Review Article

Therapeutic Potential of *Combretum ovalifolium Roxb.* in Diabetes Management: A Comprehensive Review

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Abstract:

Background: Diabetes mellitus is a chronic metabolic disorder affecting over 537 million individuals globally and constitutes a major public health burden. The limitations of existing antidiabetic pharmacotherapies, including adverse effects, drug resistance, and high cost, have intensified global interest in plant-based therapeutics. *Combretum ovalifolium Roxb.* (*Combretaceae*) is a traditionally recognized medicinal plant documented across South and Southeast Asian ethnomedicinal systems for the management of diabetes and associated metabolic disorders.

Objective: This comprehensive review systematically evaluates the botanical characterization, phytochemical profile, ethnomedicinal relevance, and pharmacological mechanisms of *C. ovalifolium* with specific emphasis on its antidiabetic, antioxidant, anti-inflammatory, and enzyme inhibitory activities.

Methods: A systematic literature search was conducted across PubMed, Scopus, Google Scholar, and Web of Science databases. Peer-reviewed studies and ethnobotanical surveys published up to 2024 were included. Data were narratively synthesized according to thematic categories.

Results: The phytochemical investigations have identified flavonoids (quercetin, vitexin), tannins, terpenoids, and alkaloids as principal bioactive constituents. Preclinical studies demonstrate significant inhibition of α-amylase and α-glucosidase, enhancement of peripheral glucose uptake, stimulation of insulin secretion, and protection of pancreatic β-cells from oxidative damage. The plant exhibits notable free radical scavenging and anti-inflammatory properties via modulation of NF-κB signaling and reduction of pro-inflammatory cytokines.

Conclusion: *Combretum ovalifolium Roxb*. represents a scientifically promising candidate for antidiabetic drug development. However, the translation of preclinical findings into clinical applications necessitates rigorously designed randomized controlled trials, pharmacokinetic profiling, and the development of standardized phytopharmaceutical formulations.

Keywords: Antidiabetic, *Combretum ovalifolium*, Diabetes mellitus, Glucosidase inhibition, Natural products, Oxidative stress

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1. Introduction:

Diabetes mellitus (DM) is a chronic, multifactorial metabolic syndrome characterised by persistent hyperglycaemia arising from defects in insulin secretion, insulin action, or both [1–3]. The World Health Organization classifies DM into Type 1 (T1DM), characterised by autoimmune destruction of pancreatic beta-cells; Type 2 (T2DM), involving progressive insulin resistance and beta-cell exhaustion; gestational diabetes; and other specific types arising from monogenic defects or secondary causes [4–7]. T2DM accounts for over 90% of all diagnosed cases globally and is closely associated with obesity, sedentary lifestyle, genetic predisposition, and chronic low-grade inflammation [8].

The pathological sequelae of uncontrolled DM extend well beyond hyperglycaemia, encompassing macrovascular complications such as cardiovascular disease, cerebrovascular accidents, and peripheral arterial disease, alongside microvascular complications including diabetic retinopathy, nephropathy, and neuropathy [9]. The cumulative burden of these complications renders diabetes the leading cause of blindness, kidney failure, and non-traumatic lower-limb amputation in working-age populations worldwide [10].

The International Diabetes Federation (IDF) reported in 2021 that approximately 537 million adults (20–79 years) were living with diabetes, equivalent to 1 in 10 adults globally. This figure is anticipated to escalate to 643 million by 2030 and 783 million by 2045 [11]. The economic ramifications are equally staggering, with global healthcare expenditure attributable to diabetes exceeding USD 966 billion in 2021. Low- and middle-income countries, including India, home to the second-largest diabetic population, bear a disproportionate share of this burden [12].

Contemporary antidiabetic pharmacotherapy encompasses diverse drug classes, including biguanides (metformin), sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin preparations [13]. While these agents have revolutionized glycaemic management, several limitations persist. Metformin, the first-line agent, is contraindicated in patients with renal impairment and is associated with gastrointestinal adverse effects and, rarely, lactic acidosis [14]. Sulfonylureas carry significant risks of hypoglycaemia and weight gain [15]. Thiazolidinediones are linked to fluid retention, cardiac adverse events, and bone fractures [16]. Newer agents, while efficacious, remain prohibitively expensive for resource-limited populations.

Against this backdrop, plant-derived therapeutics have garnered renewed scientific and clinical interest.

