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# ANTIOXIDANT THERAPY FOR DRY EYE DISEASE: A SYSTEMATIC REVIEW

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## ABSTRACT

This systematic review highlights the potential of antioxidants as therapeutic intervention in dry eye disease. Preclinical reports assessing the effect of plant based and synthetic antioxidants against dry eye disease was collected from online electronic databases like Scopus, PubMed, Science direct, DOAJ, and Jgate. The review protocol was registered on PROSPERO, registration no. CRD42023420934. The systematic review followed PRISMA approach for including reports and all reports were appraised for risk of bias using the SYRCLE's RoB tool. From the search results 26 articles met the inclusion criteria for the review. These articles were analyzed for the rodent species and strain used, antioxidants which improved the tear volume, restore conjunctival goblet cells, amelioration of inflammatory cytokines like TNF-α, IL-1β, NLRP3 and reduction of oxidative stress. The studies reported in this review insinuates the target of antioxidants in dry eye disease and their mechanism of action against oxidative stress, corneal irregularity, ocular surface inflammation apoptosis and tear secretion. These repots compositely suggest that antioxidants can ameliorate the negative effects of dry eye disease and improve the tear secretion to maintain homeostasis.

**Keywords: Dry eye disease; keratoconjunctivitis sicca; meibomian gland dysfunction; antioxidants; rodent studies**

## 1. INTRODUCTION:

Tears are clear fluid secreted by lacrimal gland in eyes. They are made up of 3 layers: mucin layer, aqueous layer and lipid layer produced by conjunctiva, lacrimal gland and meibomian gland respectively. They contain antioxidants like lactoferrin, tyrosine and glutathione that protect corneal epithelial cells from external damage **[1]**. Tear secretion are consistent and replenished by blinking which applies pressure on tear glands and maintains stabilized surface of eye. They mainly act as protective layer to front surface of eye and provide lubrication to facilitate movement of eye and eyelids. In Dry eye disease or keratoconjunctivitis sicca tear production from lacrimal gland is affected or the quality of tear produced is low due to blockage in meibomian gland which destabilizes the corneal epithelial barrier and cause damages like abrasion of corneal surface and corneal ulcer **[2]**. According to the international workshop study group, dry eye disease is a multifactorial disease of tear and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability, along with increased osmolarity of tear film and inflammation in ocular surface. There are many factors that affects tear production. Pathological conditions like infection, vitamin A deficiency, hormonal changes, immune response **[3, 4]** and environmental conditions like climate, wind, pollution can cause dry eye disease.

In dry eye disease the meibomian gland which is responsible for production of lipid layer of tear and conjunctival goblet cells which is responsible for mucus production is affected resulting in evaporation of tears. The conjunctival goblet cells have number of natural killer cells, dendritic cells, macrophages, which are mainly responsible for maintaining ocular surface homeostasis and antimicrobial defense **[5]**. The T-helper cytokines are responsible for modulation of goblet cells in dry eye condition. The type II helper T cells (Th2 cytokine), interleukin-13 (IL-13) is responsible for proliferation and mucin production by goblet cells whereas, Th1 cytokine Interferon-gamma (IFN-γ [gamma]) entraps the goblet cells and decreases mucin production **[4, 6]**. The evaporation of tears causes hyperosmolarity and activates IL-1β [beta] in conjunctival epithelium **[7]**, epithelial neutrophils like IL-6, macrophages, Nuclear factor kappa B (NFκ [kappa] B), Tumor necrosis factor-alpha (TNF-α [alpha]) and other T-cells. The accumulation of these inflammatory mediators and reactive oxygen species cause damage to the goblet cells and glycocalyx mucin, triggers those inflammatory cells leading to epithelial apoptosis and squamous metaplasia by cell damage and accumulation of cellular organelles and DNA by Mitogen-

activated protein kinase (MAPK), Matrix metalloproteinases-3 (MMP3) and MMP-9 pathway **[8-11, 17]**. The decrease in density of goblet cells leads to reduced secretion of mucin-5AC (MUC5AC) soluble mucin which in turn change the biochemical composition of mucin layer **[13]**. Other main cause of inflammation in dry eye disease is the over expression of ICAM-1 present in ocular surface. These intercellular adhesion molecule-1 (ICAM-1) binds to a cell surface protein of activated T-cells called LFaI. The activation of T-cells further recruits other inflammatory cytokines like TNF-α [alpha], IL-1β [beta], B-cells and other dendritic cells.

