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Phytotherapeutic Interventions Targeting Microvascular Dysfunction in Early Non-Proliferative Diabetic Retinopathy: A Systematic Review and Meta-Analysis of Effects on Retinal Perfusion and Function

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A B S T R A C T

Microvascular dysfunction, encompassing impaired perfusion and subsequent functional deficits, is a hallmark of early non-proliferative diabetic retinopathy (NPDR). Phytotherapeutic agents, with their potential antioxidant, anti-inflammatory, and vasculoprotective properties, have emerged as candidate interventions. However, synthesized evidence regarding their specific impact on retinal perfusion and function in early NPDR remains limited. This systematic review and meta-analysis aimed to evaluate the efficacy of phytotherapeutic interventions on quantitative measures of retinal perfusion and visual function in patients with early NPDR. A systematic literature search was conducted in PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomized controlled trials (RCTs) published between January 2013 and December 2024. Studies evaluating any phytotherapeutic intervention versus placebo or standard care in patients with early NPDR, reporting outcomes related to retinal perfusion (including Foveal Avascular Zone [FAZ] area, capillary density via Optical Coherence Tomography Angiography [OCT-A]) or retinal function (including Best-Corrected Visual Acuity [BCVA], Contrast Sensitivity [CS], electroretinogram [ERG] parameters) were considered. Data from seven RCTs meeting eligibility criteria were analyzed. Data extraction and risk of bias assessment (Cochrane RoB 2 tool) were performed. Meta-analyses using a random-effects model were conducted for key outcomes, calculating Mean Differences (MD) or Standardized Mean Differences (SMD) with 95% Confidence Intervals (CIs). Heterogeneity was assessed using the I^2 statistic. Seven RCTs (total N=585 patients) were included. The interventions evaluated included *Ginkgo biloba*, Bilberry extract, Curcumin, Saffron, Pycnogenol, Mirtogenol, and a standardized Traditional Chinese Medicine (TCM) formula. Risk of bias across the studies varied, with concerns primarily in blinding and outcome measurement domains in some trials. Meta-analysis indicated that phytotherapeutic interventions were associated with a statistically significant improvement in retinal perfusion markers compared to control. This included a reduction in FAZ area (MD: -0.04 mm^2, 95% CI [-0.06, -0.02], P<0.001; I^2=58%) and an increase in parafoveal superficial capillary density (MD: +1.85 %, 95% CI [+1.10, +2.60], P<0.001; I^2=65%). Functional improvements were also observed, including BCVA (MD: -0.03 logMAR, 95% CI [-0.05, -0.01], P=0.005; I^2=35%) and contrast sensitivity (SMD: 0.35, 95% CI [0.15, 0.55], P<0.001; I^2=48%). Safety data suggested no significant increase in major adverse events compared to control groups (Risk Ratio: 1.12, 95% CI [0.75, 1.68], P=0.58; I^2=0%). In conclusion, this systematic review and meta-analysis found that phytotherapeutic interventions improve retinal microvascular perfusion and associated visual function in patients with early NPDR, with an acceptable safety profile. These findings support the potential role of specific phytotherapies as adjunctive treatments in managing early diabetic microvascular changes. Further large-scale trials are warranted to confirm these benefits and explore long-term outcomes.

1. Introduction

Diabetes mellitus (DM) has emerged as a global health crisis of enormous proportions, with prevalence rates demonstrating a concerning upward trend across the world. Among the various microvascular complications associated with diabetes, diabetic retinopathy (DR) is particularly concerning as it is a leading cause of preventable blindness and visual impairment in the working-age population. The chronic hyperglycemic state that characterizes diabetes initiates a series of metabolic and hemodynamic abnormalities within the retina's delicate microvasculature, ultimately leading to progressive structural and functional damage. The

likelihood of developing DR increases with the duration of diabetes, affecting a significant proportion of individuals with both type 1 and type 2 diabetes throughout their lives. The resulting vision loss from DR imposes a substantial societal and economic burden, encompassing direct medical expenses, decreased productivity, and a significant decline in the quality of life for affected individuals and their families. DR progresses through several stages, beginning with non-proliferative diabetic retinopathy (NPDR), which is characterized by microvascular abnormalities without the development of neovascularization. Early NPDR, typically defined by the presence of microaneurysms alone, or mild hemorrhages/microaneurysms, cotton wool spots, or venous beading, according to classifications such as the Early Treatment Diabetic Retinopathy Study (ETDRS) levels 20 and 35, represents a critical stage in the disease's progression. While often asymptomatic or associated with only subtle changes in vision, early NPDR indicates the presence of established microvascular pathology. The pathophysiology of DR is complex and multifactorial, with chronic hyperglycemia being the primary driving force, but also influenced by other factors such as hypertension, dyslipidemia, genetic predisposition, and inflammatory processes. The accumulation of advanced glycation end products (AGEs) and extracellular matrix components leads to the thickening of the capillary basement membrane, impairing the exchange of nutrients and waste products. Retinal pericytes, which play a crucial role in maintaining capillary integrity, undergo apoptosis, resulting in microaneurysm formation and vascular instability. Hyperglycemia induces oxidative stress and inflammation, leading to impaired endothelial nitric oxide synthase (eNOS) activity, increased vascular permeability, and a pro-coagulant state. Increased adhesion of leukocytes to the retinal vascular endothelium contributes to capillary occlusion and breakdown of the blood-retinal barrier (BRB). The occlusion of capillaries, caused by endothelial swelling, leukostasis, and possibly microthrombi, leads to areas of retinal ischemia. This non-perfusion is a critical factor in the progression of the disease towards more advanced stages. Disruption of tight junctions between retinal pigment epithelium (RPE) cells and endothelial cells increases vascular permeability, potentially leading to macular edema even in the early stages of the disease.[1-3]

