ISSN 2150-5330 (online)

World Journal of *Gastrointestinal Pathophysiology*

Bimonthly Volume 15 Number 5 September 22, 2024



Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Pathophysiology

Contents

Bimonthly Volume 15 Number 5 September 22, 2024

REVIEW

Haghshenas L, Banihashemi S, Malekzadegan Y, Catanzaro R, Moghadam Ahmadi A, Marotta F. Microbiome as an endocrine organ and its relationship with eye diseases: Effective factors and new targeted approaches. *World J Gastrointest Pathophysiol* 2024; 15(5): 96446 [DOI: 10.4291/wjgp.v15.i5.96446]

World Journal of Gastrointestinal Pathophysiology

Bimonthly Volume 15 Number 5 September 22, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Pathophysiology*, Georgios D Koukoulis, MD, MSc, PhD, Consultant Surgeon, Department of General Surgery, General Hospital of Larissa, Larissa 41221, Greece. georgios.koukoulis@gmail.com

AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pathophysiology* (*WJGP*, *World J Gastrointest Pathophysiol*) is to provide scholars and readers from various fields of gastrointestinal pathophysiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGP mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal pathophysiology and covering a wide range of topics including disorders of the esophagus, stomach and duodenum, small intestines, pancreas, biliary system, and liver.

INDEXING/ABSTRACTING

The *WJGP* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lei Zhang*; **Production Department Director:** *Xu Guo*; **Cover Editor:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Pathophysiology

ISSN
ISSN 2150-5330 (online)

LAUNCH DATE
April 15, 2010

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Kusum K Kharbanda, Tsutomu Nishida, Somchai Amornyotin

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2150-5330/editorialboard.htm

PUBLICATION DATE
September 22, 2024

COPYRIGHT
© 2024 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2024 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: office@baishideng.com https://www.wjgnet.com

World Journal of Gastrointestinal Pathophysiology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Pathophysiol 2024 September 22; 15(5): 96446

DOI: 10.4291/wjgp.v15.i5.96446

ISSN 2150-5330 (online)

REVIEW

Microbiome as an endocrine organ and its relationship with eye diseases: Effective factors and new targeted approaches

Leila Haghshenas, Sara Banihashemi, Yalda Malekzadegan, Roberto Catanzaro, Amir Moghadam Ahmadi, Francesco Marotta

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Wu L

Received: May 7, 2024
Revised: September 4, 2024
Accepted: September 13, 2024
Published online: September 22, 2024
Processing time: 136 Days and 0.6 Hours

Leila Haghshenas, Department of Clinical Bioinformatics, Harvard Medical School, Boston, MA 02115, United States

Sara Banihashemi, Department of Bioscience, School of Science and Technology, Nottingham Trend University, Nottingham NG1 4FQ, United Kingdom

Yalda Malekzadegan, Department of Microbiology, Saveh University of Medical Sciences, Saveh 3919676651, Iran

Roberto Catanzaro, Department of Clinical and Experimental Medicine, University of Catania, Catania 95123, Catania, Italy

Amir Moghadam Ahmadi, Department of Neuroimmunology, Thomas Jefferson University Hospital, Philadelphia, PA 19107, United States

Francesco Marotta, Department of Human Nutrition and Food Sciences, Texas Women University, Milano 20154, Italy

Co-corresponding authors: Leila Haghshenas and Francesco Marotta.

Corresponding author: Leila Haghshenas, PhD, Assistant Professor, Department of Clinical Bioinformatics, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, United States. leilahagh@yahoo.com

Abstract

Microbiome is an endocrine organ that refers to both the complicated biological system of microbial species that colonize our bodies and their genomes and surroundings. Recent studies confirm the connection between the microbiome and eye diseases, which are involved in the pathogenesis of eye diseases, including age-related macular disorders, diabetic retinopathy, glaucoma, retinitis pigmentosa, dry eye, and uveitis. The aim of this review is to investigate the microbiome in relation to eye health. First, a brief introduction of the characteristics of the gut microorganisms terms of composition and work, the role of dysbiosis, the gut microbiome and the eye microbiome in the progression of eye illnesses are highlighted, then the relationship among the microbiome and the function of the immune system and eye diseases, the role of inflammation and aging and the immune system, It has been reviewed and finally, the control and treatment goals of microbiome and eye diseases, the role of food factors and

supplements, biotherapy and antibiotics in relation to microbiome and eye health have been reviewed.

Key Words: Dysbiosis; Gut microbiome; Eye diseases; Inflammation; Diabetic retinopatyhy; Aging; Nutrient supplementation

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In this article, we reviewed the content of the studies conducted in the field of intestinal microbiome and eye diseases and stated that the intestinal microbiome acts like an endocrine gland that regulates hormonal and humoral factors to regulate the innate immune system in processes related to metabolism. We reviewed dysbiosis, which causes changes in small secretory molecules in the digestive area and intestinal lumen leakage and the occurrence of diseases in all body organs, including eye diseases. We investigated latest important studies related to environmental, food and drugs in relation to intestinal microbiome and eye diseases.

Citation: Haghshenas L, Banihashemi S, Malekzadegan Y, Catanzaro R, Moghadam Ahmadi A, Marotta F. Microbiome as an endocrine organ and its relationship with eye diseases: Effective factors and new targeted approaches. *World J Gastrointest Pathophysiol* 2024; 15(5): 96446
URL: https://www.wjgnet.com/2150-5330/full/v15/i5/96446.htm
DOI: https://dx.doi.org/10.4291/wjgp.v15.i5.96446

INTRODUCTION

The microbiome is an significantly complicated biological system of microbial species that it is contained in our body, their genome, and the surroundings they live[1]. Hence, the microbiome alludes to each microorganisms and their action, which contains of microbial metabolites and hereditary components[2]. Totality of genomes of a microbiota, regularly utilized to depict the entity of microbial traits (= functions) encoded with the aid of using a microbiota[3]. These microbial elements account for more than one hundred trillion microorganisms that encode more than three million genes and a big range of metabolites. Therefore, for the reason that our body interacts symbiotically with organisms, it performs primary immune and metabolic capabilities[4], being influenced by dietary style, quality of life and environmental factors[5].

In that produces secretions that are distributed throughout the body through the bloodstream or lymph, it produces both hormonal factors and humoral factors and regulates the innate immune system in a metabolism-dependent manner. This presence is necessary for digestion and energy production, and independent of metabolism, such as signaling factors. Metabolites and products that are formed during processes like fermentation such as short chain fatty acids (SCFAs), conversion of bile acids, conversion of choline and L-carnitine to trimethylamine (TMA), can contribute to the occurrence of conditions like increased insulin resistance and increased inflammation, increased intestinal permeability and diseases such as atherosclerosis cardiovascular diseases and stroke[6].

Moreover, dysbiosis by changing the production of small molecules that are secreted in the digestive tract, such as ghrelin, YY peptide, GLP-1, glucagon and other molecules that are related to the feeling of satiety or play a role in accelerating the emptying of the stomach and reducing appetite can affects on the intestinal leakage and also causes the desire to consume more food and obesity. Obesity is associated with several metabolic dependent diseases in different organs: Cardiovascular diseases, type 2 diabetes, non-alcoholic fatty liver disease, colorectal, breast, endometrial, kidney, esophagus, ovary, prostate, pancreas and stomach, esophageal reflux, asthma, arthritis and depression and anxiety[7] and Alzheimer's disease[8].

Dysbiosis by changing homeostasis leads to changes in the absorption of iron and selenium, iodine and minerals, and changes in the absorption of vitamins play a role in the weakness of the immune system and changes in thyroid activity and can lead to thyroid cancer[9] and several other diseases[10]. In addition, recent years have provided a increasingly growing frame of experimental and clinical evidences highlighting how gut microbiota dysbiosis may play an initiating and probable perpetuating role in a number of ocular diseases, hence establishing the concept of an eye-gut axis[11].

Two percent to five percent of individuals through inflammatory bowel illness have eye problems[12]. A few considers have illustrated the presence of a gut-eye hub in which intestine microscopic organisms impact resistance at removed locales, counting the eye[13]. In this consider we are going examine more fine points of interest of the response of the immune system and defense additives in connection to the intestinal and eye microbiome. In addition, we would have a look at the connection between dysbiosis, inflammation and maturing and eye illnesses along side the part of the microbiome situations, nourishment, probiotics, prebiotics, postbiotics and utilitarian nourishments, vitamins and supplements and anti-microbials on eye wellbeing.

DIGESTIVE MICROBIOME VARIETY AND FACTORS AFFECTING IT

The microbiome varies from person to person and changes in anybody determines the composition of the intestine

microbiome because of components related from pregnancy to birth, maturing, environment, use of anti-microbials and eating habits[14].

The microbiome regulates the physiological capacities of the have, contains digestion system and the improvement and support of resistant homeostasis. The human gut microorganisms differs in classification and function in each of the anatomical regions of the gastrointestinal (GI) tract, because these areas have different characteristics in terms of physiology, pH, oxygen tension, digestive flow rate, substrate availability and host secretions[15].

Molecular science advances have given the microbial phyla show within the intestine microbiome and their evaluation by analyzing DNA and RNA extracted from stool tests. It has been found that the intestinal microbiome incorporates some phyla such as *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *Verrucomicrobia* where the two phylums *Firmicutes* and *Bacteroidetes* represent the bigger part of the intestinal microbiome. The *Firmicutes* phylum contains the most species of *Lactobacillus*, *Bacillus*, *Enterococcus* and *Ruminococcus*, with *Clostridium* forming, majority of this phylum primarily contains *Prevotella* and *Bacteroides* genera. The phylum *Actinobacteria* is normally found in the microbiome and was primarily composed of the class *Bifidobacterium*[4].

Intestine microbial imbalance influences the host and contributes to the pathogenicity or progression of a wide range of harmful effects in different organs[16]. For the establishment of the immune system and physiological improvement, intestinal colonization of microbiota is fundamental in early life[17].

Gestational age at birth, mode delivery (caesarean or physiological), nourishing and duration of breastfeeding, as well as life-style, geographic area, hereditary traits of the infant, utilize of anti-microbials[18], eat less and utilization of drugs influence the intestine microbial populace[19].

THE RELATIONSHIP AMONG DYSBIOSIS, INFLAMMATION AND EYE DISEASES

Pathological properties that make intestinal dysbiosis and alter microbial metabolites disrupt the immune system metabolism, important to lead to inflammatory and immune system diseases. Dysbiosis refers to modification within the quali-quantitative composition of microbiome communities. The commensal microorganisms in intestine track directs the development of the mucosal immune system though the harmful microbiome may cause immune diseases, *i.e.* an awkwardness through the commensal and pathogenic microbiome that can incline to inflammatory diseases[20].

The digestive tract microbiome impacts the homeostasis and immune system either regionally and systemic. Expanded intestinal permeability (leaky gut) and microbial translocation results in systemic inflammatory aggravation[21]. Enterocytes, or intestinal epithelial cells, create a barrier that selectively regulates the exchanges among he internal and external surroundings of the lumen, toxins, antigens, as well as the absorption of nutrients, vitamins and water *via* intercellular and paracellular transport mechanisms[22]. Intestinal mucosal membrane permeability is associated with paracellular trafficking of microbial agents and increased immune response tolerance against non-self antigens[23]. Intestinal dysbiosis may also additionally become to end result in altering zonulin, the modulator of physiological intestinal permeability[24] which causes moieties of luminal contents to pass through the epithelial lining. This phenomenon would then trigger proinflammatory cytokine factors that further increase intestinal membrane permeability, allowing for a massive influx of microbial antigens and substances that prompt T cells. Then, depending of the genetic predisposition of the host, those T cells are possibly to remain in the GI tract and cause inflammatory bowel diseases (Crohn's disease, irritable bowel syndrome and other undefined inflammatory bowel diseases) or migrate to specific organs and igniting infection, low-grade inflammation[25,26] and overt GI illnesses[27]. In addition, intestinal dysbiosis can cause the production of an inflammatory lipopolysaccharide (LPS), that is a glycolipid withinside the outer membrane of Gram-negative microorganisms and it is a common endotoxin composed of the O antigen[28]. The release of LPS inside the intestinal area and its passage into the blood explains LPS-associated toxicity, *i.e.,* endotoxemia[29]. LPS can enter the circulatory system directly or with the aid of an increased intestinal permeability[30]. Lipid A stimulates signaling cascades and a wide range of pro- inflammatory pathways, for example nuclear factor kappa-B (NF-kB) and prolongs oxidative stress after coupling to Toll-Like receptor (TLR) 4[31,32]. Increased oxidative stress may lead to systemic and retinal disease[33]. It is noteworthy that the first part of the GI tract, the oral region, serves as a gateway for foreign bacteria and bacteria that reside in the mouth and potentially affect distant organs such as the eye can concurrently lead to age-related macular degeneration (ARMD), glaucoma, and diabetic retinopathy (DR)[34]. For example, it has been observed that in the presence of an exposed periodontal pathogen community, it can gain access, possibly evade autophagy, and stably proliferate in retinal pigment epithelial (RPE) cells as one of the mechanisms leading to DR and ARMD[35].

RELATIONSHIP BETWEEN DYSBIOSIS AND DR

A 2010 study looked at the effect of gut microbiota on diabetes establishing an association between *Firmicutes* and *Bacteroidetes* in Danish diabetics as in comparison to non-diabetic people. In this way, their ratio was found to be notably decreased, while the ratio of Bacteroidetes increased withinside the intestines of patients with type 2 diabetes[36].

An imbalance of the intestine microbiome has been linked to many eye illnesses which include uveitis[37], glaucoma [38] and ARMD[39]. In addition, Beli *et al*[40] reported that by altering gut microbiome through intermittent fasting can prevent retinopathy and extend lifespan in mice. The prevalence of diabetes and retinopathy associated with intestine microbe dysbiosis is now convincingly related.

In a study by Huang *et al*[41], 16S rRNA gene sequencing was used to achieve a complete composition of intestine microbiota in stool samples from seventy five individuals, who include diabetic sufferers without overt retinopathy (DM) as well as patients with retinopathy (DR) with different grades have been analyzed. The severity of healthy people with the same age and sex without latest history of probiotic, prebiotic or antibiotic use were also selected as the healthy control (HC) group. In every group, they additionally compared different genera and families of bacteria in the DM and DR and HC group and with every different.

In Huang *et al*'s study[41], fundus by ophthalmoscopy confirmed a grossly ordinary structure in the DM and HC groups, but confirmed retinal vascular lesions, microaneurysms, hemorrhages, cotton wool spots, and lipid secretions in DR group. Optical coherence tomography pictures confirmed ordinary histological form in DM and HC groups, while macular edema, retinal thickening and retinal detachment were evident in DR group. With reliable diagnostic accuracy, they recognized 16 phyla in all samples, in which *Firmicutes*, *Actinobacteriota*, *Proteobacteria* and *Bacteroidota* were the maximum dominant phyla in every group with greater than 99% abundance. In general, through evaluating the relative frequency of every phyla some of the 3 groups, only *Firmicutes* and *Desulfobacterota* phyla confirmed a great difference [41]. In particular, the abundance of Firmicutes and associated *Clostridiaceae* was decreased in DM and DR groups than in healthy individuals. In addition, *Bacteroidetes* were greater considerable in DR than in DM and HC groups[42].

