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Review Article

Microbial Signatures and Metabolic Mediators in Diabetic Retinopathy: The Emerging Gut-Retina Connection

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Abstract

Background: Diabetic Retinopathy (DR), a major cause of preventable blindness, has been increasingly linked to systemic inflammation and metabolic dysregulation. Emerging evidence highlights the gut- retina axis, where gut microbiota composition influences retinal health through inflammatory and neurovascular pathways. Dysbiosis, characterized by reduced microbial diversity and Diminished Short- Chain Fatty Acid (SCFA)-producing bacteria, may exacerbate retinal damage via chronic inflammation and vascular dysfunction.

Methods: A comprehensive literature search was performed in PubMed and Semantic Scholar using the terms gut microbiome and diabetic retinopathy. Filters targeting relevant journals (including Frontiers in Microbiology, PLOS ONE, International Journal of Molecular Sciences and Microorganisms) were applied. English-language, free full-text articles were included. Abstracts were screened for relevance and a PRISMA-based review framework guided study selection and synthesis.

Results: Current evidence supports that gut dysbiosis contributes to DR through mechanisms involving metabolic endotoxemia, impaired SCFA signaling and bile acid dysregulation. These alterations amplify inflammation, disrupt the blood-retinal barrier and promote angiogenesis. Interventions such as probiotics, prebiotics, dietary modulation and fecal microbiota transplantation demonstrate potential in restoring microbial balance and mitigating disease progression. Specific microbial signatures also show promise as predictive biomarkers of DR severity.

Conclusion: The gut microbiome emerges as a modifiable determinant of diabetic retinopathy. Targeting gut-derived metabolites and microbial pathways may open novel therapeutic and preventive avenues for preserving retinal health in diabetes.

Keywords: Diabetic Retinopathy; Gut Microbiome; Short-Chain Fatty Acids; Gut-Retina Axis; Dysbiosis

Abbreviations

DR: Diabetic Retinopathy; SCFA: Short-Chain Fatty Acid; DME: Diabetic Macular Edema; DM: Diabetes Mellitus; PDR: Proliferative Diabetic Retinopathy; LPS: Lipopolysaccharides; PAMP: Pathogen-Associated Molecular Patterns; TLR4: Toll-Like Receptor 4; NLRP3: NOD-Like Receptor Family Pyrin Domain-Containing 3; BRB: Blood Retinal Barrier; VEGF: Vascular Endothelial Growth Factor; FMT: Fecal Microbiota Transplant

Introduction

Diabetic Retinopathy (DR) and its major complication, Diabetic Macular Edema (DME), are leading causes of vision loss globally and across the Asia-Pacific region. As the most common organ-specific complication of Diabetes Mellitus (DM), DR remains a

principal cause of preventable blindness among the adult working population [1]. The onset and progression of this condition are increasingly associated with systemic changes driven by chronic inflammation and metabolic dysfunction. Research has uncovered the integral role of the gut microbiome -comprised of trillions of microorganisms residing in the digestive tract in influencing the pathogenesis of DR. Dysbiosis or an imbalance in gut microbial communities, has been implicated in the exacerbation of diabetic complications, including DR [2,3].

The idea of a "gut-retina axis" suggests that what happens in our gut may ripple far beyond digestion, potentially shaping how our eyes function and age. When the gut microbiome falls out of balance, a state often called dysbiosis, the intestinal barrier can become more permeable. This "leaky gut" effect may allow bacterial products to enter the bloodstream, stirring up low-grade inflammation throughout the body. Such chronic inflammation, researchers suspect, could play a meaningful role in the onset and progression of diabetic DR [4,5]. Experimental models have illustrated how modifications in gut microbiota composition can directly influence retinal health through inflammatory pathways and neurovascular integrity [6,7]. It has been shown that certain bacterial populations, particularly those producing Short-Chain Fatty Acids (SCFAs), play protective roles against inflammatory processes that can lead to deterioration of retinal structures associated with DR [8,9]. Among the many substances produced by gut microbes, Short-Chain Fatty Acids (SCFAs), particularly butyrate, acetate and propionate have drawn considerable interest for their apparent anti-inflammatory and neuroprotective effects. These molecules don't just nourish the intestinal lining; they also seem to communicate with immune cells through specific receptors, subtly tuning inflammatory pathways. By doing so, they may help preserve the integrity of blood vessels and ease inflammatory stress in retinal tissue [8,10]. Specifically, butyrate has been indicated to inhibit Histone Deacetylase (HDAC) activity, a critical pathway influencing retinal cell differentiation and gene expression, thereby underscoring the multifunctional aspects of SCFAs in neuroprotection and retinal health [11].

