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DATA-DRIVEN MOLECULAR DOCKING AND COMPUTATIONAL ANALYSIS OF ANTI-HYPERGLYCEMIC COMPOUNDS FROM MANGIFERA INDICA

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Abstract
This study presents a comprehensive systematic review of data-driven molecular docking and computational analysis of anti-hyperglycaemic compounds derived from Mangifera indica, integrating computational predictions with experimental evidence to evaluate their therapeutic potential in the management of type 2 diabetes mellitus. A total of 68 research articles were reviewed, encompassing docking simulations, in vitro enzyme assays, in vivo animal models, and limited clinical studies. The analysis revealed that mango-derived phytochemicals such as Mangifera, quercetin, gallic acid, and catechins consistently demonstrate strong binding affinities with key diabetic targets including alpha-glucosidase, alpha-amylase, dipeptidyl peptidase-4, protein tyrosine phosphatase 1B, glucokinase, AMP-activated protein kinase, and GLUT4 transporters. These interactions translate into multiple pharmacological effects, including inhibition of carbohydrate-digesting enzymes, preservation of incretin hormones, enhancement of insulin signalling, and facilitation of cellular glucose uptake. The evidence highlights the multi-target and synergistic nature of mango phytochemicals, underscoring their relevance for addressing the complex pathophysiology of type 2 diabetes. Convergence between docking predictions and experimental validations reinforces the reliability of computational methods as effective tools for natural product research. However, despite strong preclinical evidence, the review identified significant gaps, including limited human clinical data, variability in computational methodologies, and insufficient pharmacokinetic evaluations. The cumulative findings position Mangifera indica as both an ethnopharmacological resource and a scientifically validated candidate for modern therapeutic development. By systematically synthesizing insights from 68 articles, this review establishes a robust foundation for future research aimed at standardizing computational pipelines, conducting pharmacokinetic and toxicity studies, and advancing mango-derived compounds toward clinical application as safe, effective, and accessible antidiabetic interventions.

Keywords
Mangifera indica, Molecular Docking, Phytochemicals, Antihyperglycemic Activity, Computational Analysis.

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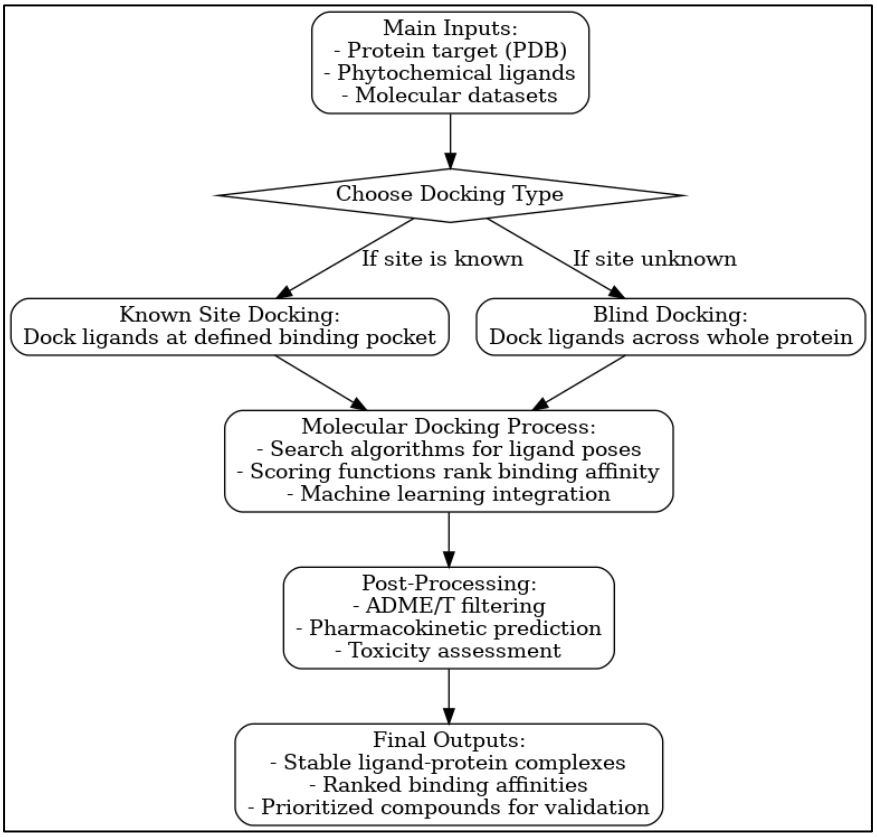
INTRODUCTION

