Review Article

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Nutraceuticals for Prevention of Ophthalmic Diseases

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Abstract

This review focuses on the vitamins, minerals and antioxidants that have been described for reducing the risk of eye related diseases. Nowadays there is insufficient source to recommend routine nutritional supplementation in healthy adults for prevention age related eye disease. Consumption of antioxidant rich foods and nutraceutical formulas reduced the risk of macular degeneration. Many formulated dietary supplements that are sold in the market were clinically proved for their efficacy to treat eye disease. Nutraceutical can offer some therapeutic potential in glaucoma management but to lack of clinical trials examine their benefits for glaucoma limits their current therapeutic use. There is many complications to treat cataract by surgery such as it may raise the intraocular pressure, iris prolapse, cystoid macular edema and Posterior Capsular Opacification (PCO). Therefore as an alternative food and nutraceutical is the best natural way to cure the eye diseases because of their presumed safety and therapeutic effects.

Keywords: Age-related macular degeneration; Glaucoma; Cataract; Antioxidants; Dietary supplements

Introduction

In elderly people visual impairment is considered as health problems that significantly disturbs quality of life of millions worldwide. In developed countries, the most common cause of blindness in worldwide is age-related macular degeneration. By the year 2050, in US the prevalence of AMD is anticipated to increase to 22 million while the global prevalence is predictable to increase to 288 million by the year 2040. Glaucoma is the second main cause of blindness after cataract. It is concomitant with increased ocular pressure and when left untreated, patients may experience their sight completely loss. It is usually characterized by structural changes to the optic nerve head. In worldwide around 45 million people are blind, beyond 17.6 are cataract cases. As per national blindness survey, prevalence of blindness was reported about 8% in the age group more than 50 [1].

Literature Review

Ophthalmic diseases

Age related macular degeneration: ARMD is an eye disease which is related to retina, due to this disease, the part of the retina called the macula is damaged. Due to damage of macula, the fine points are not clear. When it becomes growing, it destroys the central vision which is necessary for reading books, recognizing faces, watching television, sewing driving and performing other daily everyday jobs. It leads to severe vision loss in adults over age 50. Conventionally ARMD is classified into two types mainly dry (non-exudative, non-neovascular) form which is more common and presents as geographical atrophy in its advanced stage. Wet (exudative, neovascular) form which is relatively less common but is associated with rapid advance to vision loss [2].

According to a recent clinical classification ARMD is divided into:

- Early AMD (Drusen size more than 63 µm less than 125 µm).
- Intermediate AMD (Drusen size more than 125 µm).
- Late AMD (Neovascualr AMD and geographical atrophy).

Its prevalence probable to rise as a consequence of exponential population ageing. Prevalence of AMD differs from 1.2% to 29.3%. Three population based studies-the beaver dam eye, the rotterdam and blue mountain eye. The study report the prevalence rates to be 1.7% in US, 1.4% in Australia and 1.2% in Netherland respectively. Jayshree MP report that higher prevalence was noted in females. Dry AMD was noted more than wet AMD and late AMD was seen less than early AMD. Jayshree diagnosed 120 patient with ARMD and revealed that when the age of subjects increased prevalence also increased and most of them were in the age group of 60-70. Early AMD (71.7%, n=86) and late AMD was seen 28.3% (n=34).

Ritu Sharma, et al., conclude that prevalence of dry AMD (20.5%) is evident in the population of Punjab which is facilitated individually by age (≥ 66 yrs), DBP (>80 mmHg), alcohol drinking and smoking. Nupura, et al., reviewed and reported various antioxidants, vitamins, minerals, age related eye disease study like formulas and berry extracts [3].

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Antioxidants

Xanthophylls: Phylloxanthins are the compounds belonging to the carotenoid group. They are mainly found in dark green leafy vegetables and in egg yolk. They are yellow pigments because these carotenoids exists in high concentration in the macula that occur widely in nature and form one of two major division of the carotenoid group, the other division is formed by the carotene. Xanthophyll mainly composed of macular pigments-lutein and zeaxanthin as well as β carotene are known to have protective effects against eye diseases include AMD, cataract and retinitis pigmentosa [4].

