

Special Article - Cataract Clinical Cases and Images

Age Related or Senile Cataract: Pathology, Mechanism and Management

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Thiruvananthapuram, 695581, Kerala, India**Received:** April 04, 2016; **Accepted:** June 09, 2016;**Published:** June 15, 2016**Abstract**

Cataract is a serious eye disease accounts for the major cause of blindness globally. It is characterized by the loss of transparency and opacification of eye lens; an opaque lens scatters the light as it passes through it and prevents the sharpness of the image in the retina and vision becomes blurred. Cataractogenesis is associated with numerous factors acting over many years. The major reason lies behind the formation of cataract is the damage induced by free radicals, reactive oxygen/ nitrogen species to the crystalline lens. In this review, we have discussed the different events and mechanisms associated oxidative damage in the lens that gives rise to cataractogenesis, the present treatment procedures and management of cataract.

Keywords: Cataract; Eye; Lens; MAPK pathway; Oxidative stress

Introduction

The visual system is the various components of eyes functioning in the process of vision by reacting to light, gain information about their environments and help to recognize the outer world by the process of visual perception and the resulting perception is called vision or sight. Vision is one of the most complex functions and it requires the cooperation of many intricate parts and the eye is made up of three coats. The outer layer or tunica externa or tunica fibrosa composed of the cornea and sclera. The middle layer or tunica media or tunica vasculosa or uvea consists of the choroid, ciliary body and iris. The inner layer or tunica interna or tunica nervosa or retina is the light-sensitive tissue layer equipped with photoreceptors. Within these coats are the aqueous humour, the vitreous body and the flexible lens. The aqueous humour is a clear fluid that is contained in two areas: the anterior chamber between the cornea and the iris and the posterior chamber between the iris and the lens. The lens is suspended to the ciliary body by the suspensory ligament (Zonule of Zinn) made up of fine transparent fibers. The vitreous body is a clear jelly that is much larger than the aqueous humour present behind the lens, and the rest is bordered by the sclera, zonule and lens. Vision begins when light rays are reflected off an object and enter the eyes through the cornea, the transparent outer covering of the eye. The cornea bends or refracts the rays that pass through a round hole called the pupil. The iris, or colored portion of the eye that surrounds the pupil, opens and closes to regulate the amount of light passing through. The light rays then pass through the lens, which actually changes shape so it can further bend the rays and focus them on the retina at the back of the eye. The retina is a thin layer of tissue at the back of the eye that contains millions of tiny light-sensing nerve cells called rods and cones, for bright light and dim light respectively. These cells in the retina convert the light into electrical impulses. The optic nerve sends these impulses to the visual cortex in the brain where a composite image is produced [1].

The lens plays a crucial role in focusing unimpeded light on the retina. Eye lens is a biconvex, transparent, elastic, avascular structure

that is located just behind the iris and the pupil that receives all its nutrients from aqueous and vitreous humor. The lens is suspended in place by the zonular fibers, which attach to the lens near its equatorial line and connect the lens to a ring of muscular tissue, called the ciliary body. 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 lens is capable of changing its 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 by the process, accommodation [2]. The lens is flexible and its curvature is controlled by ciliary muscles through the zonules.

Structurally, the lens has three main components; capsule, epithelium and fibers. The capsule is the transparent, elastic, acellular basement membrane that completely encloses the whole cell mass and is the thickest basement membrane of the body. It is made up of type IV collagen and glycosaminoglycans and its main function is in the process of accommodation by molding the shape of the lens in response to tension from zonules [3]. The lens epithelium represents a single sheet of cuboidal cells just beneath the capsule at the anterior surface of the lens and the intercellular communication between the adjacent epithelial cells is through gap junctions. These monolayered cells regulate most of the homeostatic functions such as nutrient and ion transport, energy metabolism etc. in the lens and maintain the transparency of the lens. The fibers are long, thin, transparent cells form the bulk of the lens that the epithelial cells elongate, divide and differentiate to form the regularly arranged lens fibres. The new lens fibres are laid on the older deeper fibres and are formed throughout the life. Lens fibers arranged in zones, the cytoplasm of the cells of superficial bow region and the newly formed lens fibres contain nucleus, mitochondria, golgi complex, rough endoplasmic reticulum and polysomes and later on, all the light scattering organelles undergo an in built suicide process that minimizes light scatter and favors transparency [4].