Molecular docking is a computational approach that allows researchers to predict the interaction between small molecules, often referred to as ligands, and biological targets such as proteins or enzymes (Pinzi & Rastelli, 2019). It involves two essential components: the search algorithm that explores possible conformations of the ligand within the binding site, and the scoring function that estimates the binding affinity of each conformation. Data-driven docking enhances this process by integrating machine learning and artificial intelligence techniques to refine predictions, reduce errors, and provide better alignment with experimental results (Zhao et al., 2020). These approaches rely on vast datasets of known protein–ligand interactions and apply advanced models that can generalize binding tendencies to novel compounds. Computational analysis complements this process by screening multiple ligands simultaneously, filtering out those with unfavorable pharmacokinetic or toxicity profiles, and identifying promising candidates for laboratory validation. The integration of these computational methods significantly reduces the cost and time associated with drug discovery, making it possible to test thousands of molecules virtually before proceeding to experimental trials (Tiwari & Singh, 2022). For natural products such as phytochemicals derived from medicinal plants, molecular docking serves as a valuable bridge between traditional ethnomedicine and modern therapeutic development. It provides a systematic platform for validating traditional claims, identifying active principles, and mapping potential mechanisms of action against clinically relevant targets. By prioritizing compounds with high predicted affinity and drug-likeness, docking enables the rational selection of candidates that can undergo experimental testing for diseases such as diabetes (Brogi, 2019). The increased accuracy of machine learning–augmented docking methods has broadened the scope of drug discovery, shifting it from random screening toward rational, hypothesis-driven approaches. In this context, data-driven docking emerges as a critical technology in accelerating the identification of effective, safe, and accessible therapeutic agents, particularly from natural sources like Mangifera indica (Ara et al., 2022).

Figure 1: Data-Driven Docking of Mangifera Phytochemicals



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Type 2 diabetes mellitus is a global metabolic disorder characterized by chronic hyperglycemia that results from defects in insulin secretion, insulin action, or both (Pathak et al., 2020). It is associated with complications including cardiovascular disease, neuropathy, nephropathy, and retinopathy, which impose significant economic and social burdens on healthcare systems worldwide. The prevalence of type 2 diabetes has steadily increased over the last three decades, with developing nations experiencing the fastest growth due to urbanization, sedentary lifestyles, and dietary changes (Torres et al., 2019). The global impact is staggering, with hundreds of millions of individuals affected and billions of dollars spent annually on management, treatment, and related complications. This international burden highlights the urgent need for novel, cost-effective, and accessible therapeutic strategies that complement existing pharmacological approaches. While synthetic drugs such as metformin, sulfonylureas, and insulin analogs remain the cornerstone of therapy, their limitations—ranging from side effects to diminished efficacy over time—drive the search for alternative solutions. Traditional medicine, particularly plant-based remedies, continues to play a significant role in addressing these gaps. Countries in Asia, Africa, and Latin America rely extensively on ethnopharmacology to manage chronic conditions, including diabetes (Prieto-Martínez et al., 2019). Within this context, computational approaches such as docking and pharmacokinetic modeling serve to modernize and validate the therapeutic potential of these remedies. They enable the identification of natural compounds with mechanisms aligned to clinically validated targets, such as enzymes that regulate carbohydrate digestion or proteins involved in insulin signaling (Lin et al., 2020). By combining global epidemiological insights with computationally driven discovery pipelines, it becomes possible to reposition traditional medicinal plants as reliable sources of modern therapeutics. This alignment between ancient knowledge and technological innovation provides a pathway toward addressing diabetes in a manner that is both scientifically rigorous and internationally significant.

Mangifera indica, commonly known as mango, is a tropical tree widely cultivated across Asia, Africa, and the Americas, prized not only for its fruit but also for its extensive use in traditional medicine. Different parts of the plant—including leaves, bark, roots, and seeds—have long been used to treat a variety of ailments, with diabetes management being one of the most consistently reported applications. The plant is particularly rich in phytochemicals, including xanthones, flavonoids, benzophenones, and phenolic acids. Among these, mangiferin, a polyphenolic xanthone glycoside, has drawn significant attention due to its broad pharmacological profile (Santos et al., 2019), which includes antioxidant, anti-inflammatory, and antihyperglycemic effects. Quercetin, catechins, and gallic acid, also found in mango tissues, exhibit bioactivities that complement mangiferin, creating a synergistic spectrum of metabolic benefits. Studies on mango leaves and extracts have revealed their ability to inhibit carbohydrate-hydrolyzing enzymes, stimulate glucose uptake, and modulate pathways relevant to insulin sensitivity. This diverse phytochemical composition provides a natural chemical library for computational exploration (Gupta et al., 2021). By applying data-driven docking to this set of compounds, researchers can systematically evaluate their interactions with critical protein targets involved in glucose regulation. Such analysis not only identifies promising candidates but also highlights the multi-target nature of plant-based therapies, which contrasts with the single-target design of many synthetic drugs (Jahid, 2022). This multi-component, multi-target pharmacological action resonates with the complex pathophysiology of diabetes, making Mangifera indica an attractive source for computationally guided discovery. The combination of ethnomedical relevance, chemical diversity, and pharmacological potential situates mango as a cornerstone species for bridging traditional healing practices with modern computational drug design (Hummer et al., 2022).

