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Review Article

Plant-Derived Flavonoids from Couroupita Guianensis As Therapeutic Agents in Diabetes Mellitus & Diabetic Retinopathy: Mechanistic Insights, Pharmacological Potential & Future Perspectives: A Review

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Diabetes mellitus (DM) is a chronic, progressive metabolic disorder characterized by persistent hyperglycemia arising from impaired insulin secretion, peripheral insulin resistance, or a combination of both defects. Among its numerous micro- and macrovascular sequelae, diabetic retinopathy (DR) constitutes one of the foremost causes of preventable blindness in the working-age population worldwide. Conventional pharmacotherapy, comprising insulin replacement, oral hypoglycemic agents and anti-vascular endothelial growth factor (anti-VEGF) intravitreal therapy, is frequently limited by cumulative toxicity, high cost, and an inability to fully arrest disease progression. Consequently, plant-derived phytoconstituents, particularly flavonoids, have attracted considerable scientific interest as multi-targeted therapeutic alternatives. *Couroupita guianensis Aubl*. is a tropical medicinal plant whose flowers, leaves and bark are rich in bioactive flavonoids such as quercetin, kaempferol, rutin, luteolin and pelargonidin glycosides. These constituents have been reported to exert antidiabetic effects through inhibition of carbohydrate-hydrolyzing enzymes, free-radical scavenging, suppression of pro-inflammatory signaling, protection of pancreatic β-cells, and attenuation of the oxidative and angiogenic pathways implicated in diabetic retinopathy. This review consolidates current knowledge of the phytochemical profile, molecular mechanisms, retino-protective pathways and translational prospects of flavonoid-rich *Couroupita guianensis* extracts, with the aim of supporting their further development as adjunct or alternative agents in the management of diabetes and its ocular complications.

Keywords: *Couroupita guianensis*; Flavonoids; Diabetes mellitus; Diabetic retinopathy; Oxidative stress; Antidiabetic phytotherapy.

INTRODUCTION

Diabetes mellitus represents one of the most rapidly expanding non-communicable diseases globally, with prevalence projected to rise substantially over the coming decades as a consequence of sedentary lifestyles, and increasing obesity rates. The disorder is characterized not merely by elevated blood glucose but by a constellation of downstream biochemical derangements that progressively damage multiple

organ systems. Chronic hyperglycemia is now well recognized as the principle driver of both macrovascular complications, such as coronary artery disease and stroke, and microvascular complications, including nephropathy, neuropathy, and retinopathy. Among these, diabetic retinopathy remains a leading cause of irreversible vision loss in adults of working age.