Further, it was reported that *Clostridium* has a negative relationship with fasting glucose, insulin and plasma triglycerides and a positive relationship with adiponectin and excessive-density lipoprotein, which are all intently associated with diabetes. Therefore, it is speculated that the prevalence of diabetes and retinopathy can also be related to decrease of those useful bacteria[41].

Desulfobacterota are organisms that could reduce sulfur compounds through the different DsrAB sulfite reduction pathway[43] and take part in butyrate degradation through carrying out a β-butyrate oxidation pathway, suggesting that *Desulfobacterota* are concerned withinside the catabolic balance of reactions[44]. Therefore, it can be hypothesized that *Desulfobacterota* can promote LPS to induce an inflammatory damage or exacerbate abnormalities of energy metabolism, each of them are involved in diabetes[41].

Blautia and *Lactobacillus* genera were more abundant in individuals with diabetes and were greater abundant in DM group than DR group[38,44,45].

Wang *et al*[46] reported that *Blautia* was positively correlated with tauroursodeoxycholic acid (TUDCA) levels. TUDCA, a farnesoid X receptor (FXR) antagonist, regulates glycolipid metabolism through its receptor for FXR and the bile acid G protein-coupled membrane receptor (TGR5). TGR5 is present in primary retinal ganglion cells (RGCs), and activation of TGR5 can prevent retinopathy and prolong the life span of db/db mice, so diabetic sufferers with higher *Blautia* expand less retinopathy.

Lactobacillus is a common probiotic with immunomodulatory and antioxidant properties that play a role in the mechanism of DR[47].

This study also showed that some drugs used to treat diabetes have critical outcomes on changes in the intestine microbiome. For example, Wu *et al*[48] suggested that metformin notably impacts the intestine microbiome (consisting of extended *Bifidobacterium*) to enhance glucose tolerance and enhance antidiabetic effects. *Eubacteriaceae* showed a positive correlation with fasting glucose levels and have been notably abundant in diabetic sufferers, specifically in the DR group. In addition, an increase in the levels of Bifidobacterium and Lactobacillus and a decrease in the levels of *Escherichia Shigella* and *Faecalibacterium* were found in the DM and DR groups as in comparison to the HC group[49].

THE RELATIONSHIP AMONG DYSBIOSIS, EYE MICROBIOME, IMMUNITY AND FACTORS AFFECTING ITS CHANGES

Ocular microbiota, microorganisms present in the eye are common and pathogenic. Commensal microbiota play a crucial function in regulating host physiology, inducing and growing the immune system.

The floor of the eye is constantly in contact with the outside environment and diverse pathogens. Common microorganism isolated from eye spots are gram-positive strains of bacteria such as coagulase-negative *Staphylococcus*, *Propionibacterium*, *Streptococcus*, *Diphtheroid* and *Micrococcus*. In the normal floor of the eye, some strains which are considerable in intestinal flora which include *Escherichia coli*, *Enterococcus*, *Bacillus* and *Lactobacillus* are found less. Fungal isolates and Gram-negative strains such as *Haemophilus*, Neisseria, *Pseudomonas* are much rarer, however, they can be isolated from the floor of the eye without causing symptoms such as inflammation or infection. Physiological conditions of the disease along with retinal vascular damage can lead to microbial invasions that are circulating withinside the blood.

Retinal vascular leakage is one of the early pathological manifestations of DR. DR has been shown to be affected also by the microbiome. Each disorder has a unique relationship with intraocular microbiome, which shows that there is a relationship among intraocular microbiota and eye health and disease[50].

Age and sex hormones are amongst the modulators in eye microbiota. Dry eye syndrome (DES) is described as a condition related to the lack of homeostasis and hyperosmolarity withinside the tear layer, causing inflammation in the eye surface and vision impairment, which is promoted by inflammatory cytokines and the infiltration of inflammatory cells into the conjunctiva and lacrimal glands. The most common cause of dry eye is meibomian gland disorder which is a modified autoimmune-progressive disease. Despite some report of beneficial effect by oral and systemic antibiotics, a review conducted by the American Academy of Ophthalmology concluded that there was only scant evidence to indicate their efficacy against side effects. A Cochrane review comprising about 3500 cases of dry eye cases ended up suggesting there was little evidence that over-the-counter drops provided any significant benefit as compared to placebo[50]. In 2007 it was shown a significant quali-quantitative change between the corneal microbiome population of subjects with dry eye

as opposed to those without, specifically identifying *Klebsiella oxytoca* and *Bacillus spp.* most of the bacteria were coagulase negative *Staphylococci*[51].

This overgrowth correlated with a reduction of mucin-generating goblet cells in the eye as well as observed in dysbiotic GI tract. Dysbiosis is involved in various diseases related to systemic inflammation, inflammatory bowel disease and several eye diseases such as uveitis, glaucoma and ARMD[52]. Some microbial species of the intestinal microbiota can degrade glycans in the host's mucous secretions and mucin secreted by goblet cells or destroy epithelial cells[53], Cholinergic neurotransmitters stimulate mucin reflex secretion. Lacrimal gland secretion is regulated by nerves, androgens and growth factors from the family of epidermal growth factors[52].

Based at the outcomes of targeted 16S rRNA gene sequencing, there are presently 52 identified bacterial phyla stated, with about five to seven phyla recognized to reside withinside the mammalian GI tracts. Among those, 4 most important phyla *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* dominate and occupy as much as 97% of the whole bacteria. A entire and balanced bacterial environment forms due to ideal interactions some of the different bacterial phyla [54].

In a 2022 study by Watane *et al*[55], it was found that all individuals with dry eye disease had a decrease in the phyla *Firmicutes* and an increase in the phyla *Proteobacteria*, *Actinobacteria*, and *Bacteroidetes* compared to control individuals. People with Sjogren's dry eye compared to control people, an increase in phylogenetic diversity was observed without relation to age or co- immune diseases. The above emphasized the link between gut associated lymphoid tissue, mucosal associated lymphoid tissue and corneal associated lymphoid tissue, to mention only some stations. All the above paved the way to a rationale of gut-eye microbiota intervention. The oral supplementation of omega-3 fatty acids was tested for their prebiotic properties and endowed by some initial positive reports. However, probably due also to uneven i7clusion criteria, this approach has so far conflicting results despite more recent large studies[56,57]. Interestingly, a combination of fish oil, lactoferrin protein, zinc, vitamins C and E, lutein, amino acid γ-aminobutanoic acid, and Enterococcus faecium wb2000 bacteria on dry eye disease significantly improved clinical symptoms during an 8-week trial[58]. In addition to promoting intestinal probiotic bacteria, curcumin extract has been proposed to inhibit hyperosmolarity in human corneal epithelial cells and also reduce the expression of inflammatory cytokines in a mouse model[59]. Regarding clinical interventions with oligosaccharides, a randomized controlled trial using a combination of probiotics and fructo-oligosaccharides as a tear substitute, significantly improved symptoms in dry together with a beneficial change of ocular surface microbiota[60]. It has also been shown experimentally that oligosaccharide-enriched human milk protects corneal epithelial thickness to the same extent as cyclosporine in a mouse model of dry eye disease[61].

The is also interest in compounds with polyphenols for their known antioxidant, anti-inflammatory, antibacterial properties, which are used to decline along the aging process[62] and proving beneficial changes in other tissues[63]. However, more fine biochemical studies are required in after some promising positive data from blueberry or grape seed extracts for corneal diseases[64,65].

On the other hand, it has been recently reported that elevated polipyphenolic concentration of green tea may negatively affected the tear film quality with lipid oxidation and detrimental decrease in electrolyte tear concentration [66].

The prebiotic properties of quercetin in these settings have been shown to regulate immunity by increasing the tear volume, restoring the smooth surface of the cornea and increasing the density of goblet cells when used topically in mouse dry eye models[67]. In addition to these effects, resveratrol also increased levels of *Akkermansia* species, bifidobacteria and lactobacilli in mouse models[68].

Kim *et al*[69] has reported few years ago about the efficacy of a probiotic mixture based on *Lctobacillus reuteri*, *Lctobacillus casei*, *Sreptococcus thermophiles*, *Lctobacillus acidophilus* and *Bfidobacterium bifidum* in successfully treating an autoimmune model of dry eye, thus corroborating the gut ecosystem relevance in the disease and as a potential therapeutic target.

Accordingly, in the same year Chisari *et al*[70] carried out a pilot study dealing with elderly eye microbiota in subjects suffering from dry eye. The protocol implied the use of oral supplementation of a mixture of *Saccharomyces boulardii* and also *Enterococcus faecium* and the results clearly showed a significant benefit on severity reduction of the disease and symptoms paralled by improved tear tests and eye microbiota.

The above data proved also to be beneficial withinside the knowledge and treatment of Sjogren's syndrome (SS), where the reduced salivary gland secretion fuels an increased bacterial dental plaque formation. In these patients, prebiotics and probiotics have shown to inhibit cross-reactive T cells against gut peptides potentially yielding a beneficial ocular microbiome shift[71] .In another study a relationship between the quali-quantitative gut microbiome changes and soluble inflammatory markers was established, where the low Bifidobacterium counting was inversely associated to a clear pro-inflammatory pattern in the blood (high IL-17 and TNF-α)[72].

Uveitis shares with DES some pathophysiological aspects, but it is less common. Terminologically, uveitis refers to an inflammatory process of the center layer of blood vessels and eye pigment. Regarding the strength of the immune privilege concept in the context of uveitis, this word should be used cautiously. This is because this assumption may be dependent on whether the inflammation takes place in front of or behind the blood-retinal barrier (BRB). In that, the retina with its greater immunomodulatory microenvironment, lacks of immunosuppressive mediators and major histocompatibility complex (MHC) class II^+ dendritic cells may not prevent an inflammatory uveoretinitis. It appears that there is a convincing evidence that rather than a single microorganism triggering an antigenic cross-reactivity, this disease is leaning on multiple microbiota species[73].

In sufferers with illne sses such as diabetes, dyslipidemia, conjunctivitis, autoimmune ailments such as Behçet's disease and rheumatoid arthritis, SS, meibomian gland disorder and DES, show a modified ocular microbiota[53].

INFLAMMATION, POTENTIAL MECHANISMS OF INTRAOCULAR INFLAMMATION, IMMUNE AND GENETIC FACTORS AND INTRAOCULAR MICROBIOME RELATIONSHIP

Despite the eye is enforced by what is termed as immune priviledge, *i.e.*, a defensive reaction system to immune challenge based on the sequestration of tissue self-antigens in the back of blood-tissue barriers, ocular tissues are susceptible to infection and inflammatory conditions. There are two types of intraocular inflammation, acute inflammation and chronic inflammation. Acute inflammation due to pathogenic microbes after surgery or accident and causes changes withinside the permeability of the BRB and the infiltration of immune system cells which include macrophages and polymorphonuclear leukocytes. Chronic eye inflammation includes a combination of predisposing genetic (such as HLA haplotypes, A29, B27, B51, DR4 and DQ4) and environmental factors generating an enhanced leukocyte trafficking among the gut and the eye. In fact, the production of autoantibodies against endogenous antigens, the dysregulation of regulatory T cells, and the infiltration of macrophages and T lymphocytes underlie chronic intraocular inflammation, especially uveitis[74].

Uveitis occurs as an acute inflammation or chronic intraocular inflammation of an infectious or noninfectious basis and accounts for 10%-15% of severe visual impairment worldwide and as much as 15% of blindness in the United States[75].

Dysbiosis can cause overgrowth of pathogenic microorganisms that affect antigen-presenting cells (APCs; Figure 1). . In humans, uveitis is related to a MHC class I allele, human leukocyte B27 (HLA-B27), an antigen expressed on the surface of white cells. Individuals how have acute anterior uveitis contain specific intestinal microbial changes. Immature APCs engulf the microbe to mature after which migrate to the nearest lymph nodes to be recognized by CD4+ T cells, giving rise by antigenic mimicry to autoreactive lymphocytes specific for the neuroretina[76,77].

Retinal-specific T cells that are activated in this state disrupt the BRB and penetrate into the eye to secrete pro-inflammatory cytokines and chemokines and absorb inflammatory and cellular mediators. About 20 years ago, researchers found that a peptide from cow's milk casein protein (Cas) and PDSAg peptide from retinal protein S antigen have antigenic mimics[78]. Recently, the same group found an increased antibody response to Cas and PDSAg as well as an increased T cell response in the sera of patients with uveitis compared to HCs[79]. While this area still represents a therapeutic challenges, there are some worth considering data. For example, orally administered berberine has been shown to inhibit BRB breakdown induced by experimental autoimmune uveitis (EAU). This was also related to a robust modulation of the spleen transcriptome and increasing the number of immunomodulatory-endowed gut bacteria[80]. Another gut microbiota-targeted therapeutic option is represented by SCFA whose direct ingestion may yield a beneficial modulation of the gut mucosal immunity. Nakamura *et al*[81] had demonstrated that the ingestion of the SCFA propionate significantly decreased the severity of EAU probably also due to a Regulatory T cells (Treg) increase.

Intestinal commensals are also concerned in the pathogenesis of several noninfectious eye diseases including ARMD and glaucoma. ARMD is a proliferative retinal degeneration with chronic low-grade inflammation of the inner eye. In genome-wide studies, the association of genetic variants in various pathways of complement and inflammatory elements including complement factor (CF) H, CFI, ARMS2, TIMP3 and MMP9 are shown. Also in the lipid pathway such as APOE, LIPC, ABCA1 and CETP were correlated with this disease[82,83]. At least 71% of ARMD is genetically heritable [84]. This may be attributed to the interaction of genetics with environmental factors including smoking, obesity, diet and sun exposure[82]. Commensal microorganism could play a role in ARMD patients as a potential environmental influence. There are several reasons for it[85]: (1) Microbes are very effective on low-grade chronic inflammation by regulating host immunity and regulating lipid metabolism, which is involved in the pathogenesis of ARMD; (2) Drusen withinside the eyes of ARMD patients consists of anti-inflammatory components including apolipoprotein E and complement components plus amyloid β, vitronectin, immunoglobulins and C1Q; and (3) Microorganisms in the gut can send signals that have an effect on distant organs including the eye. Microbial communities in the gut, mouth, nose and pharynx have also demonstrated the potential function of mucosal floor microbes withinside the pathogenesis of ARMD and glaucoma [41,86,87]. In particular, Zhang *et al*[88] found in ARMD patients with clinical features as in comparison to healthy individuals that the number of *Firmicutes* showed a great decrease and increased levels of *Proteobacteria* and other bacteria (*i.e.*, *Escherichia-Shigella*), which metagenomic analysis showed to be related to LPS biosynthesis.