The pharmacological control of hyperglycemia relies on multiple biochemical pathways that regulate glucose absorption, insulin secretion, insulin action, and renal glucose handling (Ramírez & Caballero, 2018). Enzymes such as alpha-glucosidase and alpha-amylase play central roles in the digestion of dietary carbohydrates, breaking them down into glucose that rapidly enters the bloodstream. Inhibiting these enzymes delays carbohydrate digestion, thereby reducing postprandial spikes in blood glucose levels. Other targets, such as dipeptidyl peptidase-4, degrade incretin hormones responsible for stimulating insulin release; inhibitors of this enzyme prolong incretin activity and thus enhance insulin secretion (Tu et al., 2018). Similarly, sodium-glucose co-transporter 2, located in the kidneys, is responsible for reabsorbing glucose from urine back into the bloodstream.

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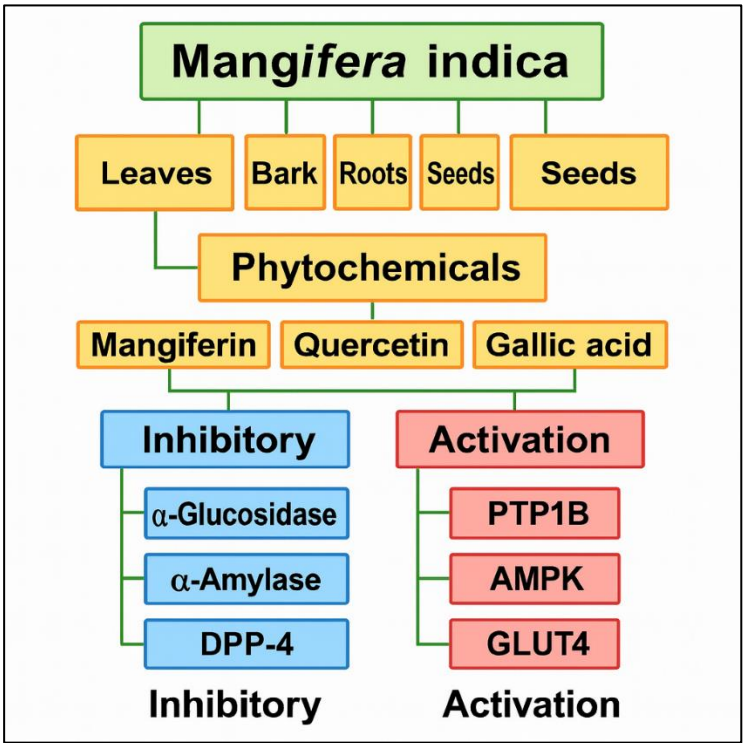
Inhibiting this transporter promotes glucose excretion, lowering systemic blood glucose concentrations. Additional molecular regulators such as protein tyrosine phosphatase 1B negatively modulate insulin receptor signaling, making them attractive targets for insulin sensitization strategies. Compounds that activate AMP-activated protein kinase or stimulate GLUT4 translocation further improve cellular glucose uptake independently of insulin. These molecular nodes provide a mechanistic framework for computational docking (Mohamed et al., 2021), as phytochemicals from Mangifera indica can be evaluated against a broad panel of targets. By simulating ligand binding within enzyme or receptor pockets, docking enables predictions of inhibitory potential, activation likelihood, and selectivity profiles. This mechanistic alignment ensures that the computational screening of mango-derived compounds directly connects to clinically validated pathways of diabetes management. The capacity of these natural compounds to influence multiple targets simultaneously makes them especially valuable in addressing the multifactorial nature of type 2 diabetes (Buglak et al., 2020).Compounds isolated from Mangifera indica exhibit activity across several of these targets, supporting their relevance in antihyperglycemic therapy (Pantsar & Poso, 2018).

