INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

**Research Article**

# A Review of Pharmacological Agents for Cataract Prevention

**Pratik Bhand, Ajay Bhagwat, Shrushti Darade*, Ishwari Borhade, Priyanka Narasale, Swapnil Auti**

*Samarth College of Pharmacy, Belhe, Pune. Maharashtra. India. 412410.*

ARTICLE INFO

Published: 28 Nov 2025
Keywords:
Cataract, Antioxidant, non-enzymatic glycation, Oxidative stress, Polyol pathway
DOI:
10.5281/zenodo.17746753

## ABSTRACT

Globally, cataracts continue to be the primary cause of blindness and visual impairment. 180 million people worldwide are thought to be sight-impaired. Of these, 37 million are blind, and with 28,000 new instances reported every day, the figure rises by one to two million per year. Fifty per cent of blindness worldwide is caused by cataracts. The percentage of children who are blind from cataracts varies greatly by location, ranging from 10% to 30%. The global average is believed to be 14%, meaning that 190,000 children are blind as a result of cataracts. The only treatment available at the moment is surgically removing the cataractous lens and replacing it with a synthetic polymer lens. Nevertheless, the prevalence is so high that the surgical facilities that are now available cannot handle the issue. Postoperative problems, including endophthalmitis, posterior capsular opacification, and uncorrected residual refractive error, may also arise. As a result, pharmaceutical interventions that preserve the lens's transparency are being sought. To define the aetiology of cataracts, a great deal of study has been done during the past 20 years. Numerous medicines have been used in an attempt to postpone the start of cataracts and reduce their progression. Regretfully, no single drug has shown clinical utility for this purpose despite significant efforts. This review highlights the various pharmaceutical approaches for preventing cataract formation and the risk factors associated with cataractogenesis.

## INTRODUCTION

### 1.1.Factors Involved in Cataract Formation

The pathophysiology of senile cataract has been associated with several risk factors. In addition to age, cataract development is caused by smoking, diabetes, gender, steroids, and nitric oxide. These risk factors have been linked to various cataract morphological types.

- **Smoking**

It is believed that smoking raises the risk of cataracts, at least in part, by increasing the

***Corresponding Author:** Shrushti Darade
**Address:** *Samarth College of Pharmacy, Belhe, Pune. Maharashtra. India. 412410.*
**Email** ✉: daradeshrushti@gmail.com
**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

oxidative stress that free radicals produced in the lens cause.[1-5] In the presence of these free radicals from tobacco smoke, they have the potential to directly harm the lens's Epithelial cell membrane and lens protein [6,7] When a person smokes or chews tobacco, a significant amount of cadmium (Cd) is taken into the body. This Cd substitutes bivalent elements like zinc (Zn), copper (Cu), and manganese from superoxide dismutase (SOD), a potent antioxidant.[8]

- **Diabetes**

Diabetes can affect the eyes in a number of ways, but cataracts are the most prevalent cause of visual loss. One of the first secondary consequences is cataractogenesis of diabetes mellitus, a severe metabolic condition marked by hyperglycemia.[2] There are a few theories as to how diabetes mellitus causes cataracts, including elevated free radical generation, aberrant glycosylation of lens proteins, and high tissue sorbitol concentrations. [9]

- **Female gender**

Several epidemiological studies that used cross-sectional data have revealed that women are more likely than men to get cataracts.[10] The reason behind Although the exact cause of the gender disparities in cataract incidence is unknown, it may be linked to the hormonal differences between men and women. One possible contributing factor is postmenopausal estrogen insufficiency. There is some indication from recent epidemiologic data that estrogen and hormone replacement therapy may help lower the incidence of age-related cataracts.[11]

- **Steroids**

It is commonly known that using steroids increases the risk of developing cataracts. There appears to be agreement that the longer the time, the larger the steroid dose of usage, the greater the chance of developing posterior subcapsular cataracts.[12] Steroids impede the cation pump in the lens capsule, which leads to an electrolyte/water imbalance that causes cataracts.[13]

- **Nitric oxide**

Although nitric oxide (NO) is not a very harmful substance by itself, it can combine with other molecules to produce more reactive chemicals. For instance, the interaction with nitric oxide (NO) produces peroxynitrite ($ONOO^-$), which damages cells extensively and may play a significant part in the development of diabetic cataracts.[14,15]In addition to the risk factors listed above, genetic variables, socioeconomic status, sunshine, ultraviolet (UV), myopia, renal failure, diarrhoea, malnutrition, illiteracy, and hypertension, Cataractogenesis has also been linked to exposure, obesity, chemical burns, glaucoma, and alcohol[16,17] [Fig. 1].

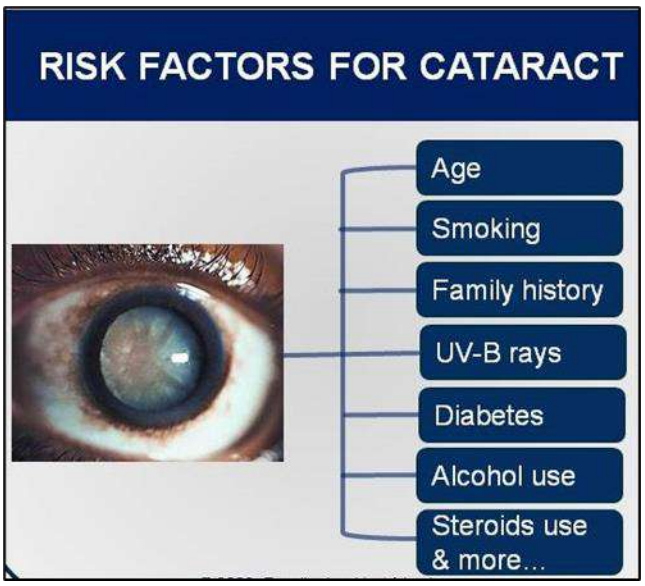



**Figure 1: Major risk factors implicated in cataractogenesis**

### 1.2. Mechanisms Related to Cataract

Human cataract development is caused by a number of intricate metabolic and physiological processes that work together to alter the refractive index. [18] Research on lens proteins shows that chemical processes, including oxidation, glycation, Schiff base formation, proteolysis, transamination, carbamylation, phosphorylation, and increased calcium levels, cause post-translational modifications in the lens proteins during cataractogenesis. [17] [Figure 2]. To promote aggregation, disruption of normal lens cell structure, and opacification, the post-translational modifications change the attractive forces between lens proteins. [2]

