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Preserving Neural Retina Through Re-Emerging Herbal Interventions

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ABSTRACT

Eye related diseases such as glaucoma, diabetic retinopathy, cataract, conjunctivitis are very common worldwide. With the current scenario India will be among the top five countries in the number of glaucoma cases. Limited discovery of successful drugs for the treatment of such diseases led scientists to look towards the use of conventional sources for treatment. Herbal extracts from Ayurveda have remained an important part of treatment regime in many parts of world even today. For this reason, local herbs possessing curative properties are still being used by local inhabitants due to its anti-inflammatory and antioxidant properties. Because retinal damage involves alterations in oxidative enzymes, blood flow changes and increase in apoptotic signals, herbal extracts are being tested for their ability to moderate antioxidant machinery and trigger neuroprotective pathways. The present review summarizes some of such herbal extracts which have been tested for their neuroprotective role in eye related diseases. The active components that exert neuroprotective effects have also been discussed along with possible mechanisms of action. J. Cell. Biochem. 115: 1659–1668, 2014.

KEY WORDS: HERBAL EXTRACT; COMPLEMENTARY MEDICINE; OCULAR; OXIDATIVE STRESS; ANTIOXIDANTS

Diseases related with retinal ganglion cell (RGC) disruption are widely prevalent. Glaucoma is the second major cause of blindness after cataract, among eye disorders, and the most common cause of irreversible blindness. By 2020, India will become second in glaucoma incidence and, therefore, there is an urgent need to improve therapeutic approaches to retinal ganglion cell damage that can be applied not only nationwide but also worldwide [Shahsuvarya, 2012]. There is evidence that dying neural cells create a toxic internal milieu which can affect healthy cells surrounding it. The essence of neuroprotection involves protection afforded to these healthy cells from damage. Glaucoma, being an irreversibly blinding disease, could benefit immensely from this strategy if it could be made to work.

RGCs are neurons present in retina. While the cell bodies of these entities are located in the retina, the axons extend along the optic nerve which connects to the visual center of brain. RGC loss is a characteristic feature of various optic neuropathies. The ultimate fate of any eye disease is RGCs death regardless of the mechanisms of damage. These could be modeled as artificially induced ischemia either due to middle cerebral artery occlusion [Shakakibara et al., 2008] (MCAO) or carotid artery occlusion (CCAO) (Shri and Bora, 2008), neurotrophin deprivation, glial activation, excitotoxicity, oxidative stress [Hyun et al., 2013], episcleral vein cauterization [Dan et al., 2011] etc. Retinal ischemia is the prominent form of injury that can artificially induce RGC death. As confirmed from previous studies ischemia results in reduced flow of blood to retina and elevated levels of free radicals such as superoxide anion, hydroxyl radical, and hydrogen peroxide, along with a progressive depletion in endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), or antioxidants, glutathione (GSH) (Makris and Rossiter, 2001). Under normal conditions, free radical generation due to various metabolic

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processes is balanced by antioxidant enzymes. Oxidative stress occurs when this balance between production of endogenous antioxidative defense systems and reactive oxygen species (ROS) is disturbed (Kumari and Augusti, 2007). Excessive free radicals cause oxidative stress, damage lipid, protein and DNA, and ultimately result in cell death. Therefore, ischemia results in deprivation of oxygen to tissue and metabolic substrates ultimately affecting waste recycling. These processes lead to homeostatic imbalance exacerbating injury. Retinal ischemia has been studied extensively because it has been proposed to be involved in number of optic neuropathies such as anterior ischemic optic neuropathy (AION), glaucoma, retinal and choroidal vessel occlusions, retinopathy of prematurity (ROP), diabetic retinopathy, and traumatic optic neuropathy (Fig. 1).

CURRENT THERAPY AND ITS LIMITATION

The process of RGC degeneration is multivariate and can occur with or without increase in IOP. Various IOP independent factors such as ischemia, deprivation of one or more trophic factors [Quigley et al., 2000], excitoxicity [Cherecheanu et al., 2013], and oxidative stress [Chrysostomou et al., 2013] could lead to this damage. The current treatments available for various optic neuropathies which results due to RGCs degeneration are not adequate and thus alternate therapies can constitute re-emergent approaches from traditional knowledge resources for damage prevention. Moreover, commercial drugs available for diseases related to RGC damage like, timolol and letanoprost, for glaucoma exhibits toxic outcomes [Pisella et al., 2004]. Studies carried out to examine metabolic properties of Timolol have shown CYP2D6 as one of the principal enzymes involved. Mainly expressed in the liver, CYP2D6 has a very low expression in eye. Thus, after topical administration of Timolol, adverse effects may follow [Volotinen et al., 2011]. Even the systemic drugs used to treat other disorders have been critically reviewed by Santaella and Fraunfelder (2007) and they have found serious ocular side effects associated with these drugs. Therefore, it is imperative that an alternative treatment strategy from among re-emerging herbal interventions derived from natural resources be explored for diseases of retina. In this context, this review discusses the studies emanating from use of *Allium cepa* and other natural products from plant sources.

