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NUTRACEUTICAL COMPONENTS OF BLUEBERRIES FOR THE PREVENTION AND TREATMENT OF DIABETIC RETINOPATHY

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Introduction

Diabetic retinopathy (DR), as a severe complication of the diabetes mellitus (DM), is the leading cause of vision loss. It develops in almost all patients with type I DM and the vast majority of type II DM patients. As of 2019, of the 463 million adults with DM, 125 million have already developed DR. In addition, the number of adults with DM will increase further, reaching 700 million in 2045, which, assuming that the prevalence of DR among adults with DM continues, will result in approximately 189 million cases of DR worldwide [1, 2].

High glucose levels in DM patients cause oxidative stress and macular edema in the area of the retina called the macula [3]. A proliferation of new blood vessels, increased ischemia and retinal detachment are occured. The first stage of DR is diagnosed when a microvascular lesions, usually microaneurysms, which are the result of dilation of the capillary walls are reveald at fundus examination [1]. For the treatment of DR, methods of non-pharmacological intervention are used – laser photocoagulation and vitrectomy, but only in the late stages of the disease, therefore the search and research of new pharmacologic drugs, especially of plant origin, for the prevention and treatment of DR in the early stages of its development, is extremely relevant.

There is a wide variety of biologically active compounds of plant origin that are less toxic, cheaper and safer and can be used as therapeutically active agents. According to Alghamdi AH. et al. (2023), there are about 600 plants whose biologically active substances are used to treat eye diseases [4]. In particular, anthocyanins – flavonoid compounds obtained from edible plants, demonstrate excellent pharmacological properties due to the simultaneous effect on numerous metabolic pathways and can act as an alternative to other methods of treatment and prevent the further development of the disease [5, 6, 7]. Many studies in vitro and in vivo have demonstrated the potential effects of anthocyanins and anthocyanin-rich foods in the prevention and/or treatment of diabetes and its complications, cancer, cardiovascular and neurodegenerative diseases [8].

Blueberry (Vaccinium myrtillus L.) is believed to have anti-diabetic properties, and its berries and leaves have been used for centuries to relieve diabetes symptoms. The known hypoglycemic effect of blueberries is a desirable effect for the prevention or control of diabetes mellitus and its complications caused by insulin resistance and functional insufficiency of B cells. Diabetes is associated with increased oxidative stress, inflammation, and dyslipidemia, and is associated with an increased risk of cardiovascular disease, cancer, and vision loss due to cataracts and DR [9].

In this review, we summarize the current state of research and future prospects for the use of anthocyanins – water-soluble flavonoid compounds of blueberries (Vaccinium myrtillus L.) for the prevention and treatment of DR. This review will help to better understand what these compounds are and how they can be used to prevent and treat DR. In the work there are used general scientific research methods, which include an analytical review of scientific sources, analysis and synthesis of literary data.

Anthocyanins

Anthocyanins and anthocyanidins belong to a large group of biologically active compounds of plant origin, known as flavonoids, which are a subgroup of an even larger group of compounds – polyphenols. Anthocyanins and anthocyanidins are found in all plant tissues, including leaves, stems, roots, flowers, and fruits. In addition to the use of anthocyanins and anthocyanidins as natural dyes, these color pigments are potential pharmaceutical ingredients with health benefits. Human and animal studies have shown that anthocyanins can reduce oxidative stress, hyperglycemia, and prevent diabetic complications, including diabetic retinopathy [10].

