Natural Therapies for Ocular Disorders Part Two: Cataracts and Glaucoma

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Abstract

Pathophysiological mechanisms of cataract formation include deficient glutathione levels contributing to a faulty antioxidant defense system within the lens of the eye. Nutrients to increase glutathione levels and activity include lipoic acid, vitamins E and C, and selenium. Cataract patients also tend to be deficient in vitamin A and the carotenes, lutein and zeaxanthin. The B vitamin riboflavin appears to play an essential role as a precursor to flavin adenine dinucleotide (FAD), a co-factor for glutathione reductase activity. Other nutrients and botanicals, which may benefit cataract patients or help prevent cataracts, include pantethine, folic acid, melatonin, and bilberry. Diabetic cataracts are caused by an elevation of polyols within the lens of the eye catalyzed by the enzyme aldose reductase. Flavonoids, particularly quercetin and its derivatives, are potent inhibitors of aldose reductase.

Glaucoma is characterized by increased intraocular pressure (IOP) in some but not all cases. Some patients with glaucoma have normal IOP but poor circulation, resulting in damage to the optic nerve. Faulty glycosaminoglycan (GAG) synthesis or breakdown in the trabecular meshwork associated with aqueous outflow has also been implicated. Similar to patients with cataracts, those with glaucoma typically have compromised antioxidant defense systems as well. Nutrients that can impact GAGs such as vitamin C and glucosamine sulfate may hold promise for glaucoma treatment. Vitamin C in high doses has been found to lower IOP via its osmotic effect. Other nutrients holding some potential benefit for glaucoma include lipoic acid, vitamin B12, magnesium, and melatonin. Botanicals may offer some therapeutic potential. *Ginkgo biloba* increases circulation to the optic nerve; forskolin (an extract from *Coleus forskohlii*) has been used successfully as a topical agent to lower IOP; and intramuscular injections of *Salvia miltiorrhiza* have shown benefit in improving visual acuity and peripheral vision in people with glaucoma.

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Introduction

Part one of this article was published in the October 1999 issue of *Alternative Medicine Review* and discussed nutritional and botanical approaches to conditions of the retina. This second part covers alternative treatments for nonretinal disorders: senile cataracts, diabetic cataracts, and chronic open-angle glaucoma.

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A large percentage of blindness in the world is nutritionally preventable.[1] The author of this comment was referring primarily to the use of vitamin A to prevent corneal degeneration associated with a vitamin A deficiency; however, there is considerable evidence that many other eye conditions, which are leading causes of vision impairment and blindness, also may be preventable with nutritional supplementation, botanical medicines, diet, and other lifestyle changes. In addition, a number of nutrients hold promise for the treatment of already existing cataracts and glaucoma.

Senile Cataracts

Senile cataracts are the leading cause of impaired vision in the United States, with a large percentage of the geriatric population exhibiting some signs of the lesion. Over one million cataract surgeries are performed yearly in this country alone.[2] Cataracts are developmental or degenerative opacities of the lens of the eye, generally characterized by a gradual painless loss of vision. The extent of the vision loss depends on the size and location of the cataract. Cataracts may be located in the center of the lens (nuclear), in the superficial cortex (cortical), or in the posterior subcapsular area. Cataracts are also classified according to their color, which is consistent with location and density of the cataract. Pale yellow cataracts are typically slight opacities of the cortex, subcapsular region, or both; yellow or light brown cataracts are consistent with moderate to intense opacities of the cortex, nucleus, or both; and brown cataracts are associated with dense nuclear cataracts.[3]

Diagnosis

Symptoms include near vision image blur, abnormal color perception, monocular diplopia, glare, and impaired visual acuity, and may vary depending on location of the cataract. For example, if the opacity is located in the center of the lens (nuclear cataract), myopia is often a symptom, whereas posterior subcapsular cataracts tend to be most noticeable in bright light.[4] Ophthalmoscopic examination is best conducted on a dilated pupil, holding the scope approximately one foot away. Small cataracts appear as dark defects against the red reflex, whereas a large cataract may completely obliterate the red reflex. Once a cataract has been established, a referral for slit-lamp examination, which provides more detail on location and extent of opacity, is recommended.
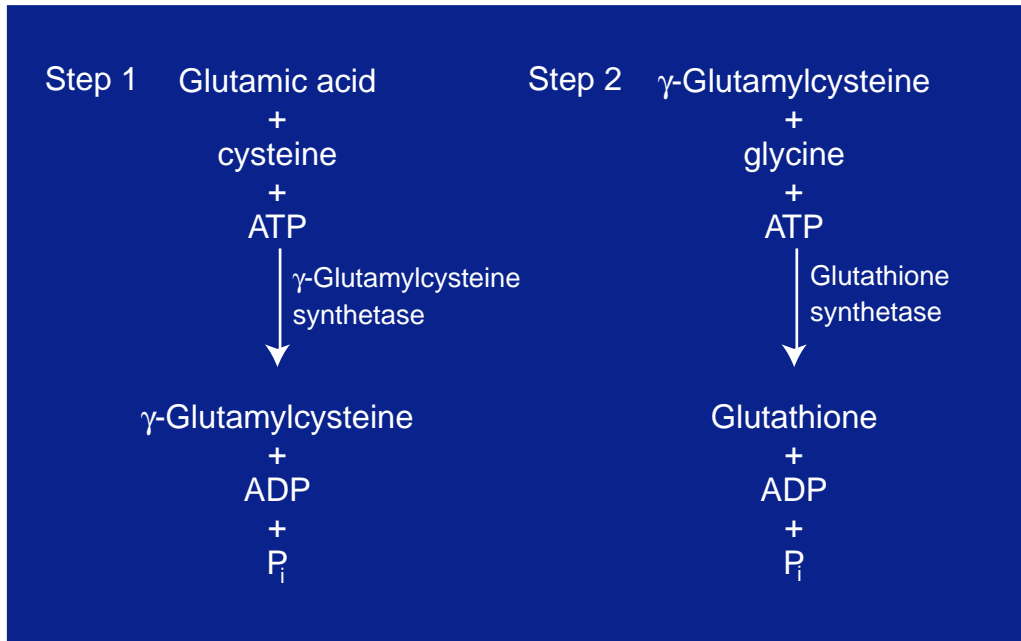
Etiological/Risk Factors

Factors contributing to cataract formation include aging, smoking,[5] exposure to UV-B and ionizing radiation,[6] oxidative stress (secondary to other risk factors such as aging or smoking),[7] dietary factors,[8] increased body weight (above 22-percent body fat), central obesity,[9] and family history. Medications and environmental exposures which may contribute to cataract formation include steroids, gout medications, and heavy metal exposure. Cadmium, copper, lead,[10] iron, and nickel[11] have all been found in cataractous lenses. A high level of cadmium in the lens is associated with smoking and can contribute to accumulation of other heavy metals.[10] Conditions which predispose to cataracts include diabetes, galactosemia, neurofibromatosis, hypothyroidism, hyperparathyroidism, hypervitaminosis D, infectious diseases such as toxoplasmosis, and several syndromes caused by chromosomal disorders.[2]

Mechanisms Involved in the Pathophysiology of Cataracts

Cataracts are characterized by electrolyte disturbances resulting in osmotic imbalances. Derangements in the function of the membrane resulting in ion imbalance may be due to increased membrane permeability or to a depression of the Na^+/K^+ pump because of interference with the enzyme Na^+/K^+ ATPase.[12]

Figure 1: Synthesis of Glutathione in the Lens

Step 1   Glutamic acid
+
cysteine
+
ATP

γ-Glutamylcysteine synthetase

γ-Glutamylcysteine
+
ADP
+
P_i

Step 2   γ-Glutamylcysteine
+
glycine
+
ATP

Glutathione synthetase

Glutathione
+
ADP
+
P_i

Cataracts are also characterized by aggregates of insoluble proteins.[12]

Oxidative insult appears to be involved as a precipitating factor in all cataracts. Lens proteins typically remain in their reduced form. However, in cataractous lenses, the proteins are found in an insoluble, oxidized form. Oxidation may occur as a result of many factors (see Etiological Factors). Higher levels of hydrogen peroxide have been found in cataractous lenses when compared to normal controls.[13] Normally the lens contains significant levels of reduced glutathione (GSH), which keeps the proteins in their reduced form. However, there are significantly lower levels of GSH in cataractous lenses.