The receptors of the innate immune system, such as TLRs, cause an immune response withinside the retina. These receptors are placed in the retina and have an extracellular domain and an intracellular domain, the extracellular domain is hooked up to bacterial structural components which include lipids, peptidoglycans and their LPS with leucine repeats, and the cytoplasmic intracellular domain signaling. Stimulation of TLRs signaling increases NF-kB or activation of interferon factors or activation of mitogen protein kinase pathways, which express more inflammatory mediators and It can play an important function in the pathogenesis of uveitis[46].

Moreover, studies show that the predominant species of bacteria *Anaerotruncus* and *Oscillibacter*, *Ruminococcus* torques and *Eubacterium ventriosum* are more abundant in people with ARMD, in where the amino acid production pathways of arginine are increased and lead to the destruction of glutamate[35].

The commonality between heat shock proteins (HSPs; HSPs of the gut microbial population and highly conserved human HSPs makes them cross-react with human HSPs, which triggers autoimmune diseases and RGC damage[89,90].

In a 2019 study by Henein and Khaw[91], it was found that the levels of HSP-27 and HSP-60 specific T cells and antibodies were higher in each primary open angle glaucoma (POAG) and normal tension glaucoma patients when compared to age-matched healthy individuals. The pathophysiological reasons of these changes are multifactorial and involving also multigenetic mechanisms. The underlying dangers of elevated intraocular pressure (IOP) and POAG have been defined in relation to the role of tyrosine kinase signaling, lipid metabolism, mitochondrial function, and developmental processes. Age and increased IOP are the most important risk factors for glaucoma, but mechanisms beyond pressure-induced neurodegeneration are involvealsod. It seems that the proximity of immune cells along the digestive tract and the dysfunction of the retinal blood barrier in stressful conditions are other possibilities of this case. Data are

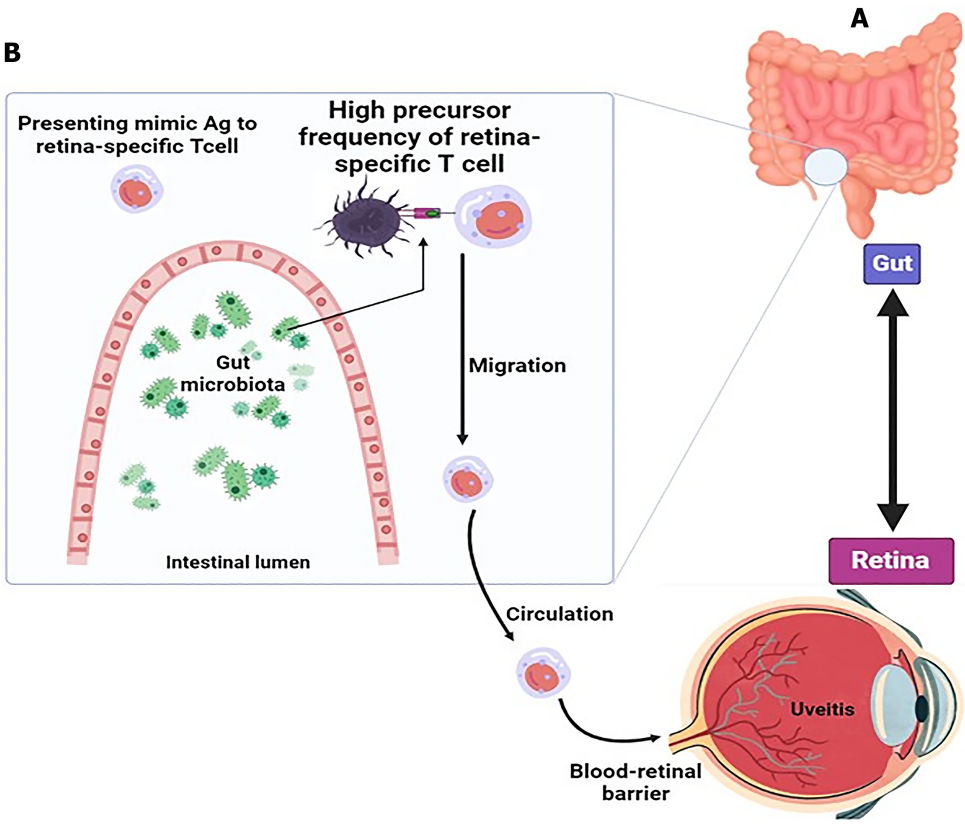


Figure 1 Activation of specific autoreactive T cells by microbiota and development of uveitis. A: Gut connection with retina in uveitis; B: Mechanism of retina-specific T cell activation by gut microbiome. Uveitis is caused by the retina-specific autoreactive T cells activated by microbiota. The gut lipopolysaccharide exhibits many retina-specific autoreactive T lymphocytes in the periphery. Antigen-presenting cells present gut microbiota-derived products that to these T cells may resemble Ag. Retina-specific T cells become activated, migrate to the eye, and pass through the blood-retina barrier leading to inflammation of the retina. Citation: Horai R, Caspi RR. Microbiome and Autoimmune Uveitis. *Front Immunol* 2019; 10: 232. Copyright ©The Author(s) 2019. Published by Frontiers Media SA[166].

accumulating on the growing evidence there exists a commensal microbiome as an integral component of the retinal environment which can also additionally suffer from subtle intraocular microenvironment changes. These may be modifying the retinal immune reaction regulation and overcoming the suppressive mechanisms leading to retinal degeneration. A "dual-hit" hypothesis has been postulated, *i.e.*, from gut to retina. The TLRs-mediated recognition by the microbial pathogen-associated molecular pattern in the resident microglia in the retina give raise to a surge of proinflammatory secretome and MHC II. Once the retina undergoes a chronic innate immunity activation, the infiltrative homing of peripheral primed T cells takes place with breaking the BRB and this is suggested also to occur for blood-brain barrier [92].

Experimental data with POAG rats have clearly shown that this condition was invariably associated with a decresed microbial diversity and an altered gut microbial metabolomics (*e.g.*, significantly increased *Akkermansia*, *Romboutsia*, *Bacteroides* and *Verrucomicrobia* phylum) which correlated with the status of RGCs. These data confirmed the similar clinical findings together with a major decrease of Lactobacillus in patients with POAG[93].

Experimental and clinical studies also agree in suggesting that increased bacteria in glaucoma were all active mucus degraders, especially in a fiber-poor diet[94], and this, on its turn, favoring inflammatory-related genera inversely related to RGC density. In recent years, dysbiosis in glaucoma has also staged as a key player in guiding the peripheral immune system while also having part in the T cells activation. In aid of the hypothesis of a bacteria-sensitization of T-cell response in glaucoma progression, a completely elegant review by Chen *et al*[95] highlighted how even transient IOP elevations were consistent enough to break the BRB and generating a retinal infiltration from CD4+ T-cells triggering glaucomatous neurodegeneration-prone HSP-specific CD4+ T-cell responses.

As one of the intestine metabolites, also bile acid composition showed in POAG a higher level of some specific bile acids (3A,7A-dihydroxycholanoic acid)[40] as compared to health control and, as also somehow similarly noted in Parkinson's disease[96].

An interesting bridging hypothesis has been suggested early this year by Pezzino *et al*[97] who reported the data linking obesity and elevated body mass index associated to high IOP and glaucoma. Obesity index being the best predictor of worsening IOP either in an Asian[98]and in a European population[99].

As a matter of fact, obesity is associated to a proinflammatory cytokine profile and to gut and oral dysbiosis both facilitating bacterial translocation with also endotoxic activity and associated to glaucoma[100].

Indeed a further recent work where authors found that TMA, a gut bacteria metabolite, concentration in acqueous humor of glaucomatous patients was significantly high thus potentially promoting the progression of glaucoma by impairing smooth muscle-based trabecular meshwork filtration and enhancing hypoxia[101].

In addition, studies show that there is an association between *Helicobacter pylori* (*H. pylori*) and glaucoma, as determined by measuring increased antibody titers in POAG patients. Intestinal dysbiosis confers susceptibility to *H. pylori* infection, and this has indeed been reported in a recent meta-analysis[102]. It is interesting to note that the successful eradication of *H. pylori* can lead to a partial improvement of IOP[103]. The by-products of intestinal microorganisms play a role in the stimulation of microglial cells in the central nervous system (CNS), their regulation and function, and their maturation and differentiation[91].

In a study using fermented corn supernatant rich in probiotic bacteria, changes in the gut microbiome in mice modulated the retinal immune response and protected RGCs[104].

Another study showed that increased levels of arginine play a role in causing retinal degeneration and changes in intestinal microbiota[105].

Changes in gut microorganisms, for instance a loss of bacteria that affect fatty acid length, have been linked to ARMD [35]. Their production byproducts may regulate intraocular inflammation by transiting lymphocytes from the gut to the eye[106].

Inflammatory processes associated with intestinal dysbiosis in the elderly have been shown to cause premature senescence of retinal cells, leading to neovascularization and impaired vascular repair through inflammatory factors and angiogenesis[107,108].

Another retinal disorder involving the gut microbiome is retinitis pigmentosa (RP). This study found that changes in gut microorganisms composition were associated with RP[109].

Different cells withinside the innate and adaptive immune system express different elements that act to activate G protein-coupled receptors and regulate gene expression. SCFAs are histone deacetylase inhibitors. Other metabolites of nuclear receptors are receptors consisting of pregnane X receptor, vitamin D receptor and liver X receptors[110].

RELATIONS WITH AGING AND GUT MICROBIOME AND EYE DISEASES

The intestinal epithelium, which contains factors including IgA secretory immunoglobulins, the intestinal layer, and antimicrobial peptides, is necessary to hold homeostasis. Aging influences the composition of the gut microbiome by changing this barrier. With increasing age, these changes increase and the diversity and richness of intestinal microbes decreases[111].

Aging causes stem cells to decline and the body loses its capacity to repair tissues and cells[112]. During aging, because of host elements which includes genetics, nutrition, intestinal growing older and immune system, living environment, drug exposure, *etc.*, it causes a gradual change of intestinal microorganisms[113]. Proteolytic bacteria increase and saccharolytic bacteria decrease[114], resulting withinside the onset of many age-associated diseases, which includes neurodegenerative diseases[115].

Low-grade infection is manifested with the aid of using expanded expression of inflammatory cytokines and transcription elements consisting of IL-6, TNF-α, and NF-κB[116].

Aging is determined and moderated through the surroundings[117]. In a 2021 Yoon *et al*[118] study, it become determined that intestine dysbiosis is related to age and inflammation and continual illnesses in the aged and contributes to the pathophysiology and exacerbation of dry eye disease. In univariate evaluation on this look at, the genera of *Firmicutes*, *Proteobacteria* and *Cyanobacteria*, *Firmicutes*/*Bacteroidetes* and *Alistipes*, *Bacteroides*, *Prevotella*, *Paraprevotella* and *Helicobacter* had been related to the degree of dry eye.

Zhang *et al*[88] in 2023, In the case of age-associated macular degeneration (AMD), that's the primary reason of vision loss in humans over 50 years of age, suggested that the intestine microorganisms performs a function withinside the pathogenesis of eye diseases and isn't the same as healthy people.

In 2017, Wen *et al*[119] confirmed that age- and gender-associated variations have an effect on the conjunctival microbiome and might modify ocular floor immune homeostasis *via* adjustments in its shared microbiome. In this observe, there has been a selected distinction in the variety of microorganisms, their metabolic features and the frequency of antibiotic resistance genes among the young and old groups. They stated that growing older impacts the ocular floor microbiome. *Propionibacterium acnes* (*P. acnes*) turned into located in 88% of healthy volunteers, at the same time as *Staphylococcus epidermidis* turned into located in 73%. Epidermidis reduced considerably from male to woman, whilst *Escherichia coli* extended drastically in the female group. *Staphylococcus haemolyticus*, *Micrococcus luteus* and *Escherichia coli* withinside the aged in comparison to the younger groups, and an extensive lower in Ochrobactrum anthropi, *Mycoplasma hyorhinis* and *P. acnes* from young to old.

In Chen *et al*'s study[120] on the role of microbiome dysfunction in the pathogenesis of many neurodegenerative diseases and the relationship between the gut microbiome and glaucoma, it is reported that the gut microbiome of glaucoma patients has a higher level of Dysgonamonadaceae, and a decrease level of *Barnesiellaceae*. This microbiome pattern causes SCFAs to be produced more in stool and blood samples. Deletion of glaucoma patient-particular intestine microbiome microorganism decreased RGC and retinal microglia activation and inflammatory cytokine overproduction, whilst SCFAs remedy decreased microglia activation. Studies have also shown that estrogen is protective in models of RGC injury and indeed, a still poorly addressed area is the association between menopause and glaucoma. In this regard a mixed phytochemical[121] and probiotics intervention[122] can be envisaged.

Further discount of intestine microbiome microorganism in those patients decreased retinal microRNAs which include MiR-122-5p, which turned into related to inhibition of retinal inflammation *via* neurodegeneration. In addition, they confirmed that transplantation of fecal microbiome from glaucoma patients exacerbated microglia activation and will increase retinal inflammation and adjustments the expression of retinal microRNAs which results in retinal inflammatory response[120].

In 2021, Alam *et al*[121] confirmed that food-borne *Listeria monocytogenes* (*L. monocytogenes*), which causes gastroenteritis, septicemia, meningitis, and chorioamnionitis, is associated with excess mortality in old age and altered gut microbiota in old age. It increases after infection and causes dysbiosis. Major bacterial phyla including *Bacteroidetes* and *Firmicutes*, they are no longer significantly increased at some stages of aging or infection, while *Verrucomicrobia*, *Clostridaiceae* and *Lactobacillaceae* are reduced in aged mice. *L. monocytogenes* infection spreads *Porphyromonadaceae* and *Prevotellaceae* species, even *Ruminococcaceae* and *Lachnospiraceae* in adult mice, while *Blautia* and *Alistipes* reduced after infection in adult and old mice. Butyrate-producing and immunomodulatory microorganism including *Pseudoflavonefractor* and *Facalybacteriomethans* were enhanced in aged mice, which contribute to up-regulation of intestinal inflammatory mRNA in aged mice. Histological evaluation of gastric tissues confirmed many lesions in aged mice with Listeria infection. Common species along with *Lactobacillus*, *Clostridial* and *Ackermansia* were more in mice with inflammation, but their frequency decreased in old mice. Changes in these microorganisms reduce and destroy beneficial substances inside the intestine. Therefore, aging can also affect the composition of gut microorganisms and increase the risk of invasive monocytogenes infection.

