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Review

Hypercholesterolemia-induced ocular disorder: Ameliorating role of phytotherapy

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ABSTRACT

The ocular region is a complex structure that allows conscious light perception and vision. It is of ecto-mesodermal origin. Cholesterol and polyunsaturated fatty acids are involved in retinal cell function; however, hypercholesterolemia and diabetes impair its function. Retinal damage, neovascularization, and cataracts are the main complications of cholesterol overload. Dietary supplementation of selected plant products can lead to the scavenging of free reactive oxygen species, thereby protecting the ocular regions from the damage of hypercholesterolemia. This review illustrates the dramatic effects of increased cholesterol levels on the ocular regions. The effect of phytotherapy is discussed in relation to the different regions of the eye, including the retina, cornea, and lens.

Introduction

It is important to understand how to target the risk factors involved in a hypercholesterolemic diet to prevent the development of atherosclerosis, the marker of severe organ diseases, as well as cardiovascular complications via elevated levels of plasma oxidized low-density lipoprotein (LDL) levels [1,2]. Oxidized LDL (10–200 μg/mL) augments the activity of acetylcholinesterase after 24 h treatment and also increases the intracellular reactive oxygen formation causing cell damage [3]. Dietary oxidized cholesterols are absorbed in the enterocytes; the synthesis of chylomicron cholesterol also occurs in the enterocytes [4]. It has been reported that CD-36–deficient mice exhibited apparent increases in synthesis of chylomicron in the small intestine [5]. Recently, it was revealed that tumor necrosis factor (TNF)-α increased CD-36, which facilitated the passage of fatty acids [6]. Ocular regions, including the retina, cornea, and lens, are subjected to oxidative stress in both diabetes and hypercholesterolemia; therefore supplementation of phytochemical nutrients may inhibit the progress of metabolic syndrome by improving the antioxidant defense. The susceptibility of the retina to oxidative damage is attributed to the presence of polyunsaturated fatty acids (PUFAs) in its membrane bilayers, periodic light exposure, and its high metabolic rate with increase demand of oxygen supply. Hypercholesterolemia is associated with the increase of lipid peroxidation and reduction of retinal blood flow, causing retinal ischemia [7,8]. These have led to increases in the microvasculature within the retina and cornea as assessed by elevated levels of vascular endothelial growth factor (VEGF), the stimulator of endothelial cells (ECs) to migrate, proliferate, and form blood capillaries [9]. In vitro studies of human RPE culture exhibited increased lipid deposits in Bruch's membrane (BM) interfering with the alteration of retinal blood barriers similar to those observed in age-related macular degeneration (AMD) [10].

Ocular structures and function

The eyeball is ensheathed externally by the sclera. The conjunctiva lines the sclera in front of the cornea as well as the back surfaces of the eyelids and eyeball. The lens is situated behind the iris, and changes its shape to accommodate light onto the retina. The cornea forms stratified epithelium with Bowman's layer, stroma, Descemet's membrane, and Descemet's endothelium. Internally, the retina, which is the sensory part, is composed of the pigment epithelium and the neurosensory region (photoreceptor, bipolar, horizontal, amacrine, interplexiform, and ganglion cells) in association with glial cells (Müller cells, astrocytes, and microglia). Two kinds of photoreceptors are distinguished: rods for nocturnal vision and cones for diurnal vision [11]. The photoreceptors are composed of inner and outer

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segments. The outer segment is internally lined by tightly packed stacked membrane that contains the rhodopsin, which converts light photons into an electrical signal [12]. Photoreceptors receive input from the horizontal and bipolar cells in the inner nuclear layer (INL) [13,14]. The INL also possesses cell bodies of Müller glial, bipolar cells, amacrine, and horizontal cells. The inner plexiform layer (IPL) localizes at the interphase between ganglion and inner nuclear cells contain bipolar axons, ganglion, and amacrine cells [15]. Two other microglia cells—Müller cells and astrocytes—are present and are able to preserve the synaptic activity by the uptake and metabolization of extracellular neurotransmitters including glutamate and γ-aminobutyric acid (GABA) [16,17].

The retinal pigmented epithelium (RPE), a simple cuboidal epithelium, serves as protection against toxic agents, phagocytosis of terminal photoreceptor outer segments, elimination of waste products, and formation of vitamin A metabolites in the vision cycle (Fig. 1) [18]. Each RPE cell possesses numerous, long apical microvilli between the photoreceptors, and basal infolding membranes localized on BM [19]. It is also characterized by melanin-containing organelles, which mainly appear in the apical cell surface, often within the microvilli protecting the retina from intensive light exposure [20].

The BM is situated beneath the RPE and at the interface of choriocapillaris. It plays a role in promoting the exchange of biomolecules, nutrients, oxygen, fluids, and metabolic waste products between the retina and the general circulation. The pentalaminar structure of the BM is composed of choriocapillaris, outer collagenous layer, elastic layer, inner collagenous layer, and a basement membrane of the RPE (Fig. 2) [21]. In many mammalian species, the choroidal circulation supplies the inner and outer retina because retinal blood vessels are absent, as in the Guinea pig, or sparse, as in the rabbit [22].

