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Postbiotic Metabolites from Indigenous Fermented Medicinal Plants as Candidate Modulators of the Gut–Retina Axis in Early Diabetic Retinopathy: A Mechanistic Review and Research Roadmap

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ABSTRACT: Approximately a quarter of the world's diabetics suffer from DR, with 160 million patients anticipated by 2045, but there is no effective treatment beyond glycemic control for its earliest, non-proliferative form. In the last five years, another area of research has developed a view of a "gut-retina axis," where gut dysbiosis, gut barrier dysfunction, and circulating bacterial metabolites contribute to retinal inflammation and vascular biology in the same way that the gut-brain axis influences neurological outcomes. Simultaneously, the notion of postbiotics, defined as inactive microorganisms and/or components with proven health benefits, has developed into an established, ISAPP-managed class of molecules, different from probiotics, prebiotics, and isolated metabolites. This review unites these two areas of research with a third, previously underappreciated line of research: the biochemistry of local fermented herbal medicines. Examples of the former include the Ayurvedic tradition of Asava-Arishta remedies and various regionally fermented drinks, such as Raabadi and Kanji, which have been used clinically for many centuries but never explored from a retinal perspective. From existing literature on the link between gut dysbiosis and diabetes and DR, the pathophysiology of NPDR driven by the oxidative stress and AGEs-RAGE interaction, and the categories of

active metabolites formed through fermentation of medicinal plants, we appraise the literature and the mixed trial results concerning probiotics and synbiotics in glucose management, leading to the conclusion that a standardized postbiotic approach is more favorable compared to living organism methods. Based on all of the above, we develop an explicit five-step hypothesis about how postbiotic metabolites may help maintaining gut-retina axis homeostasis in early DR, and we propose a sequential in vitro, animal and human study to test the hypothesis. The article does not provide any new experimental data but provides an approach based on the literatures in different but mature fields that were not yet connected.

1. INTRODUCTION

Diabetic retinopathy, according to the latest estimations, is estimated to be occurring in approximately one out of every four individuals with diabetes around the globe, and sight-endangering forms of diabetic retinopathy in one out of every ten. According to one extensively cited meta-analysis, there will be an estimated increase in the population suffering from DR from about 103 million in 2020 to more than 160 million by 2045, along with the parallel increase in the prevalence of diabetes, whose International Diabetes Federation's estimates now exceed 500 million in adults [20][22]. This burden is not shared equally; according to the latest Global Burden of Disease estimates, South Asia and China have a disproportionate share, and the burden due to disability has almost tripled since 1990 in the age group of working individuals. These happen to be regions with extensive history of fermenting medicinal plants [12] [17] [18].

In terms of clinical staging, DR ranges from mild, moderate, and severe NPDR to PDR and DME. In terms of treatments that have been shown to work, anti-VEGF drugs, steroids, and PRP are indicated only for DME and advanced disease, by design, because they act on established neovascularization or oedema and not on the processes preceding it. Treatment of early NPDR involves, in reality, glycaemic and blood pressure control, and regular monitoring. There is no adjunct treatment which has been approved which targets the process of neuroinflammation and subclinical leakage of the retina before microvascular damage becomes clinically evident. That is the area this review aims to address even though the content below deals with mechanism of action and not trial results.

Concurrent with this timeframe, the concept of microbiota axes specific for particular organs has developed from a gut-brain fascination into an expanded paradigm including the gut-liver, gut-lung, and recently the gut-eye axis. Specifically, the literature on reviews of gut dysbiosis in diabetes-related retinopathy has exploded since around 2022 [21]. Alongside this has been the development of postbiotics which, as officially defined by the International Scientific Association of Probiotics and Prebiotics in 2021, are “an inanimate microorganism and/or its components which confer a demonstrated health benefit to the host [1] [2] [11].” Where this has yet to be explored in the existing scientific literature, as far as we are aware, is the overlap between these two areas and a third: namely, the possibility of postbiotics from endogenous fermented medicinal plants, a hybrid category involving both microbial fermentation and plant phytochemistry and one which has thousands of years of known history [3] [4] [10].

