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Nutritional supplement for eyes: for prevention & treatment of cataract

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ABSTRACT

Cataract is multifactorial diseases associated with several risk factors and it is responsible for 50% of blindness worldwide. At present, the only remedy for cataract is surgery. However the incidence is so large that the available surgical facilities are unable to cope up with the problem because of postoperative complications such as posterior capsular opacification, endophthalmitis and uncorrected residual refractive error. In India alone around 30 million people suffer from cataract. Thus, the expense and unavailability of surgery mean that non-surgical medical therapy or nutritional treatment to inhibit the formation or slow the progression of cataracts is an important goal in experimental eye research to benefit patients and reduce the huge economic burden. The present Article reviews the role of Nutritional supplements for eyes to prevent Cataract.

Keywords: Nutritional supplements, Eye disorders, Cataract.

INTRODUCTION

Ayurveda is believed to be prevalent since last 5000 years . It is one of the most noted systems of medicine in the world. Ayurveda is based on the hypothesis that everything in the universe is composed of five elements viz. space, air, energy, liquid and solid. These elements exist in the human body in combined forms like *Vata* (space and air), *Pitta* (energy and liquid) and *Kapha* (liquid and solid). *Vata*, *Pitta* and *Kapha* together are called *Tridosha* (three pillars of life). Some important herbs from ayurveda include *Rauwolfia serpentina*,

Asparagus racemosus, *Cassia angustifolia*, *Sesamum indicum*, *Holarrhenaantidysenterica*, *Withania somnifera*, *Aconitum napellus* and *Piper longum* etc.[1]

Natural products, including plants, animals and minerals have been the basis of treatment of diseases from time immemorial. History of medicine dates back practically to the existence human civilization. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies. The history of medicineincludes many ludicrous therapies. Nevertheless, ancient wisdom has been the basis of modernmedicine and will remain as one important source of future medicine and therapeutics. The future of natural products drug discovery will be more holistic, personalized and involve wise use of ancient and modern therapeutic skills in a complementary manner so that maximum benefits can be accrued to the patients and the community.[2]

Plants have played a crucial role in maintaining human health and improving the quality of human life for thousands of years. The World Health Organization has estimated that 80% of the earth's inhabitants rely on traditional medicine for their health care needs, and most of this therapy involves the use of plants extracts or their active components. Therefore, therapeutic approach of several traditional medicines is rather more holistic. Majority of fundamental concepts of their medicinal systems still cannot be explained using modern tools.[3]

Medicinal plants sector has traditionally occupied an important position in the sociocultural, spiritual and medicinal area of rural and tribal lives of India. The global thrust areas for drugs from medicinal plants include disease conditions, whose incidence is unavailable or unsatisfactory. International market of medicinal plants is over US $ 60 billion per year, which is growing at the rate of 7% annually.[4]

Traditional Vs orthodox medicine

Traditional remedies invariably involve crude plant extracts containing multiple chemical constituents, which vary in potency from highly active (e.g. *Digitalis* leaf) to very weak (e.g. *Cinnamon* bark). In contrast, orthodox medicine relies heavily on single (or a very small member of) chemically well-characterized active ingredients exhibiting selective activities at, in many cases, well-established biological targets. These medicines are generally very potent and many exhibit fairly narrow windows between an effective and a toxic dose. Orthodox medicines are formulated into doses that are carefully standardized for bioavailability. Amongst our most invaluable orthodox medicines derived from compounds in higher plants are analgesic agents (e.g. morphine and codeine), antimalarial treatments (e.g. quinine), antitumour drugs (e.g. vincristine and taxol) and asthma therapies (e.g. cromoglycate).[5]

Diseases and disorders of the eyes

Cataracts are opacities of the lens. While some are small and do not require any treatment, others may be large enough to block light and obstruct vision. Cataracts usually develop as the aging lens becomes more and more opaque, but cataracts can also form congenitally or after injury to the lens. Diabetes is also a risk factor for cataract.

Presbyopia is the age-related loss of accommodation, which is marked by the inability of the eye to focus on nearby objects. The exact mechanism is still unknown, but age-related changes in the hardness, shape, and size of the lens have all been linked to the condition.

Ectopia lentis is the displacement of the lens from its normal position.

Aphakia is the absence of the lens from the eye. Aphakia can be the result of surgery or injury, or it can be congenital.

Nuclear sclerosis is an age-related change in the density of the lens nucleus that occurs in all older animals.

Age-related macular degeneration (AMD) is a disease that blurs the sharp, central vision you need for "straight-ahead" activities such as reading, sewing, and driving. AMD affects the macula, the part of the eye that allows you to see fine detail. AMD causes no pain.

Amblyopia is the medical term used when the vision in one of the eyes is reduced because the eye and the brain are not working together properly. The eye itself looks normal, but it is not being used normally because the brain is favoring the other eye. This condition is also sometimes called lazy eye.

Microphthalmia is a disorder in which one or both eyes are abnormally small.

Anophthalmia is the absence of one or both eyes. These rare disorders develop during pregnancy and can be associated with other birth defects.

Refractive errors include nearsightedness and farsightedness, eye conditions that are very common. Most people have one or more of them. Refractive errors can usually be corrected with eyeglasses or contact lens.

Blepharitis is a common condition that causes inflammation of the eyelids. It can affect the inside or outside of the eyelids. The condition can be difficult to manage because it tends to recur.

Dry eye occurs when the eye does not produce tears properly, or when they evaporate too quickly. Dry eye can make it difficult to do some activities, such as using a computer or reading for an extended period of time, and it can decrease tolerance for dry environments, such as the air inside an airplane.

