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# SELECTED HERBAL GALACTAGOGUES IN INDONESIAN POSTPARTUM CARE: A NARRATIVE REVIEW INTEGRATING PRODUCT STANDARDIZATION, MATERNAL FACTORS, AND INFANT OUTCOMES

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*Ocular Drug Delivery*

## *Abstract*

*Diabetic retinopathy (DR) is a progressive neurovascular complication of diabetes and a major cause of preventable visual impairment. Although intravitreal anti-vascular endothelial growth factor therapy, corticosteroids, laser photocoagulation, and vitreoretinal surgery have improved outcomes, treatment burden, cost, invasiveness, variable response, and limited access sustain interest in complementary strategies. Herbal-derived compounds, including curcumin, resveratrol, quercetin, anthocyanins, crocin, naringin, baicalein, and berberine, target several mechanisms implicated in DR, such as oxidative stress, inflammation, blood-retinal barrier failure, angiogenesis, mitochondrial dysfunction, and retinal neurodegeneration. However, biochemical or histological improvement does not automatically establish clinically meaningful retinal benefit. Multimodal imaging can provide objective structural and vascular endpoints that connect pharmacological mechanisms with tissue-level response. This narrative review integrates experimental and clinical evidence on herbal-derived therapies with color and ultra-widefield fundus photography, optical coherence tomography (OCT), OCT angiography (OCTA), fluorescein angiography, adaptive optics, and emerging quantitative imaging. Preclinical findings are consistently favorable, but human imaging evidence remains limited. Notably, an OCTA-based randomized trial of curcumin-piperine improved systemic oxidative-stress markers without significant OCT or OCTA change, whereas recent animal studies reported improved retinal structure and vascular density. This contrast illustrates the central translational gap. Future studies should use standardized extracts, pharmacokinetic characterization, prespecified imaging endpoints, centralized image grading, adequate follow-up, and comparison with standard care. Herbal-derived products should currently be considered investigational adjuncts rather than replacements for established DR therapy.*



## INTRODUCTION

Diabetic retinopathy (DR) is among the most consequential microvascular complications of diabetes because it can progress silently before causing irreversible visual loss. A global meta-analysis estimated that 22.27% of people with diabetes had DR in 2020, corresponding to approximately 103 million adults, with the number projected to rise to about 160 million by 2045 (Teo et al., 2021). The clinical spectrum extends from mild nonproliferative abnormalities, including microaneurysms and small hemorrhages, to diabetic macular edema (DME), retinal nonperfusion, and proliferative disease with neovascularization. These phenotypes arise from interacting vascular, inflammatory, metabolic, and neuronal processes rather than from a single pathological pathway.

Current treatment is effective but incomplete. Tight systemic control remains fundamental, while intravitreal anti-vascular endothelial growth factor (VEGF) agents are central to the management of center-involved DME and selected stages of proliferative DR. A large comparative trial demonstrated that aflibercept, bevacizumab,

and ranibizumab can improve visual acuity, although the magnitude of benefit varies with baseline visual function and treatment requires repeated monitoring and injections (Diabetic Retinopathy Clinical Research Network, 2015). Laser photocoagulation, corticosteroids, and vitreoretinal surgery retain important roles. Nevertheless, invasiveness, cost, recurrence, injection burden, incomplete response, and unequal access have encouraged investigation of adjunctive therapies capable of acting earlier and across multiple biological targets.

Phytochemicals are attractive in this context because many display antioxidant, anti-inflammatory, antiangiogenic, and neuroprotective activities. Yet enthusiasm must be tempered by major translational problems: extracts differ in composition, active compounds often have poor oral bioavailability, doses used in animals may not be clinically achievable, and apparent molecular improvement may not translate into better retinal structure or vision. An evaluation based only on serum oxidative markers, cultured cells, or retinal histology therefore risks overstating clinical relevance.