Parker *et al*[122] in 2022 show that fecal microbiota transfer, from among younger and elderly mice changed the recipient microbiota composition with a composition such as the donor, enriched for specific bacterial species, and changed the metabolic ability of the ensuing intestine microbial composition. They are show that elderly donor microbiota transfer to younger mice drives inflammation and lack of integrity withinside the intestinal epithelial barrier extended systemic and tissue markers of inflammaging, and upregulated inflammation withinside the retina and brain. The transferred elderly microbiota and ensuing recipient microbiota composition have been outstanding through enrichment for *Prevotella*, *Lacnospiraceae* and *Facecalibaculum* species and depletion of long-chain fatty acid synthesis. Conversely, switch of elderly mice with younger donor microbiota, which become outstanding through enrichment *Bifidobacteria*, *Eubacteria*, and *Akkermansia* species, and enrichment for B vitamin biosynthesis and also lipid synthesis pathways reversed inflammatory modifications in the elderly intestine, brain, and retina[123]. They also showed that transplantation of an elderly donor's microbiota affected extended intestinal concentrations of TNF and broader surrogate biomarkers of epithelial barrier permeability (I-FABP, LBP), which contribute to intestinal barrier integrity and promote systemic inflammatory responses.

Transplantation of young donor microbiota reduced the number of Iba-1 + microglia within the CNS of elderly recipients, whereas aged donor microbiota expanded Iba-1+ cells within the CNS of younger recipients. These dramatic changes in microglial activation could recapitulate expansion and/or contraction in the total number of microglial cells, or modulation of Iba-1 + expression in resident populations, or both[124-126].

Intestinal dysbiosis has been associated with an increased risk of infection. Imbalances in gut microbial community structure associated with adverse inflammatory responses are increasingly associated with disease processes that affect many body systems. Overall, given the studies reviewed in this section on the relationship between aging, the immune system, and the microbiome, how dysbiosis affects human aging and disease is becoming clear. It is becoming more apparent that the link between gut dysbiosis and age-related diseases may lie in the way the gut microbiome interacts with the gut mucosa and the systemic immune system, given that these networks share a common reciprocal relationship [127].

MICROBIOME CONTROL AND TREATMENT GOALS AND EYE DISEASES

Natural supplements effective on dry eyes, ARMD and other eye diseases

A study by Rowan *et al*[128] showed that clostridials were associated with a "high glycemic diet" in patients with ARMD, while Bacteroidetes were associated with a "low glycemic diet" and protected against disease. In the study by Fernandes *et al*[129] and Oubaha *et al*[130] it was also reported that hyperglycemia causes changes in the intestinal barrier that lead to destruction of immune system homeostasis, a chronic systemic inflammatory process, and even retinal vascular involvement.

Overall, human and animal model studies have shown that gut microbial composition is influenced by dietary vitamins and omega-3 polyunsaturated fatty acids[131] in ARMD[132].

Scientific evidence shows that nutritional carotenoids have an important effect on the regulation of intestinal microbiota and human health, and this is due to pro-vitamin a activity and antioxidant function. Beta-carotene, α-carotene, lycopene, astaxanthin, lutein, zeaxanthin, beta Cryptoxanthin, α-cryptoxanthin, γ-carotene, and fucoxanthin are common human dietary carotenoids found in fruits and vegetables and seafood. Carotenoid consumption reduces the risk of cancer, cardiovascular diseases, eye diseases and many other diseases. Diet has the potential for dietary therapeutic strategies for microbial design and stability[133].

Epidemiological studies have shown that diet is a modifiable ARMD risk factor, and nutrient modification is a particularly appealing adjuvant treatment for ARMD. Recently, the age-related eye disease study part 2 was concluded and demonstrated further benefit with the addition of lutein and zeaxanthin as a replacement for the β-carotene of the previous generation formulation. Lutein is a carotenoid found in green leafy vegetables, avocados, and eggs, and is purported to have protective effects against ARMD as well as benefits for visual and cognitive health. Recent studies have

indicated significant variation in serum lutein among individuals and that GI microbial profile may potentially contribute to lutein status[133,134].

A 2019 study showed that *Dialister*, *Ruminococcus*, *Gemmiger* and *Phascolarctobacterium* together with *Bacteroides eggerthii, Ruminococcus torques* differ in serum lutein levels and are increased in people with ARMD. This suggested a relationship between these microbes and Lutein is availability[135].

In a 2022 study, Grant *et al*[136] showed that consumption of fish, fruits, vegetables and a low glycemic index resulted in a healthier retina in old age.

Zhang *et al*[137], stated that omega-3 fatty acid supplementation could target AMD.

Epidemiological studies have shown that consuming fermented foods is related to a reduced risk of type 2 diabetes, metabolic syndrome, and heart disorder at the side of improved weight management. Microorganisms in those foods are recommended to make contributions to those health advantages. Among these, the starter culture organisms of yogurt are Streptococcus thermophilus and *Lactobacillus delbruecki* of the bulgaricus subspecies, in addition to *Bifidobacterium* and *Lactobacillus* strains, which are added due to their probiotic properties. In contrast, for other fermented foods, including sauerkraut, kimchi, and miso, fermentation is initiated through independent microbes present in the raw materials[138]. A higher knowledge of the relationship among gut microbes could offer new therapeutic targets for eye disorders[139].

By healing the gut surroundings and balancing the microbial population[140,141], probiotics have created a new therapeutic goal for various eye diseases[142].

Lactobacillus paracasei (*L. paracasei*) KW3110 has been used in experimental and clinical trials. Consumption of this bacterium suppresses cell death[143] and has anti-inflammatory effects on retinal epithelial cells and decreases cytokines and chemokines[144].

Prebiotics were defined by a panel of experts in 2016[145]. Fructo-oligosaccharides, inulin and galacto-oligosaccharides have beneficial effects on human health due to fermentation. They increase lactobacillus and bifidobacteria, which with useful products cause absorption of calcium, less protein fermentation, reduction of pathogenic bacteria, strengthening of intestinal lining and immune system[146].

Studies have shown the relationship between intestinal microbiota in SS and dry eye severity. Gut microbiota is less diverse in dry eye patients[147].

Chisari *et al*[70] study showed that faecium LMG S-28935 and *Saccharomyces boulardii* MUCL 53837 improve mental symptoms by increasing tear secretion and can reduced tear breakup time in another study, bifido increased tear secretion and tear breakup time in addition to changing eye microbiota in dry eye patients[62].

In the study by Kawashima *et al*[58] facium WB2000 with fish oil improved subjective symptoms by increasing tear secretion in dry eye patients.

In the study by Tavakoli *et al*[148] in 2022, MULTIBIOTIC™ probiotics (Medlab Pty Ltd., Botany, NSW, Australia) and maltodextrin (placebo) were used, which reduced dry eye symptoms.

Given the connection between the ocular mucosa and the gut, we hypothesize that inflammation of the ocular surface will also improve, thereby reducing the signs and symptoms of dry eye. Modulation of intestine microbiome modulates proteins expressed by lacrimal glands by increasing IL-10 and decreasing IL-1β and IL-6[147,148].

Research in functional foods uses postbiotics, a combination of metabolic substances released by microorganisms on cells such as *L. paracasei* KW3110[143], exopolysaccharides, enzymes such as glutathione peroxidase, SCFAs[149] directly or indirectly health increase the host[150].

In a 2018 study by Morita[143], administration of *L. paracasei* KW3110 improved eye fatigue induced by visual display terminal loads at high levels of eye fatigue by reducing retinal cell death.

Postbiotics perform their function by modulating the intestinal microbiome and increasing epithelial barrier functions, modulating local and systemic immune responses, modulating systemic metabolic responses and systemic signaling through the nervous system, and protect the cell wall against the destruction of enzymes, GI and immune attack protection[151].

Diet affects the richness and diversity of microbiota, polyphenols in wine and tea and vitamin D can balance beneficial bacteria .Dietary fibers, inulin, galacto-oligosaccharides, arabinoxylan and oligofructose promote beneficial microbes and reduce harmful species[152].

The association of vitamin D and various eye diseases, including myopia, ARMD, glaucoma, DR, and DES (DES) has been investigated in several studies. Thyroid eye disease (TED), uveitis, retinoblastoma (RB), and cataracts discuss vitamin D metabolism in the eye. We searched two research databases for articles examining the association between vitamin D deficiency and various eye diseases. There is evidence of an association between vitamin D and myopia, AMD, DR and DES. But the available evidence for the association with other eye diseases such as glaucoma, TED and RB is limited. Vitamin D affects the homeostasis of mineral metabolism and has antioxidant and anti-inflammatory properties. It also plays a role in anti-angiogenesis, cell cycle modulation, including cell proliferation, differentiation and apoptosis. VDR and vitamin D regulatory enzymes are present in ocular tissues. Ocular tissues can activate and regulate vitamin D, indicating the importance of vitamin D in maintaining eye health[153].

RELATIONSHIP BETWEEN ANTIBIOTIC USE AND EYE DROPS, MICROBIOME AND EYE DISEASES

Antibiotics cause the destruction of beneficial microbial species and the overgrowth of pathogenic species such as C difficile and changes in digestive metabolism[154,155].

Antibiotics kill sensitive species. The study of patients treated with broad-spectrum antibiotics shows that the microbial load of stool samples during treatment with b-lactams was associated with an increase in bacteroidetes

compared to *Firmicutes*. Drugs are metabolized in the intestine by large amounts of cytochrome p450 cyp enzymes, especially chromogranin, which increase certain microbial species[156]. Studies show that *Eubacterium aerofaciens*, *Desulfomonas pigra* and *Streptomyces coelicolor* A3, has cytochrome CYP family genes. C-type cytochromes in *Geobacter sulfurreducens* are active in electron transfer to iron (III) oxides. *Eubacterium lentum* contains cytochromes a, b and c and a pigment that binds to carbon monoxide[157].

According to studies, the administration of some antibiotics in mice (ampicillin, vancomycin, metronidazole, and gentamicin) in corneal abrasions caused an abnormal gene expression profile, which caused a decrease in corneal nerve density. Specifically, CCR2-corneal macrophages were reduced in antibiotic-treated mice. However, after discontinuation of antibiotics, stool transplantation, and probiotics, corneal macrophages were restored and corneal nerve fibers were regenerated. The author concluded the importance of probiotic supplementation whenever an antibiotic treatment for corneal damage is instituted[158].

One note of caution for uncontrolled use of antibiotics come from an experimental work by Möhle *et al*[159] where the daily use of antibiotics caused a decreases hippocampal neurogenesis and memory retention. To obtain a complete restoration of these abnormalities it was needed a synergy of gut flora reconstitution, plus wheel running exercise or probiotics.

A 2022 study from Columbia University found out that the microbiota of unilateral POAG patients treated with oreservative-added eye drops showed that alpha diversity and relative abundance of Gram-negative microbes are significantly higher as opposed to the gram-positive predominant microbes observed in the control eye and in HCs. Moreover, the metagenomic study suggested also that the treated glaucoma patients displayed an increased synthesis of LPS. This finding may be tentatively explained by the presence of the preservative benzalkonium chloride which acts as a detergent of potential bacterial overgrowth into the eye drops bottle[160].

Indeed, a similar study has very recently proven that eye drop therapy does not modify the eye microbioma but a very few (about 10%) were using preservative containing topical treatment[161].

Lim *et al*[162] raised some concern in the use of topical prostaglandins (PG) in glaucoma in that he unveiled that the eyelid microbiome of patients under PG was different as compared to naïve-POAG individuals, it creates problems about the eyelid surrounding of individuals using these drugs suggesting that this change may require some careful long term investigation.

In a study in Finland, children were treated with macrolides including erythromycin, roxithromycin, azithromycin and clarithromycin. These antibiotics can lead to a decrease in the diversity of intestinal microbiota, changes in metabolic activity and the abundance of antibiotic-resistant organisms, and have effects such as antibiotic diarrhea and recurrent C difficile infections[163].

Evidence also shows that exposure to antibiotics affects the cognitive immune system and the nervous system of the digestive system[164]. The vascular and neural mechanisms of retinal toxicity by aminoglycosides such as gentamicin are unclear. Gentamicin is a strong acid whose toxicity may be influenced by pH or by destroying the acidic environment of the lysosome and disrupting RPE metabolism[165].

CONCLUSION

In this review, we have described the relationship between the microbiome and health and eye diseases by reviewing prominent studies. We described how intestinal microbial imbalances are associated with various diseases and investigated the relevance of common gut and eye microbes on the mechanism of immune development and homeostasis in the development of eye diseases. The eye is affected by gut microbiota in association with changes in the immune system with an inflammatory component. We study eye surface microbes in pathological conditions, injury and surgery and their imbalance and changes in relation to eye diseases, ARMDs, RP, glaucoma, DR, dry eye and we checked uveitis. The retina is a very delicate organ with an inability to regenerate cells in old age. The use of antibiotics and chemotherapy drugs also has a toxic impact on the cells of the eye area, which, with the mechanism of action on the extracellular matrix and lysosomes and metabolism, causes many side effects, including dry eyes, mild redness of the eyes, itching, hemorrhage, retinal infection, neuritis in some cases. The function of microbiota in modulating homeostasis processes creates new methods for therapeutic purposes and pathology of extraintestinal diseases, including eye diseases. In addition, the intestine microbiota plays an essential role in nutrient absorption and metabolism. It produces vitamins K and B, which are essential for bacteria. In addition, it seems that the intestine microbiota can influence the metabolism of polyphenols and influence their biological activity. People with old age are severely affected by changes in the intestinal microbiome, eyes and chronic inflammatory diseases including diabetes, obesity, rheumatoid arthritis, Alzheimer's, Parkinson's and multiple sclerosis, intestinal inflammation and cardiovascular diseases and other diseases such as Behçet's syndrome and Sjogren's, stated that these diseases are specifically inflammatory diseases of the immune system related to the changes in the intestinal microbiome. Studies that show the effect of probiotics, prebiotics, and synbiotics on the gut and eye microbiota, and which modulate inflammation and homeostasis, have been reviewed. Changes in intestinal microbes and the use of beneficial microbes investigated in studies, the use of probiotics, prebiotics, postbiotics and fermented foods and foods containing essential vitamins and supplements, the misuse of antibiotics and even transmission fecal microbiota in elderly people, it seems that they have the potential to be used in the treatment of eye diseases and preventive strategies.

FOOTNOTES

Author contributions: Haghshenas L has cooperated in all aspects of writing and sending the article for publishing and corrections; Banihashemi S and Malekzadegan Y have cooperated in the selection of figures and content analysis; Ahmadi AM has cooperated in writing the text; Catanzaro R and Marotta F have cooperated in reviewing and approving the article and guiding the topic and selecting the reference of articles.

Conflict-of-interest statement: The authors declare no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country of origin: United States

ORCID number: Leila Haghshenas 0000-0002-4883-5977; Roberto Catanzaro 0000-0003-4852-9125.

