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# DIGITAL SCREEN USE AND DRY EYE DISEASE: THE ROLE OF MUCINS, DIETARY NUTRIENTS AND PHYTOCHEMICAL CONSTITUENTS IN DRY EYE DISEASE RELIEF

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**Keywords:**

DED, Digital screen, Mucin, Dietary nutrients, MUC5AC

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**ABSTRACT:** Dry eye disease (DED) is one of the most common conditions in today's digitalized society. DED is associated with decreased tear production, an unstable tear film, and ocular inflammation. Due to the COVID-19 pandemic, the use of digital screens (computers, laptops or smartphones) for work, study or entertainment has increased. As a result, the constant use of digital screens affects the eyes and makes everyone, including youth in the modern era, more susceptible to dry eye disease (DED). Alterations in mucin production are considered one of the most important causes contributing to dry eye disease. MUC5AC, a gel-forming mucin, acts as a surface active agent on the ocular surface and facilitates an evenly distributed tear film that moisturizes the conjunctival epithelium. The prolonged use of artificial tears and other allopathic medications results in specific adverse effects. Therefore, dietary nutrient intake and nutraceutical supplementation with active ingredients can be considered a safe and effective therapy for the treatment of dry eye disease. In conclusion, this review focused on some nutrients and active phytochemical constituents that enhance MUC5AC production in the treatment of dry eye disease.

**INTRODUCTION:** Dry eye disease (DED) is considered a multifactorial disorder characterized by loss of tear film homeostasis and the appearance of ocular symptoms such as hyperosmolarity and unstable tear film on the ocular surface. In addition, inflammation and damage to the ocular surface and abnormalities of neurosensory organs play an etiologic role [1]. DED may also occur due to decreased tear secretion due to hypofunction of the lacrimal gland, which correlates with oxidative stress and inflammation and changes in mucin levels [2].

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Severe DED can lead to impaired work productivity and quality of life (impaired driving, reading and screen productivity) [3]. Worldwide, the prevalence of DED ranges from 5% to 50% according to population based studies. With age, the prevalence of DED increases and is more common in women than in men, due to the effect of certain female hormones on the lacrimal gland, meibomian gland and ocular surface [4].

External factors outside the body and prolonged use of digital screens (smartphones, tablets, laptops, and computers) are one of the most common external factors causing DED [5]. Previous research studies have observed a significant decrease in tear volume, tear film instability, hyperosmolarity, increased release of inflammatory cytokines, increased oxidative stress markers, and decreased mucin secretion, ocular surface damage, and redness of the bulbar region, which are directly

related to prolonged use of digital screens [6]. The risk of developing DED is significantly higher in elderly and in individuals who spend more than four hours per day in front of a screen. Mucins are high molecular weight glycoproteins composed of various sugar chains linked to a core protein called apomucin [7]. Mucins are one of the major components of mucus that maintains a healthy moist surface [8].

Mucins are classified into secreted mucins (gel-forming and soluble mucins) and membrane-associated mucins. MUC5AC is a gel-forming mucin that is thought to be secreted by the goblet cells of the conjunctival epithelium of the ocular surface and released into the tear film as a scaffold [9]. In some studies, people suffering from DED have been found to have decreased MUC5AC content in tears, which is associated with lower levels of MUC5AC transcripts in the conjunctival epithelium.

It is suggested that a decrease in MUC5AC mucins in tears may affect tear film stability and normal ocular surface physiology, as gel-forming mucins are primarily responsible for maintaining fluid on the ocular surface epithelium [10]. Prolonged use of the primary treatment for dry eye symptoms, such as artificial tears along with topical corticosteroids, as well as the use of other marketed medications to relieve inflammation and increase tear secretion, has been associated with adverse effects [11]. Oxidative stress is considered to be one of the major factors in the occurrence of DED. Symptoms of DED can be alleviated by reducing oxidative stress with oral vitamin or antioxidant therapy. Supplementation of active phytochemicals with antioxidant activity may be helpful in alleviating DED caused by oxidative stress. Therefore, there is great interest in investigating the efficacy of oral supplementation of natural products to prevent the adverse effects of long-term use of eye drops. The current review mainly focused on the effects of digital screen use on DED, and better intake of nutrients and supplements with active phytochemical constituents that promote mucin synthesis may be helpful in alleviating DED.