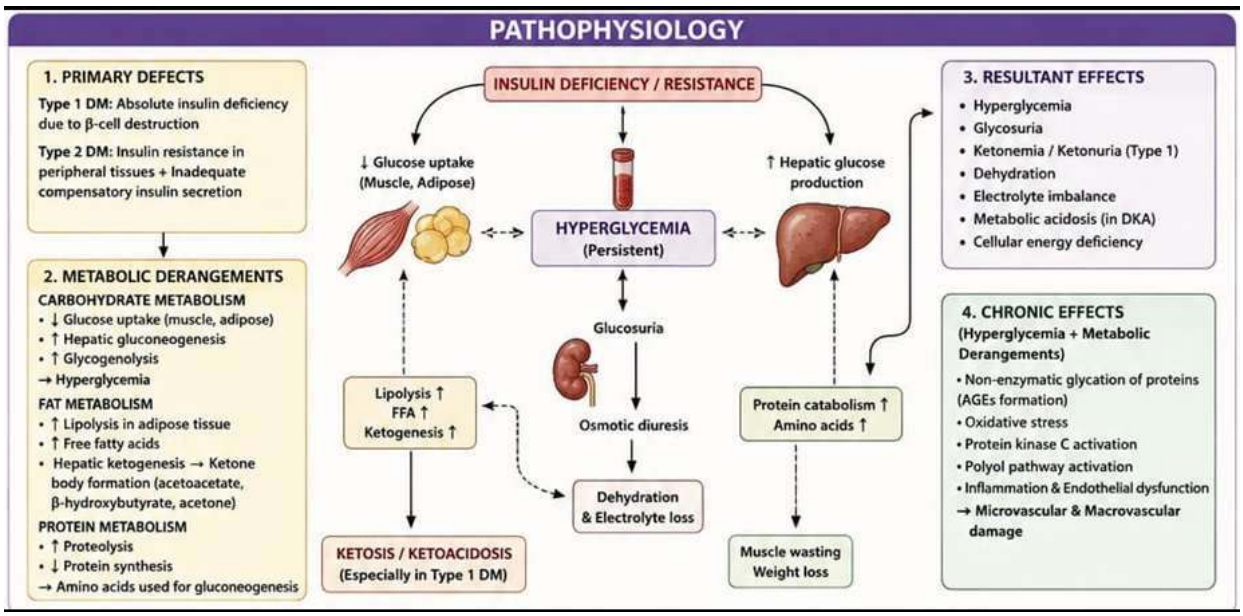


Fig. No. 1: Pathophysiology of Diabetes mellitus

The pathogenesis of diabetic retinopathy is multifactorial and involves the convergence of several interrelated biochemical cascades. Sustained hyperglycemia promotes excessive generation of reactive oxygen species (ROS), activation of pro-inflammatory cytokine pathways, mitochondrial dysfunction, accumulation of advanced glycation end-products (AGEs), and progressive structural damage to the retinal microvasculature. These processes act synergistically rather than in isolation, producing a self-perpetuating cycle of oxidative and inflammatory injury that culminates in capillary occlusion, neovascularization, and, ultimately, vision-threatening complications such as macular oedema and vitreous hemorrhage. Current management strategies for diabetes and its ocular complications are largely centered on insulin therapy, oral hypoglycemic agents, and, in advanced retinopathy, anti-VEGF intravitreal injections or laser photocoagulation. While effective in controlling glycaemia and slowing disease progression, these interventions are frequently associated with long-term adverse effects, considerable financial cost, and an inability to completely halt the underlying pathological process. Such limitations have intensified interest in plant-derived bioactive compounds as complementary or alternative therapeutic strategies. Flavonoids, a structurally diverse class of polyphenolic phytochemicals, have emerged as particularly promising candidates owing to their capacity to simultaneously modulate several of the biochemical pathways implicated in diabetes pathogenesis and retinal damage, including enzyme inhibition, antioxidant defense, anti-inflammatory signaling, and anti-angiogenic activity. *Couroupita guianensis*, a medicinal plant with a long history of traditional use, and examines the phytochemical basis, mechanistic pathways, and preclinical pharmacological evidence supporting its potential application in the management of diabetes mellitus and diabetic retinopathy. The review further outlines existing research gaps and proposes directions for future investigation to facilitate the translational development of this botanical resource.

Botanical Description Of *Couroupita Guianensis*

- ***Couroupita guianensis*** **Aubl**. (Lecythidaceae), commonly known as the cannonball tree, is a medium to large deciduous tropical species characterized by its distinctive cauliflorous habit and large, spherical, woody fruits. Native to South

and Central America, the species is widely cultivated across tropical regions, including India, where it holds cultural and religious significance and is frequently planted near temple premises.

- **Tree architecture: -**The trunk is cylindrical with greyish-brown, fissured bark and can attain heights of up to 35 m. The lower trunk bears a dense, tangled network of vine-like branches, while the root system is extensive, deep-seated, and well-anchored.
- **Foliar characteristics**: - Leaves are simple and alternately arranged, typically clustered in spiral or apical whorls at branch termini. Laminae are elliptic to ovate or oblong, measuring 8–31 cm in length, with margins ranging from finely serrate to nearly entire. The leaf texture is leathery, with a smooth to slightly pubescent abaxial surface, particularly along the venation.

Fig. No. 2: Leaves & flowers of *Couroupita guianensis* Aubl.

