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Review Article

Exploring the Mechanisms and Therapeutic Potential of *Rhus chinensis* Mill in Managing Type 2 Diabetes Mellitus: A Comprehensive Review

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ABSTRACT

The ethnomedicinal plant *Rhus chinensis* Mill., used extensively throughout Asia, has drawn scientific interest due to its potential use in treating Type 2 Diabetes Mellitus (T2DM). This comprehensive review investigates the molecular pathways, bioactive components, and therapeutic potential of *R. chinensis* in glycemic control and metabolic regulation. The study synthesizes phytochemical analyses, recent *in vitro* and *in vivo* research, and current scientific insights to identify gaps in translational research. Phytochemical profiling reveals a rich presence of gallotannins, phenolic acids, flavonoids, and triterpenoids with strong anti-inflammatory, enzyme-modulatory, and antioxidant properties. Recent studies indicate antidiabetic effects through mechanisms such as increasing insulin sensitivity, inhibiting hepatic gluconeogenesis, promoting glucose uptake through AMPK activation, and inhibiting α-glucosidase and α-amylase. Evidence also suggests benefits regarding dyslipidemia, inflammation, and gut microbial modulation. *R. chinensis* emerges as a compelling natural candidate for integrative T2DM management; however, well-designed clinical trials are needed to validate efficacy, optimize dosing, and ensure long-term safety.

Keywords: α-glucosidase, antioxidant, DPP-IV, *Galla chinensis*, polyphenols, *Rhus chinensis*, type 2 diabetes mellitus.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), which is marked by increasing prevalence, substantial morbidity, and huge socioeconomic costs, has become one of the most urgent global public health issues. Chronic inflammatory disease, oxidative stress, dyslipidemia, and increasing end-organ damage are among the metabolic dysregulations linked to type 2 diabetes, which is characterized by persistent hyperglycemia brought on by a combination of insulin resistance and insufficient pancreatic β-cell production. There were an estimated 445 million people with type 2 diabetes globally in 2020, according to recent estimates, and this figure is expected to increase significantly over the next several decades. By 2050, the burden is predicted to reach 730 million if current prevalence rates stay the same; alternate scenarios indicate significantly larger burdens under adverse trends (Guzman-Vilca and Carrillo-Larco, 2024). Global dietary changes, obesity, sedentary lifestyles, urbanization, and population aging are the main causes of this growth (Yu *et al*., 2025). The frequency of problems connected to type 2 diabetes is rising in tandem with the prevalence. The global incidence of Chronic Kidney Disease (CKD) linked to Type 2 Diabetes (T2DM) has more than doubled since 1992; in 2021 alone, 2.01 million new cases of CKD T2DM were reported. Instead of only increasing incidence, a large portion of this growth is ascribed to demographic changes, such as aging populations and longer life expectancies (Cao *et al*., 2025). Other significant causes of the illness burden include metabolic comorbidities, peripheral vascular disease, retinopathy, neuropathy, and cardiovascular disease (Mahe *et al*., 2024). Although new therapeutic approaches have been launched in recent years, obstacles still exist in the management of type 2 diabetes. Although metformin as a first-line treatment is still useful, new guidelines place more emphasis on early combination therapy, especially for patients with increased cardiovascular or renal risk, in order to meet glycemic targets more quickly and prevent long-term complications (IDF, 2025). Because of their dual benefits on glycemia and cardiorenal protection, novel medicines like Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are being incorporated earlier in treatment algorithms (Caturano *et al*., 2025). Beyond medication, lifestyle changes continue to

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be essential: losing weight, improving one's diet, getting more exercise, and lowering modifiable risk factors like obesity and poor diet are all crucial for management and prevention. However, there are many obstacles to adherence to lifestyle therapies, such as the intricacy of dietary recommendations, financial limitations, a lack of patient education, and a low use of digital health tools or mobile health (mHealth) applications (Alrasheeday *et al*., 2024; Dsouza SM *et al*., 2024). Furthermore, self-management becomes more difficult even in cases when medical access is good due to the interaction of comorbidity, psychological variables, and treatment load (Rana *et al*., 2022; Padma and Abdul, 2024).

R. chinensis Mill. or Chinese sumac (*Anacardiaceae*), has a long history in East Asian traditional medicine and is gaining attention from scientists as a source of bioactive polyphenols that may have metabolic advantages. Gallotannins, gallic acid, and other phenolic compounds with tenable molecular connections to glycemic control (e.g., enzyme inhibition, antioxidant, and anti-inflammatory activities) are abundant in *R. chinensis* fruits and galls, according to contemporary phytochemical investigations (Figure 1). Preclinical research suggests a number of ways that *R. chinensis* extracts may improve important pathophysiological aspects of type 2 diabetes. Intestinal α-glucosidase, which reduces postprandial glucose excursions, was strongly inhibited in early enzyme-targeted studies. Later fractionation work showed inhibitory activity against both α-glucosidase and DPP-IV, indicating dual effects on incretin metabolism and carbohydrate digestion (Liu *et al*., 2021). Improvements in fasting glycaemia, insulin signalling, and hepatic glycolipid dysregulation are reported by additional *in vivo* studies in diet and chemically induced rodent models. Transcriptomic/protein data implicate the AMPK, IRS1/PI3K/AKT, and SREBP-1 pathways (Liu *et al*., 2023). All of these findings point to a multi-targeted pharmacology that may be useful in the treatment of Type 2 Diabetes (T2D): inhibition of digestive enzymes, modification of antioxidant/anti-inflammatory responses, and enhancement of hepatic insulin signalling.

