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Intralipid Eye Drops for Cataract Treatment?

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Abstract

Cataract is the leading cause of world blindness. Mitochondrial targeting of compounds with universal types of antioxidant activity represents a promising approach for treating a number of ROS-related ocular diseases of the aging eye and can be implicated in the management of cataracts. Intralipid can improve the anti-oxidative capacity and reduce the oxidative damage on the aging cataract lens.

Intralipid eye drops are first suggested for cataract treatment in the medical literature.

Keywords: Cataract; Eye Drops; Intralipid; Intralipid Eye Drops

Oil Eye Drops

Ocular inflammatory diseases, such as uveitis, scleritis, episcleritis and dry eye syndrome are commonly treated with eye drop formulations. In the present study, attempts were made to prepare aceclofenac oil formulations to evaluate its transcorneal permeation and anti-inflammatory effect. Ophthalmic solutions of aceclofenac with or without (0.5% v/v) benzyl alcohol were formulated in different vegetable oilsand permeation studies were carried out. Aceclofenac ophthalmic solution in linseed oil containing benzyl alcohol exhibited maximum permeation (4.42% in goat, 4.26% in sheep and 3.94% in buffalo) through corneas under study. The partition characteristics of aceclofenac in linseed oil reinforced the results of permeation studies. The optimized formulation (linseed oil containing benzyl alcohol) showed better stability profile. Linseed oil aceclofenac formulation showed significant inhibitory effect on ocular inflammation induced by arachidonic acid in rabbit eyes ($p<0.05$) and hence it can be considered as a potential approach for treatment of ocular inflammatory conditions [1].

To evaluate the effectiveness of topical 1% cyclosporine eye drops diluted in either of the two vehicles-olive and linseed oil-and that of the oils themselves in treating experimentally-induced kerato conjunctivitis sicca (KCS) in rabbits.

KCS was induced in 25 New Zealand rabbits using 1% atropine sulfate eye drops for 7 days before treatment and throughout the treatment period (12 weeks). The rabbits were divided into five groups: one control (C) group without KCS induction and four treatment groups in which KCS was induced and treated topically with olive oil (O), linseed oil (L), cyclosporine in olive oil (CO), and cyclosporine in linseed oil (CL). The animals were evaluated using Schirmer tear test 1 (STT), the fluorescein test (FT), tear-film break-up time (TBUT), the rose bengal test (RBT), and histopathological analysis.

Values of STT and TBUT significantly decreased 1 week post-induction ($p<0.05$) and were similar to initial values after the 4th week of treatment, in all groups. After KCS induction, there was significantly less corneal damage in group L than in group CL, as assessed FT and RBT. Histopathology demonstrated that Groups L and CL presented less

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edema and corneal congestion. There was no significant difference in the goblet cell density (cells/mm2) between the groups (p=0.147).

Cyclosporine diluted in olive oil or linseed oil was effective in the treatment of KCS, although it had better efficacy when diluted in linseed oil.

Linseed oil presented better effectiveness, whether associated or not, than olive oil. These results may contribute to the creation of novel topical ophthalmic formulations for KCS treatment in future [2].

The purpose of this study was to determine the clinical impact of using SYSTANE BALANCE Lubricant Eye Drops (Alcon, Fort Worth, TX), an oil-in-water emulsion, as a rewetting eye drop in symptomatic contact lens wearers.

Subjects who had previously experienced contact lens discomfort (CLD), with a mean lens wearing history of 18.6±12.8 years, were randomly assigned to use a Test (SYSTANE BALANCE Lubricant Eye Drops; n=76) or control (habitual non-lipid contact lens rewetting eye drop; n=30) drop over their contact lenses within 5 min of lens insertion and then subsequently at 2 hr intervals up to a maximum of 4 drops per eye daily for a 1-month period. Assessments of subjective comfort, comfortable wearing time, lid wiper epitheliopathy (LWE), and corneal staining were conducted at baseline and after 1 month, after 6 hr of lens wear.

Comfort, wearing time, LWE, and corneal staining all showed statistically significant improvements in the test group using SYSTANE BALANCE Lubricant Eye Drops at the 1-month visit compared with baseline data (all P<0.01) and compared with the control group at the 1-month visit (P<0.01, P=0.01, P<0.01, and P=0.03, respectively).

The use of SYSTANE BALANCE Lubricant Eye Drops as a rewetting drop in a group of wearers who experienced symptoms of CLD improved subjective comfort scores, increased comfortable wearing time, and reduced signs of LWE and corneal staining, when compared with the use of non-lipid-containing contact lens rewetting eye drops [3].

To compare the efficacy of 0.03% tacrolimus eye drops diluted in two different vehicles (linseed oil and olive oil) for the treatment of kerato conjunctivitis sicca (KCS) in dogs.

This study included 60 dogs. Of this group, 20 were healthy and allocated to the control group, and 40 were diagnosed with bilateral KCS and randomly allocated to either the TO (tacrolimus in olive oil) or the TL (tacrolimus in linseed oil) groups. Ophthalmic examinations, Schirmer Tear Test-1 (STT-1), Tear Film Break-up Time (TBUT) and Fluorescein Test (FT) were carried out monthly, along with cytological and histopathological examinations at the beginning and end of the study.

The clinical signs, corneal ulcers, Schirmer Tear Test-1 values, and Tear Film Break-up Time values improved in both groups after one month of treatment. Cytological examination at the end of the study showed decreased lymphocytes, neutrophil, metaplastic, and squamous cell counts in both groups, while the histopathological analysis showed decreases in lymphocytes and neutrophils and an increase in goblet cell density (cells/mm2). The decreases in neutrophil count were more significant (p<0.05) in the TL group for both types of examination.

In sum, 0.03% tacrolimus eye drops diluted in olive oil and linseed oil were effective in the treatment of kerato conjunctivitis sicca. None of the evaluated parameters differed significantly between the two groups, except for neutrophil count which was significantly lower in the TL group. Thus, linseed oil may be considered as an alternative diluent for tacrolimus eye drops [4].

To investigate the therapeutic effects of mineral oil (MO) and hyaluronic acid (HA) mixture eye drops on the tear film and ocular surface in a mouse model of experimental dry eye (EDE).

Eye drops consisting of 0.1% HA alone or mixed with 0.1%, 0.5%, or 5.0% MO were applied to desiccating stress-induced murine dry eyes. Tear volume, corneal irregularity score, tear film break-up time (TBUT), and corneal fluorescein staining scores were measured at 5 and 10 days after treatment. Ten days after treatment, goblet cells in the conjunctiva were counted after Periodic acid-Schiff staining.