- **Floral morphology**: The species exhibits one of the most structurally complex floral architectures among angiosperms, with flowers borne in long, pendulous racemes arising directly from the trunk (cauliflory). Each flower possesses six large, fleshy petals, rose-pink to red or orange adaxially and yellow abaxially. The androecium is dimorphic, comprising (i) a central ring of short, fertile, pollen-producing stamens, and (ii) a curved, anemone-like hood of staminodes (sterile stamens) that mimics a pollen reward to attract pollinators such as carpenter bees, thereby facilitating pollen transfer from the fertile ring. The ovary, centrally positioned, morphologically resembles a miniature Shiva linga—a feature of particular ethnobotanical interest. Floral fragrance is most pronounced during early morning and evening hours.
- **Fruit characteristics**: Fruits are heavy, globose, woody structures 20–25 cm in diameter, resembling cannonballs, hence the common name. They develop directly on the trunk and main branches, with individual trees capable of bearing over 100 fruits simultaneously. Each fruit comprises a hard outer pericarp enclosing hundreds of flattened seeds embedded within a malodorous, gelatinous white pulp. Fruit maturation requires approximately 12–18 months.

Fig. No. 3: Fruit of *Couroupita guianensis* Aubl.

Geographical Distribution and Traditional Use

- Couroupita guianensis, popularly referred to as the Cannonball tree, or Nagalingam in several Indian languages, is indigenous to the tropical regions of South America but has been widely naturalized and cultivated across India, Sri Lanka, Africa, and Southeast Asia owing to its ornamental and religious significance.

- Within India, the species is commonly cultivated in the southern states of Karnataka, Kerala, Tamil Nadu, Andhra Pradesh, and Telangana, where it is frequently planted in temple precincts and botanical gardens.

- Ethnobotanical surveys indicate that virtually every part of the plant, including the flowers, leaves, bark, fruit pulp, and roots, has traditionally been employed in folk and indigenous medicine systems for the management of inflammatory conditions, microbial infections, gastrointestinal ulcers, diabetes, and impaired wound healing.

- This broad spectrum of traditional applications provides an empirical rationale for the systematic pharmacological investigation of the plant, and underpins the growing scientific interest in its phytochemical constituents

Taxonomical Study of *Couroupita Guianensis* Aubl

Table. No. 1: Taxonomical classification of *Couroupita guianensis* Aubl.

Taxonomical Rank	Classification
Kingdom	Plantae
Sub-kingdom	Tracheobionta (Vascular plants)
Division	Magnoliophyte (Flowering plants)
Class	Magnoliopsida (Dicotyledons)
Order	Ericales
Family	Lecythidaceae
Genus	Couroupita
Species	Couroupita guianensis Aubl

It's commonly known as Cannon Ball Tree

Synonyms: Ayahuma, Sala Tree (in some regions)

- **Scientific Description:** Couroupita guianensis is a tropical flowering tree belonging to the family Lecythidaceae. It is native to the rainforests of Brazil, Guyana, and other parts of tropical South America. The species is well recognized for its large spherical fruits resembling cannonballs and highly aromatic flowers. Various parts of the plant, including flowers, leaves, bark, and fruits, contain diverse phytoconstituents such as flavonoids, alkaloids, terpenoids, and phenolic compounds, which have attracted considerable interest due to their antioxidant, anti-inflammatory, antimicrobial, and antidiabetic potential. This plant is particularly relevant in phytopharmacological research because its flavonoid-rich extracts may contribute to

oxidative stress reduction, β-cell protection, and prevention of diabetic complications such as Diabetic Retinopathy.

Phytochemical Composition of *Couroupita Guianensis*

Phytochemical screening of various parts of *Couroupita guianensis* has revealed a chemically diverse profile comprising flavonoids, phenolic acids, alkaloids, sterols, and several minor bioactive constituents. The phytochemical profile of C. guianensis varies considerably across plant organs, reflecting tissue-specific biosynthetic activity.

Table. No. 2: Phytochemical Composition of C. guianensis

Phytochemical Class	Representative Compounds Identified
Flavonoids	Quercetin, kaempferol, rutin, luteolin
Phenolic acids	Rosmarinic acid, caffeic acid
Alkaloids	Couroupitine
Sterols	β-Sitosterol, campesterol
Other constituents	Isatin, indirubin, tryptanthrin

1. **Floral phytochemistry**: The intensely aromatic flowers constitute a rich reservoir of volatile organic compounds and phenolic acids. Predominant volatile constituents include eugenol, linalool, nerol, geraniol, and (E, E)-farnesol, which are collectively responsible for the characteristic fragrance and documented antifungal activity. Phenolic acids identified include caffeic acid, p-coumaric acid, and o-coumaric acid, alongside flavonoid glycosides such as quercetin and pelargonidin derivatives.

