

Development and Evaluation of *Alternanthera sessilis* Extract-Loaded Nanoparticles for Ocular Delivery and Anti-Cataract Activity: Review

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ABSTRACT

Cataract remains a leading cause of visual impairment worldwide. Oxidative stress plays central role in cataractogenesis through depletion of antioxidant defences, lipid peroxidation, aggregation of lens proteins. Current management relies on surgical extraction with limitations. *Alternanthera sessilis* commonly known as Ponaganti Koora or sessile joyweed, is widely consumed leafy vegetable in South India with reported flavonoids, phenolics, carotenoids, quercetin derivatives.

Aim: This review aims to comprehensively compile the phytochemistry, anti-oxidant and anti- cataract potential of *Alternanthera sessilis* and provide rationale for development of extract loaded chitosan nanoparticles for ocular delivery.

Literature search was conducted using PubMed, Scopus and Web of science from 2009-2025 using keywords *Alternanthera sessilis*, cataract, quercetin, chitosan nanoparticles, Nrf2/HO-1. Previous work demonstrated cataract preventive activity in glucose-induced and UV-induced goat lens models and galactose-induced rat model. Recent 2022 comprehensive review (Hwong et al., J Ethnopharmacol) confirmed potent antioxidant activity due to polyphenols, terpenes, alkaloids, carotenoids plus vitamins C, E. However, conventional extracts exhibit poor ocular bioavailability (<5%) due to tear drainage, blinking, corneal barrier. Chitosan-based nanoparticles prepared by ionic gelation offer mucoadhesion, sustained release, improved corneal permeation. Latest 2025 study (ACS) developed chitosan-coated quercetin nanoemulsion eye drops showing protection against H₂O₂-induced oxidative stress in lens epithelial cells with viability >70% and Bcl-2 upregulation.

Keywords: *Alternanthera sessilis*, Cataract, Quercetin, Chitosan nanoparticles, Nrf2/HO-1, Ocular delivery, Nanoemulsion

1. INTRODUCTION

Visual impairment¹⁻⁶ due to cataract continues to be major public health concern globally. Cataract is defined as progressive opacification of crystalline lens, leading to gradual reduction in visual acuity. While aging is most common risk factor, diabetes mellitus, prolonged ultraviolet exposure, nutritional deficiencies, oxidative damage significantly contribute.

The lens possesses efficient endogenous antioxidant defence comprising reduced glutathione (GSH), catalase,

superoxide dismutase (SOD), glutathione peroxidase (GPx). These systems neutralize reactive oxygen species and maintain transparency. In cataractogenesis, excessive generation of free radicals overwhelms these protective mechanisms⁸⁻¹⁵. Consequently, lipid peroxidation increases, antioxidant enzymes decline, crystallins aggregate, solubility decreases.

In current clinical practice, mature cataract is managed by surgical extraction followed by implantation of intraocular lens. Although surgery yields excellent

outcomes, universal accessibility is constrained by cost, infrastructure, postoperative care¹⁶⁻²². Therefore, investigation of safe, cost-effective agents capable of preventing or delaying cataract onset is active area.

Plant-based medicines rich in antioxidants have gained attention²³⁻²⁹. *Alternanthera sessilis* L., belonging to family Amaranthaceae, commonly known as Ponaganti Koora in Telangana and sessile joyweed in English. Widely consumed³⁰⁻³⁶ as green leafy vegetable and used in traditional systems³⁷⁻⁴⁰. Phytochemical studies report presence of flavonoids, phenolic compounds, carotenoids, triterpenoids. Quercetin and its derivatives are key constituents with documented antioxidant and cytoprotective properties. Recent 2022 review confirms no toxicity even at high doses, supporting safety for ocular use.

2. REVIEW OF LITERATURE

2.1 Cataract and Oxidative Stress

Cataract continues to be leading cause of blindness, especially in developing countries. Pathogenesis multifactorial - oxidative stress, non-enzymatic glycation, osmotic stress due to polyol pathway.