Multimodal imaging offers a bridge between pharmacology and clinical ophthalmology. Color fundus photography records visible lesion burden; OCT quantifies retinal thickness, fluid, and microstructural integrity; OCTA measures capillary perfusion without dye; fluorescein angiography identifies leakage, ischemia, and neovascular activity; and emerging techniques provide cellular, metabolic, or computational phenotypes. This review examines how these modalities can evaluate herbal-derived therapies in DR, identifies what has and has not been demonstrated in humans, and proposes an imaging-centered framework for future interdisciplinary research.

Figure 1 summarizes the translational logic of this review, linking chemically defined herbal candidates to plausible mechanisms, retinal tissue targets, and measurable multimodal imaging endpoints.

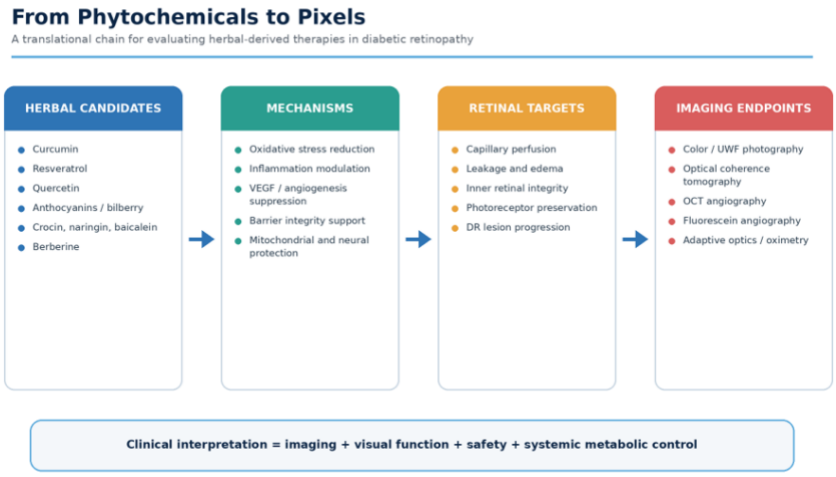


Figure 1. Translational chain linking herbal-derived candidates, biological mechanisms, retinal targets, and multimodal imaging endpoints in diabetic retinopathy.

## NARRATIVE REVIEW APPROACH

A focused narrative search of PubMed/MEDLINE and publisher-indexed records was conducted for literature available through 18 August 2026. Search combinations included “diabetic retinopathy,”

"phytochemical," "herbal medicine," individual compounds, "fundus photography," "optical coherence tomography," "OCT angiography," "fluorescein angiography," "retinal imaging," "nanoparticle," and "drug delivery." Priority was given to human trials, prospective imaging studies, original experimental studies that linked a phytochemical to retinal outcomes, and recent drug-delivery research. Additional landmark imaging and treatment studies were included to establish clinically meaningful endpoints. Because this was a narrative review, study selection was interpretive rather than exhaustive, and no formal meta-analysis or risk-of-bias score was performed. Evidence was synthesized according to compound, mechanism, level of evidence, imaging modality, and translational limitation.

## DIABETIC RETINOPATHY AS A NEUROVASCULAR AND IMAGING-DEFINED DISEASE

Chronic hyperglycemia activates several interconnected injury pathways, including excess reactive oxygen species, advanced glycation, protein kinase C signaling, mitochondrial dysfunction, and inflammatory transcription. These processes injure endothelial cells and pericytes, alter glial function, reduce tight-junction integrity, and destabilize the blood-retinal barrier. VEGF and inflammatory mediators promote vascular permeability, leukocyte adhesion, capillary closure, edema, and eventually pathological neovascularization. Simultaneously, neuronal and glial injury can occur before advanced vascular lesions. OCT segmentation studies have shown selective thinning of inner retinal layers in people with type 1 diabetes and minimal DR, supporting an early neurodegenerative component (van Dijk et al., 2009).