**Epidemiology of Dry Eye Disease:** Globally, the incidence of DED is considered as a major cause of ocular disease. Similar to the global incidence, there are slight variations in the incidence of DED in India depending on the different demographic characteristics.

Some population-based studies reported that the prevalence rate of DED is 32% in northern India and 1.46 % in southern India [12, 13]. In addition, one of the clinical studies in western India found that the recurrence rate of DED is 34.26% [14]. Some studies reported that womens (especially postmenopausal women) and elderly are more prone to dry eye disease [15].

Some Meta-analysis studies reported that in Asia, the incidence of DED is 16.4% in men and 21.7% in women [16]. The use of digital screens is increasingly common In the current generation due to the regular use of laptops, computers, video games, and smartphones [17]. In some meta-analysis studies, the estimated incidence of DED among digital screen users ranged from 9.5% to 87.5% [18].

Therefore, increasing use of digital screens may lead to increased dry eye symptoms even at younger ages [19]. The incidence of eye dryness has been reported to be high during the COVID-19 pandemic due to the extensive use of digital devices for work-from-home and online education [20].

**Risk Factors of Dry Eye Disease:** The main risk factors for the occurrence of dry eye disease include older age [21], female gender [22] and postmenopausal women [23].

In addition, some other clinical conditions such as diabetes mellitus [24], hepatitis-C associated cirrhosis [25], connective tissue diseases [26], antihistamine use [27], post-traumatic stress disorder and depression [28], vitamin A and vitamin D deficiency [29], and long-term contact lens use [30] may also be considered risk factors for dry eye disease.

Environmental factors (humidity and air pollution) and external factors (prolonged exposure to light sources and reading) also act as environmental risk factors for DED [31, 32] (see **Fig. 1**). The use of Visual display terminal (VDT), occupational use of computers and laptops, and Smartphones are also important risk factors for the occurrence of DED in modern times [20, 33].