Advanced glycation end products (AGE) appear to play a role in cataract formation. Researchers have tested the hypothesis that the major AGE formed in the lens has an EDTA-like structure, capable of binding to copper. They found copper binding was 20-30 percent greater in the older, cataractous lens protein fractions than in young, non-cataractous fractions. The pro-oxidant copper precipitates further oxidation,

creating a vicious cycle. The researchers hypothesized that, "chelation therapy could be beneficial in delaying cataractogenesis."[14] Other researchers have confirmed the involvement of transition metals, copper and iron, as instigators of ascorbyl and hydroxyl radical formation in cataracts.[15]

The Role of Glutathione in Lens Metabolism

In order to fully understand the mechanisms involved in cataract formation and the link to nutritional prevention, it is important to understand the role glutathione and its enzyme co-factors play in metabolism within the lens. *In vitro* studies of incubated lenses from animals as well as humans have helped elucidate the mechanisms involved.

The lens of the eye is avascular, depending entirely on passive diffusion, active transport, and intra-lens synthesis for nutrients and other substances important for metabolism. As a result, the content of the surrounding intraocular fluids (aqueous humor) is relevant. While levels of GSH are high in the lens, they are relatively low in the aqueous humor; thus, glutathione appears to be synthesized within the lens. Glutathione is composed of the amino acids cysteine, glutamic acid, and glycine, and its synthesis within the lens takes place in two steps (Figure 1). Cataractous lenses can demonstrate dramatic decreases in GSH, as much as 81 percent, when compared to normal lenses.[3] Researchers have examined

this phenomenon in an attempt to determine whether low GSH is due to decreased synthesis or increased degradation. Decreases in the enzymes involved in both synthesis (γ-glutamyl transferase) and recycling (glutathione reductase) of GSH from oxidized glutathione (GSSG) lend credence to the theory that synthesis is diminished in cataractous lenses.[3] These same researchers found a decrease in the activity of enzymes of GSH degradation (glutathione peroxidase and glutathione s-transferase) which should result in an increased rather than a decreased accumulation of GSH. They therefore concluded that the loss of activity of these enzymes was not enough to offset the losses associated with decreased synthesis. They also did not rule out the possible loss of GSH from the lens via membrane leakage.

There are several ways in which glutathione or its depletion can affect the opacity of the lens. A review by primary researchers on glutathione metabolism and its relationship to cataract formation outlines three possible mechanisms of cataract prevention by glutathione:[16] (1) maintaining sulfhydryl (SH) groups on proteins in their reduced form preventing disulfide cross-linkage; (2) protecting SH groups on proteins important for active transport and membrane permeability; and (3) preventing oxidative damage from hydrogen peroxide (H_2O_2).
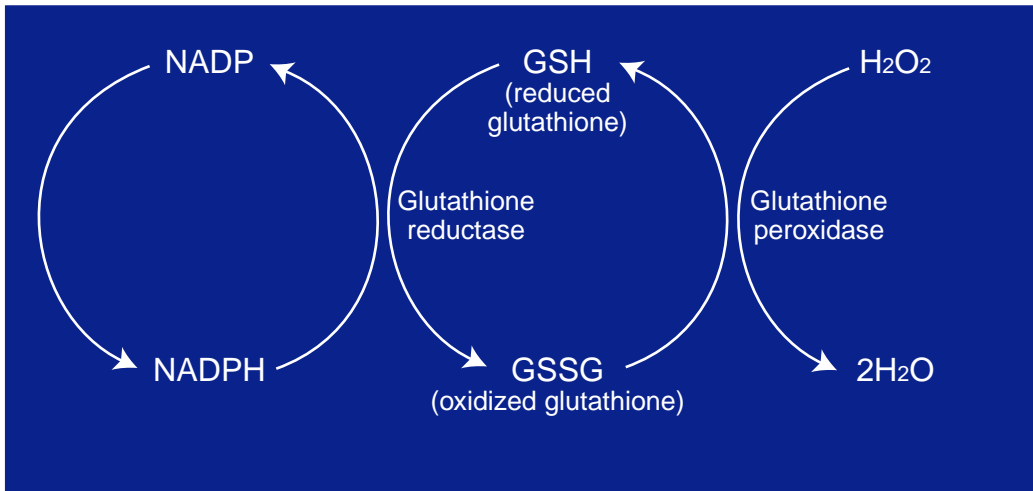
Considering the first mechanism by which GSH can protect lenses from opacities, there is an increase in high molecular weight (HMW) proteins in cataractous lenses. These protein aggregates contribute to lens opacity and are found particularly in dense cataracts. Reddy and Giblin examined x-ray-induced cataracts in rabbits and found increased levels of disulfide bonds, confirming their assertion that oxidation of SH groups resulted in disulfide bond formation and HMW proteins. They also found that SH groups on proteins only become oxidized when levels of GSH drop below some critical level.[16] Other researchers

have found an increase in disulfide bonds in human cataractous lenses.[17]

Maintaining normal cell volume and transport of electrolytes are important factors in lens transparency. Glutathione may play a role in maintaining normal lens permeability and active cation transport by protecting sulfhydryl groups in the cell membrane from oxidation. Oxidation of SH groups on the surface of the cell membrane results in increased permeability, and oxidation of important SH groups of Na^+/K^+ ATPase impedes active transport. Reddy et al examined the effect of GSH depletion on rabbit lenses and found it directly led to increased membrane permeability.[18] While GSH depletion did not directly impair active transport, it resulted in increased susceptibility of the Na^+/K^+ pump to oxidative damage by H_2O_2. Oxidation of GSH resulted in a 70-percent decrease in active transport and a two-fold increase in membrane permeability. Other experiments have found that lens-epithelial-GSH needs to be depleted by about 60 percent for these changes to occur. The authors point out that, "the lens has a remarkable ability to regenerate reduced glutathione." However, they found that, although the change in membrane permeability was reversible with the regeneration of GSH, the decrease in pump activity was irreversibly affected.[16]

H_2O_2 is found in the aqueous humor in humans as well as other species. GSH is involved in detoxifying this reactive oxygen species to water in a coupled reaction involving NADPH (Figure 2). Without detoxification the peroxide radicals would damage the lens membranes and susceptible protein groups. The researchers found both normal human and rabbit lenses with high GSH content were rapidly able to detoxify H_2O_2 in culture medium.[16] Lenses pretreated with methyl mercury, which decreased the concentration of GSH by 75 percent, were less able to detoxify the peroxide radicals.

Figure 2: Metabolism of Hydrogen Peroxide by Glutathione

NADP

GSH (reduced glutathione)

H_2O_2

Glutathione reductase

Glutathione peroxidase

NADPH

GSSG (oxidized glutathione)

$2H_2O$

Other researchers have postulated a possible diffusion problem. Normally GSH is synthesized and regenerated in the lens cortex and then diffuses to other areas of the lens. Cataracts of the elderly are primarily in the nucleus. Researchers examined normal human lenses *in vitro* and found the older ones appeared to have a barrier to diffusion of GSH from the cortex to the nucleus.[19]

Specific Nutrients and Prevention of Cataracts

Oxidation of lens proteins is part of the pathophysiology of cataracts. Therefore, it is no surprise that antioxidants may help prevent the formation of cataracts.