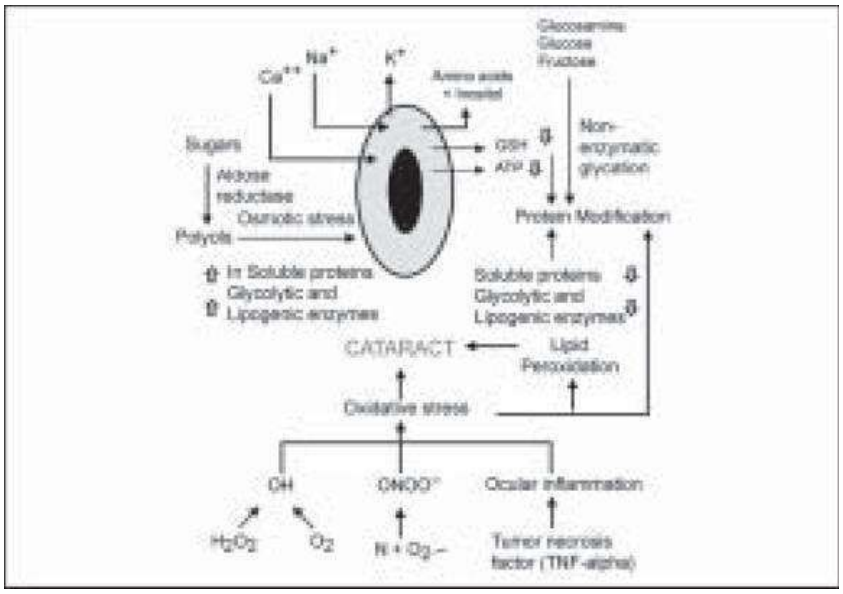



**Figure 2: Mechanisms associated with cataractogenesis**

This article describes the function of the following pathways in the development of cataracts among the various mechanisms put out for cataractogenesis.

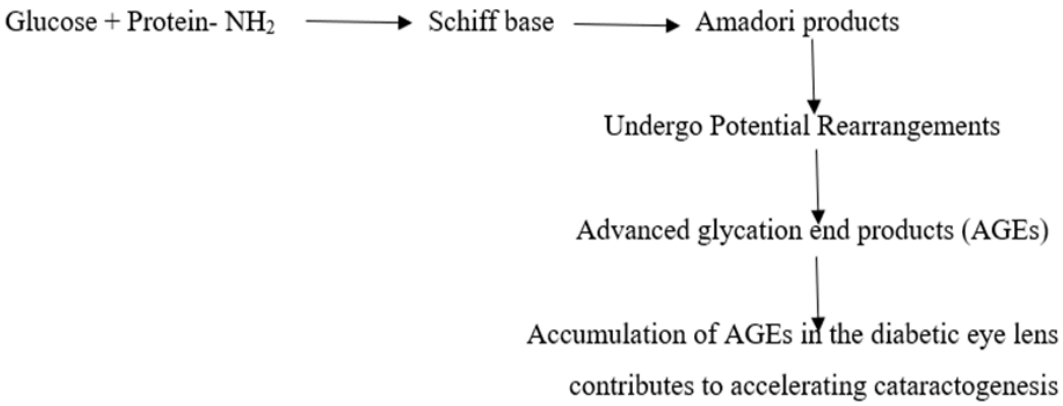
a. non-enzymatic glycation

b. Oxidative stress

c. Polyol pathway

➢ **Non-enzymatic glycation**

When blood glucose levels are high, some of the extra glucose reacts non-enzymatically with proteins or other components of tissue or blood, raising the pace of non-enzymatic glycation in the body. [19] Long-lived molecules, extracellular matrix, eye lens crystallins, and chromosomal DNA are the main causes of chronic, permanent problems that are not affected by blood glucose correction. Advanced products of non-enzymatic glycation are crucial to the development of sugar cataract because of their distinctive chemical characteristics. As the first stage of the intricate Maillard process, the synthesis of advanced glycation end products (AGEs) starts with the attachment of a glucose carbonyl group to a free amino group of proteins or amino acids to produce a labile Schiff base adduct. The unstable Schiff base levels rise quickly, and equilibrium is reached after a few hours. Schiff base adducts, once created, undergo a gradual chemical rearrangement over several weeks to create an Amadori product that is more stable but still chemically reversible [20] [Flow chart No. 1].




**Flow chart No.1:**

Because Amadori products might potentially undergo a wide spectrum of rearrangements, specific chemical identification of AGE proteins has proven challenging. Immunological and chemical evidence suggests that the gradual build-up of AGEs in the diabetic eye lens accelerates the development of cataracts in both diabetic humans and hyperglycaemic experimental animals. [21, 22]

➢ **Oxidative stress**

The pathogenesis of cataract is significantly influenced by oxidative stress of cataract [23]. An imbalance could lead to oxidative stress between the generation of ROS (reactive oxygen species) and the antioxidant defence systems within cells. Within the cells of the ROS may cause a spike in harmful metabolic processes in the eyes. such as severe protein degradation leading to intracellular protein aggregation and peroxidation of membrane lipids, precipitation, which ultimately results in lens opacification. [24, 25] The redox set point of the single layer of lens epithelial cells rapidly shifts from a strongly reducing to an oxidising environment when the eye is exposed to oxidative stress. Significant damage to the DNA and membrane pump systems occurs almost simultaneously with this alteration. This is

followed by the death of epithelial cells through necrotic and apoptotic processes, which results in cataract. [26, 27]

➢ **Polyol pathway**

Diabetic cataracts progress by a different process than senile cataracts. The buildup of polyols inside the lens is the main contributing element. Insulin is not necessary for glucose and other simple carbohydrates to penetrate some bodily tissues, such as the lens of the eye. Sugar can diffuse passively into the lens due to its high concentration in the aqueous humour in diabetics. The lens's enzyme aldose reductase changes glucose into sorbitol or galactose into galactitol [Fig. 4]. These polyols are unable to collect or convert into fructose by diffusing passively out of the lens. An osmotic gradient created by the buildup of polyols promotes the diffusion of fluid from the aqueous humour.

Pharmacological Strategies for Prevention of Cataract: Drugs have been developed that are aimed at interacting at the level of altered lens metabolism and lens pathophysiology. The anticataract agents claimed to be effective in vitro, in vivo and in epidemiological studies may be broadly classified in the following categories:

A. Aldose reductase inhibitors

B. Non-steroidal anti-inflammatory drugs

C. Agents acting on glutathione

D. Vitamins, minerals, antioxidants and herbal drugs

E. Miscellaneous agents

➢ **Aldose reductase inhibitors (ARI)**

The goal of ARI is to obstruct the glucose metabolic pathways that cause diabetic vascular impairment. Their part in preventing diabetic cataract in animals is now widely recognised. [28, 29] Aldose reductase has been reported to be inhibited by a wide variety of synthetic and natural substances. By binding to aldose reductase, these so-called ARI prevent the synthesis of polyols. Since the enzyme aldose reductase is very slow with glucose, the justification for employing sorbitol-lowering medications has diminished with time. Moreover, sorbitol does not build up in adult human lenses cultured in high glucose conditions. Several ARI are known to have anticataract potential and to postpone the cataract caused by galactose in several experimental animals. [30] Alrestatin, sorbinil, sulindac, naproxen, aspirin, Tolrestat, statin, and bioflavonoids are a few of these.

