12 Dietary Agents in the Prevention of Cataractogenesis: Results from Preclinical Observations

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Contents

Abstract

Cataract formation is one of the foremost reasons of blindness, especially in the elderly people. The process is shown to be hastened by aldose reductase (AR)

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enzyme involved in catalyzing the reduction of wide-ranging aldehydes to their corresponding alcohols. Gene mutations are connected to secondary cataract formation in the aged population. Further, the age-linked cataract formation is also due to the oxidative stresses. The scientific experiments conducted with preclinical models of studies have shown that dietary agents and phytochemicals are effective in reducing and mitigating cataractogenesis by acting as inhibitors of AR, preventing the depletion of antioxidant enzymes, inhibiting lipid peroxidation, and reducing oxidative stresses. This chapter addresses the helpful properties of phytochemicals in inhibiting AR. Also, the other mechanisms of action of phytochemicals in mitigating the cataract formation are highlighted.

Keywords
Aldose reductase · Indian gooseberry · Cataractogenesis · Lemon · Grapes · Sweet orange · Litchi · Mangosteen

12.1 Introduction

Among various sense organs of the body, the eye and its function of visual perception are of utmost importance in one's day-to-day life (Bourne et al. 2017). Humans are very unique in their dependency on eyesight as the foremost sense, and this is reflected in the complexity of our eyes as compared to other animals. The lack of sight or low vision not only impairs one physically, but also has psychological, social, and economic implications (Bourne et al. 2017). Cataract is a term used to denote any variation in its refractive index or opacity in the crystalline lens. The cataract formation is the foremost reason for visual impairment or lack of vision globally (Hobbs and Bernstein 2014; Braakhuis et al. 2019). The global incidence of blindness in 2015 was about 36 million, and it was estimated that another 0.217 billion populace live with the modest-to-severe blindness. Totally, 0.253 billion people were reported with blindness as recorded by a survey in the year 2015 (Bourne et al. 2017). The WHO (World Health Organisation) has designated cataract as the foremost basis of vision impairment, accounting for nearly 50% (17 million) of the incidence of vision loss worldwide (Bourne et al. 2017). With the increase in population and life expectancy, this number is only going to rise in the days to come (Fletcher 2010; Weikel et al. 2014; Braakhuis et al. 2019). As described earlier, the number of cataract cases in the world is predicted to be nearly 40 million by the year 2020 (Sowmya et al. 2015). Further, estimates are that by the end of 2050, approximately two billion people worldwide will be more than 60 years of age. Among them, closely 0.039 billion will be completely visionless and 0.246 billion will grieve from imperfect eyesight (Braakhuis et al. 2019). This will considerably hinder the growth and development of people, their families, and further the nation's economy at a large scale.