Glaucoma is a group of diseases that can damage the eye's optic nerve and result in vision loss and blindness. Open-angle glaucoma is the most common form of the disease.[11]

Anatomy of eye lens

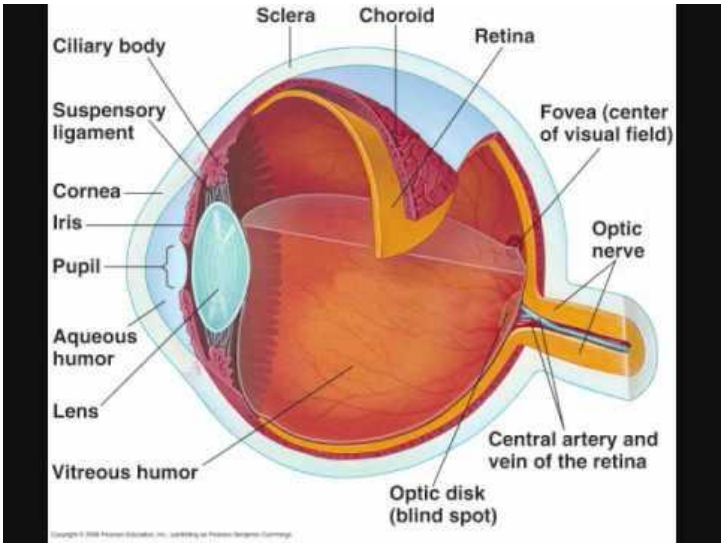

Fig.1 Anatomy of eye

The crystalline lens is a transparent, biconvex structure in the eye that, along with the cornea, helps to refract light to be focused on the retina. The lens, by changing shape, functions to change the focal distance of the eye so that it can focus on objects at various distances, thus allowing a sharp real image of the object of interest to be formed on the retina. This adjustment of the lens is known as accommodation. It is similar to the focusing of a photographic camera via movement of its lenses. The lens is flatter on its anterior side.

The lens is also known as the *aquula* (Latin, *a little stream*, dim. of *aqua*, *water*) or *crystallinelens*. In humans, the refractive power of the lens in its natural environment is approximately 18 dioptres, roughly one-third of the eye's total power.

Position, size, and shape of lens

The lens is part of the anterior segment of the eye. Anterior to the lens is the iris, which regulates the amount of light entering into the eye. The lens is suspended in place by the suspensory ligament of the lens, a ring of fibrous tissue that attaches to the lens at its equator[12, 13] and connects it to the ciliary body. Posterior to the lens is the vitreous body, which, along with the aqueous humor on the anterior surface, bathes the lens. The lens has an ellipsoid, biconvex shape. The anterior surface is less curved than the posterior. In the adult, the lens is typically circa 10 mm in diameter and has an axial length of

about 4 mm, though it is important to note that the size and shape can change due to accommodation and because the lens continues to grow throughout a person's lifetime.[14]. In many aquatic vertebrates, the lens is considerably thicker, almost spherical, to increase the refraction of light. This difference compensates for the smaller angle of refraction between the eye's cornea and the watery medium, as they have similar refractive indices.[15]

Even among terrestrial animals; however, the lens of primates such as humans is unusually flat. In reptiles and birds, the ciliary body touches the lens with a number of pads on its inner surface, in addition to the zonular fibres. These pads compress and release the lens to modify its shape while focusing on things at different distances; the zonular fibres perform this function in mammals. In fish and amphibians, the lens is fixed in shape, and focusing is instead achieved by moving the lens forwards or backwards within the eye. [16]

Structure and function of lens

The lens has three main parts: the lens capsule, the lens epithelium, and the lens fibers. The lens capsule forms the outermost layer of the lens and the lens fibers form the bulk of the interior of the lens. The cells of the lens epithelium, located between the lens capsule and the outermost layer of lens fibers, are found only on the anterior side of the lens.

PARTS OF LENS ARE AS FOLLOWS-

Lens capsule

The lens capsule is a smooth, transparent basement membrane that completely surrounds the lens. The capsule is elastic and is composed of collagen. It is synthesized by the lens epithelium and its main components are Type IV collagen and sulfated glycosaminoglycans (GAGs). The capsule is very elastic and so causes the lens to assume a more globular shape when not under the tension of the zonular fibers, which connect the lens capsule to the ciliary body.

The capsule varies from 2-28 micrometres in thickness, being thickest near the equator and thinnest near the posterior pole. The lens capsule may be involved with the higher anterior curvature than posterior of the lens.[13]

Lens epithelium

The lens epithelium, located in the anterior portion of the lens between the lenscapsule and the lens fibers, is a simple cuboidal epithelium. The cells of the lens epithelium regulate most of the homeostatic functions of the lens. As ions, nutrients, and liquid enter the lens from the aqueous humor, Na+/K+ ATPase pumps in the lens epithelial cells pump ions out of the lens to maintain appropriate lens osmolarity and volume, with equatorially positioned lens epithelium cells contributing most to this current. The activity of the Na+/K+ ATPases keeps water and current flowing through the lens from the poles and exiting through the equatorial regions.[17]

The cells of the lens epithelium also serve as the progenitors for new lens fibers. It constantly lays down fibers in the embryo, fetus, infant, and adult, and continues to lay down fibers for lifelong growth. [18]

Lens fibers

The lens fibers form the bulk of the lens. They are long, thin, transparent cells, firmly packed, with diameters typically between 4-7 micrometres and lengths of up to 12 mm long. The lens fibers stretch lengthwise from the posterior to the anterior poles and, when cut horizontally, are arranged in concentric layers rather like the layers of an onion. If cut along the equator, it appears as a honeycomb. The middle of each fiber lies on the equator. These tightly packed layers of lens fibers are referred to as laminae. The lens fibers are linked together via gap junctions and interdigitations of the cells that resemble "ball and socket" forms.

The lens is split into regions depending on the age of the lens fibers of a particular layer. Moving outwards from the central, oldest layer, the lens is split into an embryonic nucleus, the fetal nucleus, the adult nucleus, and the outer cortex. New lens fibers, generated from the lens epithelium, are added to the outer cortex. Mature lens fibers have no organelles or nuclei. [18]

Accommodation: changing the power of the lens

The lens is flexible and its curvature is controlled by ciliary muscles through the zonules. By changing the curvature of the lens, one can focus the eye on objects at different distances from it. This process is called accommodation. At short

focal distance the ciliary muscle contracts, zonule fibers loosen, and the lens thickens, resulting in a rounder shape and thus high refractive power. Changing focus to an object at a greater distance requires the relaxation of the ciliary muscle, which in turn increases the tension on the zonules, flattening the lens and thus increasing the focal distance. The refractive index of the lens varies from approximately 1.406 in the central layers down to 1.386 in less dense layers of the lens. This index gradient enhances the optical power of the lens.