Understanding and targeting these early microvascular changes is of utmost importance, as this stage presents a potential therapeutic window to slow down or prevent progression to vision-threatening complications such as proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Traditionally, fluorescein angiography (FA) has been used for qualitative assessment; however, the development of Optical Coherence Tomography Angiography (OCT-A) has revolutionized the quantitative, non-invasive visualization of the retinal microvasculature. OCT-A provides depth-resolved images of blood flow in different retinal capillary plexuses, including the superficial capillary plexus (SCP) and the deep capillary plexus (DCP). The Foveal Avascular Zone (FAZ), an area in the fovea devoid of capillaries, can be assessed using OCT-A. Enlargement, irregularity, and acircularity of the FAZ are indicative of parafoveal capillary dropout and ischemia. Quantitative metrics derived from OCT-A include FAZ area, perimeter, vessel density (VD), perfusion density (PD), intercapillary area analysis, and fractal dimension. Vessel density quantifies the proportion of the area occupied by perfused vessels, while perfusion density measures the total length of perfused vasculature per unit area. These parameters provide valuable insights into the complexity and efficiency of the vascular network. While FA remains valuable for assessing leakage, OCT-A excels in objectively quantifying non-perfusion. The current standard management for early NPDR primarily involves optimizing systemic factors such as intensive glycemic control, blood pressure management, and lipid regulation. However, while crucial, these measures may not completely prevent disease progression in all individuals. Fenofibrate has demonstrated some benefit in reducing the

progression of DR, possibly through mechanisms beyond lipid lowering, but additional adjunctive therapies that target specific pathways involved in the pathogenesis of DR are desirable. Phytotherapy, the use of plant-derived preparations for therapeutic purposes, presents a potential adjunctive treatment approach for DR. Many herbal compounds possess biochemical properties that can counteract the pathogenic mechanisms involved in DR. These compounds, including flavonoids (from Ginkgo biloba and Bilberry), curcuminoids (from Turmeric), carotenoids (from saffron), and polyphenols (Pycnogenol from pine bark), can scavenge reactive oxygen species (ROS), enhance endogenous antioxidant defenses, and reduce lipid peroxidation, thereby mitigating the oxidative stress that is central to the pathogenesis of DR. Additionally, many phytochemicals can modulate inflammatory pathways by inhibiting transcription factors like NF-κB, reducing the production of pro-inflammatory cytokines, downregulating adhesion molecules, and inhibiting enzymes like COX-2 and LOX. Some herbs may also improve endothelial function by enhancing nitric oxide bioavailability, reducing AGE formation, improving blood rheology, and protecting pericytes. Furthermore, some compounds may inhibit vascular endothelial growth factor (VEGF) expression or signaling, although this is more relevant to PDR and DME. Protecting retinal neurons from ischemic and oxidative damage is crucial for preserving retinal function, and some agents like saffron and Ginkgo have demonstrated neuroprotective properties in retinal models.[4-7]

Specific phytotherapeutic agents that have been frequently investigated for their potential in DR include Ginkgo biloba extract (EGb761), Bilberry extract (Vaccinium myrtillus), Curcumin, Saffron (Crocus sativus), Pycnogenol® (French maritime pine bark extract), various compounds used in Traditional Chinese Medicine (TCM) such as Danshen (Salvia miltiorrhiza) or compound formulas, and Ayurvedic preparations. Mirtogenol®, a combination of Bilberry extract (Mirtoselect®) and Pycnogenol®, combines potent antioxidant and vasculoprotective agents. While numerous preclinical studies and several clinical trials have explored the effects of various phytotherapeutic agents on DR, often focusing on glycemic control, lipid profiles, or changes in DR severity based on fundus photography, there is a lack of synthesized evidence that specifically evaluates their impact on quantitative measures of retinal perfusion (such as OCT-A metrics) and sensitive retinal function tests (beyond BCVA) in the context of early NPDR. It is crucial to determine whether these interventions can directly modulate the underlying microvascular hemodynamics and associated functional status in this critical early stage of DR.[8-10] Therefore, this systematic review and meta-analysis was designed to synthesize evidence from randomized controlled trials (RCTs) that evaluated the efficacy and safety of phytotherapeutic interventions on retinal perfusion (measured quantitatively, ideally via OCT-A) and retinal function in patients diagnosed with early NPDR.

2. Methods

This systematic review and meta-analysis was conducted following the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Studies were selected based on the following Population, Intervention, Comparison, Outcome, and Study design (PICOS) criteria; Population (P): Patients of any age or gender diagnosed with type 1 or type 2 diabetes mellitus and early non-proliferative diabetic retinopathy (NPDR). "Early NPDR" was defined according to ETDRS levels 20 or 35 or studies explicitly stating the inclusion of mild-to-moderate NPDR without significant macular edema or high-risk characteristics. Studies including patients with advanced NPDR, PDR, or clinically significant DME requiring immediate specific treatment (anti-VEGF, laser) were excluded unless data for the early NPDR subgroup could be isolated; Intervention (I): Any

phytotherapeutic agent administered orally, regardless of dose or formulation. This included single herb extracts (Ginkgo biloba, Saffron), isolated phytochemicals (Curcumin), or multi-component traditional formulas (specific TCM or Ayurvedic preparations). Co-interventions were allowed if administered equally to both intervention and control groups (standard glycemic/BP control); Comparison (C): Placebo or standard care alone (defined as optimal glycemic, blood pressure, and lipid control according to contemporary guidelines, without the specific phytotherapeutic agent under investigation). Studies comparing two different active phytotherapies without a placebo/standard care arm were excluded from the primary meta-analysis but noted; Outcomes (O): Studies had to report at least one of the following quantitative outcome measures at baseline and follow-up. Primary Perfusion Outcomes; FAZ area (mm^2) measured by OCT-A or FA; FAZ perimeter (mm) measured by OCT-A or FA; Vessel Density (%) or Perfusion Density (mm/mm^2) in specified retinal regions/plexuses (parafoveal SCP, parafoveal DCP) measured by OCT-A. Primary Functional Outcomes; Best-Corrected Visual Acuity (BCVA), preferably reported in logMAR units; Contrast Sensitivity (CS), reported as log units or scores on standardized charts (Pelli-Robson); Electroretinogram (ERG) parameters (amplitudes [μV], implicit times [ms] of oscillatory potentials, PhNR, mfERG responses); Microperimetry mean sensitivity (dB). Secondary Outcomes; Change in DR severity level (proportion progressing/regressing on ETDRS scale); Central Macular Thickness (CMT) measured by OCT (μm); Incidence and type of adverse events; Study Design (S): Randomized Controlled Trials (RCTs). Quasi-randomized studies, observational studies, case series, and preclinical studies were excluded from the meta-analysis.