There was no significant difference in the tear volume between desiccating stress-induced groups. The corneal irregularity score was lower in the 0.5% MO group compared with the EDE and HA groups. The 0.5% and 5.0% MO groups showed a significant improvement in TBUT compared with the EDE group. Mice treated with 0.1% and 0.5% MO mixture eye drops showed a significant improvement in fluorescein staining scores compared with the EDE group and the HA group. The conjunctival goblet cell count was higher in the 0.5% MO group compared with the EDE group and HA group.

The MO and HA mixture eye drops had a beneficial effect on the tear films and ocular surface of murine dry eye. The application of 0.5% MO and 0.1% HA mixture eye drops could improve corneal irregularity, the corneal fluorescein staining score, and conjunctival goblet cell count compared with 0.1% HA eye drops in the treatment of EDE [5].

Treatments for dry eye disease in increasing order of severity include artificial tears, anti-inflammatory agents, immunosuppressants, punctal plugs, serum eye drops, contact lenses, and surgery [6,7]. We developed low-concentration homogenized castor oil eye drops for the treatment of patients with noninflamed obstructive meibomian gland dysfunction (MGD), a major cause of lipid-deficiency dry eye, and assessed the safety, stability, and efficacy of the eye drops.

Randomized, double-masked, placebo-controlled crossover clinical trial. Forty eyes of 20 patients with non-inflamed MGD. After a preliminary study of eye drops containing castor oil, 2% castor oil and 5% polyoxyethylene castor oil (emulsifier) were mixed to formulate homogenized oil eye drops. The patients were assigned randomly to receive oil eye drops or placebo six times daily for 2 periods of 2 weeks each.

At the end of each treatment period, we assessed symptoms, tear interference grade, tear evaporation, fluorescein and rose bengal scores, tear break-up time (BUT), and meibomian gland orifice obstruction. Safety and stability tests were also performed.

Symptom scores, tear interference grade, tear evaporation test results, rose bengal scores, tear BUT, and orifice obstruction scores after the oil eye drop period showed significant improvement compared with the results after the placebo period. No complications attributable to the eye drops were observed. The oil eye drops were stable when stored at 4 degrees C.

The results indicate that castor oil eye drops are effective and safe in the treatment of MGD. The possible mechanisms of this treatment are improvement of tear stability as a result of lipid spreading, ease of meibum expression, prevention of tear evaporation, and the lubricating effect of the oil eye drops [8].

Aqueous eye-drop solutions are still the most common formulations for topical ocular drug delivery, since they are the simplest, easiest and cheapest ocular dosage forms to produce. The main drawbacks of these conventional ocular dosage forms are that they are rapidly eliminated from the ocular surface following instillation, resulting in a low ocular bioavailability (less than 1%) of the drugs, and are limited to water soluble compounds. Variants with viscosifying agents, penetration enhancers or spreading surfactants have not fundamentally changed the paradigm. Suspensions, gels and negatively charged oil-in-water (o/w) nano emulsions were developed to improve ocular bioavailability of lipophilic or poorly water soluble drugs. Among them, o/w nanoemulsions were demonstrated to be effective ocular drug delivery vehicles [9-14].

Cyclosporine administration is very effective in the case of immunological diseases of the cornea, conjunctive or uvea. Moreover, it is widely used in the case of high-risk rejection corneal transplantation. Cyclosporine 2% eye drops are prepared following a particular formulation including one part commercially available cyclosporine oral solution (Sandimmun) diluted in four parts of sterile castor oil. Manufacturing procedures maintain the sterile state of the preparation with a laminar airflow hood placed in a particulate controlled room, with pharmacists, technicians and clerical personnel wearing sterile clothes. Physical and chemical monitoring during and after manufacture for each batch guarantees the process and minimizes the risk of batch rejection. Chemical analysis of cyclosporine is conducted using a validated stability-indicating high-performance liquid chromatographic assay (reverse-phase). Blood dosages taken after the first administration at the 24th hour (after administration of the 6th drop) check for systemic integration.

Cyclosporine 2% eye drops are fairly stable: 12 months after manufacturing, concentrations result in levels not statistically different from concentrations measured the day of preparation. After a daily regimen of six drops in the eye, cyclosporine 2% eye drops have a very low systemic bioavailability, because the blood concentrations only reach the detection limit of the fluorescence polarization immunoassay used for cyclosporine drug monitoring. This explains the absence of systemic toxicity.

Cyclosporine 2% eye drops can be available in the hospital pharmacy. The eye drops are stable at room temperature and can be delivered up to 12 months after manufacture. No local adverse effects have been noted, probably in relation with the very low concentration of ethanol in the ocular preparation [15].

To evaluate and compare the efficacy of a lipid-based lubricant eye drop formulation (hydroxypropyl guar/propylene glycol/phospholipid [HPG/PG/PL]) with preservative-free saline for the treatment of dry eye. This was a prospective, multicenter, randomized, single-masked, parallel-group phase 4 clinical study. Patients ≥ 18 years diagnosed with dry eye received 1 drop of saline 4 times daily (QID) for 15 days during a run-in phase, followed by randomization. Patients then instilled HPG/PG/PL or saline QID through day 35 and as needed through day 90. Change in tear film break-up time (TFBUT), change in total ocular surface staining (TOSS) score, and Impact of Dry Eye on Everyday Life (IDEEL) were evaluated on day 35.

Increase in TFBUT from baseline to day 35 was assessed during the interim and final analyses. Mean±SE difference between the HPG/PG/PL (n=110) and saline groups (n=100) was 1.3±0.4 seconds (interim analysis; 95% confidence interval [CI] 0.5-2.1 seconds; p=0.0012) and 1.0±0.3 seconds (final analysis; 95% CI 0.4-1.6 seconds; p=0.0011), demonstrating the superiority of HPG/PG/PL. The mean±SE difference between the HPG/PG/PL and saline groups for IDEEL treatment effectiveness scores was 16.0±3.6 (95% CI 8.9-23.1; p<0.0001). No significant differences in TOSS scores or IDEEL inconvenience scores were observed between treatment groups.

Thirty-five days of QID HPG/PG/PL treatment resulted in a statistically significant improvement in TFBUT and IDEEL treatment effectiveness scores compared with saline but not in TOSS or IDEEL treatment inconvenience scores. HPG/PG/PL was well-tolerated by patients [16].