2. **Leaf phytochemistry**. Foliar tissue functions as a significant site of secondary metabolite accumulation, particularly compounds implicated in cellular protection. Notable constituents include pentacyclic triterpenoids and sterols—α-amyrin, β-amyrin, friedelin, botulinic acid, and β-sitosterol—together with fatty acids such as linoleic acid and triterpenoid esters (e.g., β-amyrin palmitate). Leaves are additionally characterized by high concentrations of tannins, saponins, and phytosterols.

3. **Fruit pulp and seed phytochemistry**: The fleshy fruit pulp is a substantial source of antioxidant and bioactive compounds, including carotenoids, which contribute to pigmentation and free-radical scavenging capacity. Steroidal constituents such as campesterol and stigmasterol have been identified, alongside organic acids (malic, citric, and tartaric acid) and glycosides, including anthocyanins and cardiac glycosides.

The therapeutic potential of *Couroupita guianensis* is largely attributed to its flavonoid-rich composition. Flavonoids are low-molecular-weight polyphenolic compounds characterized by a common diphenyl propane (C6–C3–C6) skeleton, which confers strong antioxidant, enzyme-modulatory, and anti-inflammatory properties. By virtue of their phenolic hydroxyl groups, these compounds function as potent free-radical scavengers capable of neutralizing reactive oxygen and nitrogen species generated during states of metabolic stress. In addition, several flavonoid constituents have been shown to interact with key enzymes and signaling intermediates involved in glucose homeostasis, thereby contributing to their observed antidiabetic activity. The co-occurrence of phenolic acids, sterols, and alkaloid derivatives may further contribute synergistically to the overall pharmacological profile of the plant, although the relative contribution of each compound class warrants further isolation-based investigation.

Flavonoids as Antidiabetic Agents

- **α-Glucosidase and α-Amylase Inhibition Mechanism:** One of the principal mechanisms by which flavonoids exert anti-hyperglycemic activity is through competitive inhibition of carbohydrate-hydrolyzing enzymes, particularly α-glucosidase and α-amylase. These enzymes are responsible for the breakdown of dietary

polysaccharides and oligosaccharides into absorbable monosaccharides within the intestinal lumen. By binding to the catalytic sites of these enzymes, flavonoids such as quercetin and kaempferol delay the enzymatic hydrolysis of starch, thereby slowing glucose liberation and subsequent intestinal absorption. The net physiological consequence of this inhibitory action is a blunted postprandial glycaemia excursion, which is of particular therapeutic relevance given that postprandial hyperglycemia is a major contributor to the cumulative glycaemia burden and associated vascular complications observed in diabetic patients. Sequentially, this mechanism may be conceptualized as a stepwise reduction in starch digestion, decreased glucose absorption across the intestinal epithelium, attenuated elevation of blood glucose, and, cumulatively, improved long-term control of disease progression.

- **Protection of Pancreatic β-Cells:** Sustained hyperglycemia generates excessive reactive oxygen species within pancreatic β-cells, which possess comparatively limited intrinsic antioxidant defense capacity relative to other cell types. This renders β-cells particularly vulnerable to oxidative injury, ultimately leading to functional impairment and progressive cell death, a process that further compromises insulin secretory capacity and accelerates disease progression. Flavonoids isolated from *Couroupita guianensis* have been reported to mitigate this oxidative insult through several complementary mechanisms: neutralization of reactive oxygen species via direct radical scavenging, stabilization of β-cell membrane integrity, enhancement of glucose-stimulated insulin secretion, and attenuation of experimentally induced oxidative damage, such as that produced by alloxan in preclinical models. Collectively, these cytoprotective actions support a role for flavonoid-rich extracts in preserving residual β-cell mass and function during the course of diabetic pathology.