There is still very little clinical evidence, despite encouraging mechanistic and animal findings demonstrating the glycemic and metabolic advantages of polyphenol-rich fruit extracts in mice and biochemical models. Before suggesting *R. chinensis* as a treatment or nutraceutical for individuals with type 2 diabetes, it is necessary to fill in the gaps in the existing research, which is primarily preclinical, diverse in terms of extract type and dosage, and frequently devoid of standardized phytochemical characterisation or long-term safety data. Therefore, standardized extracts, dose-finding, safety monitoring, and well-designed human pharmacokinetic and randomized controlled studies are of utmost importance. In light of these difficulties, studies have increasingly concentrated on early prognosis, individualized treatment plans, and holistic care models in addition to new therapies. Better knowledge of the pathophysiological foundations (genetic, epigenetic, and environmental) and advancements in predictive modelling (e.g., integrating clinical risk factors, artificial intelligence) are encouraging and could aid in bridging the gap between scientific discovery and clinical implementation (Ghosh *et al*., 2025). The burden of type 2 diabetes is quickly increasing and is a complex, multifaceted disease. Gaps in management, access, and putting knowledge into practice still exist despite advancements in prevention and therapy. This lays the groundwork for investigating supplemental treatments, such as plant-derived substances like *R. chinensis*, whose multi-mechanistic potential may enhance current approaches to lessen the course and severity of disease (Clemente-Suárez *et al*., 2025).

METHODOLOGY

A thorough review of literature was conducted using various research databases, including Scopus, Web of Science, Google Scholar, Science Direct, and PubMed. Relevant articles that were published between 2001 and 2025 were found using relatable keywords, including *Rhus chinensis*, galla chinensis, phytoconstituents of *Rhus chinensis*, pharmacology and therapeutic activity of *Rhus chinensis* anti-diabetic activity, and vice versa. We only observed and selected the peer-reviewed research and review papers. Studies about ethnomedicinal importance, phytochemical studies, *in vitro* and *in vivo* studies, and mechanisms of action of *Rhus chinensis* relevant to the treatment of diabetes were taken into consideration for our study. Articles that are not relevant with metabolic diseases or antidiabetic activity were excluded. All the data were systematically analyzed and studied and were able to identify the major bioactive components, its pharmacological relevance and lastly identify the research gaps.

RESULTS

Ethnomedicinal uses of *rhus chinensis*

In Traditional Chinese Medicine (TCM), the galls of *R. chinensis* ("Wu Bei Zi") are highly prized. They have been traditionally used to treat diarrhea, night sweats, chronic cough, rectal prolapse, uterine bleeding, and excessive perspiration (Djakpo and Yao, 2010). Decoctions of the galls are believed to act as potent astringents due to their high tannin content, making them effective in controlling bleeding and secretions (Thingbaijam *et al*., 2023). In Indian ethnomedicine, particularly in the Northeastern states (Assam, Manipur, Meghalaya), the fruits are consumed for their digestive, antidiabetic, and anti-inflammatory properties (Heirangkhongjam and Ngaseppam, 2018). The fruits of *R. chinensis* are edible and consumed fresh, dried, or processed. In Northeast India, particularly Manipur and Assam, the fruits are made into chutneys, pickles, beverages, and condiments, valued for their sour taste and high vitamin C content (Heirangkhongjam *et al*., 2019). In parts of China, the galls are also utilized as a food additive for their antioxidant and preservative properties. The galls of *R. chinensis* are rich in tannins (40-70%), making them historically important in dyeing, ink production, tanning leather, and as natural preservatives (Zhang *et al*., 2022). In rural communities, powdered galls have also been applied topically to treat oral ulcers, wounds, and skin infections (Djakpo and Yao, 2010).

Phytochemical constituents of *R. chinensis*

R. chinensis (fruit, leaf, stem, and especially the galls sold as Galla chinensis) is chemically rich in hydrolyzable tannins (gallotannins), simple phenolics (gallic acid and derivatives), flavonoids (myricetin and quercetin glycosides), small phenolic acids (protocatechuic acid), and assorted triterpenoids/other minor constituents (Djakpo and Yao, 2010) (Table 1). The gall (Galla chinensis) is particularly concentrated in gallotannins (e.g., pentagalloylglucose and related oligogalloyl glucoses) and free gallic acid; fruit and leaf extracts commonly yield flavonols (myricetin derivatives, quercetin glycosides), methyl gallate, and other phenolic acids (Figure 2) (Huang *et al*., 2012). Analytical fractionation studies correlate specific constituents (e.g., myricetin-galloyl glycosides, di-O-galloyl-glucosides) with biochemical activities such as α-glucosidase and DPP-IV inhibition and AGE suppression (Table 1).

Mechanistic pathways related to antidiabetic action

α-Glucosidase and α-Amylase Inhibition

Carbohydrate-hydrolyzing enzymes α-glucosidase and α-amylase play a major role in postprandial glucose excursions. α-Amylase breaks down starch into oligosaccharides, while α-glucosidase catalyzes disaccharide hydrolysis and releases glucose. Inhibiting these enzymes slows carbohydrate digestion and glucose absorption, decreasing postprandial hyperglycemia, a key therapeutic strategy in Type 2 Diabetes Mellitus (T2DM). Conventional inhibitors (e.g., acarbose, miglitol, voglibose) have clinical efficacy but are frequently limited by gastrointestinal side effects. As a result, natural inhibitors derived from dietary or medicinal plants are under active investigation as safer alternatives (Salehi *et al*., 2019). Activity-guided fractionation and phytochemical profiling reveal that gallic acid, methyl gallate, Pentagalloyl Glucose (PGG), quercitrin, and myricetin derivatives are among the most active compounds. Molecular docking analyses show that gallotannins (PGG) and flavonoid glycosides bind to the catalytic sites of α-glucosidase and α-amylase, creating stable hydrogen-bond networks that block substrate access. The polyhydroxylated nature of these phenolics allows for numerous binding interactions, which explains why *R. chinensis* phenolic fractions are more potent than single-compound standards such as gallic acid (Zhang *et al*., 2021).

