Mini Review

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Macular Degeneration and the Pharmacology of Lycium Berries

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ABSTRACT

The pharmacology of carotenoids, flavonoids and polysaccharides is discussed in terms of their effects on the gut, immune cells and retinal functions. It is suggested that the use of goji berries may be superior to isolated, purified carotenoids and vitamins in the prevention of macular degeneration.

Keywords: Macular degeneration; zeaxanthin, Neovascularization; Flavonoids; Goji Berry Polysaccharides

Abbreviations: VEGF: Vascular Endothelial Growth Factor; BDNF: Brain Derived Neurotrophic Factor; TNF: Tumor Necrosis Factor; LBPs: *Lycium Barbarum* Polysaccharides

Mini Review

The retina is the light sensitive organ in the back of the eye. It is composed of 18 layers that contain neurons, Muller cells, ganglion cells, amacrine cells and other cells [1]. The retina also contains its own vasculature that supplies up to 25% of the oxygen and nutrients required by the retina [2]. The choroid, located between the retina and sclera, is the vascular layer of the eye and supplies the remaining 75% of the oxygen and nutrients needed by the retina [3]. The retinal macula and its central fovea are involved in sharp central vision and color perception. Retinal diseases decrease vision and can lead to blindness. Macular degeneration is an age-related loss of central vision that is a cause of blindness in many people. Lifestyle, age and family history are prominent causes of macular degeneration [4]. Diet, smoking, high blood cholesterol, high blood pressure, lack of exercise and obesity are risk factors for the disease. Diabetic retinopathy is also a risk factor for macular degeneration [5]. The incidence of type 2 diabetes increases every year due to obesity [6], thereby increasing the risk of macular degeneration. Half of type 2 diabetes patients develop retinal pathology [7].

Late stage macular degeneration is described as a "wet" or "dry" form. The dry form is more common and progresses more slowly but can lead to wet macular degeneration. The wet form is the leading cause of blindness in people over 60. The dry form is diagnosed by the presence of pigment clumps called drusen, small yellow deposits under the retina [8,9]. These drusen deposits may be the result of slow leakage from choroidal blood vessels. The wet form is diagnosed by visualizing extracellular fluid and blood in the macula that leaks out of blood vessels from the choroid. This visualization can be done with fluorescein dye, indocyanine green dye or optical coherence tomography [8,9]. Fluorescein dye can demonstrate the presence of leaking blood vessels and new blood vessels in the macula, called neovascularization. Inflammation of blood vessels in the macula with resultant leakage is a major cause of macular degeneration [8,9]. The retina attempts to repair itself following damage from drusen and neovascularization. Astrocytes and Muller cells form scars in the macula that repair the channels carved by extravasation of blood and fluids. This scarring can impair vision [8]. Treatment of wet macular degeneration involves antibodies against vascular endothelial growth factor (VEGF). Pegaptanib, ranibizumab, bevacizumab and aflibercept are the anti-VEGF antibodies used to inhibit neovascularization, fluid extravasation and restore vision in many patients [8,9]. These expensive drugs have greatly improved therapy for macular degeneration. However, they are also toxic and can increase strokes, hemorrhage and mortality [8].

There have been at least two clinical trials of vitamins and dietary supplements in the treatment of macular degeneration, AREDS and AREDS2. The AREDS study found that a combination of vitamin C, vitamin E, β-carotene, zinc and copper significantly decreased the risk of developing macular degeneration in patients with extensive or moderate drusen accumulation [10]. Due to the increased risk of lung cancer in patients receiving β-carotene, a new formulation containing lutein and zeaxanthin was tested in AREDS2 [11]. Lutein and zeaxanthin were found to be as good as β-carotene at preventing macular degeneration. Based on these trials, vitamin and mineral supplements are available that contain 10mg of lutein and 2mg of zeaxanthin in each tablet, as well as 500mg of Vitamin C, 400 U of Vitamin E, 25mg of zinc and 2mg of copper. Inflammation of the retinal vasculature is important in macular degeneration [7,8]. This inflammation involves neutrophils and monocytes that infiltrate into the retina [12-14]. Neutrophils adhere to retinal endothelial cells and transmigrate into the macula due to the presence of integrin β1 in early macular degeneration [12]. In diabetes, hyperglycemia and NADPH oxidase stimulate neutrophil extracellular trap formation on retinal endothelial cells [13]. This allows neutrophils to adhere and penetrate the macula, inducing inflammation. Monocytes are attracted into the macula by chemokines [14]. Once monocytes have penetrated the macula, they induce inflammation and neovascularization [14].