Lens is an unusual organelle in its composition that with

extraordinarily high protein content and low water content and this enables the lens to have a refractive index considerably greater than its fluid environment. Transparency of the lens is made possible by various factors such as normal physiology of epithelial cells, regular arrangement of the lens fibers, architecture of structural and functional proteins etc. Any alteration in the normal architecture of eye lens is associated with the change in the clarity of the lens or opacification and eventually forms the cataract. It is a significant visual impairment globally and as per the latest statistical records of World Health Organization (WHO), the total number of persons with visual impairment worldwide in 2010 was 285 million and cataract is responsible for 51% of world blindness, which represents about 20 million people [5]. Cataracts may be congenital, age related or secondary. Congenital cataracts, which are present at the birth and are, the less common cataract. The main types of age-related cataracts are nuclear sclerosis, cortical and posterior subcapsular. Nuclear cataracts form in the center of the lens and cause the nucleus to become hard or sclerotic with the deposition of brown pigment. Cortical cataracts are due to the opacity lens cortex and posterior subcapsular cataracts attack the back of the lens adjacent to the capsule. Secondary cataracts are caused by diseases like glaucoma and diabetes or medications such as steroids and radiations [6]. Cataract is associated with the gradual reduction of visual quality and is accompanied by a series of pathways that associated with imbalance in oxidant-antioxidant status [7], membrane lipid peroxidation [8], defected cellular communication [9], ion imbalance [10], modification, aggregation and accumulation of proteins [11,12], lenticular cell death [13,14] inflammation [15,16] etc. Hence, based on a variety of model systems; including cell/ organ culture, animal and human studies, the review focused on exploring the various pathways relating to the pathology of cataract, current treatment modalities and therapeutic preventive measures.

Mechanism of Cataract Formation

Oxidant-antioxidant imbalance

As lens is an organelle that exposed to light throughout the life time and prone to oxidative attack induced by reactive oxygen/nitrogen species (ROS/RNS) [17,18], it is equipped with an efficient antioxidant system for defending these oxidative/nitrosative stress. The major enzymatic antioxidants in the lens are superoxide dismutase [19], Catalase [20], glutathione peroxidase [21], glutathione reductase, glutathione-S-transferase [22], thioredoxin system etc. [23] and non-enzymatic antioxidants are reduced glutathione [24], ascorbic acid, Vitamin A, E etc. [25-28]. These antioxidants protect lens from damage induced by toxic radicals/species and oxidative stress is a metabolic state in which excessive levels of highly reactive and unstable compounds overwhelm the ability of antioxidants that quenches them. Decline in the activity of all these enzymes and molecules are reported in the formation of cataract [29,30].

Stress signaling

NFκB is a ubiquitous transcription factor activated by ROS. Normally it is located in the cytoplasm in an inactive complex with inhibitor kappa B (IκB) and oxidative stress induce the release of IκB resulting in translocation of NFκB to the nucleus and it binds to DNA control elements and thus influences the transcription of specific genes associated with stress signaling and cell death. NFκB-mediated pathway is reported to present in lens epithelial cells

