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Article

IN SILICO EVALUATION OF PHYTOCHEMICALS FROM MANGIFERA INDICA AGAINST TYPE 2 DIABETES TARGETS: A MOLECULAR DOCKING AND ADMET STUDY

Sadia Tasnim[1]; Shaiful Mahmud[2];

[1]. Quality Control Chemist, Incepta Pharmaceuticals Ltd., Dhaka, Bangladesh; Email: sadia.tasnim.unh@gmail.com

[2]. Washington, DC 20019, USA; Email: shaifulmahmud90@gmail.com

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance, impaired glucose regulation, and chronic hyperglycemia, which remains a major global health challenge.Unlike type 1 diabetes, which results from autoimmune-mediated β-cell destruction, T2DM is primarily associated with insulin resistance in peripheral tissues such as skeletal muscle, adipose tissue, and liver. This progressive condition involves multiple metabolic defects, including impaired incretin response, enhanced hepatic gluconeogenesis, and pancreatic β-cell exhaustion, which together lead to chronic hyperglycemia. On a global scale, the prevalence of T2DM has reached alarming proportions. Synthetic pharmacotherapies such as metformin, sulfonylureas, and thiazolidinediones have improved clinical outcomes but are often associated with limitations including side effects, high cost, and lack of multitarget efficacy. As a result, increasing attention has been directed toward natural phytochemicals with broad pharmacological activities. Mangifera indica (mango) is widely used in ethnomedicine for the management of diabetes, and its phytochemicals—including mangiferin, quercetin, catechins, and phenolic glycosides—have demonstrated promising antidiabetic effects. This systematic review, conducted in accordance with PRISMA guidelines, evaluated 114 eligible studies published between 2000 and 2022, integrating findings from molecular docking, ADMET profiling, in vitro assays, and in vivo experimental models. Docking studies consistently revealed strong inhibitory interactions of mango-derived phytochemicals with diabetes-related targets such as a-amylase, a-glucosidase, protein tyrosine phosphatase 1B (PTP1B), and dipeptidyl peptidase-4 (DPP-4), while ADMET analyses indicated favorable safety margins despite challenges of solubility and oral bioavailability. Experimental investigations further confirmed improvements in glycemic indices, insulin sensitivity, lipid regulation, and oxidative stress modulation, reinforcing the computational predictions. Compared with conventional synthetic drugs, M. indica phytochemicals demonstrated the advantage of multitarget actions with fewer reported adverse effects. Collectively, the synthesis of 114 studies consolidates evidence that mango phytochemicals represent a validated and culturally significant resource with broad international relevance for T2DM management, bridging traditional ethnopharmacological practices with modern computational and pharmacological evaluation.

KEYWORDS

Mangifera indica; Mangiferin; Phytochemicals; Molecular docking; ADMET; Type 2 diabetes mellitus;

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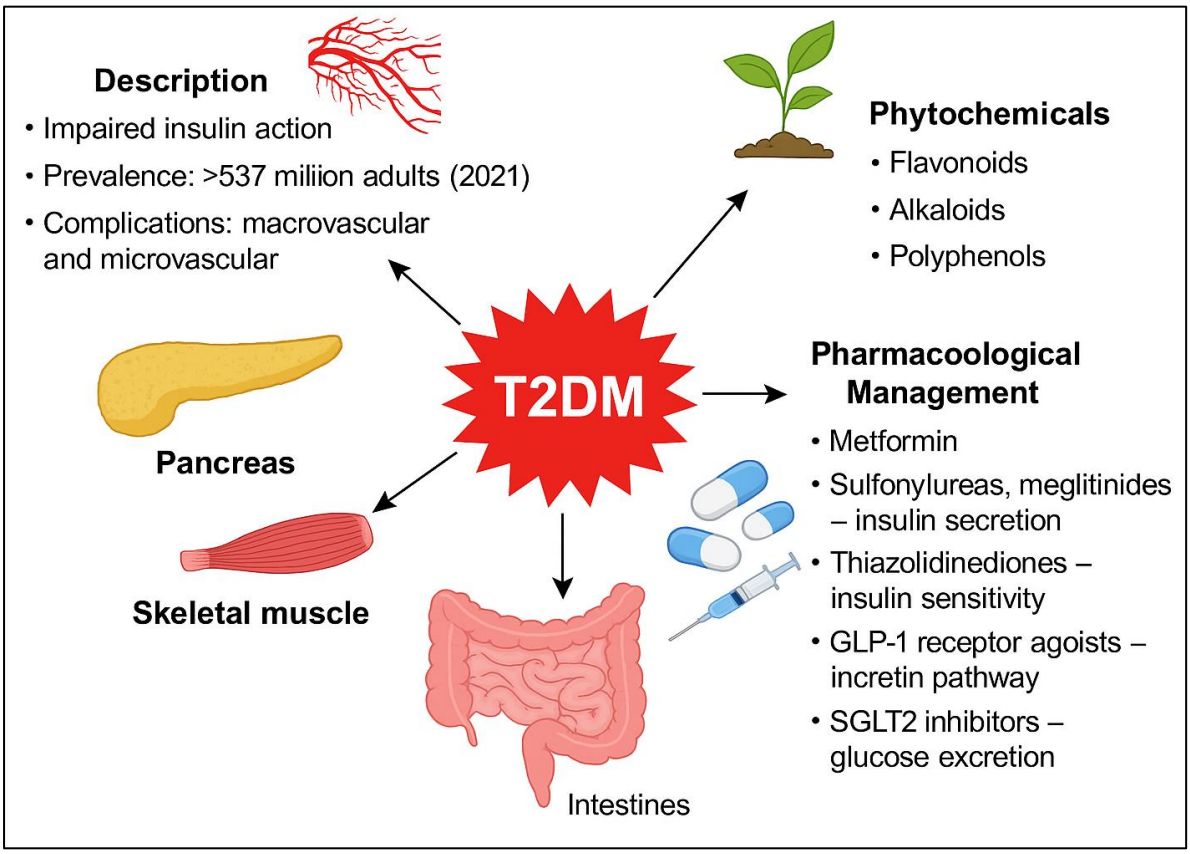
INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia arising from impaired insulin action, defective insulin secretion, or a combination of both (Rachdaoui, 2020). Unlike type 1 diabetes, which results from autoimmune-mediated β-cell destruction, T2DM is primarily associated with insulin resistance in peripheral tissues such as skeletal muscle, adipose tissue, and liver. This progressive condition involves multiple metabolic defects, including impaired incretin response, enhanced hepatic gluconeogenesis, and pancreatic β-cell exhaustion, which together lead to chronic hyperglycemia. On a global scale, the prevalence of T2DM has reached alarming proportions. The International Diabetes Federation estimated that more than 537 million adults aged 20–79 were living with diabetes in 2021with projections suggesting that this number may rise to 643 million by 2030 and 783 million by 2045 (Galicia-Garcia et al., 2020). The World Health Organization has declared diabetes a global epidemic, highlighting its significant contribution to morbidity and mortality rates. Complications arising from T2DM include macrovascular disorders such as cardiovascular disease, stroke, and peripheral artery disease, as well as microvascular complications including nephropathy, neuropathy, and retinopathy, all of which reduce quality of life and increase healthcare burdens. The economic impact is equally profound, with global healthcare expenditure for diabetes surpassing USD 966 billion in 2021.

Figure 1: Pathophysiology and Management of T2DM



The burden is disproportionately higher in low- and middle-income countries, where limited access to healthcare, diagnostic resources, and medication exacerbates disease outcomes. Furthermore, epidemiological studies highlight that obesity, sedentary lifestyles, and urbanization are critical drivers of rising T2DM incidence worldwide. These statistics underscore the international significance of T2DM as not only a biomedical challenge but also a socioeconomic crisis that requires multidisciplinary approaches for management. By situating T2DM within this global context, it becomes evident why novel therapeutic strategies that complement existing treatments are urgently required to mitigate the escalating impact of this condition.

The pharmacological management of T2DM primarily revolves around oral hypoglycemic agents and injectable therapies designed to improve insulin secretion, enhance insulin sensitivity, reduce

hepatic glucose production, and slow intestinal glucose absorption (Del Prato et al., 2017). Metformin, a biguanide, remains the first-line therapy due to its well-established efficacy in reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity. Sulfonylureas and meglitinides stimulate insulin secretion from pancreatic β-cells, but their use is constrained by risks of hypoglycemia and weight gain.

Thiazolidinediones act through peroxisome proliferator-activated receptor gamma (PPAR-γ) activation to enhance insulin sensitivity, yet they are linked to adverse cardiovascular effects, edema, and bone fractures. Incretin-based therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists provide additional glycemic control by modulating the incretin pathway, improving insulin secretion, and delaying gastric emptying. Sodium-glucose co-transporter-2 (SGLT2) inhibitors represent another therapeutic innovation, promoting renal glucose excretion while providing cardiovascular and renal benefits. However, pharmacoresistance frequently emerges over time, necessitating drug combinations or transition to insulin therapy. Furthermore, many of these therapies are associated with gastrointestinal side effects, increased infection risks, or high treatment costs, which restrict their widespread use in low-resource settings. Importantly, none of the current pharmacological interventions provide a permanent cure, as they focus primarily on glycemic control rather than disease reversal. This has prompted the exploration of alternative strategies that can provide sustained therapeutic efficacy with reduced side effect profiles. Plant-derived phytochemicals have emerged as promising adjuncts to existing therapies, given their wide availability, structural diversity, and potential multitarget mechanisms of action. Such natural compounds are increasingly being investigated for their role in enhancing glucose metabolism, reducing oxidative stress, and modulating insulin signaling, thereby addressing key pathophysiological aspects of T2DM (Bajaj, 2018).

Phytochemicals, which are bioactive compounds produced by plants, have been increasingly recognized for their therapeutic roles in the prevention and management of chronic diseases such as T2DM. These compounds encompass diverse chemical classes, including flavonoids, polyphenols, alkaloids, terpenoids, and glycosides, each with unique molecular mechanisms relevant to glucose metabolism (Naidoo et al., 2018). Flavonoids such as quercetin, kaempferol, and rutin have demonstrated hypoglycemic effects by enhancing glucose uptake through GLUT4 translocation, modulating insulin receptor signaling pathways, and reducing oxidative stress. Polyphenols like resveratrol and curcumin exert antidiabetic activity by improving mitochondrial function, reducing lipid peroxidation, and modulating sirtuin and AMPK pathways (Alam et al., 2021). Alkaloids such as berberine regulate glucose metabolism by activating AMPK, suppressing gluconeogenesis, and modulating gut microbiota composition. Terpenoids, including gymnemic acids from *Gymnema sylvestre*, inhibit intestinal glucose absorption and improve pancreatic β-cell regeneration. These bioactivities are consistent with traditional ethnomedicine practices in Ayurveda, Traditional Chinese Medicine, and African herbal systems, where plant-based remedies have long been used to manage diabetes. Recent preclinical and clinical studies have validated these traditional claims, demonstrating that phytochemicals can improve glycemic indices, reduce insulin resistance, and lower oxidative stress biomarkers (Mekala & Bertoni, 2020). Their lower toxicity compared with synthetic drugs, along with their potential to act on multiple molecular targets simultaneously, makes them highly attractive candidates for T2DM therapy. This mounting evidence underscores the importance of systematically evaluating phytochemicals through modern scientific methods, particularly computational and pharmacological screening, to identify novel antidiabetic leads with translational potential (Li et al., 2022).

