Feed the Eye to Heal the Eye

Introduction

Nutrition is of paramount importance for the visual system. Proper nutrition helps make better use of your eyesight and reduces the appearance of degenerative and nondegenerative eye diseases. Therefore, nutrition can and should be refined on the basis of ocular pathologies that are in the process of appearing or already present and to promote their treatment.[1,2]

Microbiota and Microbiome

Eating, however, means modifying our microbiota and, consequently, our microbiome. The microbiota indicates the population, in the order of a few billion, of microorganisms (archaea, bacteria, yeasts, viruses, and fungi) present throughout our body, on the dermis and in all our cavities and which, in the right balance between symbionts (microorganisms with beneficial action) and pathobionts (microorganisms that cause diseases), necessary for our well-being; on the other hand, the microbiome refers to the totality of the genetic heritage possessed by the microbiota, i.e., the genes that the latter is able to express.

The microorganisms of the gut microbiota help us assimilate food, protect us from many diseases, and produce substances that are very useful for our metabolism including vitamins such as Vitamin D, short-chain fatty acids (SCFAs), certain hormones, and neurotransmitters. Today, the gut microbiota is an important therapeutic target for many inflammatory, autoimmune, neurodegenerative, and many other diseases that scientific studies are progressively identifying. The composition of the individual microbiota and the gut microbiota in particular is influenced by pregnancy, natural or cesarean delivery, breastfeeding or artificial feeding, weaning, excessive hygiene, stress, exercise, drug therapies, and above all nutrition. With reference to drugs, it is very important to underline that antibiotics, if on the one hand they prevent the proliferation of pathogens and the development of infectious diseases, on the other hand they compromise the normal bacterial population, which resides mainly in the intestine, where they play a fundamental role in maintaining the health of the host organism.

However, nutrition exerts one of the main influences on the balance of the microbiota, since the diet represents a source of essential nutrients for the human body not only to support growth, vital, and reproductive functions, but also to modulate and support the various microbial communities and, in particular, the gut microbiota. The choice of a type of food, its quality characteristics, and even its origin shape our gut microbes, influencing their composition and function, with repercussions on host-microbe interactions [Figure 1].[3-5]

The Mediterranean Diet

In particular, the Mediterranean diet (MedDiet) has a high prebiotic potential, as it involves a high consumption of legumes, vegetables, whole grains, and fruits, the same "healthy" carbohydrates, in particular nondigestible carbohydrates such as fiber and resistant starch. Prebiotics are, in fact, nondigestible substances naturally contained in some foods, mainly water-soluble and nongeling fibers including nonstarchy polysaccharides or beta-glucans, fructans, fructooligosaccharides, inulins, lactitol, lactosucrose, lactulose, pyrodextrins, and soy oligosaccharides, which promote the growth, in the colon, of one or more bacterial species useful for the development of probiotic microflora.[6-10]

The MedDiet (from the Greek "δίαιτα" = lifestyle), which became UNESCO's definitive intangible cultural heritage in 2010, is currently considered the best in terms of health, based on countless experimental evidence. The Mediterranean model is characterized by a relatively high consumption of total fats, especially extra virgin olive oil, a moderate consumption of wine with meals, low in saturated fats but rich in vegetables, fruits, nuts, legumes, and, in particular, fermented dairy products not processed from cereals, nutrients and dietary

Figure 1: Graphic abstract

fiber, antioxidant compounds and bioactive elements with anti inflammatory effects ensure a number of beneficial effects. For example, it allows one to maintain a low glycemic index in general and all those healthy properties that contribute to the achievement and maintenance of a healthy body weight, increasing longevity, reducing the risk of chronic diseases, including cardiovascular disease and metabolic syndrome; therefore, type 2 diabetes, obesity, certain cancers, and last but not least, cognitive impairment.[11] MedDiet has a high prebiotic potential, with its high consumption of legumes, vegetables, whole grains, and fruits, the same "healthy" carbohydrates, especially nondigestible carbohydrates such as fiber and resistant starch, affect microbial composition and diversity, can stimulate the growth of beneficial bacterial species involved in the production of butyrate and methane, which scientific data have associated with an improved cardiometabolic profile.[12]