Carotenes and Vitamin A: Epidemiological Evidence

Levels of nutrients, including carotenoids, have been examined in human cataractous lenses after extraction using high performance liquid chromatography. Vitamins A and E and the carotenoids lutein and zeaxanthin were found. The newer, epithelial/outer cortex layer had more carotenoids, tocopherol, and retinol (approximately 3-, 1.8-, and 1.3-fold higher, respectively) than the older, inner cortex/nuclear portion.[20] Other studies have quantified significant levels of lutein, zeaxanthin, and alpha- and gamma-tocopherol in the lens.[21]

A prospective study of the effect of carotenes and vitamin A on the risk of cataract formation was conducted as part of the Nurses' Health Study. A total of 77,466 female nurses, ages 45-71 years, were included in the study, which involved food-frequency questionnaires over a 12-year period. After other risk factors were controlled for, including smoking and age, those in the highest quintile for consumption of lutein and zeaxanthin had a 22-percent decreased risk of cataract extraction compared with those in the lowest quintile.[22]

Another cohort of the Nurses' Health Study followed 50,823 women, ages 45-67, for eight years and found women in the highest quintile of vitamin A consumption had a 39-percent lower risk of developing cataracts compared to women in the lowest quintile.[23]

In a similar study of male health professionals in the United States, 36,644 participants, ages 45-75 years, were followed for eight years with periodic dietary questionnaires. Men in the highest quintile for lutein and zeaxanthin intake had a 19-percent decreased risk of cataract extraction when smoking, age, and other risk factors were controlled for.[24] Neither the women nor the men demonstrated a decreased risk of cataract with intakes of other carotenoids (α-carotene, β-carotene, lycopene, or beta-cryptoxanthin). It is hypothesized the protective effect of the carotenoids may be due to quenching reactive

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oxygen species generated by exposure to ultraviolet light.[25]

The Beaver Dam Eye Study examined risk for developing nuclear cataracts in 252 subjects who were followed over a five-year period. Only a trend toward an inverse relationship between serum lutein and cryptoxanthin and risk of cataract development was noted.[26]

Vitamin E: Animal, Epidemiological, and Clinical Studies

As a fat-soluble antioxidant, it is reasonable to predict a positive role for vitamin E as a cataract preventive in the lens cell membrane. Animal, epidemiological, and clinical studies help confirm this hypothesis. A placebo-controlled animal study found 100 IU d-alpha-tocopherol injected subcutaneously prevented ionizing radiation damage to the lens, which did occur in rats not supplemented with vitamin E.[27] Two other animal studies using vitamin E instilled in the eyes as drops confirmed the preventive effect of vitamin E, at least when used topically.[28,29]

Several human studies have found low levels of vitamin E intake are associated with increased risk for cataract development. An epidemiological investigation examined self-reported supplementary vitamin consumption of 175 cataract patients compared to 175 matched individuals without cataracts. The cataract-free group used significantly more vitamin E (p=0.004) and vitamin C (p=0.01) than the cataract group, resulting in at least a 50-percent reduction in cataract risk in the supplemented group.[30] An Italian study compared 207 patients with cataracts to 706 control subjects in a hospital setting. Vitamin E, in addition to a number of other nutritional factors, was associated with a decreased risk for cataract.[8]

The Vitamin E and Cataract Prevention Study (VECAT) is a four-year, prospective, randomized, controlled trial of vitamin E versus placebo for cataract prevention in a population of healthy volunteers, ages 55-80 years.[31] Although results are still pending, data was collected on prior use of vitamin E and incidence of cataract in 1,111 participants. A statistically significant relationship was found between past vitamin E supplementation and prevention of cortical cataract but not nuclear cataract.[32]

The Lens Opacities Case-Control Study was designed to determine risk factors for cataracts in 1,380 participants, ages 40-79 years. Blood chemistry and levels of vitamin E and selenium were performed on all patients. The risk of developing cataracts was reduced to less than one-half (odds ratio 0.44 for nuclear cataracts) in subjects with higher levels of vitamin E.[33] Some of these same researchers examined the association between antioxidants and the risk of cataract in the Longitudinal Study of Cataract. Dietary intake, use of supplements, and plasma vitamin E levels were assessed on 764 participants. Lens opacities were examined on a yearly basis and the risk of development of cataract was 30-percent less in regular users of a multiple vitamin, 57-percent less in regular users of supplemental vitamin E, and 42-percent less is those with higher plasma levels of vitamin E.[34]

In a randomized trial of 50 patients with early cataracts, subjects were assigned to receive either 100 mg vitamin E twice daily or placebo for 30 days. There was a significantly smaller increase in the size of cortical cataracts in the vitamin E group compared to placebo. While increases of vitamin E were found in both nuclear and cortical lens homogenates after surgical removal, GSH levels were increased significantly only in those with cortical cataracts receiving vitamin E. In addition, the malondialdehyde (MDA) — a measure of oxidative stress — levels and glutathione peroxidase levels were higher in cortical cataract/vitamin E users than in the nuclear cataract/vitamin E group.[35] Some conclusions that can be drawn from this study are:

(1) vitamin E decreases oxidative stress in cataractous lenses; (2) part of vitamin E's protective effect is due to enhancement of GSH levels; and (3) vitamin E seems to be more protective for cortical than nuclear cataracts, at least in this short-term study.

Vitamin C and Risk of Cataracts

Animal experimentation has shed some light on ascorbic acid and its role in cataract formation. Cataracts induced in chick embryos by the application of hydrocortisone were prevented by the introduction of vitamin C to the developing embryo. In addition, vitamin C slowed the decline in GSH levels, which occurred with the cortisone treatment.[36]

Ascorbic acid is normally found in high concentrations in the aqueous humor and lens in humans. A group of 44 subjects were supplemented with 2 g daily ascorbic acid. Significant increases in vitamin C in lens, aqueous humor, and plasma were noted.[37] In another study, lenses were exposed *in vitro* to light, which caused an increase in superoxide radicals and subsequent damage to the Na^+/K^+ pump. The damage was prevented by addition of vitamin C in doses comparable to what would be found in the aqueous humor.[38]

In the Nurses' Health Study supplemental vitamin C for a period of 10 years or greater was associated with a 77-percent lower incidence of early lens opacities and an 83-percent lower incidence of moderate lens opacities. In this study, no significant protection was noted from vitamin C supplementation of less than 10 years.[39]

Riboflavin

Riboflavin is a precursor to flavin adenine dinucleotide (FAD), which is a coenzyme for glutathione reductase. *In vitro* evaluations of surgically removed cataracts have confirmed inactivity of glutathione reductase enzyme activity in a significant number of cataracts examined. Furthermore, the activity was restored by the addition of FAD.[40]

It is not surprising then that a deficiency of riboflavin has been implicated as a cause of cataract formation. A study of B vitamin nutritional status of cataract patients (n=37) compared to age-matched controls without cataract (n=16) found that 80 percent of those with cataracts and only 12.5 percent of control subjects had a riboflavin deficiency.[41] The same researcher tested for, but did not find, a deficiency of thiamin or pyridoxine in cataract patients. Other researchers have found a relationship between riboflavin deficiency and later-stage cataracts, but not in early cataract formation.[42] The Lens Opacities Case-Control Study found that lens opacities were associated with lower levels of riboflavin which were assessed by RBC enzyme assays and dietary intake reports.

Data collected during cancer intervention trials in Linxian, China, were assessed for nutrient effects on other conditions, including cataracts. Two randomized, double-blind, controlled studies of cataract risk resulted from the Linxian study. In the first trial 12,141 participants, ages 45-74, were supplemented for five to six years with either a multiple vitamin-mineral or placebo. There was a statistically significant 36-percent reduction in incidence of nuclear cataract for subjects ages 65-74 years given the multiple vitamin. In the second trial 23,249 participants were given one of four different vitamin/mineral combinations: (1) retinol/zinc, (2) riboflavin/niacin, (3) ascorbic acid/molybdenum, or (4) selenium/alpha-tocopherol/beta carotene. Again, the most significant effect was noted in people age 65-74, with a 44-percent decrease in nuclear cataract risk in the group taking riboflavin/niacin (3 mg riboflavin/40 mg niacin). No significant protection was noted for the other nutrient combinations or for protection from cortical cataracts.[43]

A series of case reports from the University of Georgia treated 24 cataract patients (18 with lens opacities and six with fully-developed cataracts) with 15 mg riboflavin daily.

Dramatic improvement was reported within 24-48 hours, and after nine months all lens opacities disappeared.[44] Larger, double-blind, placebo-controlled trials are needed to confirm these seemingly dramatic improvements.