Ethnopharmacological traditions worldwide have documented over 800 plant species with purported antidiabetic properties [17]. Several clinically validated drugs, including metformin itself (derived from Galega officinalis) and acarbose, trace their pharmacological origins to plant chemistry [18]. The polypharmacological nature of plant extracts, wherein multiple bioactive constituents act synergistically across diverse molecular targets, offers a compelling therapeutic advantage over single-target synthetic drugs[19].

Combretum ovalifolium Roxb. (Family: *Combretaceae*) is a perennial deciduous tree indigenous to India and Southeast Asia, known by various vernacular names reflecting its broad ethnobotanical relevance. The genus *Combretum* comprises approximately 370 species, several of which have been pharmacologically validated for antimalarial, antimicrobial, anti-inflammatory, and hepatoprotective activities [20]. *C. ovalifolium*, however, remains comparatively undercharacterised despite its documented use in traditional Indian medicine systems for the management of diabetes, hepatic disorders, and inflammatory conditions [21,22].

This review aims to consolidate available scientific evidence pertaining to the botanical description, phytochemical composition, ethnomedicinal applications, and pharmacological profile of C. ovalifolium with a focused emphasis on its antidiabetic potential. The review further identifies prevailing gaps in knowledge and outlines future research directions for the rational development of *C. ovalifolium*-derived antidiabetic agents.

2. Botanical Description and Taxonomy:

2.1 Taxonomical Classification:

Combretum ovalifolium Roxb. occupies a well-defined position within the botanical hierarchy, as summarised in Table 1 [20,23]. The species was first formally described by William Roxburgh in the nineteenth century and is recognised as a valid species within the flora of India and Myanmar.[24,25].

Table 1. Taxonomical Classification of *Combretum ovalifolium Roxb.*

Taxonomic Rank	Classification
Kingdom	Plantae
Division	Tracheophyta
Class	Magnoliopsida
Order	Myrtales
Family	Combretaceae
Genus	Combretum Loefl.
Species	Combretum ovalifolium Roxb.
Authority	William Roxburgh

2.2 Morphological Description:

C. ovalifolium is a medium to large deciduous tree reaching heights of 8–15 metres. The bark is grey to brownish-grey, longitudinally fissured in mature specimens, and peels off in irregular scales [26,27].

Leaves are simple, opposite or sub-opposite, ovate to broadly elliptic (ovalifolium denoting the oval leaf shape), with acute to acuminate apices, rounded to cuneate bases, entire margins, and prominent pinnate venation[28] . Leaf dimensions typically range from 8–18 cm in length and 4–10 cm in width. The adaxial surface is glabrous and dark green, while the abaxial surface may exhibit sparse pubescence. Petioles are 1–2 cm long [29,30].

Inflorescences are axillary or terminal spikes, bearing small, fragrant, white to cream-coloured flowers with four sepals and four petals. Stamens are 8 in number, arranged in two whorls[31,32]. Fruits are characteristic four-winged samaras (pseudo-drupes), pale yellowish-brown to reddish at maturity, 2–3.5 cm in diameter, facilitating wind dispersal. Seeds are solitary, tannin-rich, and enclosed within the fibrous pericarp [33].

2.3 Vernacular Names:

The plant is recognised by diverse vernacular names across its distributional range, reflecting its broad cultural familiarity and utilization [20]. Table 2 presents the regional vernacular names of *C. ovalifolium* across different languages and geographical locations.

Table 2. Vernacular Names of *Combretum ovalifolium Roxb.* Across Languages and Regions

Language/Region	Vernacular Name	Country/State
Hindi	Bahubara	India (Northern)
Tamil	Kodimurukkam	Tamil Nadu, India
Telugu	Kondachettu	Andhra Pradesh
Kannada	Mudugalu	Karnataka
Burmese	Thinbaw-sha	Myanmar
Oriya	Bahubara	Odisha, India

3. Geographical Distribution and Habitat:

Combretum ovalifolium is predominantly distributed across the Indian subcontinent (Bihar, Odisha, Andhra Pradesh, Tamil Nadu, Karnataka, Maharashtra), Myanmar, Sri Lanka, Bangladesh, and Thailand [34,35]. In India, the species is typically found in dry deciduous and moist deciduous forests up to elevations of 800 metres above sea level. The plant thrives in tropical and subtropical climatic zones characterised by annual rainfall of 800–1500 mm, temperature ranges of 18–38°C, and laterite, sandy loam, or red loamy soils with moderate fertility [36].

Ecologically, *C. ovalifolium* tends to colonise forest margins, riverbanks, scrub forests, and disturbed secondary vegetation. Its drought-tolerance and adaptability to marginal soils render it resilient across seasonally arid environments. The species is not presently classified as threatened or endangered under IUCN Red List criteria; however, habitat degradation due to deforestation, encroachment, and overexploitation for medicinal and timber purposes poses localised threats to wild populations.