S-Editor: Lin C
L-Editor: A
P-Editor: Zhang L

REFERENCES

1 **Marchesi JR**, Ravel J. The vocabulary of microbiome research: a proposal. *Microbiome* 2015; **3**: 31 [PMID: 26229597 DOI: 10.1186/s40168-015-0094-5]
2 **Berg G**, Rybakova D, Fischer D, Cernava T, Vergès MC, Charles T, Chen X, Cocolin L, Eversole K, Corral GH, Kazou M, Kinkel L, Lange L, Lima N, Loy A, Macklin JA, Maguin E, Mauchline T, McClure R, Mitter B, Ryan M, Sarand I, Smidt H, Schelkle B, Roume H, Kiran GS, Selvin J, Souza RSC, van Overbeek L, Singh BK, Wagner M, Walsh A, Sessitsch A, Schloter M. Microbiome definition re-visited: old concepts and new challenges. *Microbiome* 2020; **8**: 103 [PMID: 32605663 DOI: 10.1186/s40168-020-00875-0]
3 **Nagpal R**, Kumar M, Yadav AK, Hemalatha R, Yadav H, Marotta F, Yamashiro Y. Gut microbiota in health and disease: an overview focused on metabolic inflammation. *Benef Microbes* 2016; **7**: 181-194 [PMID: 26645350 DOI: 10.3920/bm2015.0062]
4 **Vaiserman AM**, Koliada AK, Marotta F. Gut microbiota: A player in aging and a target for anti-aging intervention. *Ageing Res Rev* 2017; **35**: 36-45 [PMID: 28109835 DOI: 10.1016/j.arr.2017.01.001]
5 **Martinez JE**, Kahana DD, Ghuman S, Wilson HP, Wilson J, Kim SCJ, Lagishetty V, Jacobs JP, Sinha-Hikim AP, Friedman TC. Unhealthy Lifestyle and Gut Dysbiosis: A Better Understanding of the Effects of Poor Diet and Nicotine on the Intestinal Microbiome. *Front Endocrinol (Lausanne)* 2021; **12**: 667066 [PMID: 34168615 DOI: 10.3389/fendo.2021.667066]
6 **Brown JM**, Hazen SL. The gut microbial endocrine organ: bacterially derived signals driving cardiometabolic diseases. *Annu Rev Med* 2015; **66**: 343-359 [PMID: 25587655 DOI: 10.1146/annurev-med-060513-093205]
7 **Ispas S**, Tuta LA, Botnarciuc M, Ispas V, Staicovici S, Ali S, Nelson-Twakor A, Cojocaru C, Herlo A, Petcu A. Metabolic Disorders, the Microbiome as an Endocrine Organ, and Their Relations with Obesity: A Literature Review. *J Pers Med* 2023; **13** [PMID: 38003917 DOI: 10.3390/jpm13111602]
8 **Wang X**, Sun G, Feng T, Zhang J, Huang X, Wang T, Xie Z, Chu X, Yang J, Wang H, Chang S, Gong Y, Ruan L, Zhang G, Yan S, Lian W, Du C, Yang D, Zhang Q, Lin F, Liu J, Zhang H, Ge C, Xiao S, Ding J, Geng M. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res* 2019; **29**: 787-803 [PMID: 31488882 DOI: 10.1038/s41422-019-0216-x]
9 **Liu Q**, Sun W, Zhang H. Interaction of Gut Microbiota with Endocrine Homeostasis and Thyroid Cancer. *Cancers (Basel)* 2022; **14** [PMID: 35681636 DOI: 10.3390/cancers14112656]
10 **Battson ML**, Lee DM, Weir TL, Gentile CL. The gut microbiota as a novel regulator of cardiovascular function and disease. *J Nutr Biochem* 2018; **56**: 1-15 [PMID: 29427903 DOI: 10.1016/j.jnutbio.2017.12.010]
11 **Floyd JL**, Grant MB. The Gut-Eye Axis: Lessons Learned from Murine Models. *Ophthalmol Ther* 2020; **9**: 499-513 [PMID: 32617914 DOI: 10.1007/s40123-020-00278-2]
12 **Vavricka SR**, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal Manifestations of Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015; **21**: 1982-1992 [PMID: 26154136 DOI: 10.1097/MIB.0000000000000392]
13 **Kugadas A**, Wright Q, Geddes-McAlister J, Gadjeva M. Role of Microbiota in Strengthening Ocular Mucosal Barrier Function Through Secretory IgA. *Invest Ophthalmol Vis Sci* 2017; **58**: 4593-4600 [PMID: 28892827 DOI: 10.1167/iovs.17-22119]
14 **Thursby E**, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017; **474**: 1823-1836 [PMID: 28512250 DOI: 10.1042/BCJ20160510]
15 **Nagpal R**, Mainali R, Ahmadi S, Wang S, Singh R, Kavanagh K, Kitzman DW, Kushugulova A, Marotta F, Yadav H. Gut microbiome and aging: Physiological and mechanistic insights. *Nutr Healthy Aging* 2018; **4**: 267-285 [PMID: 29951588 DOI: 10.3233/NHA-170030]
16 **Kho ZY**, Lal SK. The Human Gut Microbiome - A Potential Controller of Wellness and Disease. *Front Microbiol* 2018; **9**: 1835 [PMID: 30154767 DOI: 10.3389/fmicb.2018.01835]
17 **Koleva PT**, Kim JS, Scott JA, Kozyrskyj AL. Microbial programming of health and disease starts during fetal life. *Birth Defects Res C Embryo Today* 2015; **105**: 265-277 [PMID: 26663884 DOI: 10.1002/bdrc.21117]
18 **Zhuang L**, Chen H, Zhang S, Zhuang J, Li Q, Feng Z. Intestinal Microbiota in Early Life and Its Implications on Childhood Health. *Genomics Proteomics Bioinformatics* 2019; **17**: 13-25 [PMID: 30986482 DOI: 10.1016/j.gpb.2018.10.002]
19 **Ottman N**, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what do they do? *Front Cell Infect Microbiol*

2012; **2**: 104 [PMID: 22919693 DOI: 10.3389/fcimb.2012.00104]

20 **Shi N**, Li N, Duan X, Niu H. Interaction between the gut microbiome and mucosal immune system. *Mil Med Res* 2017; **4**: 14 [PMID: 28465831 DOI: 10.1186/s40779-017-0122-9]

21 **Rizzetto L**, Fava F, Tuohy KM, Selmi C. Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex. *J Autoimmun* 2018; **92**: 12-34 [PMID: 29861127 DOI: 10.1016/j.jaut.2018.05.008]

22 **Jain S**, Marotta F, Haghshenas L, Yadav H. Treating Leaky Syndrome in the Over 65s: Progress and Challenges. *Clin Interv Aging* 2023; **18**: 1447-1451 [PMID: 37671072 DOI: 10.2147/CIA.S409801]

23 **Ahmad R**, Sorrell MF, Batra SK, Dhawan P, Singh AB. Gut permeability and mucosal inflammation: bad, good or context dependent. *Mucosal Immunol* 2017; **10**: 307-317 [PMID: 28120842 DOI: 10.1038/mi.2016.128]

24 **Fasano A**, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Goldblum SE. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet* 2000; **355**: 1518-1519 [PMID: 10801176 DOI: 10.1016/S0140-6736(00)02169-3]

25 **Fukui H**. Increased Intestinal Permeability and Decreased Barrier Function: Does It Really Influence the Risk of Inflammation? *Inflamm Intest Dis* 2016; **1**: 135-145 [PMID: 29922669 DOI: 10.1159/000447252]

26 **Tilg H**, Zmora N, Adolph TE, Elinav E. The intestinal microbiota fuelling metabolic inflammation. *Nat Rev Immunol* 2020; **20**: 40-54 [PMID: 31388093 DOI: 10.1038/s41577-019-0198-4]

27 **Fasano A**. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F1000Res* 2020; **9** [PMID: 32051759 DOI: 10.12688/f1000research.20510.1]

28 **Salguero MV**, Al-Obaide MAI, Singh R, Siepmann T, Vasylyeva TL. Dysbiosis of Gram-negative gut microbiota and the associated serum lipopolysaccharide exacerbates inflammation in type 2 diabetic patients with chronic kidney disease. *Exp Ther Med* 2019; **18**: 3461-3469 [PMID: 31602221 DOI: 10.3892/etm.2019.7943]

29 **Guo S**, Al-Sadi R, Said HM, Ma TY. Lipopolysaccharide causes an increase in intestinal tight junction permeability in vitro and in vivo by inducing enterocyte membrane expression and localization of TLR-4 and CD14. *Am J Pathol* 2013; **182**: 375-387 [PMID: 23201091 DOI: 10.1016/j.ajpath.2012.10.014]

30 **Lighthouse J**, Naito Y, Helmy A, Hotten P, Fuji H, Min CH, Yoshioka M, Marotta F. Endotoxinemia and benzodiazepine-like substances in compensated cirrhotic patients: a randomized study comparing the effect of rifaximine alone and in association with a symbiotic preparation. *Hepatol Res* 2004; **28**: 155-160 [PMID: 15036072 DOI: 10.1016/j.hepres.2003.11.005]

31 **Asehnoune K**, Strassheim D, Mitra S, Kim JY, Abraham E. Involvement of reactive oxygen species in Toll-like receptor 4-dependent activation of NF-kappa B. *J Immunol* 2004; **172**: 2522-2529 [PMID: 14764725 DOI: 10.4049/jimmunol.172.4.2522]

32 **Boutagy NE**, McMillan RP, Frisard MI, Hulver MW. Metabolic endotoxemia with obesity: Is it real and is it relevant? *Biochimie* 2016; **124**: 11-20 [PMID: 26133659 DOI: 10.1016/j.biochi.2015.06.020]

33 **Han X**, Chen X, Chen S, Luo Q, Liu X, He A, He S, Qiu J, Chen P, Wu Y, Zhuang J, Yang M, Wu C, Wu N, Yang Y, Ge J, Zhuang J, Yu K. Tetramethylpyrazine attenuates endotoxin-induced retinal inflammation by inhibiting microglial activation *via* the TLR4/NF-κB signalling pathway. *Biomed Pharmacother* 2020; **128**: 110273 [PMID: 32460188 DOI: 10.1016/j.biopha.2020.110273]

34 **Arjunan P**, Swaminathan R. Do Oral Pathogens Inhabit the Eye and Play a Role in Ocular Diseases? *J Clin Med* 2022; **11** [PMID: 35629064 DOI: 10.3390/jcm11102938]

35 **Arjunan P**, Swaminathan R, Yuan J, Al-Shabrawey M, Espinosa-Heidmann DG, Nussbaum J, Martin PM, Cutler CW. Invasion of Human Retinal Pigment Epithelial Cells by Porphyromonas gingivalis leading to Vacuolar/Cytosolic localization and Autophagy dysfunction In-Vitro. *Sci Rep* 2020; **10**: 7468 [PMID: 32366945 DOI: 10.1038/s41598-020-64449-8]

36 **Inskeep WP**, Rusch DB, Jay ZJ, Herrgard MJ, Kozubal MA, Richardson TH, Macur RE, Hamamura N, Jennings Rd, Fouke BW, Reysenbach AL, Roberto F, Young M, Schwartz A, Boyd ES, Badger JH, Mathur EJ, Ortmann AC, Bateson M, Geesey G, Frazier M. Metagenomes from high-temperature chemotrophic systems reveal geochemical controls on microbial community structure and function. *PLoS One* 2010; **5**: e9773 [PMID: 20333304 DOI: 10.1371/journal.pone.0009773]

37 **Janowitz C**, Nakamura YK, Metea C, Gligor A, Yu W, Karstens L, Rosenbaum JT, Asquith M, Lin P. Disruption of Intestinal Homeostasis and Intestinal Microbiota During Experimental Autoimmune Uveitis. *Invest Ophthalmol Vis Sci* 2019; **60**: 420-429 [PMID: 30695094 DOI: 10.1167/iovs.18-24813]

38 **Gong H**, Zhang S, Li Q, Zuo C, Gao X, Zheng B, Lin M. Gut microbiota compositional profile and serum metabolic phenotype in patients with primary open-angle glaucoma. *Exp Eye Res* 2020; **191**: 107921 [PMID: 31917963 DOI: 10.1016/j.exer.2020.107921]

39 **Zinkernagel MS**, Zysset-Burri DC, Keller I, Berger LE, Leichtle AB, Largiadèr CR, Fiedler GM, Wolf S. Association of the Intestinal Microbiome with the Development of Neovascular Age-Related Macular Degeneration. *Sci Rep* 2017; **7**: 40826 [PMID: 28094305 DOI: 10.1038/srep40826]

40 **Beli E**, Yan Y, Moldovan L, Vieira CP, Gao R, Duan Y, Prasad R, Bhatwadekar A, White FA, Townsend SD, Chan L, Ryan CN, Morton D, Moldovan EG, Chu FI, Oudit GY, Derendorf H, Adorini L, Wang XX, Evans-Molina C, Mirmira RG, Boulton ME, Yoder MC, Li Q, Levi M, Busik JV, Grant MB. Restructuring of the Gut Microbiome by Intermittent Fasting Prevents Retinopathy and Prolongs Survival in db/db Mice. *Diabetes* 2018; **67**: 1867-1879 [PMID: 29712667 DOI: 10.2337/db18-0158]

41 **Huang Y**, Wang Z, Ma H, Ji S, Chen Z, Cui Z, Chen J, Tang S. Dysbiosis and Implication of the Gut Microbiota in Diabetic Retinopathy. *Front Cell Infect Microbiol* 2021; **11**: 646348 [PMID: 33816351 DOI: 10.3389/fcimb.2021.646348]

42 **Moubayed NM**, Bhat RS, Al Farraj D, Dihani NA, El Ansary A, Fahmy RM. Screening and identification of gut anaerobes (Bacteroidetes) from human diabetic stool samples with and without retinopathy in comparison to control subjects. *Microb Pathog* 2019; **129**: 88-92 [PMID: 30708043 DOI: 10.1016/j.micpath.2019.01.025]

43 **Waite DW**, Chuvochina M, Pelikan C, Parks DH, Yilmaz P, Wagner M, Loy A, Naganuma T, Nakai R, Whitman WB, Hahn MW, Kuever J, Hugenholtz P. Proposal to reclassify the proteobacterial classes Deltaproteobacteria and Oligoflexia, and the phylum Thermodesulfobacteria into four phyla reflecting major functional capabilities. *Int J Syst Evol Microbiol* 2020; **70**: 5972-6016 [PMID: 33151140 DOI: 10.1099/ijsem.0.004213]

44 **Hao L**, Michaelsen TY, Singleton CM, Dottorini G, Kirkegaard RH, Albertsen M, Nielsen PH, Dueholm MS. Novel syntrophic bacteria in full-scale anaerobic digesters revealed by genome-centric metatranscriptomics. *ISME J* 2020; **14**: 906-918 [PMID: 31896784 DOI: 10.1038/s41396-019-0571-0]

45 **Karlsson FH**, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, Nielsen J, Bäckhed F. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013; **498**: 99-103 [PMID: 23719380 DOI: 10.1038/nature12198]

46 **Wang Y**, Ye X, Ding D, Lu Y. Characteristics of the intestinal flora in patients with peripheral neuropathy associated with type 2 diabetes. *J*