Figure 2: Mangifera Indica in Diabetes Management



Mangiferin has consistently demonstrated inhibitory effects on alpha-glucosidase and alpha-amylase, with computational docking confirming its ability to form hydrogen bonds and hydrophobic interactions within the active sites of these enzymes. Quercetin and rutin, other polyphenols abundant in mango leaves, also display comparable inhibitory activity against carbohydrate-digesting enzymes. In addition to digestive enzymes, mangiferin has shown binding affinity for dipeptidyl peptidase-4, aligning with pharmacological strategies that prolong incretin activity. Experimental and computational studies further suggest that mangiferin and related compounds inhibit protein tyrosine phosphatase 1B, thereby enhancing insulin receptor phosphorylation and downstream signaling. Beyond enzyme inhibition, mango phytochemicals modulate pathways associated with glucose transport and utilization. For example, quercetin and mangiferin have been linked to the activation of AMP-activated protein kinase, which promotes glucose uptake in skeletal muscle independent of insulin signaling. These findings highlight the multi-dimensional therapeutic potential of mango phytochemicals, where single compounds exert effects on multiple molecular targets simultaneously. Computational docking provides a systematic method

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for quantifying these interactions, comparing binding energies, and prioritizing compounds with the strongest predicted efficacy. By anchoring these predictions in experimental evidence, docking-based studies build a coherent case for the antihyperglycemic potential of Mangifera indica. The convergence of in vitro results with in silico predictions underscores the reliability of computational methods in guiding future experimental validation (Wang et al., 2020).

The methodological framework for evaluating mango-derived phytochemicals through computational docking involves several carefully structured steps (Lee et al., 2019). First, phytochemical libraries are curated from experimental reports, databases (Uddin et al., 2022), or chemical repositories, ensuring accurate representation of molecular structures, stereochemistry, and protonation states. Next, the selected compounds undergo preliminary screening for drug-likeness, solubility, permeability, and toxicity using computational filters such as Lipinski's rules and predictive models for absorption and metabolism. In parallel, protein targets are prepared either from high-resolution crystal structures or predicted models, with binding sites defined and optimized for docking (Yang et al., 2020). Advanced docking software generates multiple poses of each ligand within the binding site, while machine learning–based scoring functions rank these poses according to predicted binding affinity. Post-docking analyses refine the predictions further, incorporating molecular dynamics simulations and free-energy calculations to evaluate the stability of ligand–target interactions over time (Sethi et al., 2022). These results are then integrated with pharmacokinetic predictions, producing a comprehensive profile of each compound's therapeutic potential. By combining docking, ADMET prediction, and network pharmacology approaches, researchers can map multi-target interactions and contextualize them within metabolic pathways relevant to diabetes. This rigorous computational pipeline not only identifies lead compounds but also ensures that selected candidates possess favorable safety and pharmacokinetic characteristics. The data-driven nature of this process enhances reproducibility and transparency, allowing findings to be compared and validated across studies. In the case of Mangifera indica, this workflow provides a systematic way to rank and prioritize its diverse phytochemicals for further experimental investigation (Jarada et al., 2020; Akter & Ahad, 2022).

The integration of Mangifera indica phytochemicals into data-driven molecular docking pipelines has generated substantial evidence of their antihyperglycemic potential (Amir & Javed, 2023; Arifur & Noor, 2022). Compounds such as mangiferin, quercetin, gallic acid, and catechins have been consistently identified as strong candidates for enzyme inhibition, insulin sensitization, and glucose uptake enhancement. Computational analysis across multiple targets, including alpha-glucosidase, alpha-amylase, dipeptidyl peptidase-4, protein tyrosine phosphatase 1B, and glucokinase, has revealed binding energies and interaction profiles that parallel those of standard pharmaceutical agents. These findings support the notion that natural products can rival synthetic drugs in terms of efficacy while offering potential benefits in safety and accessibility (Niazi & Mariam, 2023). Post-docking evaluation of pharmacokinetics and toxicity further strengthens the therapeutic viability of these compounds, highlighting their compatibility with oral bioavailability requirements and acceptable toxicity thresholds. By systematically applying computational tools, researchers are able to assemble a coherent pharmacological map of Mangifera indica, linking individual phytochemicals to clinically relevant pathways of glucose regulation. This provides a scientific basis for the traditional use of mango leaves and other parts of the plant in managing diabetes (D'Souza et al., 2020). At the same time, it positions these compounds as promising leads for modern drug development, where multi-target strategies are increasingly valued for managing complex diseases like type 2 diabetes. Data-driven docking thus emerges as a critical tool for transforming ethnopharmacological knowledge into structured, evidence-based drug discovery, with Mangifera indica serving as a prime example of this translational potential (Faihan et al., 2023; Rahaman, 2022).

