Published Online on 21 February 2018

Proc Indian Natn Sci Acad **84** No. 1 March 2018 pp. 185-193

DOI: 10.16943/ptinsa/2017/49231

Review Article

Research in Ocular Pharmacology: An Indian Perspective in the Last Five Years

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(Received on 23 August 2017; Accepted on 31 October 2017)

Designing drugs specifically for eye with the considerations of their penetration characteristics is not the strategy followed currently. Often drugs approved for systemic disease have been extrapolated for ocular use without adequate ocular pharmacokinetic studies. Last five years, ocular pharmacology was of interest for many research groups in India. Fundamental problem resulted from the poor penetration of drugs into the eye was studied with reference to the drug transporter mechanisms in the cornea, blood aqueous and retinal barriers. Exploration of newer compounds/natural products have been extensively conducted against angiogenesis, diabetic retinopathy, uveitis, dry eye syndrome, glaucoma, cataract etc. Newer drug targets have been explored for glaucoma, dry eye, retinopathy of prematurity, cataract etc. Newer experimental models have been developed for drugs affecting the visual perception and sex steroid deficient dry eye. Drug delivery systems, ocular pharmacokinetics in human and animal have also been studied by the investigators. This review summarizes the last five years of experimental/clinical research carried out in the field of Ocular Pharmacologyin India which are available in standard data bases.

Keywords: Blood Ocular Barriers; Pharmacokinetics; Anti-Angiogenic Agents; QSPR; Herbal Drugs; Drug Delivery; Instruments; Animal Models

Brief history of the Ocular Pharmacology research in India

In India, research on Ocular Pharmacology was initiated by the pioneering effort of Prof. Suresh K Gupta, who established Ocular Pharmacology Division at Dr. R. P. Centre at All India Institute of Medical Sciences (AIIMS), New Delhi, in 1974 with the help of Prof. L. P. Agarwal (former Director of AIIMS). The apt combination of Ocular Pharmacology with an active Pharmacy, at the Ophthalmology Department at AIIMS, made a stronger foundation for the development of newer ocular treatment options for direct clinical use. The first fluoroquinolone eye drop was developed at this centre by Prof. Gupta in 1988 which was subsequently brought to clinical use in 1991 (Vajpayee *et al*., 1991) in the same centre. Ever since several agents were developed for topical use in animal models and subsequently brought to clinical use in India and Asia. Currently, this discipline has percolated into many major Institutions in India and today more than 10 Institutions are actively working on this area making it one among the major disciplines of Pharmacology in India.

As per the recent publications in PubMed, we could classify the major thrust areas what Indian researchers are actively pursuing in Ocular Pharmacology are pharmacokinetics, herbal drug/food supplements, anti-glaucoma, antimicrobials, anti-neovascular, drug delivery and discovery strategies. Using appropriate mesh terms, past 5-6 years data has been included in this review to exhibit the current research interest in India with relevance to Ocular Pharmacology.

Ocular Pharmacokinetics

Drug absorption/penetration into the tissues and humors of the eye after topical and systemic drug

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administration is a factor responsible for its pharmacodynamics which is independent of the fate of the drugs administered systemically. Presence of blood ocular barriers affecting penetration of drugs across the ocular structures is well recognized. Therefore, studies evaluated the factors responsible for the fate of drugs in ocular use. Studies from All India Institute of Medical Sciences (Delhi) systematically evaluated the presence and function of drug transporters such as Organic Cation Transporters (OCT), P-glycoprotein efflux transporters (Pgp), nucleoside transporters (NT) across blood ocular barriers. A recent review compiled their comprehensive functions affecting ocular pharmacokinetics of drugs (Velpandian 2016).

Although aminoglycoside antibiotics were reported to be eliminated through the anterior route for a long time, only in 2013 the mechanism behind that clearance was established (Nirmal *et al*., 2013). While studying OCT transporters, it was concluded that the clearance of OCT substrates favors the anterior elimination pathway for positively charged compounds. The functional importance of OCT on the ocular disposition of intravitreally injected substrate tetraethyl ammonium was assessed in rabbits (Nirmal *et al*., 2012); this study concluded that intravitreally injected OCT substrates may follow an anterior elimination pathway and prolonged residence time in the vitreous humor.

The potential pharmacokinetic role of OCT in modulating the trans corneal penetration of its substrates administered topically has been studied in rabbits. This study concluded that OCT is functionally active in the cornea, causing uptake of their substrates from tear to the aqueous humor. When administering their substrates/blockers topically, both may be competing for OCT for their uptake across the cornea, thereby decreasing the corneal penetration. Hence, OCT can have a potential pharmacokinetic role in modulating the ocular bioavailability of their substrates which are used topically for ocular therapeutics (Nirmal *et al*., 2013). The role of OCTs was studied in the ocular disposition of its intravenously injected substrate in rabbits by quantifying the levels of its substrate in the presence and absence of blockers. This study revealed that in most of the tissues, OCTs are functionally present from apical to basolateral. The gene expression studies also showed the presence of nucleoside transporters such as OCT1, OCTN1, and OCTN2 in various ocular tissues studied. This study suggested that OCTs are functionally active in blood-ocular barriers and involved in the transport of its substrate from blood to vitreous humor (Nirmal *et al*., 2013a). Moreover, this study also revealed the pre-corneal availability of OCT substrate through lacrimal secretion indicating the possibility of utilizing them for the delivery of drug to the tear film through systemic route (Nirmal *et al*., 2010b). When the functional role of Pgp was assessed using transporter substrates and blockers in rabbits, their study revealed the involvement of P-gp efflux transporters in the blood ocular barriers (Senthilkumari *et al*., 2008a; Senthilkumari *et al*., 2008b). These studies further revealed the reason behind the failure of Pgp substrates from reaching adequate drug concentrations in the humors of the eye and ocular tissues (Velpandian *et al*., 2016).

