REVIEW

The nutraceutical potential of natural products in diabetic cataract prevention

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Summary
Recent reports indicate that consumption of fruits and vegetables, in particular those rich in polyphenols, decreased the incidence of diabetes mellitus type 2 as well as its associated secondary complications. Thus, the use of traditional medicines, mainly derived from plant sources, has become an attractive segment in the management of lifestyle diseases. Among many metabolic and age-related diseases, this review is devoted to debilitating eye lens opacification changes leading to diabetic cataract. The main cataractogenesis mechanisms are summarized and accordingly, the corresponding prospective anti-cataract agents are classified. The roles of antioxidants, inhibitors of non-enzymatic glycation, inhibitors of aldose reductase enzyme and inhibitors of calpain proteases are thoroughly discussed. This compilation focuses also on recent data about possible role of phytochemicals in the management of diseases and outlines nutraceutical concepts for diabetic cataract prevention. Finally, some dietary recommendations are suggested and further cataract research prospects are outlined.

Keywords
cataract; diabetes; phytochemical; polyphenol; flavonoid; nutraceutical

The use of traditional medicines, mainly derived from plant sources, has been a major part in the management of many chronic ailments including diabetes, particularly in Asian countries like China, India and Korea [1, 2]. Moreover, there is a renewed interest in recent-times knowledge, e.g. provided by ayurvedic medicine, to identify many plant sources for their therapeutic value. For example there, was a large number of plants or spices recognized to possess hypoglycemic potential [1–5].

The consumption of a diet low in fat and rich in antioxidants may reduce the risk of obesity and insulin resistance within diabetic population [6–8]. A number of recent reports indicated that consumption of fruits and vegetables, in particular those rich in polyphenols, decreased the incidence of diabetes type 2 associated with impaired insulin resistance [9, 10].

Diabetes mellitus is considered a serious risk factor for the development and progression of diabetic cataract [11]. Cataract, the opacification of the eye lens, is the leading cause of blindness – it accounts for approximately 42% of all blindness. Thus more than 17 million people are blind because of cataract and worldwide, new cases are reported daily. Moreover, approximately 25% of the elderly population over 65 and about 50% over 80 suffer from serious loss of vision because of senile cataract [12]. In USA, over 1.2 million cataract operations are performed per year; the costs being over 3.4 billion dollars [13]. Unfortunately, of some 37 million blind persons in the world, 90% live in developing countries, where malnutrition is a key cotmponent of several diseases.

Wild and cultivated plant species might make fundamental contributions to human health and nutrition by securing food supplies, meeting energy and micronutrients requirements, and providing medicinal resources [14, 15]. Since plant species and varieties have different nutrient and non-nutrient compositions [16], the dietary diversity, i.e. consumption of a variety of foods across and within food groups, was able to provide benefit to human health by improving the nutritional status and reducing risks of civilization-specific diseases [17–19].

Epidemiologic evidence suggests that both

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fruits and vegetables might also contribute to the prevention of age-related cataract [20, 21]. The first prospective cohort study from 1992 showed a strong protective effect of green leaf vegetables, particularly spinach, compared as the intake in women of the highest to the lowest quintile of consumption [22]. Similar results were reported in five other studies for spinach and/or kale and/or carotenoides and other greens [23–26]. MOELLER et al. observed a 42% decrease in nuclear opacity in high fruit consumers as compared to a low intake group [27]. CHRISTEN et al. reported a 10% to 15% decrease in cataract prevalence of women in the highest fruit and vegetable intake quintile compared to the lowest [28].

This review focuses on recent information on the possible role of phytochemicals in disease management and outlines nutraceutical concepts for diabetic cataract prevention. The main cataractogenesis mechanisms are summarized and accordingly, the corresponding prospective anticataract agents are classified and thoroughly discussed. Finally, some dietary recommendations are suggested and further cataract research directions drawn.

MECHANISMS OF CATARACTOGENESIS

The human lens is a transparent and avascular tissue composed of epithelial and fibre cells. In the lens fibres, virtually all organelles together with their component proteins are removed, while a large quantity of crystallins are synthesized. Thus, the lens fibres have the highest protein content in the body, which accounts for more than 35% of their wet weight. About 90% of the lens proteins are structural proteins called crystallins. There are three distinct families of crystallins: α-, β- and γ-crystallins.

Crystallin breakdown in the lens occurs for several reasons. Occasionally, it is a part of the normal lens maturation process [29]. It may be due to the activation of lens proteolytic enzymes [30, 31]. Non-enzymatic mechanisms are also likely to generate crystallin fragments [32]. Crystallin degradation is also necessary for the removal of denatured proteins or unfolded proteins that result from various oxidative stresses on lens. Proteasomes and ubiquitin systems in the lens are involved in the removal of oxidized proteins or peptides [33]. Despite this, truncated proteins or short peptides might accumulate in the lens because of their excessive production or because the degradation system cannot break down the fragments [34, 35].

Diabetes mellitus is considered a serious risk factor for development and progression of cataract [11]. Chronic elevation of blood glucose plays a critical role in the development and progression of major diabetic complications, while those ocular degenerative changes are the earliest to manifest. Prolonged exposure to elevated glucose causes both acute reversible changes in cellular metabolism and long-term irreversible changes in stable macromolecules. The injurious effects of hyperglycemia are characteristically primarily observed in tissues that are not dependent on insulin for glucose entry into the cell (e.g. eye lens, kidney) and, hence, are not capable of down-regulating glucose transport along with the increase of extracellular saccharide concentration.