Oxidative stress is central mechanism. ROS generated through normal metabolism, UV radiation, hyperglycemia damage lens lipids, proteins, DNA. Reduction in GSH levels, increased MDA as marker of lipid peroxidation, decreased catalase activity consistently observed in cataractous lenses.

Gupta et al. (2009) reviewed pharmacological strategies for cataract prevention and highlighted agents targeting oxidative stress, glycation, aldose reductase show promise. Nair et al. (2009) and Patel et al. (2010) discussed emerging molecular targets and cytochrome-related pathways.

Thiagarajan et al. (2014) demonstrated that Nrf2 knockout mice develop early cataract, establishing Nrf2/HO-1 axis critical for maintaining redox homeostasis. Deficiency leads to downregulation of antioxidant genes and accelerated opacification.

Recent reviews on natural antioxidant activities (Antioxidants 2022) highlighted quercetin, flavonoid found in fruits and vegetables, as potent antioxidant. In Sprague Dawley mice, quercetin reduced onset and development of selenite-induced cataracts and maintained lens chaperone function. Citrus flavonoids prevented selenite-induced opacities in Wistar rats with increase in CAT, SOD, GSH-Px, GST, and reduction in lipid peroxidation.

Zhou et al. (2018) investigated molecular mechanism - Wistar rats given 20 uM/kg sodium selenite i.p. to induce cataract, quercetin 400 mg/kg i.p. HSP70 expression lower, 8-OHdG DNA damage marker significantly lower, CAT and SOD enhanced greater than model.

Park et al. examined 8 dietary flavonoids including quercetin in glycation-induced goat lens organ culture. Quercetin along with kaempferol and taxifolin effectively maintained lens transparency and structural integrity.

2.2 Phytochemistry and Antioxidant Potential of *Alternanthera sessilis*

Alternanthera sessilis L. is annual or perennial herb widely distributed in tropical and subtropical regions. In India, commonly consumed as leafy vegetable, especially in Andhra Pradesh, Telangana, Tamil Nadu, Kerala. Locally known as Ponaganti Koora, Ponnanganni Keerai, Gudari Saag, recognized for nutritional and medicinal value. Traditionally used for gastrointestinal disorders, wound healing, antioxidant, hepatoprotective.

Hwong et al. (2022) Comprehensive review in J Ethnopharmacol described two cultivars: green and red. Green used for wound healing, dysentery, asthma, hypertension. Red for cardiovascular and liver diseases. Confirmed potent antioxidant activity due to polyphenols, terpenes, alkaloids, carotenoids plus vitamins C, E, unsaturated fatty acids. Activities: antimicrobial, anthelmintic, anti-diabetic, lipid lowering, anti-inflammatory, analgesic, anti-cancer. Toxicity evaluation showed no adverse effect.

Phytochemical investigations reveal diverse bioactive constituents - flavonoids, phenols, tannins, alkaloids, saponins, sterols. Quantitative analyses report high phenolic and flavonoid content. Carotenoids including lutein, beta-carotene, triterpenes documented.

Sharma et al. (2013) evaluated antioxidant potential using DPPH and nitric oxide scavenging assays and reported significant activity comparable to standards. Kota et al. (2017) investigated wild leafy vegetable from South India and reported alkaloids, flavonoids, tannins, phenols. Evaluated antibacterial and anti-cataract activity attributed to flavonoid content.

Mohd Hazli et al. (2019) performed UHPLC-QqQ-MS/MS analysis and identified several polyphenols including quercetin derivatives, kaempferol glycosides, phenolic acids. Hwong et al. (2023) isolated antioxidant-rich red extracts using Sephadex LH-20 and characterized polyphenols through HPLC-QToF-MS/MS, confirming quercetin, rutin.