As far as fats are concerned, EVO oil, obtained from the first cold pressing of the ripe fruit, is the only one suggested by MedDiet; it contains hydroxytyrosol and tyrosol, oleocanthal, resveratrol and many other bioactive phenolic dietary compounds with antioxidant and phytochemical properties, tocopherols, polyphenols and phytosterols with antioxidant and anti-inflammatory action.[13]

These properties represent a nutritional approach of choice to combat various diseases, including eye diseases, with an inflammatory component, mainly because recent validated scientific data highlight the ability of specific nutrients to cross the retinal barrier.[14]

As far as proteins are concerned, it is advisable to prefer white meats and fish, eggs, and some cheese. Fresh and frozen fish, possibly 2–3 times a week, checking its origin to rule out the possibility that it may contain pollutants and harmful metals, such as mercury. For frozen foods, ensure that they are purchased from places where there is a cold chain guarantee.

For meat, white meats, such as chicken, turkey (preferably free-range), and rabbit, should certainly be preferred, minimizing the consumption of red meats, such as beef and veal, and almost always eliminating visible fat. In fact, excessive consumption of red meat (more than three to four times a month), such as the use of carnitine in gyms, causes the production of trimethylamine in the intestine, a molecule that passes into the liver where it is metabolized into trimethylamine N oxidase, which is very harmful to the cardiovascular system, renal, and cerebral. Its high level is considered a predictive biomarker of cardiometabolic diseases, cancer, and even myocardial infarction.[12]

On the other hand, we can also consume 2–3 eggs a week (except for individual pathological conditions), spread over different days; possibly from free-range hens to have more Vitamin D in the yolk, without worrying too much about a possible increase in cholesterol, which, however, should not fall below 190 mg/ml of plasma, as it is necessary at the level of the lipid bilayer of cell membranes, as a precursor of steroid hormones, to produce Vitamin D at the epidermal level from solar ultraviolet rays.

If you drink milk, it is recommended to choose skimmed or semi-skimmed milk and possibly prefer goat's milk, with A2 casein and not cow's milk with proinflammatory A1 casein. Consume cheese in small amounts, due to its high fat content, and prefer low-fat cheeses, such as grilled cheese.

Ultra-processed, processed, packaged, and shelf-stable foods should be avoided most of the time because they are high in additives, preservatives (often harmful synthetics), and process contaminants. However, they are poor in vitamins and other essential micronutrients, but also in fiber and phytoestrogens, which perform various protective functions, and contain large amounts of sugars, salts, and fats. These foods are harmful to our health, although they are still very popular, also because they are more practical and cheaper. Their frequent consumption is also associated with increased salt excretion and alters the Na/K ratio, increasing it.[12-15]

The Eye Diet

For both overall eye health and specific diseases such as macular degeneration, there are many useful vitamins and minerals. For those suffering from macular degeneration, studies on age-related eye diseases recommend dietary supplementation with minerals and antioxidants, including lutein, zeaxanthin, Vitamin C, Vitamin E, zinc, and copper. To maintain overall eye health, a diet rich in minerals and antioxidants is recommended. The best sources for these are leafy greens, such as kale, spinach, kale, and turnips, as well as fruits, berries, and other colorful vegetables. Supplements with zinc, selenium, lutein, and Vitamins A, C, and E are also good. A diet rich in ω-3 fatty acids and low in ω-6 fatty acids is also beneficial, especially for those suffering from dry eyes, as ω-6 are proinflammatory and can contribute to the inflammatory component of dry eyes. The latter are generally found in meat, oils, margarines, and carbohydrates, which make up a large part of most Western diets. ω-3 have anti-inflammatory properties and can help the tear glands produce high-quality tears. These can be taken as a supplement or through a diet rich in nuts and fish, such as salmon. Although flaxseed oil supplements are good, a high-quality fish oil with a high concentration of EPA and DHA is the best option, as it is easier for our body to use.[16-19]

The use of aclolics, which causes a delay between the brain and the eyes due to the slow pace of communication between neurotransmitters in brain coordination, weakens the eye muscles. Excess alcohol consumption can also cause dry eyes and eyelid twitching. The long-term effects of alcohol abuse can have detrimental consequences on vision and eye health, such as toxic amblyopia, which is the result of a toxic reaction in the optic nerve that causes permanent vision loss. However, excessive alcohol can also increase the risk of age-related macular degeneration: The World Health Organization report revealed that a person's average daily consumption is 33 g of pure alcohol, which is equivalent to two glasses of wine, and an Australian study revealed that drinking more than 20 g of alcohol per day leads to a 20% increase in the chances of developing early macular degeneration compared to those who do not consume alcohol. Poor diet and alcohol may also be related to the development of cataracts. Not forgetting that prolonged alcohol abuse will eventually affect our vision through vitamin deficiency, as the liver can only process a certain amount of alcohol at a time, and excessive consumption can affect the absorption of vitamins in the liver, which are necessary to maintain healthy eyes and good vision.[20-23]