The corneal-protective effects of an artificial tear containing sodium hyaluronate (SH) and castor oil (CO) were evaluated on a porcine short-term dry eye model. Fresh porcine eyes with an intact cornea were treated with an artificial tear of saline, SH solution (0.1%, 0.5% or 1%), CO solution (0.5%, 1% or 5%) or a mixture solution containing 0.5% SH and 1% CO and then desiccated for 60, 90 or 180 min. To assess corneal damage, the eyes were stained with methylene blue (MB) or lissamine green (LG). The staining score of MB, absorbance of MB extracted from the cornea and staining density of LG increased significantly with increasing desiccation time in untreated and all artificial tear-treated eyes, although there were no significant differences in staining scores and absorbance of MB between eyes treated continuously with saline and 1% SH-treated ones at 60 and 90 min of desiccation or the mixture-treated eyes at 60 min of desiccation. No significant differences in the staining

density of LG were also found between continuous saline-treated eyes and ones desiccated for 60 min and treated with 1% SH and the mixture. Mild cytoplasmic vacuolations were histopathologically observed in the basal and wing cells in eyes desiccated for 60 min and treated with 1% SH and the mixture. The mixture solution containing 0.5% SH and 1% CO has protective effects against corneal desiccation similar to those of 1% SH and would be helpful as an artificial tear [17].

To investigate the efficacy of the topical application of omega-3 essential fatty acids (EFAs) and hyaluronic acid (HA) mixtures in a mouse model of experimental dry eye (EDE).

Eye drops consisting of 0.1% HA, 0.02%, or 0.2% omega-3 EFAs alone and mixture of 0.02%, or 0.2% omega-3 EFAs and 0.1% HA were applied in desiccating stress-induced murine dry eye. Corneal irregularity scores and fluorescein staining scores were measured 5 and 10 days after treatment. Levels of interleukin (IL)-1β, -17, and interferon gamma-induced protein (IP)-10 were measured in the conjunctiva at 10 days using a multiplex immuno bead assay. The concentrations of hexanoyl-lys (HEL) and 4-hydroxynonenal (4-HNE) in conjunctiva tissue were measured with enzyme-linked immunosorbent assays.

Mice treated with the mixture containing 0.2% omega-3 EFAs showed a significant improvement in corneal irregularity scores and corneal fluorescein staining scores compared with EDE, HA, 0.02% or 0.2% omega-3 EFAs alone, and 0.02% omega-3 EFAs mixture-treated mice. A significant decrease in the levels of IL-1β, -17, and IP-10 were observed in the 0.2% EFAs mixture-treated group, compared with the other groups. In the mice treated with the mixture containing 0.2% omega-3 EFAs, the concentration of 4-HNE was also lower than the other groups. Although 0.2% omega-3 EFAs alone group also had a significant improvement in corneal irregularity scores and IL-17, IL-10, and 4 HNE levels compared with the other groups, the efficacy was lower than 0.2% omega-3 mixture group.

Topically applied eye drops containing a mixture of omega-3 EFAs and HA could improve corneal irregularity and corneal epithelial barrier disruption, and decrease inflammatory cytokines and oxidative stress markers on the ocular surface. Topical omega-3 EFAs and HA mixture may have a greater therapeutic effect on clinical signs and inflammation of dry eye compared with HA artificial tears [18].

To study the efficacy of topical application of alpha-linolenic acid (ALA) and linoleic acid (LA) for dry eye treatment.

Formulations containing ALA, LA, combined ALA and LA, or vehicle alone, were applied to dry eyes induced in mice. Corneal fluorescein staining and the number and maturation of corneal CD11b(+) cells were determined by a masked observer in the different treatment groups. Real-time polymerase chain reaction was used to quantify expression of inflammatory cytokines in the cornea and conjunctiva.

Dry eye induction significantly increased corneal fluorescein staining; CD11b(+) cell number and major histocompatibility complex Class II expression; corneal IL-1alpha and tumor necrosis factor alpha (TNF-alpha) expression; and conjunctival IL-1alpha, TNF-alpha, interferon gamma, IL-2, IL-6, and IL-10 expression. Treatment with ALA significantly decreased corneal fluorescein staining compared with both vehicle and untreated controls. Additionally, ALA treatment was associated with a significant decrease in CD11b(+) cell number, expression of corneal IL-1alpha and TNF-alpha, and conjunctival TNF-alpha.

Topical ALA treatment led to a significant decrease in dry eye signs and inflammatory changes at both cellular and molecular levels.

Topical application of ALA omega-3 fatty acid may be a novel therapy to treat the clinical signs and inflammatory changes accompanying dry eye syndrome [19].

The purpose of this study was to investigate the self-micro emulsifying drug delivery systems (SMEDDS) for ophthalmic delivery of Prednisolone (PDN) to treat uveitis.

The pseudo-ternary phase diagrams were developed, and various SMEDDS were prepared using Linoleic acid as oil, Cremophore RH 40 as a surfactant, and propylene glycol as a co-surfactant. Physicochemical parameters (globule size, zeta potential, viscosity, and pH) and *in vitro* release of SMEDDS were studied. The *in vivo* efficacy of prepared formulations and the marketed drug solution was studied by administering them topically to an endotoxin-induced uveitis rabbit model.

All formulations displayed an average globule size less than 100 nm. The developed SMEDDS exhibited acceptable physicochemical behavior and displayed sustained drug release. *In vivo* studies in a rabbit eye showed a marked improvement in the anti-inflammatory activity of developed formulation compared with a marketed formulation in a uveitis-induced rabbit eye model.

The developed SMEDDS are a feasible option to conventional eye drops for its capability to improve bioavailability *via* its longer precorneal residence time and its capacity to sustain the release of the drug [20].

Eye Drops for Cataract Treatment

Cataract is the leading cause of world blindness. The only available treatment for cataract is surgery. Surgery requires highly-trained individuals with expensive operating facilities. Where these are not available, patients go untreated. A form of treatment that did not involve surgery would be a useful alternative for people with symptomatic cataract who are unable or unwilling to undergo surgery. If an eye drop existed that could reverse or even prevent progression of cataract, then this would be a useful additional treatment option. Cataract tends to result from oxidative stress. The protein, L-carnosine, is known to have an antioxidant effect on the cataractous lens, so biochemically there is sound logic for exploring L-carnosine as an agent to reverse or even prevent progression of cataract. When applied as an eye drop, L-carnosine cannot penetrate the eye. However,

when applied to the surface of the eye, N-acetylcarnosine (NAC) penetrates the cornea into the front chamber of the eye (near to where the cataract is), where it is metabolised into L-carnosine. Hence, it is possible that use of NAC eye drops may reverse or even prevent progression of cataract, thereby improving vision and quality of life.

To assess the effectiveness of NAC drops to prevent or reverse the progression of cataract.

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2016), Embase (January 1980 to June 2016), Allied and Complementary Medicine Database (AMED) (January 1985 to June 2016), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to June 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 June 2016. We hand searched the American Society of Cataract and Refractive Surgery (ASCRS) and the European Society of Cataract and Refractive Surgeons (ESCRS) meetings from 2005 until September 2015.