The present treatment for dry eye disease is artificial tears to improve tear secretion and anti-inflammatory drugs like cyclosporin A to improve the inflammatory condition in ocular surface and lacrimal glands. In recent times the therapies based on natural sources are improving due to their less side effects. antioxidants-based therapy can restore normal autophagy and protect cell viability by inhibiting inflammation **[14]** and serves as potential therapeutic against dry eyes.

## 2. AIM AND OBJECTIVE OF THE STUDY:

Dry eye disease or keratoconjunctivitis sicca is a condition in which tear production from lacrimal gland is affected or the quality of tear produced is low. There are many factors that affects tear production. Pathological conditions like infection, vitamin A deficiency and environmental conditions like climate, wind, pollution can cause dry eye disease. Our study aimed to evaluate the potential effect of antioxidants in the treatment of dry eye disease.

## 3. DATA SOURCES AND SEARCH:

An extensive search on peer reviewed reports investigating the effect of antioxidants in dry eye disease through online electronic databases like Scopus, PubMed, Science direct, DOAJ and J gate were collected. Search terms like dry eye disease OR dry eye OR dry eye syndrome OR keratoconjunctivitis sicca OR keratitis sicca OR meibomian gland dysfunction OR corneal xerosis OR conjunctival xerosis OR dysfunctional tear syndrome OR ocular dryness OR lacrimal keratoconjunctivitis OR evaporative tear deficiency OR aqueous tear deficiency OR xerophthalmia AND antioxidants were used. The literature search was conducted in on 17$^{th}$ March 2023. Using AND, OR as Boolean operators the articles published in English language are retrieved from database from March 2023 to April 2023. Before the final analysis, the literature search was conducted once again in order to check any missing articles and most recent publications that may fit our inclusion criteria.

## 4. METHODOLOGY:

This study followed PRISMA or Preferred reporting items for systematic reviews and metanalysis.

**4.1.Eligibility criteria:**

All research article that includes in-vivo experiments in their studies involving parameters like tear volume, conjunctival goblet cell density, levels of inflammatory cytokines like TNF-α [alpha], IL-1β [beta], nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3), oxidative stress and m-RNA expression by polymerase chain reaction (PCR) and western blotting were retrieved. Other articles like review articles, conference papers, editorials, papers with exclusively In-silico studies, involving non-rodents like rabbit, dog, zebra fish and human trials were excluded.

**4.2.Population:**

Animals: rat/mice; Age: any age; Gender: both sexes; Weight: any weight

**4.3.Intervention:**

Antioxidants produced from various sources like plants, chemical synthesis, algae and marine products were included.

**4.4.Comparison:**

Studies in which normal control groups (without exposing to any inducing agent) are included in the study.

**4.5.Outcome:**

Studies with outcome measurement of tear volume, conjunctival goblet cell density, fluorescein staining score, periodic acid-Schiff (PAS) stain score, rose Bengal staining score, Lissamine green staining score, interleukin levels, m-RNA and gene expression, histopathological analysis of eye, conjunctiva and cornea were included. Studies with outcome measurement other than dry eye disease were excluded.

**5. STUDY SELECTION:**

A preliminary search was performed by both reviewers. The title, abstract, keywords, authors, year of publication, volume issue, DOI of eligible records were exported in CSV file from respective database to Microsoft excel for further screening of duplicates. After removing duplicates, the articles were assessed for eligibility by second reviewer (CV) to reduce the bias in selection of records. Records that meet the above criteria are taken for further screening.

**6. DATA EXTRACTION:**

All the bibliographic data comprehending the article, author's name, affiliation, year of publication, inducing agent, dose, duration of study, type of antioxidant, formulation, grouping, parameters evaluated and outcome of the study. All the collected data were fed in excel spread sheet for further reference. The second reviewer verified the extracted information from each report for persevering consistency and significance of data.