Int Med Res 2020; **48**: 300060520936806 [PMID: 32938282 DOI: 10.1177/0300060520936806]

47 **Zeuthen LH**, Christensen HR, Frøkiaer H. Lactic acid bacteria inducing a weak interleukin-12 and tumor necrosis factor alpha response in human dendritic cells inhibit strongly stimulating lactic acid bacteria but act synergistically with gram-negative bacteria. *Clin Vaccine Immunol* 2006; **13**: 365-375 [PMID: 16522779 DOI: 10.1128/CVI.13.3.365-375.2006]

48 **Wu H**, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, Ståhlman M, Olsson LM, Serino M, Planas-Fèlix M, Xifra G, Mercader JM, Torrents D, Burcelin R, Ricart W, Perkins R, Fernàndez-Real JM, Bäckhed F. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat Med* 2017; **23**: 850-858 [PMID: 28530702 DOI: 10.1038/nm.4345]

49 **Arrieta MC**, Finlay BB. The commensal microbiota drives immune homeostasis. *Front Immunol* 2012; **3**: 33 [PMID: 22566917 DOI: 10.3389/fimmu.2012.00033]

50 **Li JJ**, Yi S, Wei L. Ocular Microbiota and Intraocular Inflammation. *Front Immunol* 2020; **11**: 609765 [PMID: 33424865 DOI: 10.3389/fimmu.2020.609765]

51 **Graham JE**, Moore JE, Jiru X, Moore JE, Goodall EA, Dooley JS, Hayes VE, Dartt DA, Downes CS, Moore TC. Ocular pathogen or commensal: a PCR-based study of surface bacterial flora in normal and dry eyes. *Invest Ophthalmol Vis Sci* 2007; **48**: 5616-5623 [PMID: 18055811 DOI: 10.1167/iovs.07-0588]

52 **Dartt DA**. Regulation of mucin and fluid secretion by conjunctival epithelial cells. *Prog Retin Eye Res* 2002; **21**: 555-576 [PMID: 12433377 DOI: 10.1016/s1350-9462(02)00038-1]

53 **Koropatkin NM**, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. *Nat Rev Microbiol* 2012; **10**: 323-335 [PMID: 22491358 DOI: 10.1038/nrmicro2746]

54 **Tsai YL**, Lin TL, Chang CJ, Wu TR, Lai WF, Lu CC, Lai HC. Probiotics, prebiotics and amelioration of diseases. *J Biomed Sci* 2019; **26**: 3 [PMID: 30609922 DOI: 10.1186/s12929-018-0493-6]

55 **Watane A**, Raolji S, Cavuoto K, Galor A. Microbiome and immune-mediated dry eye: a review. *BMJ Open Ophthalmol* 2022; **7** [PMID: 36161855 DOI: 10.1136/bmjophth-2021-000956]

56 **Giannaccare G**, Pellegrini M, Sebastiani S, Bernabei F, Roda M, Taroni L, Versura P, Campos EC. Efficacy of Omega-3 Fatty Acid Supplementation for Treatment of Dry Eye Disease: A Meta-Analysis of Randomized Clinical Trials. *Cornea* 2019; **38**: 565-573 [PMID: 30702470 DOI: 10.1097/ICO.0000000000001884]

57 **Dry Eye Assessment and Management Study Research Group**, Asbell PA, Maguire MG, Pistilli M, Ying GS, Szczotka-Flynn LB, Hardten DR, Lin MC, Shtein RM. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. *N Engl J Med* 2018; **378**: 1681-1690 [PMID: 29652551 DOI: 10.1056/NEJMoa1709691]

58 **Kawashima M**, Nakamura S, Izuta Y, Inoue S, Tsubota K. Dietary Supplementation with a Combination of Lactoferrin, Fish Oil, and Enterococcus faecium WB2000 for Treating Dry Eye: A Rat Model and Human Clinical Study. *Ocul Surf* 2016; **14**: 255-263 [PMID: 26795265 DOI: 10.1016/j.jtos.2015.12.005]

59 **Chung SH**, Choi SH, Choi JA, Chuck RS, Joo CK. Curcumin suppresses ovalbumin-induced allergic conjunctivitis. *Mol Vis* 2012; **18**: 1966-1972 [PMID: 22876123]

60 **Chisari G**, Chisari EM, Francaviglia A, Chisari CG. The mixture of bifidobacterium associated with fructo-oligosaccharides reduces the damage of the ocular surface. *Clin Ter* 2017; **168**: e181-e185 [PMID: 28612893 DOI: 10.7417/T.2017.2002]

61 **Diego JL**, Bidikov L, Pedler MG, Kennedy JB, Quiroz-Mercado H, Gregory DG, Petrash JM, McCourt EA. Effect of human milk as a treatment for dry eye syndrome in a mouse model. *Mol Vis* 2016; **22**: 1095-1102 [PMID: 27667918]

62 **Marotta F**, Pavasuthipaisit K, Yoshida C, Albergati F, Marandola P. Relationship between aging and susceptibility of erythrocytes to oxidative damage: in view of nutraceutical interventions. *Rejuvenation Res* 2006; **9**: 227-230 [PMID: 16706649 DOI: 10.1089/rej.2006.9.227]

63 **Bertuccelli G**, Zerbinati N, Marcellino M, Nanda Kumar NS, He F, Tsepakolenko V, Cervi J, Lorenzetti A, Marotta F. Effect of a quality-controlled fermented nutraceutical on skin aging markers: An antioxidant-control, double-blind study. *Exp Ther Med* 2016; **11**: 909-916 [PMID: 26998011 DOI: 10.3892/etm.2016.3011]

64 **Riva A**, Togni S, Franceschi F, Kawada S, Inaba Y, Eggenhoffner R, Giacomelli L. The effect of a natural, standardized bilberry extract (Mirtoselect®) in dry eye: a randomized, double blinded, placebo-controlled trial. *Eur Rev Med Pharmacol Sci* 2017; **21**: 2518-2525 [PMID: 28617532]

65 **Natarajan SB**, Hwang JW, Kim YS, Kim EK, Park PJ. Ocular promoting activity of grape polyphenols-A review. *Environ Toxicol Pharmacol* 2017; **50**: 83-90 [PMID: 28135653 DOI: 10.1016/j.etap.2016.12.004]

66 **Masmali AM**, Alanazi SA, Alotaibi AG, Fagehi R, Abusharaha A, El-Hiti GA. The acute effect of a single dose of green tea on the quality and quantity of tears in normal eye subjects. *Clin Ophthalmol* 2019; **13**: 605-610 [PMID: 31040641 DOI: 10.2147/OPTH.S201127]

67 **Abengózar-Vela A**, Schaumburg CS, Stern ME, Calonge M, Enríquez-de-Salamanca A, González-García MJ. Topical Quercetin and Resveratrol Protect the Ocular Surface in Experimental Dry Eye Disease. *Ocul Immunol Inflamm* 2019; **27**: 1023-1032 [PMID: 30096001 DOI: 10.1080/09273948.2018.1497664]

68 **Rodríguez-Daza MC**, de Vos WM. Polyphenols as Drivers of a Homeostatic Gut Microecology and Immuno-Metabolic Traits of Akkermansia muciniphila: From Mouse to Man. *Int J Mol Sci* 2022; **24** [PMID: 36613488 DOI: 10.3390/ijms24010045]

69 **Kim J**, Choi SH, Kim YJ, Jeong HJ, Ryu JS, Lee HJ, Kim TW, Im SH, Oh JY, Kim MK. Clinical Effect of IRT-5 Probiotics on Immune Modulation of Autoimmunity or Alloimmunity in the Eye. *Nutrients* 2017; **9** [PMID: 29068389 DOI: 10.3390/nu9111166]

70 **Chisari G**, Chisari EM, Borzi AM, Chisari CG. Aging Eye Microbiota in Dry Eye Syndrome in Patients Treated with Enterococcus faecium and Saccharomyces boulardii. *Curr Clin Pharmacol* 2017; **12**: 99-105 [PMID: 28676009 DOI: 10.2174/1574884712666170704145046]

71 **de Paiva CS**, Jones DB, Stern ME, Bian F, Moore QL, Corbiere S, Streckfus CF, Hutchinson DS, Ajami NJ, Petrosino JF, Pflugfelder SC. Altered Mucosal Microbiome Diversity and Disease Severity in Sjögren Syndrome. *Sci Rep* 2016; **6**: 23561 [PMID: 27087247 DOI: 10.1038/srep23561]

72 **Cano-Ortiz A**, Laborda-Illanes A, Plaza-Andrades I, Membrillo Del Pozo A, Villarrubia Cuadrado A, Rodríguez Calvo de Mora M, Leiva-Gea I, Sanchez-Alcoholado L, Queipo-Ortuño MI. Connection between the Gut Microbiome, Systemic Inflammation, Gut Permeability and FOXP3 Expression in Patients with Primary Sjögren's Syndrome. *Int J Mol Sci* 2020; **21** [PMID: 33228011 DOI: 10.3390/ijms21228733]

73 **Mölzer C**, Heissigerova J, Wilson HM, Kuffova L, Forrester JV. Immune Privilege: The Microbiome and Uveitis. *Front Immunol* 2020; **11**: 608377 [PMID: 33569055 DOI: 10.3389/fimmu.2020.608377]

74 **Caspi RR**. A look at autoimmunity and inflammation in the eye. *J Clin Invest* 2010; **120**: 3073-3083 [PMID: 20811163 DOI: 10.1172/JCI42440]

75 **Darrell RW**, Wagener HP, Kurland LT. Epidemiology of uveitis. Incidence and prevalence in a small urban community. *Arch Ophthalmol* 1962; **68**: 502-514 [PMID: 13883604 DOI: 10.1001/archopht.1962.00960030506014]

76 **Rosenbaum JT**, Asquith M. The microbiome and HLA-B27-associated acute anterior uveitis. *Nat Rev Rheumatol* 2018; **14**: 704-713 [PMID: 30301938 DOI: 10.1038/s41584-018-0097-2]

77 **Huang X**, Ye Z, Cao Q, Su G, Wang Q, Deng J, Zhou C, Kijlstra A, Yang P. Gut Microbiota Composition and Fecal Metabolic Phenotype in Patients With Acute Anterior Uveitis. *Invest Ophthalmol Vis Sci* 2018; **59**: 1523-1531 [PMID: 29625474 DOI: 10.1167/iovs.17-22677]

78 **Wildner G**, Diedrichs-Möhring M. Autoimmune uveitis induced by molecular mimicry of peptides from rotavirus, bovine casein and retinal S-antigen. *Eur J Immunol* 2003; **33**: 2577-2587 [PMID: 12938234 DOI: 10.1002/eji.200324058]

79 **Wildner G**, Diedrichs-Möhring M. Molecular Mimicry and Uveitis. *Front Immunol* 2020; **11**: 580636 [PMID: 33193382 DOI: 10.3389/fimmu.2020.580636]

80 **Du Z**, Wang Q, Huang X, Yi S, Mei S, Yuan G, Su G, Cao Q, Zhou C, Wang Y, Kijlstra A, Yang P. Effect of berberine on spleen transcriptome and gut microbiota composition in experimental autoimmune uveitis. *Int Immunopharmacol* 2020; **81**: 106270 [PMID: 32044663 DOI: 10.1016/j.intimp.2020.106270]

81 **Nakamura YK**, Janowitz C, Metea C, Asquith M, Karstens L, Rosenbaum JT, Lin P. Short chain fatty acids ameliorate immune-mediated uveitis partially by altering migration of lymphocytes from the intestine. *Sci Rep* 2017; **7**: 11745 [PMID: 28924192 DOI: 10.1038/s41598-017-12163-3]

82 **Fritsche LG**, Igl W, Bailey JN, Grassmann F, Sengupta S, Bragg-Gresham JL, Burdon KP, Hebbring SJ, Wen C, Gorski M, Kim IK, Cho D, Zack D, Souied E, Scholl HP, Bala E, Lee KE, Hunter DJ, Sardell RJ, Mitchell P, Merriam JE, Cipriani V, Hoffman JD, Schick T, Lechanteur YT, Guymer RH, Johnson MP, Jiang Y, Stanton CM, Buitendijk GH, Zhan X, Kwong AM, Boleda A, Brooks M, Gieser L, Ratnapriya R, Branham KE, Foerster JR, Heckenlively JR, Othman MI, Vote BJ, Liang HH, Souzeau E, McAllister IL, Isaacs T, Hall J, Lake S, Mackey DA, Constable IJ, Craig JE, Kitchner TE, Yang Z, Su Z, Luo H, Chen D, Ouyang H, Flagg K, Lin D, Mao G, Ferreyra H, Stark K, von Strachwitz CN, Wolf A, Brandl C, Rudolph G, Olden M, Morrison MA, Morgan DJ, Schu M, Ahn J, Silvestri G, Tsironi EE, Park KH, Farrer LA, Orlin A, Brucker A, Li M, Curcio CA, Mohand-Saïd S, Sahel JA, Audo I, Benchaboune M, Cree AJ, Rennie CA, Goverdhan SV, Grunin M, Hagbi-Levi S, Campochiaro P, Katsanis N, Holz FG, Blond F, Blanché H, Deleuze JF, Igo RP Jr, Truitt B, Peachey NS, Meuer SM, Myers CE, Moore EL, Klein R, Hauser MA, Postel EA, Courtenay MD, Schwartz SG, Kovach JL, Scott WK, Liew G, Tan AG, Gopinath B, Merriam JC, Smith RT, Khan JC, Shahid H, Moore AT, McGrath JA, Laux R, Brantley MA Jr, Agarwal A, Ersoy L, Caramoy A, Langmann T, Saksens NT, de Jong EK, Hoyng CB, Cain MS, Richardson AJ, Martin TM, Blangero J, Weeks DE, Dhillon B, van Duijn CM, Doheny KF, Romm J, Klaver CC, Hayward C, Gorin MB, Klein ML, Baird PN, den Hollander AI, Fauser S, Yates JR, Allikmets R, Wang JJ, Schaumberg DA, Klein BE, Hagstrom SA, Chowers I, Lotery AJ, Léveillard T, Zhang K, Brilliant MH, Hewitt AW, Swaroop A, Chew EY, Pericak-Vance MA, DeAngelis M, Stambolian D, Haines JL, Iyengar SK, Weber BH, Abecasis GR, Heid IM. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet* 2016; **48**: 134-143 [PMID: 26691988 DOI: 10.1038/ng.3448]