ALTERNATIVE THERAPEUTIC APPROACHES

According to National Institute of Health's (NIH) National Center for Complementary and Alternative Medicine (NCCAM), Complementary and alternative medicine (CAM) is a group of different medical related systems and practices which are commonly used by people around the globe, yet do not constitute the conventional approach in practice of medicine. The alternative approaches which can address the diseases of eye are needed for validation against the protection of ocular diseases. For example, various dietary supplements are known to have a direct or indirect role in the signaling pathways to protect the retina [Kiser and Dagnelie, 2008] but have not been tested widely.

Institution of complementary and alternative intervention is more frequent among developing nations and are now being regarded as re-emerging medical intervention in the face of slow pace of worldwide drug discovery. Rhee et al. (2001) reported that use of CAM among patients is approximately 5% (54 out of 1,000 patients). They also categorize the complementary and alternative therapies for glaucoma treatment into major nine branches: herbal extracts,

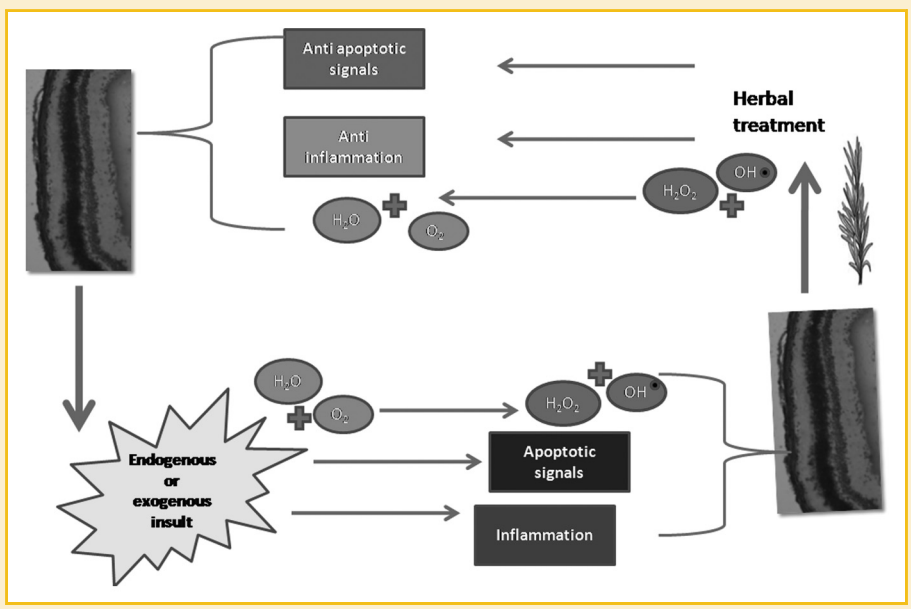

Fig. 1. Graphical abstract.

acupuncture, homeopathy, meditation, Vitamin supplementation, therapeutic touch, faith healing, exercise, and dietary modification.

Natural compounds such as grape seed extracts [Ritch, 2007], α- lipoic acid [Liu et al., 2012a], Vitamin E [Majumdar and Srirangam, 2010], curcumin [Alwan et al., 2012] have been tested from time to time to screen their neuroprotective role in retinal degenerative diseases of the brain. In contrast to singular herb centric (Chang and So, 2008) or singular disease centric [Mi et al., 2013] reviews, we have undertaken to present a critical analysis of those herbal extracts which have re-emerged as potentially efficacious agents in ocular disorders with minimal side effects. Present literature has some articles discussing different herbal interventions in ocular diseases (Wilkinson and Fraunfelder, 2011); however, the molecular mechanisms associated with neuroprotection were not emphasized in-depth. Therefore, the review summarizes the various herbal remedies and the convergent molecular mechanisms central to retinal degeneration protection.

HERBAL REMEDIES

Herbal extracts are being used from time immemorial for the treatment of various diseases. Studies have been carried out to screen the potential of natural extracts in preventing retinal degeneration.

ALLIUM CEPA

Allium cepa is a common component of our daily diet and has been widely studied for its therapeutic effectiveness due to its role as antidiabetic, antibiotic, anticancer, antiatherogenic, etc. [Helen et al., 2000]. Onions are rich in flavonoids (quercetin, myricetin, kaempferol) and organosulphur compounds (thiosulphimates and cepaenes). The antioxidant activity of *Allium cepa* is attributed to these key elements (Bhanot and Shri, 2010). Quercetin present in the onion is believed to inhibit the caspase-3-activity.The neuroprotective effect of quercetin was shown to act via wnt/-catenin pathway. Because of such an extensive study on use of *Allium cepa* in a variety of diseases and its normal uptake in body it provides an attractive agent to be tested against retinal ischemia. Besides, there are studies that showed the neuroprotective effect of *Allium cepa* in neurodegenerative and other related diseases, but it has not been adequately evaluated in models of retinal ischemia (Table I).