This biology produces measurable imaging phenotypes. Color photography captures microaneurysms, hemorrhages, cotton-wool spots, venous abnormalities, exudates, and new vessels. OCT identifies DME through increased central subfield thickness and intraretinal or subretinal fluid, while also demonstrating disorganization of retinal inner layers (DRIL), hyperreflective foci, ellipsoid-zone disruption, and ganglion-cell loss. DRIL is associated with outer-retinal disruption, increasing DR severity, and poorer visual acuity (Das et al., 2018). Hyperreflective foci also increase with DR severity and may represent inflammatory cells, lipid extravasation, or other tissue-level debris, although their biological specificity remains imperfect (Mizukami et al., 2017).

OCTA adds a vascular dimension by visualizing motion contrast from erythrocytes. DR is generally associated with lower vessel density and a larger or less regular foveal avascular zone (FAZ), particularly in the deep capillary plexus (Al-Sheikh et al., 2016). Prospective evidence indicates that OCTA parameters can predict subsequent DR progression and DME development (Sun et al., 2019). These imaging findings are not interchangeable with molecular biomarkers: a compound may lower circulating malondialdehyde yet fail to alter capillary perfusion, retinal fluid, or neural integrity. Consequently, imaging endpoints are essential for determining whether a pharmacological effect reaches the retina at a clinically relevant magnitude.

## HERBAL-DERIVED THERAPEUTIC CANDIDATES

### *Curcumin*

Curcumin, the principal polyphenolic constituent of *Curcuma longa,* is the most extensively studied herbal-derived candidate in DR. Experimental studies suggest that it reduces oxidative stress, suppresses NF-kappaB-

associated inflammation, downregulates VEGF, preserves capillary ultrastructure, and limits apoptosis. In streptozotocin-induced diabetic rats, curcumin preserved antioxidant defenses and reduced inflammatory mediators and capillary basement-membrane abnormalities (Gupta et al., 2011). A later rat study found improved retinal ultrastructure, lower VEGF expression, and a shift toward antiapoptotic signaling (Yang et al., 2018).

The imaging evidence is particularly instructive. In 2026, Hu et al. evaluated diabetic mice using OCT, OCTA, fluorescein angiography, electroretinography, and histology. High-dose curcumin improved retinal structure, increased vascular density, reduced nonperfusion and acellular capillaries, and modulated Hippo-YAP signaling and endothelial-to-mesenchymal transition (Hu et al., 2026). This study moves beyond biochemical inference because it connects molecular effects to structural, vascular, and functional readouts. Nevertheless, an animal response at high weight-adjusted doses cannot be assumed to predict human benefit.

The principal human counterpoint is an OCTA-based randomized controlled trial in nonproliferative DR. Curcumin-piperine supplementation improved total antioxidant capacity and superoxide dismutase and reduced malondialdehyde, but it did not significantly change OCT or OCTA parameters compared with placebo (Amini et al., 2024). The trial was small and relatively short, yet its neutral retinal imaging result is clinically important. It suggests that systemic biochemical activity may be insufficient, that the retinal exposure was too low, that the selected disease stage was not reversible, or that the imaging endpoints required a larger sample and longer follow-up. Curcumin is therefore promising but not clinically established for DR.

***Resveratrol***

Resveratrol is a plant-derived stilbene found in grapes, berries, and peanuts. Its proposed actions include antioxidant activity, modulation of AMP-activated protein kinase and sirtuin pathways, inhibition of inflammatory signaling, and suppression of VEGF. In diabetic mice, oral resveratrol reduced retinal vascular leakage, pericyte loss, and VEGF induction (Kim et al., 2012). In diabetic rats and high-glucose-exposed retinal endothelial cells, resveratrol also reduced inflammatory cytokines, oxidative injury, apoptosis, VEGF expression, and retinal permeability, with paraoxonase-1 implicated in the response (Chen et al., 2019).

These studies support a vasoprotective hypothesis, but most endpoints were angiographic leakage, biochemical assays, histology, or cell survival rather than standardized human OCT/OCTA metrics. Future trials should test whether resveratrol changes deep-plexus vessel density, FAZ morphology, nonperfusion index, central retinal thickness, or hyperreflective foci. Without such data, the current evidence remains preclinical.