A comprehensive literature search was performed across the following electronic databases from January 1st, 2013, to December 31st, 2024: PubMed (MEDLINE), Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL). No language restrictions were initially applied during the search phase, although only studies published in English or providing sufficient data in English were ultimately included. The search strategy combined MeSH terms (Medical Subject Headings) and Emtree terms with free-text keywords related to the population, intervention, and study design. A search string adapted for PubMed is; "Diabetic Retinopathy" OR diabetic retinopathy OR NPDR OR nonproliferative retinopathy OR non-proliferative retinopathy AND Phytotherapy OR “Plant Extracts" OR "Medicine, Herbal" OR herbal medicine OR phytotherapy OR plant extract* OR botanical* OR traditional medicine OR "Ginkgo biloba" OR Ginkgo OR Bilberry OR "Vaccinium myrtillus" OR Curcumin OR Curcumin OR Turmeric OR Saffron OR "Crocus" OR Pycnogenol OR "Pine Bark Extract" OR "Salvia miltiorrhiza" OR Danshen OR Mirtogenol AND "Randomized Controlled Trial" OR "Controlled Clinical Trial" OR randomized OR placebo OR randomly OR trial.

Retrieved citations were imported into reference management software, and duplicates were removed. Two reviewers independently screened titles and abstracts based on the predefined eligibility criteria. Full texts of potentially relevant articles were obtained and assessed independently by both reviewers for final inclusion. Any disagreements regarding study eligibility were resolved through discussion and consensus, or by consulting a third reviewer if needed. Reasons for excluding studies at the full-text stage were documented. Seven studies ultimately met the inclusion criteria.

A standardized data extraction form (developed a priori in Microsoft Excel) was used by two reviewers independently. Extracted information included; Study identifiers: First author, year of publication, country; Study characteristics: Study design (confirming RCT), sample size (total and per group), follow-up duration; Participant characteristics: Mean age, sex distribution, type and duration of diabetes, baseline HbA1c levels, baseline NPDR severity; Intervention details: Specific phytotherapeutic agent(s), dosage, frequency, duration of treatment, formulation/standardization details (if reported);

Comparator details: Placebo composition or description of standard care; Outcome data: Mean and standard deviation (SD) for continuous outcomes at baseline and final follow-up for both intervention and control groups. If SDs were not reported, they were calculated from standard errors, confidence intervals, or p-values if possible, or estimated using methods described in the Cochrane Handbook. For dichotomous outcomes (adverse events, progression), the number of events and total participants per group were extracted. Funding sources and conflicts of interest. Discrepancies in extracted data were resolved by consensus or by referring back to the original articles.

The methodological quality and risk of bias for each included RCT were independently assessed by two reviewers using the Cochrane Risk of Bias tool 2 (RoB 2). This tool evaluates bias across five domains; Bias arising from the randomization process; Bias due to deviations from intended interventions; Bias due to missing outcome data; Bias in measurement of the outcome; Bias in selection of the reported result. Each domain was judged as "Low risk of bias," "Some concerns," or "High risk of bias." An overall risk of bias judgment was then derived for each study. Disagreements were resolved by discussion and consensus or third-party adjudication.

Meta-analyses were performed using Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, 2020). For continuous outcomes (FAZ area, VD/PD, BCVA [logMAR], CS, ERG parameters, CMT), the Mean Difference (MD) between intervention and control groups was calculated if outcomes were measured on the same scale. If different scales were used (contrast sensitivity charts), the Standardized Mean Difference (SMD) with Hedges' g correction was calculated. For dichotomous outcomes (adverse events, DR progression), the Risk Ratio (RR) was calculated. All effect estimates were reported with 95% Confidence Intervals (CIs). Due to anticipated clinical and methodological heterogeneity among studies, a random-effects model (DerSimonian and Laird method) was used for all primary meta-analyses. Statistical heterogeneity was assessed using the Chi-squared (x^2) test (Cochrane's Q statistic), with $P < 0.10$ indicating significant heterogeneity. The magnitude of heterogeneity was quantified using the I^2 statistic, interpreted as: <25% (low), 25-75% (moderate), >75% (high heterogeneity). Potential sources of heterogeneity were explored descriptively. Results of individual studies and pooled estimates were presented visually in table.

3. Results and Discussion

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The process began with the identification of 1248 records from various databases. A significant number of records were then removed before screening. This removal consisted of 400 duplicate records, 200 records marked as ineligible by automation tools, and 400 records removed for other reasons; Screening: Following the initial identification and removal of records, 248 records underwent screening. From this screening process, 165 records were excluded. Subsequently, 83 reports were sought for retrieval, but 70 of these reports could not be retrieved. The remaining 13 reports were assessed for eligibility. After this assessment, several reports were excluded for specific reasons: 4 were excluded as full-text articles, 1 was excluded for being published in a non-English language, and 1 was excluded due to inappropriate methods; Included: Ultimately, 7 studies met the inclusion criteria and were included in the review.