Antioxidant effect of *Allium cepa* has already been established in previous studies (Makris and Rossiter, 2001). Kumari and Augusti (2007) have shown that *S*-methyl cysteine sulfoxide isolated from *Allium cepa* reduced the concentration of cholesterol and phospholipids in rat fed on high cholesterol diet. Antioxidant effects were further confirmed by Campos et al. (2003). Alcoholic extracts of *Allium cepa* have been reported to have wound healing activities as shown by Shenoy et al. (2009). Our earlier studies have shown that methanolic extracts of *Allium cepa* provides neuroprotection against brain ischemia-reperfusion injury and a dose of 100 mg/kg B.W. and 200 mg/kg B.W. was found to be effectively reducing cerebral infarct volume (Shri and Bora, 2008) (Fig. 2).

CURCUMIN

Curcumin is a bioactive component of turmeric which is commonly used spice in India. Retinal pigment epithelium (RPE) is an important layer of retina which provides nutrition to other retinal layer and is

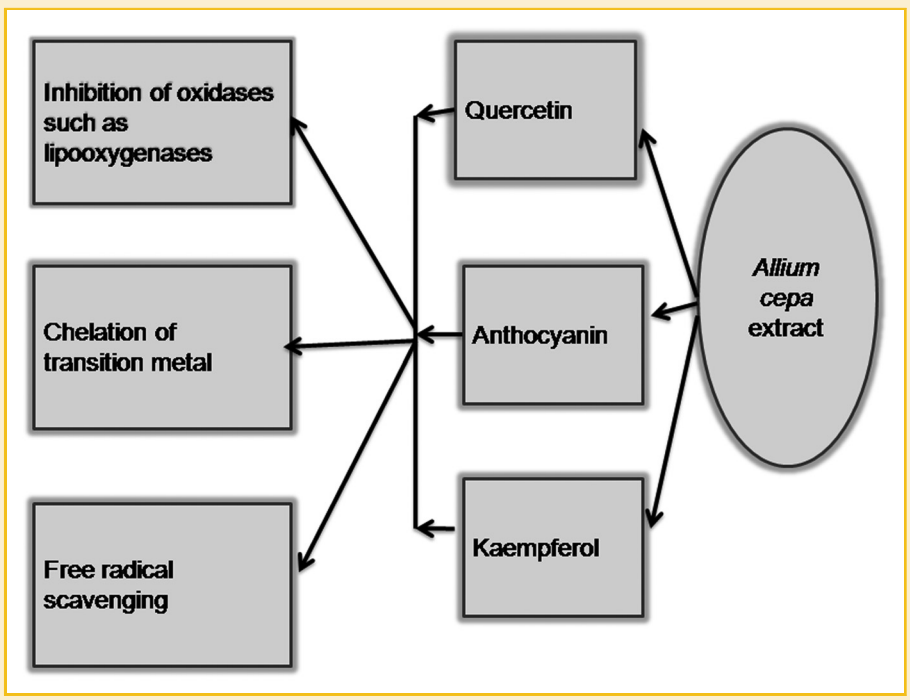

Fig. 2. Proposed mechanism for antioxidant activity of *Allium cepa* extract.

TABLE I. *Allium cepa* Extracts in Various Studies

S. no.	Model animal	Purpose	Reference
1	Gerbil	Cerebral ischemia	Hwang et al., 2009
2	Rat	Antidepressant	Shakakibara et al., 2010
3	Mice	Brain ischemia	Shri and Bora, 2008; Hyun et al., 2013
4	The brain microvascular endothelial cells(BMVECs) and astrocytes	In vitro neuroprotection against neuronal apoptosis	Dan et al., 2011
5	Mice	Diabetic neuropathy	Bhanot and Shri, 2010

