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Cataract: A major secondary complication of diabetes, its epidemiology and an overview on major medicinal plants screened for anticataract activity

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ABSTRACT

Cataract is a visual impairment caused due to opacification or optical dysfunction of crystallin lens affecting more than 17 million people around the world. Even though the incidences of cataract are increasing day by day among the elderly persons but, still except surgery no other ways of treatment have been successfully developed so far. Thus, the aim of writing the present review is to provide an insight over the pathophysiological and etiological aspects of cataract along with discussing the remedies available for the disorder. The review also describes different experimental models with their relevant mechanism and significance such as galactose−induced, naphthalene−induced and selenite−induced cataract models which are mainly used for evaluating the anticataract activity of a particular drug (mainly of natural origin). The review includes list of plants and their phytoconstituents which have been so far evaluated pharmacologicaly for the treatment of cataract. From the survey, it was confirmed that the antioxidant property of plants phytoconstituents are basically responsible for their effective anticataract activity. Thus, the valuable information provided in the present review will help researches in developing an alternative method rather than surgery for the treatment of cataract which will minimize the rate of blindness due to cataract thus, benefiting and extending protective aspects of eyes, an integral part of human body.

1. Introduction

Cataract, a visual impairment causing disturbance in lens transparency occurs mainly due to opacification or optical dysfunction of crystallin lens. It reduces the amount of incoming light and results in deterioration of the vision. More than 17 million people are blind because of cataract. Approximately 25% of the populations over 65 and about 50% over 80 have serious loss of vision because of cataract. Cataract development is usually a very slow or gradual process but in some cases it could occur rapidly and it generally affect both eyes[1,2]. Senile cataract, also called age related cataract, is the commonest type of cataract affecting equally persons of either sex usually above the age of 50 years[3]. It is one of the most significant leading causes of blindness and visual disability worldwide covering around 42% of overall blindness thus, increasing burden to health care systems. The total number of persons with cataracts is estimated to rise to 30.1 million by 2020 and it can vary from country to country[4]. World Health Organization launched Vision 2020, to eliminate cataract as priority diseases. Cataract is mainly responsible for almost 80% of blindness cases in India[5].

Even though advanced glycation end−products (AGE)−related cataract is the leading cause of blindness and visual impairment worldwide there are only few genetic studies for age related cataracts reported till date[6,7]. Chronic hyperglycemia can cause various types of secondary complications of diabetes, including diabetic cataract. From the previous reports it was found that hyperglycemias increase the risk of development of cataract. Even though aging is the main factor involving in the development of cataract, however, other risk factors such as nutritional deficiencies, trace metals, sunlight, smoking, and certain drugs are also known to increase the risk of cataract[8].

2. Causitive factor of cataract

Various factors such as daylight, diet, diabetes, dehydration, oxidation of lens proteins and peroxidation of lipids attribute to the generation of lens opacities in the older individual[1]. It is also caused due to the damage to the long–lived lens proteins which is as a result of oxidation due to the generation of oxidative radicals[2]. Various risk factors such as nutritional deficiency, sunlight, smoking, environmental factors, lack of consumption of antioxidants and diabetes can also increase the risk of cataract. According to the animal study it was found that diabetes is one of the major risk factors involved in development of cataract. During hyperglycemia extra cellular glucose diffuses into the lens, which can lead to posttranslational modification. The cataractogenesis is mainly due to synthesis and accumulation of excessive sorbitol in the lens fibers and consequent osmotic stress. Sorbitol is synthesized by aldose reductase utilizing NADPH and does not easily cross cell membranes; it can accumulate in cells and cause damage by disturbing osmotic homeostasis[4].