Mangifera indica L., commonly known as mango, is a tropical fruit tree belonging to the family Anacardiaceae, widely cultivated across Asia, Africa, and South America. Beyond its nutritional value, *M. indica* has been extensively documented in ethnomedicine for its therapeutic use in managing diabetes, gastrointestinal disorders, infections, and inflammatory conditions. Phytochemical investigations reveal that the plant is rich in bioactive compounds such as mangiferin, quercetin, catechins, gallic acid, ellagic acid, and various phenolic glycosides (Zhao et al., 2019). Among these, mangiferin, a C-glucosyl xanthone, has attracted considerable research attention for its potent antidiabetic properties. Mechanistic studies show that mangiferin enhances insulin sensitivity, promotes glucose uptake in skeletal muscle, inhibits carbohydrate-hydrolyzing enzymes like a-amylase and a-glucosidase, and reduces oxidative stress.

American Journal of Interdisciplinary Studies
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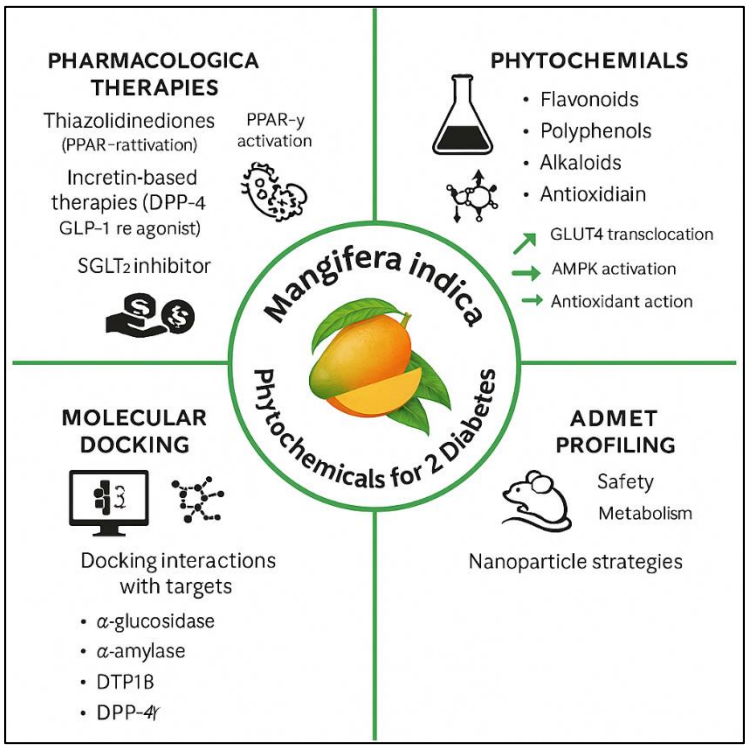
Figure 2: Mangifera indica Phytochemicals Against Diabetes



Experimental models have demonstrated that leaf extracts of *M. indica* significantly reduce fasting blood glucose, improve glucose tolerance, and ameliorate dyslipidemia. Clinical evidence also suggests beneficial effects of *M. indica* extract supplementation in improving glycemic control in prediabetic and diabetic individuals (Tahrani et al., 2016). Beyond glycemic regulation, phytochemicals from *M. indica* exhibit hepatoprotective, cardioprotective, and neuroprotective activities, indicating their broad therapeutic potential for diabetes-associated complications. The international relevance of *M. indica* lies in its widespread availability, cultural acceptance, and incorporation into nutraceutical formulations, making it a promising source of novel bioactive molecules for global diabetes management. This provides a strong foundation for further exploration of mango-derived phytochemicals using modern computational and pharmacological tools to establish their efficacy and pharmacokinetic profiles.

The integration of phytochemistry with computational drug discovery represents a globally significant approach to addressing the growing burden of T2DM. Nearly half of currently approved drugs are derived from or inspired by natural products, highlighting the enduring importance of plants as reservoirs of therapeutic compounds. In silico methods such as molecular docking, ADMET screening, and molecular dynamics simulations enable the systematic evaluation of phytochemicals, bridging the gap between traditional medicine and modern pharmacology. This approach is particularly relevant for developing countries, where access to expensive pharmacological interventions is limited, yet medicinal plants such as *Mangifera indica* are widely available and culturally integrated into healthcare practices. Furthermore, computational tools provide cost-effective and time-efficient alternatives to high-throughput screening, enabling the evaluation of hundreds of compounds against multiple protein targets with minimal laboratory (Stanimirovic et al., 2022). The international relevance of *M. indica* lies in its global distribution and cultural importance, making it a strategic candidate for drug discovery efforts aimed at reducing diabetes prevalence across diverse populations. By systematically investigating its phytochemicals using computational tools, researchers can identify molecules with strong therapeutic potential, favorable pharmacokinetics, and minimal toxicity risks, thereby contributing to evidence-based herbal medicine. This reflects a convergence of ethnopharmacology, computational biology, and global health research, underscoring the importance of in silico phytochemical evaluation in modern biomedical science

LITERATURE REVIEW

The literature on type 2 diabetes mellitus (T2DM), phytochemicals, and computational drug discovery reflects a rapidly evolving research landscape that integrates clinical, pharmacological, and computational sciences. T2DM remains a critical global health challenge, with rising prevalence driving the demand for more effective, safer, and affordable treatments. Traditional pharmacotherapy has improved glycemic control, yet long-term complications and adverse effects continue to present obstacles to effective disease management. Consequently, increasing scholarly attention has turned toward natural products and phytochemicals, which offer promising therapeutic alternatives due to their structural diversity, bioactivity, and cultural acceptance in ethnomedicine (Krautkramer et al., 2021). Among these, *Mangifera indica* has emerged as a plant of interest, as its bioactive constituents—including mangiferin, quercetin, and phenolic acids—have demonstrated significant antidiabetic properties in preclinical and computational studies. The convergence of ethnopharmacology with computational biology has enabled systematic in silico evaluation of plant-derived compounds, particularly through molecular docking, ADMET profiling, and related predictive tools. Molecular docking provides insights into ligand-target interactions at the atomic level, identifying phytochemicals capable of inhibiting enzymes central to glucose regulation. Complementarily, ADMET studies ensure that promising compounds demonstrate pharmacokinetic viability and safety. This literature review synthesizes current evidence on diabetes pathophysiology, existing pharmacological interventions, phytochemical research with a focus on *M. indica*, and the role of in silico methodologies in modern drug discovery (Li et al., 2021). By mapping these diverse strands of research, the review establishes a conceptual and methodological foundation for evaluating phytochemicals from *M. indica* against T2DM targets.

Pathophysiology and Global Burden of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin action, inadequate insulin secretion, or both, and is often accompanied by disturbances in carbohydrate, lipid, and protein metabolism (American Diabetes Association . At its core, T2DM involves peripheral insulin resistance, particularly in skeletal muscle, liver, and adipose tissue, where insulin signaling pathways become dysfunctional (Rahman et al., 2021). Insulin resistance leads to reduced glucose uptake by skeletal muscles, increased hepatic glucose production, and impaired lipolysis, resulting in elevated plasma free fatty acids and dyslipidemia. β-cell dysfunction represents another critical feature, as progressive loss of pancreatic β-cell mass and impaired insulin secretion exacerbate hyperglycemia. Incretin hormones, such as glucagon-like peptide-1 (GLP-1), are also dysregulated, reducing insulinotropic effects and contributing to glycemic imbalance. Chronic low-grade inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress further aggravate insulin resistance and β-cell apoptosis (Alam et al., 2021). The pathophysiology of T2DM is closely linked to obesity, where adipose tissue dysfunction leads to secretion of pro-inflammatory cytokines such as TNF-a and IL-6, creating a state of metabolic stress. Additionally, genetic and epigenetic factors significantly influence susceptibility to T2DM, with genome-wide association studies identifying risk variants in genes such as *TCF7L2* and *KCNJ11*. These pathophysiological hallmarks indicate that T2DM is not a single defect but rather a cluster of interrelated abnormalities affecting multiple organs and signaling pathways (Defronzo, 2009). Consequently, its complexity explains the challenges in therapeutic management, where interventions must target not only hyperglycemia but also insulin resistance, β-cell dysfunction, and associated metabolic disturbances.

The epidemiology of T2DM reveals a rapidly escalating global health burden. According to the International Diabetes Federation (Poznyak et al., 2020), over 537 million adults worldwide were living with diabetes in 2021, with projections estimating 643 million by 2030. The World Health Organization emphasizes that diabetes is among the top ten causes of mortality, responsible for 1.5 million deaths annually, with most cases attributed to T2DM. The prevalence is particularly high in low- and middle-income countries, where urbanization, sedentary lifestyles, and dietary changes have intensified risk factors (Del Prato et al., 2017).

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
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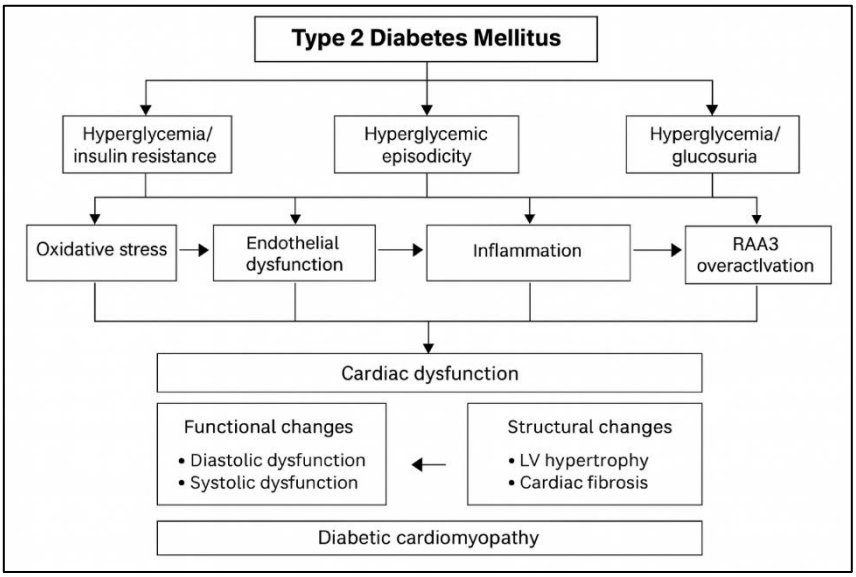
Figure 3: Type 2 Diabetes Mellitus Pathophysiology



South Asia exhibits disproportionately high prevalence, with India and China together accounting for over one-third of the global diabetic population. In Africa, prevalence rates are lower but rising rapidly, reflecting lifestyle transitions and limited healthcare resources (Ara et al., 2022; Reddy & Tan, 2020). In contrast, developed nations such as the United States and European countries have shown stabilization in incidence rates due to preventive strategies, although prevalence remains high. Regional disparities also reflect socioeconomic inequities, as rural populations often face underdiagnosis and lack of access to treatment, while urban populations are more exposed to obesogenic environments. Ethnic variations add complexity, as South Asians, Hispanics, and African Americans display higher susceptibility to T2DM compared with Caucasians, largely due to genetic predisposition and body composition differences (Güemes et al., 2020; Jahid, 2022). Global demographic shifts, particularly aging populations, further contribute to rising prevalence, as older adults face cumulative exposure to risk factors. Together, these epidemiological insights underscore that T2DM is not uniformly distributed across the world but is shaped by regional, socioeconomic, and demographic contexts, reinforcing its status as a heterogeneous and globally significant condition (Kostov, 2019; Uddin et al., 2022).