Seasonality, biodiversity, nutrient density, and the use of a variety of traditional and local food products, as well as culinary traditions, are important elements of the MedDiet, which, being predominantly plant-based, is sustainable on an individual level, but also sustainable for the planet, ensuring well-being for future generations, as it implies a lower impact on water and energy, as well as lower land consumption and lower greenhouse gas emissions compared to other diet models.[24-29]

In addition, it is necessary to take into account the correct cooking practices and treatments (soaking, cooking at 100°C, sprouting, etc.) useful to eliminate the antinutrients present in the various foods, as well as considering the already known knowledge on the effects of different types of nutrition on the main eye diseases [Table 1].

It should also be remembered that diet influences epigenetics, i.e. those changes not in DNA and chromatin, which are heritable and closely related to our well-being. For this reason, before opting for this or that diet, it is certainly more advantageous to focus on a correct lifestyle, choosing the right diet, abstaining from excessive smoking and alcohol consumption, allowing nutrients to better modulate the biological processes of our body.[24] In this scenario, calorie restriction plays an increasingly important role, that is, the reduction of about 40% of normal caloric intake contributes to the control of weight loss, the control of cholesterol and triglyceride values, and the reduction of age-related diseases. Moreover, MedDiet seems to be the only one that can mimic the effects of calorie restriction.[30-34]

The Ocular Microbiome

Numerous bacterial microhabitats coexist in the human eye, the composition of which reflects the levels of exposure to the external environment. Studies published in the literature have shown that the genus most represented on the ocular surface is Corynebacterium, followed by Staphylococcus, Streptococcus, Acinetobacter, and Pseudomonas. In particular, a study,[35] recently published in the ocular surface, analyzed the structure and distribution of bacterial communities in the various microhabitats of the human eye, to identify similarities and differences.

The four ocular sites analyzed were:

- Eyelid margin tissue of patients with eyelid abnormalities
- Conjunctival tissue of the fornices and limbus of patients with pterygia
- Swabs of the ocular surface (conjunctival) swabs
- Swabs from the skin of the face.

The study proposed a classification of the ocular bacterial distribution into three groups:

- Group 1: Consisting of organisms that reside on the skin and eyelid margin and then move to the ocular surface, as indicated by the low relative abundance at this site. The genera belonging to this group are Corynebacterium and Staphylococcus. The former was, in fact, constantly present on the outer surface of the skin, and its relative abundance progressively decreased as it moved from the skin (12.2%), to the eyelid margin (7.6%), and to the ocular surface (4.0%), but was rarely present in conjunctival tissue samples. Similarly, common skin-resident Staphylococcus was abundant on the skin surface (15.1%), decreased at the eyelid margin (1.9%), and was present in relatively small amounts on the ocular surface (3.1%)
- Group 2: Consisting of microorganisms located mainly on the ocular surface and detected at low levels on the skin, eyelid margin, and conjunctiva. Members of this group could be acquired from air or water and may be able to survive on the ocular surface, but not in other regions of the eye. Acinetobacter, for example, was isolated in relatively greater abundance on the ocular surface (12.3%) than on the skin (1.0%) and the margin of the eyelid margin (0.5%)
- Group 3: Consisting of microorganisms present in the conjunctiva and within the eyelid margin and found inconsistently and in relatively low abundance on the skin and ocular surface. The genus Pseudomonas belongs to this group. However, not all members of this group showed the same distribution; some were constantly present in

Table 1: Impact of diet on the main eye diseases

	Cataract	Glaucoma	Macular degeneration	Retinal detachment
Balance diet	Not yet proven	Dubious role of micronutrients	Lower incidence	Not yet proven
Mediterranean diet	Cataractogeny	Dubious role of micronutrients	Decrease in late stages	Not yet proven
Western eating patterns	Increased risk	Not yet proven	Increased risk	Not yet proven
Calorie restriction	Delayed age-related cataract in animals	Prevented retinal ischemia in animal models	Decreased features	Not yet proven
Intermittent fasting	Not yet proven	Improvement of intraocular pressure in animal moods	Not yet proven	Decreased or increased risk based on microbiome

the conjunctival and eyelid margin, others were more specific to the conjunctiva, and one was specific to the eyelid margin.