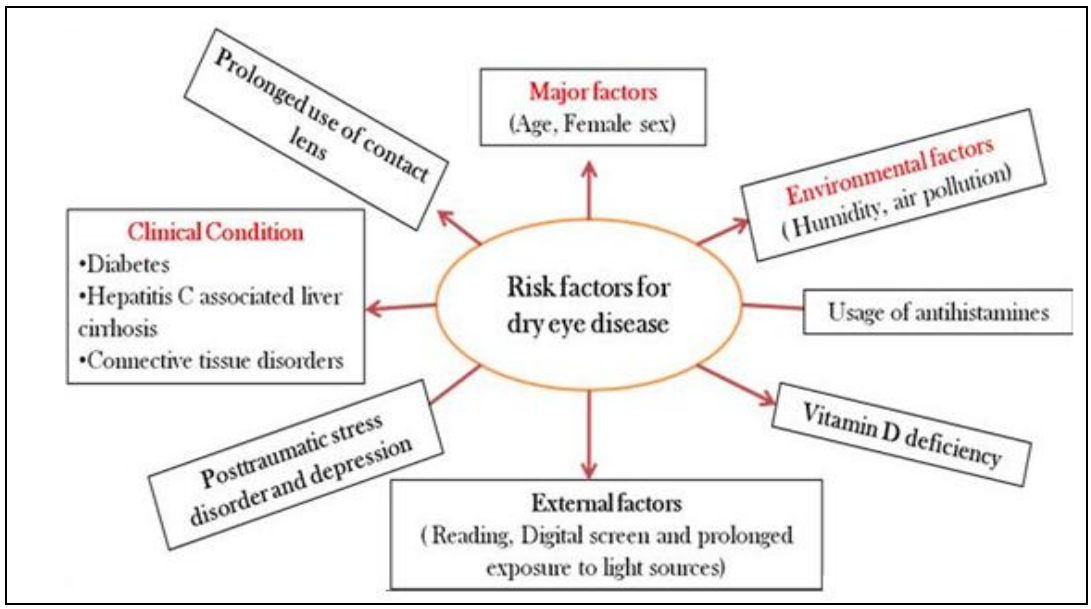


**FIG. 1: RISK FACTORS FOR DRY EYE DISEASE (DED)**

**Correlation of Digital Screen Use and Ded:** The association between DED and digital screen use is particularly noteworthy because dry eye disease can significantly affect quality of life due to ocular discomfort and visual disturbances caused by tear film instability. Long-term use of digital screens alters blinking behavior by decreasing the rate and completeness of blinking, resulting in increased ocular surface dryness [34, 35]. Evaporation of aqueous tears from the tear film during blinking is considered one of the possible mechanisms involved in the prevalence of DED. Full blinking is necessary to replenish the tear film by distributing tears and lipids from the lacrimal and meibomian glands over the ocular surface. This further initiates the DED cycle [36]. This hypothesis has been supported by a number of research studies showing that digital screen use can alter blink kinetics [37]. One study reports that the percentage of incomplete blinks is increased when playing a video game compared to baseline, which is consistent with the above hypothesis [38].

One of the main causes of dry eyes disease when using digital screens is the blue light emitted from our computers, laptops, video screens and smartphones [39]. Other causes of dry eye disease when using digital screens include decreased blink rate, screen characteristics (decreased font size, decreased contrast, excessive luminance, and small screen size), screen usage conditions (improper lighting, contact lens use, high temperature, low humidity, and direct airflow), and screen positioning (screen reflections, low and high screen position). Factors responsible for tear film and ocular surface abnormalities include decreased tear film thickness and stability, increased tear film evaporation, increased osmolarity and decreased tear film volume, abnormal tear drainage, increased corneal stress, accumulation of inflammatory markers, and increased ocular surface stress. In addition, decreased mucin secretion, increased lid margin abnormalities, decreased tear turnover rate, inefficient tear film distribution, decreased visual clarity, and decreased basal tear secretion also contribute to factors [40]. Experts suggest that dry eye may be a major cause of headache, light sensitivity, itchy eyes, eye pain and burning sensation. In addition, some studies have reported that people with migraine or post-traumatic brain injury are more prone to dry eye complications [41, 42]. It is also reported that people who sit in front of a screen for more than 5 to 8 years are at increased risk for dry eye and associated severe symptoms [43]. The pandemic COVID-19 appears to be worsening individual eye health due to a significant increase in the use of digital devices for work, education, communication, and recreation [44]. In addition, many young people are prone to dry eyes in today's digitalised world due to their frequent use of electronic devices for education and entertainment [45].

**Pathophysiology of DED:** DED is a multifactorial disease in which multiple mechanisms interact. Several risk factors, including long-term use of

digital systems and air conditioning, result in either decreased secretion of tear fluid, defined as aqueous deficient dry eye, or increased evaporation of tear fluid, defined as evaporative dry eye [46]. Many individuals suffering from DED suffer from both of these pathogenic mechanisms, which share the common condition of tear hyperosmolarity. Tear hyperosmolarity leads to further activation of mitogen-activated protein kinase (MAPK) p[38] and corneal epithelial c-Jun N-terminal kinase (JNK), nuclear factor-kB (NF-kB), and activator protein-1 (AP-1). It is also responsible for the production of pro-inflammatory interleukins (IL-1β, IL-6 and TNF-α), matrix metalloproteinases (MMPs) (MMP-3 and 9), chemokines and also induces apoptosis [47]. In general, excitation of nerve endings in the cornea and nasal passages transmits signals to the central nervous system, which in turn controls tear production and blinking of the lacrimal gland. Blinking normally compresses the meibomian glands, which produce lipids throughout the ocular surface and form the lipid layer of the tear film. In addition, the goblet cells of the conjunctiva and the ocular surface promote the formation of the mucin layer [48]. DED is mainly triggered by the hyperosmolarity and impermanence of the tear film, which initiates an inflammatory cascade process that eventually leads to damage of the epithelial and goblet cells of the eye. Eventually, the equilibrium of the tear film is lost [49]. In general, the osmolarity of the tear film in normal people is 296-302 mOsm/L, whereas in people with DED it is between 316-360 mOsm/L [50]. Thus, the hyperosmolar conditions, the inflammatory cascade promoted by immune cells and the matrix conversion factor activate oxidative stress on the ocular surface. These factors contribute to oxidative stress by producing reactive oxygen species (ROS), decreasing the activity of antioxidant enzymes (glutathione peroxidase-1 and superoxide dismutase-1), and increasing the activity of heme oxygenase-1 and cyclooxygenase-2, thereby disturbing the physiological balance between ROS and antioxidant enzymes [51, 52], as shown in **Fig. 2.** Caspases 8, 9, 3, and 7 alter the ocular surface, leading to apoptosis [53]. Apoptosis decreases tear film stability and increases corneal nerve fibre stimulation, which can lead to lacrimal gland stimulation, blinking, and other DED symptoms. These effects, in combination with the hyperosmolar environment, lead to a weakening of tear film stability [54]. In addition, damage to the conjunctival epithelium resulted in a significant change in mucin production; glycoproteins necessary for water retention and maintenance of the moist eye led to the formation of an unstable and hyperosmolar tear film [55]. People suffering from dry eyes may feel a pollutant in the eye, resulting in inflamed eyes, decreased visual activity, and inability to focus on work, especially on a computer screen [56].