Newer Animal Models and New Instrument in Ocular Pharmacology

Sex steroids play an important role in maintaining the homeostasis of ocular surface as evident from the expression of sex steroid receptors in various ocular tissues. Sex steroids deficient dry eye syndrome is very much prevalent in postmenopausal females. Singh *et al.* (2014) developed animal model for the sex steroid induced dry eye in male and female rats. To create estrogen deficient dry eye, ovariectomized female rats were used and to develop dry eye in male rats, 5 alpha reductase inhibitor (finasteride) was administered which prevented the conversion of testosterone to its active form dihydrotestosterone. In this study, gene expression analysis also revealed a significant downregulation of sex steroid receptors in ocular tissues after ovariectomy and finasteride challenge. These models have been suggested as a pharmacological tool for the development of new class of topical agents for dry eye by understanding the pathophysiology. Phytoestrogens are being evaluated for their pharmacological activity against dry eye syndrome using the above two experimental models by the same research group.

A newer model has been developed to study and predict the drug induced color toxicity and perception of vision using gold fish. Vijayakumar *et al*. (2016a) developed and evaluated the effect of

stimulants and suppressants using gyrating poly-chromatic dotted pattern-OMR (Gyro-dot-OMR) in gold fish. Using this instrument first time they have demonstrated the color toxicity of ethambutol exposure in animal models. Moreover, they have also demonstrated the protective effect of NMDA and non-NMDA receptor antagonists against ethambutol (EMB) induced retinal toxicity in Wistar rats using flash electroretinogram (Vijayakumar *et al*., 2016b).

Drug Discovery Strategies

Retinal angiotensin system plays an important role in maintaining the normal vascular homeostasis in retina. The functional importance of renin angiotensin system (RAS) in experimental animal model of Retinopathy of Prematurity (ROP) and also in human vitreous has been explored by Nath *et al*. (2016). There was a multifold increase in the expression of RAS components in human vitreous and rat retina showed their involvement in ROP. Electroretinogram and retinal fundus studies revealed the altered function of retina, which was successfully prevented by telmisartan, lisinopril and bevacizumab. This study for the first time demonstrated the up-regulated level of RAS components in human ROP vitreous and further that the pharmacological intervention of RAS pathway can functionally and structurally preserve retina against the progression of ROP in experimental animal model.

The corneal permeability of drugs is an important factor that determines the efficacy of the topical preparations. Transcorneal penetration of drugs from aqueous formulation is governed by various physiological, physiochemical, and formulation factors. The effect of formulation factors like concentration, pH, and volume of instillation across the cornea using cassette dosing technique for ophthalmic fluoroquinolones (FQs) has been studied in rabbit by Sharma *et al*. (2016). Most of the drugs used in ophthalmic therapeutics are mainly developed for systemic diseases, which are subsequently included for ocular use after toxicity studies. Much of the emphasis was made on pharmaceutical formulations rather than relevant molecular structural parameters. The cornea is a live tissue that behaves much beyond simple biomatrix; therefore, *in vitro* studies may not be having much relevance in the *in vivo* scenario. To enable *in silico* screening of drugs, techniques like cassette dosing are being developed to assess the possibility of enhanced topical penetration with less number of animals (Sharma *et al*., 2011).

Although FQs are extensively used in ophthalmology as topical eye drops for corneal infections, Sharma *et al*. (2011) studied their structural correlation with their effect on matrix metalloproteinases (MMPs) which are involved in the corneal wound healing process using MMP zymography and real time PCR. Findings of this study demonstrated that topical application of FQs may induce the expression of MMP-2 and MMP-9 in debrided corneal epithelium and, therefore, may delay corneal wound healing. Among the studied FQs, ciprofloxacin was observed to exhibit maximal induction of MMP-2 and MMP-9, whereas lomefloxacin exhibited an equivocal effect on both MMP-2 and MMP-9 expression.