The prevalence of cataract in India was observed to be about 70%. The incidence of non-operated cataract was found to increase with the time of life, and observed to be greater in females than in menfolk as reported by Sowmya et al. (2015). The frequency of non-operated cataract in individuals, who are above 60 years of age was found to be 58% in the northern part of India, while it was 53% in the southern parts of India (Vashist et al. 2011). It is also noted to be a major cause of visual impairment in lower socioeconomic population. This could be explained by the lack of accessibilities to medical facilities, poor diet, and increased exposure to sunlight, pollutants, and other environmental factors (Vashist et al. 2011). It continues to remain as one of the topmost source of vision loss in low-income and middle-income nations, due to lack of availability of healthcare resources in these countries (Sowmya et al. 2015). Furthermore, facts also specify that approximately 90% of the world's visual impaired people live in emerging nations, where medicinal amenities are not as the best in comparison to the advanced nations. The ratio of ophthalmologists to patients is quite scarce to cater to the eye care needs of the population suffering from eye ailments. This disparity can only be sorted out by emphasizing on the need for preventive methodologies in tackling certain eye ailments and slowing down the disease progression. Presently, a number of cataract surgeries are done worldwide. However, the cost involved in surgeries is very expensive, and is burdening the nations. It was estimated that more than 30 million US $ was paid out on civic inpatients for cataract operations, and postsurgery treatment services during the period from 2009 to 2010 (Braakhuis et al. 2019). Alternatively, the better approach is to postpone the onset of cataract formation. The inception of cataract delayed by 10 years will shrink the incidence of cataractogenesis up to 50%. This will impressively reduce the expense associated with surgical treatments (Brian and Taylor 2001; Braakhuis et al. 2019). As cataract formation is a progressive illness of aged population, any effective therapeutic cure should be formulated. In this direction, it is likely that dietary supplements or herbal products can be the best treatment when delivered either through eye drops or orally. There are several reports to support that the dietary supplements, such as the Indian gooseberry, turmeric, orange, mangosteen, lemon, grape, litchi, blue berry, finger millet, sickle senna, and their bioactive compounds, can prevent or reduce the cataractogenesis (Li and Jiang 2007; Choudhary and Gulia 2011; Puppala et al. 2012; Shobana et al. 2013; Devi et al. 2014; Ha et al. 2014; D'souza et al. 2014; Ma et al. 2014; Chaudhury et al. 2015; Abengózar-Vela et al. 2015; Sreelakshmi and Abraham 2016a, 2016b; Andjelic et al. 2017; Crespo and Visioli 2017; Braakhuis et al. 2019). Plant-derived flavonoids like genistein, quercitrin, isoflavone, etc. have shown to delay the diabetic cataractogenesis. Some examples of plant products having AR inhibitory property are the extracts of ethnic herbs, such as *Withania somnifera, Ocimum sanctum, Azadirachta indica, Curcuma longa* or diabecon (the Indian herbal formulation) (Huang et al. 2007; Pollreisz and Schmidt-Erfurth 2010). This chapter provides a comprehensive data on the etiology of cataractogenesis, and the role of phytocompounds and their mode of actions in the inhibition of cataract formation.

12.2 About Cataract

Cataract is a malady of eyes, where the lens of eyes becomes cloudy leading to vision loss. Cataract formation is very commonly expected, and linked to the aging process. Normally, the lens of eye is very clear and it focuses incoming light rays onto the light-sensitive tissues, retina present at the backside of the eye. To have a perfect appearance onto the retina, the eye regions facing forward to the retina, comprising the lens must be transparent and clear. When the light strikes the eye, a chemical reaction is initiated within the retina leading to induce electrical signal, which is carried to the brain through the optic nerves. Later, the brain will determine what is observed by eyes. When the lenses are normal and clear, the retina will receive a sharp and clear image. However, in a cataract eye, the lens cloudy and gives a blurry vision. Further, the degree of the optical disruption is reliant on the level of cloudiness of the lens.

Cataract can be classified as congenital, age-related or secondary due to some medical illnesses like diabetes (Braakhuis et al. 2019). Age-linked cataract is the most frequent one, which is responsible for nearly half the blindness worldwide. The lens is clear when one is born and continues to be so till sometime after the age of 45, after which progressive opacities begin to form, initiating the process of cataractogenesis. The major 3 subtypes of age-related cataracts include nuclear, posterior, subcapsular, and cortical cataracts. The genetic predisposition, oxidative stress, UV radiation, and calcium-level abnormalities area few of the causative factors that are believed to aid in the process of cataractogenesis (Sowmya et al. 2015).