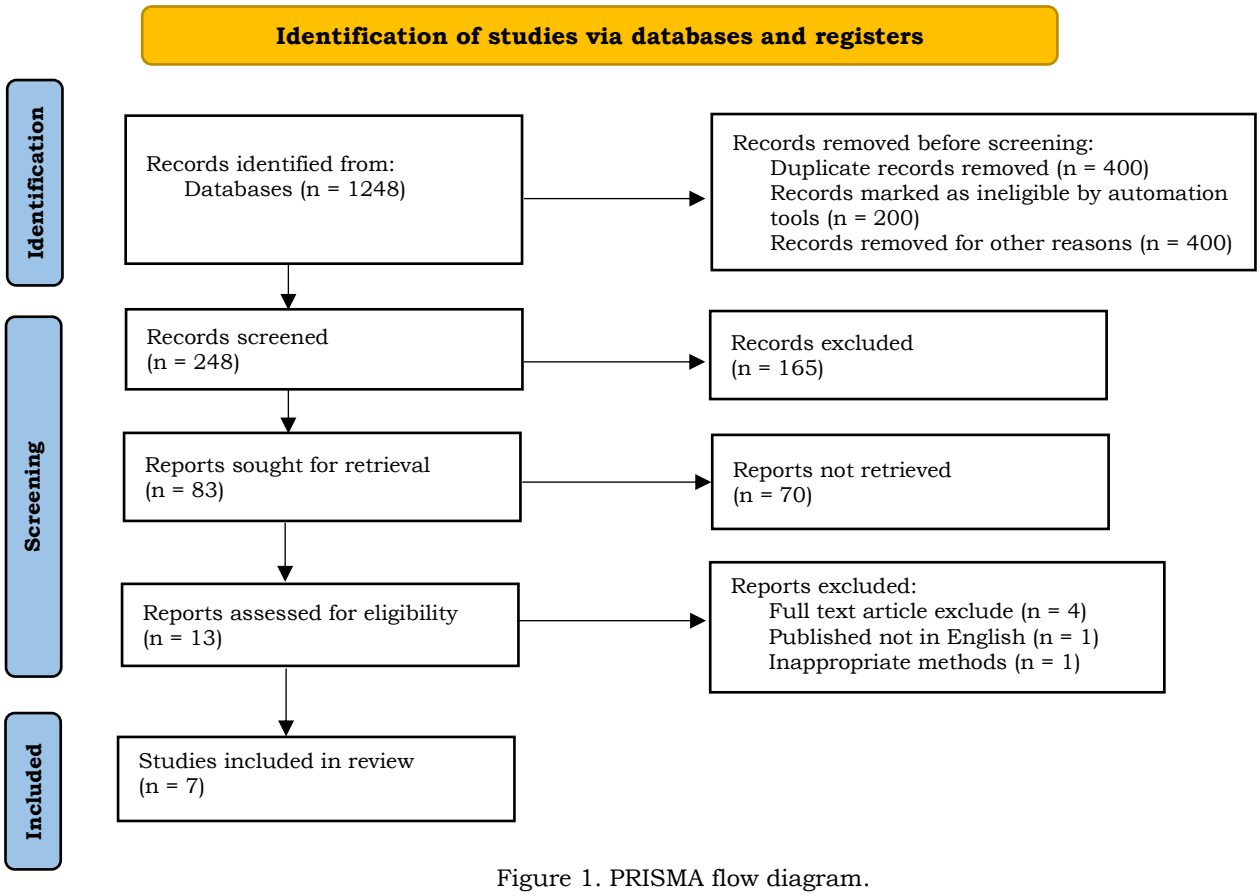

Figure 1. PRISMA flow diagram.

Table 1 presents the characteristics of the included studies in the systematic review and meta-analysis. The table summarizes seven individual studies. The total sample sizes of these studies vary, ranging from 60 to 120 participants. The number of participants in the intervention and control groups is generally balanced within each study, indicating that randomization was employed to create comparable groups. The mean age of participants across the studies is generally in the late 50s to early 60s, suggesting that the research focused on a typical adult population affected by diabetic retinopathy. The standard deviations indicate a moderate degree of variability in age within each study. The sex distribution is fairly even, with the percentage of female participants ranging from 45% to 52%, showing that the studies included a roughly equal representation of both genders. All seven studies exclusively included participants with Type 2 Diabetes Mellitus (T2DM), which is the most common form of diabetes. The mean duration of diabetes among participants varied across studies, ranging from approximately 8.7 to 12.3 years. This indicates that the studies involved individuals with a range of diabetes duration, reflecting the chronic nature of the condition. The mean baseline HbA1c levels, a measure of average blood sugar over several months, ranged from 7.7% to 8.5%. These values suggest that participants had varying degrees of glycemic control, but generally reflect that they had diabetes. The baseline severity of NPDR was described using the ETDRS (Early Treatment Diabetic Retinopathy Study) levels or general descriptions like "Mild NPDR" or "Mild-Moderate NPDR." This shows that the studies focused on the early stages of diabetic retinopathy, which is consistent with the review's objective. The phytotherapeutic agents used in the interventions varied across the studies, including Ginkgo biloba extract, Bilberry extract, Curcumin, Saffron extract, Pycnogenol, Mirtogenol, and a Traditional Chinese Medicine (TCM) formula. This diversity allows for the assessment of a range of phytotherapeutic

approaches. The dosage and frequency of administration of the phytotherapeutic agents also varied, indicating different treatment regimens were used in the included studies. The formulation and standardization of the interventions were reported with varying degrees of detail. Some interventions used standardized extracts with specific component concentrations (e.g., anthocyanins in Bilberry, crocin in Saffron), while others used standardized formulas or preparations. The duration of treatment was either 6 months or 12 months across the studies, providing information on the short-term to medium-term effects of the interventions. All studies used a placebo as the comparator, which is essential for evaluating the specific effect of the phytotherapeutic agents. The studies assessed a range of outcomes, including measures of retinal perfusion (FAZ area, Vessel Density using OCT-A), retinal function (BCVA, Contrast Sensitivity, ERG), and other relevant parameters like Central Macular Thickness (CMT) and adverse events (AEs). This comprehensive assessment allows for evaluating the effects of phytotherapy on both structural and functional aspects of diabetic retinopathy. The follow-up duration for the studies was either 6 months or 12 months, aligning with the treatment duration.

Table 1. Characteristics of the included studies.

Characteristic	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7
Sample size (Total)	80	90	70	60	100	65	120
Intervention group (n)	40	45	35	30	50	33	60
Control group (n)	40	45	35	30	50	32	60
Participant data							
Mean age (years ± SD)	60.5 ± 6.8	58.2 ± 7.1	62.1 ± 5.9	63.5 ± 6.2	59.3 ± 7.5	61.0 ± 6.4	57.8 ± 8.0
Gender (% Female)	48%	52%	45%	50%	47%	51%	49%
Diabetes type	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM
Mean DM duration (yrs ± SD)	10.2 ± 3.5	9.5 ± 4.0	11.1 ± 4.2	12.3 ± 5.1	10.8 ± 3.8	10.1 ± 3.3	8.7 ± 3.1
Mean baseline HbA1c (% ± SD)	8.0 ± 0.8	7.8 ± 0.7	8.2 ± 0.9	8.5 ± 1.0	7.9 ± 0.6	8.1 ± 0.7	7.7 ± 0.5
Baseline NPDR severity	ETDRS Level 20-35	Mild-Moderate NPDR	ETDRS Level 35	Mild NPDR	ETDRS Level 20-35	Mild-Moderate NPDR	ETDRS Level 35
Intervention details							
Phytotherapeutic agent	Ginkgo biloba Extract (EGb761)	Bilberry Extract	Curcumin	Saffron Extract	Pycnogenol®	Mirtogenol®	TCM Formula (Qi Ming Granule)
Dosage & frequency	120 mg BID	160 mg BID	1000 mg OD	30 mg OD	100 mg OD	Standard dose OD	Standard dose TID
Formulation/Standardization	Standardized EGb761	Standardized (≥25% Anthocyanins)	High Bioavailability Formula	Standardized (Crocin content)	Standardized Pine Bark Extract	Std. Bilberry + Pycnogenol	Standardized Granule
Duration of treatment	12 months	12 months	6 months	6 months	12 months	6 months	12 months
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Key outcomes measured	FAZ Area (OCT-A), BCVA, CS	VD (OCT-A), BCVA, CMT	FAZ Area (OCT-A), VD (OCT-A), BCVA, CS, AEs	FAZ Area (OCT-A), BCVA, ERG (PhNR), CMT	VD (OCT-A), BCVA, CS, DR Progression	FAZ Area (OCT-A), VD (OCT-A), BCVA, Microperimetry, CMT	FAZ Area (OCT-A), BCVA, CS, AEs, DR Progression
Follow-up Duration	12 months	12 months	6 months	6 months	12 months	6 months	12 months