Most of reviews and experimental articles highlight only the role of oxidative stress, while other mechanisms of cataractogenesis are mentioned marginally or are completely overlooked. However, multiple biochemical mechanisms contributing to opacification of the lens have beenthroughly described:

i) oxidative stress [36];
ii) non-enzymatic glycation [7];
iii) polyol pathway [37]; and
iv) activation of calpain proteases [38].

Oxidative stress and diabetic cataract

Diabetes mellitus was found to be inextricably connected with increased oxidative stress both in diabetic humans and hyperglycemic animals [39, 40]. Among the number of mechanisms proposed as a pathogenic link between hyperglycemia and diabetic complications, oxidative stress is regarded as a hypothesis superior to the others (the Maillard advanced glycation hypothesis, the aldose reductase (AR) mediates osmotic hypothesis or calcium impairments). The oxidative stress and its corresponding biochemical disturbances are summarized in Fig. 1.

Irreversible advanced glycation end products (AGE) were shown to be formed via a sequence of glycation and oxidation reactions [41, 42]. Under physiological conditions, glucose, like other α-hydroxyaldehydes, can enolize and thereby reduce molecular oxygen, catalysed by transition metals yielding reactive α-ketoaldehydes and oxidizing free radical intermediates [43]. The ketoamine Amadori product undergoes autooxidation as well, contributing to the oxidative damage of proteins exposed to hyperglycemia [44, 45].

Hyperglycemia would not only generate more reactive oxygen species (ROS) but also attenuate endogenous anti-oxidative mechanisms through glycation of scavenging enzymes and depletion of

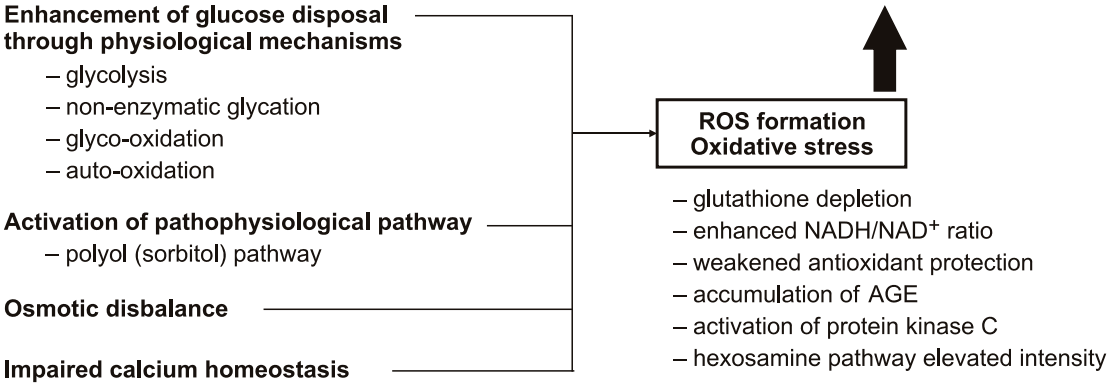

Fig. 1. The oxidative stress – unifying mechanisms of cataractogenesis.

AGE – advanced glycation end products, ROS – reactive oxygen species.

low molecular wieght antioxidants, e.g. glutathione (GSH). Shifts in redox balances due to derangement in energy metabolism of saccharides and lipids also contribute to the overt oxidative stress in diabetic individuals.

Reactive dicarbonyls, products of saccharide auto-oxidation, contribute to covalent attachment of monosacharide to protein with a high cross-linking potential. Indeed, glycation and oxidation are closely connected and the complex process is often referred to as glyco-oxidation [45].

It is now widely accepted that oxidative free-radical damage is an initiating or very early event in the overall sequence that leads to cataract [46]. Oxidative stress may cause direct modification of the inner lens proteins, such as cross-linking, aggregation and precipitation [47, 48]. Toxic aldehydes generated by peroxidation of lens epithelium and by oxidative damage of the vulnerable retina may contribute to the final damage of lens proteins, yielding opacity [49].

Advanced glycation end products (AGE) formation

Under hyperglycemic conditions, part of the glucose excess reacts non-enzymatically with proteins or other tissue or blood constituents, thus increasing the physiological rate of non-enzymatic glycation [50]. Chronic, irreversible abnormalities unaffected by normalization of blood glucose levels primarily involve long-lived molecules including extracellular matrix, eye lens crystallins and chromosomal DNA. Due to their characteristic chemical properties, advanced products of non-enzymatic glycation play a critical role in the evolution of diabetic complications.

The formation of AGE begins with the attachment of glucose carbonyl group to a free amino group of proteins or amino acids to form a labile Schiff base adduct as the first step of the complex Maillard process. Levels of the unstable Schiff base increase rapidly, and equilibrium is reached after several hours. Once formed, Schiff base adducts undergo a slow chemical rearrangement over a period of weeks to form a more stable, but still chemically reversible, Amadori product [51]. Finally, AGE are formed as a rather heterogeneous mixture of protein-bound nitrogen- and/or oxygen-containing heterocyclic compounds through a complex cascade of dehydration, condensation, fragmentation, oxidation and cyclization reactions of the intermediate Amadori ketoamine. The AGE are frequently pigmented or fluorescent and, most importantly for diabetic complications, they participate in glucose-derived cross-link formation [50, 52, 53].

Specific chemical characterization of AGE proteins is difficult, as Amadori products can theoretically undergo a large number of potential rearrangements. Immunological and chemical evidence indicates that progressive accumulation of AGE in diabetic eye lens contributes to accelerated cataractogenesis in hyperglycemic experimental animals and diabetic humans [54–58].