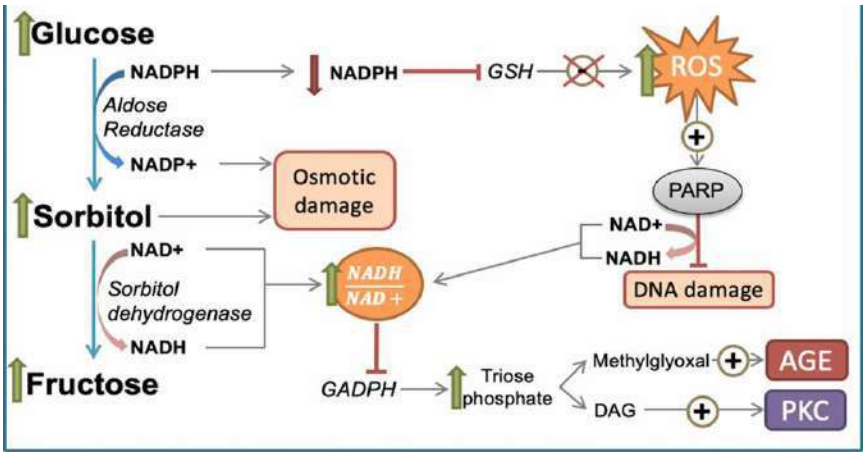



**Figure 4: Polyol pathway**

Flavonoids are among the most potent naturally occurring ARI. Various studies of in vitro animal lenses incubated in high-sugar mediums, flavonoids have found to inhibit aldose reductase.[31,32] In our previous studies, the flavonoids quercetin and myricetin have exhibited signiÞ cant delay in the onset and progression of galactose cataract in rats.[33] The flavonoids quercetrin and quercetrin-2-acetate, quercetin, rutin, hesperidin, hesperidin chalcone and naringin exhibited AR-inhibiting activity to different extents.[34] A recent study was carried out to evaluate the potential of AR-inhibiting bioflavonoids extracted from fruits of G. applanatum. [35]

A recent study done by Varma et al. showed that administration of pyruvate prevented cataract development by inhibiting the AR in diabetic rats.37 The AR-inhibiting activity in Emblica officinalis was investigated, and it was found to be better than quercetin.[38] Similarly, vitamin C also has potential as an ARI, with both animal and clinical studies showing that it minimises the levels of sorbitol.[38,39]] Gymnema sylvestre aqueous extract showed potential AR inhibition in sugar-induced cataract and had also protected the lens against osmotic damage.[40] Table 1 shows some of the most commercially available flavonoids and herbal drugs and their comparative inhibitions. Among the ARI, only sorbinil reached the advanced clinical trial stages in the cataract prevention program. However, due to the manifestation of skin rashes, the trial had to be discontinued. In spite of extensive research input, clinical trials of the sorbitol-lowering agents have not provided convincing evidence of their efficacy.

- **Non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs) have emerged as another group of drugs with anticataract potential. The Þ rst indication regarding the probable use of NSAIDs as prophylactic anticataract agents came from studies on aspirin use in patients with rheumatoid arthritis and diabetes.[41]

**Table 1: Aldose reductase inhibiting activity of some ß avonoids**

| Flavonoid | Percent inhibition |
|---|---|
| Quercetrin-2-acetate [32] | 100 |
| Quercetrin [32] | 100 |
| Quercetin [32] | 100 |
| Rutin [32] | 95 |
| Hesperidin [32] | 88 |
| Hesperidin chalcone [32] | 82 |
| Naringin [32] | 80 |
| Emblica ofÞ cinalis [37] | 82.4 |

Thereafter, a variety of NSAIDs with different chemical structures have been reported to retard the phenomenon in experimental animals. The NSAIDs extensively such as aspirin, paracetamol, ibuprofen, naproxen, and sulindac. and bendazec. [42-44] The anticataract activity of these drugs is explained by virtue of their effect on different biochemical pathways. The mechanisms associated with the protective effect of NSAIDs include acetylation, inhibition of glycosylation and carbamylation of lens proteins.

We have earlier shown that naproxen delays the onset and progression of galactose-induced cataract in rats. Moreover, naproxen was also tested for its in vivo effectiveness in rat pups developing cataracts under the oxidative inß uence of sodium selenite.[46] To explain the mechanism of action of Naproxen as an antioxidant, its effect on light-induced lipid peroxidation in isolated rat lenses was studied, and depletion of lens glutathione and a rise in malondialdehyde levels were observed.[47] It was also shown that sulindac inhibits lens Polyol to a large extent by its possible inhibiting action on lens AR.[48] Comparative studies on the anticataract activity of Various NSAIDs demonstrated that though inhibition of

lens AR by NSAIDs may be a significant factor-it does not appear to be the sole cause.[45] The hypothesis of acetylation of lens protein by aspirin does not justify the mechanism of action of other NSAIDs, such as ibuprofen do not have an acetyl group. The Results obtained so far suggest that there are several sites where NSAIDs likely act to impede cataract progression. However, their mechanisms of action need to be elucidated. action in more detail under different culture conditions and in different experimental models.

Anticataract activity of aspirin, sulindac, and naproxen eye drops was also studied, and they were found to delay both onset and progression of cataract in different models of cataractogenesis; moreover, there were no adverse side effects. Even after long-term application 49, subsequent studies further confirmed that aspirin is a potential anti-cataract agent.[50] Bendazac, a compound similar to indomethacin in its structure, emerged as a potential radical scavenger and anticataract agent. Bendazac protects lens and serum proteinsfrom denaturation in vitro and in vivo.[51, 52] 5-hydroxybendazac, a derivative, however, was found to be more effective than the parent compound in protecting lens proteins against cyanate, glucose 6-phosphate and galactose.[53] Another derivative, bendazac lysine, was found to have better absorption in animal and human studies, and it is reported to delay cataractogenesis.[54] Bendazac-lysine has undergone clinical trials, but these studies have been small and of short duration.[55] Bendazac-lysine is already available as an anticataract drug in Italy and in several other European countries, under the trade name of Carbopol. 980NF manufactured by Goodrich Limited.

- **Agents that act on glutathione:**

The most important function of GSH is to inactivate and render excess free radicals and render them harmless. GSH consists of the amino acids cysteine, glutamic acid, and glycine, and its synthesis within the lens occurs in two ATP-dependent steps [Fig. 5]. There are several ways in which GSH or its depletion can affect the opacity of the lens. A review by researchers on GSH [56].