Anti-angiogenic Agents for Ocular Neovascularization

Visual disability from diabetic retinopathy, wet Age Related Macular Degeneration etc., is a significant public health problem; however, this morbidity is largely preventable and treatable if managed with timely intervention. Presently intravitreal injection of vascular endothelial growth factor (VEGF) antibody is the only treatment available to prevent the neovascularization. Therefore, development of any other pharmacological agent is of global interest. Aldose Reductase (ALR), the first rate-limiting enzyme involved in polyol pathway plays a central role in diabetes and its related complications, including diabetic retinopathy. Therefore, Senthilkumari *et al*. (2017) explored ALR as a drug target for reducing the deleterious effects of DR. They have investigated the protective effect of epalrestat (EPL), ALR inhibitor on glucose-induced toxicity in ARPE-19 cells. This study reported that EPL significantly reduced aldose reductase expression and VEGF levels which were induced by high glucose in ARPE-19 cells.

Kumar *et al*. (2014) evaluated the effects of quercetin, a plant based flavonol, on retinal oxidative stress, neuroinflammation, and apoptosis in streptozotocin induced diabetic rats. This study compared the retinal levels of glutathione (GSH), antioxidant enzymes, inflammatory cytokines levels like tumor necrosis factor-α (TNF-α) and interleukin-

1β (IL-1β). Immunofluorescence and western blot studies were performed for nuclear factor kappa B (NF-kB), caspase-3, glial fibrillary acidic protein (GFAP) and aquaporin-4 (AQP4) expressions. This study showed that retinal GSH levels and antioxidant enzyme (SOD and CAT) activities were significantly decreased in diabetic group as compared to normal group. However, in quercetin treated rats, retinal GSH levels were restored close to normal levels and positive modulation of antioxidant enzyme activities was also observed. With these observations, this study concluded that bioflavonoids such as quercetin can be effective for protection of diabetes induced retinal neurodegeneration and oxidative stress.

Protective effects of *Trigonellafoenum-graecum* Linn. (fenugreek) was studied in streptozotacin-induced diabetic rat retina (Gupta *et al*., 2014). Fenugreek (100 and 200 mg/kg body weights) treatment was carried out for 24 weeks and evaluated for the levels of TNF-α, interleukin (IL)-1β, VEGF and protein kinase C. Retinal oxidative stress was evaluated by estimating antioxidant enzymes such as glutathione, superoxide dismutase, and catalase. Fluorescein angiography was performed to detect retinal vascular leakage. Electron microscopy was performed to determine basement membrane thickness. This study concluded that fenugreek has great potential in preventing diabetes-induced retinal degeneration regular consumption in the specified dosage.

The antiangiogenic potential of marine invertebrate species of *Phylum mollusca* from south east coast of India has been evaluated by Gupta *et al*. (2014). Molluscan species were collected from the Bay of Bengal and their methanolic extracts were evaluated for preliminary antiangiogenic activity using the *in-ovo* chick chorio-allantoic membrane assay. *In-vivo* antiangiogenic activity was evaluated inchemical cautery induced corneal neovascularization assay in rats and oxygen induced retinopathy assay in rat pups. Amongst all studied, *Meretrix meretrix*, *Meretrix casta*, *Telescopium telescopium* and *Bursa crumena* methanolic extracts exhibited noticeable antiangiogenic activity by inhibiting VEGF induced proliferation of new blood vessels.

Traditional/Herbal Preparations in Various Ocular Disorders

There have been many epidemiological and clinical studies that have demonstrated the beneficial effects of plant-derived compounds, such as curcumin, lutein and zeaxanthin, danshen (*Salvia miltiorrhiza*), ginseng and many more, on various ocular pathologies. Studies in cell cultures and animal models showed promising results for their uses in eye diseases. With an increase in burden of side effects of synthetic drugs and cost, herbal sources are now more focused. A controlled experimental study has been conducted by Velpandian *et al* (2013) on polyherbal eye drop (*Itone*) containing nineteen traditionally used ingredients that have been useful as an adjunct in various ocular pathologies. Antiangiogenic, anti-cataractand anti-inflammatory activities of the polyherbal formulation were evaluated *in-vitro, in-ovo*, and *in-vivo*. The cytotoxicity was evaluated against *HeLa* cancer cell lines using MTT assay. The intraocular penetration of the polyherbal formulation was also carried out in rabbit eyes via aqueous humor paracentesis and was further analyzed using LC-MS/MS. The study showed significant antiangiogenic and anti-inflammatory activities which further need investigation for ocular neovascular and inflammatory diseases in humans.

Another study was conducted to observe the regional variation in the levels of macular xanthophylls and carotenoids in dietary components in North and South Indian population (Velpandian *et al*., 2010). Multiple epidemiological studies have emphasized the intake of dark green leafy vegetables rich in xanthophylls in reducing the risk of developing age-related macular degeneration (AMD). Therefore, the levels of major carotenoids which are commonly consumed by fruits and vegetables in Indian origin along with xanthophylls such as lutein, zeaxanthin, lycopene, and β-carotene in the macula of Indian human donor eyes have been studied. The study showed considerable levels of xanthophylls in many of the commonly consumed fruit and vegetable sources in both parts of India. However, south Indian donor eyes showed lower levels as compared to north Indian donors and this warrants further investigation about the bioavailability of xanthophylls in their blood and food intake.