Aquatic animals must rely entirely on their lens both for focusing and to provide almost the entire refractive power of the eye as the water-cornea interface does not have a large enough difference in indices of refraction to provide significant refractive power. As such, lenses in aquatic eyes tend to be much rounder and harder.[18]

Crystallins and transparency

Crystallins are water-soluble proteins that compose over 90% of the protein within the lens. The three main crystallin types found in the human eye are α-, β-, and γ-crystallins. Crystallins tend to form soluble, high-molecular weight aggregates that pack tightly in lens fibers, thus increasing the index of refraction of the lens while maintaining its transparency. β and γ crystallins are found primarily in the lens, while subunits of α -crystallin have been isolated from other parts of the eye and the body. α-crystallin proteins belong to a larger superfamily of molecular chaperone proteins, and so it is believed that the crystallin proteins were evolutionarily recruited from chaperone proteins for optical purposes. The chaperone functions of α –crystallin may also help maintain the lens proteins, which must last a human for his/her entire lifetime.[19]

Another important factor in maintaining the transparency of the lens is the absence of light-scattering organelles such as the nucleus, endoplasmic reticulum, and mitochondria within the mature lens fibers. Lens fibers also have a very extensive cytoskeleton that maintains the ns fibers results in the lens growing more ellipsoid in shape; after about age 20, however, the lens grows rounder with time.[21]

Nourishment of the lens

The lens is metabolically active and requires nourishment in order to maintain its growth and transparency. Compared to other tissues in the eye, however, the lens has considerably lower energy demands. By nine weeks into human development, the lens is surrounded and nourished by a net of vessels, the tunica vasculosa lentis, which is derived from the hyaloid artery. Beginning in the fourth month of development, the hyaloid artery and its related vasculature begin to atrophy and completely disappear by birth.[21] In the postnatal eye, Cloquet's canal marks the former location of the hyaloid artery. After regression of the hyaloid artery, the lens receives all its nourishment from the aqueous humor. Nutrients diffuse in and waste diffuses out through a constant flow of fluid from the anterior/posterior poles of the lens and out of the equatorial regions, a dynamic that is maintained by the Na+/K+ ATPase pumps located in the equatorially positioned cells of the lens epithelium.[22]

Glucose is the primary energy source for the lens. As mature lens fibers do not have mitochondria, approximately 80% of the glucose is metabolized via anaerobic respiration. The remaining fraction of glucose is shunted primarily down the pentose phosphate pathway. The lack of aerobic respiration means that the lens consumes very little oxygen as well.[23]

General overview of Cataract

Cataracts are described as an opacification (cloudiness) of the lens that leads to the scattering of light entering the eye and a loss of vision. Cataracts, which affect more than 50 million people [24] are the most common cause of blindness in the world. In first world countries, old age is the single largest cause of cataracts: only about 5% of Caucasian Americans aged 52- 64 years have cataracts, where as 18% of those aged 65-75 and 46% of those aged 75-85 are affected by cataracts.[25] As the average life span increases, the prevalence of cataract also increases. Cataract formation cannot be prevented or reversed,[26] however it can be cured by surgical replacement of the lens. There have been significant advances in surgical techniques and refinement of intraocular lens implants which have benefited cataract patients.

In India alone around 30 million people suffer from cataract. Thus, the expense and unavailability of surgery mean that non-surgical medical therapy or nutritional treatment to inhibit the formation or slow the progression of cataracts is an important

goal in experimental eye research to benefit patients and reduce the huge economic burden. [27]

Factors implicated in cataractogenesis

Several risk factors have been identified in the pathogenesis of cataract. Apart from aging, smoking, diabetes, gender, steroids and nitric oxide are responsible for the development of cataract. These risk factors have been associated with different morphological type of cataract.

Smoking

Smoking is thought to increase the risk of cataract, at least in part by increasing the oxidative stress in the lens caused by the generated free radicals. In the presence of tobacco smoke, these free radicals may directly damage lens proteins and the fiber cell membrane in the lens.[28, 29] Tobacco leaves contain a significant amount of cadmium (Cd), which is absorbed intothe body when a person smokes or chews tobacco and this Cd replace the bivalent metals like
Zinc (Zn), copper (Cu) and manganese from super oxide dismutase (SOD), a powerful antioxidant.[30]

Diabetes

There are several ways that diabetes can affect the eyes but the most common cause of loss of vision is cataract. Cataractogenesis is one of earliest secondary complications of diabetes mellitus, a severe metabolic disorders characterized by hyperglycemia. Some mechanisms have been proposed for cataract formation in diabetes mellitus such as excessive tissue sorbitol concentrations, abnormal glycosylation of lens proteins and increased free radical production. [31]

Gender

A number of epidemiological studies using cross sectional data have shown an increased prevalence of cataract in women compared with men.[32] The cause of the gender differences in cataract occurrences is not clear but could be related to the hormonal differences between women and men. Postmenopausal estrogen deficiency may be a factor. Recent epidemiologic data provided some evidence that estrogen and hormone replacement therapy may play a protective role in reducing the incidence of age related cataract. [33]

Steroids

The association between steroid use and development of cataract is well established. There seems to be a consensus that higher the dose of steroid and longer the duration of use, the higher will be the risk for posterior sub capsular cataract.[34] Steroids cause an inhibition of the cation pump in the lens capsule and the resulting electrolyte/water imbalance is responsible for cataract formation.[35]

Nitric oxide

O2- in itself is not highly toxic but it may react with other molecules yielding more reactive compounds. For example, the reaction with nitric oxide (NO) generates peroxynitrite (ONOO-), which causes extensive cell damage and can also have an important role in diabetic cataract formation. [36, 37] Apart from the above mentioned risk factors, genetic factors, socioeconomic status, illiteracy, malnutrition, diarrhea, myopia, renal failure, hypertension, sunlight, ultraviolet exposure, obesity, chemical burn, glaucoma and alcohol.[38,39] have also been implicated in cataracogenesis.