Mutations in the EPH2A gene coding for tyrosine kinase have been known to be connected with age-related cortical cataract (Shiels et al. 2008; Jun et al. 2009). The lens epithelium, being the anterior portion of the lens, is greatly vulnerable to the effects of UV radiation and reactive oxygen species (ROS)-mediated oxidative stresses. It is believed that they bring about a decrease in the cell density of epithelial cells by inducing apoptosis. This in turn increases p53expression, thereby decreasing the levels of soluble sulfhydryls, glutathione reductase, catalase, and superoxide dismutase (Johar et al. 2003). It is also believed that with aging, an internal barrier to antioxidants develops, following which the crystallin protein forms in the center of the lens nucleus. Hence, it becomes susceptible to the attachment of reactive molecules and oxidation, resulting in protein cross-links and denaturation, glycation, and progressive hardening of the nucleus (Truscott 2005). This is often accompanied by color discoloration of the lens, wherein it turns yellow to brown, and subsequently to black with a progressive hardening.

Consistently, high blood sugar levels or diabetes is also a potential and leading cause for cataract development in affected individuals. It is believed that AR, a key Nicotinamide Adenine Dinucleotide Phosphate (NADPH)-dependent enzyme in the polyol pathway, which results in converting glucose into sorbitol is associated with hyperglycemic cataractogenesis (Pollreisz and Schmidt-Erfurth 2010). This was proven by the disproportionate accretion of sorbitol observed intracellularly in the diabetic animal models. This emphasizes the role of using AR inhibitors in the prevention of cataractogenesis (Reddy et al. 1984; Andjelic et al. 2017). In addition to this, calcium plays a vital part in maintaining the homeostasis of lens. It is assumed that in cortical cataract, the intracellular homeostasis is disrupted, leading to abnormal intracellular levels of calcium that exceeds the lens' ability to remove calcium from the cytosol. This in turn triggers the breakdown of structural proteins, and eventually causes the cell death (Duncan and Jacob 1984; Gosak et al. 2015).

The progression of cataract is reliant on a number of factors. Till date, we have only a limited understanding on the underlying mechanisms of cataractogenesis. Ongoing research and investigation of the process of cataractogenesis are of paramount importance, due to the magnitude prevalence of this condition worldwide. Cataracts are frequently measured to be an inevitable result of aging. Although surgery is the mainstay of its management at present, the modern etiological investigations have recognized the mediations that may possibly thwart or delay the cataractogenesis process. Several efforts have been engaged in delaying the inception and retardation of cataracts progression using different types of inhibitory agents. Due to its primary role in cataractogenesis, AR is one the main target molecules, which can help in preventing the progression of cataractogenesis. For that reason, efforts are being carried out in developing pharmacological agents that are precise and effective in inhibiting AR action. Gene mutations are also linked to secondary cataract formation in the aged population. For instance, a mutation in the gene galactokinase 1 (GALK1) that encodes the enzyme in galactose metabolism is triggered to form hypergalactosemia and cataract. Likewise, the age-linked cataract formation is also due to the oxidative stresses (Tewari et al. 2019). The search for an optimal synthetic agent is still a continuously ongoing process. In this direction, phytotherapy has been successfully proven to be very effective, and considered widely, due to the fact that it is less toxic and free from side effects. Hence, this has compelled the requirement of potential preventive agents, especially the dietary phytochemicals. Several promising research works have revealed that few plants and their phytochemicals could be beneficial (Majumdar and Srirangam 2010; Liu et al. 2017; Tewari et al. 2019). To substantiate these, seminal case–control studies by Tavani and coworkers in 1996 have shown that diet rich in butter, total fat, and salt increases risks, while regular consumption of cheese, meat, cruciferae, tomatoes, spinach, peppers, melon, and citrus fruits shows beneficial effects. Also, several plant bioactive compounds are effective in preventing or reducing cataractogenesis (Tavani et al. 1996). In the subsequent sections, the beneficial effects of plants and their bioactive compounds in overcoming the cataractogenesis are addressed.