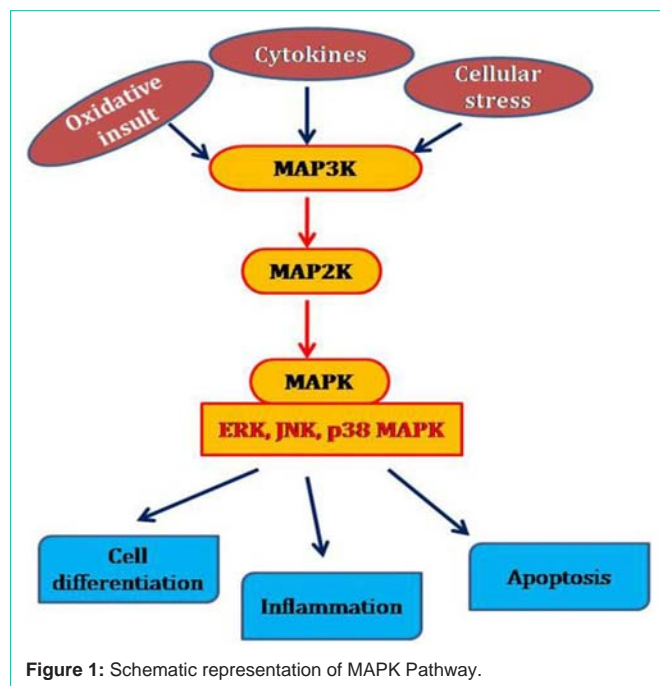


Figure 1: Schematic representation of MAPK Pathway.

exposed to hydrogen peroxide [31] and UV stress [32] indicating its role in cataractogenesis.

MAPK pathway

Mitogen-activated protein kinases (MAPKs) are serine-threonine protein kinases that play the major role in the regulation of cell proliferation, cell differentiation and cell death. MAPKs family is characterized by the conserved activation domain and specialized activation module and it comprised of extracellular signal-regulated kinases (ERK-1 and ERK-2 isoforms), the c-Jun N-terminal kinases (JNK-1, JNK-2, and JNK-3 isoforms) and the p38 MAPKs (p38α, p38β, p38γ and p38δ isoforms). Each subgroup of MAPKs is activated through a cascade of sequential phosphorylation events, beginning with the activation of MAPK kinase kinases (MAP3Ks). The MAP3Ks in turn phosphorylate and activate downstream MAPK kinases (MAP2Ks), which in turn stimulate MAPK activity through dual phosphorylation on threonine and tyrosine residues within a conserved tri-peptide motif. Activated MAPKs phosphorylate diverse substrates in the cytosol and nucleus to bring about changes in protein function and gene expression that execute the appropriate biological such as proliferation, differentiation, inflammatory responses, apoptosis etc. (Figure 1). MAPK phosphatases (MKPs), which recognize the TXY amino acid motif present in MAPKs, dephosphorylate and deactivate MAPKs [33]. MAPK pathways play discrete roles in the survival and normal functioning of lenticular epithelial cells and thus the transparency of the lens [34]. Oxidative stress is a predominant extracellular stimulus that activates MAPK pathways and many reports confirm the involvement of MAPK pathway in lens epithelial cell death and cataract formation through the disorganization of gap junctions and cytoskeletal assembly in the lens [35-37].

Protein kinase pathway

Protein kinase C (PKC) is a family of serine/threonine kinases that functions in the process of cellular signaling by phosphorylation

and like MAPKs, PKCs are activated by oxidant damage and calcium. The PKCs have been grouped into three classes (PKC α , β and γ) depending on the cofactors required for their activation. PKC γ moves to the plasma membrane following activation and phosphorylates targets such as receptors, structural proteins and gap junction proteins and reported in lens opacity [38-40].

Protein modification and removal of modified proteins

Proper arrangement of lens proteins plays the major role in the maintenance of transparency and modification of structural and functional proteins in the lens as a result of oxidation, proteolysis, transamidation, carbamylation, phosphorylation etc. is reported in the lens opacity [41].

Xanthine oxidase is a pro-oxidant enzyme normally present in ocular tissues and the raised activity of xanthine oxidase forms an important source of free radicals and is a lens oxidative stress marker [42]. Oxidants generated by xanthine oxidase system imposes cross-linking and aggregation of crystallins, loss of cellular redox balance, oxidation of DNA bases and lipid peroxidation of polyunsaturated fatty acids and inflict the damage to the lens membrane active transport pumps and implicated in cataractogenesis [43]. Proteins may contain several actual or potential sulfhydryl groups and are the potential sites for reversible oxidation-reduction reactions and thioltransferases in the lens prevent the oxidation of proteins and maintain redox homeostasis in the lens. Modification of proteins precedes a cascade of events starting with protein disulfide cross-links, alteration of protein conformation, protein/enzyme deactivation, protein solubility loss and eventually lens opacification [11,44].