DPP-IV Inhibition

Recent phytochemical and bioactivity-guided studies have identified *R. chinensis*, specifically its fruit and gall extracts, as a promising natural source of DPP-IV inhibiting chemicals. A study found that the free phenolic fraction from *R. chinensis* fruits had the highest DPP-IV inhibitory activity (IC_{50} = 66.08 ± 1.36 μg/mL), outperforming insoluble-bound and esterified phenolic fractions.[11] These findings suggest that readily extractable polyphenols, such as flavonoid glycosides and gallotannins, play an important role in modulating incretin-enzyme activity (Table 2). Chemical profiling and molecular docking analyses indicate that quercitrin, myricetin derivatives, gallic acid, and Pentagalloyl Glucose (PGG) can bind to the catalytic region of DPP-IV via hydrogen bonding and π-π interactions, stabilizing enzyme-ligand complexes and preventing incretin degradation (Liu *et al*., 2023) (Table 2). Molecular docking and in-silico studies of dietary flavonoids and related polyphenols reveal that many flavonoid scaffolds can occupy DPP-IV's active site, forming hydrogen bonds and hydrophobic/π-π interactions with residues that define the S1 pocket and nearby catalytic region, similar to small-molecule DPP-IV inhibitors (Gao *et al*., 2020; Pan J *et al*., 2022; Hossain *et al*., 2024). Docking studies on phenolic fractions from *R. chinensis* have identified quercetin and myricetin type glycosides, as well as galloyl derivatives, as ligands with favorable binding energies to DPP-IV, implying that these compounds may contribute to enzyme inhibition. However, direct structural proof that galloylated flavonoids from *R. chinensis* specifically occupy the canonical S1 hydrophobic pocket in the same orientation as synthetic inhibitors remains limited (Fu *et al*., 2022). Although there is currently no direct *in vivo* evidence linking *R. chinensis* to GLP-1 elevation, administration of phenolic-rich extracts in diabetic rodent models has been associated with improved glucose tolerance, reduced fasting glucose, and modulation of oxidative and inflammatory pathways, suggesting that DPP-IV inhibition may partially contribute to these beneficial metabolic effects (Liu *et al*., 2021).

AGE Suppression

When reducing sugars react with proteins, lipids, or nucleic acids, non-enzymatic glycation reactions produce advanced glycation end-products. Their accumulation causes oxidative stress, inflammation, and cross-linking of extracellular matrix proteins, resulting in diabetes complications such as nephropathy, retinopathy, neuropathy, and cardiovascular failure. One viable technique for decreasing the long-term implications of Type 2 Diabetes Mellitus (T2DM) is to inhibit AGE synthesis or break down existing AGE cross-links. Natural polyphenols, particularly those with high antioxidant and carbonyl-trapping characteristics, are increasingly being recognized for their efficiency as AGE suppressors (Wang *et al*., 2024; Sekowski *et al*., 2023). *In-vitro* investigations revealed that *R. chinensis* fruit extracts high in polyphenols considerably inhibit the production of AGEs in bovine serum albumin glucose models. The antiglycation action correlates positively with the total phenolic content, indicating that flavonoid glycosides, phenolic acids, and gallotannins are the primary contributors (Liu *et al*., 2021). *In vivo* studies show that supplementing streptozotocin-induced diabetic mice with *R. chinensis* extracts improve glycemic status, reduce oxidative stress, and improve renal and metabolic function, implying that these anti-diabetic and antioxidant activities may have translational significance (Liu *et al*., 2023).

Antioxidant and Anti-inflammatory Activity

The potent antioxidant profile of *R. chinensis* is distinguished by the amount of phenolic compounds present in its fruits and galls, including gallic acid, methyl gallate, quercetin, myricetin derivatives, and gallotannins. Mechanistic research shows that flavonoids and gallotannins indirectly boost endogenous antioxidant defenses while directly scavenging free radicals via electron-donating hydroxyl groups. *R. chinensis* supplementation enhanced Glutathione Peroxidase (GPx), Catalase (CAT), and Superoxide Dismutase (SOD) levels in diabetic mice while decreasing Malondialdehyde (MDA) levels, indicating *in vivo* antioxidant efficacy (Liu *et al*., 2023). *R. chinensis* has significant anti-inflammatory properties in addition to antioxidant properties. R. chinensis' gallotannin, penta-O-galloyl-β-D-glucose (PGG), suppresses NF-κB activation in LPS-stimulated macrophages (Jang *et al*., 2013). *R. chinensis* fruit extract reduced expression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and suppressed NF-κB signaling in a murine model of cholestasis (Sun *et al*., 2022). A systematic review of Rhus species further confirms that extracts can downregulate classical inflammatory mediators (e.g., TNF-α, IL-1β, IL-6) through modulation of NF-κB and MAPK pathways (Rodriguez-Castillo AJ *et al*., 2025). Also, in a gastric ulcer model, *R. chinensis* extract was shown to inhibit iNOS and reduce nuclear NF-κB p65 and p-IκBα. (Ma *et al*., 2022).