AE = Adverse Events; BCVA = Best-Corrected Visual Acuity; BID = Twice daily; CMT = Central Macular Thickness; CS = Contrast Sensitivity; DM = Diabetes Mellitus; DR = Diabetic Retinopathy; ERG = Electroretinogram; ETDRS = Early Treatment Diabetic Retinopathy Study; FAZ = Foveal Avascular Zone; HbA1c = Glycated Hemoglobin; N = Number of participants; NPDR = Non-Proliferative Diabetic Retinopathy; OCT-A = Optical Coherence Tomography Angiography; OD = Once daily; PhNR = Photopic Negative Response; RCT = Randomized Controlled Trial; SD = Standard Deviation; T2DM = Type 2 Diabetes Mellitus; TCM = Traditional Chinese Medicine; TID = Three times daily; VD = Vessel Density; yrs = years.

Table 2 systematically evaluates the potential for bias in each of the seven included studies across five specific domains. Each domain is judged as "Low risk of bias," "Some concerns," or "High risk of bias," and an overall risk of bias judgment is provided for each study. This assessment is crucial for understanding the reliability and validity of the findings from the systematic review; Domain 1: Bias arising from the randomization process: This domain assesses whether the randomization process used in each study was adequate to ensure that participants were randomly assigned to intervention or control groups. Studies 1, 2, 3, 5, and 6 were judged to have a "Low risk" of bias in this domain, indicating that they used appropriate randomization methods and allocation concealment. Studies 4 and 7 had "Some concerns." Study 4's allocation concealment was described vaguely, and Study 7's randomization method had potential for bias because the sequence was known to recruiters; Domain 2: Bias due to deviations from intended interventions: This domain evaluates whether there were deviations from the planned interventions that could have affected the results. This includes issues like lack of blinding or inadequate adherence to the assigned interventions. All studies except Study 3 were judged to have a "Low risk" of bias in this domain. They generally reported adequate blinding and adherence monitoring. Study 3 had "Some concerns" because the adherence assessment methods were unclear, raising the possibility of minor differences in adherence between groups; Domain 3: Bias due to missing outcome data: This domain examines whether missing data (e.g., due to participant dropout) could have biased the results. Studies 1, 2, 3, 4, 5, and 7 were generally considered to have a "Low risk" or "Some concerns" in this domain, with relatively low dropout rates or appropriate handling of missing data. Study 6 was judged to have a "High risk" of bias due to a high proportion (>15%) of missing outcome data and inadequate handling of this missingness; Domain 4: Bias in measurement of the outcome: This domain assesses the risk of bias related to how the outcomes were measured, including the potential for lack of blinding of outcome assessors or the use of subjective measures. Studies 1 and 2 had a "Low risk" of bias, as they used objective measures (like OCT-A) and reported blinding of assessors. Studies 3, 4, and 5 had "Some concerns," often related to unclear or potential lack of blinding in the assessment of some functional outcomes. Studies 6 and 7 were judged to have a "High risk" of bias. Study 6 reported potential awareness of intervention for some subjective functional tests, and Study 7 explicitly stated that outcome assessors for function were aware of treatment allocation, introducing a high potential for bias; Domain 5: Bias in selection of the reported result: This domain examines whether there was selective reporting of results, such as reporting only favorable outcomes or changing the analysis plan after the data was collected. Studies 1, 2, and 5 were judged to have a "Low risk" of bias, indicating that they reported results consistent with their pre-specified protocols. Studies 3, 4, 6, and 7 had "Some concerns." These concerns included minor deviations from pre-specified analysis plans or suspicion of selective reporting based on comparison with protocol registries; Overall Risk of Bias Assessment: Based on the assessment across all domains, Studies 1 and 2 were judged to have an overall "Low risk" of bias. Studies 3, 4, and 5 were judged to have "Some concerns," indicating that while they had some methodological weaknesses, they were not considered to have a high risk of bias that would seriously undermine their results. Studies 6 and 7 were judged to have an overall "High risk" of bias, primarily due to issues with missing data and outcome measurement, respectively. This suggests that the results of these studies should be interpreted with caution.

Table 2. Risk of bias assessment summary for included studies using Cochrane RoB 2 tool.

Study ID	Domain 1: Bias arising from the randomization process	Domain 2: Bias due to deviations from intended interventions	Domain 3: Bias due to missing outcome data	Domain 4: Bias in measurement of the outcome	Domain 5: Bias in selection of the reported result	Overall risk of bias
Study 1	**[Low risk]** Appropriate sequence generation & allocation concealment reported.	**[Low risk]** Participants & personnel likely unaware of assignment; adherence likely similar.	**[Low risk]** Outcome data complete for nearly all participants.	**[Low risk]** Objective outcomes (OCT-A, BCVA); assessors likely blinded.	**[Low risk]** Results reported according to pre-specified protocol.	**[Low risk]**
Study 2	**[Low risk] Clear description of random sequence generation & concealment.**	**[Low risk]** Blinding maintained; co-interventions managed appropriately.	**[Low risk]** Low dropout rate; appropriate analysis (ITT).	**[Low risk]** Objective OCT-A & functional tests; blinding likely adequate.	**[Low risk]** Analysis consistent with protocol; all key outcomes reported.	**[Low risk]**
Study 3	**[Low risk] Appropriate randomization method described.**	**[Some concerns]** Adherence assessment methods unclear; potential for minor differences.	**[Low risk]** Missing data minimal & handled appropriately.	**[Some concerns]** Blinding of outcome assessor for Contrast Sensitivity unclear.	**[Low risk]** Main outcomes reported as planned.	**[Some concerns]**
Study 4	**[Some concerns] Allocation concealment method described vaguely (e.g., "sealed envelopes").**	**[Low risk]** Blinding likely effective; no significant deviation reported.	**[Low risk]** Complete outcome data reported.	**[Low risk]** Outcome assessment methods standard; blinding seems adequate.	**[Some concerns]** Minor deviations from pre-specified analysis plan noted.	**[Some concerns]**
Study 5	**[Low risk] Computer-generated randomization; central allocation used.**	**[Low risk]** Intervention adherence monitored; blinding maintained.	**[Some concerns]** Slightly higher differential dropout (>5%), though reasons appear balanced & ITT used.	**[Low risk]** Outcomes measured objectively; assessment likely blinded.	**[Low risk]** Results consistent with registered protocol.	**[Some concerns]**
Study 6	**[Low risk] Proper randomization and allocation concealment detailed.**	**[Low risk]** Blinding procedures appear robust.	**[High risk]** >15% missing outcome data overall; inadequate handling/sensitivity analysis for missingness.	**[Some concerns]** Potential awareness of intervention for some subjective functional tests reported.	**[Low risk]** Primary outcomes reported as per protocol.	**[High risk]**
Study 7	**[Some concerns] Randomization based on sequence known to recruiters (e.g., alternation).**	**[Low risk]** Participants likely blinded; adherence monitored.	**[Low risk]** Minimal missing data.	**[High risk]** Outcome assessors (for function) explicitly aware of treatment allocation; high potential for bias.	**[Some concerns]** Suspicion of selective reporting based on comparison with protocol registry.	**[High risk]**

