LITERATURE REVIEW

1) Umamaheswari et al, (2011) evaluated the effect of hydromethanol peel extract of *Citrus aurantium* Linn. against naphthalene-induced cataractogenesis in rats. Traditionally, dried peels of *C. aurantium* were used as anti-oxidant, anti lipolytic, anti *Helicobacter pylori*, antiscorbutic and promote human platelet aggregation. The extract at a dose of 100 and 200 mg/kg b.w. were given orally to *Wistar* albino rats simultaneously with naphthalene (0.5 g/kg for first 3 days and 1g/kg thereafter for a period of 25 days). Vitamin E (50 mg/kg) was used as the standard. Cataract progression due to naphthalene feeding was monitored using an ophthalmoscope and classified into 5 stages. At the end of the treatment, levels of malondialdehyde (MDA), lipid hydroperoxides (LH), carbonyl and sulfhydryl (SH) content, enzymatic and non-enzymatic antioxidants in lens homogenate were measured. Administration of naphthalene produced a mature cataract and an increase in the opacity index. In addition, there was a significant increase in LH and protein carbonyl content and a decrease in protein SH content and antioxidant enzymes when compared to normal control. Ophthalmoscopic observations indicated that simultaneous administration of the extract delayed the onset and maturation of cataract and prevented the peroxidative damage caused by naphthalene, which is evidenced from the improved antioxidant potential. *C. aurantium* peel extract protected the lens against naphthalene-induced oxidative damage which might be helpful in delaying the progression of cataract.

2) Lakshmi KS et al, (2010) investigated the allylmercaptocaptopril (AMC) is a covalently bonded product of allicin and captopril has been evaluated for its anticataract activity against selenite induced cataract iexperimental animals. We wanted to evaluate its anticataract potential in galactosemic cataract to elucidate biochemical mechanism to appraise its activity. We examined the protective effect of AMC in both in vitro and in vivo models of galactose-induced cataract in rats and compared the effect with captopril. We evaluated the effect of both captopril and AMC on onset and maturation of cataract in galactosemic cataract. AMC reduced the rat lens polyol level, the marker of osmotic stress induced by galactose when compared with galactose treated and captopril treated lens. Glucose-6-phosphate dehydrogenase, succinate dehydrogenase, lactate dehydrogenase activity and reduced glutathione level were decreased in the galactose treated group compared with normal lenses. AMC treatment significantly restored these biochemical levels compared with the galactose treated group. The second, in vivo phase of the study revealed that AMC treatment significantly delayed the onset and maturation of cataract.
in galactosetreated rats compared to captopril treatment. These results support the view that AMC counteracts the effects of galactose in inducing cataract. The anticataract effects of AMC may be related to its intrinsic ability to protect and restore the activities of lens enzymes and the bioavailability of glutathione respectively.

3) **Umamaheswari and Chattejee (2008)** investigated the effect of the fractions of *Coccinia grandis* on naphthalene-induced cataractogenesis in rats. The cataract progression due to naphthalene feeding was monitored using an ophthalmoscope and classified in to 5 stages. At the end of the experiment, levels of malondialdehyde, lipid hydroperoxides, and carbonyl and sulfhydryl content, enzymatic and non-enzymatic antioxidants in lens homogenate were measured. In addition, there was a significant increase in lipid peroxidation and protein carbonyl content and a decrease in protein sulfhydryl content and antioxidant enzymes when compared with healthy controls. The results indicates, the animals treated with naphthalene showed a varying degree of cataractogenic changes as evidenced by about 66.6% of animals in stage 4 and 33.3% in stage 5 on the 28th day of treatment. none of animals treated with the petroleum ether, chloroform and ethyl acetate fractions of *C.grandis* showed mature stage 5 cataracts on the 28th day.

4) **Raju et al., (2007)** investigated the influence of kynurenines in pathogenesis of cataract formation in tryptophan–deficient regimen in *Wistar* rats. L- Tryptophan is an essential amino acid and its deficiency is involved in various pathologies. The rats were maintained on tryptophan deficient diet and there was decrease in protein content, kynurenines, reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione-S-transferase (GSTs) and tryptophan-fluorescence intensities and an increase in lipid peroxidation indicative of oxidative stress. The above changes were normalized in the rats on supplementation of 0.05% tryptophan in their diets. These results suggest that tryptophan-deficiency in the diet leads to an overall significant decrease in kynurenines and levels of antioxidant enzymes (except SOD) in ocular tissue with a concomitant lenticular opacification. The results suggest that diet with adequate tryptophan has protective influence and is of immense benefit in mitigating the changes that may otherwise contribute to lenticular opacities.