We planned to include randomized or quasi-randomised controlled trials where NAC was compared to control in people with age-related cataract. We used standard methodological procedures expected by Cochrane. We identified two potentially eligible studies from Russia and the United States. One study was split into two arms: the first arm ran for six months, with two-monthly follow-up; the second arm ran for two years with six-monthly follow-up. The other study ran for four months with a data collection point at the start and end of the study only. A total of 114 people were enrolled in these studies. The ages ranged from 55 to 80 years. We were unable to obtain sufficient information to reliably determine how both these studies were designed and conducted. We have contacted the author of these studies, but have not yet received a reply. Therefore, these studies are assigned as 'awaiting classification' in the review until sufficient information can be obtained from the authors.

There is currently no convincing evidence that NAC reverses cataract, nor prevents progression of cataract (defined as a change in cataract appearance either for the better or for the worse). Future studies should be randomized, double-masked, placebo-controlled trials with standardised quality of life outcomes and validated outcome measures in terms of visual acuity, contrast sensitivity and glare, and large enough to detect adverse effects [21].

Visual impairment broadly impacts the ability of affected people to maintain their function and to remain independent during their daily occupations as they grow older. Visual impairment affects survival of older patients, quality of life, can affect a person's self-ranking of health, may be associated with social and functional decline, use of community support services, depression, falls, nursing home placement, and increased mortality. It has been hypothesized that senile cataract may serve as a marker for generalised tissue aging, since structural changes occurring in the proteins of the lens during cataract formation are similar to those which occur elsewhere as part of the aging process. The published analysis revealed a strong age-dependent relationship between undergoing cataract surgery and subsequent mortality.

Nuclear opacity, particularly severe nuclear opacity, and mixed opacities with nuclear were significant predictors of mortality independent of body mass index, comorbid conditions, smoking, age, race, and sex. The lens opacity status is considered as an independent predictor of 2-year mortality, an association that could not be explained by potential confounders. Telomeres have become important biomarkers for aging as well as for oxidative stress-related disease. The lens epithelium is especially vulnerable to oxidative stress. Oxidative damage to the cuboidal epithelial cells on the anterior surface of the lens mediated by reactive oxygen species and phospholipid hydro peroxides can precede and contribute to human lens cataract formation. The erosion and shortening of telomeres in human lens epithelial cells in the lack of telomerase activity has been recognized as a primary cause of premature lens senescence phenotype that trigger human cataractogenesis.

In this study we aimed to be focused on research defining the mechanisms that underlie linkages among telomere attrition in human lens epithelial cells associated with oxidative stress, biology of the lens response to oxidative damages, aging and health, cataract versus neuroendocrine regulation and disease. The cumulative results demonstrate that carnosine, released ophthalmically from the patented 1% N-acetylcarnosine prodrug lubricant eye drops, at physiological concentration might remarkably reduce the rate of telomere shortening in the lens cells subjected to oxidative stress in the lack of efficient antioxidant lens protection. Carnosine promotes the protection of normal cells from acquiring phenotypic characteristics of cellular senescence. The data of visual functions (visual acuity, glare sensitivity) in older adult subjects and older subjects with cataract treated with 1% N-acetylcarnosine lubricant eye drops showed significant improvement as compared, by contrast with the control group which showed generally no improvement in visual functions, with no difference from baseline in visual acuity and glare sensitivity readings.

N-acetylcarnosine derived from the lubricant eye drops may be transported into the hypothalamic tuberomammillary nucleus (TMN) histamine neurons and gradually hydrolyzed. The resulting L-histidine may subsequently be converted into histamine, which could be responsible for the effects of carnosine on neurotransmission and hormone-like anti-aging and anti-cataract physiological function.

The research utilizing the N-acetylcarnosine lubricant eye drops powerful therapeutic platform provides the findings related to the intraocular uptake exposure sources as well as a timing dosage and duration systemic

absorption of said preparation from the conjunctional sac reaching the hypothalamus with activities transfer into the hypothalamic-neuroendocrine pathways affecting across the hypothalamus metabolic pathway the telomere biology and cataract disease occurrence, reversal and prevention and the average expected lifespan of an individual. Such findings can be translated into clinical practice and may provide a basis for personalized cataract disease and aging prevention and treatment approaches [22].

Cataracts in small animals are shown to be at least partially caused by oxidative damage to lens epithelial cells (LECs) and the internal lens; biomarkers of oxidative stress in the lens are considered as general biomarkers for life expectancy in the canine and other animals. Telomeres lengths and expressed telomerase activity in canine LECs may serve as important monitors of oxidative damage in normal LECs with documented higher levels of telomerase activity in cataractous LECs during cells' lifespan. Loss of functional telomere length below a critical threshold in LECs of canines during the effect of UV and chronic oxidative stress or metabolic failure, can activate programs leading to LEC senescence or death. Telomerase is induced in LECs of canines at critical stages of cataractogenesis initiation and exposure to oxidative stress through the involvement of catalytically active pro oxidant transition metal (iron) ions. This work documents that transition metal ions (such as, ferrous ions- catalytic oxidants) might induce premature senescence in LECs of canines, telomere shortening with increased telomerase activity as adaptive response to UV light, oxidative and metabolic stresses. The therapeutic treatment with 1% N-acetylcarnosine (NAC) pro drug delivery is beneficial for prevention and dissolution of ripe cataracts in canines. This biological activity is based on the findings of ferroxidase activity pertinent to the dipeptide carnosine released ophthalmically from NAC pro drug of L-carnosine, stabilizing properties of carnosine on biological membranes based on the ability of the imidazole-containing dipeptides to interact with lipid peroxidation products and reactive oxygen species (ROS), to prevent membrane damage and dilute the associated with membrane fragments protein aggregates. The advent of therapeutic treatment of cataracts in canines with N-acetylcarnosine lubricant eye drops through targeting the prevention of loss of functional telomere length below a critical threshold and "flirting" with an indirect effect with telomerase expression in LECs of canines during the effects of UV, chronic oxidative stress increases the successful rate of cataract management challenges in home veterinary care [23].

Antioxidant supplements have been suggested as a strategy to decrease the risk of age-related cataract, but there is no evidence that antioxidants can reduce the signs of the disease. Recently, we showed that the mitochondrial antioxidant SkQ1 can partially reverse cataract signs in senescence-accelerated OXYS rats. The aim of the present study was the histomorphological examination of the influence of SkQ1 eye drops on the cataract development in OXYS rats. OXYS rats received SkQ1 eye drops (250 nM) from 9 to 12 months of age.

Ophthalmoscopic examination was carried out before and after treatment. Light and electron microscopy were used for histomorphological examination. Expression of the Cryaa and Cryab genes was determined using real-time PCR. αB-crystallin expression was detected using Western blotting.

