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Cataract: A major secondary diabetic complication

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ABSTRACT
Cataract is a visual impairment occurs due to the opacification of crystalline lens. It affects around 17 billion peoples worldwide, although incidence of cataracts is increasing day by day among the elderly persons. Still today except surgery no other effective treatment have been successfully developed so far, thus this present review is focused to highlights the etiological aspects, risk factors along with possible pharmacological prevention and animal models which are widely used for screening anticataract activity. The present review includes the list of plants and their phytoconstituents which have been evaluated pharmacologically for the treatment of cataract. From the review it can be concluded that antioxidant properties of plants phytochemicals are responsible for the anticataract activity.

***Key Words*:** Cataract, aldose reductase, galactose, selenite, antioxidant.

INTRODUCTION

A cataract is opacity of the lens that interferes with vision, and is the most frequent cause of visual impairment worldwide, especially for the elderly because the incidence of cataracts increases with increasing age. From a public health perspective, it is important to identify the risk factors that affect the development and progression of cataract. Cataract is a multifactorial disease process and is induced by various toxic factors, environmental, stressors, and gene mutations. Cataract can be classified into four types; nuclear, cortical, posterior subcapsular (PSC), and mixed. Although the etiology of each cataract type remains elusive, cataracts are known from studies on many animal models and humans to be associated with damage or death of lens epithelial cells (LECs) (Li *et al.*, 1995). Cataract is the leading cause of blindness worldwide and covers around 42% of overall visual impairment. Cataract is mainly responsible for almost 80% blindness in India (Gupta *et al.*, 2009). Cataract is also produces by the advanced glycation end products (AGE) is cause of blindness world-wide (Thiagarajan *et al.*, 2003). AGE related cataract is leading cause of blindness and visual impairment worldwide. Chronic hyperglycemia can cause various types of secondary diabetic complications including diabetic cataract. Form literature it can be found that hyperglycemia increase the risk of development of cataract. Even though aging is another factor for development of cataract, other risk factor such as nutritional deficiencies, trace metals, exposure to sunlight, smoking are also responsible for development of cataract.

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CAUSES OF CATARACT

Various factor such as diabetes, oxidation of lens, dehydration, daylight, diet and lipid peroxidation attributes to the generation of lens opacification in elderly persons (Kothadia *et al.*, 2011). Other risk factors such as smoking, environmental factor, lack of consumption of antioxidants, nutritional deficiency and diabetes can also increase the risk of development of cataract. During hyperglycemia extracellular glucose diffuse into the lens, which can leads to the post-translational modification. Cataract progress forms the synthesis and accumulation of excessive sorbitol in the lens fibre and consequent osmotic stress. Sorbitol is synthesis from aldose reductase utilising the NADPH and does not cross the cell membranes; it can accumulate in the cells and can cause cell damage due to disturbing osmotic homeostasis (Gupta *et al.*, 2009). Deficient glutathione is another mechanism behind the formation of cataract. In cataract reduced glutathione level were found to be significantly reduced when compared to normal (Thiagarajan *et al.*, 2003). Oxidative stress is another mechanism involve in development of cataract, which cause the oxidation of lens protein. Reduction in concentration of glutathione, antioxidant enzymes such as catalase, superoxide dismutase (SOD), glutathione Reductase, glutathione peroxidase with increase in age where the main factor involving the generation of cataract (Graw, 2009). Diabetes causes the increased level of oxidised DNA, proteins and lipids, which are also limiting factor in various diabetic complications (Suryanarayana *et al.*, 2005). Glucose autoxidation, formation of AGE, and activation of polyol pathway cause the intracellular accumulation of sorbitol, which cause the various types of ocular lesions, alteration of membrane permeability, loss of glutathione and diminuation of protein synthesis. Also diabetic patient has polymorphism in the promoter region of aldose reductase (ARL2). gene, causing the cataract, retinopathy, and neuropathy. Production of hydrogen peroxide through glucose auto-oxidation is also associated with cataract formation (Pastene *et al.*, 2007). Aldose Reductase key enzyme of polyol pathway catalyses the reduction of glucose into sugar alcohol sorbitol, which is subsequently metabolised to fructose by sorbitol dehydrogenase. Sorbitol as an osmolyte that leads to osmotic swelling, changes in the membrane permeability, leackage of glutathione, myo-inositol, the generation of free radicals and hydrogen peroxide which primarily causing the diabetic complication such as cataract, retinopathy and neuropathy (Jung *et al.*, 2011). Hydrogen peroxide at higher concentration can cause lens opacification and tissue damage similar to that found in human cataract (Javadzadeh *et al.*, 2009)

PHARMACOLOGICAL PREVENTION

There is sufficient evidence that oxidative stress play a pilot role in mechanism of cataractogenesis, hence there is increasing interest in developing suitable antioxidant nutrient from natural or synthetic origin that could be effective in delaying or prevention the progression of cataract (Awasthi *et al.*, 1996). Presently few medicines, eye drops, exercise and glass are available to prevent the cataract. The symptom of early cataract can be improved by new eyeglasses, anti-glare sunglasses or magnifying lens, and if these measures do not help surgery is last effective treatment (Gupta *et al.*, 2009). From earlier studies, it was found that person consuming diet with high content of antioxidants can reduce the development of cataract (Jacques *et al.*, 1991). The plants and plant-derived products have been used as therapeutics in traditional medicine due to their less adverse effects and economical benefit. Currently the only available treatment for disease is surgical removal of cataractous lens and followed by replacement with synthetic implants. Efforts have been taken to explore the traditional medicine to delay and retard the progression of cataract. Several numbers of plants and synthetic compounds has been reported to possess anti-cataract activity (Rooban *et al.*, 2010).