Hepatic Glycolipid Modulation

Preclinical *in vivo* research indicates that ethanol or phenolic-rich extracts of *R. chinensis* enhance liver lipid and glucose profiles in diet-induced metabolic disease animals. In a high-fat/high-sugar (HFHSD) rat model, oral administration of an ethanol extract (600 mg/kg) reduced hepatic and plasma triglycerides and total cholesterol, increased antioxidant indices (CAT, GSH, reduced MDA), decreased HOMA-IR and abdominal adiposity, and improved histology. The extract increased p-AMPK and PPAR-α while decreasing SREBP-1 and FAS, indicating reduced de novo lipogenesis and increased fatty acid oxidation in the liver. Simultaneously, hepatic insulin signaling was enhanced (increased p-IRS1, PI3K/AKT), indicating improved hepatic glucose management. These combined effects indicate that *R. chinensis* mitigates hepatic glycolipid derangements by activating AMPK/PPAR-α and restoring IRS-1/PI3K/AKT signaling (Wu *et al*., 2021). In NAFLD models, phenolic-rich extracts were found to reduce hepatic inflammation and apoptosis, lower markers like p-p38 and p-NF-κB, decrease iNOS and COX-2 expression, and improve TG/TC, ALT/AST, and antioxidant enzyme activity. These findings suggest that AMPK activation and suppression of inflammatory MAPK/NF-κB signaling are key mechanisms. Such modification of lipid metabolism and inflammation in the liver has a direct impact on the prevention or treatment of T2DM and associated hepatic complications (Wu *et al*., 2020). In a streptozotocin HFFD murine T2DM model, ethanol extracts of *R. chinensis* fruits improved glycemia, HbA1c, dyslipidemia, insulin resistance, and islet histology; at the molecular level, the extracts repaired islet function, regulated hepatic/insulin signaling via IRS-1/PI3K/AKT, and increased nuclear translocation of Nrf2, indicating improved insulin signaling and strengthened antioxidant defenses in metabolic tissues. These alterations establish a molecular relationship between hepatic glycolipid regulation and systemic glucose control (Liu *et al*., 2023). Preclinical data suggests that *R. chinensis* extracts can activate AMPK, PPAR-α, and suppress SREBP-1/FAS to limit hepatic lipogenesis and enhance fatty-acid oxidation, restore hepatic IRS-1/PI3K/AKT signaling to improve insulin sensitivity and glucose handling, and reduce oxidative stress and inflammatory signaling (NF-κB/MAPK) to prevent progression of hepatic glycolipid-driven metabolic dysfunction. While these findings show promise for nutritional or adjuvant therapies to T2DM, more human clinical data are needed to identify the active molecule(s), their pharmacokinetics, and safety at therapeutic levels (Wu *et al*., 2021).

Gut Microbiota Modulation

Emerging research suggests that *R. chinensis*'s metabolic advantages in type 2 diabetes may be mediated via gut microbiota modification. While direct microbiota evidence in diabetes mice are limited, the hypothesis is biologically reasonable given what we know about polyphenol microbiome interactions. Polyphenols and tannins (such the gallotannins found in R. chinensis) are poorly absorbed in the small intestine and reach the colon, where resident microorganisms hydrolyze them into smaller phenolic metabolites (e.g., gallic acid) that are more accessible and biologically active (Correa *et al*., 2019). Microbial-transformed phenolics can regulate carbohydrate metabolism by blocking α-glucosidase and signaling pathways. They may also have antioxidant and anti-inflammatory properties. Furthermore, polyphenols can selectively promote or inhibit specific bacterial taxa, as well as influence microbial metabolic activity, such as the production of short-chain fatty acids, which have been shown to strengthen the intestinal barrier, reduce endotoxin translocation, and improve insulin sensitivity (Morrison DJ *et al*., 2016; Feng *et al*., 2022). Therefore, it is possible that *R. chinensis* could modulate gut microbial composition and function in ways that contribute to its systemic glycemic and metabolic effects, though rigorous preclinical and clinical studies combining *R. chinensis*

Table 1: Some important phytoconstituents and their activity reported in *Rhus chinensis*.