***Quercetin***

Quercetin is a flavonoid present in onions, apples, berries, and many medicinal plants. In diabetic rats, quercetin increased retinal layer thickness and ganglion-cell survival while reducing inflammatory mediators, VEGF, and adhesion molecules. Induction of heme oxygenase-1 appeared central to this protection (Chai et al., 2021). A more recent study combined electroretinography and OCT with microbiome analysis and found that quercetin preserved outer nuclear layer thickness and retinal function while activating nuclear factor erythroid 2-related factor 2 signaling and modifying the gut-retina axis (Liu et al., 2024).

Quercetin therefore illustrates the value of pairing mechanistic and imaging data. OCT can demonstrate preservation of neural tissue, while electroretinography tests whether structure is accompanied by functional rescue. However, the evidence again comes from animal models, and the dose, formulation, and systemic metabolic effects complicate attribution of benefit to a direct retinal action.

***Anthocyanins and Bilberry***

Anthocyanins are pigmented polyphenols concentrated in blueberries, bilberries, and other dark fruits. In diabetic rats, blueberry anthocyanins reduced retinal reactive oxygen species and malondialdehyde, increased glutathione and antioxidant-enzyme activity, and suppressed VEGF and interleukin-1beta through Nrf2/heme oxygenase-1 signaling (Song et al., 2016). A standardized *Vaccinium myrtillus* extract reduced fluorescein leakage and preserved tight-junction proteins without lowering blood glucose, supporting a direct effect on the blood-retinal barrier rather than an exclusively systemic glycemic mechanism (Kim et al., 2015).

The imaging relevance is clear: fluorescein leakage is a direct vascular endpoint, and future human studies could add OCT fluid volumes, OCTA perfusion, and ultra-widefield nonperfusion. Nevertheless, commercial bilberry products vary substantially in anthocyanin content, extraction, and purity. Results from a standardized experimental extract cannot be generalized to uncharacterized supplements.

***Crocin, Naringin, Baicalein, and Berberine***

Crocin, a carotenoid constituent of saffron (*Crocus sativus*), reduced oxidative stress and inflammatory activation in high-glucose- and fatty-acid-exposed microglial cells through PI3K/Akt signaling (Yang et al., 2017). This mechanism is relevant because activated microglia may contribute to neuronal and vascular injury, but direct clinical retinal imaging evidence in DR remains absent.

Naringin, a citrus flavonoid, reduced retinal inflammation, oxidative stress, glial activation, and ganglion-cell loss in diabetic rats by suppressing NF-kappaB activation (Liu et al., 2017). Baicalein, derived from *Scutellaria species*, reduced microglial activation, VEGF expression, vascular leakage, and ganglion-cell loss in another diabetic rat model (Yang et al., 2009). Both compounds demonstrate multi-target activity but require pharmacokinetic and imaging-based validation in humans.

Berberine is an isoquinoline alkaloid present in several medicinal plants. Leukocytes from patients with diabetes induced retinal endothelial-cell death ex vivo, while berberine reduced leukocyte-mediated injury and inflammatory activation (Tian et al., 2013). More recently, berberine improved retinal structure on OCT and suppressed NLRP3 inflammasome-associated proteins in diabetic rats (Li et al., 2025). These findings provide a plausible anti-inflammatory bridge from human cells to animal imaging, but they do not yet establish clinical efficacy or ocular safety at therapeutic exposures.

***Macular Carotenoids***

Lutein and zeaxanthin are dietary xanthophylls rather than medicines in the conventional sense, but they are relevant phytochemicals because they accumulate in the macula and filter blue light while supporting antioxidant defense. A small study in nonproliferative DR reported increased serum lutein and zeaxanthin after supplementation and assessed visual acuity, contrast sensitivity, and foveal thickness (Hu et al., 2011).

The study suggests feasibility but is insufficient to define disease modification. Larger masked trials using OCT, OCTA, and standardized macular-pigment measurement are needed.