ANIMAL MODEL TO ASSESS ANTI-CATARACT ACTIVITY

Various animal models have been used for the screening the plants against cataract. Out of that galactose induced cataract is commonly used, it produces the large amount of reduced form, galactitol and finally into glucose. Furthermore galactitol is not subsequently metabolised as compared to the sorbitol. In this model it is supposed that factor initiating galactose cataracts in young rats are similar to those involve in the human galactose cataract model. Three mechanism involve in the formation of cataract are oxidation, polyol pathway and non enzymatic glycation (Kinoshita, 1990). Naphthalene induced cataract is similary used to test herbal drugs as anticataract due to its similarities to that of age related cataract in humans. Naphthalene is converted into stable compound naphthalene-1,2-dihydrodiol and its metabolism to 1,2-napthoquinone by an enzyme dihydrodiol dehydrogenase. Epithelial mitochondrion is the target of 1,2-nathoquinone toxicity. Formation of the 1,2- napthoquinone is considered as underlying mechanism of cataract development in naphthalene induced animal model. Aldose reductase is the key enzyme in the metabolism of naphthalene

Table 1: List of plants with anticataract potential.

Plant name with family	Parts of plant and extract/fraction	Mechanism of action	References
Adhatoda vasica (Acanthaceae)	Aqueous, ethanol and chloroform extracts	Aldose reductase activity	(Cacche and Dhole, 2011)
Allium cepa (Liliaceae)	Juice	Reduces the oxidative stress	(Javadzadeh *et al.*, 2009)
Cassia fistula (Acanthaceae)	Aqueous, ethanolic and chloroform extracts	Aldose reductase activity	(Cacche and Dhole, 2011)
Angelica dahurica (Umbellifereae)	byakangeleisin and furanocoumarin from the roots	Inhibits the galactitol and sorbitol accumulation	(Shin *et al.*, 1998)
Citrus aurantium (Rutaceae)	Hydromethanol peel extracts	Prevent the peroxidative damage	(Umamaheshwari *et al.*, 2011)
Cochlospermum religiosum (Cochlospermaceae)	Isorhmnetin -3-glucoside, bioactive flavonoids form leaves	Inhibits the oxidative stress	(Devi *et al.*, 2010)
Emilia sonchifolia (Asteraceae)	Flavonoids	Inhibits the oxidative damage and lens opacification	(Lija *et al.*, 2006)
Erigeron annuus (Asteraceae)	Caffeoylquinic acids and four flavono-ids from ethyl acetate soluble fractions of stems and leaves	Prevent the lens opacity	(Jang *et al.*, 2010)
Ginko biloba (Ginkgoaceae)	Extract of plant	Inhibit the oxidative sterss	(Ertekin *et al.*, 2004)
Momordica charantia (Cucurbita-ceae)	lyophilized extracts	Inhibit the oxidative damage	(Rathi *et al.*, 2002)
Moringa oliefera (Moringaceae)	flavonoids fractions of leaves	Inhibit the oxidative damage and reduces the lipid peroxidation.	(Sasikala *et al.*, 2010)
Ocimum sanctum (Lamiaceae)	Extract of plant	inhibition of polyol accumulation	(Halder *et al.*, 2003)
Origanum vulgare	Extract of plant	Inhibit the oxidative damage and reduces the lipid peroxidation.	(Dailami *et al.*, 2010)
Pterocarpus marsupium (Fabaceae)	aqueous extract	Inhibits the diabetes induced cataract	(Vats *et al.*, 2004)
Silybum marianum (Compositae)	seeds extract	Inhibit the oxidative damage	(Huseini *et al.*,2004)
Trigonella foenum graceum (Fabaceae)	Seed extract	Inhibit the generated oxidative stress	(Lija *et al.*, 2006)
Vitex negundo (verbanaceae)	flavonoids fraction	Inhibits the oxidative stress	(Rooban *et al.*, 2011)
Withania somnifera (solanaceae)	Extract of plant	Inhibits the oxidative stress	(Thiagarajan *et al.*, 2003)

(Germansky and Jamall, 1988). Selenite induced cataract is model for oxidative stress induced cataract. Selenite cataract is occurs due to the acute exposure of the selenite to the lens at particular age which cause the nuclear cataract (Huang *et al.*, 1982). Furthermore selenite induced oxidative stress causes the nuclear opacity through the calpain proteolysis of lens protein. It is strong sulfhydryl oxidant and it is resembles cataract caused by oxidative stress. Similar to human senile cataract, this type of cataract is accompanied by decrease in activities of the antioxidants enzymes such as superoxide dismutase, glutathione peroxidase (Shearer *et al.*, 1997).