These carotenoid act in the biological system as ability to filter short wavelength light which may help to protect the outer retina and retinal pigment epithelium from oxidative stress, a modulator in the signal transduction pathways, keeper of redox balance and aid in cell membrane stability. The association between AMD risk and lutein and zeaxanthin has been explored in several large scale epidemiological studies. Hock Eng Khoo, et al., noted that the high intake of xanthophyll containing foods has been attributed to the elevated levels of plasma lutein and zeaxanthin [5]. The elevated level of plasma helped to prevent AMD in the elderly. Johnson, et al., suggested that consumption of lutein is recommended to be higher than zeaxanthin amongst all age groups. According to the eye disease control study, advanced AMD risks are reduced by 43% in those participants who are in the highest quintile of dietary carotenoid intake when compared with the lowest quintile. Participants in the top tertile of intake (≥ 942 µg/day) had a decreased risk of incident neovascular AMD and those with above intakes (743 µg) had a reduced risk of reticular drusen. In 2006, ARMD study concluded that xanthophyll diets helps to protect against intermediate AMD in female patients less than 75 yrs. of age.

Hock Eng, et al., showed that serum concentration of lutein and zeaxanthin are essential for smokers than the non-smokers they have lower macular pigment optical density and shows inflammation of macular pigment among heavy smokers was higher than the non-smokers. Measurement of Macular Pigment Optical Density (MPOD) helps to measure the non-invasive retinal lutein and zeaxanthin [6].

Omega-3 fatty acids: Main omega 3-fatty are Alpha-Linolenic Acid (ALA-short chain), Docosahexaenoic Acid (DHA-long chain) and Eicosapentaenoic Acid (EPA-long chain). Omega 3 fatty acids plays an important role in reducing the strokes or incidence related to cardiovascular disease. In these 3 omega fatty acids, DHA is present in high concentration in the photoreceptor segment of the retina and due to deficiency of DHA it has been involved in AMD onset. For advanced AMD, higher intake of DHA and EPA were associated with a lower risk of progression. Those participants who intake highest omega 3-long chain polyunsaturated fatty acids were approx. half as to be expected to take neovascular AMD at baseline [7].

The risk of hemorrhagic stroke is potentially augmented by antithrombotic effect of fish oil. With simultaneous administration of agents like warfarin and aspirin, high dose of fish oil does not increase the risk of bleeding. The FDA issued an advisory statement that pregnant women, breast feeding mothers and children avoid eating seafood high in mercury. Fish oil supplements are generally regard as safe because most industrial purification process eliminate these toxins [8].

Berry extracts

US department of agriculture published that blueberry shows good antioxidant properties among 100 common food items and claim to protect eyes from AMD. Another berry wolfberry (Goji berry) also shows protecting properties which has been long used in Traditional Chinese Medicine (TCM). Most of the products of berry extracts should not be recommended because there are no legal requirement for quality controls of these extracts [9].

Vitamins

It is an essential micronutrient that an organism needs in small quantities for proper functioning but those who consumed increased amounts of fruits and vegetables rich in vitamin A helps to reduce the risk the stage of AMD.

Vitamin C: It is recognized as ascorbic acid. It is one of the safest and effective antioxidant that protects protein, lipids, carbohydrates and nucleic acids from free radicals and Reactive Oxygen Species (ROS) damage. San Giovanni, et al., revealed that a reduced likelihood of neovascular AMD in subjects reporting high intake of β carotene, vitamin C and vitamin E. Christen, et al., reported that users of vitamin C had a higher risk of macular degeneration than the users of vitamin E [10].

Vitamin E: It is powerful and effective antioxidant that helps to repair damage cells and scavenges the free radicals. William G, et al., revealed that long term alternate day use of 600 IU of natural source vitamin E had no large beneficial or harmful effects on risk of AMD. Due to deficiency it may lead to lipofuscin accumulatioz, retinal damage and loss of photoreceptors [11].

Minerals

Zinc: In studying eye tissue samples, it is found that deposits, which are hallmarks of ARMD, contain large amounts of zinc. Zinc supplements are mainly given to patients to help boost weak immune systems. Dietary self-administration of zinc (200 mg) daily for up to 24 months had also proven to reduce the visual loss as compared to the placebo group [12]. According to the systemic review conducted by Vishwanathan, et al., examined the evidence on zinc intake from foods for prevention ARMD and conclude that zinc treatment may be effective in preventing progression to advanced AMD. Zinc supplementation alone may not be sufficient to produce clinically changes in visual perception.