- **Mechanisms of cataract prevention are:**

1. Maintaining sulfhydryl (SH) groups on proteins in their reduced form, preventing disul de cross-linkage

2. Protecting SH groups on proteins important for active transport and membrane permeability

3. Preventing oxidative damage from H2O2

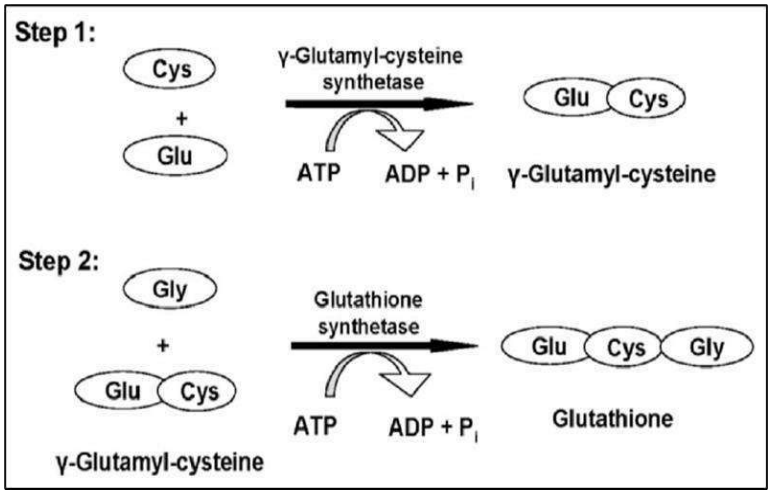



**Figure 5: Synthesis of glutathione within the lens**

GSH concentration decreases with age in the lens and more markedly in cataract.[34] GSH has been reported to control calcium inß ux and protect lens protein against damaging effects of osmotic and oxidative stress. [5,57]. A Large amount of Research has been done on antioxidants and vitamins, and the role of GSH in preventing cataract has been reported. A recent study shows that vitamin E protects the anti-oxidative defence mechanism indirectly or directly by increasing levels of GSH.[58] The anticataract effect of melatonin PSI (a scavenger of free radicals) was demonstrated, and the study concluded that the effect is due to its stimulatory effect on GSH production.[59] Clinical trials on Phaken, a preparation containing three constituents of amino acids GSH plus arginine, inositol, pyridoxine and ascorbic acid, have demonstrated improvements in visual performance. acuity, but due to a high dropout rate, no clear-cut conclusions could be drawn. [60]

- **Vitamins, minerals, antioxidants and herbal drugs:**

It is generally known that vitamins, particularly vitamin C or ascorbic acid, which is crucial to lens biology as a UV filter and antioxidant, may help prevent cataracts. [61] Ascorbate concentrations in the lens decreased as a result of vitamin C deficiency in the diet. [62] Ascorbate prevents galactose cataract, according to a study conducted on guinea pigs. [63] In a similar vein, another study shows that ascorbate consumption raises vitamin C levels in rat lenses. [64] Additionally, vitamin E plays a significant role in the antioxidant status of lenticles. Numerous studies have assessed vitamin E's anticataract potential and discovered that it is effective against UV radiation, steroids, and galactose-induced cataract. [58, 65–67] The precursor to flavin adenine dinucleotide (FAD), a coenzyme for the manufacture of glutathione reductase, is riboflavin. In vitro assessments of surgically excised cataracts have confirmed that glutathione reductase enzyme activity is inactive in a significant majority of the cataracts analysed. [68] Additionally, the addition of FAD restored the activity. A study comparing the B vitamin nutritional status of age-matched controls without cataracts (n = 16) and cataract patients (n = 37) revealed that only 12.5% of control subjects and 80% of cataract patients had a riboflavin deficiency. [69]

- **Minerals:**

The excessive free radical attack implicated in the development of cataract can be prevented by dietary intake of micronutrients such as zinc, copper and manganese. Copper and zinc are required for the catalytic activity of metal proteins and SOD.[70] Plasma levels of zinc and copper were found to be significantly low in cataract patients.[69] Selenium is an integral part of the enzyme glutathione peroxidase. A decrease in glutathione peroxidase activity has been found in the lenses of selenium-deficient rats.[71]

- **Antioxidants:**

It is commonly acknowledged that oxidative stress plays a significant role in the development of cataracts. [72–74] Because superoxide is transformed into the harmful chemical hydrogen peroxide, oxidative stress is linked to an increase in reactive oxygen species and is known to hasten the development of cataracts. Antioxidant enzymes like glutathione peroxidase, superoxide dismutase, and catalase stop this process. One important preventive measure against oxidation-related cataractogenesis is the use of antioxidants. The impact of dietary antioxidant supplements on cataract incidence has been the subject of numerous epidemiological and interventional investigations. • Carotenoids are natural lipid-soluble antioxidants. It is reported that persons

with a high intake of carotene reduce the risk of cataract[75] and the relationship between nuclear cataract and intakes of α-carotene, β-carotene, lutein, lycopene and cryptoxanthin stratifying by gender and by regular multivitamin use.[76] All carotenoids, including lycopene antioxidative activity and exert a protective effect against various diseases.[77] In previous studies, we found that lycopene protects against oxidative stress-induced experimental cataract[74] and prevents sugar-induced diabetic cataract.[57] • Turmeric's key ingredient, curcumin, has been demonstrated to have antioxidant properties both in vitro and in vivo. [78] Curcumin's effect on cataracts has also been demonstrated. Curcumin postponed the development of diabetic cataracts caused by streptozotocin and galactose [79]. [80] Curcumin also stopped cataract development brought on by oxidative stress. [81]

A new synthetic pyridoindole called stobadine has been shown in numerous experiments to be an effective antioxidant [82] and to shield bovine serum albumin from glycol oxidative harm. It has been demonstrated that stobadine can postpone the onset of diabetic cataract. [84]

- **Herbal drugs:**

Investigating the potential of utilising our natural resources to postpone the start and progression of cataracts has received a lot of attention in recent years. It has been observed that medicinal herbs and their preparations have antioxidant qualities and provide cataract protection. The aqueous extract of Ocimum sanctum has been demonstrated by *Gupta et al.* to have promising anticataract action against oxidative stress-induced experimental cataractogenesis. Restoring the antioxidant defence system increased the protective effect. [85] The aqueous extracts of Pterocarpus marsupium and Trigonella foenum-graceum, two well-known herbal antidiabetic medications, have a positive anticataract effect. [86]

Proanthocyanidin extract from grape seeds effectively inhibited the development of cataracts in rats, according to a recent study. [87] Emilia sonchifolia's flavonoids alter the lens's opacity and oxidative stress in cataracts caused by selenium. [88] Dregea volubilis is a medicinal plant that has long been used to cure a variety of eye conditions. Its potential anticataract effect has now been scientifically demonstrated, and it has also been discovered that the effect is caused by the triterpenoid aglycone drevogenin D. [89] Bilberry, also known as Vaccinium myritillus, has long been used to treat a variety of eye disorders. [34] A combination of bilberry and vitamin E prevented the progression of cataracts up to 96% in a clinical trial report of 50 individuals with senile cataracts. [90]

Certain herbal drugs, especially Ginkgo biloba extract, have been found to possess potential therapeutic effects in radiation-induced cataract.[91] Most of the studies conducted focus on green tea, Camellia sinensis. and the explained antioxidative potential is the major mechanism in the prevention of cataractogenesis. *Gupta et al.* have demonstrated that green tea protects against selenite-induced cataract and acts mainly by preserving the antioxidant defence. system.[92] It was also presented that the oxidative potential of green tea retards the progress of cataractogenesis. [93] Recently, both green tea and black tea have been shown to delay the development of diabetic cataract, also by hypoglycemic effect.[94] The recent study reveals that E. officinalis, also known as amla, used against diabetes, is also effective in delaying the progression from diabetic cataract.[95] The herbal formulation Diabecon is used for diabetics, contains 25 herbal drugs. inhibited the sugar-induced lens opacity in organ culture and

also showed that the effect is mainly due to Gymnema sylvestre, which is one of its constituents.[40] A study by our laboratory on polyherbal preparation, Chyavanprash, containing about 35 natural herbs. including amla), found it to be protective against steroid-induced opacities in the lens of the chick embryo.[96] (Table 2) summarises potential vitamins, antioxidants and herbal drugs for the prevention and treatment of cataract.