Involvement of the polyol pathway

Under physiological conditions, the bulk of glucose is metabolized through the glycolytic pathway and the pentose shunt. When hyperglycemia occurs, glucose disposal through these pathways tends to increase [59]. In addition, an increased amount of glucose is converted into sorbitol by the enzyme aldehyde reductase (AR) via polyol pathway, normally operating for converting aldehydes into alcohols at physiological glucose concentrations [60]. Sorbitol does not easily cross cell membranes and can accumulate in cells and cause

damage by disturbing osmotic homeostasis. Intralenticular accumulation of polyols produced in hyperglycemic conditions has long been suggested to be a major factor in acute models of sugar cataract.

The fact that AR is responsible for initiating the cataractous process provides an explanation for the difference in the rate of cataract progression observed between diabetic and galactosemic rats. First, galactose is a better substrate than glucose for AR so that polyol is formed faster from galactose than from glucose. Second, galactitol formed in the AR reaction is not further metabolized by sorbitol dehydrogenase, as is sorbitol in the diabetic state. Since fructose can be further metabolized and can leak from the lens, the sorbitol pathway intermediates in the diabetic state never accumulate to the level of polyol found in the galactosemic lens. Therefore, there is a greater osmotic change in the lens of galactosemic rats and consequently, the rate of cataract development is more rapid [61–66].

The increased flux of glucose via polyol pathway has also consequences for the overall antioxidant status of the lens leading to depletion of GSH as a result of competition between AR and glutathione reductase for NADPH [67, 68]. The NADPH depletion combined with leakage of GSH and compounds essential for its synthesis, such as amino acids and ATP, results in a significant fall in lenticular GSH levels, an important intralenticular antioxidant [69–71].

Calcium homeostasis impairment

Accumulating data from animal models of diabetes and from patients with diabetes reveal that intracellular calcium levels are increased in most diabetic tissues. Thus, altered intracellular Ca metabolism may represent a common, underlying abnormality linking the metabolic, cardiovascular, ocular and neural manifestations of the diabetic disease process [72].

Premature visual impairment due to lens opacification is a debilitating characteristic of untreated diabetes. Lens opacification is primarily due to the insolubilization of crystallins, proteins essential for lens optical properties.

Calpains are a family of Ca-dependent cysteine proteases under complex cellular regulation. By making selective limited proteolytic cleavages, they modulate the activity of enzymes, including the key signalling molecules, and induce specific cytoskeletal rearrangements, accounting for their roles in cell motility, signal transduction, vesicular trafficking and structural stabilization. The activation of these intracellular cysteine proteases requires the presence of Ca and, since the elevated levels of lens Ca is a condition associated with diabetic cataractogenesis, the Ca homeostasis attracts the attention of researchers.

Shearer et al. [73] proved the first that calpain-induced proteolysis of the N-terminal arms of β-crystallin polypeptides leads to a loss of normal oligomerization of β-crystallin polypeptides and formation of abnormal insoluble aggregates, possibly stabilized by hydrophobic interactions. Fukiage et al. [74] observed in young rodent cataracts, that influx of Ca led to activation of calpain proteases. Actived calpains then truncated crystallins by limited proteolysis and finally led to insolubilization and precipitations of crystallins, which can be regarded a key event in cataractogenesis. In another recent study, Biswas et al. suggested that a major cause of this insolubilization may be the unregulated proteolysis of crystallins by calpains [75].

Maintenance of a low intracellular Ca content is essential for maintaining lens clarity, because Ca elevation is a critical factor in the process of lens opacification in the sugar cataract. Cataract formation is followed by increased lens permeability, which subsequently leads to Ca accumulation [76–78]. Since the lens is an avascular organ, it requires cellular mechanisms to ensure metabolite transport to all cells. Other mechanisms for maintenance of Ca levels in the lens might also exist. For example, altered regulation of both selective and non-selective ion channels such as L-type Ca-channels and Na-Ca exchangers may have a critical role in Ca homeostasis. On the other hand, it is unlikely that ATPase pumps are involved in ion mobilization within the lens nuclear region, mainly due to the low metabolic activity in this region [79].

NATURAL COMPOUNDS EFFICACIOUS IN CATARACT PREVENTION

At present, the only remedy from the cataract is the surgical removal of the opaque lens and its substitution with a clear one made of synthetic polymers. However, in the United Kingdom half of the patients put on waiting lists for operation will die before getting surgery [12]. In USA, over 1.3 million cataract operations are performed annually at a cost of 3.5 billion dollars. In developing countries there is simply no sufficient number of surgeons to perform cataract operations. Besides significant costs of operation and possible complications, an artificial lens does not have the overall optical qualities of a normal lens [80]. This is the

reason for highly required biochemical solutions or pharmacological intervention that will maintain the transparency of the lens. It is estimated that a delay in cataract formation of about 10 years would reduce the prevalence of vision disabling cataract by about 45% [81]. Such a delay would enhance the quality of life for much of the world's older and diabetic population and substantially diminish both the economic burden due to disability and surgery related to cataract.

Unfortunately, no definitive pharmacological therapy is available nowadays, and thus the only solution for the patient with advanced cataract is surgery, with all its disadvantages. Nevertheless, there are certain measures and treatment modalities, resulting from the aforementioned discussion on possible molecular mechanisms of cataractogenesis, which can improve the visual outcome of this disabling eye disease. For a generalized scheme see Fig. 2.

The role of antioxidants

The first way how to prevent cataractogenesis is to reduce the oxidative stress by antioxidants. Antioxidants may generally act at different levels, e.g. by preventing the formation and/or eliminating already created ROS by scavenging, trapping and quenching them, or by binding metal ions into inactive chelates. The lens may defend itself against oxidative stress by means of endogenous antioxidants like vitamin C, vitamin E, carotenoids, and antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and Se-dependent GSH peroxidase [46, 82].