Role of lipid metabolism in retinal function

Long-chain (LC) PUFAs represent the main structural components of the retina. LC-PUFAs serve as precursors for the synthesis of eicosanoids, which maintain the cell structure and functions. Light sensitivity of the retinal rod photoreceptors was found significantly depleted in newborns deficient in ω-3 fatty acid. Fatty acids also are involved in rhodopsin function, rod and cone development, and neuronal dendritic attachments [23]. Phosphatidyl ethanolamine (PE) is the main class of glycerophospholipid present in the vertebrate retina and the outer segment membranes of the rod [24].

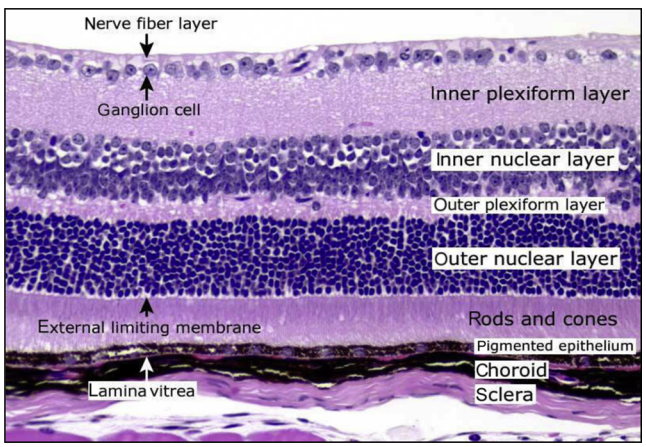

Fig. 1. Retina histologic structure.

There is an active physiological relationship between these photoreceptors, RPE, and choriocapillaris. Both the RPE and the BM/choroid are rich in phosphatidyl choline, PE, phosphatidyl inositol, and phosphatidyl serine [25]. It controls the lipid metabolism of the photoreceptors by activating membrane outer segments, and perfusion via choriocapillary. The expression of native LDL in RPE cells may facilitate the lipid metabolism of the RPE–photoreceptor complex [26]. A large cholesterol-rich lipoprotein containing apolipoprotein (apo)B, is secreted by the RPE and accumulates in BM during aging [27]. ApoE and apoB, are the main components secreted by RPE, [28] and are transported by LDL and high-density lipoprotein (HDL) [29]. Several studies have also mentioned that the RPE contains LDL receptors (LDLRs) giving it higher affinity for lipoproteins (LDL) and lipids requirement to the retina [30].

Light responses in photoreceptors are activated by cGMP phosphodiesterase at the periphery of the stacked membranes through changes in phosphoinositide levels [31]. Lipid metabolism plays a great role in the outer segments of the visual rod. Phospholipid turnover is tightly regulated by phosphorylation–dephosphorylation reactions [32]. Cholesterol is abundant in all of the neural retinal layers [33], being markedly increased in the IPL compared with that of the photoreceptor outer segment [34]. Cholesterol was found to directly enhance presynaptic differentiation and transmitter release [35].

Hypercholesterolemia and ocular disease

Hypercholesterolemia is closely associated with atherosclerosis, which causes decreased antioxidant levels, enhancing the generation of free radicals especially in patients with type 2 diabetes and hypercholesterolemia [36]. The increased level of cholesterol in arterial lumen was found to increase inflammatory injury through the formation of prooxidative changes in the cells of the arterial wall and development of atherosclerosis [37]. During hypercholesterolemia, chylomicrons are hydrolyzed into chylomicron remnants (cholesterol-rich particle, 100 and 1000 nm in size) that are picked up by the apoE receptors of the liver parenchyma, especially in the space of Disse through the fenestrated sinusoidal endothelium [38,39], they undergone de novo synthesis [40] and are involved in the pathogenesis of atherosclerosis. Diabetes was found to increase dyslipidemia similar to hypercholesterolemia and both have been associated with cardiovascular defects [2,41], with an increase in levels of lipid biomarkers such as total cholesterol (TC), HDL, LDL, and triacylglycerol (TG) and a decrease in HDL [42,43]. Both diseases also developed long-term vascular complications, especially angiogenesis. In patients with diabetes, angiogenesis was associated with retinopathy [44]. In hypercholesterolemia, there was apparent decrease of myocardial vascular density and an increase of endothelial damage [45], which result from ischemia, an increase of oxidative stress [46], and a reduction in the expression of tissue endothelial NOS [47] (Fig. 3).

In this review, we illustrated the role of hypercholesterolemia in retinal damage, neovascularization, and lenticular cataracts.

Bruch's membrane and retinal damage

Familial hypercholesterolemia (FH) is a genetic disease that affects 1 in 400 individuals in the Dutch population. FH results from mutations in the *LDLR* gene [48]. It has been reported that FH was characterized by an abnormal increase of serum LDL