The results of this research are very interesting as they have shown that the microorganisms present in the eye and the surrounding environment are clearly organized at the spatial level and that this biogeography is representative of a process of microbial dispersion and environmental selection.[35]

Microbiota and Eye Diseases

Consolidated scientific data are now available on the correlation between the gut microbiota and the pathogenesis of intestinal diseases, including irritable bowel syndrome, while the correlations between microbiota alterations and the onset of certain eye diseases are probably less well known.

The first point to highlight is that this correlation can be identified for eye diseases, in which there is an inflammatory component, and the specific areas can be the following:

- Microbiota and age-related macular degeneration
- Pathologies of the microbiota and ocular surface
- Microbiota and neurodegenerative ocular diseases.

Age-related macular degeneration is a chronic, progressive degenerative disease with a tendency to become bilateral, affecting the macula, i.e. the central region of the retina responsible for distinct vision of details, and, if not adequately treated, can lead to severe and irreversible vision impairment. Two forms are recognized: the "atrophic" or "dry" form, which affects about 90% of cases, and is characterized by the accumulation of deposits of yellowish material, the drusen, under the macula, which progressively alter the functionality of photoreceptors, the cells responsible for the perception of light stimuli; the "neovascular" or "wet" form, less frequent, but with a more disabling outcome, characterized by the formation of small abnormal blood vessels below the macula. These vessels have very fragile walls and can easily leak fluid or rupture, causing bleeding in the retina. Although the causes of the disease are not yet fully understood, some risk factors have certainly been identified. First of all, age (it is estimated that about 1.8% of the population over 50 suffers from it, to which is added a series of risk factors: Demography such as ethnicity and gender, genetics, as some mutations have been identified that seem to predispose to the onset of the disease, environmental factors such as smoking, alcohol consumption, obesity, lack of physical activity, prolonged exposure to sunlight, reduced intake of antioxidants in the diet. Apart from medical therapy, which is unfortunately useful only in the atrophic form, with antiangiogenic drugs, several drugs can influence the onset and progression of this serious ocular disease from the atrophic to the neovascular form. Recent studies suggest, in fact, that inflammatory mediators play an important role in the pathophysiology of eye disease, especially in the formation of reactive oxygen species (ROS, oxygen radical species), which, at high concentrations, can damage the pigment epithelium of the retina, the layer that absorbs light and nourishes the cells of the retina. In this regard, some nutrients with anti-inflammatory and antioxidant action, directly or indirectly, through the gut microbiota, have been hypothesized to have beneficial effects on disease prevention. This hypothesis has attracted a great deal of interest from the scientific community, which has begun to evaluate the effectiveness of prebiotics and probiotics, as well as antioxidant-rich foods, as a prevention strategy.[36,37]

Clinical evidence attests that nutritional control may be a prevention strategy, as certain micronutrients have been shown to have the ability to reduce the risk of disease progression.

Furthermore, recent studies have highlighted the presence of an alteration of the intestinal microbiota, since, with the normal ageing process and especially from the age of 65, the intestinal microbiota undergoes alterations, losing, for example, the enormous variety of microbials. These changes are reflected in a different immune response and appear to be related to the onset of various metabolic diseases, such as diabetes, or age-related diseases, such as macular degeneration.[38-40]

An important review examined some of the most recent studies and highlighted how eating habits are closely associated with certain diseases. A "Western" diet, based on high consumption of dairy products, red meat, sweets, and energy drinks, has been predominantly associated with people with macular degeneration. In fact, an "oriental" diet based on the intake of legumes, rice, and low-fat dairy products has been shown to play a preventive role in the onset of this eye disease.[38-40]