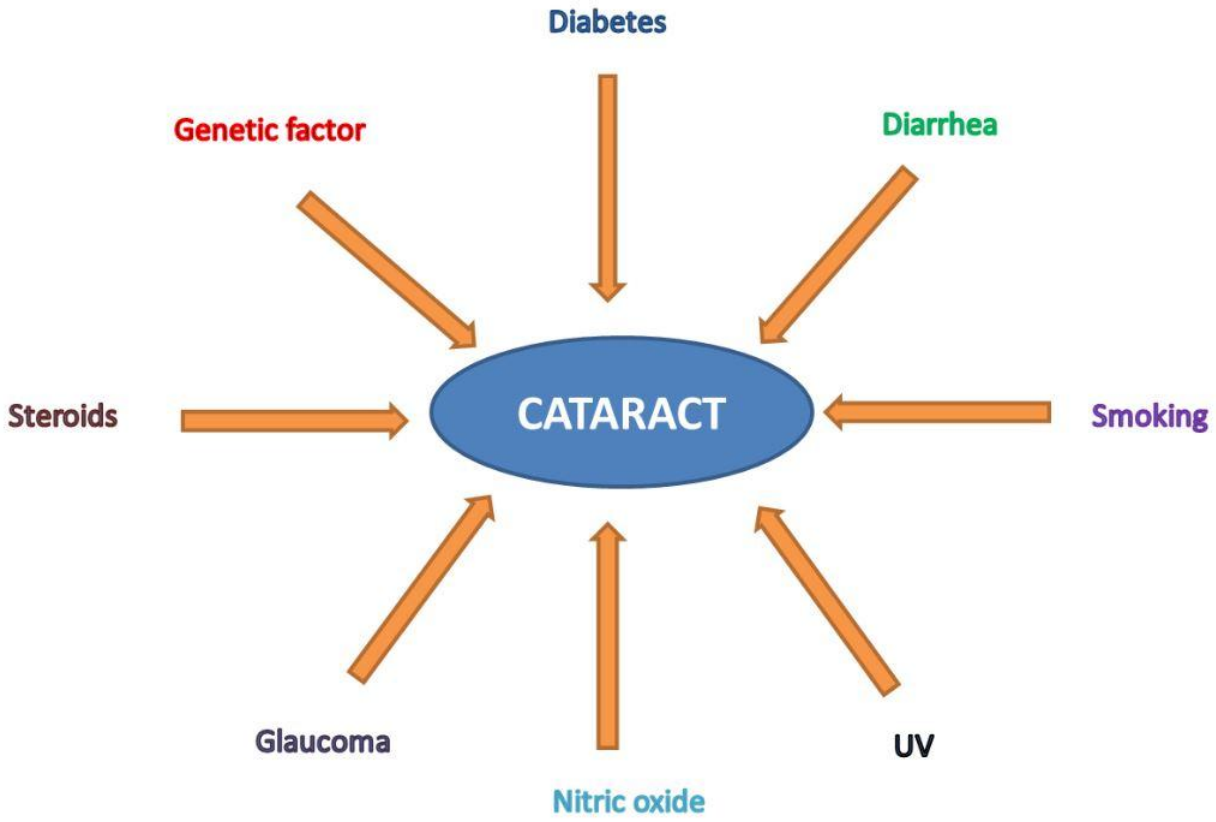

Fig. 1 Major risk factors implicated in cataractogenesis

Etiology of cataract

Developing anti-cataract agents has been difficult because cataract is not a single disease with a single aetiology. There are three major categories of cataract (nuclear, cortical, and posterior sub-capsule), each of which is multifactorial in aetiology and highly variable in severity and rate of progression. Further complicating the situation, the factors contributing to age-related cataractogenesis are a combination of pathological and normal aging processes, which have no obvious borders to distinguish them. Cataracts may be prevented if the mechanisms of formation are known. Based on the available knowledge of the biology of the normal lens and the cataractogenic process, three hypotheses have been proposed for the aetiology of cataract and three approaches have accordingly been adopted in the design of anti-cataract agents. [27]

Hypothesis for cataract

The first hypothesis is that chronic oxidative stress is a major factor in the aetiology of age related cataract. Experimental evidence suggests that oxidative stress due to the generation of free radicals plays a role in the pathogenesis of cataracts and that the process can be prevented or ameliorated by antioxidants. Therefore, agents with anti-oxidative properties have received the most attention. Such compounds comprise of three categories including antioxidant vitamins (e.g., E, C, β-carotene); functional mimics of antioxidant enzymes; and a wide variety of low molecular weight compounds with antioxidant activity. [40]

The second hypothesis is that phase separation phenomena are integral to cataract development. Phase separation results from non-covalent attractive interactions between proteins in concentrated solutions, creating protein-rich and protein poor regions. In the lens, formation of such domains creates light scattering, leading to cataract. Two

putative phase separation inhibitors, pantethine and the radio protective phosphorothioate WR-77913, were tested in several acute animal models of cataract and displayed the delay of the onset of cataract. [41]

The third hypothesis is the "protease hypothesis". Calcium activated neutral enzymes, calpains, can induce proteolysis and truncate crystalline to precipitate and scatter light to form cataract.[42] Therefore, research on calpain inhibitors is another approach to prevent or inhibit cataract formation. It has been reported that, when lambs with an inherited cataracts were treated with eye drops containing the calpain inhibitor SJA6017 for 4 months, progression of cataracts were slowed down in treated eyes compared with non-treated eyes.[43]

Models proposed to study cataract

In order to study cataracts and possible treatments for cataracts, a number of *in vivo* animal models have been developed. For example, administration of L-buthionine sulfoximine, a specific inhibitor of glutathione biosynthesis, to preweanling mice (aged ≤ 12-days) provides a model system for the induction of cataracts by depletion of lens glutathione.[44] The strong sulfhydryl oxidant, selenite, has been used to produce cataract in rats.[45] This selenite-induced cataract model has been extensively utilized to demonstrate that calpain-induced proteolysis causes truncated crystallins to precipitate and scatter light.

Other *in vivo* experimental animal models such as hyperbaric oxygen, and UVA light, have also been utilized to investigate the mechanism of formation of human senile nuclear cataract.[46]

There are also *in vitro* models of cataract where cataract is induced in cultured lenses, for example, H2O2-induced cataract in cultured lenses from rabbit.47 and rat 48 diamide (a thiolspecific oxidant)-induced cataract in Sprague-Dawley rat cultured lens model.49 Ionomycin cataract in rat cultured lens model, 50 4-bromo-calcium ionophore A23187 (Br-A23187)-induced cataract in guinea pig and rabbit cultured lens model 51 and sugar xylose-induced cataract in rhesus monkey lens model[27]. These studies have established the underlying premise that a lens organ culture model system can be used to screen potential anti-cataract agents. The lens, which is a vascular and non-innervated *in vivo*, can be maintained in a fully viable state in organ culture. Opacity can be induced in cultured lenses by various chemical or environmental perturbations, and prevention or inhibition of opacification can be observed after addition of appropriate agents to counteract the cataractogenic stresses.[27] Sheep lenses are considered to be more appropriate models of the humans lens than the rodent lenses commonly used for lens research. Rats and mice have lenses which are smaller than human and are spherical in shape compared to the flattened disc shape of the human lens. Also in sheep and human, the biconvex lens shape is altered by the ciliary muscle whereas the lens is moved backwards and forwards to focus light on the retina in the rodent eye.[52]