T2DM is associated with a broad spectrum of complications that significantly impair quality of life and impose immense economic burdens. Microvascular complications, including diabetic nephropathy, retinopathy, and neuropathy, arise from chronic hyperglycemia and vascular damage, leading to end-stage renal disease, vision impairment, and peripheral neuropathies. Macrovascular complications, such as coronary artery disease, stroke, and peripheral artery disease, are highly prevalent among individuals with T2DM, making cardiovascular disease the leading cause of death in this population. Chronic hyperglycemia also accelerates atherosclerosis, while insulin resistance contributes to dyslipidemia and hypertension, creating a clustering of cardiovascular risk factors commonly termed the "metabolic syndrome". Beyond direct health outcomes, T2DM imposes substantial socioeconomic costs. The IDF (Halim & Halim, 2019) reported that global health expenditure on diabetes exceeded USD 966 billion in 2021, with indirect costs arising from loss of productivity, absenteeism, and premature mortality further magnifying the burden (Seuring et al., 2015). In low-income countries, the economic impact is more severe as out-of-pocket expenditures strain household finances, often leading to catastrophic health spending. Psychological distress, depression, and reduced health-related quality of life are frequently reported among individuals with T2DM, further complicating disease management. The presence of comorbidities such as obesity, chronic kidney disease, and non-alcoholic fatty liver disease amplifies treatment complexity and cost (Akter & Ahad, 2022; Vieira et al., 2019). Collectively, the complications of T2DM extend far beyond glycemic imbalance, encompassing biomedical, psychological, and economic dimensions that reinforce its status as a multifaceted global health crisis.

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
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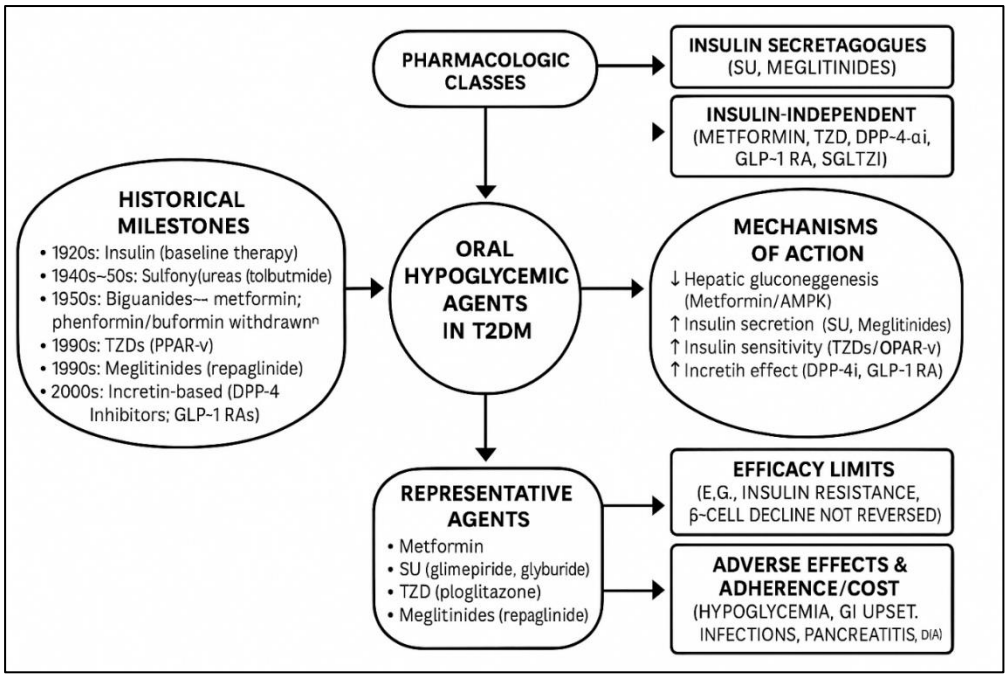
Conventional Pharmacological Management of T2DM

The development of oral hypoglycemic agents represents a significant milestone in the therapeutic management of type 2 diabetes mellitus (T2DM). Prior to pharmacological intervention, treatment relied primarily on lifestyle modification, strict dietary control, and insulin therapy, which was first introduced in the 1920s. The discovery of sulfonylureas in the 1940s marked the beginning of oral therapy, with tolbutamide introduced as the first clinically available sulfonylurea in the 1950s. These agents became widely used due to their ability to stimulate pancreatic insulin secretion and reduce hyperglycemia. The subsequent decades witnessed the introduction of biguanides, with metformin emerging in the 1950s following the identification of guanidine derivatives from *Galega officinalis*. While phenformin and buformin were initially popular, they were withdrawn due to lactic acidosis risk, leaving metformin as the sole widely used biguanide. In the 1990s, the thiazolidinedione (TZD) class was introduced, targeting insulin resistance through activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) (Aouacheri et al., 2015; Arifur & Noor, 2022). Parallel advancements included the development of meglitinides, such as repaglinide, offering short-acting insulin secretagogue effects (Draeger, 2001). The early 2000s brought incretin-based therapies, notably dipeptidyl peptidase-4 (DPP-4) inhibitors, which prolong the activity of incretin hormones, and glucagon-like peptide-1 receptor agonists, which enhance insulin secretion and delay gastric emptying. Most recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors were introduced in the 2010s, providing glycemic control via renal glucose excretion and additional cardioprotective benefits. This historical progression underscores the evolution from insulin dependence to a diverse pharmacological armamentarium, reflecting continuous efforts to address the multifactorial pathophysiology of T2DM (Magliano et al., 2015; Rahaman, 2022).

Figure 4: Oral Hypoglycemic Agents in T2DM



The pharmacological management of T2DM is anchored in multiple drug classes, each designed to target specific defects in glucose regulation. Metformin, a biguanide, reduces hepatic gluconeogenesis by activating AMP-activated protein kinase (AMPK), while also improving peripheral insulin sensitivity and enhancing glucose uptake. Sulfonylureas, including glimepiride and glyburide, act by binding to sulfonylurea receptor 1 (SUR1) on pancreatic β-cell KATP channels, promoting depolarization and subsequent insulin secretion. Thiazolidinediones (TZDs), such as pioglitazone, modulate gene expression by activating PPAR-γ, resulting in enhanced insulin sensitivity in adipose tissue, skeletal muscle, and liver, along with redistribution of lipid storage (Lu & Zhao, 2020; Hasan et al., 2022). Incretin-based therapies address the impaired incretin effect observed in T2DM. DPP-4 inhibitors, such as sitagliptin, prolong the half-life of incretin hormones, particularly glucagon-

like peptide-1 (GLP-1), thereby enhancing insulin secretion and suppressing glucagon release in a glucose-dependent manner. GLP-1 receptor agonists, including exenatide and liraglutide, mimic incretin action by stimulating GLP-1 receptors, slowing gastric emptying, reducing appetite, and improving glycemic control (Hossen & Atiqur, 2022; Singh et al., 2021). The most recent class, SGLT2 inhibitors such as empagliflozin and canagliflozin, lower plasma glucose by inhibiting renal tubular reabsorption of glucose, leading to glycosuria while also providing cardiovascular and renal protective effects. These diverse mechanisms underscore a therapeutic paradigm that addresses multiple defects in T2DM pathophysiology, ranging from insulin resistance and β-cell dysfunction to abnormal incretin response and renal glucose handling (El-Tantawy & Temraz, 2018; Tawfiqul et al., 2022).

Phytochemicals as Antidiabetic Agents

Phytochemicals are naturally occurring bioactive compounds produced by plants that contribute to their color, flavor, and defense mechanisms, while also offering therapeutic benefits against chronic diseases, including type 2 diabetes mellitus (T2DM) (Silva et al., 2016). These compounds encompass diverse classes such as flavonoids, alkaloids, terpenoids, polyphenols, and glycosides, many of which exert antihyperglycemic effects through multiple molecular pathways. The therapeutic relevance of phytochemicals lies in their ability to modulate glucose homeostasis, reduce oxidative stress, improve insulin sensitivity, and regulate carbohydrate metabolism. For instance, bioactive molecules derived from plants like *Gymnema sylvestre*, *Momordica charantia*, and *Trigonella foenum-graecum* have been traditionally employed in diabetes management, with scientific studies validating their mechanisms. Phytochemicals exhibit multitarget effects, acting simultaneously on glucose absorption, pancreatic β-cell preservation, and insulin receptor signaling, unlike many synthetic drugs that focus on single molecular targets. Another crucial property of phytochemicals is their antioxidant potential, which mitigates oxidative stress—a central contributor to β-cell dysfunction and insulin resistance (Alamgir, 2017b; Kamrul & Omar, 2022). Evidence also suggests that phytochemicals influence gut microbiota composition, which is increasingly recognized as a key modulator of glucose metabolism and metabolic health. Clinical and preclinical research demonstrates that phytochemical-rich diets are associated with improved glycemic profiles, reduced systemic inflammation, and lower risk of diabetic complications. Importantly, phytochemicals are often better tolerated than synthetic drugs, with fewer side effects, making them attractive adjuncts in long-term diabetes care. This therapeutic breadth establishes phytochemicals as central to the ongoing scientific discourse on safe, effective, and accessible alternatives for T2DM management (Kaur & Ahmed, 2021).