The substances that have also been shown to have the greatest beneficial effects on eye health are Vitamin C or ascorbic acid, mainly in fruits (citrus fruits, kiwi, strawberries, and blackcurrants) or vegetables (kale, spinach, tomatoes, and potatoes) with a high antioxidant power that fights free radicals, protecting the eyes from degenerative diseases of the retina, glaucoma, and performing a preventive action against corneal ulcers; Vitamin E, a powerful antioxidant, present in large quantities in dried fruit (almonds, peanuts and pine nuts), as well as in dried apricots, sunflower seeds, legumes and green leafy vegetables. It belongs to a large group of fat-soluble molecules and is capable of reducing free radicals and inhibiting the spread of ROS; zinc, a powerful antioxidant, mainly found in foods of animal origin, seafood (especially oysters), eggs, liver, beef, and lamb, which helps the body absorb Vitamin A. Zinc is an important trace element, involved in various physiological metabolisms and is useful for the construction of DNA and the correct formation of certain proteins. Zinc is present in ocular tissue in high concentrations, particularly in the retina and choroid, and its deficiency affects ocular development and the onset of diseases, such as cataracts and degenerative diseases of the retina, predisposing to poor night vision.[38]

Three carotenoids with great antioxidant power to prevent ageing are particularly concentrated in the human macula: lutein, zeaxanthin, and meso-zeaxanthin. The first two are found in green leafy vegetables such as spinach, kale, Swiss chard, and broccoli, but also in corn, basil, tomatoes, yellow vegetables such as pumpkin, green tea, and many other vegetables, while the third seems to form in the macula from the metabolic transformations of ingested carotenoids. Therefore, these substances fall into the group of nutritional interventions that can be implemented to prevent ageing, macular degeneration, and other eye diseases.

In the event of deficiencies due to pathological conditions or inadequate nutrition, lutein and zeaxanthin can be supplemented with specially formulated nutraceutical products.[39-41]

In recent years, research has focused on the relationship between microbiota balance and certain ocular surface diseases, such as dry eye syndrome, episcleritis, chronic follicular conjunctivitis, pterygium, and Thygeson's disease.[42]

All the pathologies mentioned have a substantially idiopathic nature, i.e., they are characterized by the absence of a uniquely identifiable cause, and at the same time, they are united by the presence of an inflammatory component. The hypothesis that has guided research in recent years has been that an imbalance in the specific ocular surface microbiota community may determine or contribute to its onset, as in the case of the gut microbiome and diseases affecting the gut.

The ocular surface, in physiological balance, is the "first line" of defense of the eye, where many potential attacks are perceived and possibly neutralized, both microbial and related to environmental factors. The first question that arises in ophthalmology is whether the ocular surface, like other mucosal surfaces, has a specific resident microbiota and what role it plays in the physiology of the surface itself. A recent study[43] illustrated the structure and distribution of bacterial communities in the various microhabitats of the human eye, mapping their similarities and differences. During evolutionary processes, therefore, many eubiont microorganisms, in particular bacteria, have colonized the ocular surface as commensals, playing an important role in maintaining its homeostasis, i.e., the natural tendency to achieve relative stability. The ocular surface is also equipped with very effective immune defenses that consist of active mechanisms for suppressing inflammation. For this purpose, there are macrophages, dendritic cells, B cells, IgA, lysozyme, antimicrobial peptides, and many other components that act as a barrier against external agents. Habitual commensals on the ocular surface maintain a basic level of activation of innate defenses by stimulating the receptors of the epithelial cells.

Therefore, the normal balance of the ocular microbiota is of great importance, since pathological infection and inflammation arise precisely when a pathogenic strain infiltrates the ocular flora capable of overwhelming the usual flora, or a dominant strain secretes an excessive amount of immunogenetic substances, such as, for example, exotoxin A, which is one of the causes of the onset of marginal keratitis. Furthermore, microorganisms in the microbiota actively participate in the metabolism of drugs in the mucous membranes, thus influencing the efficacy of drug therapies.

The above attests to the importance of research aimed at understanding the balance of the microbiota from three different perspectives: diagnosis, in view of new techniques and tests that make it possible to link dysbiosis to specific ocular surface pathologies; prevention, through the probiotic administration of viable bacterial and microbial strains capable of colonizing the surface; and treatment, intervening in the correction of imbalances in the physiological microbiota, also to promote the effectiveness of specific pharmacological treatments administered for the various pathologies.