**Table 1.** Representative herbal-derived candidates and imaging-related evidence.

| Candidate | Principal proposed actions | Evidence level | Reported imaging or tissue endpoint |
|---|---|---|---|
| Curcumin | Antioxidant; anti-inflammatory; anti-VEGF; antiapoptotic | Animal studies; one small human trial | OCT/OCTA/FFA benefit in mice; no OCT/OCTA change in the human trial |
| Resveratrol | Anti-VEGF; sirtuin signaling; vascular protection | Cell and animal studies | Leakage, pericyte loss, VEGF, and histology |
| Quercetin | HO-1/Nrf2 activation; anti-inflammatory; neuroprotective | Cell and animal studies | OCT thickness and electroretinography in rats |
| Bilberry/anthocyanins | Nrf2/HO-1 activation; barrier preservation | Mainly animal studies | Fluorescein leakage, tight-junction proteins, histology |
| Crocin/naringin/baicalein | Microglial modulation; antioxidant and anti-inflammatory effects | Cell and animal studies | Histology, leakage, and ganglion-cell measures |
| Berberine | Anti-leukostasis; anti-inflammatory; NLRP3 suppression | Human ex vivo and animal studies | Rat OCT structure; endothelial-cell survival ex vivo |

## MULTIMODAL IMAGING FOR EVALUATING THERAPEUTIC RESPONSE

### *Fundus Photography and Ultra-Widefield Imaging*

Color fundus photography remains the foundation for DR grading because it documents visible lesion burden and enables longitudinal comparison. Ultra-widefield (UWF) imaging extends assessment into the retinal periphery, where clinically important lesions may be missed by standard fields. Predominantly peripheral lesions on UWF imaging were associated with a higher four-year risk of DR progression in a prospective cohort (Silva et al., 2015). UWF fluorescein angiography further quantifies nonperfusion and peripheral vascular abnormalities; greater nonperfusion was associated with subsequent disease worsening even after adjustment for baseline severity (Silva et al., 2022). In herbal trials, fundus photography could determine whether an intervention changes lesion counts or DR severity, while UWF imaging could test effects on peripheral ischemia. These outcomes require masked reading-center grading because subtle apparent improvement may reflect field selection or image quality rather than biology.

### *Optical Coherence Tomography*

OCT is the most practical structural endpoint for interventional studies. Central subfield thickness and fluid volumes are relevant to DME, but a phytochemical trial should not rely on thickness alone. DRIL, hyperreflective foci, ellipsoid-zone integrity, external limiting membrane continuity, ganglion-cell complex thickness, and retinal nerve fiber layer thickness may capture inflammatory and neuroprotective effects. For early DR without edema, preservation of inner retinal layers may be more appropriate than expecting a reduction in central thickness. Automated segmentation should be reviewed manually because edema, exudates, and poor fixation can produce errors.

### *Optical Coherence Tomography Angiography*

OCTA is especially aligned with herbal candidates that claim vascular protection. Candidate outcomes include superficial and deep capillary vessel density, perfusion density, FAZ area and circularity, peripapillary

capillary density, fractal dimension, and widefield nonperfusion index. Because deep-plexus vessel density and FAZ abnormalities worsen across DR stages, these metrics may detect change before conventional visual acuity (Al-Sheikh et al., 2016). However, repeatability depends on device, layer, scan size, signal strength, and algorithm. Cross-device studies show that some vessel-density measurements are more reproducible than others (Levine et al., 2020). Artifact burden is also high in DR, particularly in severe disease; loss of signal, displacement, masking, motion, and segmentation errors can bias measurements (Wang et al., 2024). Trials should therefore prespecify acquisition protocols, quality thresholds, segmentation correction, and analysis software.

***Fluorescein Angiography and Emerging Modalities***

Fluorescein angiography remains valuable for leakage, capillary nonperfusion, microaneurysms, and neovascular activity. Unlike OCTA, it demonstrates dynamic leakage but requires intravenous dye. Its use is justified in selected trials when the proposed mechanism involves barrier stabilization or antiangiogenesis. Adaptive optics can visualize photoreceptors and microvasculature at near-cellular resolution; photoreceptor abnormalities have been demonstrated in regions of deep capillary nonperfusion in diabetic macular ischemia (Nesper et al., 2017). Retinal oximetry, hyperspectral imaging, and fundus autofluorescence may add metabolic information, but their endpoints require further validation.