Studies have shown that patients with DR often display reduced levels of SCFAs, suggesting a direct link between gut microbiome composition and retinal health outcomes. For instance, alterations in SCFA production correlate significantly with inflammatory biomarkers associated with retinal degeneration [2,5]. Furthermore, modulation of gut microbiota through dietary strategies, such as increased intake of plant-based fibers, has demonstrated beneficial effects on both microbiome composition and SCFA levels, providing a potential avenue for therapeutic intervention in DR management [4,11].

The interplay between microbiome-derived metabolites, particularly SCFAs and retinal health presents a novel perspective that may inform future therapeutic strategies aimed at managing and preventing DR through microbiota modulation. This study attempts to provide an update as well as review the current literature on Gut microbiome and its relationship with Diabetic retinopathy.

Methodology

English only articles from Pubmed and Semantic Scholar were searched using the search terminologies: Gut Microbiome and Diabetic retinopathy. Journal specific filters targeting Diabetes, Frontiers in Microbiology, Frontiers in Endocrinology, PLOS-1, International journal of molecular sciences and micro- organisms were applied in semantic scholar. Abstracts were screened for relevance and articles without abstracts as well as articles where the abstracts were not relevant to the area of focus were excluded. Free full text articles were included and cross-references were studied when found relevant. A PRISMA format of review was done which is shown in Fig. 1.