Other B Vitamins

Pantethine is the active coenzyme form of pantothenic acid (vitamin B5). Several animal studies have found pantethine can prevent chemically-induced cataracts if given within eight hours of exposure to lens insult.[45-47] The proposed mechanism of action was the prevention of the formation of insoluble proteins in the lens.[45]

Folic acid has been found to be low in those prone to cataracts. An Italian epidemiological survey found those in the highest quintile for folic acid consumption were only 40 percent as likely to develop cataracts than those in the lowest quintile.[8]

Selenium and Cataracts

A decrease in glutathione peroxidase activity has been found in the lenses of selenium-deficient rats. Concomitantly, an increase in MDA and free radicals was also noted in both the selenium-deficient and vitamin-E deficient groups.[48] Evaluation of selenium levels in humans has found lower than normal levels of selenium in sera and aqueous humor in cataract patients.[49] The significance of low serum levels is unclear and the relationship between selenium and cataract risk demands further evaluation.

Dietary Factors in Cataract Risk

Several epidemiological studies have found dietary links to increased or decreased risk of cataract. An Italian in-hospital study examined dietary patterns and incidence of cataract extraction. Significant inverse relationships were seen between meat, spinach, cheese, cruciferous vegetables, tomatoes, peppers, citrus fruits, and melon. An increased risk was found in those with the highest intakes of butter, total fat, salt, and oil (except olive oil).[8] The Nurses' Health Study found regular consumption of spinach and kale was moderately protective for cataracts in women.[22] The Health Professionals Follow-up Study found spinach and broccoli decreased risk of cataract in men.[24]

Bilberry and Cataracts

Vaccinium myrtillus or bilberry has a long history of use for various eye conditions. The active components, flavonoid anthocyanosides, are potent antioxidants with a particular affinity for the eye and vascular tissues. The anthocyanosides are typically concentrated in a 25-percent standardized extract. In a report of 50 patients with senile cataracts, a combination of bilberry, standardized to contain 25-percent anthocyanosides, (180 mg twice daily) and vitamin E, in the form of dl-tocopheryl acetate, (100 mg twice daily) for four months stopped the progression of cataracts in 96 percent of the subjects treated (n=25) compared to 76-percent in the control group (n=25).[50]

Melatonin

The pineal hormone, melatonin, is a potent antioxidant and because of its known antioxidant effects, several animal studies have been conducted to determine its effect on prevention of cataracts. Injections of melatonin have been found to inhibit both chemical- and UVB-induced cataracts.[51-53] In the UV-B and melatonin study cataract formation and MDA levels were significantly lower than the UV-B only group, leading the researchers to conclude, "These results suggest that melatonin may protect against the UVB-induced cataract development by directly quenching lipid peroxides and indirectly by enhancing the production of the endogenous antioxidant GSH."[51]

In studies examining chemically-induced cataracts, the animals were administered buthionine sulfoxamine (BSO), a known inhibitor of GSH synthesis. Half were treated

with melatonin and half were not. In one study, 18/18 rats given BSO alone developed cataracts compared to only 1/15 in the group treated with melatonin.[52] In the other study, 16/18 in the BSO-only group developed cataracts, whereas only 3/18 treated with melatonin developed cataracts.[53] The researchers were unsure whether the protection was due to a direct free-radical scavenging effect or to a stimulation of GSH production by melatonin.

Diabetic (Sugar) Cataracts
### Polyol Accumulation

Some of the mechanisms involved in the formation of diabetic cataracts are somewhat different from senile cataracts. The accumulation of polyols within the lens is a primary contributing factor. Certain tissues of the body, including the lens of the eye, do not require insulin for glucose or other simple sugars such as galactose to enter. In diabetes sugar is in high concentrations in the aqueous humor and can diffuse passively into the lens. The enzyme aldose reductase within the lens converts glucose to sorbitol or galactose to galactitol (Figure 3). These polyols cannot diffuse passively out of the lens and accumulate or are converted to fructose. The accumulation of polyols results in an osmotic gradient, which encourages diffusion of fluids from the aqueous humor. The water drags sodium with it and the swelling and electrolyte imbalances result in cataract formation.

Flavonoids as Aldose Reductase Inhibitors

A number of compounds, both natural and synthetic, have been found to inhibit aldose reductase. These so-called aldose reductase inhibitors (ARIs) bind to aldose reductase, inhibiting polyol production.[54] As a group, flavonoids are among the most potent naturally occurring ARIs. Several evaluations of *in vitro* animal lenses incubated in high sugar mediums have found flavonoids to inhibit aldose reductase.[55,56]

A group of researchers examined the effect of an orally administered ARI in inhibiting polyol accumulation. They reported the arrest of cataracts in galactosemic rats by oral feeding of a synthetic ARI.[57] Building on this research, another group studied the effect of a

Figure 3: The Polyol Pathway
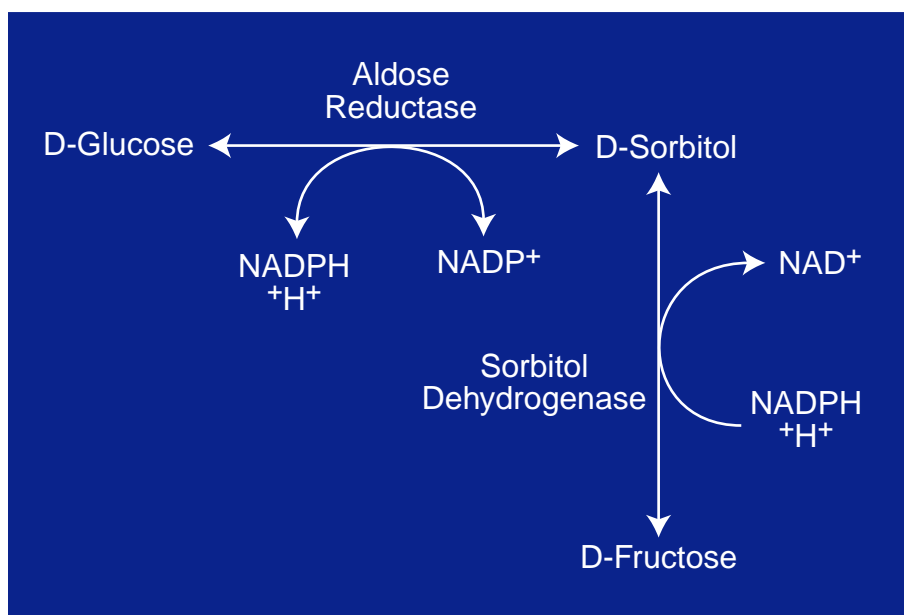
flavonoid ARI, quercetrin (a glycoside of quercetin). Rats were divided into two groups, one receiving lab chow only, while the experimental group was fed quercetrin in rat chow plus

Table 1: The Aldose Reductase Inhibitor Activity of Some Flavonoids.[60]

Flavonoid	Molar Concentration	Percent Inhibition
Quercetrin-2-acetate	10^{-4} 10^{-5} 10^{-6} 10^{-7}	100 100 100 87
Quercetrin	10^{-4} 10^{-5} 10^{-6} 10^{-7}	100 95 88 55
Quercetin	10^{-4} 10^{-5} 10^{-6} 10^{-7}	100 83 60 15
Rutin	10^{-4} 10^{-5} 10^{-6} 10^{-7}	95 95 20 10
Hesperidin	10^{-4} 10^{-5} 10^{-6} 10^{-7}	88 10 0 0
Hesperidin chalcone	10^{-4} 10^{-5} 10^{-6} 10^{-7}	82 10 0 0
Naringin	10^{-4} 10^{-5} 10^{-6} 10^{-7}	80 59 0 0

comparable (average 380 mg/100 mL), had not developed cataracts by the 25th day.[58] A French study examining the effect of oral doses of quercetin did not find an inhibition of cataract formation in diabetic animals.[59] In the positive study quercetrin rather than quercetin was used, the former administered in a water suspension which was undoubtedly more absorbable. The latter study was in French with only the abstract available so a dosage comparison was not possible.