SkQ1 completely prevented the cataract development in OXYS rats, and in some of the animals diminished the signs of the disease. Light and electron microscopy showed that SkQ1 attenuated the (typical for cataract) alterations in the lens capsule and epithelial cells, ameliorated disturbances of the hexagonal packing geometry of lens fibers, and improved ultrastructure of the epithelial cells. The levels of mRNA of α-crystallins genes which encode small heat shock proteins αA- and αB-crystallin that play a central role in maintaining lens transparency were significantly lower in the OXYS rats' lenses than in Wistar rats (control). SkQ1 normalized the level of mRNA of Cryaa, and significantly increased the level of Cryab mRNA as well as αB-crystallin protein in the lens of OXYS rats to the level of the control Wistar rats.SkQ1 eye drops hold promise as a treatment of cataract [24].

The search for anti-cataract drugs has been continuing for decades; some treatments no longer exist but antioxidants are still of much interest. The primary function of the human lens, along with the cornea, is to refract light so that it is correctly focused onto the retina for optimum image quality. With age, the human lens undergoes morphological, biochemical and physical changes leading to opacification. Age-related or senile cataract is one of the main causes of visual impairment in the elderly; given the lack of access to surgical treatment in many parts of the world, cataract remains a major cause of sight loss. Surgical treatment is the only means of treating cataract; this approach, however, has limitations and complications [25].

Cataract Mitochondria

The aging eye appears to be at considerable risk from oxidative stress. A great deal of research indicates that dysfunctional mitochondria are the primary site of reactive oxygen species (ROS). More than 95% of O2 produced during normal metabolism is generated by the electron transport chain in the inner mitochondrial membrane. Mitochondria are also the major target of ROS. Cataract formation, the opacification of the eye lens, is one of the leading causes of human blindness worldwide, accounting for 47.8% of all causes of blindness. Cataracts result from the deposition of aggregated proteins in the eye lens and lens fiber cell plasma membrane damage, which causes clouding of the lens, light scattering, and obstruction of vision. ROS-induced damage in the lens cell may consist of oxidation of proteins, DNA damage, and/or lipid peroxidation, all of which have been implicated in cataractogenesis. This study is an attempt to integrate how mitochondrial ROS are altered in the aging eye along with those protective and repair therapeutic systems believed to regulate ROS levels in ocular tissues and how damage to these systems contributes to age-onset eye disease and cataract formation. Mitochondria-targeted antioxidants might be used to effectively prevent ROS-induced oxidation of lipids and proteins in the

inner mitochondrial membrane *in vivo*. As a result of the combination of weak metal chelating, OH and lipid peroxyl radicals scavenging, reducing activities to liberated fatty acid, and phospholipid hydroperoxides, carnosine and carcinine appear to be physiological antioxidants able to efficiently protect the lipid phase of biologic membranes and aqueous environments and act as the anti-apoptotic natural drug compounds The new ophthalmic compositions, including N-acetylcarnosine, acting as a pro drug of naturally targeted to mitochondria L-carnosine endowed with pluripotent antioxidant activities combined with mitochondria-targeted rechargeable antioxidant (either MitoVit E, Mito Q, or SkQs) as a potent medicine to treat ocular diseases. Such specificity is explained by the fact that developed compositions might be used to effectively prevent ROS-induced oxidation of lipids and proteins in the inner mitochondrial membrane *in vivo* and outside mitochondria in the cellular and tissue structures of the lens and eye compartments. Mitochondrial targeting of compounds with universal types of antioxidant activity represents a promising approach for treating a number of ROS-related ocular diseases of the aging eye and can be implicated in the management of cataracts [26].

Age-related cataract is associated with oxidative stress and death of lens epithelial cells (LECs) whose survival is dependent on functional mitochondrial populations. Oxidative stress-induced depolarization/damage of LEC mitochondria results in increased reactive oxygen species (ROS) levels and cell death suggesting the need for a LEC mechanism to remove mitochondria depolarized/damaged upon oxidative stress exposure to prevent ROS release and LEC death. To date, a mechanism(s) for removal of depolarized/damaged LEC mitochondria has yet to be identified and the importance of eliminating oxidative stress-damaged mitochondria to prevent LEC ROS release and death has not been established. Here, we demonstrate that Parkin levels increase in LECs exposed to H2O2-oxidative stress. We establish that Parkin translocates to LEC mitochondria depolarized upon oxidative stress exposure and that Parkin recruits p62/SQSTM1 to depolarized LEC mitochondria. We demonstrate that translocation of Parkin results in the elimination of depolarized/damaged mitochondria and that Parkin clearance of LEC mitochondria is dependent on its ubiquitin ligase activity. Importantly, we demonstrate that Parkin elimination of damaged LEC mitochondria results in reduced ROS levels and increased survival upon oxidative stress exposure. These results establish that Parkin functions to eliminate LEC mitochondria depolarized/damaged upon oxidative stress exposure and that elimination of damaged mitochondria by Parkin is important for LEC homeostasis and survival. The data also suggest that mitochondrial quality control by Parkin could play a role in lens transparency [27].

Cataract is the leading cause of irreversible blindness worldwide. Increasing evidence indicates that oxidative stress is an important risk factor contributing to the development of cataract. Moreover, the enhancement of the antioxidant defense system may be beneficial to prevent or delay the cataractogenesis. The term oxidative stress has been defined as a disturbance in the equilibrium status of oxidant/antioxidant systems with progressive accumulation of reactive oxygen species (ROS) in intact cells. Superfluous ROS can damage proteins, lipids, polysaccharides, and nucleic acids within ocular tissues that are closely correlated with cataract formation. Therefore, prevention of oxidative stress damage by antioxidants might be considered as a viable means of medically offsetting the progression of this vision-impairing disease. Molecular hydrogen has recently been verified to have protective and therapeutic value as an antioxidant through its ability to selectively reduce cytotoxic ROS such as hydroxyl radical (OH). Hitherto, hydrogen has been used as a therapeutic element against multiple pathologies in both animal models and human patients. Unlike most well-known antioxidants, which are unable to successfully target organelles, hydrogen has advantageous distribution characteristics enabling it to penetrate bio membranes and diffuse into the cytosol, mitochondria, and nucleus. Consequently, we speculate that hydrogen might be an effective antioxidant to protect against lens damage, and it is important to further explore the biological mechanism underlying its potential therapeutic effects [28].