thus indispensible for proper growth and survival of retina. RPE damage due to oxidative stress is one of the various factors responsible for pathogenesis leading to Age related macular degeneration. Woo et al. (2012) studied the effect of curcumin in RPE cells and they found that curcumin induces elevated expression of heme oxygenase 1 enzyme which provide defense against oxidative stress. Similar protective effect was reported against ischemia/reperfusion injury and photoreceptor degeneration. Wang et al. (2011) studied the neuroprotective effect against neurovascular damage and hypothesized that this result can be attributed to inhibitory effect of curcumin on NF-kB and STAT-3 responsible for degeneration. P23H-rhodopsin transgenic mouse, model for photoreceptor damage, when supplemented with curcumin also showed improved retinal structure and presents curcumin as potential therapy for diseases of photoreceptor degeneration [Vasireddy et al., 2011]. Anti-inflammatory role of curcumin has been established in endotoxin induced uveitis model in rabbits, where pretreatment with *C. longa* along with *B. aristata* has shown reduced levels of inflammatory mediators and aqueous humor a common symptom of uveitis [Gupta et al., 2008]. Curcumin exhibits its neuroprotective action through regulating NF-κB, AKT pathways influencing the inflammatory responses to various retinal injuries. Studies have shown that curcumin protection against light induced photoreceptor degeneration is mediated through reduction of expression levels of pro-inflammatory genes such as *Timp1*, *Icam1*, *Mmp3*, *Ccl2*. Besides, curcumin also reduces the expression level of genes related to oxidative stress (Ho-1) and apoptosis (Fos l1). Thus, regulation of genes related to inflammatory pathway support the immunomodulatory role of Curcumin [Mandal et al., 2009].

GINKO BILOBA

The ginkgo tree is a native of remote mountains of China, Japan, and Korea. Leaves and seeds of the tree generally have medicinal value which is believed to be due to presence of flavanoids and terpenoids [Mesbah et al., 2005]. Ginko biloba extract (GBE) extract EGb 761 has flavanoids kempferol, quercetin, and isorhamnet [Ritch, 2000]. The polyphenolic flavonoids possess antioxidant properties and the terpenoids inhibit platelet activating factor [Mozaffarieh et al., 2008].

In vitro studies have supported the neuroprotective nature of GBE against retinal cells. Studies on retinal pigment epithelium cells have shown increased expression of HIF-1and vascular endothelial growth factor (VEGF) in presence of GBE [Oh et al., 2013] while retinal explants culture reported increased survival of retinal ganglion cells by protecting cells from caspase activated apoptosis [Wang et al., 2012]. EGb 761, when administered to rats in which cataract was induced by selenium, prevented progression of disease. The chemical stress was ameliorated by ROS scavenging that inhibits the oxidation of proteins [Thiagarajan et al., 2002].

Pretreatment with GBE was shown to reduce the loss of retinal ganglion cells in chronic glaucoma induced in rat [Hirooka et al., 2004]. Herbal mixture containing *Ginko biloba* as one of the component supported the inhibition of caspase activity by extract in optic nerve transaction model in hamsters [Cheung et al., 2004]. GBE has also been found effective against dexamethasone induced ocular hypertension. The extract reduced the elevated IOP in rabbits and protected trabecular meshwork cells from adverse effect of dexamethasone. Further, cultured human trabecular cells, pretreated with GBE before dexamethasone showed reduced anti-Fas ligand-induced apoptosis [Jia et al., 2008]. GBE was also found helpful in survival of RGC cells after optic nerve crush in rats. Intra-gastral applications of extract applied after optic nerve crush protected RGC cells from damage and survival rate was found to be dosage dependent [Ma et al., 2009]. Additional studies by Juarez et al. (2008) have reported *G. biloba* to be effective against retinopathy of prematurity induced in both mouse and rat, adding credence to the potential of alternative therapies for diseases of retina.

VACCINIUM MYRTILLUS (BILBERRY)

Bilberry is a herb with very high anthocyanin content. Anthocyanins provide bilberry extract ability to combat oxidative stress as shown by study on cataract [Yamakoshi et al., 2002]. Anthocyanosides have positively charged oxygen which scavenges negatively charged electrons readily [Bagchi et al., 2006]. Antioxidant properties were further confirmed by increased level of MDA, GSH, and SOD in mouse model of endotoxin induced uveitis (UIV). Mouse treated with lipopolysaccharide (LPS) showed elevated level of nitric oxide (NO) which was reduced by bilberry extract [Yao et al., 2010]. In another study on UIV model, pretreatment with bilberry extract resulted in improved vision by preventing photoreceptor function impairement. Treatment with bilberry extract also increases the electroretinogram response in treated group. The underlying mechanism that prevented this retinal degeneration is believed to include prevention of STAT3 activation thereby reducing inflammation-related rhodopsin damage. Besides anti-inflammatory effect, antioxidative property exhibited by extract is also believed to help in ameliorating the ROS and damage to retina [Miyake et al., 2012].

In vitro studies have provided evidence for protective role of bilberry extract against RGCs. RGC-5 cells when treated with sydnonimine hydrochloride, known to elevate levels of peroxynitrite, have shown activation of ROS and neurotoxicity. Bilberry

treatment inhibited the neurotoxic effect induced by the compound. The neuroprotective effect of extract was further tested in mouse model of chemically induced retinal damage. Upon *N*-methyl-D-aspartic acid (NMDA) treatment ganglion cell layer damage was ameliorated by bilberry extract [Matsunaga et al., 2009].