The effect of a novel flavonoid, venoruton (a mixture of mono-, di-, tri-, and tetrahydroxyethylrutosides) has been investigated in healthy rat lenses and compared with diabetic cataract modeled in vitro. The protective effect of venoruton was suggested to be related to antioxidant activity against ROS [83].

SANDERSON et al. [84] showed that low micromolar concentrations of a naturally-occurring flavonoid, quercetin, inhibited cataractogenesis in a rat lens organ cultured model exposed to the endogenous oxidant hydrogen peroxide. Quercetin was active both when incubated in the culture medium together with hydrogen peroxide, and was also active when the lenses were pre-treated with quercetin prior to oxidative insult.

SURYANARAYANA et al. [85] tested the effect of curcumin and its source, turmeric, on streptozotocin (STZ)-induced diabetic cataract in rats. Although neither curcumin nor turmeric prevented STZ-induced hyperglycemia, as assessed by blood glucose and insulin levels, slit lamp microscope observations indicated that these supplements delayed the progression and maturation of cataract. Curcumin and turmeric treatment appeared to have countered the hyperglycemia-induced oxidative stress, because there was a reversal of changes with respect to lipid peroxidation, reduced GSH, protein carbonyl content and activities of antioxidant enzymes in a significant manner. Also, treatment with turmeric or curcumin appeared to have minimized osmotic stress, as assessed by polyol pathway enzymes. Most importantly, aggregation and insolubilization of lens proteins due to hyperglycemia was prevented by turmeric and curcumin. Later on, JAIN et al. [37] validated on an erythrocyte cell model that curcumin prevented protein glycosylation and lipid peroxidation caused by high glucose levels. Their study also suggests that curcumin may inhibit oxygen radical production caused by high glucose concentrations in a cell-free system, and increase glucose utilization in

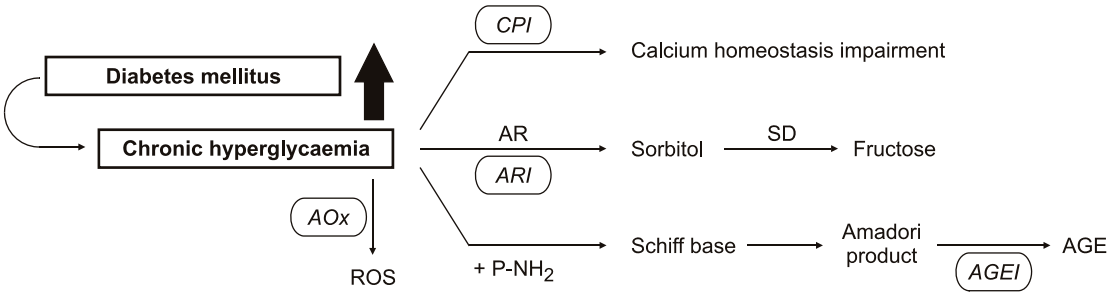

Fig. 2. The possible sites of action for natural compounds to succeed in diabetic cataract prevention.

AGE – advanced glycation end products; AGEI – AGE inhibitors; AOx – antioxidant; AR – aldose reductase enzyme; ARI – inhibitors of aldose reductase enzyme; CPI – calpain proteases inhibitors, P-NH_2 – schematic molecule of protein with amino group; ROS – reactive oxygen species; SD – sorbitol dehydrogenase.

erythrocytes. This provides evidence for a novel mechanism by which curcumin supplementation may prevent the cellular dysfunction associated with diabetes.

Taurine has an antioxidant capacity and its level in diabetic cataractous lens is markedly decreased. Therefore, SON et al. [86] investigated whether taurine is a part of the antioxidative defense mechanism involved in protecting the lens against high glucose-induced oxidative stress and tissue damage. Lenses, isolated from male Sprague-Dawley rats, were cultured in high glucose medium (55.6 $mmol \cdot l^{-1}$) for 6 days as a model of high glucose-induced cataractogenesis. Two days pretreatment of cultured lenses with 30 $mmol \cdot l^{-1}$ taurine significantly reversed the level of protein carbonylation and GSH to those of controls. Therefore, taurine might spare GSH and protect the lens from oxidative stress induced by a high concentration of glucose.

NAKANO et al. [87] examined in their study the effect of dietary antioxidants, such as astaxanthin and flavangenol, and a combination of both, in counteracting oxidative stress in STZ-induced diabetes. The degree of cataract formation in the flavangenol and even more in mix groups tended to be lower than the control group. Thus, such a combination may be beneficial in preventing the progression of diabetic complications.

Finally, ARNAL et al. [88] explored a novel approach by investigating the effect of antioxidant lutein, alone or combined with insulin, on the progression of eye lens opacity in STZ-diabetic rats for a period of 12 weeks. The combined treatment was useful in preventing the development of cataracts, supporting its use in diabetes management, in particular when a tight metabolic control is difficult to achieve.

Selenite-induced cataract (oxidative stress model) is an extremely rapid and convenient model for nuclear cataract in rats [89]. Major events of selenite-induced cataract are loss of Ca homeostasis, generation of ROS, lipid peroxidation, calpain activation, insolubilization of proteins, decreased concentrations of water-soluble proteins and GSH [90]. Thus, selenite-induced cataractogenic model, both under in vitro and in vivo conditions, is frequently used to test potencial anti-cataract substances [91].