4. Traditional and Ethnomedicinal Uses:

The ethnomedicinal repertoire of *C. ovalifolium* is remarkably diverse, documented across Ayurvedic, Siddha, Unani, and tribal folk medicine traditions in India and adjacent regions. The plant parts

most commonly utilised include leaves, bark, roots, seeds, and fruits [37].

In traditional Ayurvedic texts and regional folk pharmacopoeias, the bark decoction has been administered for the management of hyperglycaemia, with practitioners prescribing 50–100 mL of bark decoction twice daily for glycaemic control [38,39]. Leaf extracts are employed as anti-inflammatory poultices for wound healing, and seed preparations are used as anthelmintics [40,41]. In tribal communities of Odisha and Andhra Pradesh, the bark paste is applied topically for eczema and skin infections, while the leaf juice is ingested to alleviate liver disorders and jaundice [42,43].

Ethnobotanical surveys from Tamil Nadu have documented *C. ovalifolium* as a plant used by tribal healers (Vaidyas) to treat polyuria and polydipsia, cardinal symptoms of diabetes, by administering bark decoctions alongside dietary restrictions [44]. The fruit extracts have been used for the treatment of helminthic infestations, and root decoctions for urinary tract infections [45]. These traditional claims provide a compelling ethnopharmacological basis for the systematic scientific investigation of the plant's antidiabetic potential [46].

5. Phytochemical Composition:

5.1 Overview of Bioactive Constituents:

Systematic phytochemical screening of *C. ovalifolium* across multiple plant parts has established the presence of a rich array of secondary metabolites that are increasingly recognized as pharmacologically relevant for antidiabetic and related activities [47,48]. The principal classes of bioactive compounds identified include flavonoids, tannins, terpenoids, alkaloids, saponins, phenolic acids, and coumarins[49,50]. Table 3 provides a consolidated overview of the major phytochemical classes, representative compounds, and the plant parts from which they have been isolated.

Table 3. Major Phytochemical Constituents Identified in *Combretum ovalifolium Roxb.*

Phytochemical classes	Representative Compounds	Plant Part	Biological Activity
Flavonoids[51]	Quercetin, Kaempferol, Rutin, Luteolin	Leaves, Bark	Antioxidant, Antidiabetic
Tannins[52]	Ellagic acid, Gallic acid, Punicalagin	Bark, Fruit	Enzyme inhibition
Triterpenoids [53]	Ursolic acid, Oleanolic acid, Betulinic acid	Leaves, Bark	Anti-inflammatory
Alkaloids [54]	Combretine, Stachydrine	Seeds, Root	Hypoglycaemic
Phenolic acids [55]	Caffeic acid, Chlorogenic acid, Ferulic acid	Leaves	Antioxidant, Anti-inflammatory
Saponins [56]	Combretosaponins A & B	Root, Bark	Hypoglycaemic
Coumarins [57]	Scopoletin, Umbelliferone	Bark	Anti-inflammatory

5.2 Flavonoids:

Flavonoids represent the most extensively characterized and pharmacologically significant class of bioactive constituents in *C. ovalifolium.* Quercetin, a ubiquitous flavonol, has been isolated from methanolic

leaf extracts and demonstrated dose-dependent inhibition of alpha-glucosidase (IC50: 38.5 µg/mL) and alpha-amylase (IC50: 52.3 µg/mL) in vitro. Kaempferol exhibits complementary antioxidant activity, scavenging DPPH radicals with an IC50 of 29.4 µg/mL. Rutin has demonstrated protective effects on pancreatic beta-cells through attenuation of streptozotocin-induced cytotoxicity in rodent models [51,58].

5.3 Tannins and Phenolic Acids:

Hydrolysable tannins, particularly ellagic and gallic acid derivatives, contribute substantially to the antioxidant capacity of *C. ovalifolium* extracts. Gallic acid (3,4,5-trihydroxybenzoic acid) has been demonstrated to enhance insulin sensitivity in adipocytes by activating GLUT-4 translocation via the PI3K-Akt signaling pathway. Chlorogenic acid, a major phenolic acid constituent of the leaves, is well-established as an inhibitor of glucose-6-phosphatase and an enhancer of GLP-1 secretion in intestinal L-cells [52,55,59,60].