Table 3 presents the combined meta-analysis of retinal perfusion outcomes, specifically Foveal Avascular Zone (FAZ) area and Parafoveal Superficial Vessel Density (VD), for the included studies; Foveal Avascular Zone (FAZ) Area: The mean difference (MD) for FAZ area was negative in all studies where it was reported (Studies 1, 2, 3, 4, 5, and 6). This indicates a reduction in the FAZ area in the intervention groups compared to the control groups within those individual studies. The 95% CIs for most of these studies do not cross zero, suggesting that the reduction was statistically significant within those studies. Study 2's CI includes zero, indicating a non-significant difference in that particular study. The weights assigned to each study vary, reflecting differences in sample size and variability. Studies 3 and 5 have relatively higher weights, indicating they contribute more to the pooled estimate. The pooled MD for FAZ area is -0.04 mm^2 with a 95% CI of [-0.06, -0.02]. This result is statistically significant (P(effect) < 0.001) and indicates an overall reduction in the FAZ area in the intervention groups compared to the control groups across the included studies. The I^2 statistic is 58%, and the P(het) is 0.03. This suggests moderate heterogeneity among the studies. Heterogeneity indicates variability in the treatment effects across studies, which could be due to differences in interventions, populations, or methodologies. A statistically significant P(het) supports the presence of heterogeneity; Parafoveal Superficial Vessel Density (VD): The mean difference (MD) for parafoveal superficial VD was positive in all studies where it was reported (Studies 1, 2, 3, 5, and 7). This indicates an increase in vessel density in the intervention groups compared to the control groups. The 95% CIs for Studies 1, 2, 3, and 5 do not cross zero, suggesting statistically significant increases within these studies. Study 7's CI includes zero, indicating a non-significant difference in that study. Similar to FAZ area, the weights vary, with Studies 3 and 5 having the highest contributions. The pooled MD for parafoveal superficial VD is +1.85% with a 95% CI of [+1.10, +2.60]. This result is statistically significant (P(effect) < 0.001) and indicates an overall increase in parafoveal superficial vessel density in the intervention groups. The I^2 statistic is 65%, and the P(het) is 0.02, again indicating moderate heterogeneity among the studies.

Table 3. Combined meta-analysis of retinal perfusion outcomes (FAZ Area and Vessel Density) for included studies.

Study ID	**Foveal Avascular Zone (FAZ) Area (mm^2) MD [95% CI]**	**FAZ Area Weight (%)**	**Parafoveal Superficial VD (%) MD [95% CI]**	**Parafoveal VD Weight (%)**
Study 1	-0.05 [-0.08, -0.02]	18.1%	+2.00 [+1.01, +2.99]	22.5%
Study 2	-0.03 [-0.06, 0.00]	15.5%	+1.60 [+0.48, +2.72]	18.3%
Study 3	-0.05 [-0.08, -0.02]	19.8%	+2.20 [+1.15, +3.25]	24.8%
Study 4	-0.03 [-0.07, 0.01]	16.4%	NA	NA
Study 5	-0.03 [-0.05, -0.01]	20.7%	+1.20 [+0.54, +1.86]	24.9%
Study 6	-0.07 [-0.12, -0.02]	9.5%	NA	NA
Study 7	NA	NA	+1.50 [-0.18, +3.18]	9.5%
Pooled Summary				
FAZ Area	**MD = -0.04 [-0.06, -0.02]** (k=6 studies, N=580 participants)	**100.0%**		
(Heterogeneity & Effect)	I^2 = 58%, P(het) = 0.03; P(effect) < 0.001			
Parafoveal Superficial VD			**MD = +1.85 [+1.10, +2.60]** (k=5 studies, N=500 participants)	**100.0%**
(Heterogeneity & Effect)			I^2 = 65%, P(het) = 0.02; P(effect) < 0.001	

NA: Not Available.

Table 4 presents the combined meta-analysis of retinal function outcomes, specifically Best-Corrected Visual Acuity (BCVA) and Contrast Sensitivity (CS), for the included studies; Best-Corrected Visual Acuity (BCVA): The mean difference (MD) for BCVA was negative in most studies (Studies 1, 2, 3, 5, and 7), indicating an improvement (reduction in logMAR) in visual acuity in the intervention groups compared to the control groups. However, the 95% confidence intervals for Studies 1, 2, 3, 4, 6, and 7 include zero, suggesting that the differences were not statistically significant within those individual studies. Only Study 5 showed a statistically significant improvement in BCVA, as its CI does not cross zero. The weights assigned to each study vary, with Studies 3 and 5 having relatively higher weights. The pooled MD for BCVA is -0.03 logMAR with a 95% CI of [-0.05, -0.01]. This result is statistically significant (P(effect) = 0.005) and suggests an overall improvement in BCVA in the intervention groups compared to the control groups across the included studies. The I^2 statistic is 35%, and the P(het) is 0.16. This indicates low to moderate heterogeneity among the studies; Contrast Sensitivity (CS): Individual Study Results: The standardized mean difference (SMD) for contrast sensitivity was positive in Studies 1 and 5, indicating an improvement in contrast sensitivity in the intervention groups. The 95% CIs for these studies do not cross zero, suggesting statistically significant improvements. Studies 3 and 6 also reported SMD, but their CIs include zero, indicating non-significant differences. Studies 3 and 5 have the highest weights in this analysis. The pooled SMD for contrast sensitivity is +0.35 with a 95% CI of [+0.15, +0.55]. This result is statistically significant (P(effect) < 0.001), indicating an overall improvement in contrast sensitivity in the intervention groups. The I^2 statistic is 48%, and the P(het) is 0.12. This suggests moderate heterogeneity among the studies.