Senile cataract is a clouding of the lens in the aging eye leading to a decrease in vision. Symptoms may include faded colors, blurry vision, halos around light, trouble with bright lights, and trouble seeing at night. This may result in trouble driving, reading, or recognizing faces. Cataracts are the cause of half of blindness and 33% of visual impairment worldwide. Cataracts result from the deposition of aggregated proteins in the eye lens and lens fiber cells plasma membrane damage which causes clouding of the lens, light scattering, and obstruction of vision. ROS induced damage in the lens cell may consist of oxidation of proteins, DNA damage and/or lipid peroxidation, all of which have been implicated in cataractogenesis. The inner eye pressure (also called intraocular pressure or IOP) rises because the correct amount of fluid can't drain out of the eye. With primary open-angle glaucoma, the entrances to the drainage canals are clear and should be working correctly. The clogging problem occurs further inside the drainage canals, similar to a clogged pipe below the drain in a sink. The excessive oxidative damage is a major factor of the ocular diseases because the mitochondrial respiratory chain in mitochondria of the vital cells is a significant source of the damaging reactive oxygen species superoxide and hydrogen peroxide. However, despite the clinical importance of mitochondrial oxidative damage, antioxidants have been of limited therapeutic success. This may be because the antioxidants are not selectively taken up by mitochondria, but instead are dispersed throughout the body, ocular tissues and fluids' moieties. This work is an attempt to integrate how mitochondrial reactive oxygen species (ROS) are altered in the aging eye, along with those protective and repair therapeutic systems believed to regulate ROS levels in ocular tissues and how damage to these systems contributes to age-onset eye disease and cataract formation. Mitochondria-targeted antioxidants might be used to effectively prevent ROS-induced oxidation of lipids and proteins in the inner mitochondrial membrane *in vivo* [29].

The aging eye appears to be at considerable risk from oxidative stress. Lipid peroxidation (LPO) is one of the

mechanisms of cataractogenesis, initiated by enhanced promotion of oxygen free radicals in the eye fluids and tissues and impaired enzymatic and non-enzymatic antioxidant defenses of the crystalline lens. The present study proposes that mitochondria are one of the major sources of reactive oxygen species (ROS) in mammalian and human lens epithelial cells and that therapies that protect mitochondria in lens epithelial cells from damage and reduce damaging ROS generation may potentially ameliorate the effects of free radical-induced oxidation that occur in aging ocular tissues and in human cataract diseases. It has been found that rather than complete removal of oxidants by the high levels of protective enzyme activities such as superoxide dismutase (SOD), catalase, lipid peroxidases in transparent lenses, the lens conversely, possess a balance between per oxidants and antioxidants in a way that normal lens tends to generate oxidants diffusing from lenticular tissues, shifting the redox status of the lens to become more oxidizing during both morphogenesis and aging. Release of the oxidants (O(2)(-)·, H(2)O(2) , OH·, and lipid hydroperoxides) by the intact lenses in the absence of respiratory inhibitors indicates that these metabolites are normal physiological products inversely related to the lens life-span potential (maturity of cataract) generated through the metal-ion catalyzed redox-coupled pro-oxidant activation of the lens reductants (ascorbic acid, glutathione). The membrane-bound phospholipid (PL) hydroperoxides escape detoxification by the lens enzymatic reduction. The lens cells containing these species would be vulnerable to peroxidative attack which trigger the PL hydroperoxide-dependent chain propagation of LPO and other damages in membrane (lipid and protein alterations). The increased concentrations of primary LPO products (diene conjugates, lipid hydroperoxides) and end fluorescent LPO products were detected in the lipid moiety of the aqueous humor samples obtained from patients with cataract as compared to normal donors. Since LPO is clinically important in many of the pathological effects and aging, new therapeutic modalities, such as N-acetylcarnosine pro drug lubricant eye drops, should treat the incessant infliction of damage to the lens cells and biomolecules by reactive lipid peroxides and oxygen species and “refashion” the affected lens membranes in the lack of important metabolic detoxification of PL peroxides. Combined in ophthalmic formulations with N-acetylcarnosine, mitochondria-targeted antioxidants are promising to become investigated as a potential tool for treating a number of ROS-related ocular diseases, including human cataracts [30].

Antioxidants specifically addressed to mitochondria have been studied to determine if they can decelerate senescence of organisms. For this purpose, a project has been established with participation of several research groups from Russia and some other countries. A new type of compounds (SkQs) comprising plastoquinone (an antioxidant moiety), a penetrating cation, and a decane or pentane linker has been synthesized. Using planar bilayer phospholipid membrane (BLM), we selected SkQ derivatives with the highest permeability, namely plastoquinonyl-decyl-triphenylphosphonium (SkQ1), plastoquinonyl-decyl-rhodamine 19 (SkQR1), and methylplastoquinonyldecyltriphenylphosphonium (SkQ3). Anti- and prooxidant properties of these substances and also of ubiquinonyl-decyl-triphenylphosphonium (MitoQ) were tested in aqueous solution, detergent micelles, liposomes, BLM, isolated mitochondria, and cell cultures.

In mitochondria, micromolar cationic quinone derivatives were found to be prooxidants, but at lower (sub-micromolar) concentrations they displayed antioxidant activity that decreases in the series SkQ1=SkQR1>SkQ3>MitoQ. SkQ1 was reduced by mitochondrial respiratory chain, i.e. it is a rechargeable antioxidant. Nanomolar SkQ1 specifically prevented oxidation of mitochondrial cardiolipin. In cell cultures, SkQR1, a fluorescent SkQ derivative, stained only one type of organelles, namely mitochondria. Extremely low concentrations of SkQ1 or SkQR1 arrested H(2)O(2)-induced apoptosis in human fibroblasts and HeLa cells. Higher concentrations of SkQ are required to block necrosis initiated by reactive oxygen species (ROS). In the fungus Podospora anserina, the crustacean Ceriodaphnia affinis, Drosophila, and mice, SkQ1 prolonged lifespan, being especially effective at early and middle stages of aging. In mammals, the effect of SkQs on aging was accompanied by inhibition of development of such age-related diseases and traits as cataract, retinopathy, glaucoma, balding, canities, osteoporosis, involution of the thymus, hypothermia, torpor, peroxidation of lipids and proteins, etc. SkQ1 manifested a strong therapeutic action on some already pronounced retinopathies, in particular, congenital retinal dysplasia. With drops containing 250 nM SkQ1, vision was restored to 67 of 89 animals (dogs, cats, and horses) that became blind because of a retinopathy. Instillation of SkQ1-containing drops prevented the loss of sight in rabbits with experimental uveitis and restored vision to animals that had already become blind. A favorable effect of the same drops was also achieved in experimental glaucoma in rabbits. Moreover, the SkQ1 pretreatment of rats significantly decreased the H(2) O(2) or ischemia-induced arrhythmia of the isolated heart. SkQs strongly reduced the damaged area in myocardial infarction or stroke and prevented the death of animals from kidney ischemia. In p53(-/-) mice, 5 nmol/kgxday SkQ1 decreased the ROS level in the spleen and inhibited appearance of lymphomas to the same degree as million-fold higher concentration of conventional antioxidant NAC. Thus, SkQs look promising as potential tools for treatment of senescence and age-related diseases [31].