- **Miscellaneous Agents:**

Different materials with different chemical structures and It has been discovered that some characteristics have a protective effect against cataract in different experimental models. A study was conducted with pyruvate, a compound of metabolic origin and having an alpha-keto-carboxyl group. It was discovered effective in preventing the development of cataracts in diabetics [97] as well as in selenite [98] models of experimental cataracts. A study was also carried out using alpha-ketoglutarate and discovered an extremely strong anticataratogenic effect in selenite-induced cataract [98] ACE inhibitors have been shown to provide defence against free radical damage under a variety of experimental circumstances [99] Lisinopril and enalapril's anticataract efficacy was recently assessed in vitro using glucose-induced cataract and found to Significant protection. A decrease in malondialdehyde in the treated lens led the study to conclude that the effect might be due to the antioxidant and free radical scavenging activity. [100] Age-related cataracts can be effectively prevented and treated using N-acetylcarnosine, which is marketed as the ophthalmic medication Can-C. In recent clinical research, it was demonstrated to provide an effective, safe, and long-lasting improvement in vision while shielding the crystalline lens from oxidative stress. N-acetylcarnosine acts as a time-release prodrug form of L-carnosine that is resistant to hydrolysis with carnosinase when Can-C is applied topically.

N-acetylcarnosine has the capacity to function as a universal antioxidant in vivo due to its capacity to defend against oxidative damage in the lipid phase of biological cellular membranes and in the aqueous environment by a gradual intraocular turnover into L-carnosine. The clinical Effects of a topical solution of Can-C on lens opacities were studied in elderly dogs and individuals with cataracts associated cataracts. These findings demonstrated that N-acetylcarnosine.

It is successful in treating age-related cataract reversal. and prevention in both canine and human eyes [101]. There have long been reports of the protective effects of alpha lipoic acid [102], pantethine [103], DL-penicillamine [104], and deferoxamine [105], but sadly, none of these medications have proven clinically assessed. Many anticataract medications, such as Itone (a blend of 19 herbal remedies, including triphala and tulsi),[106-109] as well as a few other herbal remedies, are accessible in India without any evidence of their effectiveness; therefore, thorough scientific research is needed to determine the effectiveness of these herbal remedies.

Numerous areas of research on anticataract medications are progressing, and some medications have advanced to the point of clinical testing. Additionally, several organisations are attempting to look at the anticataract effects of both synthetic and natural medications.[110-117] Our initial research on the usage of a unique combination of a few antioxidants and herbal medications has shown promising results. It appears likely that some of these substances will be demonstrated to be effective in postponing or decreasing the onset of cataracts in the future.

## CONCLUSION

Numerous studies on the prevention and treatment of vitamins, minerals, herbal medications, and nutritional supplements have been conducted in vitro, in vivo, and epidemiologically of cataracts. The majority of research is still in its early stages, despite the fact that a number of medications may be able to treat cataracts. However, more extensive and prospective clinical research is required about the use of herbal medications and nutrients to treat cataracts. Similarly, therapeutic intervention is limited by the potential for toxicity linked to prolonged exposure to most medications. Positive reports exist regarding the topical application of these medications with negligible or no adverse effects. Preventing or delaying cataract blindness in humans through such an application will prove to be a significant accomplishment.

### Conflicts Of Interest

There are no conflicts of interest or disclosures regarding the manuscript.

## ACKNOWLEDGMENT

The authors sincerely thank Samarth College of Pharmacy, Belhe, University Libraries, and all other sources for their cooperation and advice in writing this review.

## REFERENCES

1. Gupta SK, Joshi S, Velpandian T, Len A, Prakash J. An update on pharmacological perspectives for prevention and development of cataract. Indian J Pharmacol 1997; 29:3-10.
2. Kyselova Z, Stefek M, Bauer V. Pharmacological prevention of diabetic cataract. J Diabetes Comp 2004; 18:129-40.
3. WHO. Prevention of avoidable blindness and visual impairment. Provisional agenda item 4.9. EB117/35, 117th Session 22 December 2005.
4. Shamanna BR, Muralikrishnan R. Childhood cataract: Magnitude, Management, Economics and Impact. Comm Eye Health 2004; 17:17-8.
5. Varma SD, Hegde KR. Effect of α-ketoglutarate against selenite cataract formation. Exp. Eye Res 2004; 79:913-8.
6. Sulochana KN, Punitham R, Ramakrishnan S. Effect of cigarette smoking on cataract: Antioxidant enzymes and constituent minerals in the lens and blood of humans. Indian J Pharmacol 2002; 34:428-31.
7. Lindblad BE, Hakansson N, Svensson H, Philipson B, Wolk A. Intensity of smoking and smoking cessation in relation to risk of cataract extraction: A prospective study of women. Am J Epidemiol 2005; 162:73-9.
8. Ramakrishnan S, Sulochana KN, Selvaraj T, Abdulrahim A, Lakshmi M, Arunagiri K. Smoking of beedies and cataract: Cadmium and vitamin C in the lens and blood. Br J Ophthalmol 1995; 79:202-6.
9. Aksoy H, Keles S, Kocer I, Akcay F. Diabetic cataract and the total antioxidant status in aqueous humour. Clin Chem Lab Med 2001; 39:143-5.
10. McCarty CA, Mukesh BN, Fu CL, Taylor HR. The epidemiology of cataract in Australia. Am J Ophthalmol 1999; 128:446-65.
11. Christine Y, Paul M, Robert GC, Panchapakesan J, Elena R, Angela MH. Hormone replacement therapy, reproductive factors, and the incidence of cataract and cataract surgery: The Blue Mountains Eye Study. Am J Epidemiol 2002;155:997-1006.
12. Jaime ED, Eric Dotzel, Abbot FL. Steroid-induced cataract: New perspectives from in vitro and lens culture studies. Exp Eye Res 1997;65:507-16.