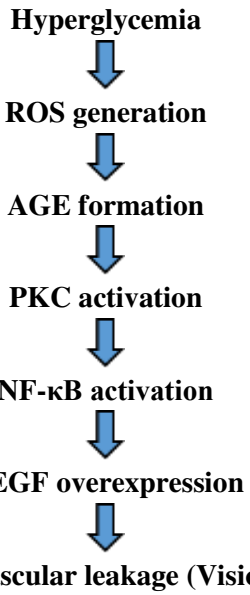
Oxidative Stress and Diabetes Pathophysiology

Persistent hyperglycemia is a potent stimulus for the excessive generation of reactive oxygen species through several interconnected biochemical routes, including mitochondrial electron transport chain dysfunction, auto-oxidation of glucose, and activation of the polyol and protein kinase C pathways. The resultant state of oxidative stress, defined as an imbalance between pro-oxidant generation and antioxidant defense capacity, contributes to widespread cellular injury. Specific consequences include direct oxidative damage to nuclear and mitochondrial DNA, peroxidative degradation of membrane lipids, oxidative modification of structural and functional proteins, induction of programmed cell death (apoptosis), and progressive endothelial dysfunction, the latter being a critical early event in the development of diabetic vascular complications. Flavonoids counteract this oxidative burden through multiple, mutually reinforcing antioxidant mechanisms. At the molecular level, the phenolic hydroxyl groups present on the flavonoid backbone are capable of directly donating hydrogen atoms or electrons to neutralize free radicals, thereby terminating chain-propagating oxidative reactions. In addition, several flavonoids chelate transition metal ions such as iron and copper, which would otherwise catalyze the generation of highly reactive hydroxyl radicals via Fenton-type chemistry. Beyond their direct radical-scavenging properties, certain flavonoids have also been implicated in the upregulation of endogenous antioxidant defense systems, including enzymes regulated through the Nrf2 signaling pathway, further amplifying their cytoprotective potential against hyperglycemia-induced oxidative injury.

Pathophysiology of Diabetic Retinopathy

Diabetic retinopathy develops as a consequence of chronic hyperglycemia-induced microvascular injury within the retinal vasculature, mediated through a cascade of interrelated molecular pathways. As outlined schematically below, sustained hyperglycemia initiates excessive reactive oxygen species generation, which in turn promotes the formation of advanced glycation end-products. These AGEs interact with their cognate receptor (RAGE) to activate protein kinase C (PKC) and nuclear factor-kappa B (NF-κB) signaling cascades, culminating in

the overexpression of vascular endothelial growth factor (VEGF). Elevated VEGF activity disrupts the integrity of the blood-retinal barrier, leading to vascular leakage, retinal oedema, and, in advanced stages, pathological neovascularization and consequent vision loss.



Several discrete but interconnected molecular pathways have been implicated in the pathogenesis of diabetic retinopathy:

- AGE RAGE signaling: The accumulation of advanced glycation end-products and their interaction with the receptor for AGEs (RAGE) promotes oxidative stress and chronic low-grade inflammation within retinal tissue.
- Protein kinase C (PKC) pathway: - hyperglycemia-induced diacylglycerol accumulation activates PKC isoforms, which subsequently impair retinal blood flow and increase vascular permeability.
- Mitogen-activated protein kinase (MAPK) signaling: This pathway amplifies inflammatory gene expression and contributes to retinal capillary cell apoptosis.
- Polyol pathway: Excess glucose flux through aldose reductase depletes cellular NADPH reserves, compromising antioxidant capacity and promoting osmotic and oxidative cellular stress.
- Poly (ADP-ribose) polymerase (PARP) activation: oxidative DNA damage triggers PARP overactivation, depleting cellular energy stores and exacerbating retinal cell dysfunction.
- VEGF-mediated angiogenesis: upregulated VEGF expression drives both vascular hyperpermeability and pathological neovascularization, representing the principal therapeutic target of current anti-VEGF interventions. Collectively, these pathways converge on a common end-point of progressive retinal microvascular compromise, underscoring the rationale for therapeutic strategies, such as flavonoid administration, capable of simultaneously modulating multiple nodes within this interconnected network.