Varma and associates performed an *in vitro* experiment to determine which aspects of flavonoids conferred the most ARI activity, and ultimately which flavonoids were the most potent in that respect.[60] Their earlier more limited research had found quercetin, quercetrin, and myricitrin to possess the most potent ARI activity.[56]

In the more recent experiment 44 flavonoids and their derivatives were examined for the ability to inhibit aldose reductase and polyol accumulation in rat lenses incubated in the sugar xylose. All flavonoids tested exhibited some inhibitory activity. The two most potent inhibitors were derivatives of quercetin, quercetrin and quercetrin-2-acetate, the latter the most potent ARI inhibitor known. Table 1 demonstrates some of the most common commercially available flavonoids and their comparative inhibitions. In decreasing order of potency they include quercetin, rutin, hesperidin and hesperidin chalcone, and naringin. Although inhibition was also noted by isoflavones, catechins, coumarins, and anthocyanins, they were found to be much less potent than flavones. When dissolved, flavones easily convert to their corresponding chalcone by the opening of the center or B-ring of the flavone structure. Because this may occur *in vivo* as well, the researchers tested hesperidin and hesperidin chalcone and found their inhibitory

an additional 70 mg oral quercetrin daily in aqueous suspension. Three days after beginning flavonoid supplementation diabetes was chemically induced and three days later lenses were assessed for sorbitol and fructose. The flavonoid group demonstrated a 50-percent inhibition of sorbitol and fructose accumulation. The control group developed cataracts by the tenth day, whereas the group receiving quercetrin, although their blood sugar was

potencies were nearly identical (Table 1). The chalcones, being more water-soluble and thus more absorbable, may represent a more logical means of oral administration. In their review Varma and associates outline a number of structural factors contributing to ARI activity. In the final analysis, the pentahydroxy (five OH groups) flavones conferred the most potent effect.

Vitamin C

Ascorbic acid also has potential as an aldose reductase inhibitor. An experiment was conducted in which guinea pigs were fed a normal, high vitamin C diet with 10-percent galactose or a scorbutic diet (devoid of vitamin C) plus 10-percent galactose. The lens epithelium of scorbutic animals had 2.5 times as much galactitol (the polyol of galactose) on day 4 than those animals fed vitamin C in their diets.[61]

A human study, although not on cells of the lens, found oral vitamin C at low doses of 100-600 mg daily was able to normalize sorbitol levels in red blood cells within 30 days in individuals with type 1 diabetes.[62]

Oxidative Stress and Diabetic Cataracts

As with senile cataracts, oxidative stress plays an important role in the pathogenesis of diabetic cataracts. Levels of glutathione peroxidase and vitamin C have been found to be deficient in the lenses of diabetics. Lenses of humans with diabetes were found to be more susceptible to oxidation of proteins, a condition exacerbated by concurrent retinal disease.[63]

Glutathione in Diabetic Cataracts

Evidence of other mechanisms at work besides sorbitol accumulation is offered by the work of Ross et al. They found that GSH, either *in vitro* in lens incubation medium or *in vivo* when injected into diabetic rats, was able to halt progression of diabetic cataracts despite sorbitol, glucose, and fructose accumulation.[64]

Lipoic Acid

In both *in vitro* lenses incubated in a glucose medium and in diabetic animal models, lipoic acid (LA) has been found to prevent cataract formation.[65] Lipoic acid has potent antioxidant effects in both its oxidized form (LA) and reduced form, dihydrolipoic acid (DHLA). It is this property which undoubtedly is responsible for much of its protective effect in diabetic cataracts. Packer, one of the foremost researchers on lipoic acid, hypothesizes that LA enters the lens (via a fatty acid carrier) and is converted to DHLA. DHLA has the potential to regenerate ascorbic acid from ascorbyl radicals; the ascorbic acid can then regenerate vitamin E from tocopheryl radicals. Alternately, he hypothesized LA could directly spare vitamins C and E. The increases in vitamins C and E would result in decreased utilization of GSH and a relative increase in its levels in the lens.[63] Due to its antioxidant effects and sparing of GSH and vitamins E and C, lipoic acid has been found to prevent chemically-induced, non-diabetic cataracts in animal models as well.[65]

Another mechanism by which lipoic acid may prevent cataracts in diabetes is via inhibition of aldose reductase, which was determined in an *in vitro* experiment.[66] The researchers also noted the ability of aldose reductase inhibitors, including lipoic acid, to chelate transition metals such as copper. This may be another way by which ARIs prevent cataracts and other complications of diabetes.

Protein Glycosylation/AGE Generation in Diabetic Cataracts

While glycosylated proteins (proteins with glucose attached) and subsequent formation of AGE have been implicated in many diabetic complications, there is disagreement as to how much they contribute to diabetic or

Table 2: Nutrients and Botanicals for the Prevention and Treatment of Cataracts

Supplement	Mechanism of Action
Glutathione	Deficiency noted in cataractous lenses; important component of the innate antioxidant system in the lens
Vitamin A	Higher levels associated with a decreased risk for cataract
Carotenes (Lutein and Zeaxanthin)	Antioxidant; higher levels associated with decreased risk for cataract
Vitamin E	Antioxidant; increases glutathione; supplementation associated with prevention
Vitamin C	Preserves glutathione levels; protects the Na+/K+ pump; long-term supplementation (>10 years) protective
Riboflavin	Precursor to FAD, a coenzyme for glutathione reductase which recycles GSH
Bilberry	Anthocyanoside antioxidants; study with vitamin E halted cataract progression
Quercetin	Aldose reductase inhibitor – diabetic cataracts
Lipoic Acid	Spares vitamins C and E, increasing GSH levels; inhibits aldose reductase and prevents protein glycosylation – diabetic cataracts

and ultimately prevented cataract formation.[67] *In vitro* studies have also found lipoic acid prevents protein glycosylation, providing yet another mechanism whereby LA may prevent cataracts.[72]

Table 2 summarizes potential nutritional and botanical treatments for cataracts.

Chronic Open-Angle Glaucoma

Currently, there are approximately two million cases of glaucoma in the United States, but due to its insidious nature, only half may be diagnosed.[4] Chronic open-angle glaucoma is the most common type, accounting for 60-70 percent of cases. It is the leading cause of blindness among African Americans[2] and the second leading cause of blindness in the U.S. population as a whole.[4] Another type, acute angle-closure glaucoma, is a medical emergency and will not be addressed here. Glaucoma is characterized by a neuropathy of the optic nerve, usually due to increased intraocular pressure (IOP). The increased pressure is due to an obstruction in the normal outflow of fluids from the aqueous humor, with most of the outflow normally occurring in the anterior chamber angle (Figure 4).

galactosemic cataracts. Some researchers have found increased levels of glycosylated proteins and AGE associated with diabetic cataracts,[67,68] while others have not found a strong correlation.[69,70]

Despite the controversy, several natural substances that inhibit protein glycosylation have been found to attenuate cataract formation *in vitro* and in animal models. Acetyl-L-carnitine, which has been found to be lower than normal in the lens of diabetic animals, was found in calf lenses *in vitro* to inhibit formation of glycosylated proteins by 42 percent and AGE formation by 70 percent.[71] The proteins became acetylated instead, preventing glucose from attaching. Pyruvate, a normal tissue metabolite, given orally to diabetic rats decreased protein glycosylation