LYCIUM BARBARUM POLYSACCHARIDE

Lycium barbarium also known as wolfberry is a medicinal plant with fruit and leaves of the plant having high medicinal value. Polysaccharides present in these plant parts are known to have antioxidant, anti-aging, and anti-tumor properties [Liu et al., 2012b].

The neuroprotective effects of *Lycium barbarum* have been tested in in vitro studies on cortical neuronal cell cultures [Ho et al., 2010]. Li et al. (2011) showed that pre-treatment with an extract from wolfberries (*Lycium barbarum* polysaccharides, LBP) could effectively protect the retinal layers from neuronal death, apoptosis, disruption of blood retinal barrier and oxidative stress in retinal I/R injury. Further, in another study it was also postulated that LBP could prevent damage to RGCs from hypertension-induced ischemic injury [Mi et al., 2012]. In vivo studies to screen the potential effect of extract on protecting retinal ganglion cells from elevated ocular pressure were carried out by Chan et al. (2007) in rats by using laser photocoagulator elevated IOP model and the results suggested *Lycium barbarum* extract to be protective against such damage.

CROCETIN

Crocetin is biochemically an aglycone of crocin and usually found in stigma of saffron and gardenia fruit. In vitro and in vivo studies on crocetin have revealed a promising therapeutic role of the carotenoid in retinal damage. RGC-5 cells treated with hydrogen peroxide or tunicamycin rescued cell damage with the treatment of 3 μM concentration of crocetin. Photoreceptor damage in mice model by light exposure was also counteracted by the crocetin administration. Protective effect of crocetin is believed to be due to inhibition of caspase 3 and caspase 9 which are responsible for cell death by apoptosis [Yamauchi et al., 2011]. Ohno et al. (2012) further evaluated the crocetin role in NMDA damaged retina and reported that oral administration improved the ERG responses in treated mice as compared to controls. The protective effects of crocetin (found in the saffron crocus, *Crocus starus* and in gardenia fruit *Gardenia jasminoides)* against the retinal ischemia induced by ligation of the pterygopalatine artery (PPA) and the external carotid artery (ECA) was also evaluated by Ishizuka et al. (2013) and found to be neuroprotective. Further studies can shed more light on its mechanism of action.

ASTAXANTHIN

Astaxanthin is a carotenoid that has characteristic oxidation properties. In vitro and in vivo studies carried out by Nakajima et al. (2008) have shown low level of oxidation in astaxanthin treated groups. The adverse effect of NMDA treatment in mice i.e. thinness of ganglion cell layer was overcome by astaxanthin treatment. Also in RGC culture studies cell viability after treating RGC-5 cell line with hydrogen peroxide was more in astaxanthin treated group. Astaxanthin, when given orally to the rats, with induced elevated ocular pressure, showed reduced retinal injury as compared to the control ones. Electrophysiological analysis of visual evoked potential (VEP) revealed that astaxanthin administration decreased the VEP in experimental animal when compared to controls [Cort et al., 2010]. In another study on cultured retinal ganglion cells, astaxanthin, a carotenoid pigment, was found to inhibit the neurotoxicity induced by H2O2 or serum deprivation. The attenuation of retinal cell damage by astaxanthin is possibly due to its antioxidant properties. The levels of oxidative stress marker such as 8-hydroxy-2-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) were also found to be downregulated after astaxanthin treatment [Dong et al., 2013].

BRAZILIAN GREEN PROPOLIS

Propolis is a resinous compound prepared by honeybees from bark of trees. Shimazawa et al. (2005) have elucidated the neuroprotective role with both in vivo and in vitro studies against retinal damage. They found that neurotoxicity induced by hydrogen peroxide and staurosporin was counteracted by propolis and RGC-5 cells viability was maintained in the culture. Similarly, the NMDA treated mice showed reduced retinal damage when propolis was administered intra-peritoneally to the mice. Later, it was determined that the protective effect was due to antioxidant properties of propolis which reduced the oxidative stress [Inokuchi et al., 2006]. Choroidal neovascularization is a characteristic of various eye related diseases such as age-related macular degeneration, diabetic retinopathy, the retinopathy of prematurity. VEGF is a well known angiogenic factor which activates various signal cascade pathways [Cort et al., 2010]. The study has revealed that propolis exerts its protective effect by acting on angiogenic processes and preventing angiogenesis. The angiostatic property of the propolis is believed to be due to its caffeoylquinic acid derivatives [Chikaraishi et al., 2010]. Thus, these findings suggest that propolis has a potential to be protective and therapeutic agent against diseases caused by angiogenesis.