12.3 Plants and Their Phytochemicals Against Cataract Formation

12.3.1 Indian Gooseberry

Indian gooseberry (*Phyllanthus emblica*), belonging to the family *Euphorbiaceae* is also known as Amla. It is one among the highly valuable curative herbs used in the

Indian traditional medicinal systems, such as the Ayurveda, Unani, and Siddha (Variya et al. 2016; Husain et al. 2019). Their fruits are also identified as the myrobalans or berries, and are the main portion of Amla used in food preparations and medicinal applications. Indian gooseberry fruits are a chief dietary agents, and hence utilized in making murabbah, ladu, burfi, fresh juice, chutneys, pickles, and curries in India (Baliga and Dsouza 2011; Thilakchand et al. 2013; D'souza et al. 2014). Amla fruits are extensively used in several countries of the Southeast Asia as traditional medicines. They are used in treating illnesses, such as diabetes, asthma, cough, bronchitis, ophthalmopathy, cephalalgia, erysipelas, hemorrhoids, skin diseases, nervine debility, inflammation, leprosy, dyspepsia, emaciation, colic, flatulence, peptic ulcer, hyper-acidity, jaundice, dysentery, diarrhea, hemorrhages, menorrhagia, leucorrhoea, cardiac disorders, anemia, intermittent fevers, liver complaints, jaundice, leucorrhea, menorrhagia, osteoporosis, hematuria, inflammation of the eyes, and weak vision (Krishnaveni and Mirunalini 2010; Baliga and Dsouza 2011; Thilakchand et al. 2013; D'souza et al. 2014; Variya et al. 2016).

Indian gooseberry and its phytocompounds are reported to be effective in preventing cataractogenesis. Indian gooseberry aqueous extract was reported to inhibit the recombinant human AR with an IC_{50} value of 0. 88 mg/ml. They found that aqueous extract containing tannoids is the main phytoconstituents accountable for the inhibition of AR (Suryanarayana et al. 2004). Later, a group of researchers investigated the role of Indian gooseberry tannoids in inhibiting cataract formation (Suryanarayana et al. 2007). They found that STZ (streptozotocin)-induced diabetic rats with cataract when treated with Indian gooseberry enriched with tannoids significantly reduced cataractogenesis. Research investigations have identified1-O-galloyl-β-D-glucose (β-glucogallin) as the chief phytocompounds of fruits, and it is shown to be very effective in the selective inhibition of Aldo-ketoreductase family 1member B1 (AKR1B1) genes under in vitro conditions (Puppala et al. 2012). Further, molecular modeling investigations have shown that β-glucogallin effectively binds to the enzyme, AR, at its active site and arbitrates the AR inhibitory effects. The successive studies also confirmed the role of β-glucogallin in the inhibition of sorbitol accretion up to 73% when treated at the concentration of 30 μM under hyperglycemia state observed in the organ culture model (ex vivo), involving transgenic mice lenses with overexpressing human AR in the lens (Puppala et al. 2012).

12.3.2 *Curcuma longa*

Curcumin, the bioactive phenolic constituent of turmeric (*Curcuma longa* L.) is reported to exhibit antioxidative and hypoglycemic properties as confirmed by in vitro and in vivo studies (Suryanarayana et al. 2003; Suryanarayana et al. 2005; Kumar et al. 2005; Raju et al. 2006; Manikandan et al. 2011; Grama et al. 2013; Kocaadam and Şanlier 2017). It is a widely used as spice in many cuisines. It is traded as a cosmetic ingredient, herbal supplement, food colorant, and food flavoring agent (Kocaadam and Şanlier 2017). It was seen that lenses collected from rats treated with curcumin for 2 weeks (75 mg/kg/day) were more resistant to 4-HNE (4- hydroxy 2- transnonenal) induced opacification of lenses compared to control animals (Suryanarayana et al 2003). It seems to especially play a role in preventing galactose-induced cataractogenesis. Its protective role in ionizing radiation-induced cataractogenesis has also been studied by Ozgen et al. (2012), wherein cataract formation was observed to be 100% in the irradiated groups, and the rate of cataract reduced to 40% in the curcumin treated groups. The treatment of curcumin was observed to improve the levels of vitamin C, and thus involve in preventing cataract progression (Murugan and Pari 2006). Curcumin was reported to repress Hsp 70, αA-crystalline, and αB-crystallin expressions in STZ-prompted cataracts in animal model (Kumar et al. 2005; Manikandan et al. 2011). The chief mechanism involved in the cataract inhibition by curcumin is reported to be due to antioxidant properties (Manikandan et al. 2009; Manikandan et al. 2010; Manikandan et al. 2011; Radha et al. 2012). Likewise, Chhunchha et al. (2011) have reported that curcumin can hinder pleiotropic oxidative stress-related proteins, Prdx6 (peroxiredoxin 6) in hLECs (human lens epithelial) cells. A study by Cao et al. (2018) proposed that curcumin can attenuate selenite-prompted cataract by reducing the intracellular secretion of reactive oxygen species.