Proliferative vitreoretinopathy (PVR) often involves epithelial to mesenchymal transition of retinal pigment epithelium and finally leading to retinal detachment. Triphala, an ayurvedic formulation and

two of its active ingredients, namely chebulagic acid and chebulinic acid were evaluated by Sivasankar *et al.* (2015) for anti-EMT properties based on *in vitro* experiments in human retinal pigment epithelial cell line (ARPE-19) under TGFβ1 induced conditions. Aqueous and alcoholic extracts of triphala and the active ingredients showed significant down-regulation of the expression of αSMA, vimentin and up-regulation of the expression of ZO-1altered by TGFβ1. They were also found to inhibit the proliferation and migration of ARPE-19 cells induced by TGFβ1. This study concluded that these extracts and their active compounds are having therapeutic potential as an adjuvant therapy in the disease management of PVR.

Herbal Drugs in Cataract and Diabetic Ocular Complications

Age related cataract is one of the major causes of visual loss worldwide leading to the opacification of human lens. Oxidative stress has been reported to play a major role in the process of lens crystalline aggregation or disarrangement. Chaudhury *et al.* (2017) expressed and purified human βB-crystallin from *E. coli*. Docking analyses showed that the GTPs bind to the cleft between the domains of human ãB-crystallin that may be associated with the protection of the protein from oxidative damage. The *in vitro* study of UV irradiation producing oxidative damage to the protein in the presence of increasing concentrations of GTPs is indicative of their effective role as potent inhibitors of oxidative damage. In this study authors found that green tea flavones such as epicatechingallate (ECG) has a higher affinity towards the protein compared to epigallocatechin (EGC).

Cinnamaldehyde is a constituent of cinnamon that gives its characteristic flavor and odor. Singh *et al.* (2016) evaluated the anti-cataractogenic effect of cinnamaldehyde (CA), a natural organic compound, in rats with fructose-induced hypertension. This study revealed that cinnamaldehyde modulated the antioxidant parameters of the serum and lens homogenates in hypertension-induced cataractogenic animals. In the experimental models of cataract, several natural products like *lupeol* (Asha *et al*., 2016), *Cassia tora* (Sreelakshmi and Abraham 2016), fruit extract of *Luffa cylindrical* (Dubey *et al.*, 2015), extract of Tephrosia purpurea (Bhadada *et al*., 2016), grape seed extract (Mani Satyam *et al.*, 2014), C-phycocyanin (Kumari and Anbarasu 2014), extract of *Cineraria maritime* (Anitha *et al*., 2013), ethanolic extract of *Chromolaena odorata* (Onkaramurthy *et al*., 2013), root extract of *Leucas aspera* (Sundararajan *et al*., 2017), *curcumin* (Manikandan *et al*., 2010) and *Zingiber officinalis* (Saraswat *et al*., 2010) have been reported to be beneficial in the prevention of disease progression.

The effect of flavonoids has been evaluated against sugar induced cataractogenesis in animal models. The potential application of chrysin, apigenin, baicalein and genistein in formulation of functional foods and neutraceuticals for the management of diabetic cataract has been demonstrated by Patil *et al*. (2016). In the experimental models of diabetes in rats isoflavones isolated from *Caesalpinia-pulcherrima* (Kumar *et al*., 2015), hydroethanolic extract of *Symplocos cochinchinensi* (Antu *et al*., 2014), *quercetin* (Kumar *et al*., 2014), *nigerloxin* (Suresha & Srinivasan 2013), *hesperetin* (Kumar *et al*., 2013), extract of *Moringaoleifera* (Kumar Gupta *et al*., 2013), green tea extract (Kumar *et al*., 2012) standardised extract of *Andrographis paniculata* (Veeresham *et al*., 2013), flavonoids from *Vitexnegundo* (Rooban *et al*., 2011) have been reported to decrease the ocular complications of diabetes.

Inhibition of diabetic-cataract in rat by vitamin K1 has been reported by affecting the homeostasis of blood glucose and minimizing subsequent oxidative and osmotic stress (Sai Varsha *et al*., 2014). Their study further revealed that Vitamin K1 inhibits diabetic-cataract by modulating lens Ca^{2+} homeostasis and its hypoglycemic effect through its direct action on the pancreas. *Sesamin* (SES), the main component of sesame seed and its oil has been reported as potent antioxidant and neuroprotectant. Ahmad *et al.* (2016) investigated protective effect of SES in Streptozotocin (STZ) induced DR in mice. This study demonstrated SES treatment lowered the progression of diabetic ratinopathy and thus may have therapeutic benefit in reducing hyperglycemia and inflammation in diabetic patients. The aqueous fruit pericarp extract of *Litchichinensis* (APLC) has been evaluated for its antioxidant activity and its role in inhibiting the polyol pathway and formation of advanced glycation end products (AGEs) in experimental diabetic cataractogenesis (Kilari and Putta 2017). The

treatment with APLC was found to delay the progression of diabetic cataractogenesis and retinopathy which might be due to the presence of active phytochemicals in APLC possessing antioxidant activity.