Artificial intelligence can support screening, segmentation, and quantitative phenotyping. Deep-learning systems can detect referable DR from fundus photographs (Gulshan et al., 2016), and newer models can segment nonperfusion and the FAZ on widefield OCTA (Le Boite et al., 2025). AI outputs should not be accepted uncritically: training-domain shift, image artifacts, and algorithm-generated vessels or boundaries can create false biological signals. Radiology expertise is valuable here for image harmonization, quantitative feature extraction, reproducibility, and blinded image analysis. MRI is not a routine DR outcome, but it may support translational studies of ocular drug residence or delivery systems; MRI has been used to assess the permanence of natural-polysaccharide ophthalmic hydrogels in vivo (Fernandez-Ferreiro et al., 2015).

**Table 2.** Suggested imaging endpoints for future phytochemical trials.

| Modality | Core endpoint | Best use in herbal-derived therapy studies |
|---|---|---|
| Color/UWF photography | DR severity, lesion counts, peripheral lesions | Long-term disease progression and peripheral phenotype |
| OCT | Central thickness, fluid, DRIL, hyperreflective foci, ellipsoid zone, RNFL/GCC | Edema, inflammation, photoreceptor integrity, and neuroprotection |
| OCTA | Vessel density, FAZ, fractal dimension, nonperfusion index | Microvascular protection and early perfusion change |
| FFA/UWF-FA | Leakage, ischemia, neovascularization | Blood-retinal barrier stabilization and antiangiogenic activity |
| Adaptive optics/oximetry | Photoreceptor mosaic and oxygen-related metrics | Exploratory cellular and metabolic effects |
| AI/radiomics | Automated segmentation and multivariable image signatures | Scalable quantification and response prediction after external validation |

## FROM PHARMACOLOGICAL SIGNAL TO IMAGING EVIDENCE

An imaging-centered interpretation should follow a causal sequence. First, the intervention must be chemically defined and reach a plausible systemic or ocular exposure. Second, it should modify a prespecified

biological target, such as oxidative stress, inflammation, VEGF signaling, or tight-junction integrity. Third, that mechanism should correspond to a retinal phenotype. An anti-permeability effect should reduce angiographic leakage or OCT fluid; a microvascular protective effect should stabilize OCTA vessel density or nonperfusion; and a neuroprotective effect should preserve inner retinal or photoreceptor structure and ideally visual function.

The curcumin literature demonstrates why this sequence matters. Rat and mouse studies show molecular, histological, OCT, OCTA, angiographic, and functional benefit, but the human trial demonstrated biochemical improvement without significant retinal imaging change (Amini et al., 2024; Hu et al., 2026). A balanced conclusion is not that imaging disproved curcumin, nor that animal data proved efficacy. Rather, the tested human regimen did not yet produce a measurable retinal effect under the study conditions. The next experiment should address exposure, duration, disease stage, sample size, and endpoint sensitivity instead of repeating broad biochemical measurements.

***Temporal Hierarchy of Response***

Therapeutic response should be separated into temporal layers because biochemical, vascular, structural, and clinical changes do not occur simultaneously. Target engagement—such as a reduction in oxidative stress or an increase in antioxidant capacity—may appear within weeks, but it only confirms biological activity. OCTA perfusion indices, angiographic leakage, or OCT hyperreflective foci may change later and can serve as intermediate evidence that the molecular effect has reached the retina. Durable preservation of retinal thickness, neural layers, photoreceptor integrity, DR severity, and vision generally requires longer observation. A short trial should therefore avoid presenting a serum biomarker change as proof of retinal protection, while a long trial should not rely exclusively on a noisy exploratory imaging metric.