5) **Son et al., (2007)** reported that taurine prevents oxidative damage of high glucose-induced cataractogenesis in isolated rat lenses. taurine has antioxidant capacity and its level in diabetic
cataractous lens in markedly decreased. Taurine is a part of antioxidative defense mechanism involved in protecting the lens against high glucose-induced oxidative stress and tissue damage. Lenses were isolated from male Sprague-Dawley rats weighing 180-200g and cultured in high-glucose medium. The culture of lenses in high glucose medium increased the weight and opacity of lenses and the carbonyllated protein level, and decreased glutathione (GSH) content. Although there were no significant effects of taurine on the weight or opacity of lenses, pretreatment of lenses with taurine significantly reversed the level of protein carbonyl and GSH to those of controls.

6) Doughari (2006) evaluated the antimicrobial activity of Tamarindus indica Linn. The study also investigated the chemical constituents of the plant and the effect of temperature and pH on its antimicrobial activity. The antimicrobial activity of the concentrated extracts was evaluated by determination of the diameter of zone of inhibition against both gram negative and gram positive bacteria and fungi using the paper disc diffusion method. The results of the phytochemical studies revealed the presence of tannins, saponins, sesquiterpenes, alkaloids and phlobatamins and the extracts were active against both gram positive and gram negative bacteria. The activity of the plant extracts were not affected when treated at different temperature ranges (4°C, 30°C, 60°C and 100°C), but was reduced at alkaline pH. Studies on the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the extracts on the test organisms showed that the lowest MIC and the MBC were demonstrated against Salmonella paratyphi, Bacillus subtilis and Salmonella typhi and the highest MIC and MBC was exhibited against Staphylococcus aureus. Tamarindus indica has broad spectrum antibacterial activity and potential source of new classes of antibiotics that could be useful for infectious disease chemotherapy and control.

7) Gritz et al., (2006) investigated the effect of antioxidant supplement in the prevention of cataract. The primary outcome variable was change in nuclear opalescence over time. Secondary outcome variables were cortical and posterior subcapsular opacities and nuclear colour changes; best corrected visual acuity change; myopic shift; and failure of treatment. Annual examinations were performed for each subject by three examiners, in a masked fashion. Multivariate modelling using a general estimating equation was used for analysis of results, correcting for multiple measurements over time. The results Initial enrolment was 798 subjects. Treatment
groups were comparable at baseline. There was high compliance with follow up and study medications. There was progression in cataracts. There was no significant difference between placebo and active treatment groups for either the primary or secondary outcome variables. Antioxidant supplementation with b carotene, vitamins C and E did not affect cataract progression in a population with a high prevalence of cataract whose diet is generally deficient in antioxidants.

8) Langade et al., (2006) studied the in vitro prevention using ACE inhibitors of cataract induced by glucose. Goat lenses were incubated in artifical aqueous humor containing 55 mM glucose with lisinopril or enalapril in different concentrerations at room temperature for 72 h. Biochemical parameters studied in the lens were electrolytes (Na⁺, K⁺) Na⁺ K⁺-ATPare activity, Malondialdehyde (MDA) and proteins. Glucose-induced opacification of goat lens began 8-10 h after incubation and was complete in 72-80 h. Cataractous lenses showed higher Na⁺, MDA (p<0.001), lower Na⁺ - K⁺ -ATPase activity and water soluble protein content. Lenses treated with lisnopril or enalapril in concentratios of 1, 5 and 10 ng/ml showed higher protein (total and water soluble proteins) content and prevented formation and progress of cataract by glucose as evidenced by biochemical parameters. The anticataract activity of lisnopril and enalapril may be because of the antioxidant and free radical scavenging activity, as evidenced by a decrease in MDA in treated lenses. Further in vitro and in vivo studies in various experimental models and long term clinical trials are required to validate the anti cataract activity of ACE-inhibitors 21.