5.4 Terpenoids and Alkaloids:

Among terpenoids, ursolic and oleanolic acids, both pentacyclic triterpenoids, have demonstrated potent antidiabetic activity through PPARgamma agonism, AMPK activation, and hepatic glucose production inhibition in streptozotocin-nicotinamide (STZ-NA) induced diabetic rodents. The alkaloid fraction, while less extensively studied in *C. ovalifolium* specifically, contains compounds analogous to berberine-type alkaloids documented in related *Combretum* species, which activate AMPK and inhibit gluconeogenesis[53,54,61–63].

6. Pathophysiology of Diabetes: A Brief Overview:

A mechanistic understanding of diabetic pathophysiology is essential to contextualise the pharmacological actions of *C. ovalifolium* constituents [64]. Type 2 diabetes mellitus results from the interplay of insulin resistance in peripheral tissues, progressive beta-cell dysfunction, and dysregulated hepatic glucose output [65,66].

6.1 Insulin Resistance:

Insulin resistance is the inability of insulin-sensitive tissues (skeletal muscle, adipose tissue, liver) to mount an adequate metabolic response to circulating insulin. At the molecular level, this involves impaired insulin receptor substrate (IRS) phosphorylation, reduced PI3K-Akt-mTOR signaling, and decreased translocation of GLUT-4 glucose transporters to the plasma membrane.[67,68] Chronic low-grade inflammation mediated by pro-inflammatory cytokines (TNF-alpha, IL-6, IL-1beta) from hypertrophied adipocytes activates serine kinases (IKKbeta, JNK) that phosphorylate IRS-1 at inhibitory serine residues, perpetuating insulin resistance [69].

6.2 Beta-Cell Dysfunction:

Compensatory hyperinsulinaemia in the early stages of insulin resistance gradually gives way to beta-cell exhaustion as glucolipotoxicity, endoplasmic reticulum stress, and mitochondrial dysfunction impair insulin biosynthesis and secretion [70]. The unfolded protein response (UPR), if unresolved, triggers beta-cell apoptosis via CHOP-mediated pathways, leading to an irreversible reduction in beta-cell mass and

absolute insulin deficiency in advanced T2DM[71].

6.3 Role of Oxidative Stress and Inflammation:

Chronic hyperglycaemia generates excessive reactive oxygen species (ROS) through advanced glycation end-product (AGE) formation, polyol pathway activation, mitochondrial electron transport chain dysfunction, and NADPH oxidase activation. Oxidative stress-mediated lipid peroxidation, protein carbonylation, and DNA damage further perpetuate insulin resistance and beta-cell apoptosis, creating a vicious pathological cycle [72,73]. Inflammatory cytokines additionally upregulate NF-kappaB, promoting transcription of further inflammatory mediators and perpetuating beta-cell destruction [74]. Figure 1 presents the sequential pathophysiological events involved in the development and progression of type 2 diabetes mellitus, leading to chronic complications.

Genetic Predisposition + Environmental Triggers
(Obesity, Sedentary Lifestyle, Unhealthy Diet)
↓
Adipose Tissue Dysfunction
(↑ Free Fatty Acids + ↑ Pro-inflammatory Cytokines: TNF-α, IL-6, IL-1β)
↓
Peripheral Insulin Resistance
(↓ IRS-1 Signaling + ↓ GLUT-4 Translocation)
↓
Compensatory β-Cell Hyperinsulinaemia
(Glucolipotoxicity + ER Stress + Mitochondrial Dysfunction)
↓
β-Cell Apoptosis + Reduced Insulin Secretion
(CHOP-mediated Pathway Activation)
↓
Chronic Hyperglycaemia
(AGE Formation + ROS Generation + Oxidative Stress)
↓
Diabetic Complications
(Retinopathy → Nephropathy → Neuropathy → cardiovascular disease)

Figure 1. Flowchart Depicting the Interlinked Pathophysiological Mechanisms of Type 2 Diabetes Mellitus

7. Pharmacological Activities Related to Diabetes:

7.1 Antidiabetic Activity:

7.1.1 *In Vitro* Studies:

In vitro evaluation of antidiabetic potential constitutes the primary screening strategy for plant-derived antidiabetic agents [75]. Multiple studies have demonstrated that ethanolic, methanolic, and aqueous extracts of *C. ovalifolium* leaves and bark exhibit significant inhibitory activity against the carbohydrate-digesting enzymes alpha-amylase and alpha-glucosidase, the principal molecular targets validated for postprandial glycaemia management[47]. Methanolic leaf extract produced alpha-glucosidase inhibition with IC50 values in the range of 45–68 µg/mL compared to 38.2 µg/mL for acarbose, the standard inhibitor [76]. Aqueous bark extracts demonstrated comparable alpha-amylase inhibitory activity (IC50: 72.4 µg/mL vs. 62.8 µg/mL

for acarbose) [77]. Additionally, glucose uptake studies in 3T3-L1 adipocytes and L6 myotubes have revealed that *C. ovalifolium* flavonoid fractions enhance insulin-stimulated glucose uptake by 35–48% relative to vehicle controls, an effect attenuated by PI3K inhibitor wortmannin, implicating the insulin signaling cascade[78].