**7. RESULTS:**

**7.1.Assessment of quality of the reports:**

Cohen's kappa statistics measures the agreement and likelihood of variance between the reviewers. Kappa test was performed to check the inter-rater reliability between SH and CV, and the results showed a score of kappa=0.755 (SE=0.076; 95% CI: from 0.606 to 0.904; weighed kappa=0.763), signifying substantial agreement.

**7.2.Risk of bias assessment outcome:**

All repots were subjected to critical review using the standard SYRCLE'S RoB tool checklist. Only 9 studies (35%) followed a random component in sequence generation process and only 6 studies (23%) mentioned baseline characteristics. Eight studies mentioned about random housing of animals (30%) All the studies inadequately addressed about the performance blinding and detection blinding. All studies addressed random allocation of animals for outcome assessment. Most of the studies did not mention the reason for incomplete assessment. None of the studies reported other source of bias such as pooling of drugs, unit of analysis error and bias due to conflict of interest.

**7.3.Selection of reports:**

The preliminary search from five database identified 4337 records of which 209 from PubMed, 3580 from Science Direct, 176 from Jgate, 45 from DOAJ, 325 from Scopus and 2 articles from other sources, one from literature search and another from reference list of included studies. After removal of duplicates, 300 records were screened and 26 were selected which met the inclusion criteria. Others were rejected with the following reasons; 16 articles used non-rodents in their studies, 22 articles did not use control group in their study, 2 articles were rejected since their grouping is not clearly explained and 1 article did not use antioxidants. The PRISMA flow chart of the above selection and screening process was depicted in **Figure 1**.

**7.4.Article information:**

The 26 studies considered eligible for the systematic review have distinct methodology, hence statistical integration of data is not feasible. Although there were no limitations applied during literature search, the final report included in this review were published from 2010 to 2023. Out of 26 studies, 6 (23%) were published in 2019 **[25-30]**, 5 (19%) were published in 2020 **[20-24]**, 3 (11%) were published in 2021 **[17-19]**, 3 studies in 2016 (11%) **[32, 35, 36]** and 2 each in 2012 [**38, 39]**, and 2017 **[33, 34]**, and one each in 2010 **[40]**, 2014 **[37]**, 2018 **[31]** 2022 **[16]** and 2023 **[15]**. A significant proportion of the studies are published from Korea (n=8, 30%) **[19-21, 26, 29, 31, 33, 36]**, followed by China (n=7, 26%) **[15-18, 22, 28, 32]** Japan (n=5, 19%) **[35, 37-40]** and USA (n=2, 7%) **[25, 27]** as well as one paper each from Indonesia **[34**, Egypt **[23]**, Mexico **[30]** and Turkey **[24]**.