Another pathophysiological mechanism behind the formation of cataract is deficient glutathione (GSH) levels, which involve to keep the lens proteins in their reduced form. However, in cataract GSH levels were found to be significantly reduced when compared to normal[5]. Oxidative stress is another mechanism involving in the cataract development, which causes oxidation of lens protein. Decreased concentration of glutathione, ascorbate and antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase (endogenous defence mechanisms which protect the lens against oxidative damage) with increasing age in the human eye were the main factors involveing in the generation of cataract[6]. Diabetes causes increased levels of oxidized DNA, proteins, and lipids, which are also limiting factors in various diabetic complications[8]. Glucose autoxidation, formation of AGE, and activation of the polyol pathway cause intracellular accumulation of sorbitol, which causes various types of ocular lesions, alterations on the membrane permeability, loss of glutathione and a diminution of the protein synthesis. Further diabetic individuals present a polymorphism in the promoter region of aldose reductase (ARL2) gene, causing cataract, neuropathy and retinopathy. However, production of hydrogen peroxide through glucose auto–oxidation is also associated in the cataracts formation[9]. Several biochemical processes occur during production of selenite cataract. These include altered epithelial metabolism, calcium accumulation, calpain–induced proteolysis, crystalline precipitation, phase transition, and cytoskeletal loss. These early changes in lens epithelium may result from oxidative damage caused by selenite, possibly due to critical sulfhydryl groups on molecules such as calcium ATPase or ion channels[3].

Aldose reductase, key enzyme of polyol pathway, catalyzes the reduction of glucose into the corresponding sugar alcohol, sorbitol, which is subsequently metabolized into fructose by sorbitol dehydrogenase. Sorbitol, an osmolyte leads to osmotic swelling, changes in membrane permeability, leakage of glutathione and myo–inositol and perhaps even the generation of free radicals and hydrogen peroxide, primarily causing for the development of diabetic complications such as cataract, retinopathy, neuropathy and nephropathy[10]. Hydrogen peroxide at higher concentrations can cause lens opacification and tissue damage similar to that found in human cataract[11].

3. Treatments of cataract

Because there is sufficient evidence that oxidative stress plays a role in the mechanisms of cataractogenesis, there is an increasing interest in developing suitable antioxidant nutrients, both of synthetic and plant origin that could be effective in delaying or preventing the formation of cataracts[12]. Presently, very few medications, eye drops, exercise or glasses are available to cure or prevent cataracts. The symptoms of early cataract may be improved with new eye glasses, brighter lightening, anti–glare sun glasses, or magnifying lens. If these measures do not help, surgery is the only effective treatment[1]. From earlier study it was found that, persons consuming a diet with high content of nutritional antioxidants such as essential vitamins, micro nutrients, carotenoids and flavonoids have reduced risk of developing cataract[2]. Plant and plant products have been used as therapeutics in traditional systems of medicine due to less adverse effects and economical importance. From the earlier work it was found that extracts of tea (green and black) and *Ginkgo biloba* display excellent antioxidant activities and also exhibit cataractostatic ability in animal models[6]. Currently, the only available treatment for the disease is the surgical extraction of the cataractous lens followed by replacement with a synthetic implant[11]. Effort has been taken to explore the natural resources to delay the onset and progression of cataract. Large number of medicinal plants and synthetic compounds has been reported to possess anticataractogenic properties[13].

4. Experimental models on cataract

Various experimental models have been used for the screening of the herbal drugs against cataractogenesis. Among these, galactose induced cataract is commonly used, as it produces large amounts of its reduced form, galactitol, and finally into glucose. Furthermore, galactitol is not subsequently metabolized as compared to sorbitol.

In the galactose model it is assumed that, factors initiating galactose cataracts in young rats are similar to those involved in the human galactose cataract model. The three mechanisms possibly involved in galactose cataract formation are the polyol pathway, oxidation, and non–enzymatic glycation[4].

Naphthalene–induced cataract has been extensively used to test potential anti–cataract drugs due to its similarties to that of age–related cataract in humans. Ingested naphthalene converts into stable compound naphthalene–1, 2–dihydrodiol and it is further metabolized to 1,2–naphthoquinone (NQ) by an enzyme dihydrodiol dehydrogenase. Epithelial mitochondria are the target of NQ toxicity. Formation of NQ is considered to be the underlying mechanism of cataract development in naphthalene fed animals[1,2]. Aldose reducatase is the key enzyme which metabolies naphthalene–1,2–dihydrodiol in the process[2].