Selenite-induced oxidative stress-mediated cataractogenesis has been shown to be prevented by antioxidative agents such as caffeic acid phenethyl ester [92] and extract of *Ocimum sanctum* [36]. Furthermore, GUPTA et al. [93] evaluated the the anti-cataract potential of polyphenolic compounds present in green tea (*Camellia sinensis*). Another nutritional antioxidant, lycopene, was also tested [94] and was shown to protect against experimental cataract development by virtue of its antioxidant properties. Resveratrol, a phytoalexin produced naturally by several plants, was able to suppress selenite-induced oxidative stress and cataract formation in rats [95]. Among potential anti-cataract agents, positive outcomes for good antioxidant activities were found for the flavonoid fraction from *Emilia sonchifolia* [96], acetyl-L-carnitine (ALCAR) [97] and for a naturally occurring polyphenol ellagic acid [98].

A herbal remedy was recommended by JAVADZADEH et al. [99]. In their study, intraperitoneal injection of aqueous garlic extract into rats appeared to effectively prevent selenite-induced cataract in vivo. Surprisingly for onion, a further work of JAVADZADEH et al. [38] testing instillation of onion juice into the rat eyes (one drop of 50% diluted fresh juice of crude onion, applied every 8 hours into the right eye for 14 days), also showed effective prevention of selenite-induced cataract formation. The prevention of selenite-induced cataractogenesis was also declared by rutin [100], by an extract of the oyster mushroom *Pleurotus ostreatus* [101] and also by curcumin [102, 103]. Recently, ROOBAN et al. [104] tested phytochemical antioxidants isolated from *Vitex negundo*. ELANCHEZHIAN et al. [105] again carried out an experiment to investigate the possibility of ALCAR to prevent selenite-induced cataractogenesis by regulating the expression of antioxidant CAT genes and apoptotic caspase-3, EGR-1 and COX-I genes. The expression of lenticular caspase-3 and EGR-1 genes appeared to be up-regulated, as inferred by detecting increased mRNA transcript levels, while that of COX-I and CAT genes appeared to be down-regulated (lowered mRNA transcript levels) in the lenses of cataract-untreated rats. However, in rats treated with ALCAR, the lenticular mRNA transcript levels were maintained at near normal levels.

WANG et al. [106] undertook a study to evaluate the anti-cataract potential of *Crataegus pinnatifida* (hawthorn tree) leaves extract. In vitro antioxidant nitric oxide production inhibition, AR inhibition and superoxide radical-scavenging activities were tested, and major compounds in *C. pinnatifida* leaves extract were characterized, namely, nine flavonoids were identified by high definition mass spectrometry. Finally, the topical administration of *Crataegus pinnatifida* leaves extract eye drops alternately three times a day in rat pups with selenite-induced oxidative stress significantly increased serum SOD and CAT activities and tended to reduce malondialdehyde level compared

with control group. The antioxidant enzyme SOD, CAT, and GSH activities in lens showed a significant increase.

Sasikala et al. [107] investigated the protective effects of the flavonoid fraction of *Moringa oleifera* leaves (FMO) on selenite cataract in vivo. FMO effectively prevented the morphological changes and oxidative damage in lens. FMO maintained the activities of antioxidant enzymes and sulfhydryl content and prevented ROS generation and lipid peroxidation. FMO was effective in preventing cataractogenesis in selenite model by enhancing the activities of antioxidant enzyme, reducing the intensity of lipid peroxidation and inhibiting free radical generation.

Ikewuchi et al. [108] tested the leaves of *Acalypha wilkesiana* used in Southern Nigeria for the management of hypertension and diabetes mellitus. They detected twenty nine known flavonoids by gas chromatographic analysis and found out that the aqueous extract of the leaves was hypoglycemic, positively influenced the hemopoietic system as well as positively influenced the integrity and function (dose dependently) of liver and kidney of the diabetic rats. It also improved the lipid profile and had no deleterious effect on red cell morphology. It protected against oxidative stress in ocular tissues. All these highlights support the use of *Acalypha wilkesiana* in traditional health practices for the management of diabetes mellitus.

Inhibitors of non-enzymatic glycation

As a second possibility of delaying cataract, protection of critical amino groups of long-lived proteins is offered. An efficient inhibitor of non-enzymatic glycation should inhibit glucose-derived AGE generation and cross-links formation. Happily, the research of AGE inhibitors intensifies and the progress is obvious.

Recently, Kumar et al. [109] investigated the antiglycating potential of cumin in vitro and its ability to modulate the chaperone-like activity of α-crystallin vis-à-vis the progression of diabetic cataract in vivo. Slit lamp examination revealed that supplementation by cumin delayed the progression and maturation of STZ-induced cataract in rats. Cumin was effective in preventing glycation of total soluble protein and α-crystallin in diabetic lens. Interestingly, feeding cumin to diabetic rats not only prevented loss of chaperone activity but also attenuated the structural changes of α-crystallin in lens. These results indicate that cumin has antiglycating properties, which may be attributed to the modulation of chaperone activity of α-crystallin, thus delaying cataract in STZ-induced diabetic rats.

Yoo et al. isolated from the ethyl acetate extract of the flowers of *Erigeron annuus* a novel 2,3-dioxygenated flavanone, erigeroflavanone, as well as eight known flavonoids and two known γ-pyranone derivatives [110]. All of the isolates were subjected to in vitro bioassays, which proved their inhibitory activity against AGE formation and rat lens aldose reductase (RLAR).

Also the leaf extract of *Nelumbo nucifera* exerted potent antioxidant effects as well as marked inhibitory effects for RLAR and AGE formation, corresponding to high values of total phenolic content and total flavonoid content. Thus Jung et al. [111] concluded that it may be potentially used in the development of therapeutic or preventive agents for diabetic complications and oxidative stress-related diseases.