Selenium: It helps in reducing the risk of AMD. Glutathione peroxidase act as mediator to reduce hydrogen peroxides which is present inside the cell. A low intake of dietary selenium is known to cause a reduction of total Polyunsaturated Fatty Acids (PUFAs) in the retinal pigment epithelium and retinal rod outer segments of laboratory animals [13].

		Plant products	Provitamins has to be metabolized into an active form	Important for rhodopsin which act as an antioxidant
B-complex	Thiamin (B1)	Animal/Plant products	Some flavonoids may antagonize vitamin B1	Involved in catabolism of amino acids, carboxylase, cell division and growth and DNA synthesis
C	Ascorbic acid	Plant products	Oxidized form of vitamin is reduced by glutathione which maintain vitamin C in reduced form	Important for non-enzymatic antioxidant
D	Cholecalciferol	Sunlight exposure	In the liver vit. D is converted to 25-hydroxyvitamin D which is used as a biomarker	Responsible for intestinal absorption of several minerals such as Ca, Mg and Zn

Coenzyme Q: The production of Adenosine Triphosphate (ATP) by oxidative phosphorylation give the cofactor and of that the electron transport chain, a membrane stabilizer gives an essential of coenzyme Q.

Table 4: The compound protects retinal cells against oxidative stress *in vivo* and *in vitro*.

1	Nucci and colleagues	On intraocular administration of coenzyme Q, it was observed by microdialysis that it affords neuroprotection in the retina of rats subjected to ischemia preventing glutamate increase
2	Lee and colleagues	Compound inhibits glutamate excitoxicity and oxidative stredd mediated mitochondrial alteration in glaucomatous DBA/2J mice. It is also preserved mitochondrial DNA content and mitochondrial transcription factor A in the retina
3	Noh and colleagues	Coenzyme Q protects the Optic Nerve Head (ONH) astrocytes against stress mediated mitochondrial dysfunction or variation in glaucoma
4	Nakajima and colleagues	Retinal Ganglion Cells (RGC-5) is a combination of coenzyme Q and trolox and referent of water soluble vitamin E which prevents the cell damage more effectively than the alone
5	Parisi and colleagues	On administration of coenzyme Q with vitamin E in open angle glaucoma indicates a favorable effect on the retinal function with enhancement of the visual corticol responses

Flavonoids: Flavonoids are used to demonstrate anti-inflammatory and neuroprotective effect that may reduces damage from oxidative stress and it is a large family of phytonutrient compound widely distributed and grouped into five main categories (flavonols, flavan-3-ols, flavones, flavanones and anthocyanidins).

It also give the beneficial effects on multiple disease states including cancer cardiovascular diseases and neurodegenerative disorders. In the studies of *in vivo* and *in vitro* also reported the beneficial effects of flavonoids in ocular diseases that shows meta-analysis with no statistically significant effect of flavonoids on lowering intraocular pressure.

Nakayama and colleagues demonstrated the neuroprotective potential give the three types of flavonoids compound is kaempferol 3-O rutinoside (niclotiflorin), quercetin 3-O rutinoside (rutin) and quercitrin using rat under stress conditions (hypoxia, excessive glutamate levels and oxidative stress. Due to these stress conditions all compounds considerably increased the RGC survival rate but nicotiflorin and rutin were more active than quercetrin.

Citicoline: It is a natural constituents of all cells that serves phosphatidyl choline synthesis and attenuates free fatty acids release and re-established the level of cardiolipin phospholipid components of inner mitochondrial membrane and also increases neurotransmitter levels in a central nervous system and the retina that gives and improvement of retinal and of the visual pathway function in patients with glaucoma.

For example, in partial crush injury of rat optic nerve model practical in was found effective in rescuing RGC and their axons *in vivo* against delayed degeneration triggered by optic nerve crush. Citicoline increase retinal expiration of apoptotic regulating protein Bcl2, indicating one of the mechanism which may be engaged in the neuroprotective effect of a compound. Moreover after intravitreal injections of kainic acid, citicholineg counteracts increase expression of NOS isoforms and decreased ERK1/2 kinase activation caused by KA, as it is rescued damage of a disease through anti apoptotic effect probably acting as an BDNF mimic that was affected with the reduction of expression of active forms of caspase 9 and 3.