Constituent	Chemical Class	Plant Part Reported	Reported Activity	References
Gallic acid	Phenolic acid	Galls, fruits	Major phenolic contributing to antioxidant activity	(Li *et al*., 2022; Zhang *et al*., 2022)
Methyl gallate	Phenolic ester	Galls, fruits	Antioxidant and antimicrobial; abundant in galls	(Li *et al*., 2022)
Pentagalloyl-glucose (PGG)	Gallotannin	Galls	Key hydrolyzable tannin; anticancer and enzyme-inhibitory	(Li *et al*., 2022)
Ellagic acid	Phenolic derivative	Galls, fruits	Formed from ellagitannins; strong antioxidant	(Li *et al*., 2022)
Quercetin-3-O-rhamnoside (quercitrin)	Flavonoid glycoside	Fruit	Major flavonoid; anti-lipase, antioxidant	(Zheng *et al*., 2022)
Myricetin-3-O-rhamnoside	Flavonoid glycoside	Fruit	Lipid-modulating and antioxidant activity	(Zheng *et al*., 2022)
Quercetin (aglycone)	Flavonoid	Fruit, stems	Anti-inflammatory and antioxidant	(Li *et al*., 2022)
Myricetin (aglycone)	Flavonoid	Fruit, stems	MS-reported flavonol with strong antioxidant activity	(Zheng *et al*., 2022)
Kaempferol-3-O-hexoside	Flavonoid glycoside	Fruit	Reported in UHPLC-MS profiling	(Zheng *et al*., 2022)
Luteolin-7-O-glucoside	Flavonoid glycoside	Fruit	Anti-inflammatory potential	(Zheng *et al*., 2022)
Catechin / Epicatechin	Flavan-3-ols	Fruits, galls	Antioxidant phenolics	(Li *et al*., 2022)
Gallotannin mixtures	Hydrolyzable tannins	Galls	Dominant bioactive fraction	(Li *et al*., 2022)
Urushiols	Phenolic lipids	Bark, stems (genus level)	Phenolic lipids common in *Rhus* species	(Li *et al*., 2022)
Lariciresinol-type lignans	Lignans	Root, bark	Reported in butanol extracts	(Li *et al*., 2022)
Betulonic acid	Triterpenoid	Root, stem	Potent anticancer triterpenoid	(Li *et al*., 2022)
Betulinic acid	Triterpenoid	Root, stem	Cytotoxic and chemopreventive	(Li *et al*., 2022)
Moronic acid / Oleanane triterpenoids	Triterpenoids	Stem, root	Broad anticancer potential	(Li *et al*., 2022)
6-Pentadecylsalicylic acid	Long-chain phenolic	Root, stem	Rare long-chain phenolic with antithrombotic effects	(Li *et al*., 2022)
Citric acid	Organic acid	Fruit	Major organic acid	(Zheng *et al*., 2022, Singh *et al*., 2019)
Malic acid	Organic acid	Fruit	Nutritional organic acid	(Zheng *et al*., 2022, Singh *et al*., 2019)
Crude polysaccharides	Polysaccharides	Fruit	Immunomodulatory/ nutraceutical value	(Sun *et al*., 2022)
Fisetin	Flavonoid	Stem	Anti-inflammatory and anticancer	(Li *et al*., 2022)
Phenolic benzofuranones	Benzofuran derivatives	Stem	Rare phenolics identified in fractions	(Li *et al*., 2022)
β-Sitosterol and sterols	Phytosterols	Stem, bark	Common sterol constituents	(Li *et al*., 2022)
Gallic acid esters (various)	Galloyl esters	Galls, fruits	Multiple esterified phenolics	[(Li *et al*., 2022)
Galloyl-glucose oligomers	Gallotannins	Galls	Several oligomeric gallotannins	[(Li *et al*., 2022)

Constituent	Chemical Class	Plant Part Reported	Reported Activity	References
Minor triterpenoid saponins	Saponins	Root, stem	Reported in targeted phytochemical screens	(Li *et al.*, 2022)
Pyrogallol and small phenolics	Simple phenolics	Fruits, galls	Hydrolysis-derived phenolic products	(Zheng *et al.*, 2022)
Mixed flavonol glycosides	Flavonoids	Fruits	Several rhamnosides/hexosides	(Zheng *et al.*, 2022)
Trace alkaloids and phenylpropanoids	Various	Multiple parts	Minor compounds detected in full-profile analysis	[Li *et al.*, 2022]

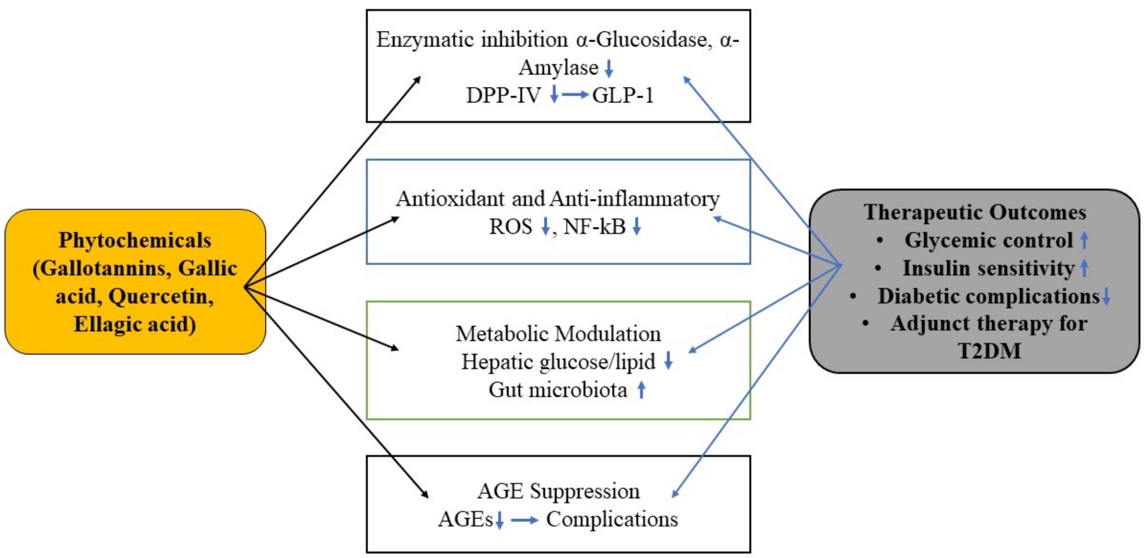

Figure 1: Mechanistic pathways of phytochemicals found in *R. chinensis* in lowering problems in T2DM.

intervention with microbiome sequencing and metabolomics are still needed.

