioactive components of FXT and provide a foundation to optimize a new medicine with minimum constituents, high efficacy, and easy quality control.

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Section snippets

Animals and reagents

Male Sprague-Dawley (SD) rats weighing 230 to 250 g (SCXK [Jing] 2007-0001) were purchased from Vital River (Beijing, China). The animal experiment protocol was in accordance with the statement for the *Use of Animals in Ophthalmic and Vision Research* by the Association for Research in Vision and Ophthalmology and approved by the Institutional Animal Care and Use Committee of Beijing University of Chinese Medicine. Rats were acclimatized for one week before experiments, housed in a 12-h ...

cFXT treatment had no effects on body weight and blood glucose level in STZ rats

As shown in Fig. 1, rats in the STZ groups were found to gain less weight during the 24-week period than the control rats, and this phenomenon was not reversed by 44.8 mg/kg or 22.4 mg/kg cFXT treatments ($F_{(3,211)}=37.961$, $P<0.01$, Fig. 1A). Meanwhile, sustained high blood glucose levels were induced by STZ treatments. The increased blood glucose levels were not affected by 44.8 mg/kg or 22.4 mg/kg cFXT treatments ($F_{(3,211)}=78.109$, $P<0.01$, Fig. 1B). ...

cFXT treatment reduced HXBJJ and WBV, but not PV, in STZ rats

As shown in Fig. 2, STZ treatment led to enhanced ...

Conclusion and discussion

In this study, a combination of the main constituents of Fufang Xueshuantong Capsule (cFXT) proved to have the majority of pharmacological effects possessed by the herbal formula FXT (Duan et al., 2013). That is, cFXT reduced STZ-induced retinal lesions in rats by decreasing HXBJJ and WBV levels, and attenuating the proliferation of acellular capillaries. Furthermore, cFXT inhibited AR activity, and rectified the over expression of VEGF, ICAM-1, and ET-1 and the hypo-expression of PEDF in the ...

Conflict of interest

The authors declare that there are no conflicts of interest. ...

Acknowledgments

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