PLANT PRODUCTS AGAINST CATARACTS

Based on literature assessment from earlier studies it was found that disturbance in the oxidative state in lens can be corrected by giving antioxidant such as ascorbic acid and besides also in body there are enzymatic and non enzymatic antioxidant system to protect cellular orgenelles from free radicals (Bhuyan *et al.*, 1981). Hyperglycemia generates the reactive oxygen species, which causes the lipid peroxidations and thus play major role in development of diabetic secondary complications in kidney, blood vessels, eye and nerve (Patel *et al.*, 2011). The natural antioxidant such as ascorbic acid, vitamin E, and carotinoids have been screened and it was found that antioxidant has protective action against cataract. Flavonoids found in various food and beverages have strong antioxidant and anticataract activity (Durukan *et al.*, 2006; Patel *et al.*, 2011). one isoflavoniod glycoside isolated from ethyl acetate soluble fraction of *Viola hondoensis* was screened for aldose reductase inhibitory activity and it was found that it possess potent aldose reductase inhibitory potential (Chung *et al.*, 2008). Tea a major source of dietary quercetin and other flavonoids had been reported to have anticataract activity; and ability of isoflavone gentisin in delaying the progression of cataract induced by the dietary galactose has been reported (Vinson and Zhang, 2005). Therefore development of pharmacologically and biochemically tested compound would be of great importance for the management of diabetic complication.

PLANTS WITH ANTICATARACT ACTIVITY

A list of plants with anticataract potential is given in table 1.

DISCUSSION

Cataract is disorder associated with several risk factors such as diabetes, aging etc. For the treatment of cataract there is no medicine available except surgery. However it has also some complication such as posterior capsular opacification, endophthalmitis and uncontrolled residual refractive errors (Javadzadeh *et al.*, 2009). So this type of therapeutic approach can reduces health burden. In last few years researchers are trying to find out the phytoconstituents that could beneficial against the cataractogenesis. From earlier studies it was found that *Ocimum sanctum* possess significant antioxidant potential with anticataract activity (Devi *et al.*, 2010). Reduction in glutathione level is another mechanism for retardation of cataract. Several phytoconstituents from herbal origin may indirectly inhibits the consumption of glutathione or it can stimulate the glutathione synthesis which may be due to modulating effect on enzymes that affects glutathione level in lens architecture. In another study, it was found that *Trigonella foenum-graceum* can enhance the glutathione level due to inhibition of consumption of glutathione (Gupta *et al.*, 2010). Several factors are involved in generation of cataract, but exact mechanism of cataract formation is still unknown. Several researchers are trying to determine the mechanism of cataract formation by use of different *In vitro* and *In vivo* models. Amongst all the experimental models, the galactose induced cataract model is widely used due to similarity of this model to that of galactose induced human cataractogenesis (Gupta *et al.*, 2009; Suryanarayana *et al.*, 2005). Human cataract is not single disease but it is group of disease involve many risk factor. Oxidative stress is main mechanism behind cataract formation and in which antioxidant level is found to be less as compared to normal person. According to previous studies, it was found that significant increased level of free radicals and low concentration of glutathione content were observed in aqueous humor. Many study shows that flavonoids, a group of phytoconstituents with antioxidant properties can prevent the oxidative damage and cataract progression. Onion a flavonoids rich staple food is example in which major flavonoids are identified for antioxidant properties including quercetin, quercetin-4-glucoside and quercetin-3,4'-diglucoside (Javadzadeh *et al.*, 2009). According to world health organisation (WHO) reports it seems that about 80% of world population are uses herbal medicine for health needs (Kim *et al.*, 2010). Many studies have done to identify the natural or synthetic compound that inhibit aldose reductase and flavonoids are found to most potent aldose reductase inhibitors (Constantino *et al.*, 1999). Plant phytochemicals including polyphenols, which are currently regarded as natural antioxidant they are important for human health against various types of enzymes, which reduces the blood glucose level in diabetes, and are capable of reducing the oxidative stress by scavenging the free radicals and prevention cell damage (Vishvanath *et al.*, 2010; Girija *et al.*, 2011).

CONCLUSION

This review provides the relevant update information about the pathophysiological aspects of cataract, risk factor involved and suitable treatment available for cataract. It also provides the database of plants and their phytoconstituents responsible for anticataract activity. Since eye is unique organ, it is constantly exposed to oxidative stress and protection of lens from these is critical for essential. So far, no single compound has found wide spread acceptance for these indication, although many compound have been screened. Thus, there is need for further research in this area. Therefore, this review enables as an important segment for development of effective medicine for treatment of cataract.

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