Carbonylation of proteins is a metal accelerated modification of proteins occurring in the side chain of amino acids such as lysine, arginine, proline or histidine and is a widespread indicator of severe oxidative damage an irreversible oxidative damage leading to the loss of protein function. carbonylated proteins tend to form high molecular-weight aggregates that are resistant to degradation, accumulate as damaged or unfolded proteins and carbonyls are reported in the lenses of cataractous lenses [45].

Crystallins are the predominant structural proteins in the lens constitute about 90% of water soluble proteins of the lens and add to the transparency and refractive properties by its proper packaging. The three main crystallin types found in the lens are α , β , and γ crystallins. Crystallins tend to form soluble, high molecular weight aggregates that pack tightly in lens fibres, thus increasing the index of refraction of the lens while maintaining its transparency. α crystallins are the major crystallins comprised of α A and α B crystallins have chaperone function [46,47] involved in remodeling and protection of the cytoskeleton, inhibition of apoptosis and resistance towards oxidative stress [48] (Andley 2007). Also, the molecular association of β and γ crystallins form dense packaging and this minimizing light scattering and provides an optimum in the transparency of lens [49]. Several studies have described extensive truncation of human lens α , β , and γ Crystallins during cataract development through several modifications such as aggregation and cross-linking which leads to protein insolubilization [50,51].

Intermediate filaments are the major cytoskeletal elements responsible for the transparency of the lens and the main intermediate filaments are filensin, phakinin and phakinin. Filensin and phakinin

forms complex with α A and α B crystallins and they together termed as beaded filaments and vimentin forms a network in the lens that functions in the lens architecture and also interacts with flensing [52]. Degradation of filensin and phakinin and vimentin deamidation was reported in the age-related cataract lenses [53,54].

Gap junctions are transmembrane aqueous channels that connect the cytoplasm of neighboring cells and allow the passage of molecules up to the size of 1 kDa between the connected cells and they respond to a variety of factors, such as Ca^{2+} levels, voltage, pH and phosphorylation events [55,56]. Different arrangements of gap junctions exist between the different regions of epithelial cells, between the fiber cells, and between the epithelial and fiber cells [57]. Connexins are a family of four-pass transmembrane proteins that assemble in groups of six to form hemichannels or connexons and two hemichannels then combine to form a gap junction. The combination of different connexins differs in the physiological properties, including unitary conductance, permeability, gating, and regulation by different protein kinase-dependent pathways. Connexins play the major role in the lens transparency and cataract that they maintain the intracellular symphony in the lens. With defective hemichannels and gap junction, metabolite supply and catabolite removal reduced the metabolic center of the lens; epithelial cells become malfunctioned resulting in vision impairment. Connexins 43, 46 and 50 are the major connexins in the lens although their distribution varies among lens epithelia and fibers. Although connexins are phosphoproteins, many abnormal phosphorylation patterns of connexins are reported in opaque lenses. All the connexin gap junctions and hemichannel functions are affected by oxidative stress and implicated in the formation of cataract [58]. Connexins are prone to phosphorylation by PKCs and nitrosylation by nitric oxide [59]. PKC-dependent phosphorylation of Ser368 in Cx43 affects its channel behavior, which leads to the decreased intercellular communication and altered permeability [60,61].

Transglutaminase 2 is an inducible transamidating acyltransferase that catalyzes Ca^{2+} dependent protein modifications by inducing of covalent cross-links between peptide bound glutamine and lysine residues and is up-regulated often in cells undergoing oxidative stress and apoptosis [62,63]. Deamidation and further denaturation of crystallins are implicated in the pathology of cataract [64,65]. Deamidation causes unfolding of α Crystallin molecules; partially unfolded protein may possess increased exposure to key hydrophobic residues, which are involved in the chaperone activity [66].