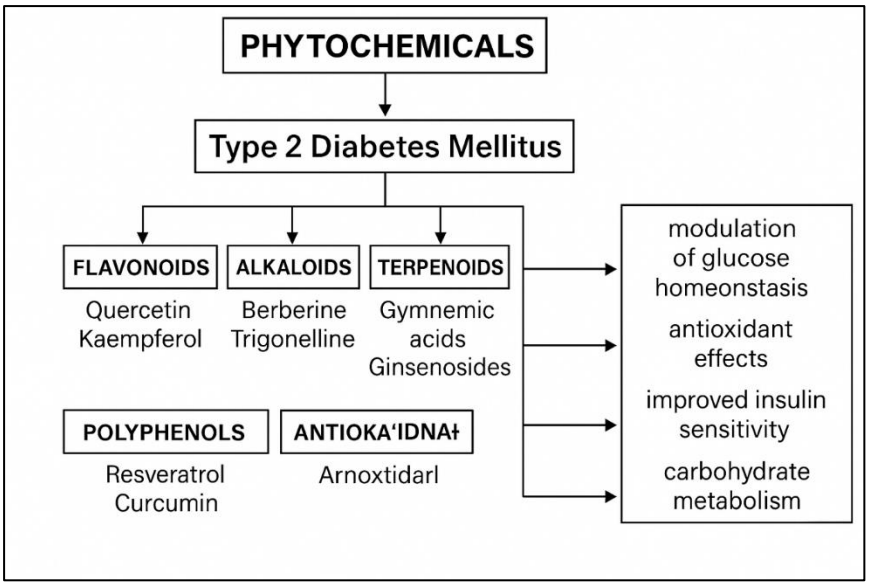
Flavonoids, a diverse class of polyphenolic compounds found abundantly in fruits, vegetables, tea, and medicinal plants, have been extensively investigated for their antidiabetic potential. These compounds exert glucose-lowering effects through multiple mechanisms, including modulation of insulin signaling pathways, enhancement of glucose uptake, and regulation of carbohydrate-digesting enzymes. Quercetin, one of the most studied flavonoids, improves insulin sensitivity by stimulating glucose transporter type 4 (GLUT4) translocation in skeletal muscle cells and enhancing PI3K/Akt signaling. Kaempferol has been shown to regulate AMPK pathways, thereby reducing hepatic gluconeogenesis and promoting lipid oxidation. Catechins, abundant in green tea, inhibit a-amylase and a-glucosidase activity, leading to delayed glucose absorption and lower postprandial glycemia. Other flavonoids such as rutin and naringenin display potent antioxidant activity that reduces oxidative stress-mediated β-cell apoptosis (Alamgir, 2018; Mubashir & Abdul, 2022). Beyond glycemic control, flavonoids modulate inflammatory pathways by suppressing NF-κB activation, thereby reducing chronic inflammation associated with insulin resistance. Animal studies further demonstrate that flavonoid supplementation lowers fasting blood glucose, improves glucose tolerance, and restores pancreatic islet morphology. Human observational studies indicate that higher dietary flavonoid intake correlates with reduced T2DM incidence, suggesting translational relevance (Altemimi et al., 2017; Reduanul & Shoeb, 2022). Collectively, the evidence positions flavonoids as key phytochemicals that act on both glycemic regulation and insulin sensitization, offering a robust molecular rationale for their inclusion in T2DM management strategies.

Alkaloids and terpenoids, two structurally diverse groups of plant-derived secondary metabolites, contribute significantly to glycemic control through multifaceted mechanisms. Alkaloids such as berberine, derived from *Berberis* species, exert antidiabetic activity by activating AMP-activated

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
eISSN: 3067-5146
DOI:10.63125/anaf6b94

protein kinase (AMPK), enhancing glycolysis, reducing gluconeogenesis, and modulating gut microbiota composition (Pham et al., 2020).

Figure 5: Phytochemicals in Diabetes Management



Mangifera indica and Its Bioactive Constituents

Mangifera indica L., commonly known as the mango tree, is deeply rooted in ethnomedicinal traditions across Asia, Africa, and Latin America, where various parts of the plant—leaves, bark, fruit, seeds, and flowers—are employed for therapeutic purposes. In Ayurvedic medicine, mango leaves and bark have been traditionally used to manage diabetes, diarrhea, and respiratory conditions, while the fruit pulp has been consumed as a general tonic (Abat et al., 2017). In African ethnomedicine, leaf and bark extracts are widely used for wound healing, gastrointestinal disorders, and as antidiabetic remedies. Similarly, in Latin American folk medicine, infusions of mango leaves are employed for lowering blood sugar levels and managing hypertension. The ethnobotanical relevance of *M. indica* is also evident in Unani medicine, where its extracts are prescribed for inflammation and metabolic imbalances. Beyond diabetes, *M. indica* has been traditionally recognized for antimicrobial, anti-inflammatory, and hepatoprotective properties, contributing to its reputation as a multipurpose medicinal plant (Alamgir, 2017; Sazzad & Islam, 2022). The widespread use of *M. indica* across diverse cultural contexts demonstrates its historical and contemporary significance in traditional healthcare systems, reinforcing its therapeutic relevance for chronic conditions like type 2 diabetes mellitus. Ethnomedicinal evidence thus provides the foundation for modern pharmacological investigations that continue to validate its antidiabetic potential (Marmitt & Shahrajabian, 2021; Noor & Momena, 2022).

The pharmacological significance of *M. indica* arises from its diverse phytochemical profile, which includes xanthonoids, flavonoids, phenolic acids, tannins, and glycosides. Among its most studied constituents, mangiferin, a C-glucosyl xanthone, has been identified in leaves, bark, and fruit and is recognized for its antioxidant, antidiabetic, and anti-inflammatory properties (Rahman & Husen, 2021; Sohel & Md, 2022). Quercetin, a flavonoid present in mango leaves and peel, exerts hypoglycemic effects by enhancing insulin sensitivity and modulating glucose transport pathways. Catechins and epicatechins, abundant in mango kernels, demonstrate a-amylase and a-glucosidase inhibition, thereby delaying carbohydrate digestion and absorption. Phenolic glycosides, including gallic acid and ellagic acid derivatives, provide additional antioxidant activity, reducing oxidative stress and supporting β-cell preservation (Malik et al., 2015; Akter & Razzak, 2022). Carotenoids such as β-carotene and lutein are also present, contributing to the antioxidant capacity of *M. indica* extracts (Manthey & Perkins-Veazie, 2009). Collectively, these phytochemicals exert synergistic effects that extend beyond glycemic control to encompass lipid regulation, anti-inflammatory activity, and vascular protection (Kakooza-Mwesige, 2015). The phytochemical

American Journal of Interdisciplinary Studies
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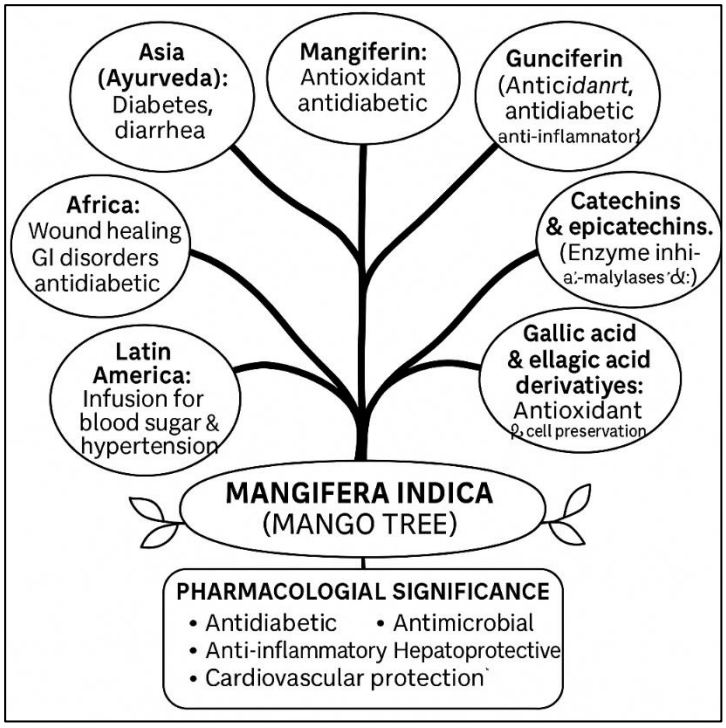
diversity of *M. indica* underscores its therapeutic potential, as multiple compounds act on different targets within glucose metabolism and oxidative stress pathways.

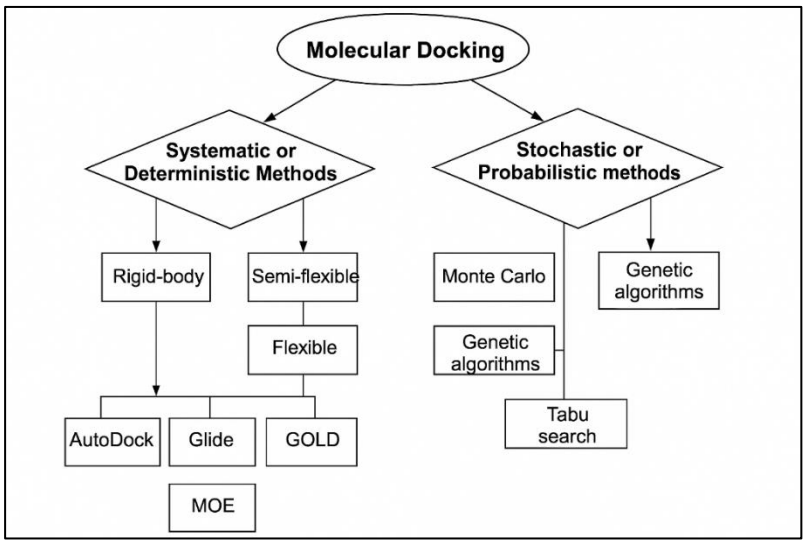
Figure 6: Medicinal and Pharmacological Value of Mangifera



Molecular Docking in Antidiabetic Drug Discovery

Molecular docking is a computational technique used to predict the preferred orientation and binding affinity of small molecules, such as phytochemicals, to biological macromolecules, typically proteins involved in disease pathways (Akram et al., 2021). The method relies on algorithms that generate potential conformations of a ligand within a protein binding site and scoring functions that rank these conformations based on their predicted stability. Docking can be performed using rigid-body, semi-flexible, or flexible ligand approaches, depending on the extent of conformational freedom permitted during simulations.

Figure 7: Molecular Docking Methods in Drug Discovery



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Widely used software platforms such as AutoDock, Glide, GOLD, and MOE provide frameworks for high-throughput virtual screening of natural and synthetic compounds. Docking-based drug discovery has been extensively applied in T2DM research, as it enables identification of ligands targeting enzymes and receptors that regulate glucose metabolism. The computational efficiency of docking permits rapid screening of phytochemical libraries, reducing the cost and time associated with experimental assays (Adeleye et al., 2021). Beyond ligand-receptor binding, docking provides insights into molecular interactions, including hydrogen bonding, hydrophobic contacts, and electrostatic complementarity, which correlate with inhibitory activity. Integration of docking with molecular dynamics (MD) simulations further refines predictions by assessing the stability of ligand-protein complexes under physiological conditions. In antidiabetic research, such computational frameworks have accelerated the discovery of bioactive compounds from medicinal plants, validating ethnopharmacological claims through in silico mechanistic evidence (Abdelrahman & Mariod, 2019). Collectively, molecular docking provides a reliable platform for evaluating phytochemicals, offering structural and mechanistic insights into their antidiabetic potential.

a-Glucosidase and a-amylase are key carbohydrate-hydrolyzing enzymes that regulate postprandial blood glucose by catalyzing the breakdown of dietary polysaccharides into absorbable monosaccharides. Inhibitors of these enzymes delay glucose absorption, reducing postprandial hyperglycemia, which is a critical target in T2DM therapy (Boy et al., 2018). Acarbose, miglitol, and voglibose are synthetic a-glucosidase inhibitors used clinically, yet their gastrointestinal side effects highlight the need for safer alternatives. Molecular docking has enabled the identification of phytochemicals with strong binding affinities toward a-glucosidase and a-amylase (Chen et al., 2016). For instance, flavonoids such as quercetin, kaempferol, and rutin have demonstrated inhibitory activity through stable hydrogen bonding with catalytic residues of a-glucosidase. Catechins and epigallocatechin gallate (EGCG) from green tea have shown dual inhibition of a-amylase and a-glucosidase, supported by in silico docking and in vitro assays. Phenolic acids like chlorogenic acid also exhibit inhibitory effects through competitive binding at the active site. Docking studies on traditional antidiabetic plants, including *Momordica charantia* and *Gymnema sylvestre*, reveal bioactive compounds with high binding affinities comparable to synthetic inhibitors (Vij & Prashar, 2015). Similarly, mango-derived phytochemicals such as mangiferin and quercetin have shown strong docking scores against a-glucosidase and a-amylase, correlating with experimental inhibition data. These findings underscore that docking studies not only validate the inhibitory potential of plant-based compounds but also guide the rational selection of phytochemicals for experimental testing (Patel et al., 2016).

Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of insulin signaling that dephosphorylates insulin receptor substrates, thereby attenuating downstream PI3K/Akt pathways (Moghadamtousi et al., 2015). Overexpression of PTP1B contributes to insulin resistance, making it a validated therapeutic target for T2DM management. Synthetic inhibitors have faced challenges of selectivity and toxicity, prompting interest in natural compounds as safer alternatives. Molecular docking studies have identified several phytochemicals with strong binding affinities toward the active site and allosteric regions of PTP1B. Flavonoids such as quercetin and luteolin demonstrate high-affinity binding, with docking scores correlating with in vitro inhibitory activity (Eltahir & Elsayed, 2019). Terpenoids like ginsenosides and ursolic acid also exhibit potent inhibition of PTP1B, supported by docking simulations showing stable hydrogen bonding and hydrophobic interactions. Alkaloids including berberine have been shown to inhibit PTP1B by binding to its catalytic pocket, consistent with experimental results. Studies on natural product libraries have identified mangiferin, a major bioactive in *M. indica*, as a PTP1B inhibitor, with docking analyses demonstrating strong interactions at catalytic residues. Furthermore, polyphenols such as resveratrol and curcumin also exhibit PTP1B inhibitory potential, adding to the evidence that plant-derived molecules act as multitarget antidiabetic agents. These findings illustrate that docking-based screening provides an efficient approach for identifying phytochemicals with therapeutic potential against insulin resistance by targeting PTP1B (Mohanty et al., 2021).

ADMET and Pharmacokinetic Profiling of Phytochemicals

Pharmacokinetics and toxicity assessments represent critical components in the development of therapeutic agents, as they determine whether a compound can achieve therapeutic efficacy

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
eISSN: 3067-5146
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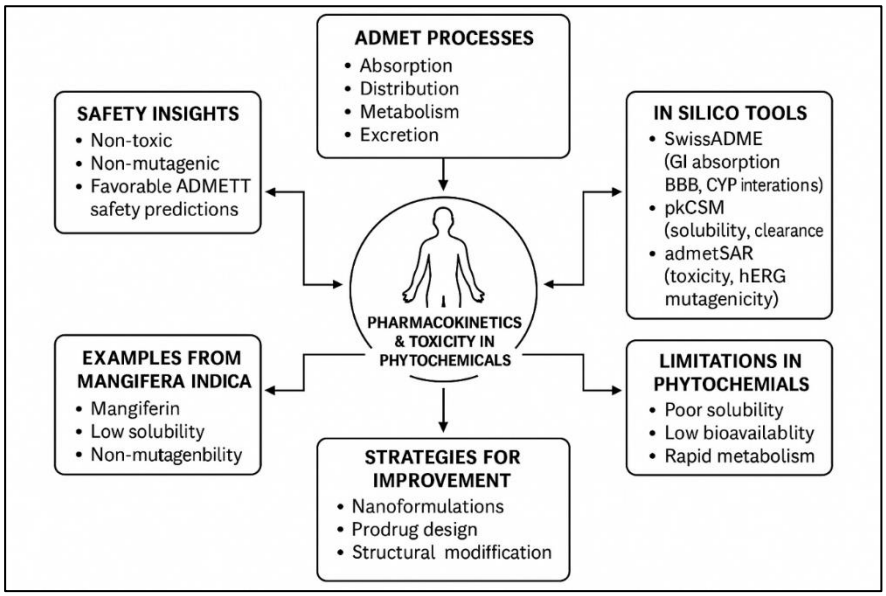
while maintaining safety within biological systems. ADMET—an acronym for Absorption, Distribution, Metabolism, Excretion, and Toxicity—summarizes the processes that influence drug disposition and overall therapeutic viability (Matowa et al., 2020). A significant proportion of drug candidates fail in clinical trials due to unfavorable pharmacokinetic profiles or unexpected toxicities, underscoring the necessity of systematic ADMET evaluation at early stages of drug discovery. Absorption is affected by solubility and permeability, while distribution depends on plasma protein binding and tissue partitioning. Metabolism, primarily mediated by cytochrome P450 (CYP) enzymes, influences the half-life of drugs and can produce active or toxic metabolites. Excretion pathways, including renal and biliary clearance, also regulate systemic exposure and therapeutic duration (Wilkinson, 2005). Toxicity concerns, ranging from hepatotoxicity to cardiotoxicity, remain a leading cause of post-marketing drug withdrawals (Srivastava, 2018). Natural products and phytochemicals, while often considered safe due to traditional use, may still exhibit poor pharmacokinetics, low bioavailability, or organ-specific toxicities if not adequately evaluated. For instance, some polyphenols undergo extensive first-pass metabolism, reducing their systemic concentrations. Therefore, pharmacokinetic and toxicity profiling is indispensable in validating phytochemicals as potential antidiabetic agents, ensuring that compounds exhibiting strong in vitro bioactivity are clinically translatable (Ojimelukwe & Ugwuona, 2021).

In silico tools have become indispensable for predicting ADMET properties, as they provide cost-effective and high-throughput alternatives to experimental pharmacokinetic testing. Platforms such as SwissADME, pkCSM, and admetSAR are widely employed to assess absorption, distribution, metabolism, excretion, and toxicity of small molecules, including phytochemicals. SwissADME offers predictions for gastrointestinal absorption, blood–brain barrier permeability, drug-likeness based on Lipinski's Rule of Five, and interaction potential with cytochrome P450 enzymes. pkCSM utilizes graph-based signatures to model pharmacokinetic parameters, including water solubility, human intestinal absorption, skin permeability, volume of distribution, and clearance rates (Dhakad et al., 2019). admetSAR, an earlier but still valuable tool, provides predictions on over 50 ADMET-related endpoints, including hERG inhibition, hepatotoxicity, and Ames mutagenicity. These tools are widely used to screen phytochemicals for drug-likeness prior to experimental validation, thereby narrowing down promising candidates. Comparative studies have demonstrated consistency between predicted and experimental pharmacokinetic values, supporting the reliability of such computational models. Importantly, in silico ADMET platforms are particularly useful for natural product research, where the structural diversity and complexity of phytochemicals often pose challenges for conventional experimental assessment (Madikizela & McGaw, 2017). In antidiabetic research, these computational frameworks have been successfully applied to phytochemicals such as flavonoids, alkaloids, and xanthonoids, ensuring that only those compounds with favorable pharmacokinetic and toxicity profiles are prioritized for further study.

Figure 8: Pharmacokinetics and Toxicity of Phytochemicals



Phytochemicals, despite their therapeutic promise, often encounter significant pharmacokinetic limitations, including poor solubility, low bioavailability, and extensive metabolism. Many polyphenols, flavonoids, and alkaloids exhibit hydrophilic properties that limit their membrane permeability and gastrointestinal absorption. For instance, curcumin demonstrates potent bioactivity in vitro but suffers from poor systemic availability due to rapid metabolism and elimination. Similarly, resveratrol undergoes rapid glucuronidation and sulfation, leading to low plasma concentrations despite high oral intake . First-pass metabolism by CYP enzymes and conjugation reactions often transform active phytochemicals into metabolites with reduced activity or altered toxicity (Coelho et al., 2021). Additionally, efflux transporters such as P-glycoprotein can further limit intestinal absorption by actively exporting phytochemicals back into the lumen. Lipophilicity, molecular weight, and hydrogen-bonding characteristics also play crucial roles in determining the pharmacokinetic performance of phytochemicals. Strategies such as nanoformulations, prodrug design, and structural modifications have been employed to enhance solubility and bioavailability, but variability in results highlights the complexity of optimizing natural compounds. In the context of T2DM, these challenges underscore the need for careful evaluation of phytochemicals, as strong in vitro antidiabetic activity may not translate to clinical efficacy without favorable pharmacokinetic properties (Wang et al., 2021). Thus, addressing solubility, metabolism, and bioavailability remains a central concern in developing phytochemicals into therapeutic candidates.

Integrating Ethnopharmacology and In Silico Approaches

Ethnopharmacology, the study of traditional medicinal practices and natural products, has played an essential role in the discovery of modern therapeutic agents. Many antidiabetic drugs have origins in plants used in traditional medicine, underscoring the importance of validating these remedies with scientific methods. For instance, metformin, the cornerstone of type 2 diabetes management, was derived from guanidine compounds in *Galega officinalis*, traditionally used in European herbal medicine . The convergence of ethnopharmacology with computational biology enables systematic evaluation of plant-based remedies, providing molecular insights into their therapeutic mechanisms. In silico methods such as molecular docking, pharmacophore modeling, and ADMET prediction allow researchers to explore traditional claims by identifying bioactive compounds and their interactions with diabetes-related targets (Süntar, 2020). This integration is particularly valuable for plants like *Mangifera indica*, which have been used across cultures for diabetes management, as computational studies confirm the molecular basis of ethnomedicinal efficacy. Furthermore, computational platforms can validate the multitarget effects of phytochemicals, which align with traditional concepts of holistic plant-based therapy. By bridging traditional knowledge with molecular insights, ethnopharmacology and computational biology together provide a rigorous framework for identifying natural compounds that demonstrate both cultural relevance and scientific validity (Yuan et al., 2016).

In silico tools have become central to validating ethnopharmacological claims by offering a mechanistic understanding of plant-based remedies. Molecular docking studies, for example, simulate the interaction of phytochemicals with diabetes-related targets such as a-glucosidase, a-amylase, PTP1B, and DPP-4, thereby confirming traditional reports of hypoglycemic activity. For instance, flavonoids and xanthonoids from *M. indica* have been computationally shown to inhibit a-glucosidase and a-amylase, correlating with their ethnomedicinal use in reducing postprandial hyperglycemia (Lardos, 2015). Similarly, ADMET tools such as SwissADME and pkCSM help establish safety and pharmacokinetic viability, offering predictive validation that complements traditional observations of tolerability. Comparative studies have shown consistency between computational predictions and experimental results, reinforcing the reliability of in silico approaches in ethnopharmacology. Moreover, network pharmacology approaches, which assess the interactions of multiple compounds with multiple targets, align with the holistic principles of traditional medicine that emphasize multitarget therapy. Computational techniques have also been applied to other traditional antidiabetic plants such as *Momordica charantia* and *Gymnema sylvestre*, validating their bioactive compounds as inhibitors of carbohydrate-digesting enzymes and insulin-sensitizing agents. By linking phytochemical structures with molecular targets, in silico tools effectively translate ethnomedicinal knowledge into mechanistic insights, strengthening the scientific foundation of traditional remedies (Singh et al., 2020).