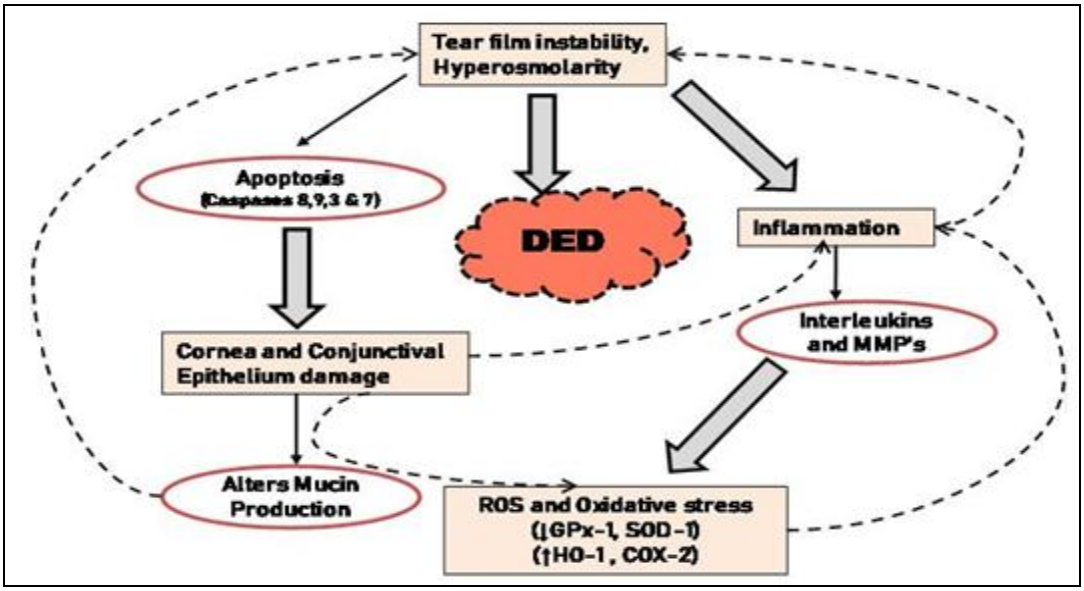


**FIG. 2: KEY FACTORS INVOLVED IN PREVALENCE OF DED. THE DOTTED LINES REPRESENT THE FACTORS THAT ENHANCE TEAR FILM INSTABILITY AND OSMOLARITY. BOLD ARROWS REPRESENT THE SEQUENTIAL OCCURRENCE OF EVENTS THAT INFLUENCE THE INCIDENCE OF DRY EYE DISEASE**

**Mucins and Dry Eye Disease (DED):**

**Overview of Mucins:** Mucins have been identified as the largest glycoproteins and are composed of oligosaccharide carbohydrates that make up the majority of their molecular weight. Mucins have an apomucin protein core consisting of tandem repeats of the amino acids serine, threonine, and proline [57]. Epithelial cells, including endothelial cells, goblet cells, leukocytes, and epithelial glands of the gastrointestinal tract, produce mucins. They are also found in the ear epithelium and on the ocular surface [58] and form gel-like structures covering the epithelial cell surfaces of the stomach, respiratory tract, genitourinary tract, and digestive tract [59].