Polyunsaturated fatty acids: The essential fatty acids of polyunsaturated are omega 3 and omega 6 both are concentrated in the phospholipids of a cell membranes throughout the human body, but especially in the brain, heart, retina and testes. Essentials of omega 3 and 6 hour of the special interest due to their reported anti-inflammatory, hypolipidemic and vasodilatory capacities. Some of the diets with increases omega 3 and decrease with omega II favor and increase in IOB reducing synthesis of the PG after leading to the decrease in uveoscleral outflow. Schenebelen and colleagues confirmed that a sixth month of supplementation with the combination of omega 3 and omega 6 phase is more effective than single supplementation since EPA+DHA (docosahexaenoic acid)+gamma linolenic acid diet combination preventive retinal cell structures and decrease in glial cell activation induced by the elevation of IOP in rats.

Cataract

Clouding of the eye's natural lens, results in the loss of vision, due to aging, infection in newborn babies, injury or poor development prior to birth or during childhood, to prevent cataract there is urgent need for inexpensive, non-surgical approaches such as therapeutic action.

- Antioxidants or ROS scavengers
- Aldose reductase inhibitors
- Antiglycating agents
- Inhibitors of lens epithelial cell apoptosis

Antioxidants

To prevent cataract, various antioxidants are used as flavonoids, carotenoids, ascorbic acid, tocopherol, caffeine and pyruvate.

Flavonoids: Flavonoids are C6-C3-C6 compounds with fifteen carbon atoms. It exert antioxidant effects due to their ability to scavenge free radicals, donate hydrogen and act also as singlet oxygen quenchers and metal ion chelators. Examples-myrcetin, quercetin, rhamnetin, morin, diosmetin, naringenin, apigenin, catechin, kaempferol and flavones. Obtained from fruits such as apple, grapes, bananas, cherries and from green leafy vegetables. Flavonoids are also referred as vitamin P, they are found as a highly potent inhibitors of aldose reductase. The best described biological activity of this group covered by number of excellent reviews (Table 5).

Table 5: Flavonoids inhibits xanthine oxidase production.

Authors	Reviews
Hamasaki	Flavonoids inhibits xanthine oxidase, the enzyme responsible for superoxide anion production
Nagao	3-methyl quercetin was found to inhibit xanthine oxidase, even more efficiently than the aglycone form of quercetin
Bors and Michael	Presence of 3 hydroxyl group increases the radical scavenging activity
Butkovic	Flavonoids were found to scavenge efficiently the model free radicals of 2,2-diphenyl-1-picrylhydrazyl and α,γ-bisdiphenylene-β phenylallyl
Amic	Quercitin is the most scavenger of reactive oxygen species

Vitamins: Robertson JM, et al. revealed that cataract patients tended to have lower serum levels of vitamin C and E than the control subjects.

Biochemical evidence suggests that oxidative stress caused by accumulation of free radicals is involved in the pathogenesis of senile cataracts, therefore it might be expected that vitamins C and E prevent or retard the process (Table 6).

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Table 7: Component of vitamins.

1	Vitamin A	It is a component of the protein rhodopsin which helps to see in light conditions
2	Vitamin E	Alpha tocopherol is a component of vitamin E which has powerful antioxidant properties
		Corn oil and wheat germ oil are common source of vitamin E
3	Vitamin C	It has also antioxidant property that helps protect against oxidative damage. It preserves glutathione level and protect the Na/k pump they are mainly found in amla and other citrus fruits
4	Vitamin B	It helps to reduce the rate of nuclear cataract which occur deep in its centre or nucleus

Carotenoids: From family of 700 compounds of carotenoid, 20 have been detected in human plasma and tissues from these two lutein and zeaxanthin are two dietary carotenoids which are present in human eye lens. It has been reported that these compounds can filter harmful short wave blue light which reduce H_2O_2 mediated damage of lens protein, lipid and DNA and function as antioxidants by stabilize membrane integrity. Astaxanthin is one of the carotenoid which has 100 fold higher antioxidant activity than alpha tocopherol, due to this it is called as 'super vitamin E'. An *in vivo* study conducted in quails confirmed that lens carotenoid can be increased by dietary intake of zeaxanthin and in streptozotocin-induced diabetic rats showed that intake of lutein supplementation was effective in preventing and progression of cataract.