Anthocyanins are the glycosylated form of anthocyanidins and are formed as a result of the addition of sugars to various side groups of the flavylium ion. The position, nature and number of sugar fragments and their acylation, as well as the position and number of hydroxyl groups and the degree of their methylation lead to different types of anthocyanins [11, 12, 13, 14]. The main difference between anthocyanin and anthocyanidin is that anthocyanin is a water-soluble vacuolar pigment whereas anthocyanidins are sugar-free analogues of anthocyanin. Twenty-seven naturally occurring anthocyanidins have been identified, but six of them account for approximately 92% of all reported anthocyanidins [15]. The most common anthocyanidins are cyanidin (3,3',4',5,7-pentahydroxyflavylium chloride), delphinidin (3,5,7-trihydroxy-2-(3,4,5,trihydroxyphenyl)-1-benzopyrylium chloride), malvidin (3,4',5,7-Tetrahydroxy-3',5'-dimethoxyflavylium chloride), peonidin (3,4',5,7-tetrahydroxy-3'-methoxyflavylium chloride), petunidin (3,3 '4', 5,7-pentahydroxy-5'-methoxyflavylium chloride) and pelargonidin (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-1-benzopyrylium chloride) [16]. The distribution of these anthocyanidins in fruits and vegetables is 50%, 12%, 12%, 12%, 7% and 7%, respectively [17,18]. Anthocyanins have structures consisting of two aromatic rings connected by three carbon atoms in an oxygenated heterocycle (i.e., a chroman ring containing a second aromatic ring at position 2) [19]. In fig. 1. The general structural formula of anthocyanins is shown.

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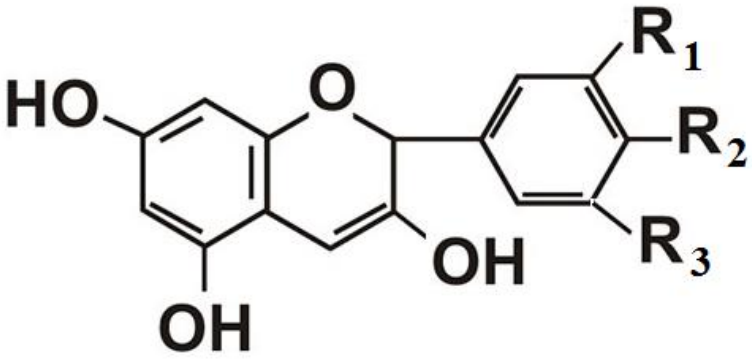

Figure 1. Chemical structure of anthocyanins: two benzoin rings separated by a heterocyclic ring.

There are more than 1,000 types of anthocyanins in nature, all of which are derived from 27 aglycones of anthocyanidins [20]. Anthocyanins show a wide spectrum of chemical diversity. As reported, of the nearly 700 studied anthocyanins, about 300 are acylated with one or more aromatic or aliphatic acyl groups, while about 100 of them contain both aromatic and aliphatic groups [15, 20, 21, 22,].

Anthocyanins can be absorbed and detected in animal or human plasma, while anthocyanidins have low bioavailability. An increase in the number of attached sugars in the aglycone can negatively affect the ability of anthocyanins to bind to various targets. The main limitation of the use of anthocyanins in clinical therapy arises from their low bioavailability, instability at physiological pH and their massive transformation into metabolites after absorption [23, 24]. The stability of anthocyanins is also affected by factors other than pH, namely temperature, concentration, light, oxygen, solvents, the presence of enzymes, metals or other ions [22]. It were found that Anthocyanins from blueberry (Vaccinium myrtillus L.) rapidly degrade to 25% of the initial amount at 60 °C [25], while the half-life of anthocyanins from sweet potato (Ipomoea batatas L.) is 111.6 hours at the same temperature [26].

Anthocyanins are able to absorb light in the ultraviolet (280–400 nm) and blue range (360–500 nm) [27], which may explain the protective effect of anthocyanins against light-induced damage to human retinal cells [28, 29, 30]. In fact, the benefits of anthocyanins for vision and eye health were among the first properties of anthocyanins that have continued to attract the interest of consumers and the scientific community. More attention has been paid to the effects of anthocyanins on vision after the hypothesis that the night vision of British Royal Air Force pilots during World War II was improved due to their regular intake of blueberry jam at breakfast [31].