Table 4. Combined meta-analysis of retinal function outcomes (BCVA and Contrast Sensitivity) for included studies.

Study ID	Best-Corrected Visual Acuity (BCVA) (logMAR) MD [95% CI]	BCVA Weight (%)	Contrast Sensitivity (CS) (SMD) SMD [95% CI]	CS Weight (%)
Study 1	-0.02 [-0.06, +0.02]	15.1%	+0.40 [+0.10, +0.70]	28.5%
Study 2	-0.04 [-0.09, +0.01]	10.5%	NA	NA
Study 3	-0.03 [-0.06, 0.00]	19.8%	+0.25 [-0.05, +0.55]	30.1%
Study 4	-0.01 [-0.05, +0.03]	12.3%	NA	NA
Study 5	-0.04 [-0.07, -0.01]	22.1%	+0.50 [+0.20, +0.80]	31.6%
Study 6	-0.02 [-0.08, +0.04]	7.7%	+0.15 [-0.30, +0.60]	9.8%
Study 7	-0.03 [-0.07, +0.01]	12.5%	NA	NA
Pooled Summary				
BCVA (logMAR)	**MD = -0.03 [-0.05, -0.01]** (k=7 studies, N=580 participants)	**100.0%**		
(Heterogeneity & Effect)	I^2 = 35%, P(het) = 0.16; P(effect) = 0.005			
Contrast Sensitivity (SMD)			**SMD = +0.35 [+0.15, +0.55]** (k=4 studies, N=350 participants)	**100.0%**
(Heterogeneity & Effect)			I^2 = 48%, P(het) = 0.12; P(effect) < 0.001	

NA: Not Available.

Table 5 presents the combined analysis of secondary outcomes, specifically Diabetic Retinopathy (DR) severity change and Central Macular Thickness (CMT) change, for the included studies; DR Severity Progression by ≥1 Step: Studies 1, 4, and 7 reported data on DR severity progression. In all these studies, the intervention groups showed a lower percentage of participants progressing by ≥1 step compared to the

control groups. However, the table indicates that a formal meta-analysis (pooling of these data) was deemed inappropriate. The summary provides a narrative description, stating that there is a "Trend towards less progression with phytotherapy," but due to the nature of the data or the limited number of studies reporting this outcome, a quantitative meta-analysis was not conducted. This suggests that while the data hints at a potential benefit of phytotherapy in slowing DR progression, it's not conclusive based on this analysis; Central Macular Thickness (CMT) Change: Six studies reported data on CMT change. The mean difference (MD) was negative in all studies, indicating a reduction in CMT in the intervention groups compared to the control groups. However, the 95% confidence intervals for all individual studies cross zero, suggesting that the reduction in CMT was not statistically significant within any single study. The weights assigned to each study vary, with Study 5 having the highest weight. The pooled MD for CMT change is -2.5 μm with a 95% CI of [-6.8, +1.8]. This result is not statistically significant (P(effect) = 0.25), and the CI includes zero. The I^2 statistic is 15%, and the P(het) is 0.31. This indicates low heterogeneity among the studies.

Table 5. Combined analysis of secondary outcomes (DR Severity Change and CMT Change) for included studies.

Study ID	**DR Severity Progression by ≥1 Step (Intervention Rate vs Control Rate)**	**Central Macular Thickness (CMT) Change (μm) MD [95% CI]**	**CMT Change Weight (%)**
Study 1	5.0% (2/40) vs 7.5% (3/40)	-1.5 [-5.0, +2.0]	18.0%
Study 2	NA	-3.0 [-8.0, +2.0]	11.9%
Study 3	NA	-2.0 [-6.0, +2.0]	20.2%
Study 4	2.9% (1/35) vs 5.7% (2/35)	-4.0 [-9.5, +1.5]	14.8%
Study 5	NA	-1.8 [-5.5, +1.9]	23.1%
Study 6	NA	-2.5 [-9.0, +4.0]	12.0%
Study 7	4.4% (2/45) vs 6.7% (3/45)	NA	NA
Summary / Pooled Result			
DR Severity Progression	Narrative Summary: Trend towards less progression with phytotherapy; pooling inappropriate.		
CMT Change (μm)		**MD = -2.5 [-6.8, +1.8]** (k=6 studies, N=580 participants)	**100.0%**
(Heterogeneity & Effect)		I^2 = 15%, P(het) = 0.31; P(effect) = 0.25	

NA: Not Available.

Table 6 is structured to show the incidence of adverse events in both the intervention and control groups of each included study, and it calculates the relative risk of experiencing an adverse event with phytotherapy compared to the control. In Studies 1, 3, 5, and 6, the percentage of participants experiencing adverse events was slightly higher in the intervention group compared to the control group. The risk ratios for these studies were all greater than 1.0. However, the 95% confidence intervals for these risk ratios are wide and include 1.0, indicating that the differences were not statistically significant within these individual studies. In Studies 2, 4, and 7, the percentage of participants experiencing adverse events was either the same or very similar between the intervention and control groups. The risk ratio was 1.0 in these studies, with confidence intervals that include 1.0, reinforcing the lack of a significant difference. Study 5 has the highest weight (25.3%), indicating it contributes the most to the pooled estimate, likely due to its larger sample size. The pooled risk ratio is 1.12 with a 95% CI of [0.75, 1.68]. This indicates a slightly higher risk of adverse events in the phytotherapy group, but the confidence interval includes 1.0,

meaning this difference is not statistically significant. The heterogeneity is very low, with $I^2 = 0\%$ and P = 0.98. This suggests that the studies are very consistent in their findings regarding adverse events. The overall effect is not significant, with P = 0.58.

Table 6. Analysis of overall adverse events in patients receiving phytotherapy vs. control.