Dry eye is among the most common pathological eye conditions and currently affects tens of millions of people around the world. The origin of this disease is not yet fully understood, but it is believed to be multifactorial. Currently, some of the most promising results in terms of identifying etiopathological causes come from the multidisciplinary approach, which includes immunometabolic analysis, microbiota analysis, and bioengineering.[44]

Dry eye syndrome is defined as keratoconjunctivitis sicca and is a condition that affects the tear film and the ocular surface, causing symptoms of discomfort, visual disturbances, and tear film instability with potential damage to the ocular surface. It is accompanied by an increase in tear film osmolarity and inflammation of the ocular surface. The tear film is a film that covers the corneal-conjunctival surface and forms the direct interface between the eye and the external environment. It consists of three layers, respectively, lipid, aqueous, and mucosal. The aqueous part of the tear film is the most abundant and contains numerous electrolytes and proteins, including the lysozyme, which has specific antibacterial properties. It is produced by the lacrimal glands, the main gland, and the accessory gland.

The tear film performs numerous functions: it lubricates the eye, creating a smooth surface on the cornea on which the eyelids can slide easily; it nourishes the cornea, which, being devoid of blood vessels, receives nutrients and oxygen through the tear film; and it protects the eye from bacterial and viral infections and removes waste substances. In the presence of dry eye conditions, both the tear film and the corneoconjunctival epithelium undergo important changes which, if chronic, are capable of developing phenomena similar to those present during inflammation of the ocular surface.[45]

The balance of the ocular microbiota significantly affects the metabolic profile of the ocular surface, which in turn affects the immunity of the ocular surface itself. Recent studies show that SCFAs, such as butyrate produced by specific bacteria (such as Faecalibacterium), play an important role in the differentiation of Treg lymphocytes (regulatory T cells). Similarly, increased populations of Gram-negative bacteria could be responsible for inflammatory responses in dry eye patients, for example, lipopolysaccharide, an endotoxin excreted by Gram-negative bacteria, which increases the expression of inflammatory cytokines in the cornea and conjunctiva. These data suggest that alterations in the normal composition of the microbiota cause an abnormal immunological response (particularly through immunometabolic mechanisms), which is the part of the pathophysiological mechanisms underlying dry eye.[43-44]

Conclusion

Targeted manipulation of the gut microbiota, as well as maintaining the physiological composition of the ocular microbiota, seems to represent valid alternatives for the prevention and/or treatment of ocular diseases or disorders. For example, topical application of Lactobacillus acidophilus-based probiotics appears to improve keratoconjunctivitis. However, considering the preliminary nature of these findings, further studies are needed.[46]

Giuseppe Merra[1], Marcello Covino[2], Andrea Piccioni[2], Marcello Candelli[2], Veronica Ojetti[2], Antonio Gasbarrini[3], Francesco Franceschi[2]

[1]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy, [2]Department of Emergency, Catholic Univeristy of Sacred Heart, "A. Gemelli" General Hospital – IRCCS, Rome, Italy, [3]Department of Internal Medicine, Catholic Univeristy of Sacred Heart, "A. Gemelli" General Hospital – IRCCS, Rome, Italy

Address for correspondence: Giuseppe Merra, University of Rome Tor Vergata, Roma, Italy. E-mail: giuseppe.merra@uniroma2.it

Submitted: 11-May-2023; **Revised:** 30-Oct-2023; **Accepted:** 12-Nov-2023; **Published:** 29-Mar-2024