Lycium Barbarum (Solanaceae)

Goji berries from *L. barbarum* have been used in China for at least 2,000 years for aging and eye problems [15, 16]. The normal dose of goji berries is 5-12g [16], usually steeped in *Chrysanthemum* tea. Each gram is about 3 goji berries. High levels of zeaxanthin are found in goji berries, about 1.87mg/g of dried berries [16,17]. The zeaxanthin is present mostly as esters of palmitic acid. Goji berries also contain vitamin E and many other pharmacologically active compounds that may play roles in the prevention of macular degeneration. California has goji berries also. A recent publication found zeaxanthin and other active compounds in *L. andersonii* and *L. cooperi* from California [18]. California goji berries have been important medicines to California Indians for centuries. Goji berries have been used medically for macular degeneration, antioxidant effects, immune modulation, anti-inflammation and other effects [16]. The wide-ranging uses of goji berries suggests that several active compounds may be present that account for its clinical efficacy. Goji berries have been tested in a double blind; placebo controlled clinical trial (RCT) of retinitis pigmentosa [19]. Goji berries prevented cone cell death and macular thinning. An RCT of a goji berry extract in elderly patients found that macular characteristics improved [20]. Macular hypopigmentation and drusen accumulation were not as severe in the goji berry group. Clearly, additional RCTs are required to test the effects of goji berries in macular degeneration.

Zeaxanthin

Zeaxanthin is a xanthophyll carotenoid like lutein and cryptoxanthin. These are yellow pigments that absorb blue light. Lutein and zeaxanthin are isomers of each other, differing by the placement of a double bond. Natural sources include green, leafy vegetables like kale, chard and mustard greens. Administration of 15g of goji berries daily for 28 days increased human plasma zeaxanthin levels 2.5-fold [16]. Zeaxanthin binds to high density lipoprotein and is transferred to the retina by a scavenger receptor [21]. This mechanism allows zeaxanthin to concentrate in the retina, especially the macula. Administration of zeaxanthin in a multi-vitamin and mineral form has been examined in clinical trials. A recent meta-analysis of all the clinical trials that found a zeaxanthin containing multi-vitamin mineral mixture may delay the progression of advanced macular degeneration [22]. This delay may be especially found in people exposed to more than normal oxidative stress, such as smokers, alcoholics and people who do not eat foods high in carotenoids. Some carotenoids, such as β-carotene are precursors for retinal, which is concentrated in rod cells and is necessary for vision.

Zeaxanthin has antioxidant effects that may protect retinal cells from the damaging effects of UV light [23]. It also increases human plasma brain derived neurotrophic factor (BDNF) and decreases human IL-1β [24]. Zeaxanthin may protect human retinal arteriolar endothelial cells thereby decreasing leaks into the retina [25]. BDNF supports the functions of retinal ganglion cells perhaps through a sigma-1 receptor or tropomyosin receptor kinase B mechanism [26, 27]. IL-1β is an inflammatory protein that damages the retina by promoting chemokine production by Muller cells and the retinal pigmented epithelium [28]. IL-1β damages Muller cells by causing the nuclear accumulation of glyceraldehyde-3-phosphate dehydrogenase [29]. IL-1β induces forehead transcription factor O1 which damages human retinal microvascular endothelial cells [30], perhaps increasing the leakiness of retinal blood vessels. Zeaxanthin has several mechanisms of protection of the retina and the retinal microvasculature. It decreases IL-1β levels, thereby protecting Muller cells and preventing retinal scarring. It also protects endothelial cells, preventing neovascularization.