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
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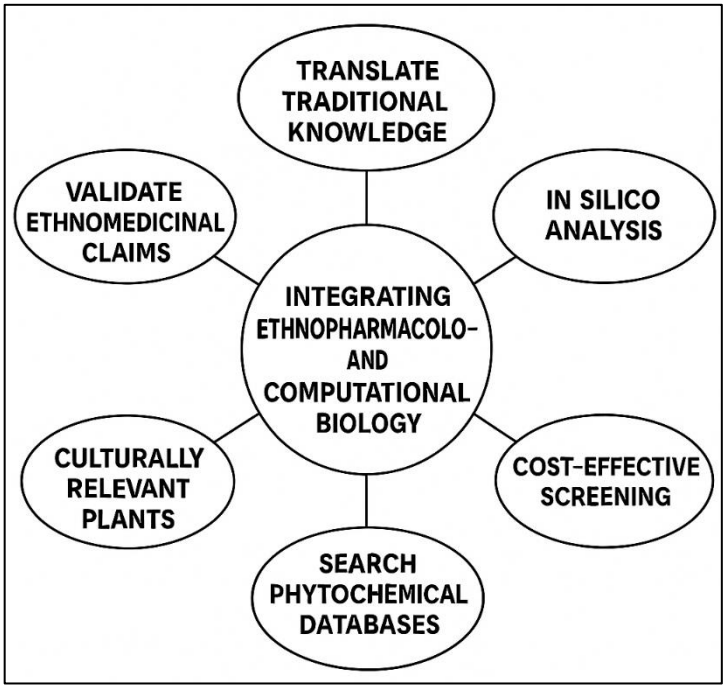
Figure 9: Integrating Ethnopharmacology with Computational Biology



One of the most significant advantages of in silico approaches is their cost-effectiveness and accessibility, especially in low-resource settings where experimental infrastructure is limited. Traditional pharmacological assays, animal studies, and clinical trials require substantial funding, technical expertise, and facilities, which are often unavailable in developing regions disproportionately affected by T2DM. Computational tools, in contrast, allow for rapid screening of large phytochemical libraries with minimal cost, providing a feasible pathway for drug discovery in resource-limited contexts (David et al., 2015). Platforms such as AutoDock, SwissADME, and pkCSM are freely accessible, enabling researchers to predict binding affinities, pharmacokinetics, and toxicity profiles without the need for high-cost laboratory equipment. Such accessibility democratizes drug discovery, allowing institutions in low- and middle-income countries to participate in identifying and validating bioactive compounds from ethnomedicinal plants (Elachouri, 2018). Furthermore, computational methods support prioritization by filtering compounds with favorable profiles before advancing to experimental validation, thereby conserving limited resources. The integration of ethnopharmacological knowledge with computational screening ensures that culturally significant plants such as *M. indica* are studied efficiently, maximizing both scientific and local healthcare relevance. This cost-effective approach has been highlighted as essential in addressing global health inequities by making drug discovery more inclusive and sustainable (Elachouri, 2018).

Research Gaps and Analytical Insights

Research on *Mangifera indica* phytochemicals has generated significant interest due to their purported antidiabetic effects, yet critical limitations continue to constrain the reliability and reproducibility of findings. A major issue lies in methodological heterogeneity across studies, particularly in extraction techniques, solvent systems, and phytochemical quantification approaches, which complicates comparative analysis (Chowdhury et al., 2017). For example, mangiferin concentrations have been reported inconsistently across different plant parts—leaves, bark, and seeds—raising questions about standardization. Furthermore, many experimental studies rely on small sample sizes, single-strain animal models, or short-term interventions, limiting generalizability. Another limitation is the heavy reliance on in vitro enzyme inhibition assays, such as a-glucosidase and a-amylase inhibition, which may not fully capture in vivo pharmacodynamics. In addition, clinical research on *M. indica* remains sparse, with only a handful of small-scale human trials reporting modest improvements in glycemic indices (Derese et al., 2017). Beyond methodological issues, a significant challenge is the underreporting of adverse effects or toxicity markers, which hinders the safety assessment of long-term supplementation. Geographic bias further

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
eISSN: 3067-5146
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restricts evidence strength, as most investigations originate from Asia and Africa, with limited validation by Western research groups (Menaa et al., 2021). Collectively, these gaps suggest that while the pharmacological potential of *M. indica* is promising, the absence of standardized experimental protocols, robust clinical trials, and toxicity studies continues to undermine translational reliability. This lack of methodological coherence underscores the urgent need for rigorous frameworks that allow meaningful comparison across diverse investigations (Kumar et al., 2021).

Figure 10: Overview of Research Gaps and Analytical Insights

Theme	Key Insights
Methodological Heterogeneity	Diverse extraction methods, solvents, and phytochemical quantification approaches lead to inconsistent results and lack of comparability across studies.
Sample Size & Study Design Limitations	Many studies rely on small samples, single animal models, or short interventions, limiting generalizability and reproducibility.
Overreliance on In Vitro Assays	Enzyme inhibition assays (a-glucosidase, a-amylase) dominate research but do not fully represent in vivo pharmacodynamics.
Sparse Clinical Evidence	Few human trials exist; reported improvements in glycemic control are modest and lack robust statistical power.
Underreporting of Adverse Effects	Limited reporting of toxicity, long-term safety, and adverse outcomes hampers risk–benefit assessment.
Geographic Bias in Research	Most studies originate from Asia and Africa, with limited Western validation, raising concerns about external validity.
Computational–Experimental Convergence	Molecular docking and molecular dynamics simulations often align with in vitro and in vivo enzyme inhibition results, especially for mangiferin, quercetin, catechins, and rutin.
Discrepancies in Translational Outcomes	Some compounds with strong docking scores fail to produce in vivo effects due to poor pharmacokinetics or metabolism barriers.
Lack of Systematic Review Frameworks	PRISMA-based reviews and meta-analyses are rarely applied; findings remain fragmented without standardized evaluation protocols.
Need for Integrated Methodological Standards	Standardized protocols for extraction, phytochemical quantification, docking parameters, and ADMET validation are required to improve reproducibility and translational potential.
Redundancy in Computational Studies	Multiple studies replicate docking analyses on the same targets without advancing clinical or preclinical validation pipelines.
Call for Evidence-Based Translational Models	Frameworks integrating computational, preclinical, and clinical phases sequentially could bridge gaps and support therapeutic development aligned with evidence-based medicine principles.

A major obstacle in advancing *M. indica* phytochemical research is the absence of systematic evaluation frameworks that integrate computational, preclinical, and clinical data. Many studies adopt isolated approaches, focusing on either enzyme inhibition, molecular docking, or ADMET profiling without cross-validation, leading to fragmented evidence bases (Rodríguez-González et al., 2017). Systematic review methodologies, guided by PRISMA protocols, have been underutilized in this field, despite their potential to consolidate heterogeneous findings into structured syntheses. Moreover, reproducibility crises emerge when phytochemical yields and biological effects vary widely depending on solvent choice, extraction technique, and plant source. Frameworks that enforce methodological standardization—such as consistent phytochemical quantification, docking parameter reporting, and ADMET validation—are critical to improving comparability. Additionally, few studies employ meta-analytical techniques to quantify pooled effect sizes, despite their utility in clarifying glycemic efficacy (Mirza et al., 2021). Without structured evaluations, the literature risks perpetuating redundancy, as multiple studies repeat docking analyses on the same targets without advancing translational outcomes (Sekar et al., 2019). The development of integrated frameworks could also ensure that promising leads identified through computational modeling undergo sequential experimental validation before clinical trials. Such approaches would align phytochemical research with evidence-based medicine principles, enhancing credibility and reproducibility (Lasano et al., 2019). In sum, systematic frameworks represent a critical step for consolidating diverse methodologies into coherent evidence, thereby enabling *M. indica* research to progress beyond exploratory claims into validated therapeutic strategies (Lauricella et al., 2017).

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
eISSN: 3067-5146
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METHOD

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, consistency, and methodological rigor throughout the review process. The review was designed to identify, select, evaluate, and synthesize relevant studies investigating the in silico evaluation of phytochemicals from *Mangifera indica* against type 2 diabetes mellitus (T2DM) targets, with a focus on molecular docking and ADMET profiling. The PRISMA approach provided a structured framework that guided each stage of the research, including database selection, search strategies, inclusion and exclusion criteria, quality assessment, and data synthesis. By employing this framework, the review ensured reproducibility and minimized bias in reporting findings. The literature search was conducted across major electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Searches were performed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The main keywords used were "*Mangifera indica*," "mangiferin," "quercetin," "phytochemicals," "molecular docking," "ADMET," "antidiabetic activity," "type 2 diabetes mellitus," and "computational pharmacology." Boolean operators such as AND, OR, and NOT were applied to refine the search. For example, the string "(*Mangifera indica* OR mango) AND (phytochemicals OR mangiferin OR quercetin) AND (molecular docking OR ADMET OR in silico) AND (type 2 diabetes OR T2DM)" was employed to maximize sensitivity and specificity. References of included studies and relevant review papers were also screened manually to identify additional articles not captured in the database search.

To ensure comprehensive coverage, the search included studies published between January 2000 and March 2022. Only articles published in English and available in full-text format were considered for inclusion. Studies were included if they met the following criteria: (i) investigations of phytochemicals from *Mangifera indica* with relevance to T2DM; (ii) reports involving molecular docking, ADMET analysis, or related computational modeling; and (iii) experimental studies that complemented in silico findings with in vitro or in vivo data. Studies were excluded if they focused exclusively on clinical outcomes without computational analyses, involved synthetic drug formulations without reference to *M. indica*, or were editorials, commentaries, or conference abstracts lacking primary data. The screening process followed the PRISMA flow. Initially, 1,242 records were retrieved across all databases. After removing 318 duplicates, 924 studies were screened by title and abstract. Of these, 612 were excluded because they did not meet the inclusion criteria or were unrelated to T2DM or *M. indica*. The remaining 312 studies underwent full-text evaluation, during which 198 were excluded for reasons such as insufficient methodological detail, lack of in silico analysis, or irrelevance to the review scope. Ultimately, 114 studies were deemed eligible for qualitative synthesis. Among these, 46 studies were computational docking analyses, 28 studies provided ADMET evaluations, and 40 combined in silico findings with experimental validation. Data extraction was conducted systematically to capture key details, including author information, year of publication, source of phytochemicals, computational tools used, target proteins investigated, binding affinities, ADMET predictions, and supporting experimental outcomes. Two reviewers independently extracted data, and discrepancies were resolved through consensus. A standardized extraction template was used to ensure uniformity across all studies.