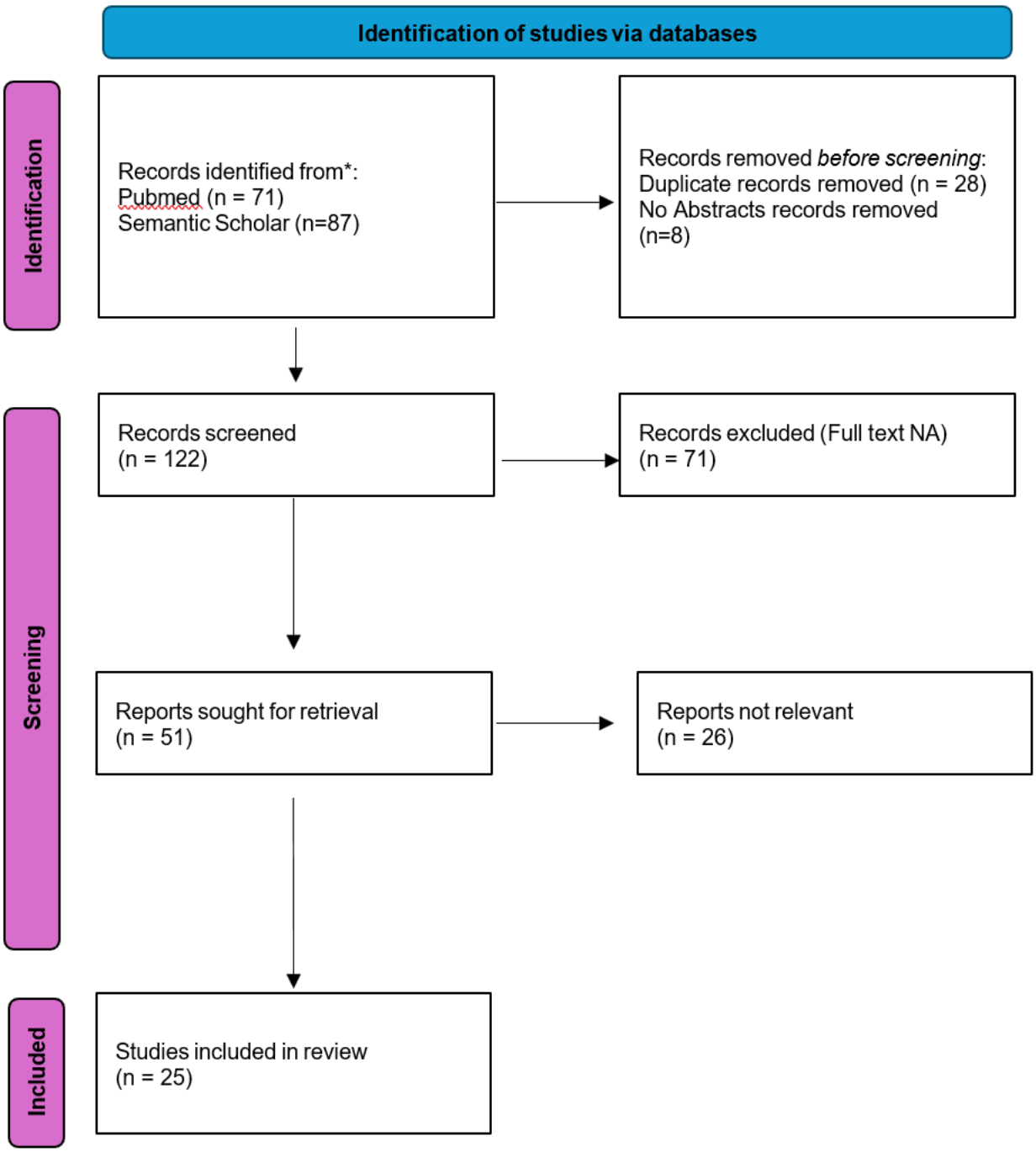

Figure 1: Identification of studies via databases.

Discussion

1. Gut dysbiosis in DR: altered diversity and taxonomic shifts

Gut dysbiosis has emerged as a crucial factor implicated in the development and progression of DR. Several studies have used human 16S rRNA sequencing data. They found that patients with DR have a notable decrease in microbial diversity. Additionally, there are changes in the types of microbes present when compared to diabetic individuals without retinopathy and healthy controls. Research indicates that the relative abundance of butyrate-producing genera, such as *Lactobacillus* and *Faecalibacterium*, is markedly diminished in DR patients, suggesting a potential link between gut health and retinal integrity [4,12,13]. The decrease in microbial diversity and certain specific genera is linked to higher local inflammation. It also leads to increased intestinal permeability. Both of these factors are known to worsen the development of DR [3,14].

Additionally, researchers have found a connection between microbial signatures and the severity of DR. Certain types of microbes are linked to more severe forms of the disease that can threaten vision. One study discovered unique patterns in the gut microbiome related to Proliferative Diabetic Retinopathy (PDR). It noted that specific microbial profiles could indicate how the condition is progressing [15,16]. The findings highlight an association between low diversity in the gut microbiota and worse clinical outcomes in DR patients, further depicting the potential use of microbiota as biomarkers for determining disease severity [17,18].

Changes in the gut microbiome can greatly affect systemic inflammation through microbial metabolites like SCFAs, which help protect vascular health. Dysbiosis is linked to lower SCFA levels, correlating with inflammation in DR. This suggests a potential therapeutic target. Adjusting the microbial composition with dietary changes or probiotics may help restore SCFA producing populations and reduce diabetic complications [8]. Moreover, correlational studies focusing on SCFA levels have proposed their role as immune regulators in the context of DR, further emphasizing the interconnectedness of gut health and ocular pathology [19].

Thus, the evolving understanding of gut dysbiosis in diabetic retinopathy signals a promising area for further exploration, where microbial diversity, taxonomic shifts and their inflammatory consequences offer insight into disease mechanisms.