For a phase II study, a practical endpoint architecture would specify one primary imaging measure aligned with the proposed mechanism, several supportive imaging measures, and at least one functional outcome. An anti-inflammatory compound might use change in OCT hyperreflective foci or edema as a mechanistic endpoint, whereas a vasoprotective compound might prioritize deep-plexus vessel density or nonperfusion. Color or ultra-widefield photography could document conventional DR progression, and visual acuity, contrast sensitivity, or electroretinography could test functional coherence. Systemic metabolic variables should be modeled as covariates because an apparent retinal benefit may result from improved glucose or blood-pressure control rather than a direct ocular effect.

Interpretation should emphasize change beyond measurement error, not merely statistical significance. OCTA vessel density and FAZ measurements are sensitive to signal strength, motion, segmentation, device software, and scan geometry; their repeatability must inform sample-size calculations and thresholds for meaningful change (Levine et al., 2020; Wang et al., 2024). A central reading center, masked graders, predefined quality criteria, and repeated scans in a subset can reduce bias. Concordant movement across mechanistically related measures is more persuasive than an isolated positive comparison among many endpoints. This hierarchy allows negative, neutral, and positive studies to refine the therapeutic hypothesis instead of forcing every imaging fluctuation into a claim of efficacy.

Imaging should also be interpreted alongside function. A small change in vessel density may not matter if visual acuity, contrast sensitivity, or retinal function is unchanged. Conversely, stable vision over a short study cannot establish protection in early DR, where deterioration is slow. Composite outcomes combining imaging, visual function, systemic control, and safety may therefore be more informative than any single marker.

Figure 2 translates these principles into a practical trial workflow and separates early target engagement from intermediate retinal imaging change and longer-term clinical benefit.

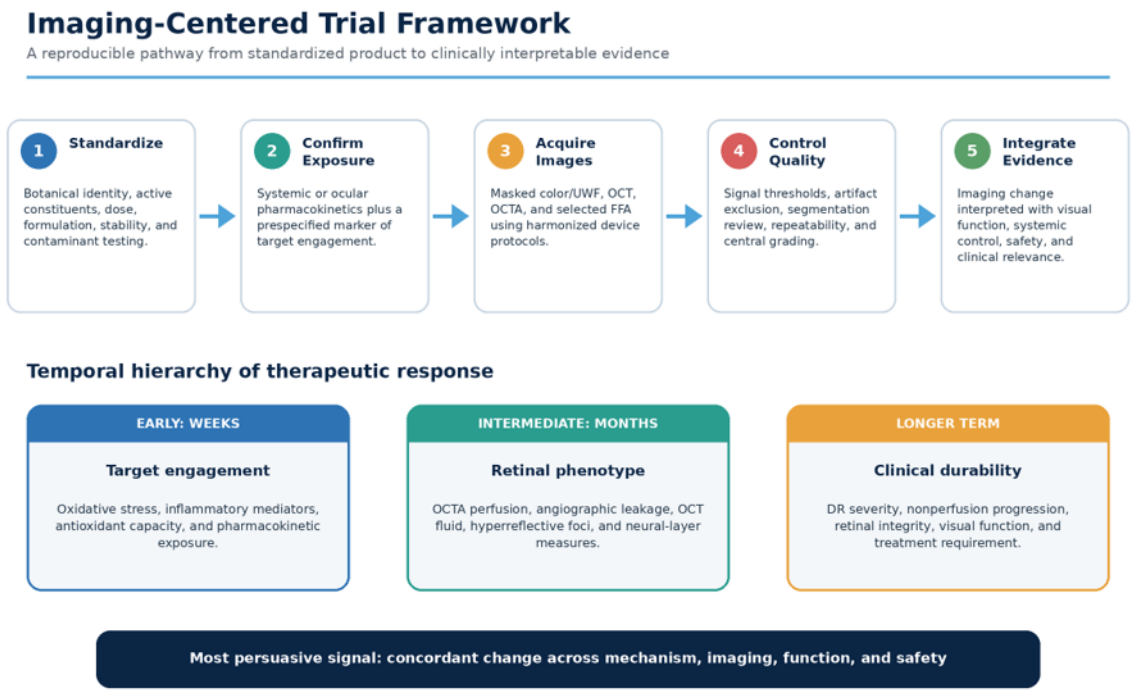


**Figure 2.** Imaging-centered framework for trials of herbal-derived therapies in diabetic retinopathy, including product standardization, exposure confirmation, multimodal acquisition, quality control, and temporally ordered outcomes.