Total anthocyanin concentration in some ocular tissues is higher than that is measured in plasma, suggesting that anthocyanins may concentrate in ocular tissues [32]. In an experimental study, the accumulation of anthocyanins in the eye tissues of animals (after 4 weeks of dietary supplementation with blueberries) demonstrated protective effects for the eyes and reversal of oxidative effects [33]. Higher concentrations of anthocyanins in some ocular tissues are observed when anthocyanins are administered intravenously, reinforcing their importance in the prevention of eye diseases [32].

Anthocyanins are widely used in folk medicine and are nutraceutical components of food supplements. They are traditionally used as phytopharmaceuticals, appetite stimulants, choleretics, as well as for the treatment of many other diseases. Bioavailability of anthocyanins as nutraceuticals is a key factor in health maintenance and disease prevention. The low bioavailability of anthocyanins causes low absorption of these compounds into the circulatory system and a high rate of excretion of anthocyanins in urine and feces, thus reducing the efficiency of anthocyanins in scavenging free radicals. Highly bioavailable anthocyanins effectively reduce lipid peroxidation in cells, thus reducing the risk of many diseases. However, the side effects of excessive anthocyanin consumption remain unknown [34, 35].

Natural sources of anthocyanins

The main natural sources of anthocyanins are blueberries (Vaccinium myrtillus L.), strawberries (Fragaria moschata L.), blackberries (Rubus caesius L.), black currants (Ribes nigrum L.), raspberries (Rubus idaeus L.). They contain from 100 to 700 mg of anthocyanins per 1 g of fresh berries. Elderberry (Sambucus nigra L.) and black rowan (Aronia melanocarpa Elliot.) berries contain anthocyanins in the amount of 1.4-1.8 g per 100 g. Cherry fruits (Prunus serasus L.) contain anthocyanins in the skin, pulp and pits. Other sources include acai (Euterpe oleracea L.), purple corn (Zea mais L.), plums (Prunus domestica L.), pomegranates (Punica granatum L.), eggplants (Solanum melongena L.), grapes (Vitis vinifera L.) [36, 37, 38, 39, 40]. Beetroot (Beta vulgaris L.), tomatoes (Solanum lycopersicum L.), red cabbage (Brassica oleracea var. capitata f. rubra), red pepper (Capsicum annuum L.) and other vegetables are rich in anthocyanins [16].

The source of anthocyanins can be the berries of the evergreen zoster (Rhamnus alaternus L. berries) and red onion (Allium cepa L.). Evergreen zoster berries contain delphinidin 3-O-rutinoside, which accounts for approximately 62.4% of the total pigments, 3-O-rutinoside derivatives of cyanidin (8.4%), petunidin (15.8%), pelargonidin (4.7%), as well as peonidin and malvidin (8.7%). The presence of the six most common anthocyanidins indicates that R. alaternus berries are a good source of anthocyanins [41]. Red onion

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anthocyanins are mainly cyanidin glucosides, acylated with malonic acid or non-acylated. Totally it has been reported about 25 different anthocyanins from red onion, including two new 5-carboxypyranocyanidin derivatives. The quantitative anthocyanin content of some varieties of red onion is reported to be approximately 10% of the total flavonoid content, or 39–240 mg/kg [42].

Blueberries have a higher anthocyanin content than other berries such as strawberries, cranberries, elderberries, cherries and raspberries [43, 44]. The American Herbal Products Association classifies blueberries as a class 1 plant, meaning they are safe to consume when used properly. Mutagenic activity has not been declared, and there are no cited contraindications to its use. Blueberries are sold in the form of fresh, frozen and dried whole berries, as well as in the form of preserves, jams, juices, increasingly liquid or powdered concentrates are sold as food supplements. Blueberries contain a variety of phenolic compounds, including flavonols (quercetin, catechins), tannins, ellagitannins, and phenolic acids, but anthocyanins make the largest contribution to its phytochemical mix. The total anthocyanin content of blueberries is usually in the range of 300-700 mg/100 g of fresh fruit, although this range depends on the variety, growing conditions and degree of ripeness of the berry [9, 45]. The degree of ripeness of berries also affects the change in total phenolic content – although the concentration of phenolic compounds is usually higher in unripe berries than in mature fruits, anthocyanins accumulate during the ripening of blueberries [9].