Intralipid for Cataract Mitochondria

Objective Glucocorticoids (GCs) can induce oxidative damage in skeletal muscles. The purpose of this study was to demonstrate a high caloric (HC) diet rich in soy oil would change the oxidative stress induced by a GC. The effect of dexamethasone (DEX) and HC diet on oxidative stress in plasma, skeletal muscles (M. pectoralis major, PM; M. biceps femoris, BF), and mitochondria were determined. The biomarkers of oxidative damage and antioxidative enzyme activity were determined. The fatty acid profile of muscles and the activities of complex I and II in mitochondria were measured. The results showed that DEX increased the

concentrations of oxidative damage markers in plasma, muscles, and mitochondria. The activity of complex I was significantly suppressed by DEX. DEX-chickens had higher proportions of polyunsaturated fatty acids and lower proportions of monounsaturated fatty acids in the PM. A HC diet decreased the levels of oxidative damage biomarkers in plasma, muscles, and mitochondria. The interaction between DEX and diet suppressed the activities of complex I and II in HC-chickens. Oxidative damage in skeletal muscles and mitochondria was the result of GC-induced suppression of the activity of mitochondrial complex I. A HC diet improved the antioxidative capacity and reduced the oxidative damage induced by the GC [32].

Mitochondriopathies (MCPs) are either due to sporadic or inherited mutations in nuclear or mitochondrial DNA located genes (primary MCPs), or due to exogenous factors (secondary MCPs). MCPs usually show a chronic, slowly progressive course and present with multi organ involvement with varying onset between birth and late adulthood. Although several proteins with signalling, assembling, transport, enzymatic function can be impaired in MCP, most frequently the activity of the respiratory chain (RC) protein complexes is primarily or secondarily affected, leading to impaired oxygen utilization and reduced energy production. MCPs represent a diagnostic challenge because of their wide variation in presentation and course. Systems frequently affected in MCP are the peripheral nervous system (myopathy, polyneuropathy, lactacidosis), brain (leucencephalopathy, calcifications, stroke-like episodes, atrophy with dementia, epilepsy, upper motor neuron signs, ataxia, extrapyramidal manifestations, fatigue), endocrinium (short stature, hyperhidrosis, diabetes, hyperlipidaemia, hypogonadism, amenorrhoea, delayed puberty), heart (impulse generation or conduction defects, cardiomyopathy, left ventricular non-compaction heart failure), eyes (cataract, glaucoma, pigmentary retinopathy, optic atrophy), ears (deafness, tinnitus, peripheral vertigo), guts (dysphagia, vomiting, diarrhoea, hepatopathy, pseudo-obstruction, pancreatitis, pancreas insufficiency), kidney (renal failure, cysts) and bone marrow (sideroblastic anaemia). Apart from well-recognized syndromes, MCP should be considered in any patient with unexplained progressive multisystem disorder. Although there is actually no specific therapy and cure for MCP, many secondary problems require specific treatment. The rapidly increasing understanding of the pathophysiological background of MCPs may further facilitate the diagnostic approach and open perspectives to future, possibly causative therapies [33].

Lenses from young and old mice were analyzed by laser scanning confocal microscopy (LSCM) with vital dyes, to determine whether age-related sub capsular and cortical cataracts were linked to the failure of lens fiber cells to degrade nuclei, DNA, and mitochondria properly and whether they result in the overproduction of reactive oxygen species (ROS) at the same sites.

As opposed to the clear DNA-free sub capsular and cortical areas of young adult mouse lenses, these areas in cataractous old mouse lenses were found to contain accumulations of nuclei, nuclear fragments, aggregated mitochondria, and amorphous DNA as cortical inclusions ($P<0.001$ between young and old lenses). These inclusions correlated spatially with age-related cataracts and with the presence of ROS. The source of such undegraded material was a large expansion of transition nuclei in the bow region and also direct involution of surface lens epithelial cells (LECs) into the underlying cortex, frequently leaving bare patches devoid of nuclei on the surface of the anterior epithelium.

Live lenses were stained vitally for DNA with Hoechst 33342. ROS and mitochondria were stained and quantified with dihydrorhodamine 123 (DHR). In fixed lenses, DNA was stained with propidium iodide (PI) or 4',6-diamidino-2-phenylindole, dihydrochloride (DAPI). The intensity and position of each probe's fluorescence was determined by LSCM. Cataract localization was ascertained by digitalized microscopy of reflected light.

In aged mice, most subcapsular and cortical cataracts colocalize with accumulations of nuclei, mitochondria, and DNA, These effects are accompanied at the same sites by the production of ROS. The condition is due to the failure of lens fiber cells in the bow region to differentiate properly into the clear fiber state and to the improper involution of cells from the anterior epithelium directly into the underlying cortex, resulting in cataractous opacities [34].

Mitochondria are critical for ocular function as they represent the major source of a cell's supply of energy and play an important role in cell differentiation and survival. Mitochondrial dysfunction can occur as a result of inherited mitochondrial mutations (e.g. Leber's hereditary optic neuropathy and chronic progressive external ophthalmoplegia) or stochastic oxidative damage which leads to cumulative mitochondrial damage and is an important factor in age-related disorders (e.g. age-related macular degeneration, cataract and diabetic retinopathy). Mitochondrial DNA (mtDNA) instability is an important factor in mitochondrial impairment culminating in age-related changes and pathology, and in all regions of the eye mtDNA damage is increased as a consequence of aging and age-related disease. It is now apparent that the mitochondrial genome is a weak link in the defenses of ocular cells since it is susceptible to oxidative damage and it lacks some of the systems that protect the nuclear genome, such as nucleotide excision repair. Accumulation of mitochondrial mutations leads to cellular dysfunction and increased susceptibility to adverse events which contribute to the pathogenesis of numerous sporadic and chronic disorders in the eye [35].

Cataract Mitochondria Aging

Mitochondria were first postulated to contribute to aging more than 40 years ago. During the following decades, multiple lines of evidence in model organisms and humans showed that impaired mitochondrial function can contribute to age-associated disease phenotypes and aging. However, in contrast to the original theory favoring oxidative damage as a cause for mtDNA mutations, there are now strong data arguing that most mammalian mtDNA mutations originate as replication errors made by the mtDNA polymerase.

Currently, a substantial amount of mitochondrial research is focused on finding ways to either remove or counteract the effects of mtDNA mutations with the hope of extending the human health- and lifespan [36].