Lee et al. obtained from the flower buds of *Magnolia fargesii* five compounds of known structures, namely, scopoletin, northalifoline, stigmast-4-en-3-one, tiliroside and oplopanone [112]. Their inhibitory activity on AGE formation and RLAR was demonstrated. Moreover, in the further experiment ex vivo, cataractogenesis of rat lenses induced with xylose was significantly inhibited by scopoletin treatment.

Soman et al. investigated the antioxidant as well as antiglycative potential of ethyl acetate extract of guava leaves [113]. Oral administration of the extract at different doses led to a significant decrease in blood glucose level. It also showed an antioxidant potential as evidenced by decreased lipid peroxidation and a significant increase in the activity of various antioxidant enzymes such as CAT, SOD, GSH peroxidase and glutathione reductase.

Jang et al. in their search directed towards the discovery of novel treatments for diabetic complications from traditional Korean herbal medicines, examined fifteen compounds, constituents of the flowers of *Platycodon grandiflorum* [114]. All the isolates were evaluated and were found to exhibit significant inhibitory activity towards AGE formation and RLAR.

In another study, Jang et al. inspected sixteen compounds from the leaves and stems of *Erigeron annuus* [115]. Among others, the tested substances included three caffeoylquinic acids and four flavonoids, which were isolated from an extract of the stems and leaves of the plant. In all the isolates, in vitro inhibitory activities on the formation of AGE and RLAR were confirmed. Moreover one of the isolated compounds, 3,5-di-O-caffeoyl-epi-quinic acid, markedly reduced AGE bovine serum albumin cross-linking in a dose-dependent manner. Furthermore, opacity

of rat lenses in an ex vivo organ culture experiment was significantly prevented when treated with this compound.

Inhibitors of aldose reductase enzyme

The third approach is the development of potential new agents to interfere with cataract formation through inhibition of accumulation of polyols in eye lens cells. A wide variety of molecules were synthesized to inhibit AR (aldose reductase inhibitors – ARI), which themselves may be acting in ways other than inhibiting the sorbitol pathway.

Although numerous synthetic ARI have been tested and shown to inhibit the enzyme, clinically those ARI have not been very successful. As ARI have considerable clinical value in ameliorating the secondary complications of diabetes, it would be of great importance to investigate their capability and to test the anti-cataractogenic effect of prospective natural sources. Therefore, evaluating phytochemicals for ARI potential may lead to the development of safer and more effective agents against diabetic complications, including cataract. Since most of the plant products and natural spices are largely free from adverse effects and are being used as a source of diet and traditional medicine, testing the ARI potential of these sources may lead to a better management of secondary complications of diabetes.

Historically, already in 1975 VARMA et al. declared flavonoids as effective ARI [116]. Quercetin, quercitrin and myricitrin were found to be significantly more potent than the previously known ARI. Their inhibitory activity was of the non-competitive type. Within their study, quercitrin effectively blocked polyol accumulation in intact rat lenses incubated in a medium with a high concentration of saccharides.

OKUDA et al. in 1982 tested thirty flavones, four isoflavones and thirteen coumarins as inhibitors of lens AR. Many of them were found to be potent inhibitors, the potencies of the two compounds being superior, namely, of axillarin (5,7,3',4'-tetrahydroxy-3,6-dimethoxyflavone) and 6,3',4'-trihydroxy-5,7,8-trimethoxyflavone (LARI 1) [117]. These two flavones inhibited AR purified from rat and bovine lenses. All the potent inhibitors had a flavone skeleton, one or two free hydroxyls in ring C, and more than three hydroxyls, free or methylated, in ring A. Thus, for the first time, the possible relationship of structures to inhibitory potencies of the compounds tested was outlined.

JUNG et al. were interested in evaluating active principles for the inhibition of AR from the rhizomes of *Belamcanda chinensis*, thus twelve phenolic compounds were isolated and tested for their effects on RLAR [118]. As a result, the isoflavonoides tectoridin and tectorigenin were identified as having the highest AR inhibitory potency. Both compounds, when administered orally at 100 $mg \cdot kg^{-1}$ for 10 consecutive days to STZ-induced diabetic rats, caused a significant inhibition of sorbitol accumulation in the tissues such as lens, sciatic nerves and red blood cells.

SURYANARAYANA et al. have assessed the inhibition of AR by tannoids from *Emblica officinalis* both under in vitro conditions in lens organ cultures and on in vivo diabetic model of cataract in rats [5]. They demonstrated that the hydrolysable tannoids of *Emblica officinalis* were responsible for AR inhibition, as enriched tannoids exhibited remarkable inhibition against both rat lens and human AR with the half-maximal inhibitory concentration (IC_{50}) of 6 and 10 $\mu g \cdot ml^{-1}$, respectively. Furthermore, the isolated tannoids influenced also osmotic changes induced by saccharides. These results indicate that exploring the therapeutic value of natural ingredients that people can incorporate into everyday life may be an effective approach in the management of diabetic complications.

Another excellent example of ARI concept came out of the study of CHUNG et al. [119]. The authors showed that water extract of *Aralia*, used commonly in Korean traditional medicine to treat diabetes mellitus, not only inhibited AR, but also acted as an antioxidant in vitro. Subsequently, these activities have a preventive effect on cataractogenesis in xylose-containing lens organ cultures and in vivo in STZ-induced diabetic rats.