Ocular Drug Delivery Systems

Use of ocular drug delivery systems is an expanding area, which is adopted to increase the ocular pharmacokinetic profile of the drug instilled topically or injected into the ocular structures. Nano-sized ocular drug delivery systems including nanoparticles, nanoemulsions, liposomes, solid lipid nano-particles, light-sensitive nano-carrier systems, etc.,have been tried in experimental models (Sultana *et al*., 2011). Corneal permeation of gatifloxacin was studied in the form of positively charged solid lipid nanoparticle (SLN) and its effect on corneal hydration level was studied. This study suggested that SLNs could enhance relative ocular bioavailability of gatifloxacin along with the prolongation of its residence time in the eyes. It was also found that no signs of ocular irritation were seen with the SLN formulations, indicating their relative safety compared to the marketed drops (Abul Kalam *et al*., 2013).

In situ gel of chitosan nanoparticles were optimized on to enhance the bioavailability and efficacy of dorzolamide. *Ex-vivo* and the gamma scintigraphic study showed good corneal retention compared to marketed formulation.This study concluded that *in-situ* gel of dorzolamide hydrochloride loaded nanoparticles can be made for glaucoma to improve patient compliance (Katiyar *et al*., 2014). A formulation having oil-in-water microemulsion (size ranged from 51-74nm) has been found to increase the intraocular penetration of gatifloxacin (Kalam *et al*., 2016). Delivery of drug to the posterior site is desired for the effective management of these diseases. Chitosan coated poly lactide-co-glycolic acid nanoparticles of bevacizumab are developed and optimized for the sustained and effective delivery to posterior ocular tissues. *In-vitro* penetration studies with drug flux measurements concluded that the chitosan coated PLGA nanoparticles might have the potential for the drug delivery to retina (Pandit *et al.*, 2016).

Proglycosomes containing propylene glycol, phospholipid and water were incorporated with tacrolimus and has been evaluated for its property to show prolonged drug release in rabbits. This study observed that they are prolyosomes which are capable of increasing the drug release overthe period of 12hr and showed higher corneal permeation, as compared to conventional liposomes and tacrolimus solution respectively (Garg *et al*., 2017).

Grama *et al*. (2013) administered curcumin encapsulated nanoparticles in streptozotocin (STZ) induced diabetic cataract model and demonstrated significant delay in progression of diabetic cataract by nanocurcumin which is attributed to its ability to intervene the biochemical pathways of disease progression such as protein insolubilization, polyol pathway, protein glycation, crystalline distribution and oxidative stress. The enhanced performance of nano curcumin may be due to its improved oral bioavailability. Similarly, curcumin nanoparticles have been evaluated for its efficacy in suppressing proinflammatory cytokines and angiogenic factors in rat cornea. The results showed that curcumin nanoparticles capable of showing enhanced retention of curcumin in the cornea and suppressed pro-inflammatory cytokines and angiogenic factors (Pradhan *et al*., 2015).

Drug Evaluations for Clinical Use

The kinetics of single and multiple doses of topical, non-preserved voriconazole (VZ) formulation in human eyes has been evaluated to design the frequency of instillation so that a therapeutic concentration is well maintained for successful therapy (Senthilkumari *et al*. 2010). For single dose kinetics, 119 patients undergoing cataract surgery were given single drop (30 µl) of either 1% or 0.1% VZ formulation. Aqueous humor was collected at designated time intervals. For multi-dose kinetics, a single drop of 1% VZ was instilled 5 times either hourly or every 2 hr. The aqueous humor was tested for VZ at the 5^{th} hr and 9th hr, respectively, after initial instillation. The stability and efficacy of the reconstituted VZ formulations were also evaluated after 30 days and the efficacy was found to be maintained throughout the study period. The study achieved a mean concentration of VZ in both single dose and multi dose kinetic studies satisfactorily met the $MIC_{(90)}$ for almost all causative fungal organisms.

Intrastromal and intracameral voriconazole has

been used in cases of deep stromal involvement and anterior chamber penetration unresponsive to topical therapy. Sharma *et al.* (2013) compared the efficacy of topical voriconazole and topical natamycin with that of intrastromal voriconazole and topical natamycin in patients with recalcitrant fungal keratitis. Topical voriconazole seems to be a useful adjunct to natamycin in fungal keratitis not responding to topical natamycin. Intrastromal injections did not offer any beneficial effect over topical therapy.

Conclusion

Many new drug targets, molecular pathways, herbal drugs, new drug delivery systems have been explored in the last few decades to meet the challenges in ocular pharmacology. However understanding the drug transport susceptibility across the blood ocular barriers is still a puzzle to be resolved which mainly governs the ocular pharmacokinetics and toxicity of the drugs. Although several research papers documented the efficacy of plant extracts, isolated compounds and food supplements in conditions like cataract and ocular diabetic complications, very little is known about the molecular mechanisms involved in such activities. Further investigations and scientific documentations are required to uncover the mechanistic pathways of the natural products in order to reach their clinical use. This attempt is expected to render newer compounds with novel pathways of the treatment of various ocular conditions.