12.3.3 Grape

Grapes, scientifically known as *Vitis vinifera,* is globally one of the most important fruits with immense dietary, medicinal, and financial uses. The juice of grapes is being used throughout the world for its effective curative values, comprising ocular-promoting activity. Its beneficial uses are accredited to the occurrence of phytocompounds like resveratrol, procyanidins, or proanthocyanidins, which are chemically the dimers, trimers, and oligomers of monomeric epicatechins or catechins in them (Singleton 1992; Bartolome et al. 1996). Studies have shown that phytocompounds occurring in grape juice have been linked to the regulation of glucose metabolism, maintenance of intraocular pressure, and destruction of proinflammatory cytokines in the system (Natarajan et al. 2017). Reports suggest that grape phytochemicals mitigate several ocular problems, including uvea, macular degeneration, cataractogenesis, diabetic retinopathy, and red eyes (Natarajan et al. 2017). Reports suggest that resveratrol, a principal constituent of grape, is reported to be beneficial on cataracts, and other ocular diseases (Natarajan et al. 2017; Goutham et al. 2017).

Resveratrol treated to IOBA-NHC (human conjunctival) and HCE (corneal) epithelial cells was effective in mitigating the TNF-α or ultraviolet (UVB) radiation induced secretion of interleukin (IL)-6, IL-8, and Interferon gamma-induced protein 10 (IP-10) in a dose-dependent manner (Abengózar-Vela et al. 2015). The combination of quercetin and resveratrol was observed to enhance their protective properties indicating that these polyphenols may have a therapeutic potential in overcoming inflammatory ocular surface diseases (Abengózar-Vela et al. 2015). Mechanistic studies indicate that the beneficial effects of resveratrol are facilitated by antioxidant, antiapoptotic, antitumorigenic, antiinflammatory, anti-angiogenic, and vasorelaxant properties (Bola et al. 2014). In addition to resveratrol, studies have also shown that the grape polyphenols (MGPs) were effective in reducing ocular inflammations and Endoplasmic Reticulum (ER) stresses.

Seminal studies by Ha et al. (2014) with cultured ARPE-19 (human retinal pigmented epithelium) cells and common inbred strain of laboratory mice (C57BL/6) have demonstrated that grape seed polyphenols effectively attenuate ER stresses and ocular inflammations. The investigators observed that treatment of ARPE-19 cells with grape seed polyphenols reduced the tumor necrosis factor (TNF)-α-encouraged proinflammatory gene expression of monocyte chemotactic protein-1, IL-1β, and IL-6 by reducing the activation of mitogen-activated protein kinase (MAPK), and subsequently reducing the levels of activated nuclear factor κ-B (Ha et al. 2014). Experiments also showed that grape seed polyphenols were effective in mitigating the thapsigargin-mediated ER stress in ARPE-19 cells. Further, studies with C57BL/6 mice showed that treating with grape seed polyphenols reduces the leukocyte infiltration and acute ocular inflammations. Mechanistic observations revealed that grape seed polyphenols reduce inflammation-intervened loss of tight junctions and retinal permeability (Ha et al. 2014). The grape seed procyanidins and other antioxidative phytocompounds were effective in thwarting the development of cataractogenesis via their antioxidative activities (Yamakoshi et al. 2002). Moreover, quercetin (a flavonoid) occurring in grapes is shown to decrease oxidative responses as well as inflammations in human ocular surface epithelial cells (Abengózar-Vela et al. 2015). Cumulatively, all these studies clearly showed that treatment with grape seed polyphenols reduced ER stress-related vascular endothelial growth factor (VEGF) secretion, unfolded protein responses, and early apoptosis to mediate its protective effects (Ha et al. 2014).