83 **Fritsche LG**, Chen W, Schu M, Yaspan BL, Yu Y, Thorleifsson G, Zack DJ, Arakawa S, Cipriani V, Ripke S, Igo RP Jr, Buitendijk GH, Sim X, Weeks DE, Guymer RH, Merriam JE, Francis PJ, Hannum G, Agarwal A, Armbrecht AM, Audo I, Aung T, Barile GR, Benchaboune M, Bird AC, Bishop PN, Branham KE, Brooks M, Brucker AJ, Cade WH, Cain MS, Campochiaro PA, Chan CC, Cheng CY, Chew EY, Chin KA, Chowers I, Clayton DG, Cojocaru R, Conley YP, Cornes BK, Daly MJ, Dhillon B, Edwards AO, Evangelou E, Fagerness J, Ferreyra HA, Friedman JS, Geirsdottir A, George RJ, Gieger C, Gupta N, Hagstrom SA, Harding SP, Haritoglou C, Heckenlively JR, Holz FG, Hughes G, Ioannidis JP, Ishibashi T, Joseph P, Jun G, Kamatani Y, Katsanis N, N Keilhauer C, Khan JC, Kim IK, Kiyohara Y, Klein BE, Klein R, Kovach JL, Kozak I, Lee CJ, Lee KE, Lichtner P, Lotery AJ, Meitinger T, Mitchell P, Mohand-Saïd S, Moore AT, Morgan DJ, Morrison MA, Myers CE, Naj AC, Nakamura Y, Okada Y, Orlin A, Ortube MC, Othman MI, Pappas C, Park KH, Pauer GJ, Peachey NS, Poch O, Priya RR, Reynolds R, Richardson AJ, Ripp R, Rudolph G, Ryu E, Sahel JA, Schaumberg DA, Scholl HP, Schwartz SG, Scott WK, Shahid H, Sigurdsson H, Silvestri G, Sivakumaran TA, Smith RT, Sobrin L, Souied EH, Stambolian DE, Stefansson H, Sturgill-Short GM, Takahashi A, Tosakulwong N, Truitt BJ, Tsironi EE, Uitterlinden AG, van Duijn CM, Vijaya L, Vingerling JR, Vithana EN, Webster AR, Wichmann HE, Winkler TW, Wong TY, Wright AF, Zelenika D, Zhang M, Zhao L, Zhang K, Klein ML, Hageman GS, Lathrop GM, Stefansson K, Allikmets R, Baird PN, Gorin MB, Wang JJ, Klaver CC, Seddon JM, Pericak-Vance MA, Iyengar SK, Yates JR, Swaroop A, Weber BH, Kubo M, Deangelis MM, Léveillard T, Thorsteinsdottir U, Haines JL, Farrer LA, Heid IM, Abecasis GR; AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. *Nat Genet* 2013; **45**: 433-439, 439e1 [PMID: 23455636 DOI: 10.1038/ng.2578]

84 **Warwick A**, Lotery A. Genetics and genetic testing for age-related macular degeneration. *Eye (Lond)* 2018; **32**: 849-857 [PMID: 29125146 DOI: 10.1038/eye.2017.245]

85 **Wen X**, Hu X, Miao L, Ge X, Deng Y, Bible PW, Wei L. Epigenetics, microbiota, and intraocular inflammation: New paradigms of immune regulation in the eye. *Prog Retin Eye Res* 2018; **64**: 84-95 [PMID: 29357307 DOI: 10.1016/j.preteyeres.2018.01.001]

86 **Rullo J**, Far PM, Quinn M, Sharma N, Bae S, Irrcher I, Sharma S. Local oral and nasal microbiome diversity in age-related macular degeneration. *Sci Rep* 2020; **10**: 3862 [PMID: 32123200 DOI: 10.1038/s41598-020-60674-3]

87 **Ho EXP**, Cheung CMG, Sim S, Chu CW, Wilm A, Lin CB, Mathur R, Wong D, Chan CM, Bhagarva M, Laude A, Lim TH, Wong TY, Cheng CY, Davila S, Hibberd M. Human pharyngeal microbiota in age-related macular degeneration. *PLoS One* 2018; **13**: e0201768 [PMID: 30089174 DOI: 10.1371/journal.pone.0201768]

88 **Zhang Y**, Wang T, Wan Z, Bai J, Xue Y, Dai R, Wang M, Peng Q. Alterations of the intestinal microbiota in age-related macular degeneration. *Front Microbiol* 2023; **14**: 1069325 [PMID: 37089564 DOI: 10.3389/fmicb.2023.1069325]

89 **Liu H**, Dicksved J, Lundh T, Lindberg JE. Heat Shock Proteins: Intestinal Gatekeepers that Are Influenced by Dietary Components and the Gut Microbiota. *Pathogens* 2014; **3**: 187-210 [PMID: 25437614 DOI: 10.3390/pathogens3010187]

90 **Wax MB**, Tezel G, Yang J, Peng G, Patil RV, Agarwal N, Sappington RM, Calkins DJ. Induced autoimmunity to heat shock proteins elicits glaucomatous loss of retinal ganglion cell neurons *via* activated T-cell-derived fas-ligand. *J Neurosci* 2008; **28**: 12085-12096 [PMID: 19005073 DOI: 10.1523/JNEUROSCI.3200-08.2008]

91 **Henein C**, Khaw PT. The interplay between inflammation, immunity and commensal microflora in glaucomatous neurodegeneration. *Ann Eye Sci* 2019; **4**: 10 [DOI: 10.21037/aes.2019.02.04]

92 **Shestopalov VI**, Spurlock M, Gramlich OW, Kuehn MH. Immune Responses in the Glaucomatous Retina: Regulation and Dynamics. *Cells* 2021; **10** [PMID: 34440742 DOI: 10.3390/cells10081973]

93 **Zhang Y**, Zhou X, Lu Y. Gut microbiota and derived metabolomic profiling in glaucoma with progressive neurodegeneration. *Front Cell Infect Microbiol* 2022; **12**: 968992 [PMID: 36034713 DOI: 10.3389/fcimb.2022.968992]

94 **Glover JS**, Ticer TD, Engevik MA. Characterizing the mucin-degrading capacity of the human gut microbiota. *Sci Rep* 2022; **12**: 8456 [PMID:

35589783 DOI: 10.1038/s41598-022-11819-z]
95 **Chen H**, Cho KS, Vu THK, Shen CH, Kaur M, Chen G, Mathew R, McHam ML, Fazelat A, Lashkari K, Au NPB, Tse JKY, Li Y, Yu H, Yang L, Stein-Streilein J, Ma CHE, Woolf CJ, Whary MT, Jager MJ, Fox JG, Chen J, Chen DF. Commensal microflora-induced T cell responses mediate progressive neurodegeneration in glaucoma. *Nat Commun* 2018; **9**: 3209 [PMID: 30097565 DOI: 10.1038/s41467-018-05681-9]
96 **Yakhine-Diop SMS**, Morales-García JA, Niso-Santano M, González-Polo RA, Uribe-Carretero E, Martinez-Chacon G, Durand S, Maiuri MC, Aiastui A, Zulaica M, Ruíz-Martínez J, López de Munain A, Pérez-Tur J, Pérez-Castillo A, Kroemer G, Bravo-San Pedro JM, Fuentes JM. Metabolic alterations in plasma from patients with familial and idiopathic Parkinson's disease. *Aging (Albany NY)* 2020; **12**: 16690-16708 [PMID: 32903216 DOI: 10.18632/aging.103992]
97 **Pezzino S**, Sofia M, Greco LP, Litrico G, Filippello G, Sarvà I, La Greca G, Latteri S. Microbiome Dysbiosis: A Pathological Mechanism at the Intersection of Obesity and Glaucoma. *Int J Mol Sci* 2023; **24** [PMID: 36674680 DOI: 10.3390/ijms24021166]
98 **Ahn MW**, Lee JW, Shin JH, Lee JS. Relationship between intraocular pressure and parameters of obesity in ocular hypertension. *Int J Ophthalmol* 2020; **13**: 794-800 [PMID: 32420228 DOI: 10.18240/ijo.2020.05.15]
99 **Garcia-Villanueva C**, Milla E, Bolarin JM, García-Medina JJ, Cruz-Espinosa J, Benítez-Del-Castillo J, Salgado-Borges J, Hernández-Martínez FJ, Bendala-Tufanisco E, Andrés-Blasco I, Gallego-Martinez A, Zanón-Moreno VC, Pinazo-Durán MD. Impact of Systemic Comorbidities on Ocular Hypertension and Open-Angle Glaucoma, in a Population from Spain and Portugal. *J Clin Med* 2022; **11** [PMID: 36233515 DOI: 10.3390/jcm11195649]
100 **Astafurov K**, Elhawy E, Ren L, Dong CQ, Igboin C, Hyman L, Griffen A, Mittag T, Danias J. Oral microbiome link to neurodegeneration in glaucoma. *PLoS One* 2014; **9**: e104416 [PMID: 25180891 DOI: 10.1371/journal.pone.0104416]
101 **Skrzypecki J**, Izdebska J, Kamińska A, Badowska J, Przybek-Skrzypecka J, Bombuy J, Samborowska E, Szaflik JP. Glaucoma patients have an increased level of trimethylamine, a toxic product of gut bacteria, in the aqueous humor: a pilot study. *Int Ophthalmol* 2021; **41**: 341-347 [PMID: 32914277 DOI: 10.1007/s10792-020-01587-y]
102 **Doulberis M**, Papaefthymiou A, Polyzos SA, Bargiotas P, Liatsos C, Srivastava DS, Zavos C, Katsinelos P, Kountouras J. Association between Active Helicobacter pylori Infection and Glaucoma: A Systematic Review and Meta-Analysis. *Microorganisms* 2020; **8** [PMID: 32545826 DOI: 10.3390/microorganisms8060894]
103 **Ala S**, Maleki I, Sanjari Araghi A, Sahebnasagh A, Shahraki A. Helicobacter pylori eradication in the management of glaucoma. *Caspian J Intern Med* 2020; **11**: 143-149 [PMID: 32509241 DOI: 10.22088/cjim.11.2.143]
104 **Fafure AA**, Edem EE, Obisesan AO, Enye LA, Adekeye AO, Adetunji AE, Nebo KE, Olusegun AA, Fafure OE. Fermented maize slurry (Ogi) and its supernatant (Omidun) mitigate elevated intraocular pressure by modulating BDNF expression and glial plasticity in the retina-gut axis of glaucomatous rats. *J Complement Integr Med* 2022; **19**: 887-896 [PMID: 34380184 DOI: 10.1515/jcim-2021-0114]
105 **Simell O**, Takki K. Raised plasma-ornithine and gyrate atrophy of the choroid and retina. *Lancet* 1973; **1**: 1031-1033 [PMID: 4122112 DOI: 10.1016/s0140-6736(73)90667-3]
106 **Chen N**, Wu J, Wang J, Piri N, Chen F, Xiao T, Zhao Y, Sun D, Kaplan HJ, Shao H. Short chain fatty acids inhibit endotoxin-induced uveitis and inflammatory responses of retinal astrocytes. *Exp Eye Res* 2021; **206**: 108520 [PMID: 33617852 DOI: 10.1016/j.exer.2021.108520]
107 **Andriessen EM**, Wilson AM, Mawambo G, Dejda A, Miloudi K, Sennlaub F, Sapieha P. Gut microbiota influences pathological angiogenesis in obesity-driven choroidal neovascularization. *EMBO Mol Med* 2016; **8**: 1366-1379 [PMID: 27861126 DOI: 10.15252/emmm.201606531]
108 **Horai R**, Zárate-Bladés CR, Dillenburg-Pilla P, Chen J, Kielczewski JL, Silver PB, Jittayasothorn Y, Chan CC, Yamane H, Honda K, Caspi RR. Microbiota-Dependent Activation of an Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site. *Immunity* 2015; **43**: 343-353 [PMID: 26287682 DOI: 10.1016/j.immuni.2015.07.014]
109 **Kutsyr O**, Maestre-Carballa L, Lluesma-Gomez M, Martinez-Garcia M, Cuenca N, Lax P. Retinitis pigmentosa is associated with shifts in the gut microbiome. *Sci Rep* 2021; **11**: 6692 [PMID: 33758301 DOI: 10.1038/s41598-021-86052-1]
110 **Kim CH**. Immune regulation by microbiome metabolites. *Immunology* 2018; **154**: 220-229 [PMID: 29569377 DOI: 10.1111/imm.12930]
111 **Branca JJV**, Gulisano M, Nicoletti C. Intestinal epithelial barrier functions in ageing. *Ageing Res Rev* 2019; **54**: 100938 [PMID: 31369869 DOI: 10.1016/j.arr.2019.100938]
112 **Reza MM**, Finlay BB, Pettersson S. Gut microbes, ageing & organ function: a chameleon in modern biology? *EMBO Mol Med* 2019; **11**: e9872 [PMID: 31410991 DOI: 10.15252/emmm.201809872]
113 **García-Peña C**, Álvarez-Cisneros T, Quiroz-Baez R, Friedland RP. Microbiota and Aging. A Review and Commentary. *Arch Med Res* 2017; **48**: 681-689 [PMID: 29229199 DOI: 10.1016/j.arcmed.2017.11.005]
114 **Bischoff SC**. Microbiota and aging. *Curr Opin Clin Nutr Metab Care* 2016; **19**: 26-30 [PMID: 26560527 DOI: 10.1097/MCO.0000000000000242]
115 **Wang HX**, Wang YP. Gut Microbiota-brain Axis. *Chin Med J (Engl)* 2016; **129**: 2373-2380 [PMID: 27647198 DOI: 10.4103/0366-6999.190667]
116 **Mangiola F**, Nicoletti A, Gasbarrini A, Ponziani FR. Gut microbiota and aging. *Eur Rev Med Pharmacol Sci* 2018; **22**: 7404-7413 [PMID: 30468488 DOI: 10.26355/eurrev_201811_16280]
117 **Soenen S**, Rayner CK, Jones KL, Horowitz M. The ageing gastrointestinal tract. *Curr Opin Clin Nutr Metab Care* 2016; **19**: 12-18 [PMID: 26560524 DOI: 10.1097/MCO.0000000000000238]
118 **Yoon CH**, Ryu JS, Moon J, Kim MK. Association between aging-dependent gut microbiome dysbiosis and dry eye severity in C57BL/6 male mouse model: a pilot study. *BMC Microbiol* 2021; **21**: 106 [PMID: 33832437 DOI: 10.1186/s12866-021-02173-7]
119 **Wen X**, Miao L, Deng Y, Bible PW, Hu X, Zou Y, Liu Y, Guo S, Liang J, Chen T, Peng GH, Chen W, Liang L, Wei L. The Influence of Age and Sex on Ocular Surface Microbiota in Healthy Adults. *Invest Ophthalmol Vis Sci* 2017; **58**: 6030-6037 [PMID: 29196767 DOI: 10.1167/iovs.17-22957]
120 **Chen S**, Wang Y, Liu Y, Li F, Chen Y, Fang X, Wen T, Xu S, Kermany D, Deng S, Li G, Zhang K, Zhang X. Dysbiosis of gut microbiome contributes to glaucoma pathogenesis. *MedComm - Future Med* 2022; **1**: e28 [DOI: 10.1002/mef2.28]
121 **Alam MS**, Gangiredla J, Hasan NA, Barnaba T, Tartera C. Aging-Induced Dysbiosis of Gut Microbiota as a Risk Factor for Increased Listeria monocytogenes Infection. *Front Immunol* 2021; **12**: 672353 [PMID: 33995413 DOI: 10.3389/fimmu.2021.672353]
122 **Parker A**, Romano S, Ansorge R, Aboelnour A, Le Gall G, Savva GM, Pontifex MG, Telatin A, Baker D, Jones E, Vauzour D, Rudder S, Blackshaw LA, Jeffery G, Carding SR. Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain. *Microbiome* 2022; **10**: 68 [PMID: 35501923 DOI: 10.1186/s40168-022-01243-w]
123 **Everard A**, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani

PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* 2013; **110**: 9066-9071 [PMID: 23671105 DOI: 10.1073/pnas.1219451110]

124 **Fransen F**, van Beek AA, Borghuis T, Aidy SE, Hugenholtz F, van der Gaast-de Jongh C, Savelkoul HFJ, De Jonge MI, Boekschoten MV, Smidt H, Faas MM, de Vos P. Aged Gut Microbiota Contributes to Systemical Inflammaging after Transfer to Germ-Free Mice. *Front Immunol* 2017; **8**: 1385 [PMID: 29163474 DOI: 10.3389/fimmu.2017.01385]

125 **Askew K**, Li K, Olmos-Alonso A, Garcia-Moreno F, Liang Y, Richardson P, Tipton T, Chapman MA, Riecken K, Beccari S, Sierra A, Molnár Z, Cragg MS, Garaschuk O, Perry VH, Gomez-Nicola D. Coupled Proliferation and Apoptosis Maintain the Rapid Turnover of Microglia in the Adult Brain. *Cell Rep* 2017; **18**: 391-405 [PMID: 28076784 DOI: 10.1016/j.celrep.2016.12.041]

126 **Leyrolle Q**, Layé S, Nadjar A. Direct and indirect effects of lipids on microglia function. *Neurosci Lett* 2019; **708**: 134348 [PMID: 31238131 DOI: 10.1016/j.neulet.2019.134348]

127 **Haran JP**, McCormick BA. Aging, Frailty, and the Microbiome-How Dysbiosis Influences Human Aging and Disease. *Gastroenterology* 2021; **160**: 507-523 [PMID: 33307030 DOI: 10.1053/j.gastro.2020.09.060]

128 **Rowan S**, Jiang S, Korem T, Szymanski J, Chang ML, Szelog J, Cassalman C, Dasuri K, McGuire C, Nagai R, Du XL, Brownlee M, Rabbani N, Thornalley PJ, Baleja JD, Deik AA, Pierce KA, Scott JM, Clish CB, Smith DE, Weinberger A, Avnit-Sagi T, Lotan-Pompan M, Segal E, Taylor A. Involvement of a gut-retina axis in protection against dietary glycemia-induced age-related macular degeneration. *Proc Natl Acad Sci U S A* 2017; **114**: E4472-E4481 [PMID: 28507131 DOI: 10.1073/pnas.1702302114]

129 **Fernandes R**, Viana SD, Nunes S, Reis F. Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy. *Biochim Biophys Acta Mol Basis Dis* 2019; **1865**: 1876-1897 [PMID: 30287404 DOI: 10.1016/j.bbadis.2018.09.032]

130 **Oubaha M**, Miloudi K, Dejda A, Guber V, Mawambo G, Germain MA, Bourdel G, Popovic N, Rezende FA, Kaufman RJ, Mallette FA, Sapieha P. Senescence-associated secretory phenotype contributes to pathological angiogenesis in retinopathy. *Sci Transl Med* 2016; **8**: 362ra144 [PMID: 27797960 DOI: 10.1126/scitranslmed.aaf9440]

131 **Costantini L**, Molinari R, Farinon B, Merendino N. Impact of Omega-3 Fatty Acids on the Gut Microbiota. *Int J Mol Sci* 2017; **18** [PMID: 29215589 DOI: 10.3390/ijms18122645]

132 **Rinninella E**, Mele MC, Merendino N, Cintoni M, Anselmi G, Caporossi A, Gasbarrini A, Minnella AM. The Role of Diet, Micronutrients and the Gut Microbiota in Age-Related Macular Degeneration: New Perspectives from the Gut–Retina Axis. *Nutrients* 2018; **10** [PMID: 30400586 DOI: 10.3390/nu10111677]

133 **Hegde PS**, Agni MB, Rai P, B MK, Km DG. Impact of carotenoids on gut microbiome: Implications in human health and disease. *J Appl Nat Sci* 2022; **14**: 1085-1099 [DOI: 10.31018/jans.v14i3.3582]

134 **Hobbs RP**, Bernstein PS. Nutrient Supplementation for Age-related Macular Degeneration, Cataract, and Dry Eye. *J Ophthalmic Vis Res* 2014; **9**: 487-493 [PMID: 25709776 DOI: 10.4103/2008-322X.150829]

135 **Dinsmoor A**, Thompson S, Edwards C, Burd N, Khan N, Erdman J Jr, Holscher H. Associations Between Serum Lutein and Human Gut Microbiota (P02-004-19). *Curr Dev Nutr* 2019; **3** (Suppl 1): nzz029.P02-004 [DOI: 10.1093/cdn/nzz029.p02-004-19]

136 **Grant MB**, Bernstein PS, Boesze-Battaglia K, Chew E, Curcio CA, Kenney MC, Klaver C, Philp NJ, Rowan S, Sparrow J, Spaide RF, Taylor A. Inside out: Relations between the microbiome, nutrition, and eye health. *Exp Eye Res* 2022; **224**: 109216 [PMID: 36041509 DOI: 10.1016/j.exer.2022.109216]

137 **Zhang AC**, Singh S, Craig JP, Downie LE. Omega-3 Fatty Acids and Eye Health: Opinions and Self-Reported Practice Behaviors of Optometrists in Australia and New Zealand. *Nutrients* 2020; **12** [PMID: 32331489 DOI: 10.3390/nu12041179]

138 **Kok CR**, Hutkins R. Yogurt and other fermented foods as sources of health-promoting bacteria. *Nutr Rev* 2018; **76**: 4-15 [PMID: 30452699 DOI: 10.1093/nutrit/nuy056]

139 **Lerner A**, Matthias T, Haimi M. [The gut feeling of the eyes: gut-eye axis]. *Harefuah* 2020; **159**: 455-457 [PMID: 32583651]

140 **Singh B**, Mal G, Marotta F. Designer Probiotics: Paving the Way to Living Therapeutics. *Trends Biotechnol* 2017; **35**: 679-682 [PMID: 28483159 DOI: 10.1016/j.tibtech.2017.04.001]

141 **Catanzaro R**, Anzalone M, Calabrese F, Milazzo M, Capuana M, Italia A, Occhipinti S, Marotta F. The gut microbiota and its correlations with the central nervous system disorders. *Panminerva Med* 2015; **57**: 127-143 [PMID: 25390799]

142 **Belizário JE**, Faintuch J, Garay-Malpartida M. Gut Microbiome Dysbiosis and Immunometabolism: New Frontiers for Treatment of Metabolic Diseases. *Mediators Inflamm* 2018; **2018**: 2037838 [PMID: 30622429 DOI: 10.1155/2018/2037838]

143 **Morita Y**, Jounai K, Miyake M, Inaba M, Kanauchi O. Effect of Heat-Killed Lactobacillus paracasei KW3110 Ingestion on Ocular Disorders Caused by Visual Display Terminal (VDT) Loads: A Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study. *Nutrients* 2018; **10** [PMID: 30096952 DOI: 10.3390/nu10081058]

144 **Morita Y**, Jounai K, Sakamoto A, Tomita Y, Sugihara Y, Suzuki H, Ohshio K, Otake M, Fujiwara D, Kanauchi O, Maruyama M. Long-term intake of Lactobacillus paracasei KW3110 prevents age-related chronic inflammation and retinal cell loss in physiologically aged mice. *Aging (Albany NY)* 2018; **10**: 2723-2740 [PMID: 30341255 DOI: 10.18632/aging.101583]

145 **Gibson GR**, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 491-502 [PMID: 28611480 DOI: 10.1038/nrgastro.2017.75]

146 **Carlson JL**, Erickson JM, Lloyd BB, Slavin JL. Health Effects and Sources of Prebiotic Dietary Fiber. *Curr Dev Nutr* 2018; **2**: nzy005 [PMID: 30019028 DOI: 10.1093/cdn/nzy005]

147 **Schaefer L**, Trujillo-Vargas CM, Midani FS, Pflugfelder SC, Britton RA, de Paiva CS. Gut Microbiota From Sjögren syndrome Patients Causes Decreased T Regulatory Cells in the Lymphoid Organs and Desiccation-Induced Corneal Barrier Disruption in Mice. *Front Med (Lausanne)* 2022; **9**: 852918 [PMID: 35355610 DOI: 10.3389/fmed.2022.852918]

148 **Tavakoli A**, Markoulli M, Papas E, Flanagan J. The Impact of Probiotics and Prebiotics on Dry Eye Disease Signs and Symptoms. *J Clin Med* 2022; **11** [PMID: 36013128 DOI: 10.3390/jcm11164889]

149 **Nataraj BH**, Ali SA, Behare PV, Yadav H. Postbiotics-parabiotics: the new horizons in microbial biotherapy and functional foods. *Microb Cell Fact* 2020; **19**: 168 [PMID: 32819443 DOI: 10.1186/s12934-020-01426-w]

150 **Choi SH**, Oh JW, Ryu JS, Kim HM, Im SH, Kim KP, Kim MK. IRT5 Probiotics Changes Immune Modulatory Protein Expression in the Extraorbital Lacrimal Glands of an Autoimmune Dry Eye Mouse Model. *Invest Ophthalmol Vis Sci* 2020; **61**: 42 [PMID: 32232342 DOI: 10.1167/iovs.61.3.42]

151 **Salminen S**, Collado MC, Endo A, Hill C, Lebeer S, Quigley EMM, Sanders ME, Shamir R, Swann JR, Szajewska H, Vinderola G. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 649-667 [PMID: 33948025 DOI: 10.1038/s41575-021-00440-6]

152 **Yang Q**, Liang Q, Balakrishnan B, Belobrajdic DP, Feng QJ, Zhang W. Role of Dietary Nutrients in the Modulation of Gut Microbiota: A Narrative Review. *Nutrients* 2020; **12** [PMID: 32023943 DOI: 10.3390/nu12020381]

153 **Chan HN**, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, Chu WK, Chen LJ, Tham CC, Yam JC, Pang CP. Vitamin D and Ocular Diseases: A Systematic Review. *Int J Mol Sci* 2022; **23** [PMID: 35457041 DOI: 10.3390/ijms23084226]

154 **Ramirez J**, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as Major Disruptors of Gut Microbiota. *Front Cell Infect Microbiol* 2020; **10**: 572912 [PMID: 33330122 DOI: 10.3389/fcimb.2020.572912]

155 **Konstantinidis T**, Tsigalou C, Karvelas A, Stavropoulou E, Voidarou C, Bezirtzoglou E. Effects of Antibiotics upon the Gut Microbiome: A Review of the Literature. *Biomedicines* 2020; **8** [PMID: 33207631 DOI: 10.3390/biomedicines8110502]

156 **Panda S**, El khader I, Casellas F, López Vivancos J, García Cors M, Santiago A, Cuenca S, Guarner F, Manichanh C. Short-term effect of antibiotics on human gut microbiota. *PLoS One* 2014; **9**: e95476 [PMID: 24748167 DOI: 10.1371/journal.pone.0095476]

157 **Bezirtzoglou EE**. Intestinal cytochromes P450 regulating the intestinal microbiota and its probiotic profile. *Microb Ecol Health Dis* 2012; **23** [PMID: 23990816 DOI: 10.3402/mehd.v23i0.18370]

158 **Liu J**, Wu M, He J, Xiao C, Xue Y, Fu T, Lin C, Dong D, Li Z. Antibiotic-Induced Dysbiosis of Gut Microbiota Impairs Corneal Nerve Regeneration by Affecting CCR2-Negative Macrophage Distribution. *Am J Pathol* 2018; **188**: 2786-2799 [PMID: 30470496 DOI: 10.1016/j.ajpath.2018.08.009]

159 **Möhle L**, Mattei D, Heimesaat MM, Bereswill S, Fischer A, Alutis M, French T, Hambardzumyan D, Matzinger P, Dunay IR, Wolf SA. Ly6C(hi) Monocytes Provide a Link between Antibiotic-Induced Changes in Gut Microbiota and Adult Hippocampal Neurogenesis. *Cell Rep* 2016; **15**: 1945-1956 [PMID: 27210745 DOI: 10.1016/j.celrep.2016.04.074]

160 **Chang CJ**, Somohano K, Zemsky C, Uhlemann AC, Liebmann J, Cioffi GA, Al-Aswad LA, Lynch SV, Winn BJ. Topical Glaucoma Therapy Is Associated With Alterations of the Ocular Surface Microbiome. *Invest Ophthalmol Vis Sci* 2022; **63**: 32 [PMID: 36036910 DOI: 10.1167/iovs.63.9.32]

161 **Priluck A**, Ramulu P, Dosto N, Quigley H, Abraham A. Validation of 16S rRNA Gene Sequencing of the Periocular Microbiome and Lack of Alteration by Topical Eyedrops. *Transl Vis Sci Technol* 2023; **12**: 32 [PMID: 36826842 DOI: 10.1167/tvst.12.2.32]

162 **Lim SH**, Shin JH, Lee JW, Lee Y, Seo JH. Differences in the eyelid and buccal microbiome of glaucoma patients receiving long-term administration of prostaglandin analog drops. *Graefes Arch Clin Exp Ophthalmol* 2021; **259**: 3055-3065 [PMID: 33961112 DOI: 10.1007/s00417-021-05218-9]

163 **Korpela K**, de Vos WM. Antibiotic use in childhood alters the gut microbiota and predisposes to overweight. *Microb Cell* 2016; **3**: 296-298 [PMID: 28357367 DOI: 10.15698/mic2016.07.514]

164 **Amoroso C**, Perillo F, Strati F, Fantini MC, Caprioli F, Facciotti F. The Role of Gut Microbiota Biomodulators on Mucosal Immunity and Intestinal Inflammation. *Cells* 2020; **9** [PMID: 32429359 DOI: 10.3390/cells9051234]

165 **Hancock HA**, Guidry C, Read RW, Ready EL, Kraft TW. Acute aminoglycoside retinal toxicity in vivo and in vitro. *Invest Ophthalmol Vis Sci* 2005; **46**: 4804-4808 [PMID: 16303982 DOI: 10.1167/iovs.05-0604]

166 **Horai R**, Caspi RR. Microbiome and Autoimmune Uveitis. *Front Immunol* 2019; **10**: 232 [PMID: 30837991 DOI: 10.3389/fimmu.2019.00232]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com



© 2024 Baishideng Publishing Group Inc. All rights reserved.