Human mucins are encoded by 22 genes, designated MUC1 to MUC22, which are differently expressed in different tissues, with higher expression in the gastrointestinal tract and lower expression in other parts of the body [60]. Mucins exhibit a complex molecular organization and are divided into secreted mucins and transmembrane mucins based on their structure and localization. Secreted mucins protect organs from external infection by forming a protective extracellular layer, whereas transmembrane mucins contribute to the protection, signaling, surveillance, and repair of damaged epithelia. The secreted mucins were further divided into gel-forming mucins (MUC2, 5AC, 5B, 6, 19) and non-gel-forming mucins (MUC7, 8). Transmembrane mucins include MUC1, 3A, 3B, 4, 12, 13, 15, 16, 17, 18, 20 and 21 [61].

**Role of Mucins on the Ocular Surface:** Mucins play a key role in maintaining the hydrophilicity of the tear film by stabilizing the tear film, decreasing surface tension, and allowing homogeneous distribution of the aqueous layer on the ocular surface. Corneal and conjunctival epithelial cells express transmembrane mucins such as MUC1, MUC4, and MUC16 [62] and epithelial goblet cells produce and secrete MUC5AC, the most abundant gel-forming mucin on the ocular surface. Various sampling methods and immunoassay techniques have been performed to determine MUC5AC levels in human tear fluid and corneal film [63]. In addition, MUC19, a gel-forming mucin, has also been detected in corneal, conjunctival, and lacrimal gland tissues [64]. Ocular mucins cleanse the eye, moisten and lubricate the corneal surface to create a smooth and refractive surface, and stabilize the tear film. They also promote disadhesion, marginal lubrication, barrier function, and epithelial integrity [65].

**Mucins role in Dry Eye Disease (DED):** HLA-DR and ICAM-1 expression are negatively correlated with the proportion of conjunctival goblet cells in DED, suggesting that the loss of these cells may be related to the severity of inflammation and its adverse effects on the ocular surface.

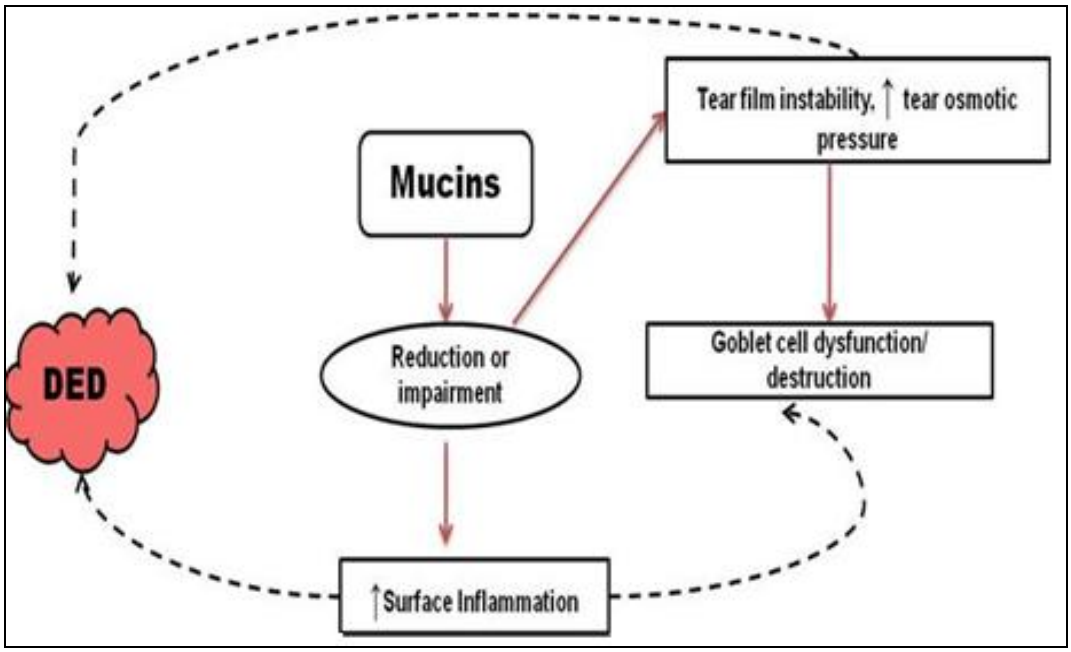


**FIG. 3: POSSIBLE ROLE OF MUCINS IN DED. RED LINES INDICATE THE EFFECT OF MUCINS ON OCULAR SURFACE AND THE DOTTED LINES INDICATE THE FACTORS RESPONSIBLE FOR INCIDENCE OF DED**