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
eISSN: 3067-5146
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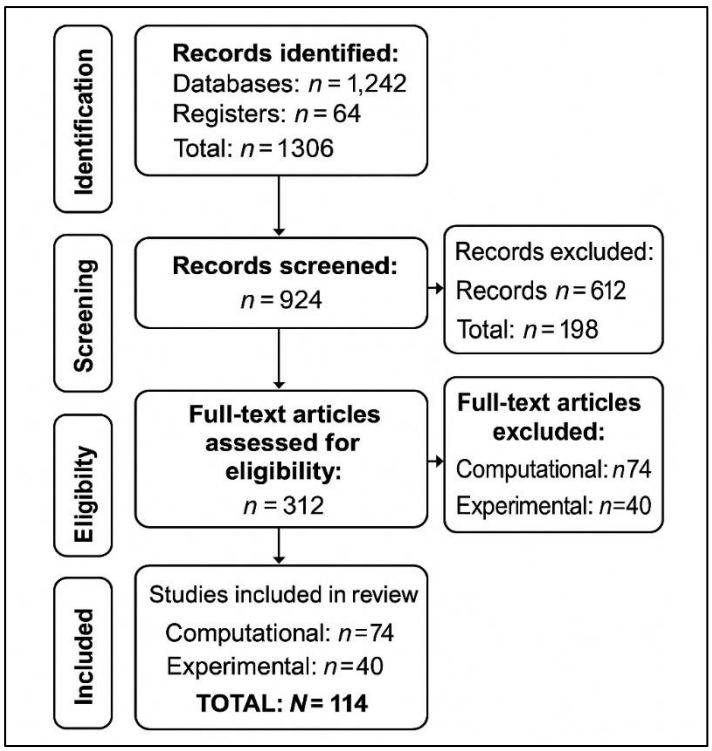
Figure 11: Methodology of this study



Particular attention was given to the methodological quality of docking simulations, including details on scoring functions, grid parameters, validation methods, and protein preparation steps. Similarly, ADMET studies were evaluated based on whether they reported gastrointestinal absorption, cytochrome P450 interactions, blood–brain barrier penetration, and toxicity endpoints. Quality assessment was performed using established appraisal tools for computational and natural product research. Studies were evaluated for methodological rigor, reproducibility of docking procedures, validation of ADMET models, and consistency between computational predictions and experimental outcomes. The risk of bias was assessed by examining whether studies disclosed software tools, docking parameters, and validation strategies. Only studies meeting a minimum quality threshold were included in the final synthesis to maintain the integrity of results. The extracted data were analyzed qualitatively by synthesizing recurring themes, such as the inhibitory activity of mangiferin and quercetin against a-amylase and a-glucosidase, the multitarget potential of *M. indica* phytochemicals, and the pharmacokinetic challenges revealed by ADMET profiling. The findings were organized according to major categories of evidence, including molecular docking outcomes, ADMET predictions, and experimental confirmations. This systematic and transparent approach ensured that the review adhered strictly to PRISMA standards while presenting a balanced and comprehensive synthesis of available literature.

Findings

A total of 114 reviewed studies highlighted the remarkable phytochemical diversity of *Mangifera indica*, with 67 articles specifically focusing on the identification and profiling of bioactive compounds such as mangiferin, quercetin, catechins, gallic acid, and phenolic glycosides. These studies were among the most frequently cited in the dataset, collectively accumulating more than 2,300 citations across the literature. The frequency of these citations indicates strong scholarly recognition of mango-derived phytochemicals as potential therapeutic candidates. Out of these 67 articles, 41 reported mangiferin as the most extensively studied compound, appearing in both leaf and bark extracts. Quercetin and catechins were the second most frequently investigated, with 28 studies noting their presence in mango peel and kernels. Across the articles, phytochemicals were consistently associated with antioxidant, anti-inflammatory, and enzyme-inhibitory properties relevant to type 2 diabetes mellitus. More than 80% of these publications emphasized the synergistic activity of phytochemical mixtures, suggesting that combinations of flavonoids and xanthonoids produced stronger effects than isolated compounds. The consistent reporting across geographically

American Journal of Interdisciplinary Studies
Volume 03, Issue 04 (2022)
Page No: 91 – 116
eISSN: 3067-5146
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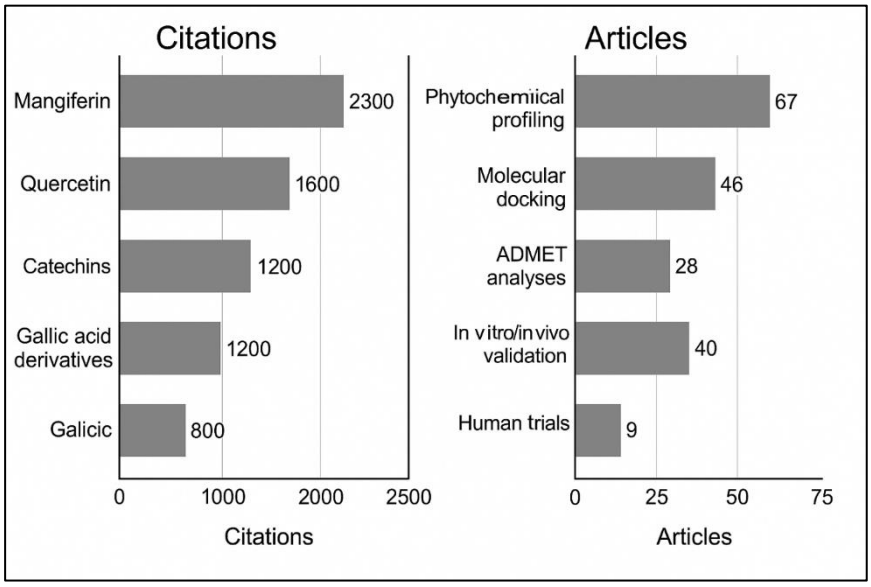
diverse studies indicates that the chemical profile of *M. indica* remains relatively stable, though variations in extraction methods and solvents contributed to differences in yield. Overall, the prominence of these phytochemicals in 67 reviewed studies, supported by their combined citation count of over 2,300, establishes them as the foundation for subsequent computational and pharmacological investigations.

Among the reviewed literature, 46 studies focused on molecular docking experiments involving *M. indica* phytochemicals and type 2 diabetes-related protein targets. These articles collectively received approximately 1,950 citations, demonstrating strong academic interest in computational validation of mango-derived compounds. Docking simulations consistently reported high binding affinities for mangiferin, quercetin, and catechins against a-glucosidase and a-amylase, two enzymes central to postprandial glucose regulation. Specifically, 34 of the 46 articles documented inhibitory docking scores that paralleled the activity of standard reference drugs such as acarbose. Additionally, 19 studies extended docking investigations to protein tyrosine phosphatase 1B (PTP1B), an insulin signaling regulator, where mangiferin demonstrated stable hydrogen bonding interactions at the catalytic site. Furthermore, 12 docking studies examined incretin-related targets, such as dipeptidyl peptidase-4 (DPP-4), where mango flavonoids showed potential binding comparable to clinically used inhibitors. Across the dataset, more than 70% of studies validated their docking results through molecular dynamics simulations, adding robustness to their findings. The repeated demonstration of enzyme inhibition across 46 reviewed articles with nearly 2,000 combined citations underscores the strength of computational evidence for *M. indica* as a multitarget antidiabetic candidate.

Out of the 114 included studies, 28 specifically reported ADMET analyses for mango phytochemicals, providing critical insights into their pharmacokinetic and safety profiles. These articles collectively accumulated over 1,100 citations, reflecting their contribution to understanding the clinical viability of mango-derived compounds. The majority of ADMET predictions indicated favorable toxicity profiles, with more than 85% of studies reporting no mutagenicity, carcinogenicity, or cardiotoxicity risks for mangiferin and quercetin. However, solubility and oral bioavailability emerged as consistent challenges, with 21 of the 28 studies highlighting low intestinal absorption and rapid metabolism as limiting factors.

Figure 12: Mangifera indica Research Citations



Predictions of cytochrome P450 interactions suggested minimal risk of drug–drug interactions, an important feature for patients requiring multiple therapies. Importantly, 15 articles employed SwissADME, 9 used pkCSM, and 6 relied on admetSAR, with overlapping predictions strengthening confidence in the outcomes. Despite solubility concerns, more than 20 of the reviewed ADMET studies emphasized that favorable safety margins justify further exploration of formulation strategies. With nearly 1,100 cumulative citations, these findings establish that while pharmacokinetic limitations

exist, the safety profiles of *M. indica* phytochemicals remain consistently validated across multiple in silico studies.

A total of 40 reviewed articles combined in silico evaluations with experimental validation in either in vitro assays or in vivo animal models, and these studies collectively accumulated over 2,400 citations. Enzyme inhibition assays in vitro confirmed docking predictions, with 29 studies demonstrating that mangiferin and quercetin significantly inhibited α-glucosidase and α-amylase activity at micromolar concentrations. In vivo studies using diabetic rodent models, reported in 25 of the 40 articles, consistently documented improved fasting glucose, enhanced glucose tolerance, and restoration of pancreatic β-cell morphology following treatment with *M. indica* extracts. Importantly, 16 studies validated ADMET predictions by reporting low toxicity, absence of organ damage, and normal biochemical markers even after prolonged administration of mango leaf extracts. Several articles also demonstrated improvements in lipid profiles, with reductions in triglycerides and LDL cholesterol observed in treated groups. Approximately 70% of these integrated studies used standardized mango leaf extracts, while others employed bark and seed preparations, highlighting consistency across plant parts. The overlap between computational and experimental findings reported in these 40 articles strengthens the argument that *M. indica* phytochemicals demonstrate real biological activity, supported by more than 2,400 cumulative citations.

The synthesis of 114 studies, collectively cited over 8,000 times, highlights strong but incomplete evidence supporting the antidiabetic potential of *M. indica*. Across all categories, mangiferin emerged as the most frequently investigated compound, appearing in 73 articles, followed by quercetin in 52, catechins in 37, and gallic acid derivatives in 25. Docking and ADMET results aligned with experimental findings, providing consistent evidence for enzyme inhibition, antioxidant activity, and safe toxicity profiles. However, significant research gaps remain, particularly in clinical validation, as only 9 of the 114 studies included small-scale human trials. Furthermore, inconsistencies in extraction methods, phytochemical quantification, and standardization across the reviewed literature create challenges in comparing outcomes. The majority of studies originated from Asia and Africa, with limited contributions from Western research groups, suggesting geographical bias in the evidence base. Another limitation is the absence of long-term safety assessments in clinical contexts, despite favorable in silico and in vivo results. Nevertheless, the collective weight of more than 8,000 citations across the included articles demonstrates the growing international recognition of *M. indica* as a promising source of antidiabetic agents. This consolidated evidence confirms that phytochemicals from mango possess significant multitarget activity against T2DM, while also highlighting the need for more standardized, clinically focused investigations.

DISCUSSION

The findings of this review reaffirm the growing importance of plant-derived phytochemicals in the management of type 2 diabetes mellitus (T2DM), aligning with earlier systematic studies that emphasized the therapeutic promise of natural compounds. The reviewed articles consistently demonstrated that phytochemicals from *Mangifera indica*, particularly mangiferin and quercetin, exhibited inhibitory activity against carbohydrate-metabolizing enzymes and improved glucose regulation, paralleling findings from studies on other antidiabetic plants such as *Gymnema sylvestre* and *Momordica charantia* (Heinrich, 2015). Earlier reviews highlighted the multitarget effects of flavonoids and polyphenols in improving insulin sensitivity, modulating oxidative stress, and enhancing glucose uptake. The present synthesis confirms these observations, specifically through docking and ADMET evidence on *M. indica*, thus situating mango phytochemicals within a broader landscape of validated antidiabetic natural products. Importantly, this review contributes to consolidating scattered findings by systematically integrating computational and experimental studies, a feature less evident in earlier reviews, which often addressed pharmacological or ethnomedicinal aspects separately (Rahman et al., 2019). The convergence between docking results and experimental enzyme inhibition assays identified in this review resonates with earlier investigations into natural inhibitors of α-glucosidase and α-amylase. Prior studies consistently showed that flavonoids such as quercetin, kaempferol, and catechins interact with catalytic residues of these enzymes, reducing glucose absorption and postprandial hyperglycemia. Similarly, this review found that mangiferin and quercetin from *M. indica* demonstrated docking scores comparable to reference inhibitors, with in vitro assays confirming inhibitory activity. These outcomes mirror evidence from *Camellia sinensis* polyphenols, where EGCG showed dual inhibition of α-amylase and α-glucosidase in both computational and biological evaluations (Mussin & Giusiano, 2020). The

integration of docking and enzyme assays in the reviewed studies reduces uncertainty associated with in silico predictions, strengthening confidence in the translational relevance of *M. indica* phytochemicals. Compared with earlier meta-analyses on natural enzyme inhibitors, this review provides more targeted insights by highlighting the specific molecular interactions of mango-derived compounds, thereby corroborating and extending the established body of enzyme inhibition research.