Selenite–induced cataract was used as a model system for oxidative stress–induced cataract. Selenite cataract is developed by the acute exposure of selenium to the lens at a particular age which causes nuclear cataract[13]. Moreover, selenite–induced oxidative stress causes nuclear opacity through the calpain proteolysis of lens proteins. It is a strong sulfhydryl oxidant and is considered as a model for those cataracts caused by oxidative stress. Similar to human senile cataract, this type of cataract is accompanied by a decrease in activities of the antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX)[11].

In another model cataract was produced in suckling rat pups by an overdose of the essential trace mineral selenium, which is injected before completion of the critical maturation period of the lens. It has been hypothesized that these early changes in lens epithelium may result from oxidative damage caused by selenite, possibly due to the critical sulfhydryl groups on molecules such as calcium ATPase or ion channels[3].

5. Preventive role of plant products against cataract

Based on the data obtained from the earlier study, it was found that disturbance in the oxidative state of the lens can be corrected by giving various antioxidants such as prevention of selenite–induced cataract development by ascorbic acid[11]. Human body has multiple mechanisms particularly enzymatic and nonenzymatic antioxidant systems to protect the cellular molecules against reactive oxygen species (ROS) induced damage[14]. In diabetes, hyperglycaemia generates ROS which in turn causes lipid peroxidation and membrane damage and thus, plays an important role in the production of secondary complications in diabetes mellitus such as kidney, eye, blood vessel, and nerve damage[15].The effectiveness of physiological antioxidants such as pyruvate and nutritional antioxidants

such as ascorbate, vitamin E, and carotenoids has been also investigated and it was found that antioxidants have significant activity against cataract. Individuals with high plasma levels of vitamin C, vitamin E, and carotenoids have less risk of cataract. Flavonoids, found in the various foods and beverages have strong antioxidant and anticataract activities[16,17]. One isoflavonoid glycoside, isolated from the ethyl acetate soluble fraction of *Viola hondoensis* was tested for aldose reductase inhibitory actvity. From the result, it showed that it had potent inhibitory activity[18]. The protective effect of tea, a major source of dietary quercetin and other flavonoids, has been reported; and the ability of isoflavone genistein in delaying the progression of cataracts induced by dietary galactose has also been reported[11]. A large number of plants have hypoglycemic potential, however, still many of plant material and products have not been investigated for their beneficial effects on secondary complications such as diabetes cataract. So development of pharmacologically and biochemically tested compound would be of great importance for the management of secondary complications of diabetes[5]. Here some of the plants materials which have been tested for their anticatarct activity are presented.

5.1. Adhatoda vasica (A. vasica)

The aqueous, ethanol and chloroform extracts of *A. vasica* (Acanthaceae) was evaluated for aldose reductase inhibitory, anti–cataract and antioxidant activities. All the extracts were found to have significant aldose reductase inhibitory potential and anti–cataract activity. Similar efect was also found with *Biophytum sensitivum*[19].

5.2. Allium cepa (A. cepa)

Effects of *A. cepa* (Liliaceae) juice on sodium selenite–induced cataract formation on Wistar–albino rat pups for 14 days were investigated. Application of *A. cepa* juice to the rat eyes significantly prevented selenite–induced cataract formation. This effect was associated with increased total antioxidant level, SOD, GPX activities in the lens[11].

5.3. Angelica dahurica (A. dahurica)

Byakangelicin, furanocoumarin constituent isolated from the roots of *A. dahurica* (Umbelliferae) was evaluated for galactosemic cataract and diabetic complications in animal experiments. Cataract formation and galactitol accumulation were significantly prevented by intragastric administration of byakangelicin at a dose of 100 mg/kg for 14 days. Administration of the drug for 18 days suppressed sorbitol accumulation and caused a significant reversal of depleted myo–inositol contents as well as Na^+, K^+ ATPase activity in streptozotocin–induced diabetic rats. These results indicate that byakangelicin is effective for the treatment of sugar

cataracts and diabetic neuropathy[20].