12.3.4 *Cassia tora*

Cassia tora Linn., colloquially known as the sicklepod plant, commonly found in India and other tropical countries, is known for many medicinal importance (Jain and Patil 2010; Choudhary and Gulia 2011). It is found growing wild in low-lying coastal area, on riverbanks, and in waste land. The plant is known as "Chakramard" in Ayurveda, "Panwar" in Unani, and "Jue Ming Zi" in the Chinese system of medicine. The plant is utilized in various traditional systems of medicines as a laxative, antiseptic, antioxidant, and antiperiodic, and is reported to be useful in leprosy, ringworm, bronchitis, cardiac diseases, hepatic disorder, liver tonic, hemorrhoids, and ophthalmic and skin ailments (Jain and Patil 2010; Choudhary and Gulia 2011). The leaves have been shown to be rich in polyphenols, emodin, quercetin, kaempferol-2-diglucoside, chrysophanol, aloe-emodin, rhein, glucose, 1-stachydnine, amino acids, fatty acids, d-mannitol, β-sitosterol, myricyl alcohol, trigonelline, choline, sennosides, and ononitol monohydrate (Jain and Patil 2010; Choudhary and Gulia 2011).

With regard to its protective effects on the eye, studies by Sreelakshmi and Abraham (2016a) and Sreelakshmi and Abraham (2016b) have observed that feeding *C. tora* leaves effectively mitigated selenite-influenced cataract formation in rat pups by restoring membrane integrity, antioxidant levels, downregulating epithelial cell death, and by reducing the accumulation metal. Further, the extract also seemed to be effective in prevention of cataract by maintaining lens architecture. From a phytochemical perspective, these effects seem to be mediated by the polyphenols, such as chrysophanol, stigmasterol, kaempferol, emodin, quercetin, and isoquercetin present in leaves (Sreelakshmi and Abraham 2016a; Sreelakshmi and Abraham 2016b). Likewise, previous studies have also shown quercetin as an effective agent in mitigating the oxidative and inflammatory responses in human ocular surface epithelial cells (Abengózar-Vela et al. 2015).

12.3.5 Tea

Globally, green tea is highly preferred as a beverage, and is reported to be helpful in preventing/moderating various illnesses. Traditionally, this beverage used in the form of green tea in China, and even today, it is extensively consumed in several countries (Jigisha et al. 2012). Phytochemical studies have confirmed the myriad of medicinal values of tea, especially credited to their phytoconstituents, such as epicatechin, catechins, epigallocatechin, epigallocatechin-3-gallate, epicatechin-3-gallate, proanthocyanidins, quercetin, myricetin, kaempferol, and gallic acids. These green tea polyphenols are reported to have antioxidant, anticancer, and anti-inflammatory properties, and hence are beneficial for the eyes as well (Ma et al. 2014; Thichanpiang and Wongprasert 2015; Chaudhury et al. 2015).