Preclinical Evidence

Preclinical studies show that *R. chinensis* fruit and gall extracts have several bioactivities that can help prevent and treat type 2 diabetic mellitus (T2DM). *In-vitro* studies on *R. chinensis* phenolic-rich fractions show significant inhibition of α-glucosidase and DPP-IV enzymes, as well as antiglycation effects, which correlate with total phenolic content, flavonoid glycosides, and gallotannins. The free phenolic fraction demonstrated the strongest enzyme inhibition in comparative assays. These fractions have strong antioxidant activity and may scavenge reactive carbonyl species in BSA-glucose AGE models, providing a molecular explanation for the antiglycation and cytoprotective benefits found in cells (Liu *et al.*, 2021). Cellular investigations suggest that gallotannins, specifically penta-O-galloyl-β-D-glucose (PGG), play a significant role. PGG and gallotannin-rich preparations suppress MyD88-dependent NF-κB activation and diminish MAPK phosphorylation (ERK, p38) in LPS-stimulated macrophages. This reduces downstream inflammatory mediators that aggravate insulin resistance. These anti-inflammatory properties complement antioxidant activities and contribute to enhanced tissue function *in vivo* (Jang *et al.*, 2013). Multiple rodent investigations have shown that oral administration of *R. chinensis* extracts improves metabolic function. In a high-fat/high-sugar (HFHSD) rat model, ethanol extract reduced hepatic and circulating triglycerides and cholesterol, improved antioxidant enzyme activities, decreased hepatic lipid accumulation on histology, and modulated key metabolic regulators, indicating reduced de-novo lipogenesis and increased β-oxidation. The extract also improved hepatic insulin signaling (IRS-1/PI3K/AKT), which links hepatic glycolipid regulation to better systemic glucose control (Wu *et al.*, 2021). *In vivo* studies have shown that phenolic-rich extracts have anti-inflammatory and cytoprotective properties in the gut and gastric mucosa. These extracts reduced colonic TNF-α/IL-1β/IL-6, iNOS and COX-2 levels, and suppressed p-NF-κB and p-MAPKs. *R. chinensis* extract reduced indomethacin-induced stomach ulcers by lowering inflammatory markers and oxidative damage. These findings highlight systemic anti-inflammatory pathways by which the plant may reduce inflammation-related aspects of metabolic illness (Zhang *et al*., 2021).

DISCUSSION

Safety and limitations

R. chinensis appears to be generally safe in preclinical animals, however its usage in type 2 diabetes management remains limited due to significant toxicological and clinical knowledge gaps. Acute and subchronic oral toxicity trials in rodents show substantial safety margins, with no death or severe organ harm at dosages up to 5,000 mg/kg for acute exposure and 30 days of repeated dosing, indicating good preliminary tolerance (Wu *et al*., 2018). Efficacy trials employing metabolically appropriate dosages, such as 600 mg/kg/day, have also shown no adverse clinical symptoms. R. chinensis compounds, particularly gallotannins and other hydrolyzable tannins, may cause gastrointestinal discomfort, impaired nutritional absorption, or possible hepatic and renal stress at high or chronic doses, according to tannin toxicology literature. Although Penta-O-Galloyl-β-D-Glucose (PGG) and gallic acid derivatives show protective properties *in vitro* and in animal, systematic investigations on their pharmacokinetics, long-term toxicity, and metabolite profiles are lacking (Jang *et al*., 2013). Furthermore, herb-drug interaction concerns have not been assessed, despite polyphenols' theoretical ability to regulate CYP enzymes and drug transporters, which is therapeutically relevant for patients receiving antidiabetic polypharmacy. While *R. chinensis* is taxonomically separate from urushiol-containing Rhus species, the genus' relationship with contact dermatitis requires vigilance while handling raw materials. Most critically, there are no human clinical safety data available, including standardized extract profiles, ADME investigations, reproductive toxicity assessments, or chronic exposure trials. Therefore, despite promising preclinical safety, the long-term use of *R. chinensis* for T2DM requires standardized preparation, rigorous toxicological evaluation, and early-phase human safety studies before clinical translation.

Translational gaps

There are several major challenges in translating promising preclinical findings of *R. chinensis* into clinical application for type 2 diabetes. Although multiple *in vitro* and animal studies demonstrate enzyme inhibition (α-glucosidase, DPP-IV), antiglycation, antioxidant, anti-inflammatory, and hepatic glycolipid-modulating effects for defined phenolic fractions or ethanol extracts (supporting biological plausibility), these data are largely preclinical and heterogeneous in extract type, dose, and endpoints, limiting direct extrapolation to humans (Liu *et al*.,2021; Liu *et al*., 2023; Wu *et al*., 2021). Safety data in rodents are reassuring at acute and subchronic timeframes (no mortality at single doses up to 5000 mg/kg and tolerability in 30-day studies), but chronic toxicology, reproductive/developmental toxicity, carcinogenicity, and comprehensive ADME/toxicokinetic profiles are lacking, which is critical for risk assessment in long-term diabetic therapy (Manach *et al*., 2005). The oral bioavailability and systemic exposure of key actives (gallotannins,

Table 2: Phytochemical classes, mechanisms, and therapeutic outcomes of *Rhus chinensis* in type 2 diabetes mellitus.

Phytochemical / Extract	Mechanism(s) of Action	Experimental Model	Key Outcomes	References
Hydrolyzable tannins (gallotannins) from Galla chinensis	Potent inhibition of α-glucosidase and α-amylase	*In vitro* enzyme assays; rodent postprandial glucose models	Reduced carbohydrate digestion; lowered postprandial blood glucose	(Shim *et al*., 2003)
Phenolic-rich fruit fractions (gallic acid, methyl gallate, flavonoids)	Inhibition of α-glucosidase and DPP-IV	*In vitro* assays	IC_{50} values in μg/mL range; enhanced incretin-action potential	(Liu *et al*., 2021)
Protocatechuic acid, myricetin glycosides	Inhibition of advanced glycation end-products (AGEs)	*In vitro* AGE assays	Suppressed AGE formation; potential vascular/renal protection	(Zhang *et al*., 2021)
Ethanolic fruit extract	Antioxidant and anti-inflammatory activities; modulation of hepatic glycolipid metabolism	High-Fat Diet (HFD)-fed rodent models	Improved hepatic steatosis; reduced triglycerides and cholesterol; enhanced insulin sensitivity	(Liu *et al*., 2021; Liu *et al*., 2023; Shan *et al*., 2024)
Crude aqueous extracts (fruit and galls)	Radical-scavenging activity; modulation of inflammatory mediators	*In vitro* antioxidant assays; rodent oxidative stress models	High antioxidant capacity; protective effects against oxidative β-cell stress	(Wu *et al*., 2021)