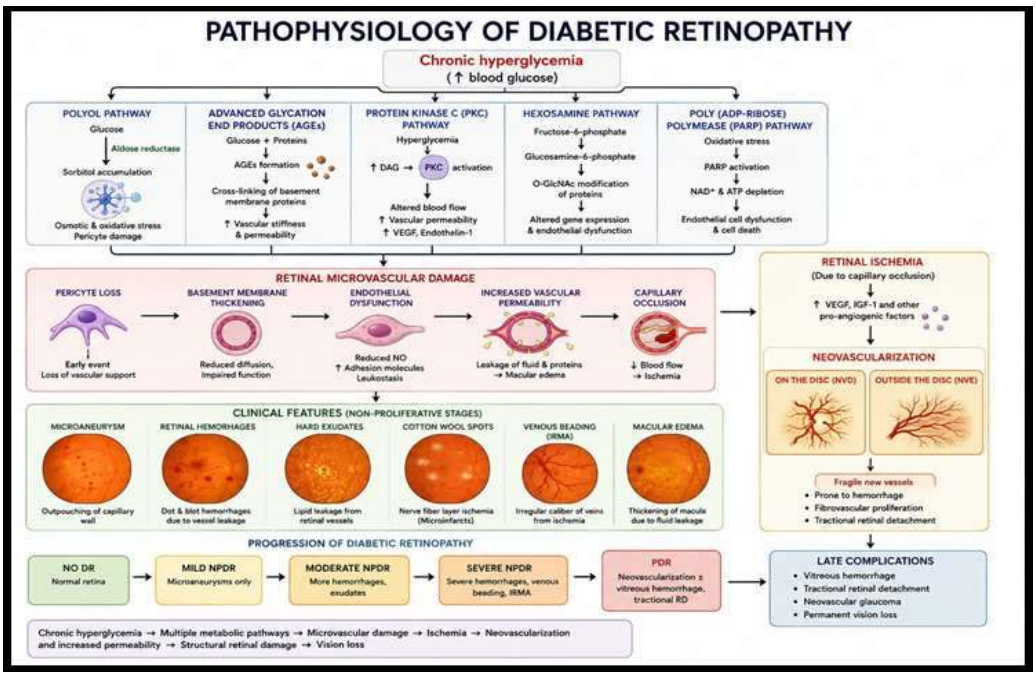


Fig. No. 5: Pathophysiology of Diabetic retinopathy

Role of Flavonoids In Diabetic Retinopathy Treatment

Given the multifactorial pathophysiology of diabetic retinopathy described above, flavonoids are particularly well suited as therapeutic candidates owing to their capacity to act simultaneously at several points within the disease cascade.

- **Neuroprotection:** Beyond their vascular effects, flavonoids exert direct neuroprotective actions on retinal ganglion and neuronal cells, limiting hyperglycemia-induced apoptotic cell death and thereby preserving retinal neuronal integrity, an aspect of diabetic retinopathy increasingly recognized as occurring in parallel with, and potentially preceding, overt microvascular damage.

- **Antioxidant:** Flavonoids mitigate hyperglycemia-induced oxidative stress within retinal endothelial cells through direct free-radical scavenging and enhancement of endogenous antioxidant defenses, thereby limiting the downstream activation of AGE- and PKC-dependent injury pathways.

- **Anti-inflammatory:** By suppressing NF-κB - mediated transcriptional activation, flavonoids reduce the release of pro-inflammatory cytokines and chemokines within retinal tissue, thereby attenuating the chronic low-grade inflammatory state that contributes to capillary dysfunction and leukocytosis.

- **Anti-angiogenic Effect:** Several flavonoid constituents have been shown to downregulate VEGF expression, thereby restricting the pathological neovascularization and vascular hyperpermeability that characterise proliferative diabetic retinopathy. This action parallels, and may potentially complement, the mechanism of existing anti-VEGF biological therapies.

Artificial Intelligence in Early Detection of Diabetic Retinopathy

Parallel to advances in phototherapeutic research, the application of artificial intelligence and machine learning methodologies has emerged as a transformative approach for the early and automated diagnosis of diabetic retinopathy from fundus photography. Hybrid computational frameworks combining deep learning architectures with optimisation-based feature selection have demonstrated considerable diagnostic promise. For example, models integrating a Restricted Boltzmann Machine for feature extraction, threshold-based U-Net architecture for retinal lesion segmentation, and a

Squirrel Search Algorithm for parameter optimization have been reported to achieve diagnostic accuracies approaching 99.2%, accompanied by high specificity and improved detection of subtle retinal abnormalities relative to conventional screening approaches. While such computational tools and the phytopharmacological strategies distinct domains of investigation, their convergence holds considerable translational promise. Artificial intelligence-based screening platforms could, in principle, facilitate earlier identification of at-risk patients, enabling timely initiation of adjunct phototherapeutic interventions such as flavonoid-based formulations before irreversible retinal damage occurs. Future interdisciplinary research integrating automated diagnostic screening with evidence-based natural product therapeutics may therefore offer a more comprehensive approach to diabetic retinopathy management.