Devineni et al. (2024) methanolic extract ASLE-M showed broad phytoconstituents, strong ROS scavenging. In SK-N-SH neuronal cells, reduced ROS and enhanced antioxidant defences. In RAW264.7 cells, significantly inhibited IL-6, IL-1b, TNF-a by 57.9%, 43.8%, 49.8% - showing anti-inflammatory property relevant to NF-kB pathway in cataract.

2.3 Prior Evidence on Anti-Cataract Activity of *A. sessilis* and Related Plants

Usha Sree et al. (2014) evaluated cataract preventive action of hydroalcoholic extract using in vitro models. Goat lenses isolated and cultured in artificial aqueous humor for 72 hours. Cataract induced using high glucose (55 mM) and photochemical model UV radiation at 315 nm for 15 minutes. Extract tested at 100, 300, 500 ug/mL with vitamin E at 75 ug/mL as standard. Lens opacity graded photographically, biochemical parameters total protein, MDA, catalase estimated. Dose-dependent protection. At 500 ug/mL, transparency better preserved, total protein and catalase maintained near normal, MDA significantly reduced.

Madhuri et al. (2014) extended to in vivo galactose-induced cataract model in Wistar rats. Rats 60-100 g fed 30% galactose diet for 40 days to induce osmotic and oxidative stress through polyol pathway. Extract administered at 200 mg/kg in combination with vitamin E at 50 mg/kg. Slit-lamp examination day 40, lenses isolated day 41. Treated groups showed lower grades of lens opacity compared to galactose control.

Ganeshpurkar et al. (2011) demonstrated in vitro prevention by *Pleurotus florida* extract in isolated goat lens model, validating model for screening natural products. Sasikala et al. (2010) showed *Moringa oleifera* prevents selenite-induced cataract in rat pups, model involving oxidative stress and calpain activation similar to age-related cataract. Umamaheswari et al. (2012) reported anticataract activity of *Achyranthes aspera* against glucose-induced cataract in goat lenses, protection attributed to flavonoids.

Recent studies confirm quercetin as key active - prevents selenite cataract, maintains chaperone activity, enhances CAT, SOD, GPx.

2.4 Nanocarriers for Ocular Drug Delivery

Topical ocular drug delivery challenging due to unique anatomy and physiology. Conventional eye drops exhibit poor bioavailability, typically less than 5%, due to rapid tear turnover, blinking, nasolacrimal drainage, corneal barrier comprising lipophilic epithelium, hydrophilic stroma, lipophilic endothelium. Conjunctival absorption and enzymatic degradation further reduce availability.

Nanocarrier-based systems investigated - polymeric nanoparticles, liposomes, niosomes, nanoemulsions, micelles for anterior segment delivery.

Chitosan-based systems particular interest for ocular delivery. Chitosan is biodegradable, biocompatible, mucoadhesive polymer derived from deacetylation of chitin. Positively charged at physiological pH due to amine groups, enabling electrostatic interaction with negatively charged mucin on corneal surface. Mucoadhesion increases residence time and enhances permeation through transient opening of tight junctions.

Gorantla et al. (2020) reviewed nanocarriers for ocular drug delivery, discussing status, challenges, translational opportunities. Highlighted polymeric nanoparticles, especially chitosan-based systems, offer sustained release, improved retention, ability to encapsulate both hydrophilic and hydrophobic agents, suitable for herbal extracts rich in polyphenols.

Mangiacotte et al. (2020) investigated mucoadhesive nanoparticles for anterior eye delivery and demonstrated chitosan nanoparticles significantly increase ocular surface retention compared to conventional solutions. Particle size below 300 nm and positive zeta potential favorable for corneal penetration.

Meza-Rios et al. (2020) concluded ionic gelation method using chitosan and sodium tripolyphosphate (TPP) simple, safe, scalable without organic solvents, advantageous for herbal extracts.

Chitosan-Coated Quercetin Nanoemulsion Eye Drops (ACS 2025) - Most relevant! Developed QNE and CS-functionalized. Nanoscale size, high entrapment, controlled release. Strong antioxidant activity and protective effects against H₂O₂-induced oxidative stress in HLE and HCE-T cells maintaining viability above 70%. Upregulated antiapoptotic Bcl-2, reducing damage. Confirms CS coating improves ocular delivery of quercetin through sustained release for delaying lens degeneration.