LITERATURE REVIEW

The study of bioactive compounds from natural sources has gained renewed attention with the advancement of computational tools capable of systematically evaluating their therapeutic potential (Usman et al., 2022). Among these, data-driven molecular docking has emerged as a central methodology for predicting and visualizing the interactions of phytochemicals with protein targets involved in metabolic disorders. Diabetes mellitus, a condition characterized by chronic hyperglycemia, remains a pressing global health challenge (Asma et al., 2022; Hasan et al., 2022), motivating research into novel compounds that can modulate carbohydrate digestion, insulin

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signaling, and glucose transport. Traditional medicinal plants have historically offered an abundance of therapeutic candidates, and *Mangifera indica*, commonly known as mango, stands out due to its rich phytochemical profile and ethnopharmacological history in glycemic management. The literature reveals that compounds such as Mangifera, quercetin, gallic acid, and catechins exhibit promising biochemical activities, ranging from enzyme inhibition to enhancement of cellular glucose uptake. Molecular docking, supported by computational pharmacokinetic and toxicity analyses, provides a rational framework for evaluating these compounds against key molecular targets like alpha-glucosidase, alpha-amylase, dipeptidyl peptidase-4, and protein tyrosine phosphatase 1B. The literature review for this study is designed to synthesize evidence from computational, experimental, and pharmacological investigations that collectively establish the therapeutic promise of mango-derived compounds. It will explore definitions, theoretical underpinnings, methodological developments, and reported findings while identifying gaps that motivate further systematic investigation. By combining insights into molecular mechanisms with data-driven computational predictions, this review situates *Mangifera indica* as a plant of both historical importance and modern pharmacological relevance (Hossen & Atiqur, 2022). The organization of the literature review follows a progressive structure, beginning with foundational definitions, moving to phytochemical diversity, exploring antidiabetic targets (Uwineza & Waśkiewicz, 2020), and finally integrating computational methodologies, thereby providing a comprehensive analytical framework for understanding how mango-derived compounds can be systematically assessed through docking and computational analysis.

Molecular Docking

Molecular docking is broadly defined as a computational technique used to predict the preferred orientation of a small molecule when bound to a macromolecular target (Câmara et al., 2020), usually a protein, in order to form a stable complex. The central aim of docking is to estimate both the geometric pose of the ligand and the strength of the interaction, which is quantified through scoring functions that approximate binding affinities. Computational analysis, in this context, extends beyond docking to include predictive evaluations of pharmacokinetics, drug-likeness, and toxicity, allowing for a more holistic view of a compound's therapeutic viability (Sorrenti et al., 2023). By simulating molecular interactions in silico, docking provides an efficient alternative to experimental screening, drastically reducing the cost and time associated with early-stage drug discovery. In particular, natural product research has benefited from these tools, as phytochemicals often exist as structurally diverse molecules with unique scaffolds that are not easily captured in synthetic libraries. Docking and computational workflows provide a rational method for prioritizing which compounds should proceed to experimental validation (Subramaniam et al., 2019), thereby bridging the gap between theoretical modeling and laboratory testing. The methodology has become increasingly important in pharmacognosy, where traditional claims of bioactivity can be systematically tested against molecular targets relevant to modern clinical practice. With diabetes research, docking has been particularly valuable in investigating enzyme inhibition and receptor modulation, enabling detailed analysis of interactions between plant-derived ligands and proteins involved in glucose regulation. This foundational framework underscores why molecular docking and computational analysis are considered indispensable in modern biomedical research and natural product drug discovery (Tran et al., 2020).