Matrix metalloproteinases (MMPs) represent a family of endopeptidases that are capable of degrading the extracellular matrix molecules and thereby of maintaining normal physiological processes such as morphogenesis and influencing cell biological activities [67] and the most widely studied MMPs in the ocular tissues are MMP 2 and MMP 9. Lens cells are capable of synthesizing MMPs upon injury to the lens, such as UV irradiation [68], oxidative stress [69] and MMPs digests type IV collagen and laminin, cleaves and aggregates β B1 crystallin and produce lens opacity [15,70].

Oxidant damage to lens proteins and its accumulation is implicated in the formation of cataract. For maintaining the transparency of lens, the damaged proteins should be removed and the process is done by the ubiquitin-proteasome mechanism. Degradation of a

protein via the ubiquitin-proteasome pathway involves tagging of the substrate protein by the covalent attachment of multiple ubiquitin molecules and the subsequent degradation of the tagged protein by the 26S proteasome. Multiple enzymes are involved in the process of ubiquitinylation through a series of ATP-dependent enzymatic steps. In this process, ubiquitin is first activated by ubiquitin activating enzyme (E1), activated ubiquitin is then passed to a ubiquitin carrier protein (E2) both via the formation of a thiol ester bond. The activated ubiquitin is then either directly linked to substrates or is linked to substrates via ubiquitin ligase (E3), targeted to 26S proteasome for proteolysis and ubiquitin is recycled [71]. Ubiquitin-dependent proteasome pathway is under the control of oxidant response and the activity of both activating and conjugating enzymes were altered in the aged lens [72,73] and amino acid residues of ubiquitin which is involved in the protein degradation mechanism is modified by oxidants [74]. All these events compromise the function of ubiquitin-proteasome pathway in the cataractous lens.

Lipid peroxidation

The integrity of lenticular membrane is one of the important factors that keep lens transparency. Lens membrane serves as an impermeable barrier to cations and is equipped with membrane ATPases for the homeostasis of water, calcium, sodium and potassium. Lipid oxidation is a major harmful consequence of ROS formation as it produces irreversible oxidative changes of membranes. It has been shown to induce disorganization of the membrane, modification of membrane proteins, alters the physiological functions of cell membranes. Lipid peroxidation has been implicated in the pathogenesis of cataract because the lethal peroxidation products induce fragmentation of soluble lens proteins and damage critical membrane structures, epithelial cell apoptosis and correlating with an increase in lens opacity and changes in the refractive properties of the lens [8,75-77].

Ion imbalance

As discussed earlier, lens membrane is equipped with various pumps for maintaining the optimal ion homeostasis. To maintain such steep ionic gradients, the lens must continually expend energy to drive sodium and calcium outward, at the same time functioning to accumulate other ions such as potassium. Cellular calcium homeostasis is achieved by a balance between the inward leak and out flow by plasma membrane Ca^{2+} ATPase and Na^+ Ca^{2+} exchanger. Progressive elevation of sodium, marked loss of potassium and several fold increment of calcium are documented in the literature in the pathology of lens opacification [78,79]. A prolonged increase in the calcium concentration would be expected to activate proteases such as calpain and could induce the formation of protein aggregates and irreversible breakdown of important structural proteins and lead to lens opacification [80-82]. The decrease of calcium ATPase activity is also reported with cataract due to lipid structural changes [83,84], increase in the oxidation of sulf-hydrul groups [85] and down-regulated ATP utilization [86].

The redox state of the cell is largely reliant on the trace elements iron and copper by virtue of their capability to go through reversible redox reactions and is maintained within strict physiological limits. Accumulation of these metals may disrupt the intracellular redox status, alter protein conformation and inhibit protein function

through metal substitution and interactions with sulfhydryl groups by catalyzing the formation of reactive hydroxyl radicals via Fenton reaction [87]. Iron and copper is implicated in the pathogenesis of cataracts by damaging lipid membranes and lens capsule, cross-linking and insolubilization of lens proteins, leakage of beta and gamma crystallins into the aqueous humor through the production of hydroxyl radicals and peroxy radicals [88-91].