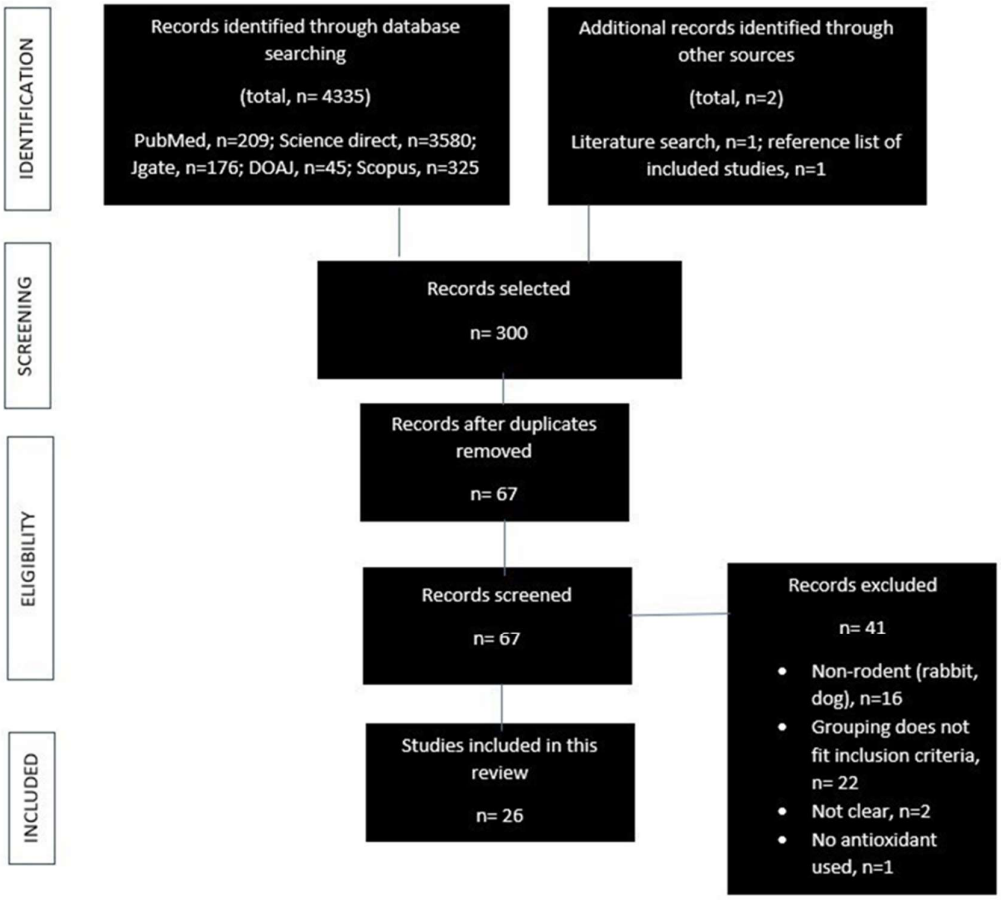


**Figure 1: The PRISMA flow diagram of the studies in this review**

### 7.5.Experimental animals:

The study outcomes of all 26 articles that met our inclusion criteria. Six out of 26 investigations used Sprague Dawley rats **[15, 20, 29, 35, 38, 40]**. Eight studies used C57BL6 strain mice **[17-19, 22, 28, 33, 36, 37,** among this one study compared the C57BL/6 strain with a wild type **[37]**. Three investigations used C57BL6J strain **[16, 27, 30]** one study used C57BL6Cr Slc strain mice **[39]**. BALB/C mice were used in one study **[21]**. Albino rats were used in one study **[23]**. B6D2F1mice in one study **[25]**. Four studies used wistar rats **[26, 31, 32, 34]** and one study did not mention any species in their paper **[24]**. 13 studies preferred male animals **[18, 21, 23, 26, 27, 29, 31, 32, 35, 37-39, 40]** and nine studies preferred female animals **[15-17, 22, 28, 30, 33, 34, 36]**. Four studies failed to mention the sex of the animal **[19, 20, 24, 25]**. The vast majority of studies induced experimental dry eye by subcutaneous or intraperitoneal injection of scopolamine hydrobromide (0.5mg-2.5mg) (n=7) **[16, 17, 19, 21, 22, 30, 33]**. Another major part of studies induced dry eye through surgical removal of lacrimal glands (n=7) **[26, 31, 32, 35, 36, 39, 40]**. Two

studies induced dry eye by controlled environment and scopolamine injection **[27, 28]**. Aged mice were used in 3 studies **[23, 37, 39]** and topical application of Benzalkonium chloride (BAC) (0.2%) to induce dry eye was used in 2 studies **[20, 24]**. Allogenic bone marrow transplant was used to induce dry eye in one study **[25]** and streptozotocin (50mg/kg, i.p) induced diabetic dry eye was induced in one study **[18]**. Ovariectomized rat was used in one study to cause atrophy in lacrimal gland **[34]**. Radiation of 2gy/min using photon 6-mv **[29]** and 100Lux blue light were used[15] each in one study.