The purpose of this review is therefore a narrowly focused one, in aid of an arguably ambitious integration. First, we briefly review the body of evidence for gut dysbiosis in type 2 diabetes and more specifically DR, including where it is actually inconsistent, because those inconsistencies are essential to the validity of the claims being made. Then we will review the oxidative stress, VEGF, and AGE/RAGE pathways of early DR pathology, after which the categories and modes of bioactivity of postbiotics will be outlined, before the specific case of indigenous fermented medicinal plants as a potentially rich but largely investigated source of postbiotics is made [5] [7] [8]. Because there is already a significant body of clinical trial data on microbiota-directed diabetes therapy, which is in fact more varied than is widely reported, we include an assessment of that body of work here. Then we put all of this together into an explicitly stated five-step mechanistic pathway linking the effects of fermented plant postbiotics to re-establishing gut-retina axis function in early DR and conclude with a translation plan. There is no new experimental evidence provided at all in Sections 6-7, only hypotheses, and we have been equally clear about what is unknown as about what is possible.

2. GUT DYSBIOSIS IN DIABETES AND DIABETIC RETINOPATHY

2.1 What 'dysbiosis' means in type 2 diabetes — and where the evidence is shakier than it looks

The intestinal microbiota of a metabolically healthy adult is composed of two phyla, namely Firmicutes and Bacteroidetes, which constitute around 80-90% of the total population, followed by Actinobacteria and Proteobacteria, as well as minor populations of Verrucomicrobia (particularly Akkermansia muciniphila). It has been extensively observed that a significant body of the T2DM research literature is concentrated on the Firmicutes to Bacteroides (F/B) ratio as an index of dysbiosis; and it would be fair to say that this literature does not concur with itself: some studies have shown the presence of high F/B ratios among T2DM patients due to insulin resistance, while other studies have shown the opposite; specifically, Larsen et al.'s study and even a 2022 systematic review of prediabetes and T2DM showed that F/B ratio was a non-relevant biomarker. What remains relatively constant across the different studies, however, is the decrease in the number of butyrate-producing taxa (Firmicutes especially) and the increase in Gram-negative, LPS-producing bacteria such as some members of Bacteroidetes and Proteobacteria. Additionally, there is evidence of the depletion of two particular types of bacteria, Akkermansia muciniphila and Faecalibacterium prausnitzii, both of which relate to barrier integrity. What this translates into is that the dysbiosis seen in diabetes can be defined functionally rather than through a taxon-specific ratio, an important consideration when it comes to developing a postbiotic therapy, detailed in section 2.3.

The functional consequence that has been studied extensively from the point of view of mechanism is metabolic endotoxemia: a chronic, low-level increase in levels of circulating LPS following its passage through an intestinal barrier rendered dysfunctional. Studies have shown that in Gambian women suffering from obesity and obesity-induced diabetes, high fasting serum LPS levels, along with an impaired ability to maintain an impermeable gut barrier (lactulose/mannitol test) and the inability to mount a normal anti-LPS antibody response exist as direct evidence for causality. The binding of LPS to CD14/TLR4 receptors of innate immunity cells activates cytokine production and, via phosphorylation of insulin receptor substrate, results in insulin resistance.

2.2 From systemic dysbiosis to the retina: the gut-eye axis specifically in DR

The axis of retinal disease research has been slow relative to hepatology or neurology in adopting the axis framework, but the gut-eye research literature has been developing rapidly ever since 2022 due to parallel progress in uveitis, age-related macular degeneration, and glaucoma which established first that eye tissue is not immunologically and metabolically separated from the gut signal pathway.As far as DR goes, the latest systematic review and meta-analysis on the matter published in 2026 based on pooling of eighteen studies (observational, cohort, and Mendelian-randomisation design) represents the most comprehensive study available up until now and it needs to be quoted literally for the sake of its precision because it is easy to exaggerate: "alpha-diversity measures, but not beta-diversity measures, significantly differed between the groups (patients with DR, diabetes patients without retinopathy and controls)."In other words: DR is not necessarily characterized by low diversity of the gut microbiome, but the diversity of its composition and function – the very function (metabolite output) being the target of postbiotics' action.