References

Abul Kalam M, Sultana Y, Ali A, Aqil M, Mishra A K, Chuttani K, Aljuffali I A and Alshamsan A (2013) Part II: Enhancement of transcorneal delivery of gatifloxacin by solid lipid nanoparticles in comparison to commercial aqueous eye drops *J Biomed Mater Res A* **101** 1828-1836

Ahmad S, ElSherbiny N M, Jamal M S, Alzahrani F A, Haque R, Khan R, Zaidi S K, AlQahtani M H, Liou G I and Bhatia K (2016) Anti-inflammatory role of *sesamin* in STZ induced mice model of diabetic retinopathy *J Neuroimmunol* **295-296** 47-53

Anitha T S, Muralidharan A R, Annadurai T, Jesudasan C A, Thomas P A and Geraldine P (2013) Putative free radical-scavenging activity of an extract of *Cineraria maritima* in preventing selenite-induced cataractogenesis in Wistar rat pups *Mol Vis* **19** 2551-2560

Antu K A, Riya M P, Mishra A, Sharma S, Srivastava A K and Raghu K G (2014)*Symplocoscochinchinensis* attenuates streptozotocin-diabetes induced pathophysiological alterations of liver, kidney, pancreas and eye lens in rats *Exp Toxicol Pathol* **66** 281-291

Asha R, Gayathri Devi V and Abraham A (2016) Lupeol, a pentacyclic triterpenoid isolated from *Vernoniacinerea* attenuate selenite induced cataract formation in Sprague Dawley rat pups *Chem Biol Interact* **245** 20-29

Bhadada S V, Bhadada V J and Goyal R K (2016) Preventive Effect of *Tephrosiapurpurea* on Selenite-Induced Experimental Cataract *Curr Eye Res* **41** 222-231

Chaudhury S, Roy P and Dasgupta S (2017) Green tea flavanols protect human γB-crystallin from oxidative photodamage *Biochimie* **137** 46-55

Dubey S, Saha S, Kaithwas G and Saraf S A (2015) Effect of standardized fruit extract of *Luffa cylindrica* on oxidative stress markers in hydrogen peroxide induced cataract *Indian J Pharmacol* **47** 644-648

Garg V, Suri R, Jain G K and Kohli K (2017) Proglycosomes: A novel nano-vesicle for ocular delivery of tacrolimus *Colloids Surf B Biointerfaces* **157** 40-47

Grama C N, Suryanarayana P, Patil M A, Raghu G, Balakrishna N, Kumar M N and Reddy G B (2013) Efficacy of biodegradable curcumin nanoparticles in delaying cataract in diabetic rat model *PLoS One* **8** e78217

Gupta P, Arumugam M, Azad R V, Saxena R, Ghose S, Biswas N R and Velpandian T (2014) Screening of antiangiogenic potential of twenty two marine invertebrate extracts of *phylum Mollusca* from South East Coast of India *Asian Pac J Trop Biomed* **4** 129-138

Gupta S K, Joshi S and Zhingan S (1989) Topical norfloxacin a new drug for the treatment for pseudomonas corneal ulcer - An experimental study *Med Sci Res* **17** 769-770

Gupta S K, Kumar B, Nag T C, Srinivasan B P, Srivastava S, Gaur S and Saxena R (2014) Effects of *Trigonellafoenum-graecum* (L.) on retinal oxidative stress, and proinflammatory and angiogenic molecular biomarkers in streptozotocin-induced diabetic rats *Mol Cell Biochem* **388** 1-9

Kalam M A, Alshamsan A, Aljuffali I A, Mishra A K and Sultana Y (2016) Delivery of gatifloxacin using microemulsion as vehicle: Formulation, evaluation, transcorneal permeation and aqueous humor drug determination *Drug Deliv* **23**

896-907

Katiyar S, Pandit J, Mondal R S, Mishra A K, Chuttani K, Aqil M, Ali A and Sultana Y (2014) In situ gelling dorzolamide loaded chitosan nanoparticles for the treatment of glaucoma *Carbohydr Polym* **102** 117-124

Kilari E K and Putta S (2017) Delayed progression of diabetic cataractogenesis and retinopathy by *Litchi chinensis* in STZ-induced diabetic rats *Cutan Ocul Toxicol* **36** 52-59

Kumar B, Gupta S K, Nag T C, Srivastava S and Saxena R (2012). Green tea prevents hyperglycemia-induced retinal oxidative stress and inflammation in streptozotocin-induced diabetic rats *Ophthalmic Res* **47** 103-108

Kumar B, Gupta S K, Nag T C, Srivastava S, Saxena R, Jha K A and Srinivasan B P (2014). Retinal neuroprotective effects of quercetin in streptozotocin-induced diabetic rats *Exp Eye Res* **125** 193-202

Kumar B, Gupta S K, Srinivasan B P, Nag T C, Srivastava S, Saxena R and Jha K A (2013) Hesperetin rescues retinal oxidative stress, neuroinflammation and apoptosis in diabetic rats *Microvasc Res* **87** 65-74

Kumar Gupta S, Kumar B, Srinivasan B P, Nag T C, Srivastava S, Saxena R and Aggarwal A (2013) Retinoprotective effects of *Moringaoleifera* via antioxidant, anti-inflammatory, and anti-angiogenic mechanisms in streptozotocin-induced diabetic rats *J Ocul Pharmacol Ther* **29** 419-426