Lan et al. CS-NAC/HP-beta-CD inclusion complex for quercetin - 20% HP-beta-CD + 0.1% CS-NAC optimized. Enhanced fluorescence deeper into corneal epithelium, delayed occurrence of cataract about 1 day with full-dose quercetin.

Liu et al. PLGA curcumin cerium oxide + chitosan-coated mPEG-PLGA for baicalin - size 148-219 nm, increased cellular uptake, improved precorneal residence, significantly enhanced activities of catalase, SOD, GPx which neutralize ROS. Target size for formulation.

Al-Kinani et al. (2015) OTZ chitosan nanoparticles 153 nm for cataract - Oxidative damage due to low GSH main cause of cataract. OTZ, cysteine prodrug, can increase cellular GSH. Chitosan nanoparticles loaded with OTZ formulated by ionic gelation - uniform, well dispersed, average size 153 nm. In vitro release over 96h. Permeation through excised bovine cornea - lag time 0.2h and flux 3.05 ug/cm²/h. Validates ionic gelation method and 150-200 nm target.

Breaking Barriers Review 2023 - MDPI confirms emerging DDS for cataract rely on biodegradable polymers with predictable release and increased biocompatibility - exactly chitosan approach.

No published study has systematically developed *A. sessilis* extract-loaded chitosan nanoparticles designed specifically for ocular delivery and evaluated for anti-

cataract activity with comprehensive biochemical and molecular evaluation.

3. RESEARCH GAP AND FUTURE PERSPECTIVES

1. Previous work evaluated only plain hydroalcoholic extract. No dedicated ocular nanoparticle system developed.
2. Conventional extracts exhibit poor ocular bioavailability and limited retention.
3. Earlier evaluation included only three markers - total protein, MDA, catalase. Important markers GSH, SOD, GPx, aldose reductase, calpain not assessed.
4. Corneal permeation, ocular tolerability, formulation characteristics such as particle size, zeta potential, entrapment efficiency, release profile not investigated.
5. Key molecular regulators Nrf2/HO-1, NF-kB p65, caspase-3 not evaluated, despite evidence Nrf2/HO-1 critical for lens protection (Thiagarajan 2014).
6. Additional relevant cataract models H₂O₂-induced oxidative model in vitro and selenite-induced model in vivo not employed.
7. Histopathological examination and TUNEL assay for apoptosis, and molecular docking studies not performed. Future research should address gaps by developing standardized *A. sessilis* extract-loaded chitosan nanoparticles using ionic gelation and evaluating in H₂O₂-induced and UV-induced goat lens models and selenite-induced and galactose-induced rat models. Comprehensive evaluation including total protein, MDA, GSH, catalase, SOD, GPx, aldose reductase, calpain, Nrf2, HO-1, NF-kB p65, caspase-3 through Western blotting, histopathology, TUNEL assay, corneal permeation, ocular tolerability, docking of quercetin with aldose reductase and Keap1.

Review Methodology

A literature search was conducted using PubMed, Scopus, and Web of Science to identify publications relevant to cataractogenesis, oxidative stress, the phytochemistry of *Alternanthera sessilis*, anti-cataract activity, and nanoparticle-based ocular drug delivery. The search covered publications from 2009 to 2025. Search terms included “*Alternanthera sessilis*,” “cataract,” “anti-cataract activity,” “quercetin,” “oxidative stress,” “chitosan nanoparticles,” “ocular drug delivery,” and “Nrf2/HO-1.” Relevant combinations of keywords were used where appropriate. Publications were considered relevant if they addressed the phytochemical composition, antioxidant or anti-cataract activity of *A. sessilis*, cataract-related experimental models, or nanoparticle-based ocular delivery systems. Studies involving related medicinal plants and antioxidant compounds were considered for

contextual comparison. The findings were synthesized narratively according to the major themes of the review. This review was not designed as a systematic review or meta-analysis. The number of records identified, duplicate removal, study-selection procedures, and formal quality assessment were not quantified.