Oxidative stress, an excess of pro-oxidants relative to antioxidants and a key factor in the gradual loss of lens transparency, is implicated in the initiation of maturity onset cataract which appears late in life and is probably not associated with congenital conditions or other diseases, such as diabetes.[53] Evidence from epidemiological studies, model systems and human lenses obtained after cataract surgery, has indicated a role for oxidation in this opacification process. This has fuelled interest in the role of diet and dietary supplements in slowing down the progression of cataract [54] concluded that dietary antioxidants have a significant impact on cataract development based on the epidemiological evidence. Experimental studies have shown that, pretreatment of the plant antioxidant, quercetin, at concentrations of 30 μM for 24 h, inhibited hydrogen peroxide-induced oxidation of the rat lens.[55, 56]

α-lipoic acid, which plays an essential role in mitochondrial dehydrogenase reactions, has recently gained considerable attention as an antioxidant. Lipoate, or its reduced form dihydrolipoate, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C, which may in turn recycle vitamin E. In addition to its antioxidant ***activities***, dihydrolipoate may exert proxidant actions through reduction of iron. α-lipoic acid administration has been shown to be beneficial in a number of oxidative stress models such as ischemia-reperfusion injury, diabetes (both α-lipoic acid and dihydrolipoic acid exhibit hydrophobic binding to proteins such as albumin, which can prevent

glycation reactions), cataract formation, HIV activation, neurodegeneration, and radiation injury. Furthermore, lipoate can function as redox regulator of proteins such as myoglobin, prolactin, thioredoxin and NF-κB
transcription factor.[57]

CLASSIFICATION OF CATARACT [58]

Congenital and developmental cataract

Congenital cataract is present at birth, and developmental cataract is that cataract which develops during the development of the lens. These type of cataracts are developed due to some disturbance, at a certain phase of growth of the lens, therefore, these types of opacities of the lens are usually stationary and they may be of various types as noted below. Underlying cause is not known but it may be due to-

· Maternal malnutrition
· Maternal infection, particularly by virus of German measles or rubella.
· Deficient oxygenation duo to placental hemorrhage.

Blue-dot cataract

· Tiny bluish white opaque spot scattered all over the lens.
· No visual disturbance.

Coronary cataract

· Club shaped opacities in the peripheral part of the cortex
· Arranged like a corona or crown.
· Develops at puberty.
· No visual disturbance.
· Axial area of the lens remains clear.

CAPSULAR OR POLAR CATARACT

Anterior capsule or polar cataract

It forms as a result of delayed formation of the anterior chamber during the development of the lens. A white plaque is formed in the anterior lens capsule in the papillary area. Sometimes, this opacity may project into the anterior chamber in the form of a pyramid, then it is called anterior pyramidal cataract.

Posterior Capsular Cataract

Due to persistence of the posterior part of the vascular sheath of the lens, the opacity is usually tiny and there is very little visual disturbance.

Sutural cataract

Tiny opaque dots situated in the Y sutures of the lens. No visual disturbance.

Coralliform cataract

Minute opacities situated in the central area of the lens, in the form of a coral. No visual disturbance.

Floriform cataract

The opacities are annular in shape arranged like petals of flowers and situated in the axial part of the lens. No visuals disturbance.

Central cataract

The nucleus of the lens shows opacity. The opacity may be granular when there is no visual disturbance or the whole of the nucleus may be opaque associated with visual disturbance. This type of cataract may be unilateral or bilateral.

Lamellar or zonular cataract

It is the most common variety of cataract in children and is bilateral. It may develop at the later part of intra-uterine life or early infancy. Sometimes it is hereditary.

Total cataract

It may be unilateral or bilateral and is usually congenital. The entire lens is opaque. The lens matter may remain soft or may liquefy to form milky fluids contained in the capsule.

Acquired cataract

Acquired cataracts develop in the intrauterine period, and the opacity generally does not enlarge or change with age. In acquired cataracts, parts of the lens almost invariably remain transparent, and visual acuity is not completely impaired. Depending on the site of the opacities, cataracts may be anterior or posterior polar (limited opacities of the capsule of the lens), lamellar, and so forth.[59]

Mechanisms associated with cataract

Loss of transparency during human cataract formation results from a variety of complex metabolic and physiological mechanisms, which act in combination to change the refractive index.[60]

Studies on lens proteins indicate that post translational modifications occurs in the lens proteins during cataractogenesis as a result of chemical actions that include oxidation, glycation, Schiff base formation, proteolysis, transmidation, carbamylation, phosphorylation, and elevated calcium levels.[61] The post translational modifications alter attractive forces between lens proteins to favour aggregation, disruption of normal lens cell structure and opacification.[62]