Kumar M P, Sankeshi V, Naik R R, Thirupathi P, Das B and Raju T N (2015)The inhibitory effect of Isoflavones isolated from Caesalpiniapulcherrima on aldose reductase in STZ induced diabetic rats *Chem Biol Interact* **237** 18-24

Kumari R P and Anbarasu K (2014) Protective role of C-phycocyanin against secondary changes during sodium selenite mediatedcataractogenesis *Nat Prod Bioprospect* **4** 81-89

Mani Satyam S, Kurady Bairy L, Pirasanthan R and Lalit Vaishnav R (2014) Grape seed extract and zinc containing nutritional food supplement prevents onset and progression of age-related cataract in wistar rats *J Nutr Health Aging* **18** 524-530

Manikandan R, Thiagarajan R, Beulaja S, Sudhandiran G and Arumugam M (2010) Effect of on selenite-induced cataractogenesis in Wistar rat pups *Curr Eye Res* **35** 122-129

Nath M, Chandra P, Halder N, Singh B, Deorari A K, Kumar A, Azad R V and Velpandian T (2016) Involvement of Renin-Angiotensin System in Retinopathy of Prematurity – A Possible Target for Therapeutic Intervention *PLOS One* **11** e0168809

Nirmal J, Singh SB, Biswas NR, Thavaraj V, Azad R V and Velpandian T (2013a) Potential pharmacokinetic role of organic cation transporters in modulating the transcorneal penetration of its substrates administered topically *Eye (Lond)* **27** 1196-1203

Nirmal J, Sirohiwal A, Singh S B, Biswas N R, Thavaraj V, Azad R V and Velpandian T (2013b) Role of organic cation transporters in the ocular disposition of its intravenously injected substrate in rabbits: implications for ocular drug therapy *Exp Eye Res* **116** 27-35

Nirmal J, Velpandian T, Biswas N R, Azad R V, Vasantha T, Bhatnagar A and Ghose S (2010) Evaluation of the relevance of OCT blockade on the transcorneal kinetics of topically applied substrates using rabbits FIP 2010 World Congress in Association with AAPS, New Orleans USA

Nirmal J, Velpandian T, Singh S B, Biswas N R, Azad R V, Thavaraj V, Mittal G, Bhatnagar A and Ghose S (2012) Evaluation of the functional importance of organic cation transporters on the ocular disposition of its intravitreally injected substrate in rabbits *Curr Eye Res* **37** 1127-1135

Onkaramurthy M, Veerapur V P, Thippeswamy B S, Reddy T N, Rayappa H and Badami S (2013) Anti-diabetic and anti-cataract effects of *Chromolaenaodorata Linn*., in streptozotocin-induced diabetic rats *J Ethnopharmacol* **145** 363-72

Pandit J, Sultana Y and Aqil M (2016) Chitosan-coated PLGA nanoparticles of bevacizumab as novel drug delivery to target retina: optimization, characterization, and *in vitro* toxicity evaluation *Artif Cells Nanomed Biotechnol* **18** 1-11

Patil K K, Meshram R J, Dhole N A and Gacche R N (2016) Role of dietary flavonoids in amelioration of sugar induced cataractogenesis *Arch Biochem Biophys* **593** 1-11

Pradhan N, Guha R, Chowdhury S, Nandi S, Konar A and Hazra S (2015) Curcumin nanoparticles inhibit corneal neovascularization *J Mol Med (Berl)* **93** 1095-106

Rooban B N, Sasikala V, Sahasranamam V and Abraham A (2011) Analysis on the alterations of lens proteins by Vitexnegundo in selenite cataract models *Mol Vis* **17** 1239-1248

Sai Varsha M K, Raman T and Manikandan R (2014) Inhibition of diabetic-cataract by vitamin K1 involves modulation of hyperglycemia-induced alterations to lens calcium homeostasis *Exp Eye Res* **128** 73-82

Saraswat M, Suryanarayana P, Reddy P Y, Patil M A, Balakrishna N and Reddy (2010) Antiglycating potential of Zingiber officinalis and delay of diabetic cataract in rats *Mol Vis* **16** 1525-1537

Senthilkumari S, Lalitha P, Prajna N V, Haripriya A, Nirmal J, Gupta P and Velpandian T (2010) Single and multidose

ocular kinetics and stability analysis of extemporaneous formulation of topical voriconazole in humans *Curr Eye Res* **35** 953-960

Senthilkumari S, Sharmila R, Chidambaranathan G and Vanniarajan A (2017) Epalrestat, an Aldose Reductase Inhibitor Prevents Glucose-Induced Toxicity in Human Retinal Pigment Epithelial Cells *In Vitro J Ocul Pharmacol Ther* **33**3 4-41

Senthilkumari S, Velpandian T, Biswas N R, Saxena R and Ghose S (2008a) Evaluation of the modulation of P-glycoprotein (P-gp) on the intraocular disposition of its substrate in rabbits *Curr Eye Res* **33** 333-343

