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# Pharmacology of plant extracts in the treatment of eye diseases

Roman Paduch

Botanical compounds have been used for centuries to treat a variety of ailments. It is related to their broad biological activity, including anti-inflammatory or antioxidant actions. Plant extracts or isolated specific ingredients are also used today for prophylaxis, supportive treatment, or for the treatment of diseases of various organs, including eyes. The following review will identify selected herbal ingredients used to treat or alleviate underlying eye conditions including age-related diabetic retinopathy (DR), macular degeneration (AMD), cataract, glaucoma, dry eye syndrome, or uveitis. Botanical compounds are an easy and non-invasive way to improve the health of the eye, but their use requires continuous research so that they do not show potential toxic effects that could damage the eye and thus impair vision [1].

New therapeutic agents aimed at combating basic eye diseases must show a number of biological activities, including anti-inflammatory, anti-apoptotic, and oxygen free radicals reducing activity. Unfortunately, trying to reconcile the necessary activities often has the consequences of unwanted side effects. Therefore, it was necessary to find an alternative source of biologically active factors with potentially lower toxicity and similar activity to compounds commonly used in ophthalmology, such as corticosteroids. Plants containing a number of factors showing the assumed biological activities were the aim of the research. The search went toward full plant extracts found in different latitudes as well as isolated specific components, most often from the group of broadly understood polyphenols. Many modern pharmaceuticals and drugs are based on basic active ingredients or secondary metabolites derived from plants. Their beneficial therapeutic effects are obtained when you include them in your daily diet or by using them as compresses or ingredients in eye drops. Their use has now also become safe due to the identification of their biochemical properties along with the molecular mechanisms of their action. This is due to the extensive ophthalmological studies performed both in cell cultures *in vitro* and in animal models *in vivo*. This allowed to obtain data enabling the introduction of these compounds as a non-invasive alternative to commonly used pharmacological therapies aimed at the treatment of basic eye diseases [1–3].

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## Age-related diabetic retinopathy (DR)

Diabetic retinopathy (DR) is a disease that occurs in people with diagnosed type I and type II diabetes associated with changes in retinal blood vessels. The blood vessels in this disease become too permeable (mainly lipid leakage), they become swollen (microaneurysms) and the appearance of new abnormal vascular structures on the retina surface can also be found. Visual impairment associated with DR is also associated with the development of diabetic macular edema (DME) and vision loss or visual impairment due to retinal detachment, vitreous hemorrhaging or neovascular glaucoma [1, 4].

In alleviating the effects of this disease, plant-derived compounds are used, which should be aimed at maintaining proper blood sugar levels. Curcumin is indicated as an agent that may protect against changes in retinal blood vessels [5] when administered with the diet. Another polyphenol with demonstrated activity in this disease is resveratrol, which can reduce early vascular lesion occurring during diabetes, reduce the production of vascular endothelial growth factor (VEGF), prostaglandins (PGs), cyclooxygenase-2 (COX-2), nitric oxide (NO) as well as oxidative stress weakening the structure of the vascular walls [1, 5]. A similar action is shown by Baicalein [6] and Pterostilbene reducing

inflammation within retina [3] or danshen (*Salvia miltiorrhiza*) improving blood-oxygen transport and absorption of retinal hemangioma [1, 2]. Improvement of the structure of blood vessels was also achieved by administering to patients extracts rich in anthocyanins as well as flavonoid proanthocyanidin polymer Pycnogenol and bioflavonoids [2, 7].

## Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) belongs to a neuro-degenerative, chronic disorder that manifests in retinal degeneration. In this disease, the degradation of the retinal pigment epithelium (RPE) occurs, leading to atrophy of photoreceptors in the macula and, consequently, disturbances in acute and central vision and blindness. The molecular basis of this disease is oxidative stress and the development of inflammation [1, 8]. Likewise, age, genetic, and environmental factors (hypertension, smoking, and obesity) may predispose to the appearance of symptoms of AMD [2, 7].

In the phytotherapeutic treatment of AMD, for example, flavonoids can be used, which due to their anti-angiogenic and anti-inflammatory effect can slow the progression of AMD. On the other hand, there are no studies unequivocally confirming that a diet rich in anthocyanins or containing *Ginkgo biloba* extract (GBE) may improve vision, limit the processes of new vessel formation or leakage of the retina microvasculature in AMD [7]. Similarly, studies conducted so far have not shown the protective activity of lutein and zeaxanthin in the development of early AMD [9]. However, if lutein and zeaxanthin were combined with other antioxidants, such as vitamins (C or E), mineral contents (zinc and copper), a potential favorable effect on macula function in AMD was demonstrated [10]. However, other studies can be found indicating that due to its antioxidant activity, lutein can be considered as a protective factor against AMD. This is explained by the action of this compound as a blue light filter after its accumulation in macula [11]. Curcumin also shows a positive protective or supportive effect in the therapy of AMD [12]. It is recognized, in the context of AMD, as a PPAR-γ agonist and thus a factor that reduces the pro-inflammatory activity of the microglia. Curcumin as a PPAR-γ activator limits the transformation and degradation of the extracellular matrix (ECM), and the migration and degradation of the retinal pigmented epithelium (RPE) and thus contributes to the limitation of the pathogenesis of AMD [5]. A positive effect in this disease was observed using the carotenoids crocin and crocetin derived from saffron (*Crocus sativus* L.). They exhibit anti-inflammatory, anti-oxidative, and neuroprotective effects and thus act as a retinal neuroprotectants. Dietary supplementation with saffron may affect the temporal improvement of retina function in AMD mainly by reducing light-induced photoreceptor degeneration [13].