Structure–Activity Relationship (SAR) Of Flavonoids

The pharmacological activity of flavonoids is closely governed by specific structural features of the flavonoid backbone, which collectively determine antioxidant potency, enzyme-binding affinity, and bioavailability:

- **Hydroxyl group substitution**: The number and position of hydroxyl groups on the flavonoid rings directly correlate with antioxidant capacity, as these groups serve as the primary site of hydrogen donation during free-radical neutralization.
- **Double bond conjugation:** The presence of a C2–C3 double bond in conjugation with a 4-oxo function stabilizes the resulting phenoxy radical following hydrogen donation, thereby enhancing overall radical-scavenging efficiency.
- **Glycoside substitution:** Glycosylation of flavonoid aglycones, while sometimes reducing intrinsic antioxidant potency, generally improves aqueous solubility and oral bioavailability, facilitating intestinal absorption and systemic distribution.

Representative flavonoid constituents identified in *Couroupita guianensis*, including quercetin, kaempferol, rutin, and pelargonidin, exemplify these structural principles and collectively underpin the plant's broad-spectrum pharmacological activity. A more detailed understanding of these structure–activity relationships may guide future efforts toward semi-synthetic optimization or targeted isolation of the most pharmacologically potent constituents.

CURRENT RESEARCH GAPS

Despite encouraging preclinical evidence, several substantial gaps remain in the current body of literature concerning *Couroupita guianensis* and its flavonoid constituents, which must be addressed before clinical translation can be considered:

- **Lack of human clinical trials:** The overwhelming majority of available evidence is derived from in vitro assays or rodent models, with no controlled clinical studies in human diabetic populations.
- **Limited retinal tissue–specific studies:** Direct experimental evidence demonstrating retinoprotective efficacy in retinal tissue or established diabetic retinopathy models remains scarce.
- **Poor extract standardization:** Variability in extraction solvents, plant part selection, and geographic or seasonal factors complicates reproducibility and comparison across studies.
- **Limited toxicity evaluation:** Comprehensive acute and chronic toxicological profiling of *Couroupita guianensis* extracts has not been systematically undertaken.
- **Lack of pharmacokinetic data:** Information regarding the absorption, distribution, metabolism, and excretion of the plant's bioactive flavonoids remains largely unavailable.
- **Limited molecular docking and in silico studies:** Computational investigations characterizing the precise binding interactions between individual flavonoids and target enzymes or receptors remain underexplored.

FUTURE PERSPECTIVES

Addressing the limitations outlined above will require a coordinated, multidisciplinary research agenda. Future investigations should prioritize the following directions:

- Isolation and characterization of individual flavonoid constituents to enable precise structure–activity and dose–response analyses.
- Development of nanoparticle-based or other novel drug delivery systems to enhance the bioavailability and target specificity of flavonoid compounds.
- Molecular docking and in silico screening against α-glucosidase and other relevant therapeutic targets to rationalize observed pharmacological activity.
- Design and execution of well-controlled clinical trials to validate efficacy and safety in human diabetic patients.
- Conduct of dedicated retinal tissue–based experimental studies to directly substantiate the proposed retinoprotective mechanisms.
- Evaluation of combination therapy approaches integrating flavonoid extracts with established conventional antidiabetic or anti-VEGF agents.

CONCLUSION

Long-term hyperglycemia remains the principal driver of diabetic retinopathy progression, acting through interconnected oxidative stress and inflammatory signaling pathways that culminate in retinal microvascular damage and vision loss. *Couroupita guianensis*, by virtue of its rich flavonoid content, represents a promising medicinal plant capable of concurrently targeting multiple nodes within the diabetic and retinopathic disease cascade. Preclinical experimental evidence to date indicates meaningful antidiabetic activity, robust antioxidant protection, preservation of pancreatic β-cell function, and a plausible mechanistic basis for the prevention of retinal vascular injury. Taken together, these findings support the considerable pharmaceutical potential of *Couroupita guianensis*-derived flavonoids; however, realization of this potential will depend on rigorous future research addressing standardization, toxicology, pharmacokinetics, and ultimately, clinical validation in human subjects.

REFERENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1): S1–S350.
2. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.
3. Michael Brownlee. The pathobiology of diabetic complications: a unifying mechanism. Nature. 2005; 414:813–820.
4. Roy Taylor. Type 2 diabetes: etiology and reversibility. Diabetes Care. 2013; 36:1047–1055.
5. Antonio Ceriello. Oxidative stress and diabetes-associated complications. Endor Pract. 2006;12(Suppl 1):60–62.
6. Michael Brownlee. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001; 414:813–820.
7. M. Porta. Diabetic retinopathy: pathogenesis and management. Lancet Diabetes Endocrinol. 2014; 2:1–12.
8. Tien Y. Wong, Chee Y. Cheung. Diabetic retinopathy. Nat Rev Dis Primers. 2016; 2:16012.
9. Renu A. Kowluru. Diabetic retinopathy: mitochondrial dysfunction and oxidative stress. Exp Diabetes Res. 2011; 2011:1–9.
10. P. K. Sharma, et al. Phytochemical and pharmacological profile of Couroupita guianensis. Pharmacogn Rev. 2015; 9:73–80.
11. M. R. Shah, et al. Medicinal properties of Couroupita guianensis: A review. J Pharmacogn Phytochem. 2018; 7:1200–1208.
12. J. C. Pradhan, et al. Ethnomedicinal uses and phytochemistry of Couroupita guianensis. J Ethnopharmacology. 2019; 231:1–15.
13. M. S. Elanchezhiyan, et al. Antidiabetic activity of methanolic flower extract of Couroupita guianensis in alloxan-induced diabetic rats. Pharmacogn Mag. 2015;11: S1–S8.
14. P. V. Rao, et al. Antioxidant and antihyperglycemic activity of Couroupita

guianensis. Asian Pac J Trop Biomed. 2013; 3:123–128.
15. M. K. Gupta, et al. Phytochemical constituents of Couroupita guianensis. Int J Pharm Sci Rev Res. 2016; 37:180–186.
16. A. L. Tapas, et al. Flavonoids as nutraceuticals: a review. Trop J Pharm Res. 2008; 7:1089–1099.
17. B. Salehi, et al. Therapeutic potential of flavonoids. Biomolecules. 2020; 10:1072.
18. M. Panche, et al. Flavonoids: an overview. J Nutr Sci. 2016;5: e47.
19. I. F. F. Benzie, S. Wachtel-Galor. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. CRC Press; 2011.
20. A. Scalbert, et al. Dietary polyphenols and health. Am J Clin Nutr. 2005; 81:215S–217S
21. M. K. Pandey, et al. Polyphenols and diabetes management. Oxid Med Cell Longev. 2019; 2019:1–18.
22. S. Y. Kim, et al. α-Glucosidase inhibitory activity of flavonoids. Food Chem. 2005; 93:557–562.
23. M. Cazarolli, et al. Mechanisms of action of flavonoids in diabetes mellitus. Mini Rev Med Chem. 2008; 8:1032–1038.
24. S. S. Alam, et al. Flavonoids in diabetes and diabetic complications. Curr Med Chem. 2021; 28:1–20.
25. J. W. Yoon, et al. β-cell protection by natural antioxidants. Diabetes Metab Res Rev. 2017;33: e2891.
26. A. P. Kowluru. Role of oxidative stress in diabetic retinopathy. Exp Diabetes Res. 2010; 2010:1–12.
27. J. A. Frank, et al. VEGF signaling in diabetic retinopathy. Prog Retin Eye Res. 2015; 49:1–29.
28. A. Ting, et al. Artificial intelligence and deep learning in diabetic retinopathy screening. Lancet Digit Health. 2019;1: e36–e48.
29. V. Gulshan, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy. JAMA. 2016; 316:2402–2410.
30. M. D. Abramoff, et al. Pivotal trial of an autonomous AI-based diagnostic system for diabetic retinopathy. NPJ Digit Med. 2018; 1:39.

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