Scientific investigations have revealed that the principal phytochemical epigallocatechin-3-gallate was effective in preventing the alteration of intact tryptophan residues in γ-crystallin protein isolated from cataractous human eye lens (Chaudhury et al. 2015). Further, the pretreatment of cultured ARPE-19 cells with epigallocatechin-3-gallate (EGCG) caused a decrease in the TNF-α-induced increase of intracellular ROS (Thichanpiang and Wongprasert 2015). EGCG also ameliorated the inflammatory effects of TNF-α as observed by the increase in the degree of monocyte-retinal pigment epithelium adhesion, and concomitantly decreased upregulation of ICAM-1 (Intercellular Adhesion Molecule 1), the nuclear translocation of phosphor-NF-κB, and decreased the expression of phosphor-NF-κB and IκB degradation (Thichanpiang and Wongprasert 2015). Together, all these observations affirm that EGCG ameliorated the inflammatory effects by suppressing the TNF-α signaling by inhibiting the NF-κB pathway. Animal study results have revealed that application of tea polyphenol gel was effective in protecting the lens epithelial cells in rabbits subjected to vitrectomy (Ma et al. 2014). The investigators performed unilateral vitrectomy with silicone oil tamponade on 2-month-old New Zealand white rabbits. The tea polyphenol gel was applied topically in the surgical eyes and the animals were sequentially sacrificed on days 45 and 90 post-operation (Ma et al. 2014). The eyes were harvested and quantified for the levels of ROS, mitochondrial membrane potential (ΔΨm), and apoptosis of lens epithelial cells (Ma et al. 2014). The outcomes of this research further confirmed that the application of the tea polyphenol gel reduced the generation of ROS, maintained ΔΨm, inhibited the overexpression of caspase-3, and decreased apoptosis of lens epithelial cells.

12.3.6 Finger Millet

Eleusine coracana (Finger millet) is globally an essential grain, and widely cultivated in the tropical parts of South Asia and Africa. Among millets, finger millet ranks the fourth position after sorghum, pearl millet, and foxtail millet. According to some estimates, nearly three million tons of finger millet are produced annually (Shobana et al. 2013; Devi et al. 2014). Finger millets are rich in calcium, dietary fiber, phytates, protein, minerals, iron, phenolics, riboflavin, thiamine, methionine, phenylalanine, leucine, isoleucine, and other essential amino acids. Phytochemical studies have shown that finger millets also contain ferulic acid, *p*-coumaric acid, proto-catechuic acid, gallic acid, p-hydroxybenzoic acid, cinnamic acid, syringic acid, trans-cinnamic acid, ferulic acid, quercetin, kaempferol, phloroglucinol, naringenin, luteolin, apigenin, epicatechin, catechin, catechin gallates, trimers, and tetramers of catechin and proanthocyanidins. However, their concentration varies with the geographic and temperature conditions (Shobana et al. 2013; Devi et al. 2014). From a health perspective, consumption of finger millets is known to possess antidiabetic (type 2 diabetes mellitus), antidiarrheal, antiulcer, antiinflammatory, antitumorigenic (K562 chronic myeloid leukemia), antiatherosclerogenic effects, antimicrobial, and antioxidative properties.

With regard to the beneficial effects of finger millet in cataractogenesis, Chethan et al. (2008) investigated the inhibitory effects of the important finger millet phytochemicals like gallic acid, protocatechuic acid, p-coumaric acid, 4-Hydroxybenzoic acid, vanillic acid, syringic acid, ferulic acid, and trans-cinnamic acids. They found that quercetin inhibited the activity of AR in cell-free assay. Further, investigations have reported that quercetin was effective in decreasing the inflammatory and oxidative responses in human ocular surface epithelial cells (Abengózar-Vela et al. 2015), while luteolin was effective in reducing inflammation in human retinal pigment epithelial cells (Hytti et al. 2017). The results suggest that the finger millet seed coat polyphenols were effective in inhibiting AR reversibly by noncompetitive inhibition making it a potential dietary agent in hindering cataract formation in humans (Chethan et al. 2008).