From a mechanistic perspective, three converging pathways have been hypothesized to explain how gut dysbiosis causes retinal dysfunction in diabetes: first, the effect of the gut microbiome on glucose homeostasis, insulin resistance, and entero-insulin release, which ultimately contributes to a deleterious systemic metabolic milieu that the retina encounters; second, the induction of TLR4 signaling through LPS, both at the systemic level and, after LPS translocation, possibly within the retinal tissue; and third, intestinal barrier dysfunction, possibly because of ACE2 deficiency seen in diabetic models [16] [19]. Neither of the three pathways alone has been shown to be sufficient, and the research community tends to consider them complementary rather than competing hypotheses.

2.3 Direct evidence that gut-derived signals reach ocular tissue

The strongest support for the existence of a true (and not simply correlated) gut-retina axis is based on studies where particular metabolites are tracked into the eye tissue. When SCFAs are delivered intraperitoneally in mice, they are detectable in the eye tissue and can significantly attenuate intraocular inflammation caused by LPS, with the SCFA receptor in the eye (GPR43) localised not only in cornea and ciliary body but also in retinal ganglion cell layer of both mice and human donor eyes. Functionally, SCFA/GPR43 signalisation reduces the production of cytokines and

chemokines mediated by activation of NF-ϰB in retinal astrocytes and corneal epithelial cells stimulated with TLR ligands, although surprisingly, the same studies revealed that SCFAs increase the ability of retinal astrocytes to stimulate T cell activation. The most directly analogous translational precedent and the one which is nearest to the hypothesis put forth here is a study carried out in 2026 in which oral supplementation with the live probiotic Lactobacillus reuteri Y7 in a light injury retinal degeneration model resulted in changes to the microbiome composition – enrichment of SCFA producing species at lower dose and Akkermansia, Parasutterella and Bacteroides at higher dose – with the improvement of gut barrier function and mitigation of retinal degeneration at the same time, the effects at the higher dose being equal to or even greater than those of dietary lutein supplementation [6].

3. PATHOPHYSIOLOGY OF EARLY DIABETIC RETINOPATHY: WHY THE EARLY-STAGE MATTERS

3.1 The oxidative-stress/VEGF autocrine loop

The biochemical mechanisms by which chronic hyperglycaemia leads to oxidative stress in the retina include four pathways which appear to be largely non-redundant: polyol pathway flux, AGE production, and the interaction of AGEs with their receptor RAGE, activation of protein kinase C, and mitochondrial production of ROS, all resulting in diminished antioxidative capabilities. The transcriptional consequence downstream of these biochemical events involves activation of NF-ϰB and AP-1, causing transcription of TNF-α, IL-1β, IL-6, ICAM-1, and VCAM-1, leading to leukostasis, capillary occlusion, and vasopermeability. The mechanism that connects oxidative stress directly with the progressive breakdown of barrier function is an autocrine loop of VEGF induction by oxidative stress: VEGF is induced in Müller cells and retinal explants by oxidative stress through VEGFR2- and Nrf2-dependent pathways, and the VEGF produced leads to induction of further VEGF production. In addition to the above pathway, there is an independent pathway specific to diabetes which involves oxidative stress-induced upregulation of urokinase plasminogen activator receptor (uPAR) via VEGF and GSK-3β/β-catenin signaling, causing direct damage to tight junctions in retinal endothelial cells, and the mechanism has been experimentally validated in diabetic rodents induced with streptozotocin.

3.2 The AGE-RAGE axis and pericyte loss

The second, partially separate pathway operates via advanced glycation end-products (AGEs) and their receptor, RAGE, which is abundantly present on the surface of retinal pericytes, endothelial cells, and resident immune cells. AGE-RAGE interaction induces NF-ϰB, TGF-β, JAK-STAT, and PI3K-Akt signalling pathways, and the most significant consequence for the retina resulting from this pathway is pericyte apoptosis. Pericytes are the mural cells supporting integrity of retinal capillaries; pericyte death represents the earliest microscopic change associated with DR, occurring before acellular capillary formation, and later neovascularization. AGE-RAGE interaction also stimulates VEGF expression via the MAPK pathway and represents the second way to enter the autocrine loop mentioned above, and leads to the elevation of the tissue factor, ICAM-1, and VCAM-1 expression on the surface of retinal endothelium.