According to Müller D., et al. (2012), who studied the anthocyanin content of commercially available blueberry juices and fresh berries, blueberries contained a maximum of 1017 mg of anthocyanins per 100 g fresh weight (7465 mg/100 g dry weight). The main anthocyanins contained in blueberry juice were delphinidin-3-O-glucopyranoside, delphinidin-3-O-galactopyranoside and cyanidin-3-O-arabinopyranoside. In contrast, fresh blueberries had higher concentrations of malvidin-3-O-arabinopyranoside and petunidin-3-O-galactopyranoside [46]. About sixteen anthocyanins were identified and quantified in fresh blueberries by ultra-performance liquid chromatography (UPLC) [47]. According to the data of the European Medicines Agency, the most common anthocyanins in blueberries are delphinidin-3-O-galactoside, which is up to 14.9%, delphinidin-3-O-arabinoside up to 15.3%, delphinidin-3-O-glucoside — up to 14.0%, cyanidin-3-O-arabinoside — 13.6% and cyanidin-3-O-glucoside, which contains up to 10.1% of the total amount of anthocyanins in blueberry fruits (Table 1) [48, 49, 50].

Table 1. Anthocyanin content in blueberries (Vaccinium myrtillus L.) [49,50,51].

The name of anthocyanins	Percentage of total anthocyanins (%)
Definidin-3-O-glucoside	13.7–14.0
Cyanidin-3-O-galactoside	9.0–9.2
Cyanidin-3-O-glucoside	8.5–10.1
Cyanidin-3-O-arabinoside	7.7–13.6
Petunidin-3-O-glucoside	6,0–8,8
Peonidin-3-O-galactoside	0,6–1,1
Peonidin-3-O-arabinoside	0,5–1,0
Malvidin-3-O-glucoside	7.9–8.4
Delphinidin-3-O-galactoside	14.3–14.9
Delphinidin-3-O-arabinoside	12.1–15.3
Petunidin-3-O-galactoside	2.1–4.0
Petunidin-3-O-arabinoside	1.3–2.6
Peonidin-3-O-glucoside	0,1–3,7
Malvidin-3-O-galactoside	2.5–3.1
Malvidin-3-O-arabinoside	1,5–2,4

Thus, blueberries are one of the most important sources of anthocyanins suitable for consumption in food, because they contain a huge number of anthocyanins, which makes them the main plant for the treatment and prevention of diabetes and its complications [51].

Pathophysiology of diabetic retinopathy

Diabetic retinopathy is a major complication of diabetes and remains the leading cause of vision loss among the working-age population. The diagnosis of DR is based on the clinical manifestations of retinal vascular abnormalities. Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is an early stage of DR where increased vascular permeability and capillary occlusion are the two main findings in the retinal vasculature. During this stage of the retinal pathology, including microaneurysms, hemorrhages, and solid exudates can be detected by fundus photography, although patients may be asymptomatic. PDR, a more advanced stage of DR, is characterized by neovascularization. At this stage, patients may experience severe vision loss when new abnormal vessels bleed into the vitreous (vitreous hemorrhage) or when traction retinal detachment is present. The most common cause of vision loss in patients with DR is diabetic macular edema (DME). DME is characterized by

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swelling or thickening of the macula due to sub- and intraretinal fluid accumulation in the macula caused by a breakdown of the hematoretinal barrier (blood-retinal barrier - BRB). DME can occur at any stage of DR and cause distortion of visual images and reduced visual acuity [52, 53, 54]. In more advanced cases of DR, retinal detachment caused by extensive neovascularization can cause irreversible vision loss.