Inflammation

Inflammation is a series complex biological response of body tissues to harmful stimuli; although Inflammation is a protective response, it is reported in various diseases. Nitric oxide (NO) is a free radical gas, signaling messenger and the role of the NO in inflammation are well established. Nitric oxide is normally present at a low concentration in the aqueous humor that bathes the lens [92]. Constitutive levels of NO production contribute normal ocular function, but in response to induction of inducible nitric oxide synthase (iNOS) by oxidant trauma, the production of NO is elevated. NO contribute to oxidation stress by developing more powerful oxidative agents such as peroxynitrite with superoxide [93] (Horton, 2003) which is highly reactive and inflicts cytotoxicity and nitrosative stress to proteins [94] and reported in cataractogenesis by type IV collagen and laminin and cleaves βB1 crystallin [18,95].

Interleukin (IL) -18 is a pleiotropic cytokine belonging to the IL-1 family induces interferon (IFN) γ , NF κB and iNOS and plays an important role in inflammatory action [96,97]. The increased generation of ROS accelerates the production of inflammatory cytokines like IFN γ in the lens through MAPK pathway. It has been reported that IFN-g leads to cataract development by causing the apoptosis of lens epithelial cells and associated with cataract development [14,98].

Lens epithelial cell apoptosis

As discussed earlier, metabolic homeostasis of a single layer of lens epithelial cells is the critical event in maintaining the transparency of the entire lens [99]. The cells have a relatively long life span under normal physiological conditions, the factors such as oxidative stress alter the viability of lenticular epithelia resulting in lens opacification. Enormous number researches confirmed the role of lens epithelial cell death as the key biochemical event underlying the process of cataractogenesis through a series of events mentioned above [14,100,101]. Oxidative damage, increased calcium level, membrane damage, inflammatory responses etc. activate lenticular apoptosis through the activation of pro-apoptotic factors, Caspases and inhibition of anti-apoptotic agents [102].

Treatment of cataract

In the modern century, surgical removal of cloudy/opaque lens and replacement with a synthetic intraocular lens is the only available treatment for cataract. Phacoemulsification, extracapsular cataract extraction and intracapsular cataract extraction are the major surgical procedures employed for cataract treatment throughout the world [103].

Phacoemulsification

It is the most common procedure used by developed countries. In this technique, a very small incision (2-3 mm) is produced on the

surface of the eye in or near the cornea. A thin ultrasound probe is inserted into the eye and uses ultrasonic vibrations (40,000 Hz) to dissolve (phacoemulsify) the clouded lens. These tiny fragmented pieces are then suctioned out through the same ultrasound probe. Once the cataract is removed, an artificial lens is placed into the thin capsular bag that the cataract previously occupied. In phacoemulsification, cataract surgery can perform in less than 30 minutes and usually requires only minimal sedation and no stitches are used to close the wound [104].

Extracapsular cataract extraction

This technique requires a larger incision so that the cataract can be removed in one piece without being fragmented inside the eye. It involves the removal of almost the entire natural lens through a large (usually 10-12 mm) incision made in the cornea or sclera, while the elastic lens capsule (posterior capsule) is left intact to allow implantation of an intraocular lens. This surgical technique requires a various number of sutures to close the larger wound and visual recovery is often slower. Manual small incision cataract surgery is an evolution extracapsular cataract extraction characterized by an appropriately constructed scleral tunnel that does not require suturing. Here the wound being relatively smaller than the above still markedly larger than a phaco wound [105].

Intracapsular cataract extraction

It involves the removal of the lens and the surrounding lens capsule in one piece and the intraocular lens is placed in front of the iris. The procedure has a relatively high rate of complications due to the large incision required and pressure placed on the vitreous body.

