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Troxerutin in the treatment of eye diseases – a proven substance rediscovered

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HIGHLIGHTS

Troxerutin has got wide spectrum of medical effects and can be used also in ophthalmology.

ABSTRACT

Troxerutin is a well and for a long time known substance, it is a semi-synthetic bioflavonoid derived from rutin. Original substance is supplied from flowers of *Styphnolobium japonicum* tree.

The author discusses actual medical effects of troxerutin, including antioxidant, anti-inflammatory, antithrombosis and protecting endothelium of small vessels. Being water-soluble, it can be used as ophthalmic drops in treatment of subconjunctival haemorrhage, vitreous haemorrhage and early stages of diabetic retinopathy.

Key words: diabetic retinopathy, subconjunctival haemorrhage, troxerutin, eye drops

INTRODUCTION

21st century is a period of constant development of new drugs, not only in ophthalmology. However, we should not forget the old, well-known substances that have been used successfully for many years. One of them is troxerutin.

OCCURRENCE AND ORIGIN

Troxerutin is a semisynthetic derivative of the natural substance – rutoside, also known as rutin or vitamin P_4 [1]. This plant-derived compound is extracted from the flowers of the Japanese pearl plant (*Styphnolobium japonicum*).
Contrary to its name, Japanese pearl is native to Korea and China. It is a tree of the bean family, related to the common *acacia robinia*. It grows up to 30 m in height. The dried, undeveloped flower buds are used in medicine [2]. Interestingly, it usually blooms in August, which is much later than other trees. It is still a rare tree in Poland.
Troxerutin belongs to the bioflavonoids and has been known as a therapeutic substance since the 19th century. It owes its popularity in medicine to its broad spectrum of action. As a substance of natural origin, it has no cytotoxic effects and low tissue toxicity [3].
Under natural conditions, it is found in coffee, tea, cereals, vegetables such as yams, tomatoes, carrots and onions, as well as fruits – oranges, lemons, limes, grapes and berries [3].

PROPERTIES OF TROXERUTIN

Troxerutin dissolves well in water, so it is easily absorbed from the gastrointestinal tract and topically from the conjunctival sac through the cornea, which is used in ophthalmology [1].
The half-life of the substance is 24 h, so it can be taken orally once a day. The daily dose according to the literature varies, ranging from 100 to 900 mg. The compound is excreted from the body in the bile, so liver disease may be a contraindication to taking it orally. Drugs containing troxerutin are safe and have few side effects. If they do occur, they usually involve gastrointestinal problems [4].