Although it is clear that diabetes-induced microvascular changes lead to pathologies that pose a serious threat to vision, the conventional view of DR as a microangiopathy is now being questioned [1]. Now it is clear that retinal neurodegeneration and inflammation occur very early in diabetes, even at the absence of clinically apparent microvascular abnormalities [1, 55, 56]. Structural neurodegenerative changes have been described, such as neuronal apoptosis, loss of ganglion cell bodies, glial reactivity, and a decrease in the thickness of the inner layers of the retina. This loss of neuronal tissue is consistent with previous functional studies that have shown neuroretinal deficits in diabetic patients, including electroretinogram abnormalities, loss of dark adaptation and contrast sensitivity, and impaired color vision. [57, 58].

In recent decades have seen some progress in the diagnosis and treatment of this common complication of diabetes. First, optical coherence tomography allows to obtain a non-invasive image of the retina, in particular the macula, with a very high resolution, thus facilitating the treatment of diabetic macular edema. Macular focal and/or retinal laser photocoagulation, applied to microaneurysms and thickened retinas, has long been the mainstay of treatment for diabetic macular edema [59]. In addition, recent advances in the understanding of the pathophysiology of DR, particularly the key role of cytokines such as vascular endothelial growth factor (VEGF), have led to the development of intraocular anti-VEGF antibodies. Anti-VEGF therapy has largely replaced laser photocoagulation for the treatment of diabetic macular edema [60]. However, intravitreal anti-VEGF therapy can be burdensome for the patient and healthcare system, often requiring monthly visits to the physician [59]. Patients with diseases of the cardiovascular system are not recommended to use anti-VEGF drugs [61].

Currently, there is no definitive treatment for DR that prevents the progression or reversal of vision loss caused by photoreceptor degeneration and retinal ganglion cell death. The main treatment options for DR are laser photocoagulation, vitreoretinal surgery, or intravitreal administration of drugs targeting vascular endothelial growth factor. However, these methods of treatment work only in late stages of DR, have short-term efficiency and cause side effects [62, 63].

Blueberry anthocyanins against diabetic retinopathy

Oxidative stress and inflammation play a significant role in the development of DR. The antioxidant and anti-inflammatory activity of anthocyanins can reduce retinopathy and vision loss [64, 65]. Anthocyanins of blueberry extract inhibit the activation of the protein STAT3 (Signal transducer and activator of transcription 3), which reduces the inflammation-related expression of rhodopsin and reduces the level of intracellular reactive oxygen species (ROS), preventing damage to photoreceptor cells and protecting visual function during retinal inflammation [29]. They protect retinal function and histological integrity by enhancing antioxidant defense mechanisms, inhibiting lipid peroxidation and proinflammatory cytokine expression, and inhibiting retinal cell apoptosis [66, 67]. One of the major blueberry anthocyanins, malvidin (Mv), and its glycosides can protect human retinal capillary cells from high glucose-induced damage [68].

Anthocyanin-enriched blueberry extracts modulate pre- or post-translational levels of heme oxygenase (HO)-1 and glutathione S-transferase-pi (GST-pi) enzymes in cultured human retinal pigment epithelial cells (RPE). As reported by Milbury PE., et al. (2007), the effects of HO-1 and GST-pi enzymes on the RPE may be due to their stimulating signal transduction to enhance protection against oxidative stress by controlling the antioxidant response element, due to a significant reduction in blood glucose concentration and increased insulin sensitivity due to the activation of adenosine monophosphate-activated protein kinase (AMPK) in white adipose tissue (WAT), skeletal muscles, and liver of diabetic mice, upregulation of glucose transporter 4 in WAT and skeletal muscles, and inhibition of glucose and lipid production in the liver [69,70]. Blueberry anthocyanins reduce retinal vascular endothelial growth factor (VEGF) expression and degradation of zonula occludens-1, occludin, and claudin-5 proteins, which are markers of diabetic retinopathy in streptozotocin-induced diabetic rats [71].