## FORMULATION, DELIVERY, AND SAFETY

Translation is limited by low solubility, rapid metabolism, uncertain retinal penetration, and variable extract composition. Piperine combinations, phospholipid complexes, nanoparticles, liposomes, micelles, nanoemulsions, and hydrogels are intended to improve exposure, but each formulation changes pharmacokinetics and potentially toxicity. A 2025 study developed nanostructured lipid carriers containing curcumin, naringenin, and alpha-lactalbumin for topical posterior-segment delivery. The formulation showed sustained release, transcorneal permeation, reduced vitreous VEGF, and preserved retinal morphology in experimental models, although retinal drug concentrations were not quantified (Nirbhavane et al., 2025). This limitation is crucial: pharmacodynamic improvement does not substitute for ocular pharmacokinetic confirmation.

Future products require botanical authentication, quantified active constituents, contaminant testing, batch consistency, stability data, and dose justification. Safety assessment should include ocular irritation, retinal toxicity, hepatic and renal effects, bleeding risk, glycemic effects, and herb-drug interactions. Patients with DR frequently use antidiabetic, antihypertensive, lipid-lowering, antiplatelet, or anticoagulant therapy, so

"natural" does not mean interaction-free. Until efficacy and safety are established, herbal-derived therapies should not be used as substitutes for clinical advice or standard ophthalmic treatment, and any adjunctive use requires professional supervision.

## RESEARCH GAPS AND FUTURE DIRECTIONS

The evidence base has four dominant gaps. First, most positive data originate from cells or rodents, whereas dedicated human imaging trials are rare. Second, interventions are heterogeneous in species, extraction, dose, formulation, and duration. Third, imaging protocols are often secondary or incompletely standardized. Fourth, many studies evaluate early biochemical change without demonstrating durable prevention of DME, proliferative disease, or visual loss.

Future trials should enroll a clearly defined phenotype, such as mild-to-moderate nonproliferative DR without center-involved DME, and stratify participants by HbA1c, diabetes duration, renal function, blood pressure, and baseline DR severity. The investigational product should have a certificate of analysis and pharmacokinetic substudy. A core imaging set could include masked color/UWF grading, OCT central thickness and neural biomarkers, and OCTA deep-plexus vessel density, FAZ morphology, and nonperfusion. Images should be acquired on the same device when possible, with prespecified signal thresholds, artifact exclusion, manual segmentation review, and centralized analysis. Follow-up should be long enough to distinguish measurement noise from biological change.

AI and radiomics may eventually identify response signatures that are not visible to human graders, but models require external validation and locked analysis plans. Interdisciplinary collaboration is therefore essential: herbal pharmacists define and standardize the intervention; ophthalmologists establish clinical relevance and safety; imaging scientists and radiologists ensure reproducible acquisition and quantitative analysis; and biostatisticians protect against false discovery. Such collaboration can transform a plausible phytochemical mechanism into evidence that is measurable, reproducible, and clinically interpretable.

## CONCLUSION

Herbal-derived compounds act on several pathways relevant to DR, and preclinical studies consistently report antioxidant, anti-inflammatory, vasoprotective, and neuroprotective effects. Curcumin currently provides the clearest example of both promise and uncertainty: multimodal imaging shows benefit in diabetic animals, while a small human randomized trial found no significant OCT or OCTA improvement. Multimodal imaging is therefore not merely illustrative; it is the critical translational test between molecular activity and retinal benefit. Standardized products, verified ocular exposure, rigorous safety assessment, prespecified imaging biomarkers, and adequately powered human trials are needed before phytochemicals can be recommended as evidence-based adjuncts. At present, they should not replace established systemic management, anti-VEGF therapy, laser, or surgery.

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