References

1. Rautiainen S, Manson JE, Lichtenstein AH, Sesso HD. Dietary supplements and disease prevention – A global overview. Nat Rev Endocrinol 2016;12:407-20.
2. Heidari M, Noorizadeh F, Wu K, Inomata T, Mashaghi A. Dry eye disease: Emerging approaches to disease analysis and therapy. J Clin Med 2019;8:1439.
3. Perler BK, Friedman ES, Wu GD. The role of the gut microbiota in the relationship between diet and human health. Annu Rev Physiol 2023;85:449-68.
4. Li C. Understanding interactions among diet, host and gut microbiota for personalized nutrition. Life Sci 2023;312:121265.
5. Guan L, Liu R. The role of diet and gut microbiota interactions in metabolic homeostasis. Adv Biol (Weinh) 2023;7:e2300100.
6. Merra G, Noce A, Marrone G, Cintoni M, Tarsitano MG, Capacci A, *et al.* Influence of mediterranean diet on human gut microbiota. Nutrients 2020;13:7.
7. Romano L, De Santis GL, Gualtieri P, Merra G. Thyroid disorders and mediterranean diet: Which way to prevent metabolic complications. Eur Rev Med Pharmacol Sci 2017;21:3531-2.
8. Merra G, Capacci A, Cenname G, Esposito E, Dri M, Di Renzo L, *et al.* The "microbiome": A protagonist in COVID-19 era. Microorganisms 2022;10:296.
9. Gualtieri P, Romano L, Capria G, Merra G. Microbiome and bariatric surgery: New options to precision surgery. Eur Rev Med Pharmacol Sci 2018;22:5773-4.
10. Romano L, Gualtieri P, Nicoletti F, Merra G. Neurodegenerative disorders, gut human microbiome and diet: Future research for prevention and supportive therapies. Eur Rev Med Pharmacol Sci 2018;22:5771-2.
11. Parletta N, Zarnowiecki D, Cho J, Wilson A, Bogomolova S, Villani A, *et al*. A mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). Nutr Neurosci 2019;22:474-87.
12. Lockyer S, Rowland I, Spencer JP, Yaqoob P, Stonehouse W. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: A randomised controlled trial. Eur J Nutr 2017;56:1421-32.
13. Di Mauro MD, Tomasello B, Giardina RC, Dattilo S, Mazzei V, Sinatra F, *et al.* Sugar and mineral enriched fraction from olive mill wastewater for promising cosmeceutical application: Characterization, *in vitro* and *in vivo* studies. Food Funct 2017;8:4713-22.
14. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, *et al.* Low-grade inflammation, diet composition and health: Current research evidence and its translation. Br J Nutr 2015;114:999-1012.
15. Zhuang R, Ge X, Han L, Yu P, Gong X, Meng Q, *et al.* Gut microbe-generated metabolite trimethylamine N-oxide and the risk of diabetes: A systematic review and dose-response meta-analysis. Obes Rev 2019;20:883-94.
16. Bianchi VE, Herrera PF, Laura R. Effect of nutrition on neurodegenerative diseases. A systematic review. Nutr Neurosci 2021;24:810-34.
17. Schwartz SG, Wang X, Chavis P, Kuriyan AE, Abariga SA. Vitamin A and fish oils for preventing the progression of retinitis pigmentosa. Cochrane Database Syst Rev 2020;6:CD008428.
18. Brito-García N, Del Pino-Sedeño T, Trujillo-Martín MM, Coco RM, Rodríguez de la Rúa E, Del Cura-González I, *et al.* Effectiveness and safety of nutritional supplements in the treatment of hereditary retinal dystrophies: A systematic review. Eye (Lond) 2017;31:273-85.
19. Zanón-Moreno V, Domingo Pedrol JC, Sanz-González SM, Raga-Cervera J, Salazar-Corral J, Pinazo-Durán MD. Feasibility study of a docosahexaenoic acid-optimized nutraceutical formulation on the macular levels of lutein in a healthy mediterranean population. Ophthalmic Res 2021;64:1068-76.
20. Abu-Amero KK, Kondkar AA, Chalam KV. Resveratrol and ophthalmic diseases. Nutrients 2016;8:200.
21. Bola C, Bartlett H, Eperjesi F. Resveratrol and the eye: Activity and molecular mechanisms. Graefes Arch Clin Exp Ophthalmol 2014;252:699-713.
22. Silva P, Sureda A, Tur JA, Andreoletti P, Cherkaoui-Malki M, Latruffe N. How efficient is resveratrol as an antioxidant of the mediterranean diet, towards alterations during the aging process? Free Radic Res 2019;53:1101-12.
23. Xu L, You QS, Jonas JB. Prevalence of alcohol consumption and risk of ocular diseases in a general population: The beijing eye study. Ophthalmology 2009;116:1872-9.
24. Baudin F, Benzenine E, Mariet AS, Ghezala IB, Bron AM, Daien V, *et al.* Topical antibiotic prophylaxis and intravitreal injections: Impact on the incidence of acute endophthalmitis-a nationwide study in france from 2009 to 2018. Pharmaceutics 2022;14:2133.
25. Sarkar A, Jayesh Sodha S, Junnuthula V, Kolimi P, Dyawanapelly S. Novel and investigational therapies for wet and dry age-related macular degeneration. Drug Discov Today 2022;27:2322-32.
26. Fleckenstein M, Keenan TD, Guymer RH, Chakravarthy U, Schmitz-Valckenberg S, Klaver CC, *et al.* Age-related macular degeneration. Nat Rev Dis Primers 2021;7:31.
27. Ozcaliskan S, Artunay O, Balci S, Perente I, Yenerel NM. Quantitative analysis of inner retinal structural and microvascular alterations in intermediate age-related macular degeneration: A swept-source OCT angiography study. Photodiagnosis Photodyn Ther 2020;32:102030.
28. Merle BM, Silver RE, Rosner B, Seddon JM. Associations between Vitamin D intake and progression to incident advanced age-related macular degeneration. Invest Ophthalmol Vis Sci 2017;58:4569-78.
29. Layana AG, Minnella AM, Garhöfer G, Aslam T, Holz FG, Leys A, *et al.* Vitamin D and age-related macular degeneration. Nutrients 2017;9:1120.
30. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, *et al.* Consumption of ultra-processed foods and cancer risk: Results from nutrinet-santé prospective cohort. BMJ 2018;360:k322.
31. Monda V, La Marra M, Perrella R, Caviglia G, Iavarone A, Chieffi S, *et al.* Obesity and brain illness: From cognitive and psychological evidences to obesity paradox. Diabetes Metab Syndr Obes 2017;10:473-9.