Figure 4: Flow of Fluids in the Eye
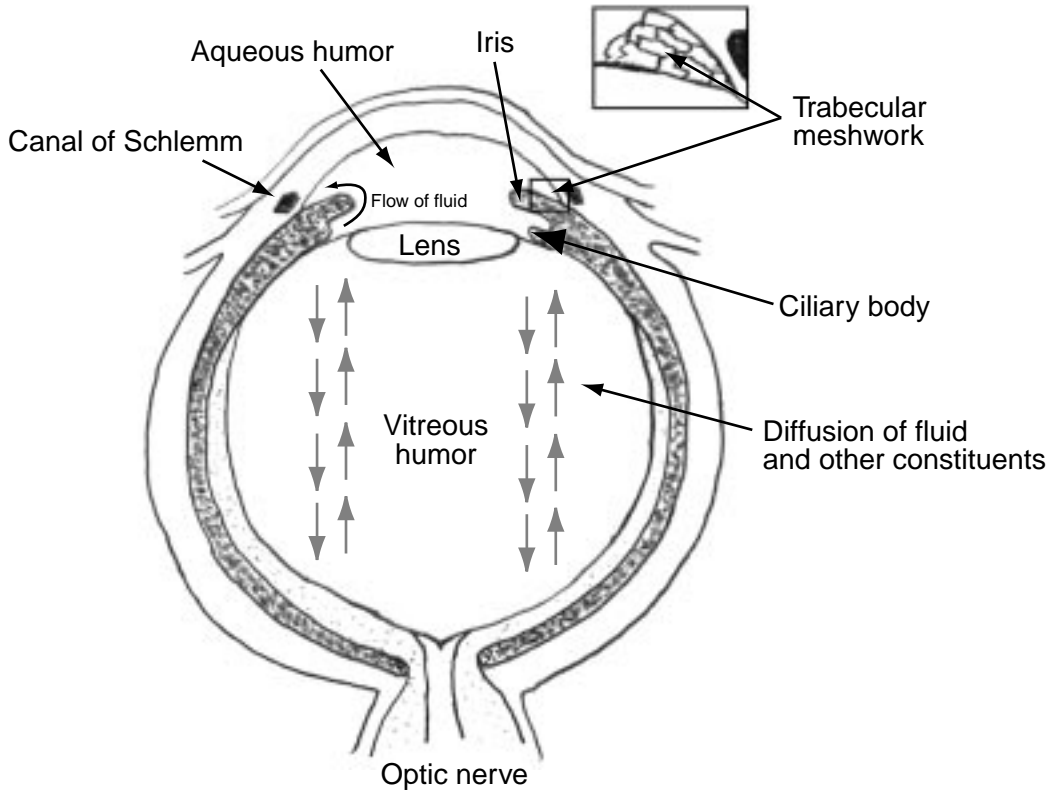
Diagnosis and Risk Factors

Although IOP screening is one factor in diagnosing glaucoma, it is a fairly insensitive test. Normal IOP ranges from 7-22 mm/Hg; however, approximately 90 percent of people with IOPs greater than 22 mm/Hg never develop glaucoma. On the other hand, some people with normal IOPs do develop optic nerve injury and glaucoma.[4] Ophthalmoscopic examination may reveal an enlarged cup within the optic disc. If glaucoma is suspected or if the patient is at high risk for developing glaucoma, referral to an optometrist or an ophthalmologist for further evaluation is essential.

Physical symptoms are usually absent in early stages. Once atrophy of the optic nerve has progressed, loss of peripheral vision occurs first; central vision is the last to be lost. Patients may complain of missing words on reading or having trouble driving due to poor peripheral vision.

Risk factors for the development of glaucoma include increased intraocular pressure, older age, family history, being of African American descent, diabetes, hypertension, and myopia.[4] Drugs associated with an increased incidence of glaucoma include corticosteroids and cholesterol-lowering drugs. As an aside, the use of scopolamine (often used by those going on a cruise to prevent seasickness) can result in acute, angle-closure glaucoma.

Pathophysiology

Normally aqueous humor is produced in the ciliary processes and flows past the lens, through the pupil, and into the anterior

chamber. Outflow occurs through the angle between the cornea and the iris, through a meshwork of trabeculae, to the canal of Schlemm (Figure 4). The canal of Schlemm is actually a very thin-walled vein that surrounds the entire eye. Because of its porous nature, large molecules are able to diffuse into the canal and, although it is a vein, it carries aqueous humor, not blood. Aqueous humor is continually being formed and reabsorbed, and it is this balance between formation and reabsorption that regulates IOP.[73]

The pathological processes involved in chronic glaucoma are not completely understood. It appears that morphological changes in collagen structure may precede increased IOP. Glycosaminoglycans (GAGs) contribute to the filtration barrier. Within the trabecular meshwork is an area called the juxtacanalicular tissue (JCT), which is the probable site of impedance to aqueous outflow in glaucoma. Researchers have compared the GAG content of the JCT in normal and glaucomatous eyes and have found some significant differences. In one study GAG content of five eyes from normal donors was compared to five with glaucoma. A significant decrease in hyaluronic acid and increase in chondroitin sulfate was found in the eyes of patients with glaucoma.[74] A similar study found trabecular meshwork of glaucomatous eyes had a 77-percent lower level of hyaluronic acid with higher levels of chondroitin sulfates in trabecular meshwork, iris, ciliary body, and sclera of eyes with glaucoma compared to normal donors.[75] The researchers postulated that the ability of normal aqueous outflow is regulated by the content of GAGs and their ability to form a highly viscous, elastic gel-like substance which acts as a filtration system.[76] Maintaining a critical level of hyaluronic acid appears to be essential for maintaining a well hydrated, semi-permeable meshwork.[77] *In vitro* research on human eyes has found a decrease in GAG synthesis, particularly hyaluronic acid, in glaucomatous eyes compared to normal eyes.[78]

Other researchers, examining human post-trabeculectomy specimens (surgical procedure for relieving increased IOP), have found evidence of a possible increase in collagen breakdown in glaucoma.[79]

Reduced antioxidant defense systems are also evident in early stage glaucoma. Much of the research on the connection between antioxidants and glaucoma has been conducted in Russia and published in Russian language journals, requiring dependence on abstracts. Levels of sulfhydryl groups, a reflection of glutathione levels, were found to be significantly lower in the aqueous humor of patients with glaucoma, particularly advanced stages of the disease, when compared to normal control subjects. Red blood cell GSH levels were also found to be lower in later stage glaucoma patients.[80] Deficiencies of sulfhydryl groups have also been found in the lacrimal fluid of later stage glaucoma patients.[81] In line with the evidence of decreased antioxidant defense systems in glaucomatous eyes is the finding of an increase in the lipid peroxidation product MDA – more than twice the normal level – in the anterior chamber of patients with glaucoma.[82]

In some patients, particularly those with normal IOP, an inadequate blood supply to the optic nerve may be contributing to damage and vision loss. These patients have a higher than normal incidence of migraines, suggesting vasospasm as an etiology.[4]

Conventional Treatment

The goal of conventional treatment is to decrease intraocular pressure to avoid damage to the optic nerve. There are a number of topical medications used, including cholinergic agonists, cholinesterase inhibitors, carbonic anhydrase inhibitors, adrenergic agonists (the newer ones are α_2-selective), β-blockers, and prostaglandin analogs. Osmotic diuretics are also used orally or IV.[4] Laser treatment may be tried instead of medications; and surgical intervention is usually a last resort

Table 3: Conventional Glaucoma Medications and Their Potential Side Effects[4,83]

Drug Category	Drug	Side Effect
Beta-blockers	timolol, levobunolol, carteolol, metipranolol, betaxolol	bronchospasm, shortness of breath fatigue, confusion, depression, impotence, hair loss, heart failure, bradycardia. Timolol has also been found to decrease HDL levels and adversely effect the total cholesterol:HDL ratio in women 60 years and older[84]
Non-selective Adrenergic Agonists	epinephrine, dipivefrin	high incidence of allergic or toxic reactions
α_2-Selective Adrenergic Agonists	apraclonidide	high rate of allergic reactions, tachyphylaxis
	brimonidine	dry mouth but less likely to cause allergic reactions
Cholinergic Agonists	carbachol	detached retina, GI disturbances, headache, frequent urination
	pilocarpine	hypertension, tachycardia, bronchial spasm
Cholinesterase Inhibitors	physostigmine, neostigmine, demecarium, echothiophate iodide, isoflurophate	The latter three in the list cause irreversible rather than reversible miosis; they may be cataractogenic; increase risk of retinal detachment.
Carbonic Anhydrase Inhibitors (oral, IV, topical)	acetazolamide, methazolamide, dichlorphenamide, ethoxzolamine	fatigue, anorexia, depression, paresthesias, electrolyte abnormalities, kidney stones, blood dyscrasias
	dorzolamide	topical so does not have the side effects of the others
Prostaglandin Analog	latanoprost	increased pigmentation of the iris; worsening of uveitis

strategy but may be used initially in patients who do not tolerate medications. Some common side effects of glaucoma medications are listed in Table 3.[4,83]

Potential Nutrient Deficiencies in Glaucoma

Deficiencies of specific nutrients have been found in patients with glaucoma, and supplementation may play a role in treatment.