## Cataract

Cataracts belong to the group of age-related diseases. It concerns the lens, which, due to abnormalities in the structure of proteins, their breakdown and the formation of clusters, limits the transmission of a pure signal and image through the lens to the retina. The problem with vision is the formation of a dense, cloudy area of proteins and pigment in the lens and therefore abnormal light refraction or even reduction of light transmission through the lens. The underlying cause of this disease is most often environmental or lifestyle-related, but it is also claimed that it may result from an inherited genetic disorder that damages the eye structure [14].

Lens clouding can be delayed or controlled by diet. It has been shown that fruits and green leafy vegetables rich in flavonoids may to some extent reduce the risk of visual disturbances, including cataract. Flavonoids such as quercetin, hesperidin, and naringin belong to the group of factors that inhibit aldose reductase. In turn, inhibition of this enzyme activity may help to reduce diabetic cataract [7]. On the other hand, it is indicated that flavonoids, such as quercetin, kaempferol, myricetin, naringenin, genistein as well as hesperidin, quercetin, rutinoside (rutin), and flavonoid fractions isolated from different plants may not be associated with a reduced risk of cataract [7, 15]. Further research in this direction is therefore necessary. There were also studies showing the effectiveness of antioxidant vitamins against development of cataract. These include vitamin C or, to a lesser extent, vitamin A [7, 9]. Moreover, it was found that lutein/zeaxanthin intake or grape seed proanthocyanidin extract (GSPE), green tea leaf extract (GTL), and resveratrol may have a protective effect on the possibility of cataract symptoms [9]. Similarly, curcumin may show therapeutic efficacy against major eye diseases, including cataract [3, 5].

## Glaucoma

It is a chronic and progressive disease involving damage to the retinal nerve fiber layer and consequently associated with morphological changes to the optic nerve. However, this disease is not limited to damage to neurons within the optic nerve, but also affects the entire optic tract and chiasm as well as primary visual cortex. Therefore, glaucoma is concerned not only with the transmission of impulses from the eyeball, but also with the brain which receives and transforms these signals. Nerve damage via retinal ganglion cell apoptosis is associated with a disturbance of the eye hydrodynamics, i.e., an increase in intraocular pressure (IOP). It is the main cause of glaucoma. However, the disease often progresses despite lowering this pressure. Therefore, new therapeutic procedures should be sought that could globally improve the visual condition of people affected by glaucoma. One of them is the use of botanical compounds showing neuroprotective or stabilizing activity in blood flow and intraocular pressure [1, 16].

In reducing the occurrence or effects of glaucoma, the effectiveness of *G. biloba* leaf extract (GBE) as a dietary supplement has been indicated. In clinical trials, administration of GBE-containing antioxidants improved blood flow in the capillaries of the retina and an increase in vessel density in this part of the eye. In animal models of chronic glaucoma, retinal ganglion cells were protected in the presence of GBE. It also inhibited the activity of free oxygen radicals released during mitochondrial oxidative stress and nitrogen radicals which could damage the eye structures [2, 7, 17]. In addition, it has been shown that epigallocatechin gallate (EGCG) may have neuroprotective effects in the retina that may have been damaged by hypoxia in the course of glaucoma [9]. In general, flavonoids have been found to stabilize collagen fibers and regulate the stability of microvessels within the eye, thus reducing the risk of the onset or progression of eye diseases, including glaucoma [7]. Lowering the risk of this disease may also result from the use of a mixture of bilberry extract and French Maritime pine bark extract, mainly due to lowering IOP and improving the stability of blood vessels [2]. Of course, it has also been shown that the use of saffron and curcuma in the diet has beneficial effects in reducing the occurrence of glaucoma [5, 11]. On the other hand, there are reports indicating no relationship between the consumption of antioxidants such as vitamins A, E, C, or the carotenoids lutein/zeaxanthin and lowering the risk of glaucoma [9].