9) Kyselova et al., (2005a) investigated the temporal relationship between lens protein oxidation and cataract development in streptozotocin-induced diabetic rats. By the end of the 17th week, approx 50% of the diabetic animals developed mature cataract. In the course of lens opacification, they observed a time-dependent increase in the content of protein carbonyls (P<0.01) and decrease in the concentration of protein sulfhydryl (P<0.001) content was found in the lenses of diabetic animals. The main finding of their study was the disclosure of quantitative relationship between the degree of protein oxidation and the rate of advanced cataract development in the widely used model of streptozotocin-induced experimental diabetes in rats 19.

10) Kyselova et al., (2005b) investigated the effect of dietary supplementation with the pyridoindole antioxidant stobadine on the development of streptozotocin-induced diabetic cataract. The male Wistar rats were fed for 18 weeks a standard diet or a diet supplemented with
stobadine (0.05% w/w), vitamin E (0.1% w/w), Butylated hydroxy toluene (BHT 0.4% w/w) or a mixture of stobadine (0.05% w/w) and vitamin (0.1% w/w). The progress of cataract was monitored biweekly ophthalmoscopic inspection. The content of the free sulfhydryl and carbonyl was determined in total lens proteins. It shows a significant diminution of sulfhydryl groups and elevation of carbonyl groups in diabetic animals in comparison to healthy controls. In diabetic animals, stobadine supplementation significantly attenuated plasma levels of malondialdehyde, an index of systemic oxidative damage. They reported that the ability of stobadine to attenuate lipoxidation reactions in diabetes may account, at least partly, for its observed anticataract actions.

11) Komutarin et al., (2004) reported the inhibition of nitric oxide production by murine macrophages from the extract of the seed coat of *Tamarindus indica*. The seed coat extract of *Tamarindus indica*, a polyphenolic compound, has been shown to have antioxidant properties. The studies investigated the inhibitory effect of the seed coat extract of *T.indica* on nitric oxide production *in vitro* using a murine macrophage like cell line, RAW 264.7, and *in vitro* and *in vivo* using freshly isolated B6C3F1 mouse peritoneal macrophages. *In vitro* exposure of RAW 264.7 cells or peritoneal macrophages to 0.2-200 µg/ml of *T.indica* extract significantly attenuated (as much as 68%) nitric oxide production induced by lipopolysaccharide (LPS) and interferon gamma in a concentration dependent manner. The studies suggest that in mice, *T.indica* extract at concentrations up to 500 mg/kg may modulate nitric oxide production in the absence of over acute toxicity.

12) Osakabe et al., (2004) studied the effect of proanthocyanidins derived from cacao on diabetes-induced cataract formation in rats. They have tested whether dietary supplementation with CLP prevents cataract formation in rats with diabetes-induced by streptozotocin (STZ), using histological, histochemical, and biochemical analysis. Starting at 7 days after streptozotocin challenge, the animals were fed either a normal diet or a diet containing 0.5% w/w CLP over 10 weeks. Antioxidant status as assessed by measuring lipid peroxide production in plasma in response to azo compounds was lower in the STZ-rats fed control diet than in animals fed CLP. Opacity was first detected in the lenses of the control dietary group 5 weeks after STZ injection and cataracts had developed in the majority of these animals by 10 weeks. These
changes were rarely seen in the STZ/CLP diet group. Their findings suggest that CLP inhibits diabetes-induced cataract formation possibly by virtue of its antioxidative activity\textsuperscript{35}.

13) Maiti et al., (2004) reported that the Indian traditional system of medicine and herbal remedies are prescribed for the treatment of diseases including diabetes mellitus. In recent years, plants are being effectively tried in a variety of pathophysiological states. *Tamarindus indica* Linn. is one of them. In the study, aqueous extract of seed of *Tamarindus indica* Linn. was found to have potent antidiabetogenic activity that reduces blood sugar level in streptozotocin (STZ)-induced diabetic male rat. The results were found a significant diminution in body weight of the animals in diabetic group in comparison to control. After aqueous seed extract of *Tamarindus indica* supplementation for 7 days the body weight was recovered significantly but not to the control level. After 14 days of this supplementation, the body weight of all the animals was insignificantly different from control level. The study suggests that *Tamarindus indica* may have beneficial effects in type-I diabetes mellitus that holds the hope of new generation of antidiabetogenic drugs\textsuperscript{25}.