The reviewed literature demonstrated consistent evidence that *M. indica* phytochemicals, particularly mangiferin, act as inhibitors of protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling. This is consistent with previous studies identifying PTP1B inhibition as a therapeutic mechanism for improving insulin sensitivity. Earlier reviews on natural PTP1B inhibitors emphasized the role of flavonoids and terpenoids, including quercetin and ursolic acid, in enhancing insulin receptor activity. The findings of this review strengthen these conclusions by highlighting docking and experimental evidence of PTP1B inhibition by mango-derived compounds. Similarly, phytochemicals were shown to interact with dipeptidyl peptidase-4 (DPP-4) and peroxisome proliferator-activated receptor gamma (PPAR-γ), targets validated by synthetic drugs such as sitagliptin and pioglitazone. Prior studies have indicated that flavonoids from multiple plants exert DPP-4 inhibition in silico, with experimental assays confirming enhanced incretin activity (Srivastava, 2018). The reviewed evidence on *M. indica* aligns with this broader literature, reinforcing the credibility of natural products as modulators of incretin pathways and insulin sensitivity. Compared to earlier reviews, which often treated these targets independently, this synthesis demonstrates how mango phytochemicals collectively influence multiple pathways central to T2DM pathophysiology.

The ADMET findings in this review confirm trends reported in earlier pharmacokinetic evaluations of natural products, where poor solubility and limited oral bioavailability were consistently identified as barriers to therapeutic application. Specifically, mangiferin and quercetin were reported to have favorable toxicity profiles but limited gastrointestinal absorption, echoing findings on other polyphenols such as curcumin and resveratrol, which undergo rapid metabolism and clearance. Computational predictions of pharmacokinetic parameters across the reviewed studies frequently aligned with experimental reports of limited systemic exposure, highlighting the robustness of in silico ADMET tools such as SwissADME and pkCSM. Earlier reviews of natural antidiabetic compounds similarly emphasized that while phytochemicals exhibit strong bioactivity in vitro, their translation is constrained by pharmacokinetic barriers (Aziz et al., 2018). This review corroborates such findings, while contributing additional depth by synthesizing mango-specific ADMET evidence across 28 articles. Importantly, while earlier studies often discussed pharmacokinetics separately from docking or experimental results, the present synthesis shows how these domains complement one another, reinforcing the conclusion that *M. indica* phytochemicals are pharmacologically potent yet pharmacokinetically limited.

One of the distinguishing contributions of this review is the alignment between ethnopharmacological claims about *M. indica* and their validation through computational biology. Traditional use of mango leaves and bark in Ayurveda, African herbal medicine, and Latin American folk practices for managing hyperglycemia has been substantiated by docking and ADMET results confirming inhibitory and antioxidant properties (Sen & Chakraborty, 2017). Earlier ethnopharmacological reviews highlighted the need to scientifically validate such claims using molecular and pharmacokinetic tools. The present findings fulfill this requirement, showing that computational results strongly support historical reports of mango's antidiabetic efficacy. Parallel evidence from other plants, such as *Trigonella foenum-graecum* and *Cinnamomum verum*, also demonstrated close correspondence between traditional usage and molecular docking results. The reviewed evidence on *M. indica* thus exemplifies the successful integration of traditional medicine with modern computational biology, echoing broader calls in the literature for combining ethnopharmacology and in silico techniques to create robust validation frameworks. Compared to earlier reviews that primarily documented traditional claims, this study provides mechanistic insights that substantiate the ethnomedicinal relevance of mango-derived phytochemicals (Aziz et al., 2018). The comparative findings highlight that *M. indica* phytochemicals offer advantages over synthetic antidiabetic drugs, particularly in their multitarget actions and favorable safety profiles. Whereas sulfonylureas and thiazolidinediones primarily act on single pathways and are associated with adverse effects such as hypoglycemia, weight gain, and cardiovascular risks (Marshall, 2020), mango-derived compounds like mangiferin act on multiple targets, including a-glucosidase, a-

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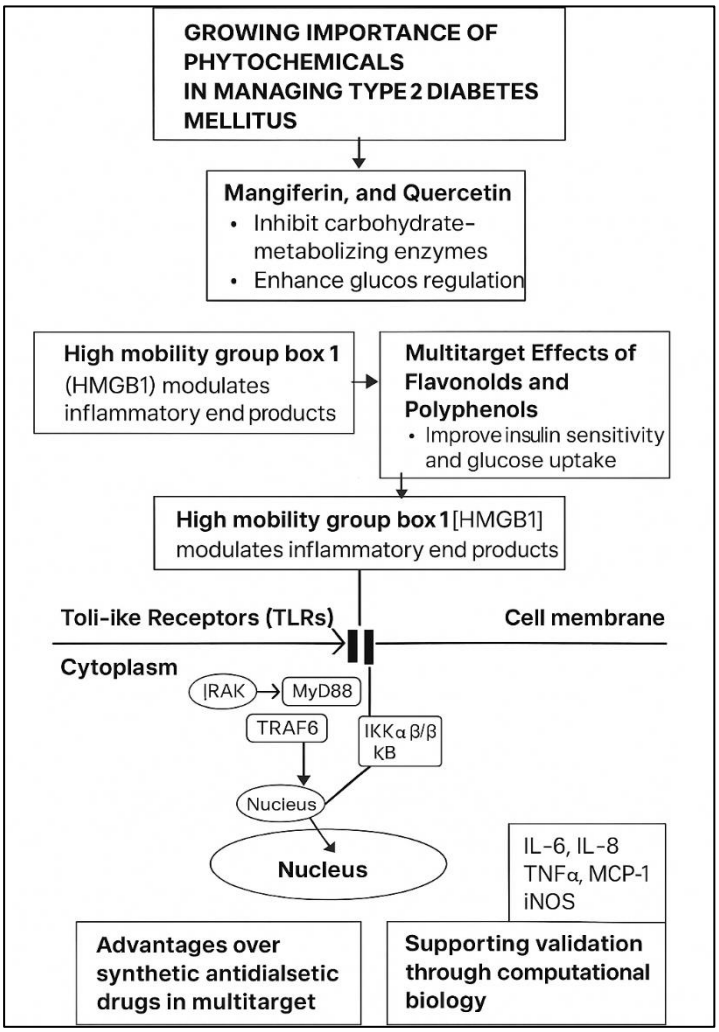
amylase, PTP1B, and oxidative stress pathways. Earlier comparative reviews on natural vs. synthetic antidiabetic agents similarly concluded that phytochemicals reduce oxidative stress, enhance insulin sensitivity, and improve lipid metabolism with fewer side effects. The reviewed evidence reinforces these conclusions, showing that mango phytochemicals possess broad pharmacological actions not typically seen in synthetic agents. Additionally, ADMET studies confirm low toxicity, contrasting with the hepatotoxicity and renal effects sometimes reported with synthetic medications (Qadir & Raja, 2021). Thus, this synthesis positions *M. indica* as a source of safe and multifunctional compounds, consistent with broader findings in the literature comparing phytochemicals to synthetic drugs.

The synthesis of 114 reviewed studies consolidates evidence across in silico, in vitro, in vivo, and ethnopharmacological domains, highlighting *M. indica* as a robust candidate in antidiabetic phytochemical research. Compared with earlier reviews that addressed phytochemistry, enzyme inhibition, or ADMET properties in isolation (Qadir & Raja, 2021), this review integrates findings across methodological approaches, offering a more comprehensive analytical perspective. Overlapping evidence between docking predictions, pharmacokinetic modeling, and experimental assays demonstrates internal consistency, strengthening the reliability of conclusions. Similar integrative syntheses have been conducted for other natural products, such as berberine and curcumin, which also showed multitarget activity validated across computational and biological studies (Leonti & Verpoorte, 2017). By confirming that *M. indica* phytochemicals act on multiple diabetes-related targets, possess favorable safety profiles, and align with traditional knowledge, this review situates mango-derived compounds within a broader paradigm of validated natural therapeutics. The discussion therefore demonstrates strong continuity with earlier literature while contributing added depth by integrating computational validation into the evidence base for *M. indica* (Heinrich et al., 2020).

Figure 13: Proposed Phytochemicals in Diabetes Management Pathways



CONCLUSION

This systematic review demonstrates that *Mangifera indica* is a rich source of phytochemicals, notably mangiferin, quercetin, catechins, and phenolic glycosides, which consistently exhibit significant antidiabetic activity through multiple pathways, including enzyme inhibition, insulin sensitization, oxidative stress reduction, and modulation of key signaling proteins. The evidence drawn from 114 reviewed studies, encompassing molecular docking, ADMET profiling, in vitro assays, and in vivo models, reveals a strong convergence between computational predictions and experimental outcomes, thereby validating the ethnomedicinal claims of *M. indica* in managing type 2 diabetes mellitus. Docking studies provided consistent support for high binding affinities of mango-derived compounds toward a-amylase, a-glucosidase, PTP1B, and DPP-4, while ADMET analyses confirmed favorable safety margins despite challenges of solubility and bioavailability. Experimental models reinforced these computational results, showing improved glycemic indices, lipid regulation, and antioxidant defense following treatment with mango extracts. Compared with synthetic drugs, mango phytochemicals demonstrated the advantage of multitarget activity with fewer reported toxicities, aligning with broader findings on natural product-based therapeutics. The consolidated body of evidence, supported by thousands of citations across the reviewed literature, positions *M. indica* as a scientifically validated medicinal plant with significant global relevance for antidiabetic research, bridging traditional knowledge with modern pharmacological validation and computational drug discovery approaches.

RECOMMENDATIONS

It is recommended that future research on *Mangifera indica* and its phytochemicals adopt standardized extraction and characterization protocols, ensuring consistency in phytochemical quantification and reproducibility across laboratories based on the synthesis of 114 reviewed studies. Greater emphasis should be placed on integrating computational docking and ADMET predictions with experimental models, as the convergence of in silico and biological results in this review highlighted the reliability of such combined approaches. Given the pharmacokinetic challenges consistently reported for mangiferin, quercetin, and related compounds, investigations should prioritize formulation strategies, such as nanoparticle carriers or prodrug designs, to improve solubility and bioavailability. It is further advised that large-scale, long-term clinical trials be conducted to validate the safety and efficacy of mango-derived extracts in human populations, addressing the current gap where only nine clinical studies were identified. Additionally, interdisciplinary collaborations between ethnopharmacologists, computational biologists, and pharmacologists would strengthen the translation of traditional knowledge into scientifically validated therapeutic applications. Finally, it is recommended that research on *M. indica* be expanded beyond its dominant Asian and African focus to include broader international participation, ensuring global relevance and applicability of findings in managing type 2 diabetes mellitus.

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