OTHER HERBAL REMEDIES

A Chinese herb Astragalus membranaceus (AME) extract, when used in animal glaucoma model, lowered the intraocular pressure significantly. AME altered the MDA and GPx levels signifying antioxidant property of extract (Horng, 2011). Another study on herb *Foeniculum vulgare,* known to have antioxidant properties, [Baliga et al., 2003] has been evaluated for treatment of glaucoma. The aqueous extract of plant administered to rabbit model of chronic glaucoma comparatively reduced IOP in treated group as compared to controls [Agarwal et al., 2008]. Similarly, *Eisenia bicyclis* is a brown algae found in Korea and Japan. In vitro and in vivo studies carried out by Kim et al. (2002) showed that ethanol extract of *Eisenia Bicyclis*, seaweed, is protective for RGC cell death caused by ischemia. Some other herbal extracts used in in-vivo animals studies are listed in Table II.

Most herbal extracts prevent the progression of apoptotic signal and promote cell survival by activating the cell survival signal cascade (Fig. 3).

MECHANISM OF ACTION

Herbal extracts preserve the retina from damage by either preventing the apoptosis of the cell or by increasing the survival signals.

TABLE II. Herbal Extracts Used in Different Animal Models

S. no.	Model	Model animal	Extract used	Reference
1	NMDA	Rat	*Hong hua*	[Romano et al., 1993]
2	Transient global ischemia	Rat	*Bacopa monniera*	[Saraf et al., 2010]
3	Transient global ischemia	Mice	*Bacopa monniera and Valeriana wallichii*	[Rehni et al., 2007]
4	IOP elevation	Rat	*Erigeron breviscapus* extract	[Lu et al., 2011]
5	IOP elevation	Rat	Curcumin	[Wang et al., 2011]
6	MCAO	Rat	*Majun Baladar*	[Yousuf et al., 2007]
7	MCAO	Rat	*Embelia ribes*	[Nazam-Ansari et al., 2008]
8	Optic nerve transaction	Hamster	*Panax quinquefolius L.* extract (PQE), *Ginkgo biloba* extract (GBE) & *Hypericum perforatum* extract (HPE),	[Cheung et al., 2004]
9	Optic nerve crush	Rat	*Paeonia* extract paeoniflorin	[Li et al., 2007]

Imbalance in ROS and antioxidant enzymes leading to oxidative stress is a common phenomenon in various optic neuropathies. Almost every herbal extract possesses an antioxidant property which is exploited in exerting neuroprotection [Ritch, 2007]. Herbal extracts inhibit the activity of oxidases such as lipoxygenases (Bhanot and Shri, 2010) in cells. On the other hand, levels of antioxidant enzymes, catalase, glutathionase, superoxide dismutase are increased [Yao et al., 2010] which help in ROS scavenging. The resulting effect includes decreased oxidative stress and restoration of homeostasis. Carotenoids present in the extracts help in absorption of short wavelength light and prevent lipid peroxidation of cell membrane (Demmig-Adams and Adams, 2013). Accumulation of transition metals in ocular tissue is known to result in retinal degeneration by catalyzing the oxidative stress mechanisms. Chelating properties of some herbal extracts have been shown to protect the retina against such damage. Chelation bound accumulated free metal renders it unavailable for toxic effects (El-Beltagi and Badawi, 2013). Besides protecting retinal cells from oxidative