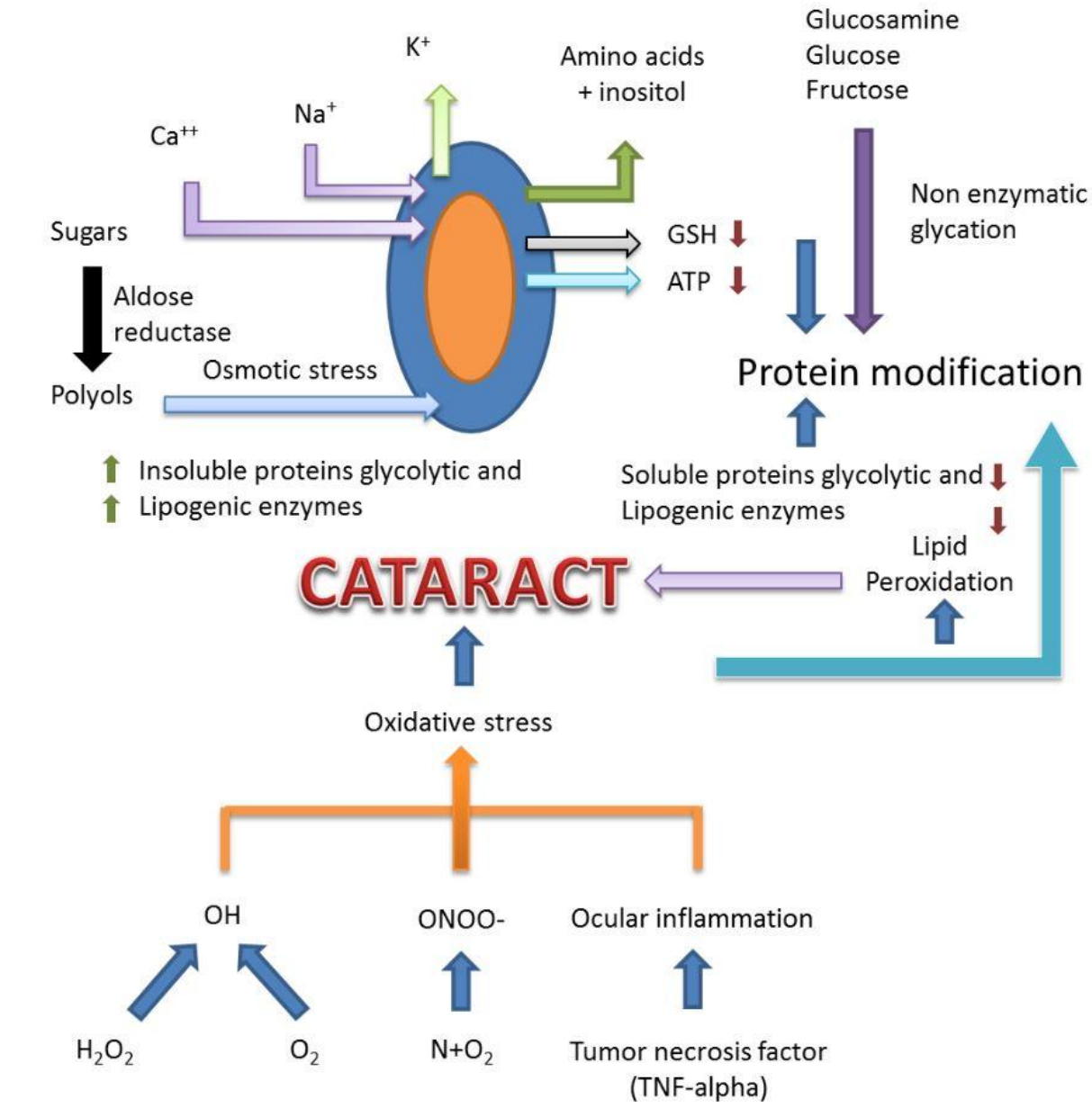

Fig. 2 Mechanisms associated with cataractogenesis

The multiple mechanisms proposed for cataractogenesis, the role of the following pathways in cataract development.

· Non enzymatic glycation
. Oxidative stress
· Polyol pathway

Non enzymatic glycation

Under hyperglycemic conditions, part of the excess glucose reacts non enzymatically with proteins or other tissue or blood constituents, thus increasing the physiological rate of non enzymatic glycation.[63] Chronic, irreversible abnormalities unaffected by normalization of blood glucose levels primarily involve long lived molecules, extra cellular 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 sugar cataract. The formation of advanced glycation end products (AGEs) begins with the attachment of a 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 Millard process. Levels of the unstable Schiff base increase rapidly, and equilibrium is reached after several hours. Once formed, Schiff base adducts undergo slow chemical rearrangement over a period of weeks to form more stable, but still chemically reversible, Amadori products. [64]

Specific chemical characterization of AGE proteins has been difficult, as Amadori products can theoretically undergo a large number of potential rearrangements. Immunological and chemical evidence indicates that progressive accumulation of AGEs in the diabetic eye lens contributes to accelerate cataractogenesis in hypoglycemic experimental animals and diabetic humans. [65,66]

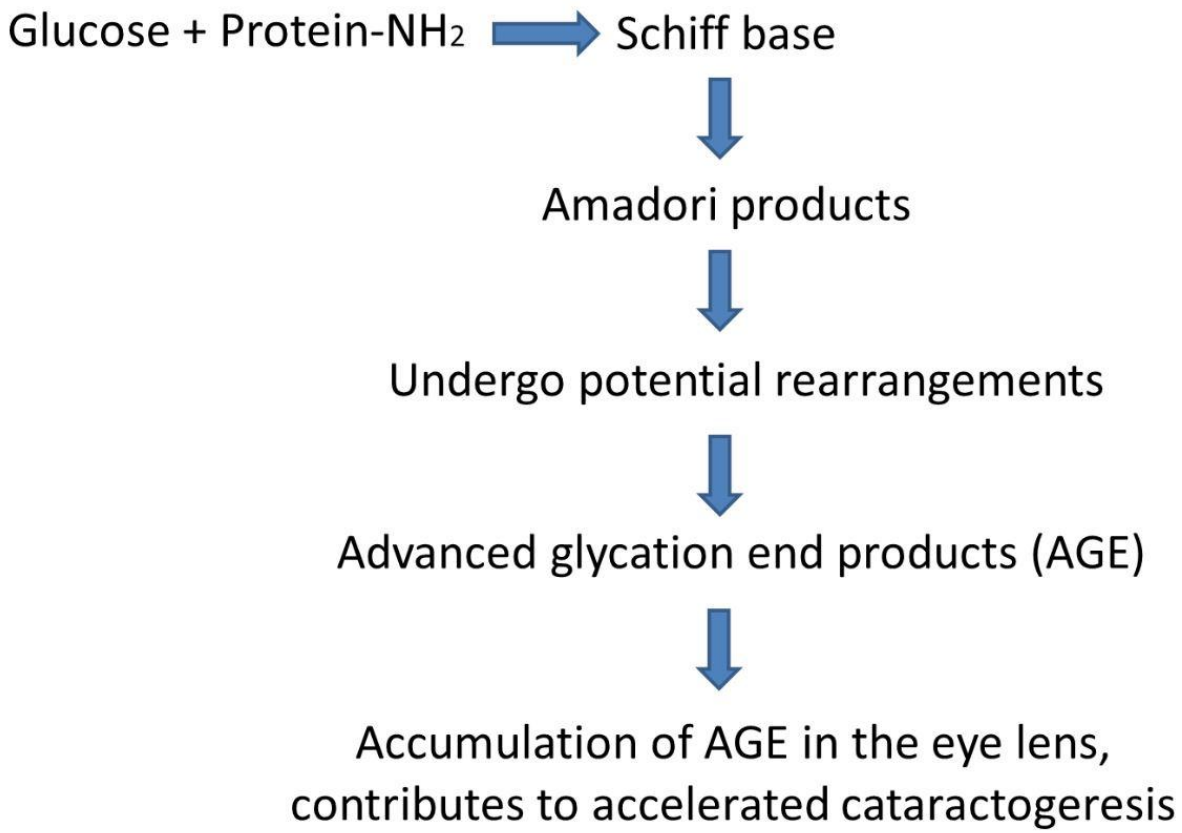

Fig. 3 Formation of advanced glycation end products

Oxidative stress

The osmotic and exogenous or endogenous oxidative stresses play an important role in the pathogenesis of cataract.[67] Oxidative stress may result from an imbalance between the production of reactive oxygen species (ROS) and the cellular antioxidant defense mechanisms. In the cells of the eyes, ROS may initiate a surge of toxic biochemical

reactions such as peroxidation of membrane lipids and extensive damage to proteins causing intracellular protein aggregation and precipitation and eventually leading to lens opacification.[68,69] On exposure of the eye to oxidative stress, the redox set point of the single layer of the lens epithelial cells quickly changes, going from a strongly reducing to an oxidizing environment. Almost concurrent with this change is extensive damage to the DNA and membrane pump systems, followed by loss of epithelial cell viability and death by necrotic and apoptotic mechanisms leading to cataract.[70,71]

