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Resveratrol and curcumin against diabetic retinopathy. Better together than apart

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HIGHLIGHTS

Polyphenols are an excellent tool in the diabetic retinopathy therapy.

ABSTRACT

The health-promoting effects of curcumin and resveratrol have been known for a long time. The most important features of polyphenols include their effect on blood vessels and participation in the neutralization of free oxygen radicals. Both resveratrol and curcumin exhibit antioxidant effects, and the combined use of both substances significantly improves their effectiveness. In the fight against diabetic retinopathy, the antiangiogenic effect of polyphenols also turn out to be important. Many researchers also point to the possibility of using resveratrol and curcumin in cancer therapy.

Key words: resveratrol, curcumin, diabetic retinopathy, antioxidant, oxidative stress

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DIABETES – THE EPIDEMIC OF OUR TIMES

Diabetes is a group of metabolic diseases characterized by elevated levels of blood glucose. Hyperglycemia is mainly caused by impaired production or malfunction of insulin, which is produced by the β cells of the pancreatic islets. Glucose disorders can have a severe impact on multiple organs, with vision-related complications being one of the most prevalent issues that hinder patients' ability to function properly [1].

The classification of diabetes distinguishes between type 1 diabetes, which is characterized by impaired insulin production, and type 2 diabetes, which is characterized by insulin resistance. In addition to type 2 diabetes, there are other specific types of diabetes, such as gestational diabetes, MODY, and LADA. Type 2 diabetes affects over 80% of patients and usually develops after the age of 40, which presents a significant therapeutic challenge in various medical fields [2].

DIABETIC RETINOPATHY

A cycle of biochemical changes that occur in the blood vessels can initiate the development of microangiopathy localized in the eyes. Diabetic retinopathy (DR) refers to a set of processes that result in abnormalities in the structure and function of the retina [3] and is now considered the primary cause of vision loss in patients over the age of 60. Hyperglycemia and alterations in metabolic pathways contribute to the development of oxidative stress and neurodegeneration, which directly impact visual quality [4].

The World Health Organization (WHO) distinguishes between non-proliferative diabetic retinopathy, with and without maculopathy, preproliferative retinopathy, and proliferative retinopathy with and without complications. Nonproliferative diabetic retinopathy (NPDR) is characterized by vascular endothelial damage, microaneurysm development, and intraretinal hemorrhages. Disruption of the blood-retinal barrier allows many pro-inflammatory cytokines and plasma proteins to penetrate, which on ophthalmic examination takes the form of hard exudates. As the disease progresses, further narrowing of the vascular lumen progresses, leading to vascular occlusion, visualized as cotton wool foci [5]. The exudate leaking from the leaking blood vessels causes retinal edema, which can eventually lead to the formation of new abnormal blood vessels and more serious retinal dysfunction, typical of proliferative diabetic retinopathy (PDR), which can include hemorrhages into the vitreous chamber and retinal detachments [6]. Preventing the effects of retinal damage in the course of diabetes is crucial and yields much better results than trying to treat advanced stages of the disease. The most important methods of prevention include regular ophthalmological visits with fundus evaluation, limiting dietary intake of sugars, ensuring physical activity tailored to individual abilities, regular blood tests, and lowering blood pressure and cholesterol levels, which are risk factors for developing DR [7].

POLYPHENOLS – RESVERATROL

Many scientific reports emphasize the importance of anti-angiogenic, antioxidant, and cytoprotective factors in maintaining proper bodily function [8]. Polyphenols are naturally occurring compounds found in plants, with resveratrol being their main representative [9].

Resveratrol is found in large amounts in red grapes, peanuts, currants, and raspberries. Polyphenols neutralize free oxygen radicals (ROS) and activate superoxide dismutase (SOD), which is a crucial protective factor against oxidative stress due to its antioxidant activity [10–12]. Polyphenols inhibit lipid oxidation and reduce thrombocyte activity, which can lower the risk of embolic complications and the development of atherosclerotic lesions [13–17].

Resveratrol has a stronger antioxidant effect than vitamin E. When combined with vitamin C or E, it exhibits synergistic effects [18, 19]. Additionally, it reduces the production of cytochromes, which are compounds with carcinogenic effects, by affecting ROS production [20].

The inhibition of cyclooxygenase 2 (COX-2) also seems to have an anti-inflammatory effect, which is significant in terms of retinal changes [21, 22]. Research projects conducted on rats in which diabetes was induced with streptozocin additionally showed a decrease in the concentrations of pro-inflammatory cytokines (IL-1, IL-6, IFN, MCP-1, NF-κB, TNF-α) and vascular endothelial growth factor (VEGF) [23, 24].