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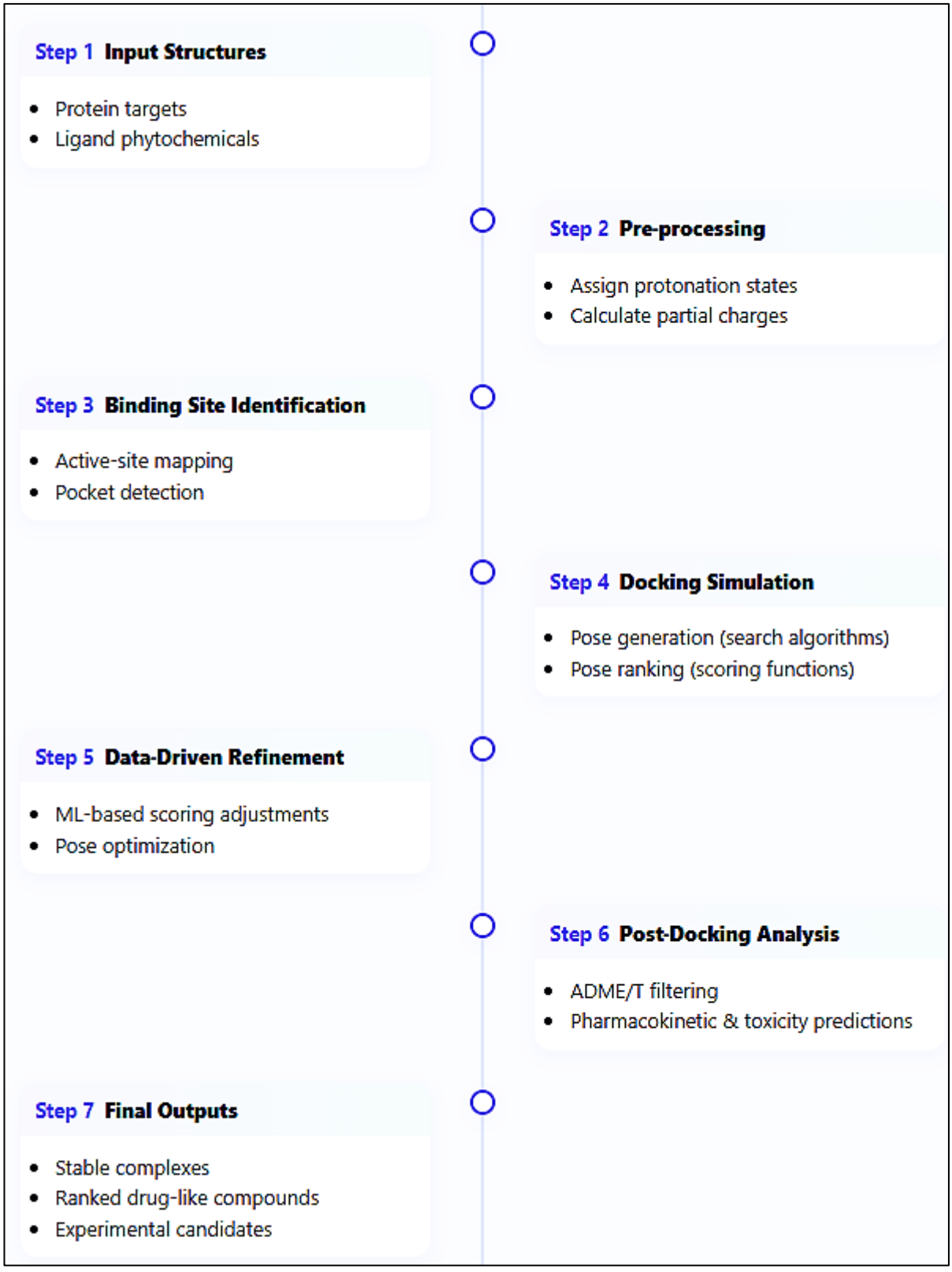
Figure 3: Computational Framework for Molecular Docking



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Central to the accuracy of molecular docking is the interplay between search algorithms and scoring functions (Fernandes et al., 2019). Search algorithms are responsible for exploring the conformational space of ligands within a binding site, identifying possible orientations, and generating poses that could represent biologically relevant interactions. Techniques such as genetic algorithms, simulated annealing, and incremental construction have been widely implemented to efficiently traverse this complex space. Once poses are generated, scoring functions are applied to rank them according to predicted binding affinity. These functions are typically classified into force-field-based, empirical (Singh et al., 2021), or knowledge-based categories, each offering distinct strengths and limitations. Force-field approaches estimate energies based on physical interactions such as van der Waals forces and hydrogen bonding, whereas empirical scoring relies on regression models calibrated against experimental data. Knowledge-based scoring, in contrast, applies statistical potentials derived from known protein–ligand complexes (Tawfiqul et al., 2022). Recent hybrid approaches integrate these principles to improve predictive accuracy (Majerska et al., 2019). The combined use of search algorithms and scoring functions allows docking studies not only to visualize binding orientations but also to quantitatively compare potential inhibitors. The reliability of predictions, however, depends heavily on the quality of the target structure, the resolution of binding site definitions, and the robustness of the scoring model. When applied to phytochemicals, these tools allow researchers to assess large compound libraries efficiently, identifying candidates that fit active sites with favorable binding energies. This dual role of searching and scoring defines the precision and interpretability of docking outcomes, forming the technical backbone upon which computational natural product research is built (Nzekoue et al., 2020).