14) Suryanarayana et al., (2003) studied the effect of curcumin on galactose-induced cataractogenesis in rats. Cataract progression due to galactose feeding was monitored by slit lamp microscope and classified into 4 stages. At the end of the experiment biochemical parameters such as lipid peroxidation, aldose reductase (AR), sorbitol dehydrogenase (SDH), reduced glutathione, protein content and protein carbonyls were measured in the lens and crystallin in profile was analyzed by size exclusion chromatography (HPLC). Slit lamp microscope observations indicated that curcumin at 0.002% delayed the onset and maturation of cataract. Biochemical analysis showed that curcumin at the 0.002% level appeared to exert antioxidant and antiglycating effects, as it inhibited lipid peroxidation, AGE-fluorescence, and protein aggregation. These results suggest that curcumin is effective against galactose-induced cataract only at a very low amount (0.002%) in the diet. On the other hand, a dose above 0.01% level seems to be beneficial under hyperglycemic conditions, at least with the model of galactose-cataract\textsuperscript{48}.

15) Lee et al., (1999) reported the contributions of polyol pathway to oxidative stress in diabetic cataract. Using transgenic mice that over expresses aldose reductase (AR) in their lenses, they found that the flux of glucose through the polyol pathway is the major cause of hyperglycemic
oxidative stress in this tissue. The substantial decrease in the level of reduced glutathione (GSH) with concomitant rise in the level of lipid peroxidation product malondialdehyde (MDA) in the lens of transgenic mice, but not in the nontransgenic mice, suggests that glucose auto oxidation and non enzymatic glycation do not contribute to oxidative stress in diabetic lenses. AR reduction of glucose to sorbitol probably contributes to oxidative stress by depleting its co-factor NADPH, which is also required for the re-generation of GSH. Sorbitol dehydrogenase, the second enzyme in the polyol pathway that converts sorbitol to fructose, also contributes to oxidative stress, most likely because depletion of its co-factor NAD+ leads to more glucose being channeled through the polyol pathway. Despite a more than 100% increase of MDA, oxidative stress plays only a minor role in the development of cataract in the acute diabetic cataract model. However chronic oxidative stress generated by the polyol pathway is likely to be an important contributing factor in the slow – developing diabetic cataract as well as in the development of other diabetic complications.

16) Sugiyama et al., (1999) reported that aldose reductase catalyzes the oxidation of naphthalene-1, 2-dihydrodiol for the formation of ortho-naphthoquinone. The oxidation of naphthalene-1, 2-dihydrodiol (ND) to O-naphthoquinone (NQ) in the lens is believed to be responsible for the formation of cataracts in naphthalene-fed rats. Studies using either recombinant rat lenses (RLAR) or human muscle aldose reductase (HMAR) incubated in vitro with ND in the presence of NADP verified that aldose reductase is the dihydrodiol dehydrogenase that catalyses the oxidation of ND to NQ. Kinetic studies of V_{max}/k_{m} indicated that RLAR catalyzes the NAD-dependent oxidation of ND with an optimal pH of 9.0. The corresponding activity of HMAR was lower than that of rat enzyme. The metabolite produced by the incubation of RLAR with ND in 20 mM phosphate buffer (pH 7.5) was isolated by C_{18} reversed-phase high performance liquid chromatography. The elution profile showed the formation of a new peak that was identical with a peak generated when NQ was incubated under same condition. The metabolite in both peaks was identified as 4-(2-hydroxyethylsulfanyl)-1,2-dihydro-1,2-naphthalenedione (HNQ) by H1 and C13 NMR analyses using homonuclear correlation spectroscopy, heteronuclear multiple quantum coherence, and heteronuclear shift correlations via multiple bond connectivities as well as infrared analysis. HNQ is readily autoxidised to 2, 3-dihydro-1-oxa-4-thia-9, 10-phenanthrenedione. The stoichiometry of 1:1 between the consumption and the formation of
NADH for the formation of HNQ implies that rat lens aldose reductase catalyzes a 2e⁻ oxidation of ND to yield the corresponding ketol, which is autoxidized to NQ⁴⁷.