2. Metabolite-mediated mechanisms: endotoxemia, SCFAs, bile acids

Metabolite-mediated mechanisms are important in the development of Diabetic Retinopathy (DR), especially with gut dysbiosis. Dysbiosis can cause increased intestinal permeability, often called "leaky gut." This allows high levels of Lipopolysaccharides (LPS) and other microbial byproducts into the bloodstream, leading to metabolic endotoxemia. This process triggers chronic low-grade inflammation, which is a key factor in the progression of DR [4,12]. Elevated LPS levels in the bloodstream have been linked to insulin resistance and systemic inflammation, contributing to metabolic derangements characteristic of diabetes and its complications, including DR [3,14]. The drop in SCFAs, especially butyrate, linked to dysbiosis really seems to impact mucosal barrier integrity and anti-inflammatory signaling. SCFAs are vital for gut health—they're not just energy sources for colonic epithelial cells but also help keep the immune system in check. When SCFA levels fall short, the intestinal barrier can weaken, making it more vulnerable to damage. This, in turn, may allow more inflammatory substances to seep through, which is definitely a concerning cycle [20,21]. Studies indicate that butyrate exerts anti-inflammatory effects by inhibiting pro-inflammatory cytokines and enhancing the production of anti-inflammatory mediators, which is particularly detrimental in the context of DR where inflammation is pivotal in disease progression [21,22].

Moreover, interactions between microbiota and bile acids are increasingly recognized as influential in modulating metabolic signaling associated with DR. Bile acids not only play a critical role in fat absorption but also act as signaling molecules that can impact glucose and lipid metabolism through their interaction with gut microbiota [23,24]. Dysbiosis can alter bile acid profiles, disrupting their metabolic signaling and leading to pathological changes that may exacerbate retinal injury and promote DR [14,19]. Impaired bile acid signaling has been associated with an increased risk of metabolic diseases and complications, highlighting the intricate relationship between gut microbiota, bile acid metabolism and retinal health [24,25].

In conclusion, metabolite-mediated mechanisms involving endotoxemia, SCFAs and bile acids represent critical pathways through which gut dysbiosis contributes to the pathogenesis of diabetic retinopathy. Targeting these pathways through dietary modifications or probiotic interventions may offer therapeutic avenues to mitigate inflammation, improve metabolic function and ultimately protect retinal health in patients with diabetes.

3. Inflammatory and immune pathways linking gut to retina

The connection between the gut microbiome and retinal health, particularly in DR, is mediated through various inflammatory and immune pathways. One significant piece of this puzzle is how microbial products and cytokines from gut inflammation can trigger systemic immune responses. For instance, Pathogen-Associated Molecular Patterns (PAMPs) such as LPS can activate Toll-Like Receptor 4 (TLR4) and the NOD-Like Receptor Family, Pyrin Domain-Containing 3 (NLRP3) inflammasome on immune cells. This priming of the immune response can extend to the retinal microvasculature, leading to increased inflammation in the retina, which is a prominent feature in the development and progression of DR [4,8].

Recent findings suggest that signals from gut microbiota can influence microglial activation in the retina. Microglia, the immune cells found in the central nervous system, are crucial for keeping retinal health in check. In animal models, studies have shown that altering gut microbiomes, such as through antibiotic administration, can lead to a reduction in retinal microglial activation and inflammation, even in diabetic contexts [15,24]. This suggests that the gut microbiome may influence neuroinflammatory responses in the retina, potentially serving as a modifiable risk factor for DR.

The systemic implications of inflammation triggered by gut dysbiosis extend beyond immune activation; they involve complex interactions that contribute to heightened oxidative stress and vascular dysfunction, exacerbating retinal pathologies like DR. Increased levels of circulating inflammatory cytokines can contribute to the breakdown of the Blood-Retinal Barrier (BRB), enhancing permeability and facilitating the progression of retinal complications [22,26]. As the gut-retina axis continues to be explored, understanding the biochemical pathways linking dysbiosis and retinal inflammation can potentially identify therapeutic strategies. Targeting gut health through dietary modifications, probiotics or other interventions may represent a novel approach for mitigating the ocular complications associated with diabetes [20,23].

The link between gut imbalance and retinal inflammation hints at a new way to look at diabetic retinopathy. If we can find ways to restore a healthier gut environment and ease the inflammation it fuels, it may open doors to treating or even preventing DR.

4. Vascular barrier and endothelial dysfunction: gut influence on BRB and angiogenesis

The integrity of the BRB is critical for preserving retinal health and function [1]. Recent evidence suggests that the gut microbiome significantly influences BRB integrity and angiogenic processes, particularly through microbiota-driven inflammation and vascular signaling.