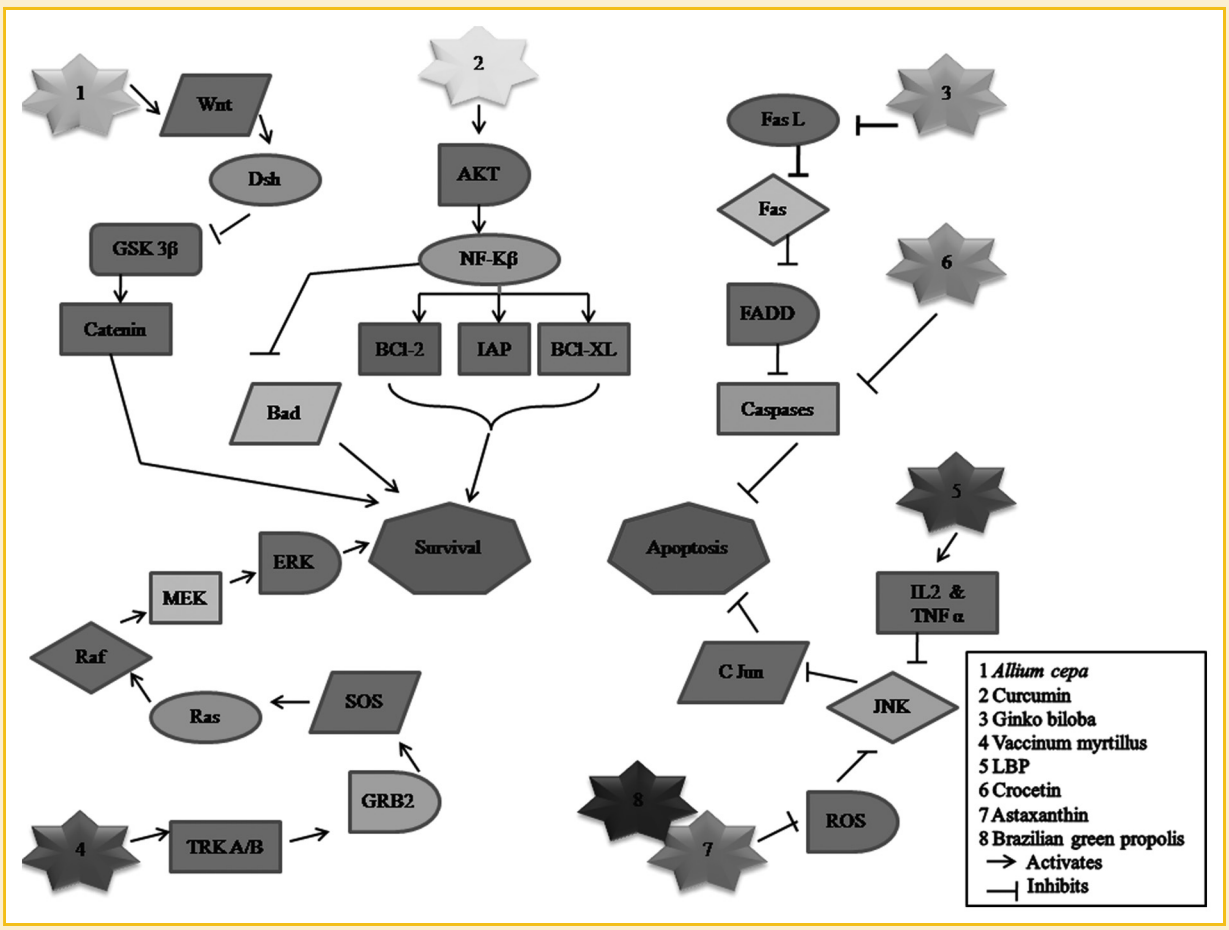

Fig. 3. Cascade of signal molecules activated/inhibited by different herbal extracts to promote cell survival.

stress, flavanoides in herbal extracts also enhance the survival of cells by elevating the expression of neurotrophic factors which are essential for normal cell functioning such as GDNF, VEGF, etc. [Zheng et al., 2000]. Immunostimulatory effects of some herbal extracts have been documented which include increased level of interleukin 2 and TNF-α resulting in retinal microglia activation (Chang and So, 2008). Herbal extracts also increase the cell survival in retina by interacting with anti-apoptotic gene *Bad* and *Bcl-XL* and decreasing caspase activity [Mi et al., 2013], thereby preventing apoptosis. Thus, herbal extracts have various mechanisms to preserve retina from neurodegeneration. These herbs and the related mechanism of action must be explored extensively for their use as therapeutic agent (Fig. 4).

CLINICAL RELEVANCE OF THE HERBAL EXTRACT

Herbal extracts are being used from time immemorial for the treatment of various diseases, however, scientific validation of these therapies still need to be evaluated. Current literature lacks research based on natural extracts [West et al., 2006]. Clinical trials of herbal extracts are very limited and thus there is a need of more and more preclinical studies on such extracts so that they can be promoted to successful clinical trials.

A herbal formulation named as Opthocare containing mixture of different herbal extracts was tested in a clinical trial. The patients who were recruited were having a wide range of ophthalmic disorders such as dry eye, pterygium, conjunctivitis, etc. The eye drop contained mixture of herbs known for their anti-inflammatory activity. In most of the patients there was an improvement with eye drop treatment [Biswas et al., 2001]. Anthocyanins purified from bilberry and blackcurrant when provided in form of capsules to participants in a clinical trial showed marked reduction in levels of NF-k-B inflammatory markers [Karlsen et al., 2007]. The marijuana effect on eye was studied and it was found to exert an effect on aqueous humor dynamics [Zhang et al., 2005].

So far, *Ginko biloba* is the herb of interest for clinicians and there have been some human studies to evaluate protective effect of this herbal extract in addressing eye related problems. Chung et al. (1999) carried out clinical trial of GBE for evaluating its efficacy against glaucoma. Patients with glaucoma were divided into two groups and treated with either GBE or placebo as a control three times daily for two days and blood flow was measured before and after treatment. The extract was shown to increase the ocular blood flow in ophthalmic artery significantly as compared to placebo.