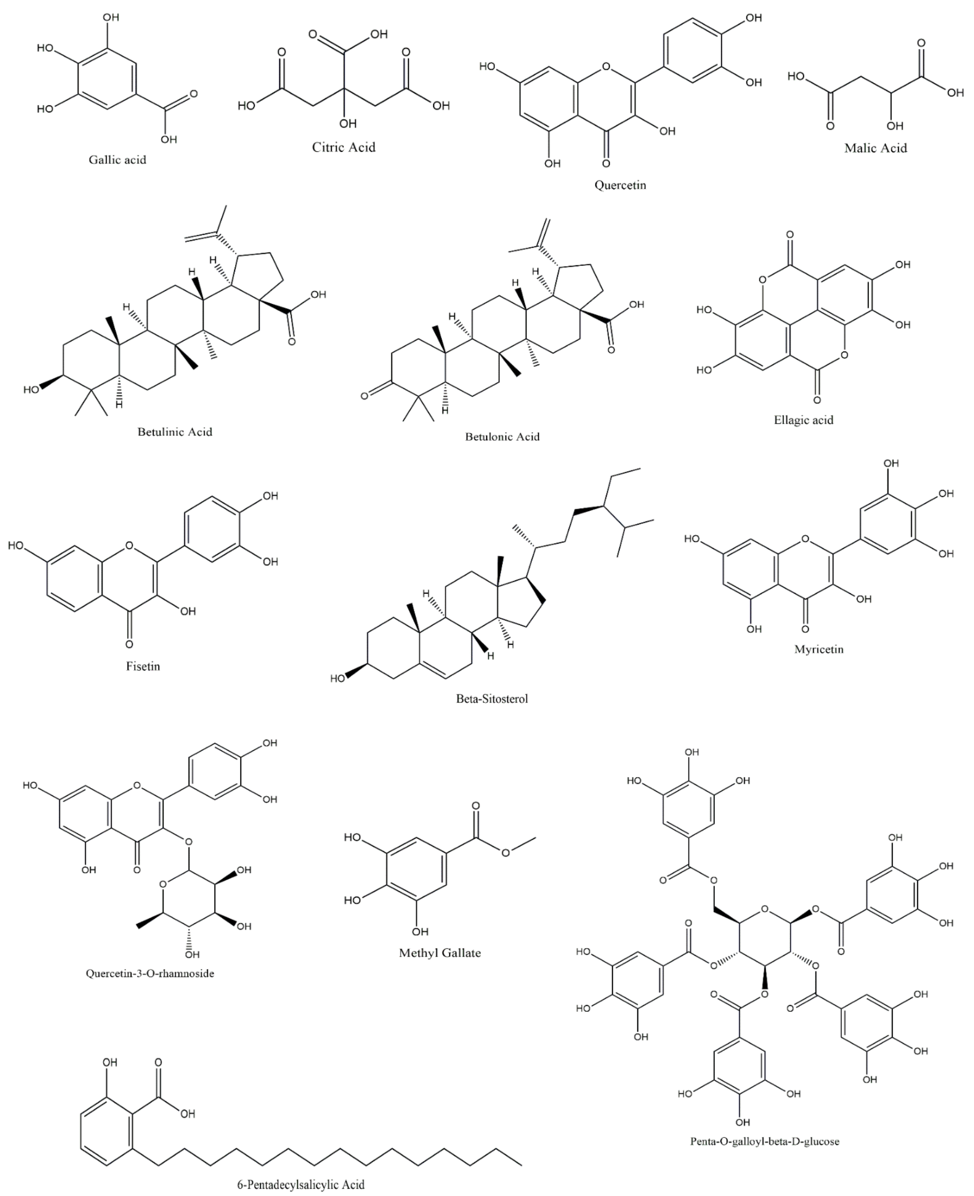

Figure 2: Chemical structures of some phytoconstituents found in *R. chinensis.*

PGG, flavonoid glycosides), the identity and activity of major *in vivo* metabolites, and the potential for clinically relevant herb-drug interactions (primarily via CYPs or transporters) are all well-known challenges for polyphenol translation in general (Jang *et al*., 2013; Zhang *et al*., 2021; Manach *et al*., 2005). Mechanistic work has identified useful molecular targets (e.g., NF-κB/MAPK suppression, AMPK/PPAR-α activation, IRS-1/PI3K/AKT restoration) but is incomplete in terms of dose response relationships, target engagement in metabolic tissues at therapeutically achievable concentrations, and validation in diabetic (rather than injury or inflammation) models for some endpoints (Wu *et al*., 2021; Zhang *et al*., 2021). Although microbiome-mediated mechanisms are likely contributors, existing evidence linking *R. chinensis* to reproducible, beneficial modifications in gut taxa or metabolites (SCFAs, microbially generated phenolics) in metabolic illness models is premature and inconsistent (Liu *et al*., 2023; D'Archivio *et al*., 2010). Finally, no well-controlled human trials have been conducted to determine efficacy, optimal formulation/dose, duration, or safety in people with T2DM; thus, extract standardization (marker compounds, manufacturing reproducibility) and regulatory-grade quality control are urgent priorities before clinical translation. These gaps, which include standardization and formulation development, rigorous chronic toxicology and PK/ADME studies, interaction testing, mechanistic confirmation at clinically relevant doses, microbiome causality experiments, and early-phase human trials, define a clear roadmap for responsibly progressing *R. chinensis* from preclinical promise to an evidence-based adjunct therapy for T2DM.