GACCHE and DHOLE evaluated anti-cataract activity of different fractions of *Catharanthus roseus, Ocimum sanctum*, *Tinospora cordifolia*, *Aegle marmelos*, *Ficus golmerata*, *Psoralea corlifolia, Tribulus terrestris* and *Morinda cetrifolia* as possible inhibitors of AR using saccharides-induced lens opacity model. Among the tested plants, water extract of *Morinda cetrifolia* exhibited significant anti-cataract potential and maximum AR inhibitory activity as compared to other phytofractions [120].

Research has gradually verified also the antidiabetic effects of ginger (*Zingiber officinale* Roscoe), an important cooking spice and herbal medicine used around the world. KATO et al. [121] isolated active compounds form ginger and those significantly suppressed not only sorbitol accumulation in human erythrocytes but also lens galactitol accumulation in galactose-fed cataract rat model.

The search for components inhibiting AR led to the discovery of active compounds contained in *Evodia rutaecarpa* Bentham (*Rutaceae*), which

is the one of the components of Kampo-herbal medicine. KATO et al. [122] isolated from the hot water extract of *Evodia rutaecarpa* an active compound, N2-(2-methylaminobenzoyl)tetrahydro-1H-pyrido[3,4-b]indol-1-one called rhetsinine. It inhibited AR with IC_{50} values of 24.1 μmol.l^{-1} and sorbitol accumulation by 79.3% at 100 μmol·l^{-1}, making it potentially useful in the treatment of diabetic complications.

CHETHAN et al. evaluated Finger millet seed coat polyphenols (FMSCP) for AR-inhibiting activity [123]. Phenolic constituents in FMSCP such as gallic, protocatechuic, *p*-hydroxy benzoic, *p*-coumaric, vanillic, syringic, ferulic, trans-cinnamic acids and quercetin effectively inhibited cataract. FMSCP was found to inhibit AR reversibly by non-competitive inhibition, thus revealing its potential in inhibiting cataractogenesis.

MERCADER et al. performed a predictive analysis of 55 newly synthesized flavonoids that possessed 2-, 7-substitutions in their benzopyrane backbone, whose activity had not yet been studied experimentally [124]. This in silico (computational approach) was based on quantitative structure activity relationship (QSAR) of an IC_{50} inhibition rates towards AR. The main result of the investigation was that the presence of a naphthyl group substituting the benzopyrane nucleus greatly increases AR inhibitory activity, while the presence of a furanyl group manifestly decreases it.

Inhibitors exhibit their anti-aldose reductase activities mainly by occupying the active site of the enzyme(s). Molecular modeling (so-called docking) studies of flavone derivatives based on the experimental data with AR reveal that they can form hydrogen bond networks with active residues by using the iodine and chlorine groups. In order to validate experimental results computationally, docking studies of new flavone derivatives synthesized were performed and their binding affinities calculated. Biological activity assessments and the outputs of carcinogenic testing indicated that 3-iodo-4-methyl-5-chloroflavone binds with highest affinity, thus making him the best flavone inhibitor against AR [125].

Inhibitors of calpain proteases

Since diabetic cataract development is both symptomatically multifactorial and biochemically complex long-term process, the prospective drug therapies to delay opacity formation need to be broader, with summative emphasis on antioxidants, antiglycating agents or suppressing polyol pathway. The last but not least proposed alternative approach might be based on blocking the entry of excess Ca by preventing osmotic gradients in conjunction with the use of channel blockers and inhibitors of calpain.

In a lens culture study, the antioxidant flavonoid quercetin showed a pronounced inhibition of Ca and Na influx, which either leads to a protection or is a consequence of action of quercetin at another site. It is likely that prevention of Ca influx is an important mechanism by which quercetin acts since increases in intracellular Ca are linked with lens opacification and activation of calpain [84]. The current data, in conjunction with epidemiological data on diet and cataract, demonstrate that quercetin could potentially play a role in reducing the incidence of cataract, further adding to the increasing body of data that suggest that dietary flavonoids may be associated with benefits to human health. The results of CORNISH et al. indicate that dietary quercetin and metabolites are active in inhibiting oxidative damage in the lens and thus could play a role in prevention of cataract formation [126]. In their study, quercetin inhibited hydrogen peroxide-induced Na and Ca influx and lens opacification.

BIJU et al. [127] evaluated the role of drevogenin D, a triterpenoid aglycone isolated from *Dregea volubilis*, in preventing selenite-induced, Ca-activated, calpain-mediated proteolysis in cultured rat lenses. The results obtained indicated that drevogenin D treatment was effective in protecting the lens proteins by controlling stress-induced protein oxidation, maintenance of Ca^{2+}-ATPase activity, Ca accumulation, lipid peroxidation and prevented calpain activation. Hence, drevogenin D can be used as a potential therapeutic agent against oxidative stress-induced cataract.

VIBIN et al. found that the flavonoid fraction of broccoli prevented selenite-induced cataractogenesis in albino rat pups [21]. Possible mechanisms of action were maintaining the antioxidant status and ionic balance through Ca^{2+}-ATPase pump, inhibition of lipid peroxidation, calpain activation and protein insolubilization. The effect observed was comparable to the reference flavonoid, quercetin. The results were found to be in agreement with the previous study using lycopene in attenuating oxidative stress-induced cataract development [93].

ROOBAN et al. repeatedly evaluated in 2009 [104] and in 2011 [128] the efficacy of the flavonoid fraction of *Vitex negundo* in preventing the toxicity induced by sodium selenite in in vitro culture conditions. Positive outcomes for cataractogenesis were registered, due to maintaining the antioxidant status, Ca homeostasis, protecting sulfhydryl groups and decreasing the oxidative stress in lens.