Flavonoids

The most abundant flavonoids in goji berries are quercetin and kaempferol [31]. The bioavailability of quercetin is low (about 2%) but increases with daily consumption of fruits and vegetables rich in quercetin [32]. Retinal uptake of quercetin has not been reported. The glucuronide metabolite of quercetin is taken up into the human brain across the blood cerebrospinal fluid barrier [33]. This implies that the glucuronide of quercetin may also penetrate the retina. However, quercetin does not have to penetrate the retina in order to have beneficial effects on the retinal vasculature. It can

exert its effects from the blood compartment. Quercetin treatments to diabetic rats decrease retinal microvascular pathology and leakiness [34]. IL-1β and tumor necrosis factorα (TNFα) levels in the retinas of diabetic rats decrease due to quercetin [35]. Retinal thinning and apoptosis of diabetic rat retinal ganglion cells are inhibited by quercetin [35]. Quercetin has several effects in the vasculature involving signal transduction and phosphorylating enzymes [32]. These effects add up to enhanced vascular health in the presence of quercetin in the blood. Quercetin also has effects on the immune system [36]. It acts directly in the gut to affect the immune system, which is the site of maturation of many immune cells. Quercetin has several mechanisms of action including altering gene transcription, inhibiting phosphorylation enzymes, inhibiting matrix metalloproteinase, suppression of the activation and accumulation of immune cells [36].

Quercetin also acts on gut bacteria, such as Verrocomicrobia, and decreases the production of active lipid metabolites produced in the gut, such as lysophosphatidylcholine [37]. Several of these lipid metabolites may damage endothelial cells throughout the body. Quercetin inhibits microRNA production in gut dendritic cells [38]. Dendritic cells are involved in regulating the immune system, especially T cells and macrophages, that are involved in inflammation in the body. The bioavailability of kaempferol is low [39]. However, it penetrates the vasculature in enough quantities to alter signal transduction mechanisms in endothelial cells [39]. It especially inhibits phosphorylation enzymes that alter intracellular redox mechanisms. Kaempferol inhibits angiogenesis in human retinal endothelial cells by inhibiting VEGF expression [40]. This may inhibit neovascularization. Kaempferol is immunostimulatory, increases IgG antibody production and Th1, Th2 immune responses [41]. The stimulation of dendritic cells in the gut may be involved in this mechanism. Kaempferol also regulates gut bacteria and their production of potentially toxic, inflammatory metabolites [42].

These actions of kaempferol in the gut appear to be responsible for its anti-inflammatory activity. Rutin is found in goji berries and is a disaccharide of quercetin. The bioavailability of rutin is very low. However, rutin acts directly in the gut to inhibit the inflammatory effects of obesity on Paneth cells and inflammatory cytokine production [43]. Rutin also stimulates humoral and cellular immune responses [44]. Rutin administration to diabetic rats protects the retina by decreasing VEGF, retinal TNFα and retinal aldose reductase [45]. In this study, rutin was detected in the retina after systemic administration. Flavonoids have several mechanisms of action in the protection of the retina. Many of these mechanisms are based in the gut. It is not surprising that flavonoids have several mechanisms of action since human beings have been eating flavonoids for the entire 200,000 years of human existence. Humans have evolved eating flavonoids which may have influenced receptor evolution in the body.

Lycium Barbarum Polysaccharides (LBPs)

LBPs make up 5-8% of the weight of dried goji berries [46]. These complex compounds have very low bioavailabilities and may act primarily in the gut. LBPs are immunostimulants by enhancing the production of B cells and chemokines [46]. T cells and macrophages are also stimulated by LBPs [46]. It is possible that stimulation of gut dendritic cells is involved in all these mechanisms [46]. LBPs modulate gut bacteria [47]. The effects of LBPs in the gut may result in immune and metabolic changes that protect the retina.

Conclusion

Focusing on zeaxanthin, lutein, minerals and vitamins in the prevention of macular degeneration provides effective therapy. However, goji berries with their arsenal of carotenoids, flavonoids and other compounds may provide superior therapy. Goji berry flavonoids and LBPs act in the gut to modulate the immune system, which may be beneficial in macular degeneration. Goji berries should be tested in more clinical trials. A gut retina axis is important in not only supplying nutrients to the retina, but also in regulating immune cells that affect the retina [48]. The use of goji berries may alter this gut retina axis in ways that decrease the progression of, or the risk of developing macular degeneration.

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