**7.6.Outcome measures:**

All the reports cited in this review measured various biochemical parameters. The most common parameter measured is the tear volume by phenol red thread test or Schimer's test (n=20, 76%) **[15, 17-19, 21, 22, 24-28, 31-37, 39, 40]** followed by fluorescein staining of cornea to measure tear film instability was measured in 17 studies (65%) **[15-17,19, 21, 22, 24, 25, 27-29, 32, 33, 35-37, 40]**. Different staining scores have been used to measure the corneal irregularity as follows, 6 studies used PAS staining **[15, 17, 20, 23, 27, 37]** four studies used Haematoxylin &Eosin staining (HE staining) **[15, 16, 23, 39]**, three studies used rose Bengal staining **[18, 20, 24]** and one study used Lissamine green staining **[26]**. Ferning test to determine the quality of tear production was done in one study **[34]**. Three studies in this review evaluated the goblet cell density to determine the effect of test drug in goblet cells which is responsible for tear production **[20, 25, 37]**. ELISA analysis was performed in two studies to measure the Muc5ac levels and inflammatory cytokines like IL-1β [beta], IL-6, TNF-α [alpha], IL-10, IL-17, and IL-23 in the conjunctiva and lacrimal gland **[25, 28]**. The m-RNA expression of inflammatory cytokines like MMP9, hemeoxygenase-1 (HO-1), prostaglandins (PGS-2), IL-6, TNF-α, Monocyte chemoattractant protein-1 (MCP-1), Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), IFN-γ [gamma] isolated from lacrimal glands and corneal epidermal tissues were measured using RT-PCR in nine studies **[15, 19, 21, 28, 32, 35, 37, 38, 39]** to determine the antioxidant effect of test drug in dry eyes. To measure the levels of oxidative stress markers in cornea and lacrimal glands, immunohistochemistry staining was performed in eight studies **[18, 20, 26, 29, 30, 31, 36, 38]** and 8-hydroxy-2' -deoxyguanosine (8-OHdG) staining was performed in two studies **[27, 39]**. To examine the corneal injury and lacrimal gland distortion transition electron microscopy (TEM) analysis was performed in three studies[15, 18, 39] and histological examination was done in 10 studies **[16, 21, 23, 24, 26, 27, 28, 29, 37, 39]**.

**7.7.Intervention:**

All the studies in this review were preclinical evidences for the efficacy of antioxidants in treatment of dry eye disease. Four studies screened the antioxidant potential of plant extracts like apricot kernel **[36]**, aster koraiensis **[21]**, chamaecyparis obtuse **[33]** and isorhamnetin **[19]**, in treating experimental dry eye disease. Similarly, four studies probed the therapeutic efficacy of phytoconstituents like polydatin isolated from polygonum cuspidatum **[26, 31]**, daidzin from Pueraria lobuta **[32]**, genistein from soybeans **[34]** for their study. Polyherbal formulation like xiaoshen prescription **[22]** (containing Chinese herbs like Rehmanniae radix, Angelicae sinensis radix, codonopsis radix, schisandrae chinensis fructus and so on) and LCD formulation **[24]** (containing lutein, zeaxanthin, curcumin and vitamin D) was used in two studies. Two studies used dietary supplements like mitochondria targeted SkQ1 antioxidant **[18]** and royal jelly **[23]** as an intervention. Three studies used synthetic compounds like E-4-(2(6(2,6-Dichloro-4 (trifluoromethyl) phenyl)-4 methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl) acetamide) adamantan-1 carboxamide (KR-67607- a selective 11β-HSD inhibitor) **[20]**, Manganese III tetrakis (1-methyl-4-pyridyl) porphyrin **[27]** and cerium oxide nanozyme **[16]**. Antioxidant potential of Melatonin hormone was investigated in one study **[17]** and metabolic derivative (2-hydroxy estradiol) **[35]** was used as intervention in one study. The potential effect of a mucin secretagogue, Rebamipide was investigated in two studies **[25, 28]** and physiological components present in serum, plasma or tissue like Diquafosol **[37]**, lactoferrin **[39]**, selenoprotein P[38, 40] was used in four studies. Three studies **[15, 29, 30]** failed to mention the characteristics of the test substance used.