Thiamin

Thiamin (vitamin B1) has been found to be deficient in some patients with glaucoma. Blood levels and dietary intakes of both vitamins C and B_1 were examined in 38 patients with glaucoma and compared to 12 controls. The glaucoma patients demonstrated a significantly lower level of thiamin (but not vitamin C), which was not a reflection of decreased intake causing the researchers to postulate an impaired absorption of thiamin in these patients.[85] As thiamin deficiency has been associated with degeneration of ganglionic cells of the brain and spinal cord, the researchers postulated a possible degeneration of the optic nerve as well.

Chromium

A deficiency of chromium has been implicated in increased IOP in humans and those afflicted with primary open-angle glaucoma have demonstrated decreased erythrocyte chromium levels.[86]

Intervention Trials of Specific Nutrients in Glaucoma

Vitamin B_{12}

While a deficiency of vitamin B_{12} has not been implicated in glaucoma, such a deficiency may cause optic atrophy and visual field defects which mimic glaucoma. An open trial of 5 mg B_{12} daily in glaucoma patients found no change in IOP with supplementation. However, there was no progression of visual field loss during five years of follow-up.[87]

Nutrients that Effect GAGs: Vitamin C and Glucosamine Sulfate

Due to the morphological changes seen in collagen structures associated with glaucoma it seems logical to explore the effect of nutrients known to exert specific influences on GAGs. Vitamin C has probably been researched more than any one single nutrient in the treatment of glaucoma. Researchers seem to be in disagreement as to whether people with glaucoma tend to have an ascorbate deficiency.[85,88] However, there is convincing research on its effectiveness in treating glaucoma.

Researchers first examined the effect of high dose IV vitamin C on animals and then humans, and found it successfully decreased IOP. IV doses used were in the range of 1 g/kg body weight; oral doses used were half that (500 mg/kg body weight).[89] A total of 49 eyes were treated, 25 with chronic open-angle glaucoma. The others included acute glaucoma, hemorrhagic glaucoma, and glaucoma secondary to another disease process. Those with chronic open-angle glaucoma responded the most dramatically. Table 4 shows the average drops in IOP two hours and 4-5 hours after a single dose of ascorbate. The higher the initial IOP, the greater the drop after ascorbate. In eyes with normal IOP, the average drop in pressure was 3.5 mmHg. Decreases in pressure were maintained for as much as eight hours. Due to the almost universal side effect of gastric upset and diarrhea from such high doses of vitamin C, the researchers studied the effect of divided daily doses (0.1-0.15 g/kg 3-5 times daily). All but one patient experienced decreased IOP during a two-week trial of divided doses and most experienced mild gastric upset and diarrhea that disappeared after 3-4 days. Use of IV vitamin C would have alleviated the gastric upset and diarrhea. Some patients who had previously been resistant to conventional drug therapy were able to maintain normal IOPs with the vitamin C regimen.

Ocular Disorders

Table 4: Decreases in IOP after Oral Ascorbic Acid at 0.5 mg/kg body weight[89]

Initial IOP	Average Pressure Decrease at 2 Hours	Average Pressure Decrease at 4-5 Hours
50-69 mmHg	16 mmHg	25 mmHg
32-49 mmHg	14 mmHg	19 mmHg
20-31 mmHg	6.5 mmHg	6.5 mmHg

A previous study of oral ascorbate did not find it effective at lowering IOP in glaucoma. The researchers, however, used only 500 mg twice daily. These same researchers successfully lowered IOP with topical use of a 10-percent aqueous solution of vitamin C.[90,91]

There are several postulated mechanisms for ascorbate's ability to lower IOP. In high doses it acts as a potent osmotic agent.[88] Vitamin C's ability to halt lipid peroxidation has also been hypothesized to play a role.[88] Vitamin C has also been found, *in vitro*, to stimulate synthesis of hyaluronic acid in trabecular meshwork from glaucomatous eyes.[78] Ascorbate has also been found to reduce the viscosity of hyaluronic acid and increase outflow through the trabeculum.[92]

Based on the observation that open-angle glaucoma may be due in part to a hyaluronic acid deficiency, a researcher has postulated a beneficial effect of glucosamine sulfate (GS) for the treatment of glaucoma.[93] He cites two case reports in which glaucoma patients given 3 g/day GS for osteoarthritis reported substantial drops in IOP. Because glucosamine sulfate is also a substrate for chondroitin sulfate, which has been found to be elevated above normal in the trabecular meshwork in glaucoma patients, it would seem to have the possible potential of further aggravation of the condition. While this author has not heard reports of exacerbation with glucosamine sulfate, close monitoring of IOP in patients with glaucoma supplemented with GS

seems warranted, not only to prevent potential harm but to monitor potential benefits of this supplement. Double-blind studies to confirm the potential benefit of GS in glaucoma are needed.

Magnesium in the Treatment of Glaucoma Caused by Vasospasm

A subcategory of glaucoma patients with normal IOP – those for which optic nerve damage is caused by vasospasm leading to decreased blood supply to the optic nerve – may benefit from supplemental magnesium. This patient group is often treated with calcium channel blocker drugs. These drugs, however, are not without side effects, including leg and periorbital edema. Ten patients, six with open-angle glaucoma and four with normal-tension glaucoma, were supplemented with magnesium, a natural calcium channel blocker.[94] All patients in this preliminary open trial suffered from cold-induced vasospasms of the extremities and all had marked visual field deficits, despite normal or drug-normalized IOP. Each subject received 121.5 mg magnesium twice daily for one month. At the end of four weeks there was a non-statistically significant trend toward improvement in visual field tests (eight improved and two deteriorated, one because of a cataract). While it is tempting to assume magnesium can improve blood supply to the optic nerve by dilating the optic blood vessels, a larger, placebo-controlled trial of this subpopulation suffering

from glaucoma and vasospasm seems warranted.

Antioxidants in Glaucoma

Low glutathione levels may contribute to some of the pathological processes seen in glaucoma. Supplementation of lipoic acid can increase glutathione in red blood cells[80] and lacrimal fluid[81] of patients with glaucoma. In a Russian controlled trial of lipoic acid, 45 patients with stage I and II glaucoma were supplemented with either 75 mg (n=26) or 150 mg (n=19) for two months. A control group of glaucoma patients (n=31) were given only local hypotensive medication. Improvement in visual function was seen in approximately 45 percent of subjects supplemented with lipoic acid.[95] As mentioned previously, vitamins C and E are also glutathione sparing. The issue of oral supplementation of glutathione is a controversial one with some researchers contending oral doses of GSH are not effective at raising plasma and tissue levels of GSH. However, both animal[96,97] and human[98] studies have found oral doses of glutathione lead to increased plasma and tissue levels.

Melatonin and Diurnal Rhythms in Intraocular Pressure

Intraocular pressure normally varies throughout the day, with the lowest pressure occurring in the very early morning hours. IOP also parallels fluctuations in cortisol levels, high cortisol conferring higher IOPs. Diurnal variations in IOP are more pronounced in people with glaucoma (>10 mmHg) compared to 3-7 mmHg variations in non-glaucomatous eyes. Because melatonin levels peak around 2 a.m., a time when IOP is on a downward trend, researchers studied its effect on IOP.[99] A series of experiments on subjects with normal IOPs and no diagnosis of glaucoma were conducted. Baseline IOPs showed maximum pressures from 4-6 p.m. and minimum pressures from 2-5 a.m. In the first experiment, exposure to bright light, which suppressed normal melatonin secretion, resulted in a blunting of the usual early-morning fall in IOP. Administration of 200 mcg melatonin to half of the bright-light group resulted in a significant drop in IOP within an hour; the effect lasted up to four hours. This experiment may have important implications, not only for possible treatment of glaucoma with melatonin, but also in regard to timing of medications. It should also be noted that beta-blockers, sometimes used for treatment of glaucoma, decrease melatonin levels. One researcher found topical use of the beta-blocker, timolol, did not work as well in the evening.[100]

Coenzyme Q10 May Prevent Cardiac Side Effects of Timolol

The beta-blocker medication timolol may have significant cardiac side effects, including bradycardia and heart failure.[4] Sixteen glaucoma patients on topical timolol were given 90 mg CoQ10 for six weeks. CoQ10 delayed the appearance of negative inotropic effects, including bradycardia, associated with timolol, preventing the negative cardiac effects of the drug without interfering with its effect on IOP.[101]

Omega-3 Fatty Acids

Epidemiological and animal studies point to a possible protective effect of omega-3 fatty acids in glaucoma. Both topical administration of prostaglandin E3 and D3 – end products of omega-3 fatty acid metabolism – and IM injections of cod liver oil – high in omega-3 fatty acids – led to decreased IOP in rabbits.[102,103] Epidemiological evidence has found a low prevalence of chronic open-angle glaucoma among Eskimos on a native diet high in omega-3 fatty acids.[104] These studies have led researchers to consider the potential for omega-3 fatty acids in the prevention and treatment of glaucoma. Further investigation is warranted.