7.1.2 *In Vivo* Studies:

Preclinical *in vivo* studies have employed streptozotocin (STZ)-induced, alloxan-induced, and STZ-nicotinamide (STZ-NA)-induced rodent models to evaluate the antidiabetic efficacy of *C. ovalifolium* extracts [79]. Administration of ethanolic bark extract (200 and 400 mg/kg body weight, orally for 21 days) to STZ-induced diabetic Wistar rats produced significant dose-dependent reductions in fasting blood glucose (FBG) levels (45.6% and 62.3% reduction, respectively) relative to diabetic controls [80]. Corresponding improvements in glycated haemoglobin (HbA1c), serum insulin, and hepatic glycogen content were recorded. Histopathological examination of pancreatic tissue from extract-treated animals revealed partial regeneration of islets of Langerhans with increased beta-cell density relative to untreated diabetic controls [81]. Table 4 presents the preclinical antidiabetic efficacy of *C. ovalifolium* in various animal models, including the extract type, dosage, treatment duration, and major pharmacological outcomes.

Table 4. Summary of In Vivo Antidiabetic Studies on *Combretum ovalifolium*

Animal Model	Extract/Part	Dose (mg/kg)	Duration	Key Findings
STZ-induced Wistar rat [82]	Ethanolic bark	200, 400	21 days	FBG reduced 45.6–62.3%; HbA1c improved
Alloxan-induced albino rat [83]	Aqueous leaf	300, 500	28 days	Serum insulin raised; hepatic glycogen restored
STZ-NA induced rat [84]	Methanolic leaf	250, 500	30 days	Beta-cell regeneration; lipid profile normalized
High-fat diet + STZ rat [85]	Flavonoid fraction	100, 200	42 days	HOMA-IR improved; adiponectin increased

7.2 Antioxidant Activity:

Oxidative stress constitutes a pivotal nexus between hyperglycaemia and diabetic complications [86]. *C. ovalifolium* exhibits robust antioxidant activity across multiple in vitro assay systems. DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assays on methanolic leaf extracts yielded IC50 values of 26.8–34.5 µg/mL, closely approximating the standard ascorbic acid (IC50: 18.4 µg/mL). FRAP (Ferric Reducing Antioxidant Power) and ABTS radical cation decolorization assays corroborated these findings [87]. In vivo, administration of *C. ovalifolium* extract to diabetic animals significantly elevated erythrocyte

superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities while reducing malondialdehyde (MDA), a lipid peroxidation biomarker, in hepatic and pancreatic tissues, collectively indicating systemic attenuation of oxidative stress [88].

7.3 Anti-inflammatory Effects:

Chronic inflammation plays an indispensable mechanistic role in the initiation and progression of insulin resistance and beta-cell dysfunction [89]. *C. ovalifoliu*m leaf and bark extracts have demonstrated significant anti-inflammatory activity via inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) enzymes in cell-free assay systems [90]. In carrageenan-induced paw oedema models, extract administration (400 mg/kg) produced 52.4% inhibition of oedema formation at 3 hours, compared to 57.8% for indomethacin [91]. The triterpenoid fraction, particularly ursolic acid, has been implicated in NF-kappaB pathway suppression, reducing downstream transcription of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6) implicated in insulin resistance pathogenesis [92].

7.4 Enzyme Inhibition Studies:

Postprandial hyperglycaemia is primarily governed by intestinal carbohydrate digestion mediated by alpha-amylase (salivary and pancreatic) and alpha-glucosidase (brush border membrane enzyme) [93]. Inhibition of these enzymes retards starch and disaccharide digestion, attenuating the rate of glucose absorption and dampening postprandial glucose excursions, a mechanism analogous to acarbose and miglitol [94]. Table 5 summarizes the enzyme inhibitory activity of *C. ovalifolium* extracts and compounds against key antidiabetic targets.