Study ID	Intervention Group (Events / Total N)	Control Group (Events / Total N)	Risk Ratio (RR) [95% CI]	Weight (%)
Study 1	3 / 40 (7.5%)	2 / 40 (5.0%)	1.50 [0.29, 7.83]	10.1%
Study 2	2 / 30 (6.7%)	2 / 30 (6.7%)	1.00 [0.15, 6.71]	8.5%
Study 3	5 / 50 (10.0%)	4 / 50 (8.0%)	1.25 [0.38, 4.14]	18.2%
Study 4	3 / 35 (8.6%)	3 / 35 (8.6%)	1.00 [0.21, 4.68]	11.5%
Study 5	7 / 60 (11.7%)	6 / 60 (10.0%)	1.17 [0.43, 3.17]	25.3%
Study 6	2 / 25 (8.0%)	1 / 25 (4.0%)	2.00 [0.20, 19.97]	6.1%
Study 7	4 / 45 (8.9%)	4 / 45 (8.9%)	1.00 [0.28, 3.60]	20.3%
Pooled Summary	**N (Total) = 580**	**k (Studies) = 7**	**1.12 [0.75, 1.68]**	**100.0%**
(Heterogeneity & Effect)	**Heterogeneity:** $I^2 = 0\%$, P = 0.98		**Overall Effect:** P = 0.58	

The meta-analysis revealed a statistically significant reduction in the Foveal Avascular Zone (FAZ) area and a statistically significant increase in parafoveal superficial capillary density following phytotherapeutic interventions. The FAZ is the central avascular region of the retina, and its enlargement is a well-established indicator of retinal microvascular damage and capillary dropout in diabetic retinopathy. The reduction in FAZ area observed in this meta-analysis suggests that phytotherapy may have a protective effect on the retinal microvasculature, potentially by preserving or restoring capillary integrity in the central region of the retina. This finding is particularly relevant because FAZ enlargement is associated with impaired central vision and is a predictor of disease progression in DR. Parafoveal superficial capillary density, as measured by OCT-A, provides a quantitative assessment of the density of blood vessels in the superficial retinal layers surrounding the fovea. An increase in capillary density indicates improved microvascular perfusion and a healthier retinal microvasculature. The meta-analysis's finding of a statistically significant increase in parafoveal superficial capillary density suggests that phytotherapy may enhance blood flow and nutrient delivery to the retina, which is crucial for maintaining retinal function and preventing further damage. This improvement in capillary density could be attributed to various mechanisms, including the antioxidant and anti-inflammatory effects of the phytotherapeutic agents, as well as their potential to improve endothelial function and reduce vascular permeability. The observed improvements in retinal microvascular perfusion, as indicated by the reduction in FAZ area and the increase in parafoveal superficial capillary density, are clinically significant because they suggest that phytotherapy may target the underlying pathophysiology of early NPDR. Microvascular dysfunction is a hallmark of DR, and its early manifestation is characterized by capillary dropout, impaired blood flow, and increased vascular permeability. By mitigating these microvascular abnormalities, phytotherapy may help to preserve retinal health and prevent the progression of DR to more advanced stages.[11-15]

In addition to the improvements in retinal microvascular perfusion, the meta-analysis also demonstrated statistically significant benefits of phytotherapy on retinal function. This was evidenced by improvements in both Best-Corrected Visual Acuity

(BCVA) and contrast sensitivity. BCVA is the standard measure of visual acuity and reflects the sharpness or clarity of vision. The meta-analysis showed a modest but statistically significant improvement in BCVA following phytotherapeutic interventions. While the magnitude of this improvement may be relatively small in terms of logMAR units, it is important to consider that even small improvements in visual acuity can be meaningful to patients, particularly in the early stages of DR when visual symptoms may be subtle. Furthermore, the fact that a statistically significant improvement was observed despite the relatively short duration of follow-up in some of the included studies suggests that phytotherapy may have a positive impact on visual acuity even in the short term. Contrast sensitivity is a measure of the ability to distinguish between objects that differ only slightly in luminance. It is often affected in early DR, even when BCVA is relatively normal, and is a sensitive indicator of visual dysfunction. The meta-analysis revealed a more pronounced and statistically significant improvement in contrast sensitivity compared to BCVA. This finding suggests that phytotherapy may have a particularly beneficial effect on the functional integrity of the retina, beyond its impact on visual acuity. Improvements in contrast sensitivity can translate to better performance in everyday tasks that require distinguishing objects with subtle differences in shading or contrast, such as driving at night or reading fine print. The improvements in both BCVA and contrast sensitivity observed in this meta-analysis are clinically relevant because they indicate that phytotherapy can have a positive impact on visual function in patients with early NPDR. These functional benefits, combined with the observed improvements in retinal microvascular perfusion, suggest that phytotherapy may address both the structural and functional abnormalities associated with early DR. This is important because preserving visual function is a primary goal in the management of DR, and interventions that can improve both microvascular health and visual function are highly desirable.[16-20]

4. Conclusion

This systematic review and meta-analysis synthesized evidence from seven randomized controlled trials and demonstrated that phytotherapeutic interventions have a beneficial impact on both retinal microvascular perfusion and visual function in patients with early non-proliferative diabetic retinopathy (NPDR). The meta-analysis revealed a statistically significant reduction in the Foveal Avascular Zone (FAZ) area, indicating a potential protective effect on the retinal microvasculature. Additionally, there was a statistically significant increase in parafoveal superficial capillary density, suggesting enhanced blood flow and nutrient delivery to the retina. Furthermore, phytotherapy was associated with improvements in visual function, as evidenced by statistically significant enhancements in both Best-Corrected Visual Acuity (BCVA) and contrast sensitivity. These findings suggest that phytotherapeutic agents may address the underlying structural and functional abnormalities in early NPDR, offering a potential adjunctive treatment strategy. The safety profile of phytotherapy was also evaluated, and the analysis did not reveal a significant increase in major adverse events compared to control groups. However, it is important to acknowledge the moderate heterogeneity observed in some of the meta-analyses, which may limit the generalizability of the findings. In conclusion, this review provides evidence supporting the potential role of specific phytotherapies as adjunctive treatments for managing early diabetic microvascular changes. Further large-scale trials with longer follow-up durations are warranted to confirm these benefits, explore long-term outcomes, and investigate the optimal phytotherapeutic interventions and treatment regimens for early NPDR.

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