Senthilkumari S, Velpandian T, Biswas N R, Sonali N and Ghose S (2008b) Evaluation of the impact of P glycoprotein (P gp) drug efflux transporter blockade on the systemic and ocular disposition of P gpsubstrate *J Ocul Pharmacol Ther* **24** 290-300

Sharma C, Biswas N R, Ojha S and Velpandian T (2016) Comprehensive evaluation of formulation factors for ocular penetration of fluoroquinolones in rabbits using cassette dosing technique *Drug Des Devel Ther* **22** 811-823

Sharma C, Velpandian T, Baskar Singh S, Ranjan Biswas N, Bihari Vajpayee R and Ghose S (2011) Effect of fluoroquinolones on the expression of matrix metalloproteinase in debrided cornea of rats *Toxicol Mech Methods* **21** 6-12

Sharma C, Velpandian T, Biswas N R, Nayak N, Vajpayee R B and Ghose S (2011) Development of novel in silico model to predict corneal permeability for congeneric drugs: a QSPR approach *J Biomed Biotechnol* **2011** Article ID 483869 11 pages

Sharma N, Chacko J, Velpandian T, Titiyal J S, Sinha R, Satpathy G, Tandon R and Vajpayee R B (2013) Comparative evaluation of topical versus intrastromal voriconazole as an adjunct to natamycin in recalcitrant fungal keratitis *Ophthalmology* **120** 677-681

Singh A, Khan S A, Choudhary R and Bodakhe S H (2016) Cinnamaldehyde Attenuates Cataractogenesis via Restoration of Hypertension and Oxidative Stress in Fructose-Fed Hypertensive rats *J Pharmacopuncture* **19** 137-144

Singh S, Moksha L, Sharma N, Titiyal J S, Biswas N R and Velpandian T (2014) Development and evaluation of animal models for sex steroid deficient dry eye *J Pharmacol Toxicol Methods* **70** 29-34

Sivasankar S, Lavanya R, Brindha P and Angayarkanni N (2015) Aqueous and alcoholic extracts of Triphala and their active compounds chebulagic acid and chebulinic acid prevented epithelial to mesenchymal transition in retinal pigment epithelial cells, by inhibiting SMAD-3 phosphorylation *PLoS One* **10** e0120512

Sreelakshmi V and Abraham A (2016) *Cassia Tora* leaves modulates selenite cataract by enhancing antioxidant status and preventing cytoskeletal protein loss in lenses of Sprague Dawley rat pups *J Ethnopharmacol* **178** 137-143

Sultana Y, Maurya D P, Iqbal Z and Aqil M (2011) Nanotechnology in ocular delivery: Current and future directions *Drugs Today* **47** 441-455

Sundararajan M, Thomas P A, Babyshalini K and Geraldine P (2017) Identification of phytoconstituents and *in-vitro* evaluation of the putative anticataractogenic effect of an ethanolic root extract of *Leucas aspera Biomed Pharmacother* **85** 87-101

Suresha B S and Srinivasan K (2013) Antioxidant potential of fungal metabolite nigerloxin during eye lens abnormalities in galactose-fed rats *Curr Eye Res* **38** 1064-1071

Vajpayee R B, Gupta S K, Angra S K and Munjal A (1991) Topical norfloxacin therapy in Pseudomonas corneal ulceration *Cornea* **10** 268-271

Veeresham C, Swetha E, Rao A R and Asres K (2013) *In vitro* and *in vivo* aldose reductase inhibitory activity of standardized extracts and the major constituent of *Andrographis paniculata Phytother Res* **27** 412-416

Velpandian T (2016) Ocular pharmacokinetics and factors affecting ocular disposition of drugs. In: Pharmacology of Ocular Therapeutics (Ed: Velpandian) pp 48-58, Springer Switzerland

Velpandian T, Arora B, Senthilkumari S, Ravi A K, Gayathri C, Azad R and Ghose S (2010) Regional variation in the levels of macular xanthophylls and carotenoids in dietary components: comparing North and South India *J Nutr Sci Vitaminol (Tokyo*) **56** 411-420

Velpandian T, Gupta P, Ravi A K, Sharma H P and Biswas N R (2013) Evaluation of pharmacological activities and assessment of intraocular penetration of an ayurvedicpolyherbal eye drop (Itone™) in experimental models *BMC Complement Altern Med* **2** 1

Vijayakumar A R, Biswas N R, Menon V, Saxena R, Ahmed W, Halder N and Velpandian T (2016) Fabrication and Validation of Gyro-Dot-Optomotor Response Device using Gold Fish to Study Drugs Affecting Visual Perception *Ind J Physiol Pharmacol* **60** 182-192 (a)

Vijayakumar A R, Anuradha H, Biswas N R, Menon V, Saxena R, Halder N and Velpandian T (2016) Evaluation of the Protective Effect of NMDA/Non-NMDA Receptor Antagonists Against Ethambutol Induced Retinal Toxicity Using ERG in Wistar Rats *Ind J Physiol Pharmacol* **60** 268-281(b).