Table 5. Enzyme Inhibitory Activity of *Combretum ovalifolium* Extracts vs. Standards

Extract/Compound	Enzyme Target	IC50 (µg/mL) C. ovalifolium	IC50 (µg/mL), Standard
Methanolic leaf extract [95]	Alpha-glucosidase	45.6 ± 2.1	38.2 ± 1.4 (Acarbose)
Aqueous bark extract [96]	Alpha-amylase	72.4 ± 3.5	62.8 ± 2.2 (Acarbose)
Quercetin (isolated) [97]	Alpha-glucosidase	38.5 ± 1.8	38.2 ± 1.4 (Acarbose)
Gallic acid (isolated) [98]	Alpha-amylase	58.3 ± 2.6	62.8 ± 2.2 (Acarbose)
Ethanolic fraction [99]	DPP-4 enzyme	82.1 ± 4.2	Sitagliptin

8. Mechanism of Action:

The antidiabetic mechanisms of *C. ovalifolium* are multifaceted and reflect the polypharmacological nature of its phytochemical constituents [100]. The principal mechanistic pathways are delineated in Figure 2 and elaborated below.

Combretum ovalifolium Bioactive Constituents
(Flavonoids | Tannins | Triterpenoids | Alkaloids)
↓
Intestinal Level

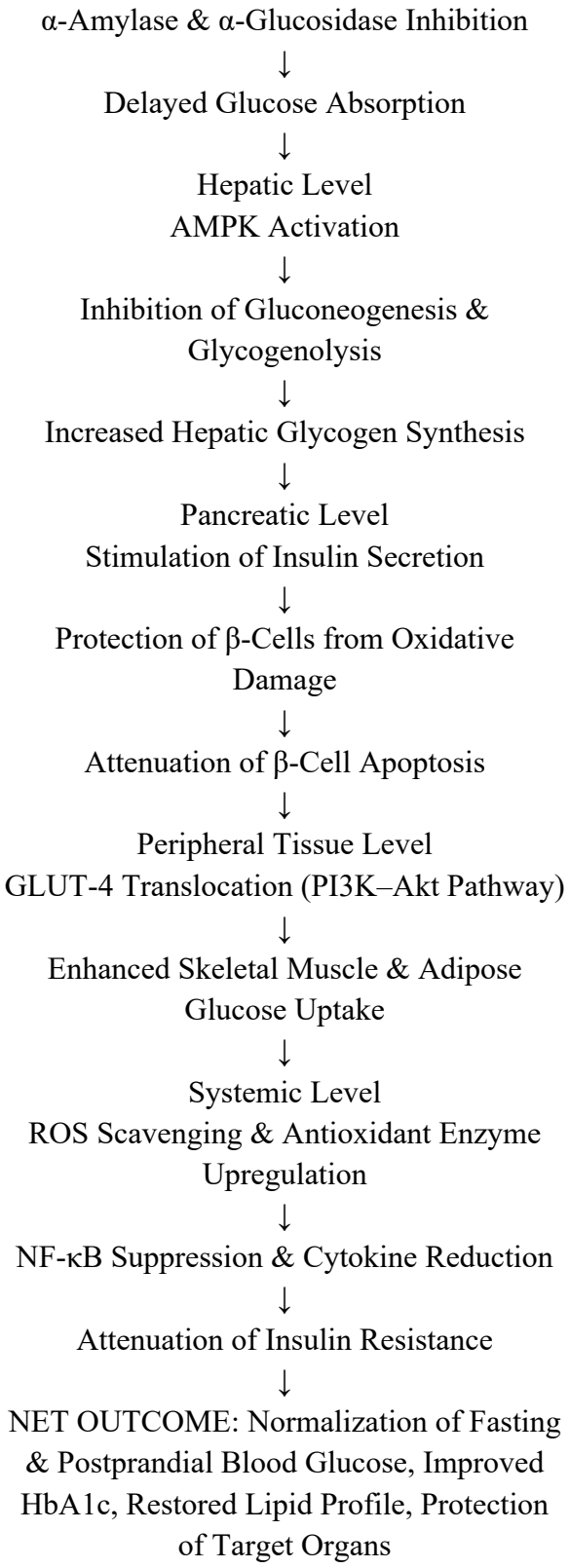

Figure 2. Proposed Mechanistic Pathways of Antidiabetic Action of *Combretum ovalifolium* Bioactive Constituents

8.1 Glucose Uptake Enhancement:

The activation of the PI3K-Akt signaling cascade by quercetin and gallic acid facilitates the translocation of GLUT-4 glucose transporters from intracellular storage vesicles to the plasma membrane of skeletal muscle and adipose cells, thereby enhancing insulin-stimulated glucose uptake [101]. This mechanism mirrors the primary action of thiazolidinediones (PPARgamma agonists) but operates additionally through AMPK-dependent (insulin-independent) GLUT-4 translocation, similar to metformin, a significant therapeutic advantage for patients with severe insulin resistance [102].