3.3 Why 'early' NPDR, specifically

Neurodegeneration of the retina and low-level gliosis and microgliosis now known to precede clinical microaneurysms and haemorrhages by a number of years – a discovery that has truly changed the way we understand this disease because DR used to be defined solely on the basis of the existence of its vascular pathologies for several decades. The above is important in respect of this review's arguments because it reveals a real, albeit limited, treatment window: a time when the underlying processes involved are predominantly inflammatory and oxidative rather than vascular, and a system treatment rather than an intraocular injection becomes mechanistically feasible. Whether a particular therapy can actually influence this development in any way at all is precisely what is to be tested according to the roadmap proposed in Section 7 and nothing in Sections 1-5 should be construed to mean that it can.

4. EXISTING CLINICAL EVIDENCE FOR MICROBIOTA-TARGETED THERAPY IN DIABETES: A CAUTIONARY BASELINE

Before presenting a new postbiotic hypothesis, it might be helpful to be honest about the performance of the most similar existing treatment modality – live probiotic and synbiotic treatment for glucose regulation in T2DM – since

the truth is that its performance has been rather varied in RCT studies and this variation should dampen hopes for any postbiotic approach in the future. Table 1 lists six different sources for the same topic.

Table 1. Representative clinical-trial and meta-analytic evidence for probiotic/synbiotic effects on glycaemic control in type 2 diabetes mellitus, illustrating the heterogeneity of the existing record

Study / synthesis	Design and size	Principal glycaemic finding
Multistrain probiotic RCT [44]	24-week RCT, n=130, T2DM	Significant reduction in HbA1c (p=0.004) and increase in HDL-c (p=0.023); non-significant trend toward lower FBG/PPBG
Probiotics/synbiotics meta-analysis [46]	Meta-analysis of RCTs, T1DM+T2DM	Significant pooled improvement in HbA1c (SMD -0.28), fasting plasma glucose (SMD -0.18) and insulin
Network meta-analysis of probiotic formulations [49]	62 RCTs pooled, T2DM	Best-performing multistrain formulations reduced FPG by up to 73.5 mg/dL and HbA1c by up to 1.59%; effect size strongly strain-dependent
Probiotic yogurt meta-analysis [47]	9 RCTs, T2DM/obesity	No significant effect on HbA1c, fasting glucose, or HOMA-IR versus conventional yogurt
16-week double-blind RCT [51]	n=213, T2DM	HbA1c and FBG improved in both probiotic and placebo arms; between-group difference not significant
Synbiotic vs probiotic-alone RCT [52]	12-week RCT, n=120, T2DM	Synbiotic (Bifidobacterium + galacto-oligosaccharide) reduced HbA1c and HOMA-IR; probiotic-alone arm showed no significant change

Two patterns emerge from the literature that are worth mentioning. First, despite small-to-moderate and statistically significant differences observed by pooled meta-analyses in HbA1c and fasting glucose, some high-quality individual RCTs, such as one involving 213 patients in 16 weeks of a double-blind study, revealed the absence of difference when a placebo group was taken into account, and a meta-analysis limited to probiotic yogurt vs. regular yogurt found that there were no statistically significant differences either. It is quite a common pattern in the field of nutraceuticals research: whereas pooled meta-analyses are influenced by heterogeneous studies, often of relatively low quality, and thus inclined to show statistical significance, large and well-blinded individual studies are more likely to have null results. Second, when effects are observed, they seem to be strain-specific and formulation-specific as opposed to a general 'probiotic effect' – a network meta-analysis of 62 clinical trials showed that the most effective multi-strain formulations could reduce HbA1c levels up to 1.59 percentage points, while others had a minimal effect; a head-to-head comparison showed that synbiotics containing Bifidobacterium animalis plus galacto-oligosaccharide outperformed the probiotics only.

The connection between this study and the current review can be made in two ways. Firstly, because it challenges the assumption that "gut microbiota modulation" can be considered a successful group of interventions on its own, without the need to prove its efficacy via rigorous placebo-controlled experiments – in essence, it questions whether a DR hypothesis based on postbiotics could make similar assumptions about its efficacy by virtue of existing in the context of the larger probiotics discussion. Secondly, it is one of the reasons – together with stability and

standardization – why this review approaches postbiotics and not live probiotics as a more viable tool: strain-dependent and formulation-dependent issues are potentially easier to solve with a characterized metabolite mixture.