Complications of cataract surgery

Although surgery is an effective measure for cataract blindness, it is not free from post-operative complications. The major risks associated with post-surgery are inflammation (swelling and redness) in the eye, swelling of the retina (cystoid macular oedema); where fluid builds up between layers of the retina at the back of the eye, swelling of the cornea- where fluid builds up in the cornea at the front of the eye; this usually clears itself, retinal detachment; a rare complication where the retina (layer of nerve cells inside the back of the eye) becomes separated from the inner wall of the eye, infection in the eye, such as endophthalmitis (a rare bacterial infection), glaucoma, secondary cataract etc. [106].

Preventive protection of cataract

Even though cataract surgical techniques are efficient treatment modalities, there are people around the globe with barriers for accessing all these facilities because of insufficient financial resources, lack of awareness etc. [107]. As cataract is a protein degenerative disorder, its irreversible nature directs vision researchers in the track of preventive protection for the management of cataract blindness. A noteworthy vision researches indicate the role of nutritional intrusion as a way to reduce the risk of cataract. As oxidative stress forms the key behind the pathological events associated with cataract, many studies have been focusing to explore the efficacy of antioxidants in the prevention of cataract. Studies recommend that optimizing intakes of lutein, zeaxanthin, B vitamins, and multivitamin supplements may be advantageous in diminishing risk of nuclear and possibly cortical

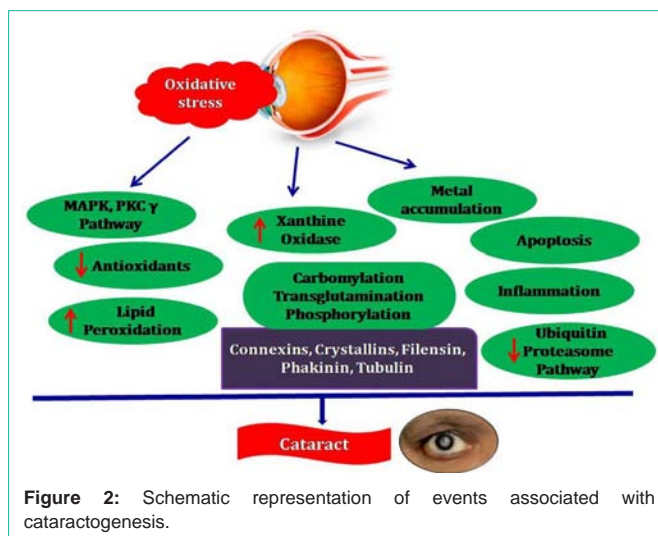


Figure 2: Schematic representation of events associated with cataractogenesis.

cataract [108]. Also many indigenous plants and plant-derived compounds have been shown to protect lens transparency in both *in vitro* and *in vivo* models such as luteol, luteolin by modulating antioxidant status and preventing apoptosis [83], rutin through blocking chaperon activity of a Crystallin [109,110], curcumin by inhibiting iNOS [111], resveratrol by lowering lipid peroxidation [112] etc. The plants reported to have anticataractogenic potential are *Cassia tora* [63,77], *Vitexnegundo* [113], *Moringaoleifera* [114], *Ginkgo biloba* [115], *Ocimum sanctum* [116] etc. Thus the incorporation of these nutrients, plants and compounds is recommended for eye health and to prevent the onset and maturation of lenticular opacities through the way of prevention by functional foods.

Conclusion

Thus, the pathophysiological position of the oxidant-antioxidant balancing systems in the lens and cataract blindness is justified here. Through MAPK pathway, oxidative damage on lens induces membrane damage, metal accumulation, protein modification and accumulation, inflammation, lenticular apoptosis, etc. (Figure 2) and all these alter the refractive properties of the lens resulting in the opacity and cataract. Although modern surgical procedures are available for the cataract treatment, it has its own limitations and complications and natural product based nutritional therapy is a newly emerging cost effective area in the field of vision research for cataract management by the way of precautionary protection.

Acknowledgement

Acknowledged to University Grants Commission (UGC), New Delhi for the financial support as a research grant.

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