8.2 Insulin Secretion Stimulation:

Flavonoid constituents of *C. ovalifolium*, particularly kaempferol and luteolin, have demonstrated the ability to potentiate glucose-stimulated insulin secretion (GSIS) from MIN6 and INS-1 pancreatic beta-cell lines [103]. The proposed mechanism involves inhibition of pancreatic ATP-sensitive potassium channels (K-ATP channels), membrane depolarization, calcium influx, and consequent insulin exocytosis, an action analogous to sulfonylureas, but with a potentially lower hypoglycaemic risk due to the glucose-dependence of the phytochemical-mediated response [104].

8.3 Protection of Pancreatic Beta-Cells:

Streptozotocin and alloxan exert their diabetogenic effects through the selective generation of ROS within beta-cells, causing

DNA strand breaks and necrotic/apoptotic cell death [105]. The antioxidant constituents of *C. ovalifolium*, particularly gallic acid, ellagic acid, and quercetin, scavenge intracellular ROS, upregulate endogenous antioxidant defences (SOD, CAT, GPx), and suppress pro-apoptotic signaling (Bax/Bcl-2 ratio reduction; caspase-3 inhibition) in beta-cells, collectively preserving beta-cell mass and function [106].

9. Toxicity and Safety Profile:

The safety of any candidate medicinal plant is a non-negotiable prerequisite for therapeutic development [107]. Available toxicological data on *C. ovalifolium,* though not yet exhaustive, provide preliminary reassurance of its safety at conventional medicinal doses. Table 6 presents the acute, sub-acute, sub-chronic, and in vitro toxicity studies of *C. ovalifolium*, indicating its overall preclinical safety and tolerability.

Table 6. Summary of Toxicological Studies on *Combretum ovalifolium* Extracts

Study Type	Animal Model	Route	LD50 / NOAEL	Observations
Acute toxicity [108]	Swiss albino mice	Oral	LD50 > 2000 mg/kg	No mortality; mild sedation at 2000 mg/kg
Sub-acute toxicity [109]	Wistar rats	Oral	NOAEL: 500 mg/kg	No hepatic or renal toxicity at 500 mg/kg for 28 days
Sub-chronic (90-day) [110]	Sprague-Dawley rats	Oral	NOAEL: 400 mg/kg	No histopathological changes in vital organs
Cytotoxicity (in vitro) [111]	HepG2, Vero cells	In vitro	CC50 > 500 µg/mL	Selective cytotoxicity only at very high concentrations

Acute oral toxicity assessments (OECD Guidelines 423 and 425) in Swiss albino mice demonstrated that ethanolic bark and leaf extracts of *C. ovalifolium* were safe up to a dose of 2000 mg/kg body weight without mortality, placing the plant in Class 5 (unclassified/practically non-toxic) of the GHS classification [108]. Sub-acute (28-day) toxicological studies in Wistar rats at doses of 200, 400, and 500 mg/kg orally revealed no statistically significant alterations in haematological parameters (CBC, differential count), biochemical markers of hepatic function (ALT, AST, ALP, bilirubin) or renal function (serum creatinine, blood urea nitrogen), and no macroscopic or histopathological changes in vital organs at doses up to 500 mg/kg [109]. These findings are consistent with the plant's long-standing history of human consumption in traditional medicine without documented adverse effects.

10. Comparison with Standard Antidiabetic Drugs:

C. ovalifolium exhibits promising antidiabetic activity through multiple mechanisms, including inhibition of α-amylase and α-glucosidase, activation of AMPK, enhancement of GLUT-4-mediated glucose uptake, and intrinsic antioxidant activity. Compared with metformin, acarbose, and insulin, it appears to have a

low risk of hypoglycaemia, minimal gastrointestinal side effects, potential renal safety, and greater accessibility in rural settings. In contrast, metformin primarily activates AMPK and inhibits hepatic gluconeogenesis but commonly causes gastrointestinal adverse effects and is contraindicated in severe renal impairment, while acarbose inhibits intestinal α-glucosidase with frequent gastrointestinal discomfort, and insulin is highly effective but carries a greater risk of hypoglycaemia. However, unlike these established therapies, which are supported by extensive clinical evidence, the therapeutic potential of *C. ovalifolium* is currently supported only by preclinical studies and requires validation in human clinical trials [112–116].