5. POSTBIOTICS: DEFINITION, CLASSES, AND THE CASE FOR STANDARDISATION OVER LIVE ORGANISMS

5.1 The ISAPP consensus

The 2021 ISAPP consensus panel consisting of eleven experts from ten different nations representing the disciplines of gastroenterology, paediatrics, metabolomics, microbiology, and regulatory affairs chose a deliberately narrow definition: 'postbiotics are defined as a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host.' There are three characteristics of this definition that are likely to go unnoticed but are important for our discussion. First, it excludes purified individual metabolites (so a pure butyrate supplement would not be a postbiotic under this definition even though butyrate as a constituent of a characterized fermentation mixture would be); second, it specifies that there must be demonstrated evidence of health benefit in the target host population, not just evidence of activity in vitro; third, it does not insist that the parent microorganism be a recognized probiotic strain, and that is exactly what allows space for the intrinsic and unstandardized microbiota of traditionally prepared fermentations to qualify, as long as they are characterized.

5.2 Why postbiotics over live probiotics for this application

Postbiotic preparations have three clear advantages over live probiotics, specifically regarding the treatment of diabetics who suffer from chronic disease and are prone to being elderly and immuno-compromised: increased stability due to thermal resistance, since inactivated preparations do not suffer from temperature instability problems faced by many commercial probiotics; reduced risk of any potential bacterial translocation or infection; and, as described in section 4 below, easier batch-to-batch standardisation due to the fact that the defined metabolites can be identified by analytic means such as LC-MS and GC-MS, whereas live organisms cannot. Bibliometric analysis of the postbiotics literature up until mid-2024 reveals a clear preponderance of reviews over original papers by a factor of about 3:1, which is in itself a statement about the state of the field: the development of concepts and regulations has been happening much faster than the experimental development, which is why this paper aims to provide some guidance in the latter regard in section 7 below.

5.3 Bioactive classes relevant to the gut-retina axis

Postbiotics are also chemically diverse and the predominance of one type over others is greatly influenced by the fermenting microorganism and substrates used. The relationship between these chemical classes of postbiotics (i.e., short-chain fatty acids, exopolysaccharides, bacteriocins and organic acids, microbial transformation of phenolic compounds, and bioactive peptides) and mechanisms for the gut-retina axis, described in Section 2, is presented in Table 2.

Table 2. Postbiotic metabolite classes and their proposed relevance to the gut–retina axis.

Postbiotic class	Representative constituents	Proposed relevance to the gut–retina axis
Short-chain fatty acids (SCFAs)	Acetate, propionate, butyrate	Bind ocular GPR43; HDAC inhibition; suppress NF-κB-driven cytokine release; support Treg differentiation and tight-junction integrity [21,22,23]
Exopolysaccharides (EPS)	LAB- and yeast-derived glucans, levans, heteropolysaccharides	Immunomodulatory and antioxidant scaffolds; contribute to mucosal barrier reinforcement [5,10]
Bacteriocins and organic acids	Lactic, acetic acids; class II bacteriocins	Selective suppression of LPS-producing pathobionts; indirect restoration of barrier-protective taxa [12,11]

Microbially biotransformed phenolics	Deglycosylated flavonoids, urolithin-like microbial metabolites, phenolic acids	Antioxidant/Nrf2-modulatory activity with the potential to interrupt oxidative-stress-driven VEGF signalling [6,7,25]
Bioactive peptides	LAB-released cryptic peptides from plant/herbal proteins	Antioxidant and putative anti-glycation activity relevant to AGE-RAGE-driven retinal injury [7,31]

6. INDIGENOUS FERMENTED MEDICINAL PLANTS AS AN UNDEREXPLORED POSTBIOTIC RESERVOIR

6.1 Traditional fermentation systems

A number of traditional medicine systems have arrived at the idea of controlled fermentation of medicinal plant material — which, in modern language, is the preparation of a complex postbiotic matrix, independent and empirical and centuries ahead of the terminology. For example, the Ayurvedic tradition known as Sandhana Kalpana is over five thousand years old and includes both Asavas (fermented herbal infusion without boiling) and Arishtas (fermented herbal decoction from a boiled extract). The process of Arishta making has a well-defined set of ratios, vessel types and the time of fermentation (from fifteen to forty-five days) specified by the Sharangdhara Samhita. This is not some folk practice outside any quality control system; as it has been stated in a review, it is 'a highly codified pharmaceutical system'. It is the kind of specification that would be required when undertaking the characterization of a modern postbiotic. Direct analysis of three types of Arishtas — Ashokarishta, Dasamoolarishta, and Aswagandharishta — showed thirty-five bacterial isolates having bile and acid resistance, hydrophobicity and autoaggregation (the latter two being relevant for the epithelial adherence), antimicrobial activity against pathogenic test strains, and the ability to produce exopolysaccharides, proteases, amylases, lipases, and cellulases.