Botanical Treatment of Glaucoma

There are several botanicals that may hold promise for the treatment of glaucoma. Most studies are merely preliminary, and larger, controlled studies are needed.

Vaccinium Myrtillus *(bilberry)*

Vaccinium myrtillus holds promise in the treatment of glaucoma, although there has been just one very limited study. Eight patients with glaucoma were given a single dose of 200 mg anthocyanosides from bilberry (most extracts are 25-percent anthocyanosides so assuming this standardization was used, the patients were given 800 mg bilberry standardized extract). Electroretinography improvements were noted.[105] Due to the fact that the article is in Italian, further details are unavailable. While this evidence is very preliminary, it is not unreasonable to imagine the anthocyanosides' collagen-stabilizing effect exerting a positive effect on the trabecular meshwork, facilitating aqueous outflow. Anthocyanosides also exert potent antioxidant effects.

Ginkgo Biloba

Forty-six patients, some with severe visual field disturbances, and some with serious retinal vascular degeneration, were given 160 mg/day Ginkgo extract for four weeks, then 120 mg/day. Progress was assessed monthly by measuring visual acuity, visual fields, fundoscopic exam, IOP, blood pressure, and pulse rate. Although only mild improvements were noted, these were deemed relevant due to the severity of the ocular damage at the beginning of the study.[106]

A potential therapeutic effect of a Ginkgo extract for the treatment of glaucoma was evaluated in a phase I, placebo-controlled, crossover trial in 11 healthy volunteers. Subjects were treated with either 40 mg Ginkgo extract three times daily or placebo for two days. Ocular blood flow via Color Doppler Imaging was measured before and after supplementation. Subjects crossed over to the other treatment after a two-week washout period. Ginkgo significantly increased blood flow to the ophthalmic artery with no change seen in the placebo group.[107] Although Ginkgo did not alter IOP, it may provide potential benefit in glaucoma patients who suffer from decreased ocular blood flow.

Coleus Forskohlii

The triterpene forskolin from the plant *Coleus forskohlii* stimulates the enzyme adenylate cyclase.[108] Adenylate cyclase then stimulates the ciliary epithelium to produce cyclic adenosine monophosphate (cAMP), which in turn decreases IOP by decreasing aqueous humor inflow.[109]

Results of studies using topical forskolin applications to decrease IOP have been mixed. A study of 2-, 1-, and 0.5-percent forskolin solutions applied to the eyes of normal rabbits found significant, dose-dependent decreases in IOP within a half hour, peaking in 2-3 hours, and lasting up to 10 hours.[110] On the other hand, a 1-percent forskolin solution failed to significantly decrease IOP in glaucomatous monkeys after two days of treatment.[111]

To date, human studies on forskolin's effect on IOP have been limited to healthy volunteers. Several studies have found it effective at lowering IOP and decreasing aqueous outflow in this population. Meyer et al compared the effect of 1-percent forskolin versus placebo in 10 healthy volunteers in a randomized, crossover trial. In the first study, both the placebo group and the forskolin group experienced a decrease in IOP, which was attributed to the local anesthetic oxybuprocaine. In the second trial, proxymetacaine was used as the topical anesthetic and forskolin was found to significantly decrease IOP compared to placebo.[112]

In 20 healthy volunteers one dose of a 1-percent forskolin solution had no effect, whereas two instillations five minutes apart led to significant decreases in IOP and aqueous

Table 5: Potential Nutrient and Botanical Approaches to Glaucoma

Supplement	Route of Administration	Mechanism
Vitamin C	IV or oral	Osmotic agent; enhance hyaluronic acid synthesis and reduce its viscosity
Vitamin B12	Oral or IM	Correct a deficiency which may cause optic nerve atrophy
Lipoic acid	Oral	Antioxidant; increase glutathione levels
Magnesium	Oral	May decrease vasospasm and increase blood supply to the optic nerve
Melatonin	Oral	Normal diurnal rhythms of IOP fluctuation reflect melatonin rhythms; antioxidant
CoQ10	Oral	Prevent cardiac side effects of timolol
Bilberry	Oral	Anthocyanosides exert antioxidant and collagen stabilizing effect
Ginkgo	Oral	Increase blood flow to the ophthalmic artery and ultimately to the optic nerve
forskolin	Topical eye drops	Decrease IOP by stimulation of cAMP
Salvia miltiorrhiza	IM or IV	Increase microcirculation to the retinal ganglions, improving visual acuity and visual fields

flow rate.[113] In eight healthy subjects one drop of forskolin significantly decreased IOP and flow rate was diminished an average of 34 percent.[114] Another study, however, did not find forskolin to have a significant effect at decreasing flow rate in a group of 15 healthy volunteers given one dose of 1-percent forskolin in each of three situations: during the day, at night while sleeping, and following pretreatment with timolol.[115]

While topical use of forskolin in animals and healthy humans appears promising, clinical studies on its use in glaucoma patients are lacking. Furthermore, while oral standardized extracts of *Coleus forskohlii* are known to raise cAMP as its mechanism of action in various disease conditions, it is not clear whether oral dosages have any effect on cAMP levels in the eye. More research on this important topic is

needed. Forskolin eye drops are available through compounding pharmacies.

Salvia Miltiorrhiza

Salvia miltiorrhiza is a commonly used botanical in Chinese medicine. Injected IV this botanical appears to improve microcirculation of the retinal ganglion cells. Two experiments on rabbits found it protected the optic nerve from the damaging effects of increased IOP, with better results when used in conjunction with a medication to lower IOP.[116,117]

In a human study, 121 patients with mid- or late-stage glaucoma with medication-controlled IOP received daily IM injections of a 2 g/mL solution of *Salvia miltiorrhiza* alone or in combination with other Chinese herbs (four different groups). After 30 days visual acuity had improved in 43.8 percent of the eyes and visual field improvement was noted in 49.7 percent of eyes. There were no significant differences among the four herbal preparations; but the effect was a statistically significant ($p<0.01$) improvement compared to 23 untreated eyes. Follow-up on 19 eyes occurred 7-30 months after the 30-day treatment and 14/19 eyes maintained or demonstrated improvement in visual fields, suggesting a possible long-term benefit from this herbal treatment. Double-blind evaluations of oral administration of Salvia seem warranted.[118]

Table 5 summarizes potential nutritional and botanical treatments for glaucoma.

Conclusions

Considerable epidemiological, *in vitro,* and animal data point to the benefit of the possible prevention and treatment of cataracts with herbal and particularly nutritional supplementation. Much of the research has been *in vitro* due to the ease of cataractous lens evaluation in this experimental model. However, there is a definite paucity of good, prospective clinical studies on the use of nutrients and botanicals for the treatment of

already existing cataracts. Maintaining normal glutathione levels seems of utmost importance in prevention of cataracts. Nutrients such as lipoic acid, vitamins C and E, and selenium increase glutathione levels or act as co-factors for glutathione-dependent enzymes. Since prevention of lens opacities is easier than treating already existing cataracts, use of these and other antioxidants to prevent cataracts should be researched more thoroughly, particularly in view of the high number of cataract surgeries performed each year and the fact that cataracts are the leading cause of visual impairment in the United States.

Even with the use of conventional medications, maintaining normal IOP and preventing damage to the optic nerve in glaucoma patients can be challenging. There are several nutrients and botanicals that hold promise in improving circulation to the optic nerve and even lowering IOP including vitamins B_{12} and C, melatonin, lipoic acid, *Ginkgo biloba*, *Vaccinium myrtillus*, topical forskolin, and IM *Salvia miltiorrhiza*. Many of these studies have been performed on normal, healthy eyes. Prospective trials on patients with glaucoma are needed.

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