13. Mayman CL, Miller D, Tijerina ML. In vitro production of steroid cataract in bovine lens. Acta Ophthalmol 1979;57:1107-16.
14. Eva MO, Stefan LM, Anders B. Glucose-induced cataract in CuZn SOD null lenses: An effect of nitric oxide? Free Radical Biol Med 2007;42:1098-105.
15. Varma SD, Hegde KR. Susceptibility of the ocular lens to nitric oxide: Implications in cataractogenesis. J Ocul Pharmacol Ther 2007;23:188-95.
16. Harding J. Cataract: Biochemistry, epidemiology and pharmacology. London: Chapman-Hall; 1991. p. 83-124.
17. Ito Y, Nabekura T, Takeda M, Nakao M, Terao M, Hori R, et al. Nitric oxide participates in cataract development in selenite-treated rats. Curr Eye Res 2001;22:215-20.
18. Clark JI. Development and maintenance of lens transparency. In: Albers EM, Jakobiec FA, editors. Principles and practice of ophthalmology. Philadelphia: W. B. Saunders; 1994. p. 114-23.
19. Brownlee M. Advanced glycation end products in diabetes and ageing. Ann Rev Med 1996;46:223-34.
20. Monnier VM. Sell DR, Nagaraj RH, Miyata S, Grandhee S, Odett I P, et al. Maillard reaction-mediated molecular damage to extracellular matrix and other tissue proteins in diabetes, ageing and uremia. Diabetes 1992;41:36-41.
21. Araki N, Ueno N, Chakrabati B, Morino Y, Horicuchi S. Immunological evidence for the presence of advanced glycation end products in human lens proteins and its positive correlation with ageing. J Biol Chem 1992;267:10211-4.
22. Duhaiman AS. Glycation of human lens proteins from diabetic and (nondiabetic) senile cataract patients. Glycoconjugate Jr 1995;12:618-21.
23. Halliwell B. Antioxidants: The basics of what they are and how to evaluate them. Adv Pharmacol 1997;38:3-19.
24. Micelli-Ferrari T, Vendemiale G, Grattagliano I. Role of lipid peroxidation in the pathogenesis of myopic and senile cataract. Br J Ophthalmol 1996;80:840-3.
25. De Haan JB, Cristiano F, Jannello RC, Kola I. Cu/Zn-superoxide dismutase and glutathione peroxide during ageing. Biochem Mol Biol Int 1995;35:1281-97.
26. Spector A. Oxidative stress-induced cataract: mechanism of action. FASEB 1995;9:1173-82.
27. Spector A. Review: Oxidative stress and disease. J Ocul Pharmacol Ther 2000;16:193-201.
28. Stribling D, Mirrlees DJ, Harrison HE, Earl DC. Properties of ICI 126536, a novel aldose reductase inhibitor, and its effect on diabetic complications in rats. Metabolism 1985;34:336-44.
29. Zenon GJ, Abobo CV, Carter BL, Ball DW. Potential use of aldose reductase inhibitors to prevent diabetic complications. Clin Pharm 1990;9:446-57.
30. Harding JJ. Pharmacological treatment strategies in age-related cataracts. Drugs Ageing 1992;2:287-300.
31. Nakai N, Fujii Y, Kobashi K, Nomura K. Aldose reductase inhibitors: Flavonoids, alkaloids, acetophenones, benzophenones, and spirohydantoins of chroman. Arch Biochem Biophys 1985;239:491-6.
32. Varma SD, Mikuni I, Kinoshita JH. Flavonoids as inhibitors of lens aldose reductase. Science 1975;188:1215-6.
33. Mohan M, Gupta SK, Agnihotri S, Joshi S, Uppal RK. Anticataract action of topical quercetin and myricetin in galactosemic rats. Med Sci Res 1988;16:685-6.

34. Kathleen ND. Natural therapies for ocular disorders, part two: Cataracts and glaucoma. Altern Med Rev 2001;6:141-66.
35. Sanghyun L, Sang HS, Kim JS, Shin KH, Kang SS. Aldose reductase inhibitors from the fruiting bodies of Ganoderma applanatum. Biol Pharm Bull 2005;28:1103-5.
36. Varma SD, Hegde KR. Prevention of cataract by pyruvate in experimentally diabetic mice. Mole Cell Biochem 2005;269: 115-20.
37. Suryanarayana P, Kumar AP, Saraswat M, Mark P, Reddy GB. Inhibition of aldose reductase by tannoid principles of Emblica officinalis: Implications for the prevention of sugar cataract. Mol Vis 2004;10:148-54.
38. Yokoyama T, Sasake H, Giblin FJ, Reddy VN. A physiological level of ascorbate inhibits galactose cataracts in guinea pigs by decreasing polyol accumulation in the lens epithelium: A dehydroascorbate-linked mechanism. Exp Eye Res 1994;58:207-18.
39. Cunningham JJ, Mearkle PL, Brown RG. Vitamin C: an aldose reductase inhibitor that normalises erythrocyte sorbitol in insulin-dependent diabetes mellitus. J Am Coll Nutr 1994;13:344-50.
40. Moghaddam MS, Kumar PA, Reddy GB, Ghole VS. Effect of Diabecon on sugar-induced lens opacity in organ culture: Mechanism of action. J Ethnopharmacol 2005;97:397-403.
41. Cotlier E, Sharma YR. Aspirin and senile cataracts in rheumatoid arthritis. Lancet 1981;1:338-9.
42. Harding JJ, Egerton M, Harding RS. Protection against cataract by aspirin, paracetamol, and ibuprofen. Acta Ophthalmol 1989;67: 518-24.
43. Gupta SK, Joshi S. Relationship between aldose reductase inhibiting activity and anti-cataract action of various NSAIDs. Dev Ophthalmol 1991;21:151-6.
44. Bono A, Millitello A, Bongiomo A. Effects of bendazac L-lysine salt on some metabolic enzymes of glutathione in the rabbit lens after x-ray irradiation. Indian J Biochem 1987;36:153-65.
45. Gupta SK, Joshi S. Naproxen: An aldose reductase inhibitor and potential anti-cataract agent. Dev Ophthalmol 1991;21:171-8.
46. Gupta SK, Joshi S. Role of naproxen as an antioxidant in selenite cataract. Opthalmic Res 1994;26:226-31.
47. Gupta SK, Joshi S. Prevention of photoperoxidation of lens lipids by naproxen. Afro Asian J Ophthalmol 1993;12:295-7.
48. Gupta SK, Agnihotri S, Joshi S. Anti-cataract action of topical sulindac (IH-indene-3-acetic acid, 5-ß uoro 2-methyl methylene) in galactosemic rats. Afro Asian J Ophthalmol 1989;8:57-61.
49. Gupta SK, Joshi S, Tandon R, Mathur P. Topical aspirin provides protection against galactosemic cataract. Indian J Ophthalmol 1997;45:221-5.
50. Eckerskorn V, Hockwin O, Muller-Breitenkamp R, Chen TT, Knowles W. Evaluation of cataract-related risk factors using detailed classiÞ cation systems and multivariate statistical methods. Dev Ophthalmol 1987;15:82-91.
51. Silvestrini B. Rationale for bendazac. In: Dermo et al, editors. Recent developments in the pharmacological treatment of cataract. Amsterdam: Kugler; 1987. p. 1-9.
52. Guglielmott i A, Capezzone De Joannon A, Cazzolla N, Marchett i M, Soldo L, Cavallo G et al. Radical scavenger activity of bendazac: An anticataract non-steroidal anti-inß ammatory agent. Pharmacol Res 1995;32:369-73.
53. Levis BS, Harding JJ. The major metabolite of bendazac inhibits the glycosylation of soluble lens proteins: A possible mechanism for a