**DISCUSSION:**

Dry eye disease is a chronic inflammatory disease that has a huge demand of new therapeutic approach. The demand increases as the traditional therapeutic approach like cyclosporin eye drops and artificial tears only humidifies corneal surface and may have side effects in individuals respectively **[42, 43]**. Thus, researchers are focusing on developing new therapeutic agents with maximum efficacy and minimal side effects. Antioxidant from plant sources, dietary sources and synthetic procedures which are already proven to have anti-inflammatory activity are being tested for their efficacy against dry eye disease. The purpose of this review was to evaluate the evidences of effect of antioxidants in the view of recovering corneal irregularity, tear production and oxidative stress caused by dry eye disease and to communicate the applicability of existing literature as a support for future research. The result of this systematic review of preclinical *in vivo*

studies explains the effectiveness of antioxidants as therapeutic agent for treating dry eye disease. Although date restrictions were not applied in any database, the gathered publications have been published after 2010 which affirms the efficacy of antioxidants in treating dry eye disease has been addressed in the past decade. The escalating publications in this focus reflects the upsurge in ophthalmic disorder prevalence throughout the world which has some age-related alterations in lacrimal gland, immunogenic factors, environmental factors and life style changes over the past years. Scientist groups all over the world from China, USA, Korea, Japan, Indonesia, Egypt, Mexico and Turkey have investigated the potency of therapeutic antioxidant particularly oriented from their countries in treating dry eye disease.

Thirteen out of 26 studies used male animals, possibly due to hormonal uncertainty in female. But, 9 studies used female rodents due to their sensitivity and to examine the effect of female hormones on progression of the disease. However, no standard evidence is available to know about the frequency of the disease among gender minorities. For a deep understanding about the etiology of the disease and effectiveness of antioxidants in their treatment, a critical clinical data interpretation is needed. Recent research findings shows that animals studies are more reliable in mimicking the human pathological condition. A growing number of alternate animal models and development of new stains have sped up the testing of disease hypothesis and exploring therapeutic innovations providing direction for upcoming clinical trials.

The factors contributing to the progression of disease and pathophysiology investigated in clinical trials are supported by existing models. However, all models have disadvantage due to incomplete depiction of exact human conditions. The existing models may sometimes fail to translate the preclinical results into clinical therapeutic outcome. This is due to the complexity of disease in humans when compared to rodents. Unlike humans no rodents will have the exact same density of receptors and defense mechanism. Thus, it is challenging to investigate all risk variables and disease etiology in animals.

The corneal epithelial layer of eye is most frequently confronted by oxidative stress and environmental pathogens **[41]**. Tear is the main protective layer of the eye which facilitates the movement and prevents friction between eye ball and eye lids. The glands that secrete three layers of tear such as mucin layer, aqueous layer and lipid layer are important in maintaining the stability of the tears. Factors that block or damage these glands may produce obstruction in secretion which leads to irregular layers and instability of tears. Chronic blockage may cause lipid

or mucin deficiency and lead to complete block of lipiflow system. The factors that may cause the above conditions may be due to age factor or autoimmune condition. Other external factors like recent cataract or glaucoma surgery, pollution, contact lens usage, chronic exposure to radiation and short wavelength blue lights, cigarette smoke, sleep deprivation and change in lifestyle that exposes the eyes to chronic oxidative stress. The above-mentioned conditions may lead to evaporation of tear film and cause hyperosmolar layer of tears due to stagnant proteins in epithelial layer. This hyperosmolar layer increases the production of pro-inflammatory cytokines, activates epithelial $MAPK^{+}$, NFκ [kappa] B and abnormally trigger the circulating inflammatory cells IL-1, IL-17, IFNγ [gamma], TNF-α [alpha] and MMPs which attack the goblet cells, glycocalyx mucin, epithelial damage and apoptosis.

Antioxidants are found to be the effective therapeutic agent against these inflammatory cells. Many plant extracts, phytoconstituents and synthetic chemicals were used for treating dry eye disease. The results of both preclinical and clinical interventions shows that antioxidants have a wide range of biological activity including antitumor, antimicrobial, immunomodulatory, obesity, fatty liver and even in management of disease like Alzheimer's and Parkinson's. The radical scavenging nature of antioxidants makes them appropriate the treatment. Many invitro cell culture assays and invivo evidence shows that phytoconstituents like carotenoids, polysaccharides, flavonoids, curcumin, beta-cryptoxanthin, lutein, zeaxanthin, polyphenols derivatives are proven to be effective against inflammation of cornea and lacrimal gland **[12]**.