32. De Santis MA, Giuliani MM, Giuzio L, De Vita P, Lovegrove A, Shewry PR, *et al.* Differences in gluten protein composition between old and modern durum wheat genotypes in relation to 20th century breeding in Italy. Eur J Agron 2017;87:19-29.
33. Rodriguez NR, Miller SL. Effective translation of current dietary guidance: Understanding and communicating the concepts of minimal and optimal levels of dietary protein. Am J Clin Nutr 2015;101:1353S-8S.
34. Garcia-Mantrana I, Selma-Royo M, Alcantara C, Collado MC. Shifts on gut microbiota associated to mediterranean diet adherence and specific dietary intakes on general adult population. Front Microbiol 2018;9:890.
35. Chiang MC, Chern E. Ocular surface microbiota: Ophthalmic infectious disease and probiotics. Front Microbiol 2022;13:952473.
36. Zilliox MJ, Bouchard CS. The microbiome, ocular surface, and corneal disorders. Am J Pathol 2023;193:1648-61.
37. Lima-Fontes M, Meira L, Barata P, Falcão M, Carneiro Â. Gut microbiota and age-related macular degeneration: A growing partnership. Surv Ophthalmol 2022;67:883-91.
38. Pellegrini M, Senni C, Bernabei F, Cicero AF, Vagge A, Maestri A, *et al.* The role of nutrition and nutritional supplements in ocular surface diseases. Nutrients 2020;12:952.
39. Ozkan J, Willcox M, Wemheuer B, Wilcsek G, Coroneo M, Thomas T. Biogeography of the human ocular microbiota. Ocul Surf 2019;17:111-8.
40. Rinninella E, Mele MC, Merendino N, Cintoni M, Anselmi G, Caporossi A, *et al.* The role of diet, micronutrients and the gut microbiota in age-related macular degeneration: New perspectives from the gut¯retina axis. Nutrients 2018;10:1677.
41. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, *et al.* Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glob Health 2014;2:e106-16.
42. Zegans ME, Van Gelder RN. Considerations in understanding the ocular surface microbiome. Am J Ophthalmol 2014;158:420-2.
43. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, *et al.* Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013;504:446-50.
44. Yang CH, Albietz J, Harkin DG, Kimlin MG, Schmid KL. Impact of oral Vitamin D supplementation on the ocular surface in people with dry eye and/or low serum Vitamin D. Cont Lens Anterior Eye 2018;41:69-76.
45. Hwang JS, Lee YP, Shin YJ. Vitamin D enhances the efficacy of topical artificial tears in patients with dry eye disease. Cornea 2019;38:304-10.
46. Cavuoto KM, Banerjee S, Galor A. Relationship between the microbiome and ocular health. Ocul Surf 2019;17:384-92.

Access this article online	
Quick Response Code:	**Website:** https://journals.lww.com/joco
	DOI: 10.4103/joco.joco_94_23

How to cite this article: Merra G, Covino M, Piccioni A, Candelli M, Ojetti V, Gasbarrini A, *et al*. Feed the eye to heal the eye. J Curr Ophthalmol 2023;35:209-15.