Oak et al. demonstrated that polyphenols in wine inhibit angiogenesis by affecting the proliferation and migration of vascular endothelial and smooth muscle cells, as well as by reducing VEGF release in vitro [25].

In contrast, Limagne et al. demonstrated that resveratrol reduces the secretion of IL-17 and factors involved in lymphocyte differentiation. This is directly associated with a decrease in angiogenesis through a reduction in VEGF secretion [26].

Resveratrol improves the tightness of intercellular junctions, reducing the formation of edema and thereby enhancing the blood–retinal barrier [27]. Brakenhielm et al. provided valuable data on the anti-angiogenic properties of resveratrol in in vivo studies that evaluated corneal neovascularization in a mouse model [28].

Disruptions in metabolic pathways and intracellular regulatory processes can lead to programmed cellular death. Polyphenols protect mitochondria from dysfunction, which prevents endothelial cell apoptosis by inhibiting metalloproteinase 9 (MMP-9) activity [29]. Resveratrol has

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been shown to have beneficial effects on the eyes due to its anti-inflammatory and neuroprotective properties. It is commonly used in conditions where oxygen free radicals and inflammation play a significant role, such as glaucoma, cataracts, diabetic retinopathy, and age-related macular degeneration (AMD) [30].

CURCUMINOIDS – CURCUMIN

Curcuminoids, classified as polyphenols, have been used for millennia. Initially, they were used as a dye and spice, but later their medicinal effects were noted [31]. Turmeric, a flowering plant of the ginger family, is also known as long oyster or Indian saffron. Curcumin is derived from its root. Curcuminoids consist of demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and curcumin [32]. Curcumin, one of the curcuminoids, possesses strong anti-inflammatory properties due to its ability to inhibit pro-inflammatory factors like NF-κB and IL-8 [33]. Curcumin has antioxidant properties that involve modulating catalase and superoxide dismutase, inhibiting the activity of enzymes that increase ROS production (such as lipoxygenase, cyclooxygenase, hydrogenase, and xanthine oxidase), and increasing the concentration of glutathione in cells [34].

Rai et al. also found that curcumin increased vitamin C and E concentrations and inhibited lipid peroxidation, resulting in reduced DNA damage in a selected group of patients with oral mucosal lesions [35].

In contrast, Lal et al. showed that orally taking curcumin 375 mg three times a day for 12 weeks by patients with chronic anterior uveitis had effects comparable to those of glucocorticosteroid therapy, but without side effects [36].

Researchers have noted that curcumin has analgesic effects by regulating cholinergic activity in nerves through its action on the nicotinic receptor (α7-nACh) [37].

Curcuminoids have been shown to lower blood glucose levels, increase tissue insulin sensitivity, and reduce body weight, supporting the use of curcumin in patients with diabetes [38]. Furthermore, a team of researchers led by Chuengsamarn has demonstrated that it has a protective effect on pancreatic cells, which may reduce the risk of pre-diabetic states progressing into full-blown diabetes [39]. Chen et al. reported that curcumin has anti-angiogenic properties due to its ability to inhibit the release of VEGF [40]. Preventing the formation of new leaky vessels is crucial in avoiding the serious consequences of proliferative diabetic retinopathy (PDR). In addition to reducing VEGF levels, curcumin regulates angiogenesis by affecting intercellular adhesion molecule 1 (ICAM- 1), cell adhesion molecules (e-selectin-1, ELAM-1), and vascular cell adhesion molecule 1 (VCAM-1) [41].

CONCLUSIONS

Curcuminoids have a wide range of health-promoting effects. They exhibit therapeutic properties in anticancer therapies, autoimmune diseases, and neurological disorders, and protect against the harmful effects of heavy metals [42].

The health-promoting effects of resveratrol and curcumin have been extensively researched for decades. Ongoing studies aim to precisely understand and utilize their mechanisms in treating and preventing various diseases of civilization. Undoubtedly, diabetic retinopathy-induced visual impairment is a significant social issue in an era of widespread obesity and metabolic disorders. Researchers are actively seeking the most effective remedy. Numerous mechanisms of action have been described for both curcumin and resveratrol. These substances affect the same pathways, complementing each other.

Lund et al. conducted in vitro study on the permeation rates of curcumin and resveratrol in cell cultures. Their findings demonstrated that co-administration of these substances resulted in a threefold increase in intestinal absorption [43].

Based on current knowledge and scientific reports, researchers commonly refer to curcumin, resveratrol, epigallocatechin gallate (EGCG), sulforaphane, and genistein as the 'Big Five' in the fight against cancer cells [44].

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