delay in cataractogenesis. Exp Eye Res 1988;47:217-25.
54. Pandolfo L, Livrea MA, Bono A. Effects of bendazac L lysine salt on X-ray-induced cataract in the rabbit lens. Exp Eye Res 1986;42: 167-75.
55. Testa M, Luliano G, Silvestrini B. Pilot study of bendazac for treatment of cataract. Lancet 1982;1:849-50.
56. Reddy VN, Giblin FJ. Metabolism and function of glutathione in the lens. Human Cataract Formation. Pitman, London (Ciba Foundation Symposium) 1984;106:65-87.
57. Gupta SK, Mohanty I, Joshi S, Trivedi D, Srivastava S. Lycope prevents sugar-induced morphological changes and modulates antioxidant status of human lens epithelial cells. Br J Nutr 2002;88:347-54.
58. Ayala MN, Soderberg PG. Vitamin C can protect against ultraviolet radiation-induced cataract in albino rats. Ophthalmic Res 2004;36:264-9.
59. Abe M, Reiter RJ, Orhii PB, Hara M, Poeggeler B. Inhibitory eff ect of melatonin on cataract formation in newborn rats: Evidence for an antioxidative role for melatonin. J Pineal Res 1994;17: 94-100.
60. Hockwin O, Weigelin E, Baur M, Boutros G. Kontrollietre Klinische studie uber die wirksankeit von Phaken als Anti-kataractmedicament. Fortschritt e der Ophthalmologie 1982;79:179-83.
61. David LW. Oxidation, antioxidants and cataract formation: A literature review. Vet Ophthalmol 2006;9:292-8.
62. Ohta Y, Niwa T, Yamasaki T. Effect of prolonged marginal ascorbic acid deficiency on lenticular levels of antioxidants and lipid peroxide in guinea pig. Int J Vitamin Nutr Res 2001;71:103-9.
63. Yokoyama T, Sasaki H, Giblin FJ, Reddy VN. A physiological level of ascorbate inhibits galactose cataract in guinea pigs by decreasing polyol accumulation in the lens epithelium: A dehydroascorbate-linked mechanism. Exp Eye Res 1994;58: 207-18.
64. Mody VC, Kakar M, Elfving A, Söderberg PG, Löfgren S. Ascorbate in the rat lens: Dependence on dietary intake. Opthalmic Res 2005;37:142-9.
65. Labgle UW, Wolf A, Cordier A. Enhancement of SDZ ICT 322 induced cataracts and skin changes in rats following vitamin E- and selenium-deficient diet. Arch Toxicol 1997;71:283-9.
66. Kojima M, Shui YB, Murano M, Nagata O, Hockwin K, Sasaki K, et al. Low vitamin E level as a subliminal risk factor in a rat model of prednisolone-induced cataract. Investig Ophthalmol Visual Sci 2002;43:1116-20.
67. Reddy GB, Nayak S, Reddy PY, Seetharam Bhat K. Reduced levels of rat lens antioxidant vitamins upon in vitro UVB irradiation. J Nutr Biochem 2001;12:121-4.
68. Horwitz J, Dovrat A, Straatsma BE, Revilla PJ, Lightfoot DO. Glutathione reductase in human lens epithelium: FAD-induced in vitro activation. Curr Eye Res 1987;6:1249-56.
69. Bhat KS. Nutritional status of thiamine, riboß avin and pyridoxine in cataract patients. Nutr Rep Inter 1987;36:685-92.
70. Nath B, Srivastava SK, Singh K. Accumulation of copper and inhibition of lactate dehydrogenase activity in human senile cataractous lens. Indian J Biol 1969;7:25-6.
71. Karakucuk S, Ertugrul Mirza G, Faruk Ekinciler O, Saraymen R, Karakucuk I, Ustdal M. Selenium concentrations in serum, lens and aqueous humour of patients with senile cataract. Acta Ophthalmol Scand 1995;73:329-32.
72. Truscott RJ. Age-related nuclear cataract-oxidation is the key. Exp Eye Res 2005;80:709-25.

73. Spector A, Wang GM, Wang RR, Li WC, Kuszak JR. A brief photochemically induced oxidative insult caused irreversible lens damage and cataract: Mechanism of action. Exp Eye Res 1995;60:483-93.
74. Gupta SK, Trivedi D, Srivastava S, Joshi S, Halder N, Varma SD. Lycopene attenuates oxidative stress-induced experimental cataract development: An in vitro and in vivo study. Nutrition 2003;19:794-9.
75. Cumming RG, Mitchell P, Smith W. Diet and cataract: The Blue Mountains Eye studies. Ophthalmology 2000;107:450-6. 76. Mares-Perlman JA, Brady WE, Klein BE, Klein R, Haus GJ, Palta M, et al. Diet and nuclear lens opacities. Am J Epidemiol 1995;41:322-34.
76. Clinton SK. Lycopene: Chemistry, biology and implications for human health and disease. Nutr Rev 1998;56:35-51.
77. Rao KE. Oxygen radical scavenging activity of curcumin. Int J Pharmacol 1990;58:237-40.
78. Suryanarayana P, Krishnaswamy K, Reddy GB. Effect of curcumin on galactose-induced cataractogenesis in rats. Mol Vis 2003;9: 223-30.
79. Suryanaraya P, Saraswat M, Mrudula T, Krishna TP, Krishnaswamy K, Reddy GB. Curcumin and turmeric delay streptozotocin-induced diabetic cataract in rats. Invest Ophthalmol Vis Sci 2005;46:2092-9.
80. Padmaja S, Raju TN. Antioxidant effect of curcumin in selenium-induced cataract of Wistar rats. Indian J Exp Biol 2004;42:601-3.
81. Horakova L, Stolc S. Antioxidant and pharmacodynamic effects of pyridoindole stobadine. Gen Pharmacol 1998;30:627-38.
82. Stefek M, Krizanova L, Trnkova Z. Oxidative modiÞ cation of serum albumin in an experimental glycation model of diabetes mellitus in vitro: Effect of the pyridoindole antioxidant stobadine. Life Sci 1999;65:1995-7.
83. Kyselova Z, Gajdosik A, Gajdosikova A, Uliena O, Mihalova D, Karasu C, et al. Effect of the pyridoindole antioxidant stobadine on the development of experimental diabetic cataract and on lens protein oxidation in rats: Comparison with vitamin E and BHT. Mol Vis 2005;11:56-65.
84. Gupta SK, Srivastava S, Trivedi D, Joshi S, Nabanita H. Ocimum sanctum modulates selenite-induced cataractogenic changes and prevents rat lens opaciÞ cation. Curr Eye Res 2005;30:583-91.
85. Vats V, Yadav SP, Biswas NR, Grover JK. Anti-cataract activity of Pterocarpus marsupium bark and Trigonella foenum-graecum seeds extract in alloxan diabetic rats. J Ethnopharmacol 2004;93:289-94.
86. Durukan AH, Everekliogl u C, Hurmeric V, Kerimoglu H, Erdurman C, Bayraktar MZ, et al. Ingestion of IH636 grape seed proanthocyanidin extract to prevent selenite-induced oxidative stress in experimental cataract. J Cataract Refract Surg 2006;32:1041-5.
87. Lij a Y, Bij u PG, Reeni A, Cibin TR, Sahasranamam V, Abraham A. Modulation of selenite cataract by the flavonoid fraction of Emilia sonchifolia in experimental animal models. Phytother Res 2006;20:1092-5.
88. Bij u PG, Devi VG, Lij a Y, Abraham A. Protection against selenite cataract in rat lens by drevogenin D: A triterpenoid aglycone from Dregea volubilis. J Med Food 2007;10:308-15.
89. Bravett, i G. Preventive medical treatment of senile cataract with vitamin E and anthocyanosides: Clinical evaluation. Ann Ott almol Clin Ocul 1989;115:109.
90. Ertekin MV, Kocccer I, Karslioglu I, Taysi S, Gepdiremen A, Sezen O, et al. Effects of oral Ginkgo biloba supplementation on cataract formation and oxidative stress occurring in lenses of rats exposed to total cranium