Microbiota-driven inflammation, characterized by elevated levels of cytokines and oxidative stress, can promote the breakdown of the BRB, thus increasing vascular permeability and the risk of macular edema in DR patients. In this context, gut dysbiosis can lead to the overproduction of pro-inflammatory cytokines, such as TNF-α and IL-6, which activate pathways that disrupt tight junction proteins essential for maintaining BRB integrity. Studies indicate that the translocation of microbial products, especially LPS, into systemic circulation can exacerbate these inflammatory responses, leading to increased vascular permeability that contributes to retinal edema and vision impairment [4,15].

Additionally, gut dysbiosis might affect angiogenic signaling pathways, like the expression of Vascular Endothelial Growth Factor (VEGF). When dysbiosis leads to increased systemic inflammation and the buildup of specific lipid metabolites, it can boost VEGF signaling. This promotes neovascularization in the retina, which is worrying because high VEGF levels are linked to the development of PDR and can result in serious vision complications [26]. Understanding how gut-derived metabolites, through their inflammatory effects, influence angiogenesis provides insight into the gut-retina axis and its implications for managing DR.

Also, it has been observed that strategies aimed at improving gut microbiota like changing diets, taking probiotics or using prebiotics might help restore barrier function and lower inflammation. These approaches could also influence angiogenic signals, offering a new way to prevent or slow down the progression of Diabetic Retinopathy (DR) [24].

The way the gut microbiome interacts with inflammation and retinal blood vessels suggests that keeping our gut bacteria in balance might matter more for eye health than we've realized. Exploring these connections could help explain why diabetic retinopathy develops in the first place and point toward treatments that protect the retina by supporting gut health.

5. Therapeutic and predictive potential: modulation of microbiome as intervention / biomarker

The therapeutic and predictive potential of gut microbiota modulation in the context of DR is an emerging area of research that offers promising avenues for intervention and biomarker development. Various approaches, such as probiotics, prebiotics, antibiotics, dietary modifications and Fecal Microbiota Transplantation (FMT), are being explored for their capacity to shift gut microbiota toward a healthier composition. These interventions could potentially halt or slow the progression of DR by addressing the underlying dysbiosis and its inflammatory consequences [4,9].

Probiotics, which are live microorganisms that confer health benefits when administered in adequate amounts, can help restore a balanced gut microbiome. They have been shown to improve gut barrier function, reduce intestinal permeability and modulate systemic inflammation all of which are crucial in the context of DR. Similarly, prebiotics, which serve as food for beneficial bacteria, can enhance the production of SCFAs like butyrate, further supporting gut health and exerting anti-inflammatory effects [24,26]. Antibiotics have been utilized to explore the causal relationships between specific microbial populations and DR, although the long-term implications and ecological impacts of antibiotic therapy must be carefully considered.

FMT, whereby stool from a healthy donor is introduced to a recipient's gastrointestinal tract, has also garnered attention to replenish diverse and beneficial microbial communities. Early studies suggest that FMT may yield positive effects on metabolic and inflammatory parameters associated with diabetic complications, including DR [6,16].

In addition to therapeutic implications, gut microbial signatures and metabolite profiles hold significant promise as biomarkers for assessing DR risk or progression. Emerging data indicate that specific microbial taxa or metabolic byproducts may correlate with disease severity and progression. For example, studies have suggested associations between reduced abundance of butyrate-producing bacteria and increased susceptibility to DR, indicating that microbial composition could serve as an early indicator of disease risk [6,16]. However, while these findings are encouraging, the current body of literature on longitudinal data linking microbiome profiles to DR progression remains limited, necessitating further research to validate these potential biomarkers [15,22]. A schematic representation of the Gut microbiome and its role in DR as well as potential therapeutic targets is shown in Fig. 2.