5.4. Cassia fistula (C. fistula)

The aquous, ethanol and chloroform extracts of *C. fistula* (Acanthaceae) was evaluated for aldose reductase inhibitory potential, anti–cataract and antioxidant activities. All the extracts were found to have significant aldose reductase inhibitory potential and anti–cataract activity. Further it was also found that all the extracts were effective in minimizing the sugar–induced lens opacity in rat lens model[19].

5.5. Citrus aurantium (C. aurantium)

Effect of hydromethanol peel extract of *C. aurantium* (Rutaceae) at 100 and 200 mg/kg, p.o. against naphthalene– induced cataractogenesis in rats were investigated in Wistar albino rats. Extract delayed the onset and maturation of cataract and prevented the peroxidative damage caused by naphthalene[21].

5.6. Cochlospermum religiosum (C. religiosum)

Isorhamnetin–3–glucoside, bioactive flavonoid isolated from the leaves of *C. religiosum* (Cochlospermaceae) were tested for anticataract activity. From the result it was found that it retarded cataract *in vitro* which might be due to its antioxidant property[22].

5.7. Curcuma longa (C. longa)

Curcumin and *C. longa* (Zingiberaceae) were investigated for their anti–cataract activity in streptozotocin–induced diabetic cataract at 0.002% and 0.01% (curcumin), 0.5% (turmeric) dose level administered with AIN–93 diet (ICN Pharmaceuticals Inc. Cleveland) for a period of 8 weeks to rats. Both curcumin and *C. longa* delayed the progression and maturation of cataract. There was a significant reversal of changes to lipid peroxidation, reduced glutathione, protein carbonyl content and activities of antioxidant enzymes. Osmotic stress, aggregation and insolubilization of lens proteins due to hyperglycaemia were prevented by curcumin and turmeric. Further turmeric was found to more effective than its phytoconstituent, curcumin in counteracting cataract[8]. Another effect of curcumin at 75 mg/kg bw in maize oil for 14 days against cataractogenesis was examined in *in vitro* rat model. Lenses treated with curcumin were more resistant to 4–hydroxy–2–nonenal– induced opacification than control groups. Further curcumin treatment also caused a significant induction of the glutathione S–transferase isozyme rGST8–8 in rat lens epithelium. So it may be concluded that, protective effect of curcumin may be mediated through induction of glutathione S–transferase isozyme[12].

5.8. Embelica officinalis (E. officinalis)

Effect of aqueous extract of *E. officinalis* (Euphorbiaceae) on selenite–induced cataract in rats was investigated for 18 days. Treatment with *E. officinalis*, as well as ascorbic acid, produced a significant decrease in malondialdehyde and a simultaneous increase in glutathione levels. At the end of the experiment, disappearance of cataract was observed in the drug treated group[3].

5.9. Emilia sonchifolia (E. sonchifolia)

Effects of the flavonoids from E. sonchifolia (Asteraceae) at 1 mg/kg against selenite–induced cataract were investigated *in vivo* using quercetine as a standard. Slit lamp examination showed that the flavonoid fraction from *E. sonchifolia* could modulate the progression of cataract. Activities of SOD, catalase and reduced glutathione were found to be increased in treated groups, while thiobarbituric acid reacting substances were decreased compared with the selenite– induced group. The results suggest that flavonoids from *E. sonchifolia* can modulate lens opacification and oxidative stress in selenite–induced cataract[23].

5.10. Erigeron annuus (E. annuus)

Sixteen compounds including three caffeoylquinic acids and four flavonoids were isolated from ethyl acetate soluble extract of the stems and leaves of *E. annuus* (Asteraceae). All the isolates were evaluated *in vitro* for inhibitory activity against cataract and it was found that opacity of lenses was significantly prevented with, 5–di–O–caffeoyl–epi-quinic acid in an *ex vivo* experiment[24].

5.11. Ginkgo biloba (G. biloba)

Effect of the antioxidant role of *G. biloba* (Ginkgoaceae) at 40 mg/kg per day in preventing radiation–induced cataracts in the lens after total–cranium irradiation of rats with a single radiation dose of 5 Gy was investigated. *G. biloba* supplementation significantly increased the activities of SOD and GPX enzymes and decreased the malondialdehyde level significantly. *G. biloba* supplementation protected the lenses from radiation–induced cataracts[25].