Efficacy of GBE and bilberry, for improving visual field, was evaluated in 332 subjects with normotensive glaucoma (NTG). Both extracts were found to increase visual acuity in the patients (Shim et al., 2012). Clinical studies on patients of NTG have showed improved vision field. 40 mg of GBE for 4 weeks improved the damage in visual field of the patients with NTG [Quaranta et al., 2003]. Further clinical trials on NTG patients using *Ginko biloba* extract have also reported increased blood flow in the

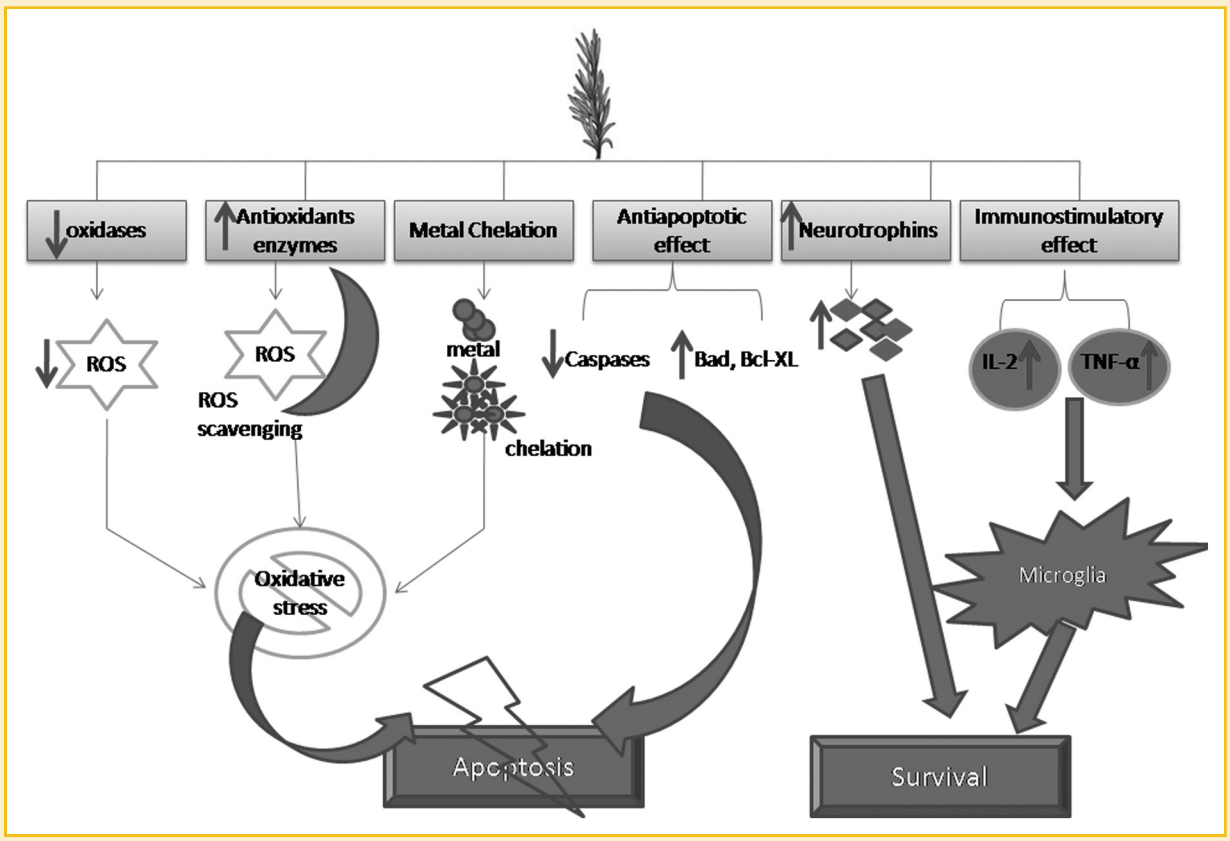

Fig. 4. Physiological and immunomodulatory pathways through which herbal extracts exerts their neuroprotection.

peripapillary area [Park et al., 2011]. Randomized control trial on 44 patients with Type 2 diabetes involving screening of GBE as a neuroprotective for eye was performed and it was revealed that the dry extract improves the microcirculation of diabetic patients. This effect was more pronounced in elderly patients [Spadiene et al., 2013].

CONCLUSION

The characteristic features of optic neuropathies include oxidative stress and cell damage. Thus, therapeutic approaches to eye diseases include not only lowering of pressure to normal level or maintaining the level of antioxidant mechanisms but also in salvaging the retinal cells. Various naturally occurring herbs possess antioxidative properties which have not been adequately explored using appropriate models. These properties of easily available herbal extracts can be tested to provide insight into treatments and mechanisms which could benefit a range of ocular diseases. Preclinical studies have revealed the effectiveness of herbal extracts for ocular diseases; however, clinical studies in the field are still lacking. The few clinical trials mentioned above have revealed the success of herbal interventions in treating the optic neuropathies. However, more preclinical and clinical studies must be carried out to collect robust data supporting the efficacy of herbal extracts in treating eye diseases especially when the synthetic drugs are not yielding any successful results. In addition, no serious side effects have been reported from the previous studies in the field. Therefore, preclinical and clinical data from further studies will help in promoting the use of herbal therapies in ocular diseases. Easy accessibility of the herbal sources may constitute a rather inexpensive strategy to combat eye disorders.

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