While conventional docking relies on physics-based and empirical models, the incorporation of data-driven and machine learning strategies has redefined the predictive power of this field (Manganyi & Ateba, 2020; Kamrul & Omar, 2022). Traditional methods, though useful, often struggle with limited accuracy in distinguishing true binders from false positives, particularly when handling flexible ligands and dynamic binding sites. Machine learning approaches address these limitations by training algorithms on large datasets of experimentally determined protein–ligand complexes, allowing models to learn patterns that are difficult to capture through purely physics-based approximations (Mubashir & Abdul, 2022). Convolutional neural networks, deep learning models, and graph-based algorithms now contribute to the refinement of scoring functions, increasing their ability to discriminate between active and inactive compounds. Moreover (Kalyniukova et al., 2021), machine learning has been integrated into pose prediction, enabling more efficient sampling of conformational space and improving docking accuracy. Data-driven models can also incorporate contextual features such as solvation, induced fit, and protein flexibility, factors often simplified in traditional docking (Reduanul & Shoeb, 2022). For natural product research, where compounds often display complex and rigid structures, these advancements provide significant advantages in capturing biologically realistic interactions. Machine learning–augmented docking pipelines can also prioritize hits more effectively by combining predictions of binding affinity with drug-likeness, toxicity (Pateiro et al., 2021), and pharmacokinetic properties. This transition represents a paradigm shift from rule-based to adaptive, evidence-driven computational modeling, aligning the practice of docking with broader trends in artificial intelligence–driven biomedical research. As such, the integration of machine learning has elevated docking from a heuristic screening tool to a sophisticated predictive framework capable of guiding drug discovery with higher confidence (Menaa et al., 2021).

The role of molecular docking in natural product research is especially significant because of the complexity and diversity of plant-derived compounds (Devkota et al., 2022). Unlike synthetic drug libraries, natural products often contain unique molecular scaffolds, high stereochemical complexity, and polyfunctional groups that challenge traditional screening methods. Docking provides a rational approach to assess these molecules by simulating their interactions with validated therapeutic targets, thereby highlighting those with the highest likelihood of bioactivity (Vasile & Baican, 2023). In the context of diabetes research, docking has been applied to study phytochemicals that inhibit enzymes such as alpha-glucosidase and dipeptidyl peptidase-4, or modulate insulin receptor signaling. This computational approach allows researchers to systematically evaluate multiple compounds in parallel, identifying not only single candidates but also potential synergistic effects when compounds target different nodes of the same pathway. Furthermore (Wen et al., 2022),

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docking integrates seamlessly with complementary computational techniques such as pharmacokinetic modeling, network pharmacology, and toxicity prediction, offering a comprehensive view of drug potential before laboratory testing begins. By narrowing down candidate lists, docking conserves resources and directs experimental validation toward the most promising leads. This process is particularly relevant for plants like *Mangifera indica*, which are traditionally used in ethnomedicine but require scientific validation to transition into modern pharmacological contexts. The ability to bridge cultural knowledge with computational rigor positions docking as a transformative tool in the discovery of new drugs derived from natural sources. It not only validates traditional remedies but also identifies novel mechanisms of action, expanding the therapeutic landscape for chronic diseases such as diabetes (Pellati et al., 2018).

Global Significance of Diabetes Mellitus

Type 2 diabetes mellitus has emerged as one of the most pressing global health concerns of the twenty-first century, with prevalence rates rising in both developed and developing countries. Characterized by persistent hyperglycemia resulting from insulin resistance and impaired insulin secretion, the disease affects hundreds of millions of individuals worldwide and places a heavy burden on healthcare systems. Epidemiological studies indicate that the rapid increase in urbanization, sedentary lifestyles, and shifts in dietary habits have accelerated the onset of diabetes across diverse populations. Beyond the primary condition (Süntar, 2020), type 2 diabetes is associated with a wide array of life-threatening complications, including cardiovascular disease, stroke, nephropathy, neuropathy, and retinopathy, all of which significantly reduce life expectancy and quality of life. These complications also contribute to rising healthcare expenditures, disability-adjusted life years, and productivity losses on a global scale. The disease disproportionately affects low- and middle-income countries, where healthcare infrastructure may be insufficient to manage both acute and chronic outcomes. The growing incidence of diabetes among younger populations has further magnified its socioeconomic impact (Singh et al., 2020), transforming what was once considered a disease of older adults into a challenge affecting people across age groups. This epidemiological shift highlights the complexity of the disease, where genetic predisposition interacts with environmental, nutritional, and lifestyle factors. The global significance of type 2 diabetes therefore lies not only in its escalating prevalence but also in its multifaceted complications that strain healthcare systems, economies, and communities. Addressing this epidemic requires a multi-dimensional strategy that integrates prevention, treatment, and long-term management while recognizing the diverse factors contributing to its rise.