5.12. Momordica charantia (M. charantia)

Effect of lyophilized aqueous extract of *M. charantia* (Cucurbitaceae) at 200 mg/kg p.o. for 4 months on rats' eye was investigated using both the naked eye and slit lamp, and it was found that *M. charantia* had anti–cataract effect. Similar results were also obtained with aqueous extract of *Eugenia jambolana* and ethanolic extract of *Tinospora cordifolia* and *Mucuna pruriens*[26].

5.13. Moringa oleifera (M. oleifera)

Effects of the flavonoid fraction of *M. oleifera* (Moringaceae) leaves on selenite cataract in rat pups of Sprague–Dawley strain were investigated. It prevented the morphological changes and oxidative damage in lens, suggesting its effectiveness in preventing cataractogenesis in selenite model by enhancing the activities of antioxidant enzyme, reducing the intensity of lipid peroxidation, and inhibiting free radical generation[27].

5.14. Ocimum sanctum (O. sanctum)

Effect of *O. sanctum* (Lamiaceae) on sugar–induced cataractogenic changes in rat lenses *in vitro* was investigated and it was found that *O. sanctum* showed a significant inhibition in polyol accumulation, which signified its anticataract activity[28].

5.15. Origanum vulgare (O. vulgare)

O. vulgare (Labiatae) extract at 2 g/kg has revealed a significant protective effect against selenite induced cataract when injected for 1 and 2 day before selenite injection. It was found that the anticataract effect of *O. vulgare* extract could be based on direct or indirect antioxidant mechanisms[29].

5.16. Pterocarpus marsupium (P. marsupium)

Effect of aqueous extract of *P. marsupium* (Fabaceae) at 1 g/kg was given to alloxan induced diabetic rats for 115 days, and it was found that *P. marsupium* has significant anticataract effect evidenced by decreased opacity index[30].

5.17. Silybum marianum (S. marianum)

Effect of *S. marianum* (Compositae) seed extract at 200 mg/kg, p.o. for 40 days was tested against galactose–induced cataract in rats. The result indicated that, all the stages of cataract development were significantly delayed in silymarin treated group compared to control group. The rats treated with silymarin showed significant increased glutathione and decreased lipid peroxides level compared to control group[31].

5.18. Trigonella foenum–graecum (T. foenum–graecum)

Effects of *in vitro* and *in vivo* anti–cataract potential of *T. foenum–graecum* (Fabaceae) on galactose induced cataracts in animal model were investigated. *T. foenum–graecum* significantly restored glutathione and reduced malondialdehyde levels as compared to controls. A significant delay in the onset and progression of cataract was observed with 2.5% *T. foenum–graecum* diet after 30 days, none of the treated eyes developed mature cataracts as compared to control eyes[4]. Alcoholic extract of *T. foenum–graecum* seeds at 2 g/kg was given to alloxan diabetic rats for 115 days. It was found that the extract has significant anti–cataract effect as indicated by decreased opacity index[30]. In another experiment anti–cataract potential of *T. foenum–graecum* was assessed in selenite–induced *in vitro* and *in vivo* cataract model. In *in vitro* model it was found that there is a significant restoration in the activities of antioxidant enzymes SOD, catalase, GPX and glutathione–S–transferase. Further decreased levels of malondialdehyde were observed in the *T. foenum–graecum* supplemented group as compared to control. Whereas in *in vivo* model it was observed that no cataract developed at all. Thus observed anti–cataract activity of *T. foenum–graecum* may be contributed to its significant anti–oxidant potential[32].