Oxidative stress occurs when the level of pro oxidants exceeds the level of antioxidants in cells resulting in oxidation of cellular components and consequent loss of cellular function. Oxidative stress is implicated in wide range of age-related disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease and the aging process itself. In the anterior segment of the eye, oxidative stress has been linked to lens cataract and glaucoma while in the posterior segment of the eye oxidative stress has been associated with macular degeneration. Key to many oxidative stress conditions are alterations in the efficiency of mitochondrial respiration resulting in superoxide (O(2)(-)) production. Superoxide production precedes subsequent reactions that form potentially more dangerous reactive oxygen species (ROS) species such as the hydroxyl radical (OH), hydrogen peroxide (H(2)O(2)) and peroxynitrite (OONO(-)). The major source of ROS in the mitochondria, and in the cell overall, is leakage of electrons from complexes I and III of the electron transport chain. It is estimated that 0.2-2% of oxygen taken up by cells is converted to ROS, through mitochondrial superoxide generation, by the mitochondria. Generation of superoxide at complexes I and III has been shown to occur at both the matrix side of the inner mitochondrial membrane and the cytosolic side of the membrane. While exogenous sources of ROS such as UV light, visible light, ionizing radiation, chemotherapeutics, and environmental toxins may contribute to the oxidative milieu, mitochondria are perhaps the most significant contribution to ROS production affecting the aging process. In addition to producing ROS, mitochondria are also a target for ROS which in turn reduces mitochondrial efficiency and leads to the generation of more ROS in a vicious self-destructive cycle. Consequently, the mitochondria have evolved a number of antioxidant and key repair systems to limit the damaging potential of free oxygen radicals and to repair damaged proteins. The aging eye appears to be at considerable risk from oxidative stress [37].

Morphological and biophysical techniques have shown that membrane derangement occurs in human cataractous lenses. The data suggest that these disruptions were globules, vacuoles, multilamellar membranes and clusters of highly undulating membranes. Deleterious structural damage of the lens fibre cell plasma membranes serve as the primary light-scattering centres that cause the observed lens opacity. Nuclear cataract, a major cause of loss of lens transparency in the aging human, has been thought to be associated with oxidative damage, particularly at the site of the nuclear plasma membrane. Phospholipid molecules modified by oxygen accumulate in the lipid bilayer, change its geometry and impair lipid-lipid and protein-lipid interactions in lenticular fibre membranes. Lipid peroxidation (LPO) is a causative and pathogenic factor in cataract. Increased concentrations of primary molecular LPO products (diene conjugates, lipid hydroperoxides, oxy-derivatives of phospholipid fatty acids) and end-fluorescent LPO products have been detected in the lipid moieties of aqueous humour samples and human lenses obtained from patients with senile and complicated cataracts as compared with normal donors. In the present study, a rapid and simple high-performance liquid chromatographic (HPLC) assay for determination of imidazole-containing dipeptides in the aqueous humour of the eye was developed. The method was applied to determine the pharmacokinetic parameters and the time-course of N-acetylcarnosine and L-carnosine-related product in the eye, following a single dosage of topical ocular administration of peptide. Utilising data from pharmacokinetic studies and the specific purity of the N-acetylcarnosine (NAC) ingredient as a source of the pharmacological principle L-carnosine, have created an ophthalmic time-release pro drug form including the US FDA-approved carboxymethylcellulose lubricant and other essential ingredients (Can-C, private label Nu-Eyes). This formulation increases the intraocular absorption of L-carnosine in the aqueous humour and optimises its specific antioxidant activity *in vivo* while reducing the toxic effects of lipid peroxides on the crystalline lens. L-carnosine that enters the aqueous humour can accumulate in the lens tissue for a reasonable period of time. The presence of L-carnosine in transparent crystalline lenses during normal aging was detected and its concentration in this case was about 25 microM. At different stages of cataract development, the level of L-carnosine drastically decreased, reaching about 5 microM in ripe human cataracts. However, administration of pure L-carnosine (1% solution) to the rabbit eye (instillation or sub conjunctival injection) does not lead to accumulation of this natural compound in the aqueous humour at the time level over 30 minutes at a concentration exceeding that in placebo-treated matched eyes, and its effective concentration is exhausted more rapidly. Use of NAC pro drug eye drops optimises the clinical effects of L-carnosine in the treatment of ophthalmic disorders (such as prevention and reversal of cataracts in human and animal [canine] eyes). The data provided predict a clinical effect with NAC ophthalmic pro drug, and show that the magnitude and duration of this effect are directly related to the bioavailability of L-carnosine released from NAC in the aqueous humour of the anterior eye segment. The ophthalmic NAC drug shows promise in the treatment of a range of ophthalmic disorders that have a component of oxidative stress in their pathogenesis (including cataract, glaucoma, dry eye, vitreous floaters, inflammatory disorders, and corneal, retinal and systemic diseases [such as diabetes mellitus and its ophthalmic complications]). There is a need for further and better collaboration between Innovative Vision Products' cataract control and ophthalmic services, improved education of people affected by cataract, a commitment that N-acetylcarnosine eye drops will be the preferred treatment before orthodox cataract surgery is attempted, and consideration of outcomes and a possible role of the NAC drug cataract treatment as source of referral for orthodox surgical, ophthalmic and optometric services [38].

To quantify changes in the lens epithelial cells and underlying lens cortex responsible for age-related cortical cataract (ARCC) in the rat.

Freshly isolated lenses were stained vitally for DNA with Hoechst 33342. Reactive oxygen species (ROS) and mitochondria were visualized and quantified by dihydrorhodamine 123 (DHR). The fluorescence was quantified using Laser Scanning Confocal Microscopy (LSCM) of vitally stained lenses. Cortical DNA was verified as such by DNAse I digestion. Cataract reflections were determined from digitalized images of light reflections taken with a low magnification light microscope, or with the LSCM.

The anterior surface epithelia of old rat lenses were full of gaps and ragged in appearance with a decrease of over 50% in lens epithelial cell (LEC) density. The surface LECs were frequently seen to have involuted into the cortex at inappropriate sites, forming deposits full of DNA, nuclear and mitochondrial debris, and abundant ROS. These involutions frequently originated near open gaps in the surface epithelia, where they appear to have detached from the capsular membrane. Cortical cataracts in the rat lenses were seen to co-localize with these LEC involutions, as had been seen previously in mice with ARCC.

ARCC in rats co-localized with inappropriate accumulations of nuclei, mitochondria, DNA, and expression of ROS in debris filled foci. These were the result of both involution of surface LECs into areas of cortical ARCC, and by an extension of the normal bow region deep into the anterior and posterior of cataractous lenses [39].

Conclusion

Intralipid eye drops are first suggested for cataract treatment in the medical literature.

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