Polyol pathway

The mechanism involved in the progression of diabetic cataracts is different from senile cataracts. The accumulation of polyols within the lens is the primary contributing factor. Certain tissues of the body, including the eye lens, do not require insulin for glucose and other simple sugars to enter. In diabetes, sugar is in high concentration 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 galctitol. These polyols cannot diffuse passively out of the lens and accumulate or converts to fructose. The accumulation of polyols results in an osmotic gradient, which encourages diffusion of fluid from the aqueous humor. The water drags sodium with it and the swelling and electrolyte imbalances result in cataract formation.

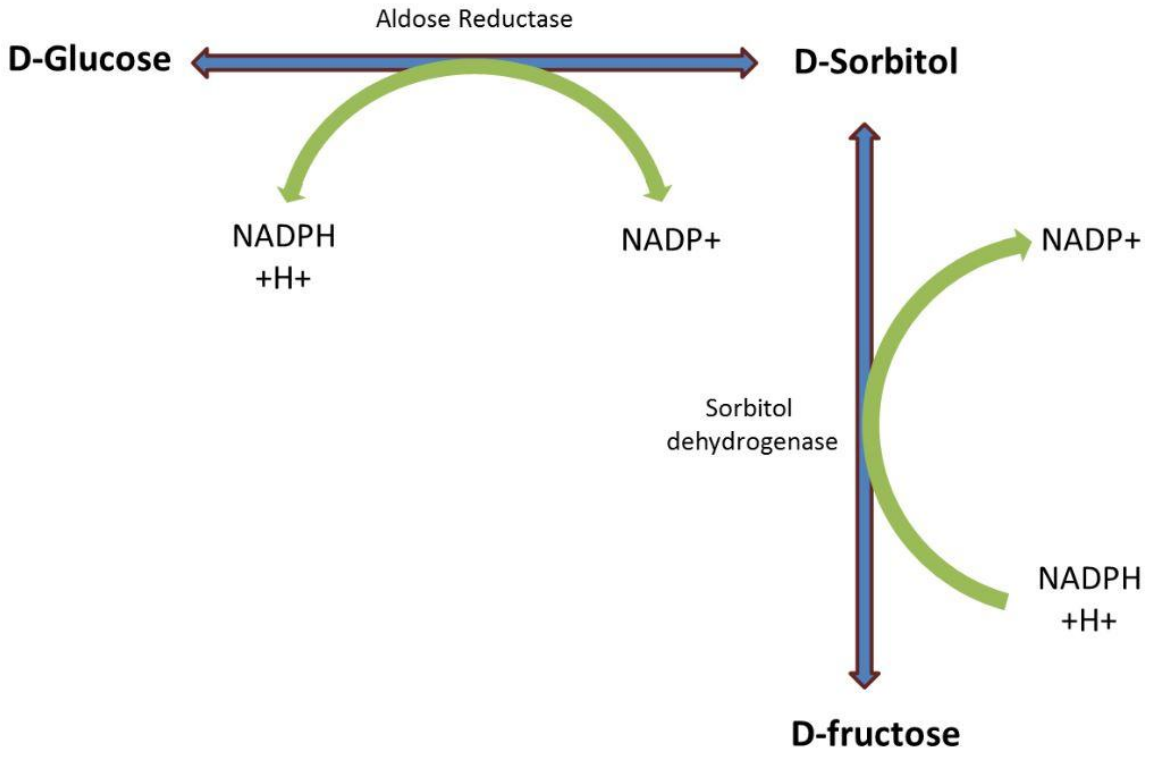

Fig4. Polyol pathway

Pharmacological strategies for prevention of cataract

Drugs have been developed which are aimed to interact at the level of altered lens metabolism and lens pathophysiology. The anticataract agents claimed to be effective *in vitro, in vivo* and in epidemiological studies may be broadly classified in the following categories:

- Aldose reductase inhibitors
- Non steroidal antiinflammatory drugs
- Agents acting on glutathione
- Vitamins, minerals, antioxidants and herbal drugs
- Miscellaneous agents

Aldose reductase inhibitors

ARIs are aimed to block the metabolic pathways of glucose responsible for diabetic vascular dysfunction. Their role in the prevention of diabetic cataract in animals is now well established.[72,73] Numerous natural and synthetic compounds have been found to inhibit aldose reductase. These so called ARI bind to aldose reductase, inhibiting polyol production. The rationale of using sorbitol -lowering agents has eroded over the years because the aldose reductase is remarkably sluggish with glucose. Furthermore, adult human lenses incubated in high glucose media do not accumulate sorbitol. There are a number of ARI known to possess anticataract potential and delay the galactose induced cataract in different experimental models. [74]

Some of these include alrestatin, sorbinil, sulindac, naproxen, aspirin, tolrestat, statil, and bioflavonoid. Flavonoids are among the most potent naturally occurring ARI. Several evaluations of *in vitro* animal lenses incubated in high sugar mediums have found flavonoids to inhibit aldose reuctase. [75,76]

Non steroidal anti-inflammatory drugs

Non steroidal anti-inflammatory drugs (NSAIDs) have emerged as another group of drugs with anticataract potential. The first indication regarding the probable use of NSAIDs as prophylactic anticataract agents came from studies on aspirin use in patients with rheumatoid arthritis and diabetes.[77] subsequently; a number of NSAIDs with diverse chemical structures were reported to delay the phenomenon in experimental animals. The NSAIDs extensively studied are aspirin, paracetamol, ibuprofen, naproxen, sulindac and bendazec.[78-80] The anticataract activity of these drugs is explained by virtue of their effect on different biochemical pathways. The mechanism associated with the protective effect of NSAIDs includes acetylation, inhibition of glycosylation and carbamylation of lens proteins.[81]

Anticataract activity of aspirin, sulindac and naproxen eye drops was also studied and they were found to delay both onset and progression of cataract in different models of cataractogenesis, moreover, there were no adverse side effects even after long term application.[82]