According to research results, 8-oxoguanine-DNA glycosylase (OGG1) protects retinal pigment epithelial cells from apoptosis induced by High concentration glucose (H-Glu) [72]. OGG1 was also found to suppress the expression of inflammatory factors and suppress inflammatory phenotypes [73]. The direct interaction of miRNA-182 (miR-182) with OGG1 induced the generation of reactive oxygen species and increased levels of Endoplasmic reticulum stress (ERS) and apoptosis in human retinal pigment epithelial cells ARPE-19 treated with H-Glu. Blueberry anthocyanins extract (BAE) was found to suppress the expression of miR-182, which is activated in DR [74, 75]. Wang C, et al. (2022) confirms that BAE, by inhibiting miR-182 expression, suppresses apoptosis, ROS production, reduces endoplasmic reticulum stress induced by high glucose in human retinal pigment epithelial cells [76].

Anthocyanins exhibit significant biological functions in protecting RPE cells from oxidative stress-induced damage after treatment with high doses of individual anthocyanins [28, 77]. Research by Paik, S.S. et al. (2012) showed that one of the blueberry extract anthocyanins, cyanidin-3-o-glucoside (C3G), reduces diabetes-induced retinal degeneration by scavenging ROS, indicating that application of 10 μM C3G performs

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the functions of restoring cellular oxidative stress without causing cytotoxicity [78].

Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that regulates cellular defense against toxic and oxidative damage through the expression of genes involved in response to oxidative stress. Activation of NRF2 makes cells resistant to inflammatory processes. In addition to antioxidant responses, NRF2 is involved in many other cellular processes, including metabolism and inflammation, allowing it to organize cellular response and adaptation to various pathological stressors to maintain homeostasis [79]. As a result of researches, it is well documented that the activation of Nrf2 by anthocyanins can increase the expression level of antioxidant enzymes and proteins such as glutaredoxin1 (Grx1), heme oxygenase-1 (HO-1), thioredoxin 1 (Trx1), and NADPH dehydrogenase 1 (NQO1) [80] and can lower blood sugar through the Nrf2/Keap1 pathway [81,82]. Since oxidative stress plays an important role in the pathogenesis and pathophysiology of DR development, the use of anthocyanins to regulate cellular redox balance may be a new proposed strategy to relieve DR [32].

Huang W., et al. (2018) reported that BAE anthocyanins can protect human retinal capillary endothelial cells from high glucose-induced damage. In particular, malvidin (Mv), malvidin-3-glucoside (Mv-3-glc), and malvidin-3-galactoside (Mv-3-gal) promoted cell growth of human retinal capillary endothelial cells, showed a significant antioxidant effect, reducing the level of ROS and increasing the activity of catalase and superoxide dismutase enzymes in human retinal capillary endothelial cells [68].

However, the chemical instability and poor bioavailability of anthocyanins limits their use. Environmental factors can significantly affect the stability of anthocyanins, including temperature, light, oxygen, enzymes, and pH. Improving the stability of anthocyanins is an important problem that needs urgent solutions. The development of effective new systems to increase the stability of anthocyanins and, therefore, their bioavailability in the human body by methods of microencapsulation, nanoencapsulation or protein complexes will help to increase their effectiveness [83, 84].

Solving the problem of stability and bioavailability of blueberry anthocyanins is possible by creating special food products. In recent decades, the use of nutraceuticals – biologically active additives to correct the chemical composition of food in order to improve the nutritional status of a person, strengthen health, and prevent a number of diseases, – has become widespread. Because of the strong seasonal availability and limited shelf life of blueberries, anthocyanins and other bioactive products derived from blueberries have become functional foods. New food developments now available include blueberry fruit juice, wine, vinegar, jam, dried fruit, pulp powder, colors and flavorings used in cakes, cookies, breads, yogurts and jellies [85].

Nutraceuticals make it possible to solve an important issue regarding the maximum satisfaction of the changed physiological needs in food substances of a sick person, as well as bypassing the damaged link of the metabolic process, which is especially important in preventive and therapeutic nutrition for diseases associated with metabolic disorders (diabetes and its complications etc.).