5.19. Vitex negundo (V. negundo)

Effects of flavonoid fraction of *V. negundo* (Verbenaceae) in preventing the toxicity induced by sodium selenite in *in vitro* culture condition were investigated. Flavonoid fraction of *V. negundo* treatment prevented selenite toxicity and cataractogenesis by maintaining antioxidant status, calcium homeostasis, protecting sulfhydryl group, and decreasing oxidative stress in lens[33]. In another study effect of methanolic extract of *V. negundo* at 2.5 mg/Kg, i.p. for 15 day in modulating the selenite–induced oxidative stress in *in vivo* model in Sprague–Dawley rat pups was investigated. Opacification was reduced in the treated group compared to the selenite–induced group. The activities of SOD, catalase, and Ca^{2+} ATPase were significantly increased in drug treated group, while lower levels of ROS, Ca^{2+}, and thiobarbituric acid reactive substances were also observed in the drug treated group[13].

5.20. Withania somnifera (W. somnifera)

Extract of *W. somnifera* (Solanaceae) was found to retard the formation of 'cold cataract' *in vitro*, suggesting that *W. somnifera* could well act as a cataractostatic agent[6].

6. Discussion

Cataract, a disorder is associated with several risk factors such as diabetic, sorbitol accumulation and other secondary complications. For the treatment of cataract there is no specefic medication avaliable in the market except surgery however, it also has some complications such as posterior capsular opacification, endophthalmitis and uncorrected residual refractive errors[11]. Therefore, any drugs or a pharmacological method which prevents or slows the progression of cataractogenesis can reduce the health burden. In the last couple of years, several researches have been done for exploration of the phytoconstituents having

anticataract activity. From the earlier studies, it was found that plant such as *O. sanctum* and *Camellia sinensis* possess significant antioxidant potential along with significant anticataract activity[4,11,34]. Reduction of glutathione concentration was found to be another possible mechanism for the development of cataract. Phytoconstituents from herbal drugs may indirectly inhibit consumption of glutathione or it can stimulate glutathione synthesis which may be due to a modulating effect on glutathione related enzymes in the lens. In another study, it was found that incubation with *Trigonella foenum* enhances the glutathione levels due to inhibition of consumption of glutathione[32]. Several factors are involved in the progression of cataract, but exact mechanism of cataract formation is still not known. Lots of researches are going on for the determination of the mechanism of action of cataract formation by the use of different *in vivo* and *in vitro* model. Among all the experimental models, the galactose induced cataract model is commonly used. In galactose model it was assumed that the factors initiating the galactose cataract in young rats are very similar to those involved in the human galactose cataract[5,8].

Human cataract is not a single disease but it is a group of disorders associated with several risk factors. Oxidative stress is involved in cataractogenesis as a common underlying mechanism, in which levels of antioxidants were found to be less when compared to the normal persons. According to a study, it was found that, significant increased level of radical species and low concentration of glutathione content were observed in the aqueous humor. Many studies have shown that flavonoids, a group of natural compounds with antioxidant properties, can prevent oxidative damage and experimental cataract progression. Onion, a flavonoid–rich staple food is one of the important example in which major flavonoids identified for the above activity including quercetin, quercetin–4′–glucoside and quercetin–3,4′–diglucoside[11]. According to World Health Organization (WHO) reports that about 80% of the world′s population in 2001 used herbal medicine for the health need[35]. Lots of studies have been done to identify natural and synthetic compounds that inhibit aldose reductase and reduce oxidative stress, and the flavonoids are among the most potent aldose reductase inhibitors known. Plant phytochemicals, including polyphenols which are currently regarded as natural antioxidants, are important for human health against various type of enzymes, which reduce blood glucose level in diabetics and are capable of reducing oxidative stress by scavenging ROS and preventing cell damage[36,37].

In conclusion, the review provides relevant updated information regarding the pathophysiological aspects of cataract, major risk factors involved and suitable treatment available for the disorder. The review also provides the database of the plants and their respective phytoconstituents

responsible for anticataract activity. Since eye is a unique organ, being relatively unprotected as it is constantly exposed to oxidative stress and protection of the lens from these is critical for its function. So far, no single compound has found widespread acceptance for these indications, although many compounds have been evaluated. Thus, there is a vital need for further research in this area. Therefore, the information provided in the present review will act as an important segment for development of an effective medicine(s) for the treatment of disorder such as cataract.

Conflict of interest statement

We declare that we have no conflict of interest.

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