Subsequent studies further confirmed that aspirin is a potential anticataract agent.[83] Bendazac, a compound resembling indomethacin in its structure, emerged as a potential radical scavenger and anticataract agent. Bendazac protects lens and serum proteins denaturation *in vitro and in vivo*.[84,85] 5- hydroxybendazac, a derivative, was found to be more effective than the parent compound in protecting lens protein against cyanate, glucose-6-phosphate and galactose.[86]

Agents which act on glutathione

The most important function of glutathione (GSH) is to deactivate and render excess free radicals and keep them harmless. GSH is composed of the amino acids cysteine, glutamic acid and glycine and its synthesis within the lens takes place in two ATP dependent steps. There are several ways in which GSH or its depletion can affect the opacity of the lens.[87] The mechanisms of cataract prevention including;

- Maintaining sulphydryl (SH) groups on proteins in their reduced form preventing disulfide cross linkage.
- protecting SH groups on proteins important for active transport and membrane permeability and
- Preventing oxidative damage from H2O2.

The concentration of GSH decreases with age in the lens and more markedly in cataract.[88] GSH has been reported to control calcium influx and protect lens protein against damaging effects of osmotic and oxidative stress .89,90 Large amount of research has been done on antioxidants and vitamins, and the role of GSH in the prevention of cataract has been reported. A recent study indicates that vitamin E protects the antioxidative defense mechanisms directly or indirectly through increased levels of GSH.[91] The anticataract effect of melatonin (a scavenger of free radical), was demonstrated which was reported to be due to its stimulatory effect on GSH production.[92]

ROLE OF NUTRITIONAL SUPPLEMENTS IN PREVENTION & TREATMENT OF CATARACT

Vitamins

The potential role of vitamins in preventing cataract is well documented, especially vitamin C or ascorbic acid which plays an important part in

lens biology, both as an antioxidant and as a UV filter.[93] Dietary deficiency of vitamin C leads to reduction in lens concentrations of ascorbate.[94] A research study on guinea pigs shows that ascorbate inhibits galactose cataract.[95]

Similarly another study reveals that intake of ascorbate increases the level of vitamin C in rat lens.[96] Vitamin E also has an important part to play in lenticular antioxidant status. A number of studies have evaluated the anticataract potential of vitamin E and found to be effective against galactose, steroids and UV radiation induced cataract.[97-100]

Minerals

The excessive free radical attack implicated in the development of cataract can be prevented by dietary intake of micronutrients such as zinc, copper and manganese. Copper and zinc are required for the catalytic activity of metal protein and SOD.[101] Plasma levels of zinc and copper were found to be significantly low in cataract patients.102 Selenium is an integral part of the enzyme, glutathione peroxidase. A decrease in glutathione peroxidase activity has been found in the lenses of selenium deficient rats. [103]

Antioxidants

It is widely accepted that oxidative stress is a significant factor in the progression of cataractogenesis.[104,105] Oxidative stress is associated with increased reactive oxygen species and is known to accelerate cataract formation since superoxide is converted to a toxic substance, namely hydrogen peroxide. This reaction is prevented by antioxidant enzymes, namely catalase, superoxide dismutase and glutathione peroxidase. Antioxidants are key prophylactic agents in preventing oxidation related cataractogenesis. A large number of epidemiological and interventional studies have been investigated for the role of dietary antioxidant supplement in the incidence of cataract.

Carotenoids are natural lipid –soluble antioxidants. It is reported that persons with a high intake of carotene reduce the incidence of risk of cataract,[106] and the relationship between nuclear cataract and intake of alpha carotene, beta carotene, lutein, lycopene and cryptoxanthin stratifying by gender and by regular multivitamin use.[107] Among all carotenoids lycopene has a high antioxidative activity and experts a protective effect in varios diseases.[108]

Curcumin, the active principle of turmeric, has been shown to have antioxidant activity *in vitro and in vivo*.[109] The effect of curcumin on cataract has also been established. Curcumin delays the onset and maturation of galactose- induced [110] and streptozotocin induced diabetic cataracts.[111] Curcumin also prevents oxidative stress induced cataract.[112]

Herbal drugs

In recent years, great emphasis has been laid on exploring the possibility of using our natural resources to delay the onset and progression of cataract. A great number of medicinal plants and their formulations are reported to possess antioxidant properties and offer protection against cataract. Herbal medicines such as *Emblica officinalis* (Euphorbiaceae), *Atropa belladonna* (Solanaceae), *Azadirachta indica* (Meliaceae), *Berberis aristata* (Berberidaceae), *Acorus calamus* (Araceae), *Butea monosperma* (Fabaceae), *Cadaba indica* (Capparaceae),*Rosa indica* (Rosaceae), *Terminalia belerica* (Combretaceae) *Vitex negundo* (Verbenaceae), *Solanum nigram* (Solanaceae), *Tinospora cordifolia* (Menispermaceae) are used in eye disorders like cataract. [6-10]

The aqueous extract of *Ocimum sanctum* possesses potential anticataract activity against oxidative stress induced experimental cataractogenesis. The protective effect was supported by restoration of the antioxidant defense system.[113] The aqueous extracts of well-known herbal antidiabetic drugs namely *Pterocarpus marsupium* and *Trigonella foenum graceum* exerted a favorable anticataract effect.[114] A recent research study found that grape seed proanhocyanidin extract effectively suppressed cataract formation in rats.[115] Flavonoids from *Emilia sonchifolia* modulate the lens opacification and oxidative stress in selenite induced cataract.116 *Dregea volubilis* is a traditionally used medicinal plant for the treatment of various eye ailments, now its potential anticataract effect has been reported which is attributed to drevogenin D, a triperpenoid aglycone.[117]

Certain herbal drugs, especially *Ginkgo biloba* extract have been found to possess potential therapeutic effect in radiation induced cataract.[118] The anticataract activity of green tea (*Camellia*

sinensis) has been studied extensively and antioxidative potential is noted to be major mechanism in the prevention of cataractogenesis.

Miscellaneous agents

Various substances with diverse chemical structures and properties are reported to have protective effect against cataract in different experimental models. ACE inhibitors have found to afford protection from free radical damage in many experimental conditions.[119] Recently, the anticataract activity of lisinopril and enalapril was evaluated in glucose induced cataract *in vitro* and found to offer significant protection. It was concluded that the effect might be due to the antioxidant and free radical scavenging activity, as evidenced by a decrease in malondialdehyde in treated lens.[120]

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