Even beyond the specific examples of Ayurvedic fermentations, there are many analogous traditional ferments in South Asia and elsewhere in the world. Raabadi, a mixed millet-barley ferment traditionally used in Haryana and Rajasthan, isolated a strain of Lactobacillus plantarum (RYPR1) with a highly unusual level of cell surface hydrophobicity (79.13%) and significant cholesterol reduction activity (59%) in vitro [15]. Kanji, a fermented black carrot or beetroot brine, has a history of use in folk medicine for digestive disorders and metabolic illnesses, consistent with its being an acidic ferment dominated by lactic acid bacteria, common to vegetable fermentations [13]. This is not a South Asian-specific trend; Lactobacillus-dominated fermentations of native plant materials such as grains, root vegetables, and others are documented from sub-Saharan Africa and show similar biopreservative and probiotics-related functions.

6.2 What fermentation actually does to the phytochemistry

One might be tempted to see 'fermentation' as a uniform procedure, but the postbiotics literature shows that this is not necessarily so – different classes of organisms such as lactic acid bacteria, yeasts, and filamentous fungi have platform-specific enzymatic cascades, and depending on the dominant organism within the fermentation, even the same substrate will produce metabolite fingerprints that differ greatly. The overall trend, however, tends to be very similar: polyphenols and flavonoids are deglycosylated and depolymerized into bioavailable smaller analogues (in some cases, these resemble urolithins, the metabolites of ellagitannins created by gut bacteria), polysaccharides undergo partial hydrolysis, while proteins in the plant or added during the fermentation are cleaved into peptide fragments exhibiting both antioxidant and anti-glycation activity in some substrates. Two examples, not connected to ocular tissue, serve to prove this point: fermented papaya preparations exhibited anti-inflammatory and immunomodulatory properties both in vivo and in vitro, and Djon Djon mushroom ferment was shown to possess ROS scavenging ability and reduced malondialdehyde content as well as enhanced catalase, collagen-I, and hyaluronic acid levels in human keratinocytes and fibroblasts under UVB and hydrogen peroxide stress, and RNA sequencing confirmed an anti-inflammatory transcriptional response rather than just an antioxidant one. These are settings of skin and immune cells rather than retina, and here we are explicitly extending our findings as opposed to reporting on what is known: but they represent actual precedent in biology, of the use of fermented postbiotic fractions from plant or fungal sources

in order to exert a measurable effect in terms of anti-oxidant and anti-inflammatory activity in host tissues suffering oxidative stress. This is the precedent that Section 6 extends below, explicitly as a hypothesis to retinal tissue under diabetes conditions.

The above preparations and their properties are listed in Table 3.

Table 3. Selected indigenous fermented medicinal plant/food preparations with documented or plausible postbiotic-relevant properties.

Preparation	Origin / substrate	Documented or plausible postbiotic-relevant features
Asava-Arishta (Sandhana Kalpana)	Polyherbal decoctions/infusions self-fermented over 15-45 days (e.g., Ashokarishta, Dasamoolarishta, Aswagandharishta)	Thirty-five bile- and acid-tolerant bacterial isolates with antimicrobial activity, exopolysaccharide and hydrolytic-enzyme production [12,13,14]
Raabadi	Fermented barley/pearl-millet flour with buttermilk (Haryana, Rajasthan, India)	Lactobacillus plantarum RYPR1 with high cell-surface hydrophobicity and hypocholesterolemic activity, suggestive of systemic metabolic modulation [15]
Kanji / Kanjika	Fermented black carrot or beetroot brine	Long-standing traditional use for digestive and metabolic complaints; acidic LAB fermentation typical of vegetable ferments [13]
Indigenous African plant ferments	Cereal- and tuber-based fermentations across sub-Saharan Africa	Lactobacillus-dominated fermentations with documented biopreservative and probiotic-relevant activity [9]