Discussion

Aldose reductase inhibitors

Polyol sorbitol accumulated in the lens that cause diabetic cataract. The enzyme aldose reductase present in the lens which converts glucose into sorbitol and the reason for accumulation of sorbitol in eye lens. To prevent the diabetic cataract aldose reductase inhibitors can be used as therapeutic agents. Some flavonoids inhibits aldose reductase activity at different extent. Mainly quercetrin and their derivatives show 100% inhibition activity. A recent study was demonstrated by Varma et al., that the administration of pyruvate prevented cataract development by inhibiting the activity of aldose reductase in diabetic rats.

Antiglycating agents

These agents' help in prevention of cataract are: Polyphenols, polysaccharides.

Polyphenols: Polyphenols are dietary antioxidants, which are commonly found in fruits, vegetables, cereals, seeds, nuts, chocolate and beverages such as coffee, tea and wine. They show strong antiglycating activity. Based on their chemical structure, these are classified as phenolic acids and flavonoids.

Terpenes, carotenoids and polyunsaturated fatty acids:

A terpene 8, 12-Labdadiene-15,16-dial (labdadiene) and 5,6-Dehydrokawain (DK) abstract from the rhizome of *Alpinia zerumbet*, which have potential to inhibit glycation-induced protein oxidation. Number of antioxidants such as carotenoids, polyunsaturated fatty acids and polysaccharides can be produced in microalgae.

Polysaccharides: The pericarp fruit (*Dimocarpus longan*) contains polysaccharide that acts as free radical scavenger which competes with glucose for binding to free amino group in proteins, which also reduces the concentration of glycation targets in proteins. Polysaccharides from pumpkin (*Cucurbita moschata*) have also shown antiglycating activity.

Inhibitors of lens epithelial cell apoptosis: Oxidative stress is the major cause of Human cell Epithelial (HPE) cell apoptosis which leads to cataract formation. Xing Chao, explored the effect of parthenolide on hydrogen peroxide induced apoptosis in Human Lens Epithelial (HLE) cells. Parthenolide is component of tanacetum parthenium. To induce apoptosis, different concentrations (50,100,200 µmol/L) of H_2O_2 were treated with HLE cells. Only the 200 µmol/L H_2O_2 caused a morphological changes such as cytoplasmic condensation and increased in intercellular gaps.

Parthenolide: Modulate apoptosis by regulating signaling pathways such as:

- Nuclear factor-kb (Involved in HOInduced damage to HLE cells)
- Phosphoinositide 3-kinase (PIK)
- Mitogen Activated Protein Kinases (MAPKs)
- Extracellular Signal Regulated Kinases (ERK1)

Both MAPKs and ERK1 increased proliferation in tumor cells and its inhibitors have become anticancer agents.

Impacts the treatment of inflammation by inhibiting nuclear factor-kb activation: Sumeer singh, had report the cataract population in south India and revealed the prevalence of cataract about 44.6%, 43.6% in the rural, urban population respectively. R Aarthi, had report that the prevalence of cataract among male was 66.9% (95% CI: 58.2%-74.8%) and 60.4% in female (95% CI: 53.7%-66.9%).

Conclusion

Nutraceutical are present in most of the food ingredients with varying concentration. By manipulating the foods, the concentration of active ingredients can be increased. By implementing one or more mechanism singly or simultaneously of nutraceutical, they play their important role in prevention of ophthalmic disease. Nutraceutical mostly followed the mechanism of antioxidants and vitamins in age related eye disease. Due to high doses of natural dietary supplements, toxicology aspects have to be considered. Due to lack of plenty evidence in elderly people for primary prevention ARMD, antioxidant supplements should not be considered regularly. Antioxidant supplements in ARMD, lutein and zeaxanthin are commonly used in diagnosed ARMD to slow the progression of ARMD. In glaucoma management, nutraceutical may provide some therapeutic potential but due to lack of clinical trials limit their current therapeutic use.

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