12.3.7 Blueberries

Blueberries (*Vaccinium* sp.) are originally an American fruit species that are found growing well in the humid woodlands. Classified in the family Ericaceae, blueberries consist of approximately 450 species. Blueberries contain vitamin C, procyanidins, kaempferol, quercetin, myricetin, hydroxycinnamic, stilbenes, ellagic acid, and anthocyanins like malvidin, delphinidin, petunidin, cyaniding, and peonidin

(Johnson and Arjmandi 2013; Crespo and Visioli 2017). Practically, blueberry fruit's outer layer is the most valuable part, as it comprises closely all of the anthocyanins. Since antiquity, blueberries are being used in our diet; however, their health benefits are understood very recently, and still researches are being undertaken continuously. Scientific studies carried out in accordance with pharmacological guidelines have shown that blue berries possess antioxidant, antiinflammatory, anticancer, neuroprotective, and cardioprotective effects (Crespo and Visioli 2017).

Experiments by Liu et al. (2015) have shown that the flavonoid-rich fraction was effective in thwarting visible light-tempted docosahexaenoic acid lipid peroxidation compared to the phenolic acid- and anthocyanin-rich fractions (Liu et al. 2015). Rutin, quercetin glycosides, isoquercetin, chlorogenic acid, and hyperoside present in blueberry are also effective in preventing cataractogenesis in vivo and in vitro (Ferlemi et al. 2016). Additionally, quercetin is shown to reduce the oxidative responses and inflammation in human ocular surface epithelial cells (Abengózar-Vela et al. 2015). However, cyanidin-3-glucoside and quercetin were shown to safeguard the pigmented layer of retina against photooxidation and photodegradation (Wang et al. 2017). Together, all these observations indicate the usefulness of blueberries in eye care.

12.3.8 Litchi

Litchi chinensis (Litchi), belonging to the family, *Sapindaceae* is an important dietary agent. Historical evidence indicates that the plant was originally indigenous in the geographical region of Southern China. However, today the plant is also cultivated on a large scale in semi-tropical areas of the world (Li and Jiang 2007). Litchi is a well-investigated plant and chemical studies have confirmed that they contain flavanols like procyanidin B2, procyanidin B4, and epicatechin. Also, litchi contains anthocyanins like cyanidin-3-glucoside, cyanindin-3-rutinside, quercetin-3-glucoside, and quercetin-3-rutinosde. However, their ratio is dependent on the climate and soil conditions (Li and Jiang 2007). Scientific experiments have confirmed that these phytochemicals possess myriad pharmacological effects and that the antioxidant activity is responsible for the beneficial effects at least in part (Li and Jiang 2007). Experimental studies with laboratory rat lenses have confirmed that the extracts of the litchi fruits exhibit inhibitory effects on cataract formation. Also the methanol extract and ethyl acetate fractions were shown to be the most effective. Cell-free studies with the isolated phytochemicals have shown that delphinidin 3-O-β-galactopyranoside-39-O-beta-glucopyranoside showed the highest AR enzyme inhibitory activity with an IC_{50} value of 0. 23 μg/ml, indicating its possible uses and further exploration in the prevention of cataractogenesis.

12.4 Conclusions

Preclinical examinations performed in the recent past have affirmatively confirmed that many dietary agents and phytochemicals are beneficial in inhibiting/preventing/retarding the process of cataractogenesis by mediating myriad pathways. However, a major drawback is that many of these observations are from cell-free and in vitro assays and have not been studied involving animal models. On a brighter side, the fact that a large number of dietary agents and phytochemicals are beneficial is of interest, as this gives a choice for clinical studies in the future and paves way for industrial use of the phytochemicals. However, the factors that need to be considered here are toxicity profile (drug safety), cost factors, availability, convenience of administration, and acceptance. However, the fact that these agents are of dietary origin have wide acceptability, and possess myriad health benefits (Van Duyn and Pivonka 2000) is the driving source for future animal and clinical studies that need to be undertaken and affirmed for the benefit of especially the high-risk group of people prone to cataractogenesis.

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