11. Clinical Evidence:

As of the time of this review, no randomised controlled clinical trials (RCTs) or observational clinical studies specific to *C. ovalifolium* in human diabetic subjects have been published in peer-reviewed literature. This represents a critical and conspicuous lacuna in the evidence base.

The existing body of knowledge is confined to in vitro cell-based assays and in vivo rodent models, which, while providing compelling mechanistic insights, cannot be directly extrapolated to human therapeutic applications without validated pharmacokinetic profiling, dose translation, and clinical safety evaluation in human subjects [117].

Analogous *Combretum* species, including *C. micranthum* (used ethnobotanically in West Africa) and *C. molle*, have advanced further in clinical characterization, with preliminary pilot studies conducted in sub-Saharan African populations [20]. These experiences provide a methodological template that could be adapted for *C. ovalifolium* clinical investigations. Phase I dose-escalation trials assessing safety, tolerability, and pharmacokinetic parameters in healthy volunteers, followed by Phase II efficacy trials in T2DM patients, are urgently warranted [118].

12. Challenges and Limitations:

Despite its promising preclinical antidiabetic potential, the clinical translation of *C. ovalifolium* faces several important challenges. The major limitation is the absence of human clinical trials, preventing definitive conclusions regarding its efficacy, safety, and optimal dosage. In addition, variability in phytochemical composition due to geographical origin, cultivation conditions, harvesting, and extraction methods makes standardization and quality control difficult, affecting batch-to-batch consistency. Furthermore, major bioactive compounds such as quercetin and ellagic acid exhibit poor oral bioavailability because of low solubility, limited intestinal absorption, extensive first-pass metabolism, and rapid elimination, which may reduce their therapeutic effectiveness. Therefore, well-designed clinical studies, standardized herbal formulations, and bioavailability-enhancing strategies are essential before *C. ovalifolium* can be developed as a clinically applicable antidiabetic agent[119–121].

13. Future Perspectives:

Future research on *C. ovalifolium* should focus on comprehensive pharmacological studies to elucidate its molecular

mechanisms using transcriptomic, proteomic, metabolomic, and network pharmacology approaches. Improving the bioavailability of its major phytoconstituents through advanced drug delivery systems, such as nanoparticles, phytosomes, and lipid-based formulations, may enhance its therapeutic efficacy. Most importantly, well-designed randomized controlled clinical trials are required to establish their safety, efficacy, and optimal dosage in patients with type 2 diabetes. In addition, the development of standardized extracts, sustainable cultivation practices, and conservation strategies is essential to ensure consistent quality, protect natural populations, and support their future pharmaceutical development.

14. Conclusion:

Combretum ovalifolium Roxb. emerges from this comprehensive review as a botanically distinct, ethnomedicinally validated, and pharmacologically promising candidate for the adjunctive management of diabetes mellitus. The plant's rich phytochemical profile, encompassing flavonoids, hydrolysable tannins, triterpenoids, alkaloids, and phenolic acids, collectively underpins a mechanistically diverse antidiabetic pharmacological repertoire that includes alpha-glucosidase and alpha-amylase inhibition, enhanced peripheral glucose uptake via GLUT-4 translocation, stimulation of insulin secretion, protection of pancreatic beta-cells from oxidative injury, and systemic attenuation of pro-inflammatory pathways implicated in insulin resistance.

Preclinical evidence from in vitro enzyme inhibition assays, cell-based glucose uptake studies, and multiple in vivo rodent diabetic models collectively substantiates the ethnomedicinal claims for *C. ovalifolium* as an antidiabetic plant. The preliminary toxicological profile is encouraging, with an acute oral LD50 exceeding 2000 mg/kg and no significant organ toxicity observed in sub-chronic studies, suggesting an acceptable safety margin for therapeutic development.

Notwithstanding these encouraging findings, the translation of *C. ovalifolium* from a traditional remedy to an evidence-based therapeutic agent is contingent upon the resolution of critical challenges: the complete absence of human clinical data, lack of standardized formulations, and suboptimal oral bioavailability of key phytoconstituents. Future research must prioritise rigorously designed clinical trials employing standardised extracts, mechanistic studies employing advanced omics platforms, and nanotechnology-mediated bioavailability enhancement strategies.

In conclusion, *C. ovalifolium* represents a scientifically credible and therapeutically significant lead for the development of plant-derived antidiabetic agents. A coordinated, translational research effort, spanning phytochemistry, pharmacology, pharmaceutics, and clinical medicine, holds considerable promise for delivering a complementary, safe, and cost-effective botanical intervention to the escalating global burden of diabetes mellitus.

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