7. A PROPOSED MECHANISTIC MODEL: LINKING FERMENTED-PLANT POSTBIOTICS TO GUT–RETINA AXIS RESTORATION IN EARLY DR

To our knowledge, there is no published work that has evaluated the effects of a postbiotic preparation of an indigenous fermented medicinal plant in any animal model of diabetic retinopathy. The following therefore constitutes a synthesis of two areas of literature: the biology of gut-retina axis in DR (sections 2-3) and postbiotics/fermented plants (sections 5-6). This synthesis represents a testable hypothesis and not a finding since each individual step of the synthesis has some level of indirect evidence behind it but their combination as a whole does not yet have any; we have enumerated the five steps in Table 4.

Table 4. Proposed mechanistic model linking postbiotic metabolites from fermented medicinal plants to gut-retina axis restoration in early diabetic retinopathy. Every linkage is a hypothesis synthesised from indirect, adjacent-context evidence; none has been tested directly in this combination

Step	Proposed mechanistic link	Supporting (indirect) evidence
1	Postbiotic bacteriocins/organic acids suppress LPS-producing pathobionts and favour barrier-protective taxa (e.g., Faecalibacterium, Akkermansia)	DR-associated dysbiosis studies; Akkermansia enrichment following probiotic supplementation in a retinal-protection model [16,17,18,24]
2	SCFA-rich fractions reinforce intestinal tight junctions and mucin output, limiting LPS translocation	Gut-retina axis reviews describing barrier disruption and metabolic endotoxemia as

		upstream drivers of systemic and ocular inflammation [16,21,42]
3	Circulating SCFAs and phenolic metabolites act at ocular GPR43 and related receptors to dampen NF-κB signalling	SCFA detection in ocular tissue; suppression of endotoxin-induced uveitis and corneal TLR responses via GPR43 [22,23]
4	Antioxidant/Nrf2-active metabolites interrupt the oxidative-stress-VEGF autocrine loop and AGE-RAGE-driven pericyte injury implicated in early BRB breakdown	VEGF autocrine and AGE-RAGE mechanistic studies in DR [25,28,31,32]
5	SCFA-driven Treg induction rebalances Th17/Treg activity relevant to ocular inflammatory disease	Mechanistic reviews of SCFA immunomodulation in ocular disease [21]

Two aspects of the model merit being stated explicitly, rather than left as an implication. First, the model is deliberately not based around a single dominant mechanism. Barrier reinforcement (step 2), direct ocular receptor signaling (step 3), blocking of the oxidative stress/AGE-RAGE-VEGF cascade (step 4), and Treg-induced immune balance restoration (step 5) are postulated as multiple parallel mechanisms, rather than a linear chain of causality – just like the literature on the DR pathophysiology considers it to be. [30] Second, the model is deliberately limited in its scope to early NPDR, rather than DR as a whole – for the reason given in Section 3.3: this is the point in time where the dominant mechanism is still significantly inflammatory/oxidative in nature, rather than structural vascular.

8. TRANSLATIONAL ROADMAP: FROM HYPOTHESIS TO EVIDENCE

However, testing of the hypothesis in Section 7 requires a phased programme; none of the below has been performed, and it is presented as merely a suggested approach, intentionally detailed enough to be implemented by a research team that has access to appropriate models.

8.1 Phase 1 — Standardisation and in vitro screening

And first, in our opinion, the most underestimated procedure of the whole is a standardisation of production of candidate preparations under reproducible, GMP-compatible fermentation conditions (controlled inoculum, temperature, time, vessel material), because variation between the batches is the number one drawback mentioned regarding conventional fermentation process in context of their application for pharmaceutical-grade preparations [14]. Next, standardised batches would require metabolite profiling by LC-MS/GC-MS to define the content of SCFA, phenolic compounds, peptides and exopolysaccharides, followed by bioactivity testing in retinal pigment epithelium (e.g., ARPE-19) and Müller glia cell lines under high glucose and oxidative stress conditions with production of ROS, VEGF and pro-inflammatory cytokines (IL-6, TNF-α), as well as tight junction markers being tested.