## Uveitis

Uveitis is an inflammatory eye disease. It is a form of eye inflammation affecting the middle layer of the tissue of the eye wall, so-called uvea including the choroid, iris and ciliary body. Uveitis usually appears as an independent disease entity, but is also associated with other systemic inflammatory diseases. The causes of this disease are most often infectious diseases, injuries, or autoimmune diseases. In addition, genetic conditions can also be the cause of uveitis [18].

Inhibition or reduction of uveitis has been demonstrated with the use of the flavonoid glycoside naringin and its aglicone: naringenin. The action of these substances is based on antioxidant and anti-inflammatory activity inhibiting the basic components of the arachidonic acid pathway related to inflammation, such as PGE2, NO, or COX-2 [2]. A similar effect in reducing inflammation in the course of uveitis has been shown for curcumin [3, 5]. It has also been shown that although catechins exhibit anti-inflammatory activity, EGCG may not be such effective in reducing the course of uveitis as naringin and curcumin [19]. Tests were also carried out on whole extracts from various plants. *Salvia hypoleuca* extracts has been shown to reduce inflammation by blocking the basic inflammatory factors (iNOS, COX-2, PGE2) involved in uveitis [20]. Polyphenol-rich blue honeysuckle extract (BHE) and aronia crude extract (ACE) have also been demonstrated in reducing inflammation by inhibiting the NF-κB-dependent signaling pathway and showing strong antioxidant properties [21, 22].

## Dry eye disease (DED) (keratoconjunctivitis sicca) (KCS)

Dry eye disease is a corneal disorder that occurs when the eye surface is insufficiently moistened due to limited tear production, rapid evaporation, or abnormal tear composition. This leads to chronic irritation and the development of inflammation, and even damage to the interpalpebral ocular surface of the lacrimal gland or the conjunctiva, resulting in severe discomfort for patients [2, 23]. It has also been shown that loss of mucins, especially MUC-4, may lead to the development of the ocular surface environment which favors the appearance of dry eye symptoms [24]. The ways to prevent the development of this disease are lifestyle changes and using eye drops. Botanical compounds are a proven eye drop additive to alleviate or eliminate the symptoms of dry eye.

One of the best ways to reduce the symptoms of this syndrome is to reduce local inflammation. Herbal extracts have been found to have the ability to reduce the symptoms of DED [25]. Many antioxidant agents reduce inflammation of the eye surface and improve the stability and composition of the tear film. They include the following polyphenols: catechin, curcumin, daidzin, quercetin, resveratrol, resveratrol with quercetin, ferulic acid, green tea polyphenols or kaempferol. Inflammatory state is also suppressed by EGCG. This component additionally limits the occurrence of the neoangiogenesis in the cornea of the eye [3, 5, 26]. In addition, antioxidants such as buckthorn oil, omega-3 essential fatty acids, anthocyanosides, astaxanthin, vitamins A, C, E, or selenoprotein P increase the production of tears, improve the stability of the tear film and thus reduce the symptoms of DED. These ingredients also reduce local inflammation mainly by limiting the concentration of pro-inflammatory cytokines and markers of oxidative stress in the tissues of the eye surface [27, 28]. However, it is not only the isolated polyphenols that may be helpful in stabilizing and eliminating DED. Whole plant extracts can also be used in the treatment of this syndrome. *Polygonum cuspidatum* (PCE) aqueous extract promotes the activity of antioxidant agents such as HO-1, SOD-1, and GPx [24]. *Chamaecyparis obtusa* (CO) extracts act in a similar way [29]. The moisturizing, anti-inflammatory, and antioxidant activity is also found from *Achyranthis radix* extract (USL) [30], *Bletilla striata* polysaccharide (BSP) [31], *Lycium barbarum* (goji berry) (GBE) [32], or *Aucuba japonica* (AJE) and aucubin [33] in studies on cells *in vitro* and in animal models. By reducing inflammation, these compounds also contribute to the reduction of apoptotic cell injury in the corneal epithelium. Thus, they are an interesting alternative as not only ingredients and dietary supplements reducing

DED, but also potential additions to the currently used treatment regimens for this syndrome.

Concluding, plant extracts as well as isolated polyphenolic components can provide a useful alternative for treating or at least reducing the adverse effects associated with eye diseases. They can be used as an addition to drugs, but also have a therapeutic effect when used as a diet or in addition to a diet. Nevertheless, special attention should be paid to the potential toxic effects of these agents, which could aggravate the damage to the eye tissues and thus aggravate the symptoms of the disease. Such effects must be detected during laboratory tests. However, the studies conducted so far indicate favorable therapeutic effects of botanical compounds in ophthalmology. They are patient-friendly ingredients while the natural formula is safe and acceptable alternative therapy model for eye diseases.

**Keywords:** Eye diseases, Natural compounds, Plant extracts, Therapeutic activity

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## Author Contributions
Roman Paduch – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Author declares no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.