Enriched with anthocyanins, blueberry extracts are used in the form of dietary supplements (DS) - food products intended for consumption in small defined quantities in addition to the usual diet. The production of DS is carried out in conditions that ensure their quality and safety for human health and guarantee compliance with the requirements of *Hazard Analysis and Critical Control Points* – a management system in which the safety of food products is considered through the analysis and control of biological, chemical and physical hazards from the production of raw materials , procurement and processing to production, distribution and consumption of finished products. Although dietary supplements are not considered medicinal products, nevertheless they are mainly manufactured at pharmaceutical enterprises, sold through pharmacy chains and specialized stores and, accordingly, occupy their place in the pharmaceutical market.

The use of blueberry anthocyanins in the form of DS has certain advantages and disadvantages, which consist in the fact that they are used mostly for preventive purposes and their therapeutic effect is usually manifested 10-14 days after the start of use. Compared to medicinal drugs, an overdose of DS does not pose a threat to the body.

The application of nanotechnology can overcome the instability of anthocyanin molecules and thus expand their application. The nanomaterials used are mainly polysaccharides, and most food-grade biopolymers can be biocompatible, biodegradable, and can be derived from a variety of sources. Anthocyanins have been found to form complexes with other polysaccharides such as cyclodextrins, starch and chitosan mainly through non-covalent bonds including hydrogen bonds, electrostatic interactions and hydrophobic bonds. Although some studies indicate a positive effect of polysaccharide-encapsulated anthocyanins, in vivo studies and clinical trials remain an unexplored area. In addition, increasing the chemical stability of anthocyanins is a complex process that requires large-scale interdisciplinary researches [86].

Thus, the analysis of the results of the conducted studies indicates that blueberry anthocyanins have the potential to prevent the progression of diabetic retinopathy and can be considered as candidates for further clinical studies for the purpose of drugs development.

Conclusion

Diabetic retinopathy, as a severe complication of diabetes, is the main cause of vision loss. Currently, there is no definitive treatment for diabetic retinopathy that would prevent the progression or reversal of vision loss caused by photoreceptor degeneration and retinal ganglion cell death. Modern methods of treatment work

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only in the late stages of the disease and cause side effects. There is an acute problem of finding new effective drugs for the treatment of diabetic retinopathy.

This review summarizes the results of research on blueberry anthocyanins, which demonstrate antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-apoptotic activity and other pharmacological properties due to the simultaneous effect on numerous metabolic pathways and can act as an alternative to other treatment methods and prevent the further development of diabetic retinopathy. Blueberry anthocyanins have the potential to prevent the progression of diabetic retinopathy and may be considered as candidates for clinical trials for drug development. However, further human studies using both blueberry extracts and individual anthocyanins are needed.

Nutraceutical components of blueberries for the prevention and treatment of diabetic retinopathy
Serhii Oliinyk, Vasyl Humeniuk, Anna Rybachuk , Petro Oliinyk

Diabetic retinopathy, as a severe complication of diabetes, is the main cause of vision loss. Currently, there is no definitive treatment for diabetic retinopathy that would prevent the progression or reversal of vision loss caused by photoreceptor degeneration and retinal ganglion cell death. For the treatment of diabetic retinopathy non-pharmacological intervention methods are used – laser photocoagulation and vitrectomy, but only in the late stages of the disease, therefore the search and research of new drugs, especially of plant origin, for the prevention and treatment of diabetic retinopathy in the early stages of its development are relevant. Anthocyanins – flavonoid compounds obtained from food plants show excellent pharmacological properties due to the simultaneous effect on numerous metabolic pathways and can act as an alternative to other treatment methods and prevent the further development of the disease. This review summarizes the results of research on blueberry anthocyanins, which demonstrate antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-apoptotic activity and other pharmacological properties due to the simultaneous effect on numerous metabolic pathways and can act as an alternative to other treatment methods and prevent the further development of diabetic retinopathy. Blueberry anthocyanins have the potential to prevent the progression of diabetic retinopathy and may be considered as candidates for clinical trials for drugs development. However, further human studies using both blueberry extracts and individual anthocyanins are needed.

Keywords: diabetic retinopathy, oxidative stress, macular edema, blueberry anthocyanins.

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