8.2 Phase 2 — In vivo proof-of-concept

A diabetic rodent model induced by streptozotocin – the same model where the VEGF/uPAR/BRB disruption pathway mentioned in Section 3.1 was first described will permit oral delivery of standardised postbiotics, with outcomes in both the gut and retinal compartments: metagenomics and SCFA in faeces; LPS and zonulin in blood serum, in keeping with the tradition established by the Gambian metabolic endotoxemia studies, histopathology and electroretinogram of the retina; Evans blue dye test for BRB permeability; and quantification of retinal VEGF and cytokines. An experiment that also incorporates an arm comparing postbiotics with live probiotics will also provide us with a means of testing a hypothesis whether the postbiotic formula preserves the efficacy of its living counterpart, an important question that cannot simply be taken for granted.

8.3 Phase 3 — Early-phase human pilot

In the event that Phases 1-2 do provide evidence for the above hypotheses, a placebo controlled pilot study in subjects with mild to moderate non-proliferative diabetic retinopathy (NPDR) could assess the effects of a standardized postbiotics preparation as an add-on to conventional treatment of hyperglycemia. With the inconsistent results obtained from glycaemic endpoints, as mentioned above in section 4, we think that it would not be ideal to power the first human trial with HbA1c; rather, an appropriate set of primary endpoints would include feasibility, mechanistic/biomarker studies of gut microbiota and metabolome changes, systemic inflammation parameters, and levels of LPS/zonulin; retinal endpoints like OCT retinal thickness, number of microaneurysms, and best corrected visual acuity could be considered exploratory secondary endpoints, because at this stage, the hypothesis is quite preliminary.

9. CHALLENGES AND LIMITATIONS

There are several limitations which directly apply to the data collected and the hypothesis based on such data, and, as we see it, the present type of review is much more helpful, rather than unhelpful, for mentioning them. The traditional methods of fermentation have real variations from batch to batch, and this issue has not been solved yet due to the standardisation of pharmaceutical production – this is not an issue solved yet and waiting only for regulatory approval. The scientific literature on the relationship between diabetes and microbiome also shows its heterogeneity: there is no consensus about F/B ratio in T2DM patients, and the most comprehensive analysis of diabetes-related meta-analysis showed inconsistent alpha-diversity results despite consistent functional changes. The track record in clinical trials for the closest existing analogy – live probiotic/synbiotic therapy for glucose regulation – is, as described in Section 4 at some length, much more complex than implied by the review literature of the area; individually-conducted RCTs may yield negative findings while meta-analyses find small but statistically significant benefit; there is no theoretical reason to believe that a postbiotic approach to DR will be any different in this regard, and the roadmap in Section 8 is constructed under this assumption. Diet, geographic location, and host genetics likely influence the baseline microbiome and postbiotic response equally, making population transfer difficult from any future Phase 3 findings. Finally, most importantly, all the mechanistic connections in Table 4 have been substantiated at this point only indirectly, through experiments carried out in related but separate settings — ocular SCFA pharmacology, one live probiotic retina degeneration model, observational DR dysbiosis associations. There has been no experiment where the fermented medicinal plant-based postbiotic treatment was used in conjunction with a model of DR or with patients with DR, and the roadmap in Section 8 is meant to be a suggested first step toward that research direction.

10. CONCLUSION

The three literatures – gut-retina axis biology in diabetic retinopathy, postbiotics biochemistry and regulation, and the indigenous pharmacology of fermented medicinal plants – individually developed well enough to warrant a review on their own, come together here in support of a common yet implicit hypothesis: that standardized postbiotic formulations of indigenous fermented medicinal plants might contribute towards the restoration of gut-retina axis balance in early, non-proliferative diabetic retinopathy, by way of correction of dysbiosis, strengthening of the intestinal barrier, ocular anti-inflammatory and antioxidant signaling and immune rebalancing via Tregs. The hypothesis currently stands completely untested, and we have aimed throughout to maintain honesty in the language regarding this fact, instead of allowing mechanistic plausibility to slip into implications of evidence. The realization of any translation value that the idea may have would involve a structured program of in vitro, animal and human studies as described in Section 8, starting with the more mundane task of standardization and chemical characterization of the candidate formulations that until now have only existed in an analytical void. Considering the considerable overlap between the areas with the highest prevalence of diabetic retinopathy and those with continuous practices of fermentation of plants for medicinal purposes, we believe that this represents a scientific path to explore rather than just speculation but still only a path, and not yet a discovery.

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