CONCLUSION

R. chinensis has emerged as a promising ethnomedicinal plant with numerous anti-diabetic properties. Its bioactive constituents, primarily gallotannins, gallic acid, and related polyphenols, have therapeutic effects by inhibiting α-glucosidase and α-amylase, suppressing DPP-IV, and attenuating Advanced Glycation End-Products (AGEs), directly targeting key enzymatic and metabolic pathways in hyperglycemia (Table 2). Furthermore, its powerful antioxidant and anti-inflammatory qualities aid in the reduction of oxidative stress and chronic low-grade inflammation, both of which play important roles in the etiology of Type 2 Diabetes Mellitus (T2DM). Additional mechanisms, including as hepatic glycolipid modulation and gut microbiota regulation, support its ability to improve systemic glucose and lipid homeostasis. Preclinical investigations consistently show effectiveness across numerous models of metabolic disorders, highlighting the pharmacological relevance of traditional applications. Importantly, safety studies indicate a wide range of tolerability at modest doses, while concerns about the high tannin content, potential for nutritional malabsorption, and allergic cross-reactivity within the *Anacardiaceae* family warrant cautious study. Despite these positive findings, major limitations persist, most notably the lack of well-designed clinical studies, heterogeneity in phytochemical composition due to environmental and processing conditions, and insufficient pharmacokinetic data. Altogether, the research suggests that *R. chinensis* is a promising option for the development of new phytopharmaceuticals for the treatment of type 2 diabetes. However, translating preclinical promise into clinical use will necessitate thorough randomized controlled studies, standardized extract formulations, and long-term safety assessments. Addressing these gaps will not only prove its therapeutic efficacy, but also make it easier to integrate into modern evidence-based healthcare while conserving its rich traditional past.

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ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; ***R. chinensis:*** Rhus chinensis; **CKD:** Chronic Kidney Disease; **SGLT2i:** Sodium-glucose co-transporter-2 inhibitors; GLP-1 **Ras:** Glucagon-like peptide-1 receptor agonists; **mHealth:** Mobile health; **DPP-IV:** Dipeptidyl peptidase-4; **AMPK:** AMP-activated protein kinase; **IRS1:** Insulin receptor substrate-1; **PI3K:** Phosphoinositide 3-kinase; AKT: Protein kinase B; **SREBP-1:** Sterol Regulatory Element-Binding Protein 1; **PGG:** Pentagalloyl glucose; **AGEs:** Advanced glycation end-products; **GPx:** Glutathione peroxidase; **CAT:** Catalase; **SOD:** Superoxide dismutase; **MDA:** Malondialdehyde; **TNF-α:** Tumor Necrosis Factor-alpha; **IL-6:** Interleukin-6; **IL-1β:** Interleukin-1 beta; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **MAPK:** Mitogen-activated protein kinase; p-**IκBα:** phosphorylated- inhibitor of nuclear factor kappa B alpha; **HFHSD:** High-fat/high-sugar; **GSH:** Reduced glutathione; **MDA:** Malondialdehyde; **HOMA-IR:** Homeostatic Model Assessment for Insulin Resistance; **p-AMPK:** phosphorylated AMP-activated protein kinase; **PPAR-α:** Peroxisome Proliferator-Activated Receptor alpha; **NAFLD:** Nonalcoholic Fatty Liver Disease; **p-p38:** phosphorylated p38 mitogen-activated protein kinase; **iNOS:** Inducible Nitric Oxide Synthase; **TG:** Triglycerides; **TC:** Total cholesterol; **ALT:** Alanine aminotransferase; AST: Aspartate aminotransferase; **MyD88:** Myeloid differentiation primary response 88; **HFFD:** High-fat, High-fructose diet; **HbA1c:** Glycated hemoglobin; **ERK:** Extracellular signal-regulated kinase, DSS: Dextran-sulfate sodium; **COX-2:** Cyclooxygenase-2; **CYP:** Cytochrome P450

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Thokchom Biona: Data collection, original draft writing, review, editing and final draft.

Kalpana Rahate: Supervision, original draft review, editing and final draft

SUMMARY

The molecular mechanisms, bioactive compounds, and therapeutic potential of *R. chine*nsis in Managing Type 2 Diabetes Mellitus are investigated in this comprehensive review. To identify gaps in translational research, the study integrates phytochemical analyses, recent *in-vitro* and *in vivo* studies, and contemporary scientific findings. Galactoannins, phenolic acids, flavonoids, and triterpenoids with potent anti-inflammatory, enzyme-modulatory, and antioxidant qualities are abundant, according to phytochemical profiling. According to recent research, antidiabetic effects can be achieved by blocking hepatic gluconeogenesis, boosting glucose absorption by activating

AMPK, inhibiting α-glucosidase and α-amylase, and improving insulin sensitivity. Additionally, research suggests benefits regarding the management of dyslipidemia, inflammation, and gut bacteria regulation. Hence, *R. chinensis* emerges as a compelling natural candidate for integrative T2DM management; however, a well-designed clinical trial is needed to validate efficacy, optimize dosing, and ensure long-term safety.

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