IN VIVO AND IN VITRO EFFECTS

The pharmacological effects of troxerutin have been confirmed both in vitro and in vivo [5].
Troxerutin has been proven to have antioxidant, anti-inflammatory, anticoagulant and anticancer activities. In addition, it exhibits nephroprotective and sugar- and lipid-lowering effects. Troxerutin also increases overall cellular sensitivity to insulin [3, 5, 6].
Clinical studies have also confirmed the efficacy of troxerutin in the treatment of venous diseases through the mechanism of endothelial cell protection and stimulation of microcirculation [3, 5].
This substance also increases the resistance of capillaries and reduces their permeability, with the beneficial effect of reducing local swelling [1]. In addition, troxerutin inhibits erythrocyte aggregation and improves erythrocyte elasticity. A derivative of natural rutin (oxerutin) is also used as a therapeutic substance in the treatment of chronic venous insufficiency of the lower extremities [7, 8]. Troxerutin also prevents tissue ischemia.
Ischemia and subsequent tissue reperfusion play a major role in the dysfunction of various cells and organs. Oxidative stress and inflammatory response, being its effects, worsen the condition of the body, and troxerutin, used in therapy, has a positive effect [5].
The medical literature reports an inhibitory effect of troxerutin on myocardial cell apoptosis after an ischemia-reperfusion incident. In patients with diabetes and heart disease, the substance shortens the periods of cardiac arrhythmias and reduces their frequency [5].
Troxerutin thus has cardioprotective, hepatoprotective and neuroprotective effects. In addition, the administration of troxerutin lowers the concentration of inflammatory cytokines: TNF-α and IL-1β [3, 5].
In experimental studies on rats in which optic nerve neuropathy was induced by methanol administration, the protective effect of rutin was demonstrated. It involves a significant reduction in inflammatory markers and oxidative stress exponents. Troxerutin attenuates oxidative stress by inhibiting membrane lipid peroxidation and increasing antioxidant enzyme concentrations [9].
Its effect on the course of chronic painful peripheral neuropathy and diabetic neuropathy is also shown [9].
A study on the time of skin wound healing conducted on rats showed that the rate of healing was faster in the study group that received topical troxerutin than in the control group. The authors emphasized that troxerutin is effective in reducing skin flap necrosis and improving its survival [10].
Rutin is a flavonoid with strong antioxidant properties based on donating protons and stabilizing free radicals. In this way, it reduces the production of reactive oxygen species. It improves vascular endothelial function by increasing nitric oxide production in human endothelial cells, which also has an antioxidative effect [9].
In diabetic rats, administration of troxerutin reduced retinal neovascularization and limited VEGF protein production [4]. In humans, high doses of troxerutin have been proven to prevent retinal venous occlusion by restoring normal rheological properties [8, 9]. In the case of venous occlusion, treatment with troxerutin has a beneficial effect on the final improvement of visual acuity [11].
Troxerutin in high doses inhibits aggregation of not only red blood cells, but also platelets, reduces blood viscosity

and improves microcirculation. In addition, it protects the endothelium of small vessels by reducing prostaglandin production and increasing collagen production [4, 11].

THE USE OF TROXERUTIN IN OPHTHALMOLOGY

The use of troxerutin in ophthalmology is due to its water solubility, action on the surface of the eye and diffusion into the anterior chamber. The substance does not penetrate the blood–brain barrier. Its mechanism of action is not fully understood. Troxerutin is believed to significantly inhibit the non-physiological action of hyaluronidase. The consequences of increased hyaluronidase activity include increased fragility and permeability of blood vessels, edema formation, and impaired substance exchange in the vascular stroma [1].

Hyaluronidases are enzymes responsible for breaking down hyaluronic acid in tissues. There are 2 types of hyaluronic acid. High molecular weight hyaluronic acid displays anti-inflammatory properties, whereas low molecular weight hyaluronic acid increases inflammation and fibrosis. Increased hyaluronidase activity results in an increase in low molecular weight hyaluronic acid, increasing inflammation and fibrosis in tissues and organs [12].

Troxerutin is available in drops for patients with selected ocular conditions. The drops contain 50 mg of the active ingredient in 1 ml of liquid and chlorhexidine gluconate used as preservative. Drops should be administered 3 times a day into the conjunctival sac. Indications for the drug include subconjunctival hemorrhages, incipient diabetic retinopathy and vitreous hemorrhages [1].

Troxerutin drops, when administered into the conjunctival sac, do not cause additional irritation that would cause a reflexive increase in tear production resulting in dilution of the drug and impairing its activity [1, 13].

Drops are the best and most common route of drug administration into the eye, but the bioavailability achieved in this way is not always satisfactory, limiting the treatment efficacy. In order to enter the eyeball, the substance has to overcome two ocular barriers: a dynamic barrier, i.e., the tear film, and a static barrier, i.e., the cornea [13].

Due to its water solubility, troxerutin administered in drops effectively penetrates through the cornea and enters the eyeball. Topical administration of troxerutin accelerates the repair processes in capillaries and keeps the eye in good condition [1].

CONCLUSIONS

Troxerutin is experiencing a renaissance in medicine, including ophthalmology, thanks to its broad, proven spectrum of action on human tissues while remaining low in toxicity. Summarizing the reports presented on its multidirectional effects, the combined topical and general administration of the drug should be considered to achieve the maximum therapeutic effect in the shortest possible time in patients with diabetes and other disorders of the small vessels of the eye.

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