In addition, inflammation may lead to altered mucin glycoproteins on the apical surface of conjunctival cells. The role of mucins in the tear film is crucial, and altered mucin expression on the ocular surface is thought to play an important role in tear film abnormality as observed in DED [66]. Several studies have found that goblet cell insufficiency and decreased MUC5AC expression are the most common alterations in DED patients. It is also known that variations in mucin concentration lead to changes in tear osmotic pressure, which in turn triggers an inflammatory response that damages the ocular surface and promotes epithelial cell death and a decrease in goblet cell and mucin function [67], as shown in **Fig. 3**. According to a cross-sectional study, professionals who use digital screens for prolonged periods of time and individuals who frequently strain their eyes have low MUC5AC concentrations in their tears [68].

**Role of Natural Diet and Phytochemical Constituents in the Management of DED:** Tear film instability and hyperosmolarity are the main causes of DED occurrence. The tear film is a mixture of molecules such as mucins, lipids and water. It is produced by the specific structures of the eye, but is also secreted from the bloodstream to a small extent. Nutrients from the diet can directly or indirectly alter the composition of the tear film by triggering changes on the ocular surface. Consequently, dietary nutrients and certain phytochemical constituents can be used to treat dry eye symptoms by increasing tear production and altering mucin concentrations.

Certain vitamins and minerals such as vitamin A, polyunsaturated essential fatty acids (PUFAs), amino acids and vitamin D have been shown to have a beneficial and therapeutic effect on the ocular surface. Vitamin A, for example, helps maintain the ocular surface epithelium, while PUFAs such as omega-3 and -6 have anti-inflammatory, regenerative and neuroprotective properties. In addition, amino acids protect the corneal structure. Therefore, the inclusion of these minerals and vitamins in the diet has been suggested as an excellent nutritional supplement in the treatment of DED, as it improves the condition of the ocular surface [69]. Phytochemical constituents from natural plants and herbs, including polyphenols may have beneficial effects in controlling pathological mechanisms of DED according to *in-vitro* and *in-vivo* studies. In some studies, epigallocatechin gallate, quercetin, resveratrol, ferulic acid and kaempferol, pterostilbene, and curcumin were found to have beneficial effects in controlling dry eye disease by controlling oxidative stress, limiting the inflammatory cascade, promoting MUC5AC production, and maintaining tear film stability [70]. In an *in-vitro* study, quercetin was reported to increase the expression and production of the MUC5AC gene in intestinal goblet cells, and this is also thought to be increased on the ocular surface [71].

Some studies have reported that oral intake of a combined dietary supplement of lutein/zeaxanthin, curcumin, and vitamin D3 improves dry eye symptoms with multiple mechanisms of action. Increased antioxidant levels and restored concentrations of protective tear proteins such as MUC5AC contribute to the supplement's ability to reduce oxidative stress and alleviate dry eyes [72].

Some studies have found that vitamin B12; vitamin C, vitamin D, vitamin E, selenium, and lactoferrin also contribute to the treatment of dry eye disease and associated symptoms. Mechanisms include down-regulation of pro-inflammatory cytokines in the conjunctiva, regulation of neuropathic pain, improvement of tear production and stability, improvement of lacrimal gland function, reduction of epithelial damage, and regulation of apoptosis [73].

Anthocyanins are increasingly used worldwide as dietary supplements for eye health. A clinical study reported that oral ingestion of anthocyanin oligomers increased therapeutic and safe efficacy in the treatment of dry eye disease by improving tear break-up time, intraocular pressure, and patient symptoms [74].

**CONCLUSION:** Dry eye disease has become more common in recent years due to prolonged use of digital screens and extended air conditioning. Long-term use of artificial tears, cyclosporine drops, fluorometholone and hydrocortisone eye drops, lactoferrin, and topical mucin secretagogues (diquafosol-tetrasodium) for dry eye has been associated with significant adverse effects. Therefore, this study primarily focused on the idea

that dietary nutritional changes and supplements containing active phytoconstituents could increase MUC5AC production and have a safe and beneficial effect in alleviating dry eye disease and its accompanying symptoms. Adequate nutrient intake and maintenance of a humidified atmosphere may be helpful in the management of dry eye in individuals who sit in front of digital screens for prolonged periods of time.

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