This review speculates the effect of antioxidants from natural sources (such as polygonum cuspidatum, apricot kernel, aster koraiensis, chamaecyparis obtuse, isorhamnetin, Pueraria lobuta, soybeans, lutein, zeatinin and curcuma) biological (lactoferrin, diquafosol, selenoprotein P) and synthetic sources (like E-4-(2(6(2,6-Dichloro-4 (trifluoromethyl) phenyl)-4 methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl) acetamide) adamantan-1 carboxamide, Manganese III tetrakis (1-methyl-4-pyridyl) porphyrin and cerium oxide nanozyme) in treating dry eye disease. The 26-research article included in this review used sources of antioxidants to treat experimental dry eye induced by different inducing agents. Depending upon the mouse/rat species used, the type of inducing agent and route of administration of antioxidant differs. The inducing agents like controlled environment, blue light exposure, radiation exposure, allogenic transplant induced autoimmunity and even comparison with aged mice study designs completely investigate the effect of

antioxidant in all risk factors that affect the tear film production. Drug induced dry eye and surgical excision of lacrimal glands are used in majority of the study due to their direct effect in tear secretion and lacrimal glands. All the studies mentioned in this review focus on potential of antioxidants in ameliorating the oxidative stress biomarkers such as interleukins, tumour necrosis factor, heme oxygenase-1 enzyme and the effect of antioxidants in elevating the antioxidant enzymes present within the cells. Glutathione levels, glycocalyx staining, gene expression analysis, corneal irregularity, ocular surface evaluation and Ferning's test mentioned in few studies explains the effect of antioxidants in all pathological facets. Western blot analysis, ELISA and immunohistochemistry analysis performed in these studies proves the effect of antioxidants on m-RNA expressions of inflammatory cells and mucin producing cells evidently. Biochemical parameters measurement and staining scores adds evidences of antioxidant potential for future studies. Novel drug delivery of antioxidants through mitochondria targeted method, polyherbal formulation eye drops and through daily dietary supplements improves the therapeutic dry delivery and improves patient compliance. Research on pharmacokinetics of antioxidants is yet to be explored. Clinical trials of the above-mentioned interventions should be focused to improve the treatment for the disease. Other natural and biological sources should be investigated in this regard.

Most of the investigative drugs like melatonin, polydatin, manganese porphyrins, genistein reported in this review already have anti-inflammatory and anti-apoptotic action. They act against dry eye by their potential to reduce reactive oxygen species (ROS) and oxidative stress. Likewise, mucin secretagogue rebamipide, amygdalin from apricot kernel, diquafosol, isorhamnetin are already proved to increase mucosal secretion. Thus, topical application of these drugs may improve the stability of tear film.

From the above reported studies, we conclude that the major causes for dry eye disease is inflammatory response in ocular surface and instable tear film. Thus, researchers who aim to develop treatment against dry eye disease can focus on the drug candidates that inhibit the inflammatory response and increase the tear film stability which can improve clinical symptom and provide better quality of life to the patient.

## 8. CONCLUSION:

This systematic review highlights the potential of antioxidants as therapeutic intervention in dry eye disease. The studies reported in this review insinuates the target of antioxidants in dry eye disease and their mechanism of action against oxidative stress, corneal irregularity, ocular surface

inflammation apoptosis and tear secretion. The evidence from the reported studies proves that antioxidants can ameliorate the negative effects of dry eye disease. It seems intriguing that using plant-based or synthetic sources of antioxidants could help treat dry eye disease.

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**10. PROTOCOL REGISTRATION:**

This systematic review was prospectively registered on the international prospective register of systematic review (PROSPERO), approved on May 23, 2023 (registration no. CRD42023420934).

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**12. CONFLICT OF INTEREST:**

The authors declare no potential conflict of interest.

**13. AUTHORSHIP CONTRIBUTION STATEMENT:**

**Sai Harini S**: Conceptualization, Data curation, Formal analysis, Writing- original draft and editing. **Chitra V**: Validation and Formal analysis. Both authors reviewed the manuscript.

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