radiotherapy. Jpn J Ophthalmol 2004;48:499-502.
91. Gupta SK, Halder N, Srivastava S, Trivedi D, Joshi S, Varma SD. Green Tea (Camellia sinensis) protects against selenite-induced oxidative stress in experimental cataractogenesis. Ophthalmic Res 2002;34:258-63.
92. Thiagarajan G, Chandani S, Sundari CS, Rao SH. Kulkarni AV, Balasubramanian D. An oxidative property of green tea and black tea and their potential ability to retard the progression of eye lens cataract. Exp Eye Res 2001;73:393-401.
93. Joe AV, Juan Z. Black and Green teas equally inhibit diabetic cataracts in a streptozotocin-induced rat model of diabetes. J Agr Food Chem 2005;53:3710-3.
94. Suryanarayana P, Saraswat J, Petrash JM, Reddy GB. Emblica officinalis and its enriched tannoids delay streptozotocin-induced diabetic cataract in rats. Mol Vis 2007;13:291-7.
95. Velpandian T, Mathur P, Sengupta S, Gupta SK. Preventive effect of Chyavanprash against steroid-induced cataract in the developing chick embryo. Phytother Res 1998;12:320-3.
96. Zhao W, Devamanoharan PS, Varma SD. Diabetes induced biochemical changes in rat lens: Attenuation of cataractogenesis by pyruvate. Diabetes Obes Metab 2000;2:165-74.
97. Varma SD, Ramachandran S, Devamanoharan PS, Morris SM, Ali AH. Prevention of oxidative damage to rat lens in vitro by pyruvate: Possible attenuation in vivo. Curr Eye Res 1995;14:643-9.
98. Elena MV, De Cavanagh EM, Inserra F, Ferder L, Fraga CG. Enalapril and captopril enhance glutathione-dependent antioxidant defences in mouse tissues. Am J Physiol Regul Integr Comp Physiol 2000;278:R572-7.
99. Langade DG, Rao G, Girme RC, Patki PS, Bulakh PM. In vitro prevention by ACE inhibitors of cataract induced by glucose. Indian J Pharmacol 2006;38:107-10.
100. Babizhayey MA, Deyev AI, Yermakova VN, Brikman IV, Bours J. Lipid peroxidation and cataracts: N-acetylcarnosine as a therapeutic tool to manage age-related cataracts in human and in canine eyes. Drugs R D 2004;53:125-39.
101. Maitra I, Serbinova E, Trischier H, Packer L. Alpha-lipoic acid prevents buthionine sulfoximine-induced cataract formation in newborn rats. Free Rad Biol Med 1995;18:823
102. Hiraoka T, Clark JI, Lixy, Thurston GM. Effect of selected anticataract agents on opacification in the selenite cataract model. Exp Eye Res 1996;62:11-9.
103. Kuck JF, Kuck KD. The Emory Mouse Cataract: The effects of cataractogenesis of alpha-tocopherol, penicillamine, triethylenetetramine and mercapto-propionylglycine. J Ocular Pharmacol 1988;4:243-51.
104. Wang Z, Hess JL, Bunce GE. Deferoxamine effect on selenite-induced cataract formation in rats. Invest Ophthalmol Vis Sci 1992;33:2511-9.
105. Gandhi, B., Bhagwat, A., Matkar, S., Kuchik, A., Wale, T., Kokane, O. and Rode, N., 2025. Formulation and Evaluation of Bilayer Tablets of Atenolol and Amlodipine for the Treatment of Hypertension. Research Journal of Pharmacy and Technology, 18(5), pp.2037-2042.
106. Bhagwat A, Lokhande A, Pingat M, Doke R, Ghule S. Strategies and Mechanisms for Enhancing Drug Bioavailability through Co-Amorphous Mixtures-A Comprehensive Review. Research Journal of Pharmacy and Technology. 2025;18(1):409-14.

107. Bhagwat A, Tambe P, Vare P, More S, Nagare S, Shinde A, Doke R. Advances in neurotransmitter detection and modulation: Implications for neurological disorders. IP Int J Comprehensive Adv Pharmacol. 2024;9(4):236-47.
108. BHAGWAT, Ajay, et al. Development of Nanoparticles for the Novel Anticancer Therapeutic Agents for Acute Myeloid Leukemia. Int J Pharm Sci Nanotechnol, 2023, 16.4: 6894-906.
109. Prajakta Shingote, Ajay Bhagwat, Aarti Malkapure, Prasad Jadhav, Akshada Thorat, Cervical Cancer: Current Perspectives on Pathophysiology, Diagnosis, Prevention, and Therapeutic Advances, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 10, 2393-2408.
110. Kadale Priyanka, Ajay Bhagwat, Bhangare Sayali, Choudhari Rutuja, Borkar Sahil., Ficus Racemosa: A Comprehensive Review of its Phytochemistry and Pharmacological Potential, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 10, 1710-1723.
111. Jyoti Bhagat, Ajay Bhagwat, Pranav Waghmode, Pratiksha Temkar, Sahil Gunjal*, Akanksha Walunj, Pranjal Shinde, Ashlesha Nikam, Sarita Kawad, Centella Asiatica In the Modern Therapeutic Landscape, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 10, 1973-1982.
112. Trupti Mate, Ajay Bhagwat, Vaishnavi Auti, Sakshi Pawar, Pravin Ambhore*, Pathophysiology of Malaria and Its Implications for Drug Resistance and Future Therapies, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 10, 1628-1640
113. Mahale N, Bhagwat A, Ghule S, Kanade S, Bhujbal S, Auti S. World Journal of Pharmaceutical. World. 2025;4(5).
114. Badhe, N., Maniyar, S., Kadale, P., Kale, R., Bhagwat, A. and Doke, R.R., Advancements in nanotechnology for glaucoma detection and treatment: A focus on biosensors, IOP monitoring, and nano-drug delivery systems.
115. Sarika Bhabad, Ajay Bhagwat, Swapnil Auti, Nikita Galande, Monika Bhosale.3d printing of pharmaceuticals: customized dosage forms and future prospects. World Journal of Pharmaceutical. World. 2025;4(5).
116. Kallur, S., Suryawanshi, A., Utarade, A., Kandalkar, P., Morde, R., Bhagwat, A. and Doke, R., 2023. Oxidative stress and neurodegenerative diseases: Exploring natural antioxidants for therapeutic potential. Int. J. Compr. Adv. Pharmacol, 8, pp.149-158.

HOW TO CITE: Pratik Bhand, Ajay Bhagwat, Shrushti Darade*, Ishwari Borhade, Priyanka Narasale, Swapnil Auti, A Review of Pharmacological Agents for Cataract Prevention, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 11, 4548-4564 https://doi.org/10.5281/zenodo.17746753