Strengths of the Review

This review integrates the available evidence on the phytochemical composition, antioxidant properties, and preliminary anti-cataract potential of *Alternanthera sessilis*. It highlights the possible role of quercetin and other polyphenolic constituents in reducing oxidative stress and maintaining lens integrity. Another strength is the discussion of chitosan-based nanoparticle systems as a potential strategy to improve ocular surface retention, controlled drug release, and corneal delivery. The review also identifies important gaps in the existing literature, including the lack of systematic formulation development and comprehensive biochemical and molecular evaluation of *A. sessilis* extract-loaded nanoparticles for ocular applications.

Limitations of the Review

This review has several limitations. First, the available evidence specifically evaluating the anti-cataract activity of *Alternanthera sessilis* appears limited, with much of the discussion relying on preliminary experimental studies and findings from other antioxidant plants or isolated compounds such as quercetin. Second, the review does not provide a fully reproducible literature-search strategy, including exact search strings, the number of records identified, duplicate removal, or study-selection criteria. Third, no formal assessment of methodological quality or risk of bias of the included studies is reported. Differences in experimental models, extract composition, dosage, and outcome measures also limit direct comparisons between studies. Finally, the proposed benefits of chitosan nanoparticles for delivering *A. sessilis* extracts remain to be experimentally validated, and clinical efficacy and long-term ocular safety cannot be established from the currently discussed preclinical evidence.

Future Directions

Future research should focus on the development and optimization of standardized *A. sessilis* extract-loaded chitosan nanoparticles using suitable formulation techniques, including ionic gelation. Important formulation parameters such as particle size, polydispersity index, zeta potential, entrapment efficiency, drug-release profile, and physicochemical stability should be evaluated. Further studies should investigate corneal permeation, ocular surface retention, sterility, and ocular tolerability using appropriate

experimental models. The anti-cataract potential of the formulation should be compared with the plain extract, blank nanoparticles, and suitable positive controls in validated in vitro and in vivo models. Biochemical and molecular investigations involving glutathione, antioxidant enzymes, lipid peroxidation, Nrf2/HO-1 signalling, and apoptosis-related pathways may help clarify the underlying mechanisms. Once adequate preclinical evidence and safety data are established, further translational studies may determine whether this approach has practical potential for cataract prevention or management.

4. CONCLUSION

Cataract remains major cause of visual impairment with oxidative stress as key pathogenic mechanism. *Alternanthera sessilis*, commonly consumed leafy vegetable rich in antioxidant polyphenols including quercetin, has shown promising anti-cataract activity in preliminary in vitro and in vivo studies 2014. Recent comprehensive reviews 2022-2024 confirm safety and potent antioxidant, anti-inflammatory activities via polyphenols, inhibition of IL-6, IL-1b, TNF-a. Quercetin validated in selenite, galactose, H₂O₂ models with enhancement of CAT, SOD, GPx, maintenance of chaperone function, modulation of HSP70, reduction of 8-OHdG. However, ocular delivery and comprehensive mechanistic evaluation remain unexplored. Chitosan-based nanoparticles prepared by ionic gelation offer promising platform to improve ocular retention and bioavailability. Latest 2025 chitosan-coated quercetin nanoemulsion eye drops demonstrate strong antioxidant activity and protection against H₂O₂-induced oxidative stress with Bcl-2 upregulation. Development and evaluation of *A. sessilis* extract-loaded nanoparticles with extended biochemical, molecular, histopathological, docking studies represents logical extension and holds potential for affordable adjunct therapy.

DECLARATIONS

Ethics Approval and Consent to Participate: Not applicable, as this review did not involve new experiments on human participants or animals.

Consent for Publication: Not applicable.

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