POSSIBLE FURTHER CATARACT RESEARCH DIRECTIONS

Todays traditional medicine increasingly embraces the idea of external natural influences on health of the individual. The common notions about nutritional influences on eye health were very well summarized in following general concepts [129]: first, there is undeniable scientific evidence, biochemical, physiological and epidemiologic, associating ocular diseases with nutrition and environment. Second, the globalization of society confronts us with the opportunity to compare etiologic cross-cultural and environmental aspects of diseases incidence and prevalence. Third, a great part of the world's population relies on plant-based alternative medicine providing valuable evidence-based data. Fourth, many of the curative approaches used today simply do not work effectively enough, and moreover they are dangerous and expensive. This has much to do with economic incentives for drug development [130]. For example, The Physician's Desk Reference suggests 120 or more drugs to treat hypertension when a few would suffice. This is a consequence of the U.S. Food and Drug Administration agency's policy: the only requirements are that a new medication should be superior to a placebo and not to other pre-existing patented medications or natural therapies. Moreover, pharmaceutical companies exert certain pressure on clinical investigators and inexpensive solutions appear to be outside of their interest.

In terms of globalization, it is important to appreciate the importance and complexity of nutrition, based on the history of medicine, multicultural and environmental perspectives. The implications to "Eye Care" in the new millenium are both evolutionary and revolutionary. Prescription drugs will probably remain the mainstays for the treatment of infections, acute inflammations, pain, pre-operative/postoperative care and rare genetic diseases because pharmaceuticals, as opposed to nutrients, provide potency and immediate relief. On the other hand, long-term use of many pharmaceuticals is associated with negative side effects, often as a result of nutrient depletion [131]. In contrast nutrients, with rare exceptions, are safe [132]. Informed patients increasingly demand the comparison of prescription drugs with safer, often inexpensive alternatives. Nutraceuticals are defined as food and/or parts of food providing medical benefits for prevention and treatment of diseases. Therapeutic doses of nutrients attempt to address the underlying physiological abnormality, resulting often in secondary improvements to general health. Unfortunately, there is little economic incentive to evaluate the effectiveness of complementary approaches.

However, concerning the application of nutrition counseling in optometric practice, possible adverse effects of certain nutrients and dosage levels have to be scientifically assessed. Nutritionists caution that large doses of virtually any vitamin or mineral may affect the body's ability to absorb other nutrients and can be associated with some health risks [133]. Thus, toxicological aspects of unusually high doses of natural dietary supplements have to be evaluated and the implication for public health considered.

Unfortunately, the majority of studies involving bioactive compounds studied only one or a few compounds at a time. However, the overall effect of a particular fruit or vegetable cannot be accounted for by one or a few components present therein. That is probably why many epidemiological and cohort studies failed to find correlations between the consumption of specific fruits or vegetables rich in a particular component [134]. The bioavailability is of course a major key factor determining the overall effect of bioactive compounds, particularly from different food matrices. Absorption of different constituents can be very complex depending upon the food matrix consumed, and investigation in this aspect might provide a better understanding for the development of a tailored approach [135–137]. Thus, future strategies should be looking into the synergistic effect of these bioactive phytochemical components, considering the whole fruit or vegetable matrix.

In relation to either diabetic, senile cataract or other ocular diseases, it is important to bear in mind the bioavailability of phytochemicals and their metabolites to the eye bulb or lens in particular. In the anterior chamber of the eye, the aqueous humour bathes the anterior surface of the lens, providing all oxygen and nutrient requirements. It is therefore most probably via this route that any dietary nutraceutical would reach the lens. Thus, facultative topical route of administration via eye-drops would be ideal for flavonoid extracts to apply. Up-to-date ophthalmic research is evolving novel platforms for sustained release of drugs, e.g. hydrogel contact lens [138] or molecularly imprinted contact lens with enhanced loading and delayed release of therapeuticals [139]. Of the many future challenges with drug research, one of the most required would be to make the routes of administration more effective.

The actual molecular interactions of polyphenols with biological systems remain mostly specu-

lative [140]. A better knowledge about the nature and biological consequences of interactions of polyphenols with cell components might contribute to the development of nutritional and pharmacological strategies focused on preventing the onset and/or the consequences of diabetic cataract [141]. Considerable attention is given to proper extrapolation of in vitro proven beneficiary action of polyphenols to in vivo conditions. In order to understand the peculiar mechanisms of action for phytochemicals at molecular level, thorough investigations are required. Luckily, as never before, laboratories in the 21st century are equipped with powerful high-resolution genomic and proteomic bio-analytical tools. The good news for all suffering from degenerative changes of eye lens proteins is that we may be closer than ever to more comprehensive results that might help to prevent cataract.

CONCLUSIONS AND RECOMMENDATIONS

Phytochemicals appear to have a potential role both manifestly in prevention and occasionally in treatment of various lifestyle diseases. This review is dedicated to debilitating eye lens opacification that lead to diabetic cataract, as one of many metabolic and age-related ailments. Additional nutraceutically oriented research is found to be necessary to establish the efficacy of the preventive and therapeutic attributes of individual phytochemicals that may be operative in ocular problems related to diabetes mellitus and/or aging. Toxicological aspects of unusually high doses of natural dietary supplements have to be considered. Future strategies should be looking into the synergistic effect of bioactive phytochemical components, specifically within the whole food matrix, including fruits and/or vegetables. More efficacious routes of administration e.g. via sophisticated eye-drops, should be thoroughly investigated. Thanks to ongoing progression in molecular biology, precise phytochemical mechanisms of action might most probably be revealed during the next decade. In the meantime, incorporating 3–5 daily servings of either berry fruits or green leaf vegetables rich in flavonoides in the diet may be regarded as a healthy choice for preserving ocular health in the challenged organism.

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