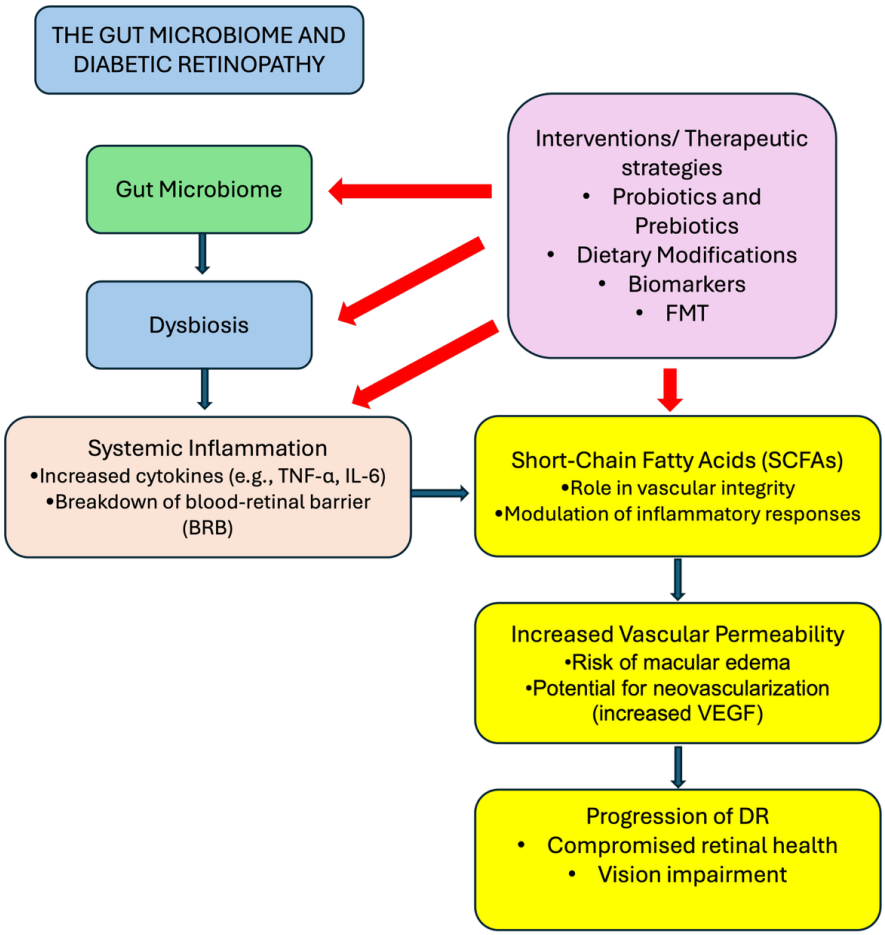

Figure 2: A schematic representation of the gut microbiome.

Adjusting the gut microbiome may offer a promising way to slow or even reduce the risk of diabetic retinopathy. Approaches such as probiotics, prebiotics or FMT appear to help restore microbial balance, though much remains to be proven. Future research could make prevention more precise, especially for those most vulnerable.

Conclusion

The review discusses the emerging relationship between gut microbiota and DR emphasizing the critical role of the gut-retina axis in ocular health. Dysbiosis, characterized by diminished microbial diversity and shifts in beneficial bacteria, contributes to systemic inflammation and compromises the blood-retinal barrier, exacerbating retinal damage. Metabolites, particularly SCFAs, play a vital role in maintaining vascular integrity and modulating inflammatory responses, indicating potential therapeutic targets.

Interventions aimed at restoring a balanced gut microbiome such as probiotics, prebiotics and dietary changes, offer promising strategies to slow DR progression. Furthermore, specific microbial profiles may serve as valuable biomarkers for assessing DR risk and progression, paving the way for personalized treatment approaches. The study has some limitations. Only recent English reports were used from the past 10 years. Additionally, since there is no sponsorship and this is a self-funded effort, it included only full free text articles but abstracts for articles were screened to look for any relevance with due diligence. There would be some landmark studies in other languages which will get overlooked as a result as well. However, the strengths of the study like attempting to search on Pubmed and Semantic scholar which are well known sources of hosting high quality articles, following a PRISMA strategy help in identifying key points to provide an update on the role of Microbiome in DR. Larger reviews where access to all articles is easily possible by larger institutions could perhaps add some more information. Overall, these findings highlight the gut microbiome as a modifiable risk factor in DR, opening new avenues for innovative therapeutic strategies that leverage the gut-retina connection.

Conflict of Interest

The author declares no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Author's Contributions

All authors have contributed equally to this work and have reviewed and approved the final manuscript for publication.

Consent For Publication

Not applicable.

Ethical Statement

This project was exempt from IRB review as it did not qualify as human subject research under federal regulations.

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