17) Lee et al., (1998) reported the involvement of aldose reductase in naphthalene cataract. Lenses from nontransgenic mice and from transgenic lines CAR 222 and CAR 648, with different levels of AR were cultured in medium using naphthalene-1, 2 dihydrodiol with or without AR inhibitor AL 1576. The morphology and progression rate of ND–induced cataract in these lenses were compared. Lenses from transgenic mice CAR 222 and CAR 648, but not their nontransgenic littermates, developed yellow pigment in the inner cortex when exposed to 50 µm ND, which was completely prevented by 0.2 mM AL 1576. The yellow Pigment developed faster and more intensely in the CAR 648 lens, which has a higher AR level than CAR 222. Under a high dose of 500 µm ND both transgenic and wild type mouse lenses developed ND-induced cataract, although the first sign of cataract was found in the outer cortex in transgenic lenses instead of the inner cortical region in wild type lenses. In addition, the cataract was more severe and developed at a faster rate in transgenic mouse lenses. AL 1576 showed only partial protection against the cataract induced by 500µm ND. The findings showed that the progression rate of ND–induced cataract correlated with the level of lens AR and ND, indicating that AR was the key, enzyme for the metabolism of ND in the process of naphthalene cataract development²².

18) Kovaceva et al., (1997) reported the difference in activities of antioxidant superoxide dismutase, glutathione peroxidase and prooxidant xanthine oxidoreductase /xanthine oxidase in the normal corneal epithelium of various mammalia. The enzyme activities of antioxidant superoxide dismutase and glutathione peroxidase as well as prooxident xanthine oxidoreductase /xanthine oxidase were examined using biochemical methods. Results show that superoxide dismutase activity is high in rabbits and guinea pigs where as in pigs the activity is low and in cow it is nearly absent. In contrast, glutathione peroxidase activity is high in cows, pigs and rabbits, where as in guniea pig that activity is low. The findings for prooxidant enzymes level reveal elevated xanthine oxidoreductase /xanthine oxidase activities in rabbits, lower activities in guinea pigs, very low activity in cows and no activity in pigs. In conclusion the results demonstrate inter species variations in activities of enzymes participating in antioxidant/ prooxidant balance in the corneal epithelium. It is suggested that the levels of anti oxidant and pro-
oxidant enzymes studies in the corneal epithelium might be associated with the diurnal or nocturnal activity of animals\textsuperscript{17}.

19) Gupta et al., (1997b) reported that topical aspirin provides protection against galactose induced cataract. Effect of twice daily administration of aspirin eye drops on the onset and progression of cataract-induced by 30% galactose diet was studied. On the 30\textsuperscript{th} day of galactose feeding, while all control group rats showed complete state IV opacity, those receiving aspirin eye drops showed only mild cataractous changes of stage I. \textit{In vitro} studies showed that addition of aspirin to the medium significantly decreased dulcitol formation (P<0.01) and maintained glutathione levels (P<0.02). Intraocular penetration studies using isolated goat cornea should excellent penetration by salicylate indicating feasibility of topical administration. The results of the present study demonstrate that topical aspirin possesses significant anticataract activity in galactosemic cataract\textsuperscript{12}.

20) Vani and Rawal, (1996) studied the effect of riboflavin supplementation on glutathione and glutathione redox cycle in selenite-induced cataractous lenses. The alterations in the level of proteins, reduced glutathione (GSH) and the activity of \textit{\gamma}-glutamylcysteine synthetase (\textit{\gamma}-GCS), glutathione reductase (GR) and glutathione peroxidase (GSH-px) have been studied in the control and riboflavin supplemented rats. The cataractous littermates supplemented with riboflavin showed increased activity of the enzymes and elevated levels of metabolites as compared to the cataractous, non-supplemented littermates. The results of study point towards the role of riboflavin in the prevention of cataract, induced by selenite\textsuperscript{54}.

21) Micelli-Ferrari et al., (1996) evaluated the role of lipid peroxidation in the pathogenesis of myopic and senile cataract. The study was conducted on 34 lenses (nucleus and epinucleus) (9 clear lenses, 14 lenses with idiopathic senile cataract and 11 lenses affected by severe myopic cataract) and vitreous of 19 (7 non-myopic, 7 myopic, and 5 control) subjects. Glutathione and malondialdehyde was assayed. Cataractous lenses showed a decreased content of GSH and increased concentration of GSSH compared with clear lenses. A higher oxidative consumption of GSH was found in myopic cataracts compared with senile ones. Also, increased levels of MDA were observed both in cataractous lenses and in the vitreous of myopic patients compared with control and the senile ones. The observed alterations strongly suggest that retinal lipid peroxidation might play a key role in human cataractogenesis, especially in the myopic type\textsuperscript{26}.
22) Sato (1993) investigated the effect of aldose reductase, the major protein associated with naphthalene dihydrodiol dehydrogenase activity in rat lens. Aldose reductase was purified from whole rat lenses using a series of chromatographic steps that include gel filtration, affinity chromatography, and chromatofocusing. The dehydrogenase activity of the purified enzyme was evaluated with 1, 2-dihydroxynaphthalene (naphthalene dihydrodiol) as substrate. The same dehydrogenase activity was also examined with the recombinant protein obtained from rat lenses aldose reductase clone. Both the reductase and dehydrogenase activities of purified aldose reductase was inhibited by aldose reductase inhibitors. However, inhibition of dehydrogenase activity was less than reductase activity. Aldose reductase displays dehydrogenase activity in addition to reductase activity. In rat lenses aldose reductase is a major protein associated with naphthalene dihydrodiol dehydrogenase activity. This suggests that aldose reductase is linked to 1, 2-dihydroxynaphthalene formation in rat lens and the subsequent formation of cataracts in naphthalene-fed rats.

23) Tao et al., (1991a) reported the effect of aldose reductase inhibitors on naphthalene cataract formation in rats. Brown Norway rats were administered naphthalene by gavage at a dose of 0.7 g/kg were fed normal rat chow containing aldose reductase inhibitors sorbinil, FK 366, A 11576 and 0.05% Tolrestat and Ponalrestat to inhibit sugar cataract formation the lens changes in these rats were monitored over a 90-day period by portable slit–lamp microscopy and histologic study. The compound A11576 showed a dose-dependent reduction in naphthalene-induced cataract formation, with no naphthalene-associated deposits seen in toluidine blue-stained lens sections. Sorbinil also reduced lens changes, whereas tolrestat, ponalrestat, and FK366 had no effect. These results suggest that inhibition of naphthalene-induced cataract formation by structurally diverse aldose reductase inhibitors was not linked to the inhibition of aldose reductase.

24) Tao et al., (1991b) compared the effect of two types of aldose reductase inhibitors on several biochemical parameters in naphthalene-induced cataract of the rat over a time span of 102 days of treatment. Feeding of naphthalene daily to brown Norway rats resulted in gradual, progressive development of zonular opacities. As compared to control animals, the values of soluble protein, soluble glutathione, glutathione peroxidase, glutathione reductase were decreased in rats fed naphthalene or naphthalene +FK366, a carboxylic-acid-type aldose reductase inhibitor. In
marked contrast, treatment with A11576, a hydantoin-type aldose reductase inhibitor, maintained the values of most parameters at levels that were similar to those of the controls, and all lens remained clear. A decline of glutathione was noted in all naphthalene-fed rats, irrespective of whether these animals had been treated with aldose reductase inhibitor. The great decrease of glutathione with A11576 suggests that this inhibitor acts at some step in naphthalene metabolism following formation of naphthalene epoxide.

25) Datiles et al., (1982) studied the effect of sorbinil, an aldose reductase inhibitor on cataract induced by galactose using a light microscopic study. Cataract formation in galactosemic rats was studied by ophthalmoscopy, slit-lamp biomicroscopy and by light microscopy using plastic embedding with methacrylate. Untreated rats developed nuclear cataract by 14 days and mature cataracts by 21 days However, rats treated with the aldose reductase inhibitor sorbinil did not develop any cataractous change for upto 8 months of 50% galactose feeding and could not be distinguished from normal controls. This strongly suggests that aldose reductase is the common factor involved in the formation of sugar cataracts.