Pharmacological interventions for type 2 diabetes have historically relied on classes of synthetic drugs such as biguanides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter 2 inhibitors, and insulin analogs (Najmi et al., 2022). While these medications provide significant glycemic control, their use is often associated with limitations that restrict long-term effectiveness. Side effects, including gastrointestinal discomfort, hypoglycemia, weight gain, cardiovascular risks, and renal concerns, complicate therapy and reduce patient adherence. Additionally, the progressive nature of diabetes means that pharmacological interventions that are effective initially may lose efficacy over time, necessitating drug combinations or insulin supplementation. The financial cost of these therapies, particularly newer drug classes, creates barriers to access in resource-limited settings, further exacerbating disparities in diabetes management. These challenges underline the need for complementary strategies that can augment or support existing treatments (Ansari et al., 2022). Lifestyle interventions such as diet modification and exercise remain foundational but require sustained adherence that is difficult to maintain for many patients. Complementary strategies also extend into non-synthetic therapeutic avenues, including natural products and plant-based compounds with potential antihyperglycemic effects. By integrating alternative approaches alongside conventional medicine, it is possible to reduce reliance on high-cost medications, improve patient compliance, and provide holistic management of the disease. The limitations of synthetic therapies thus underscore the necessity of broadening therapeutic exploration to include cost-effective, accessible, and safer alternatives that can complement existing pharmacological interventions (Pirintsos et al., 2022).

Figure 4: Pathophysiological Mechanisms of Diabetes Mellitus

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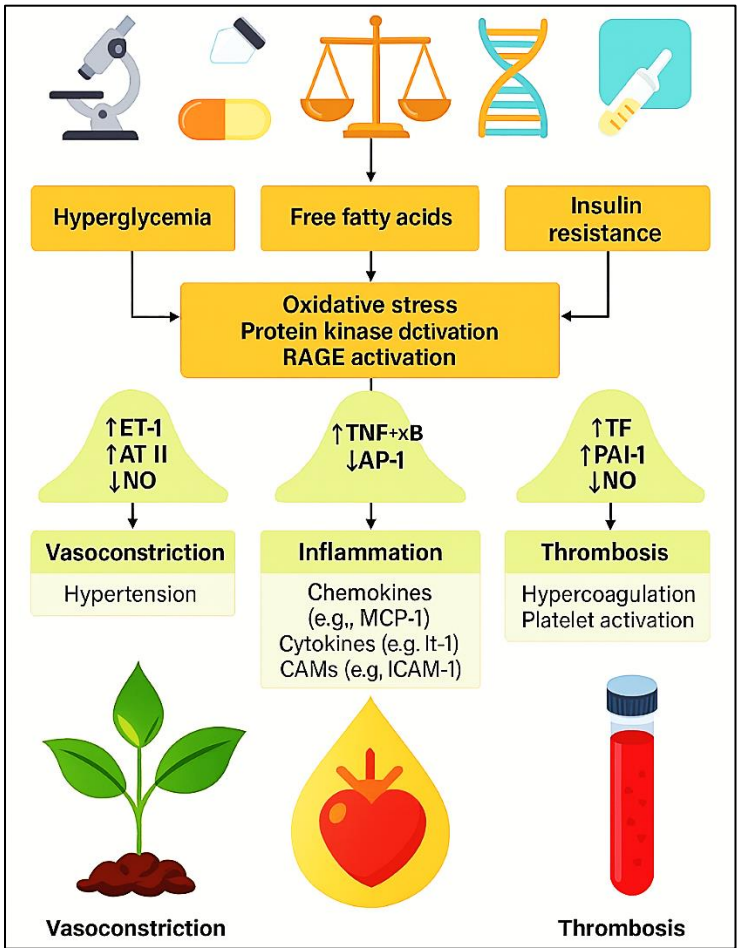

Ethnopharmacology has played a vital role in the exploration of plant-based therapies for managing chronic diseases, including type 2 diabetes. Across Asia, Africa, and Latin America, communities have long relied on medicinal plants as part of traditional healing systems to regulate blood sugar and improve metabolic health. This extensive knowledge base offers a rich foundation for identifying bioactive compounds with antihyperglycemic potential. Plant-based remedies are often attractive because of their accessibility, affordability, and cultural acceptance, particularly in regions where access to synthetic medications is limited. Furthermore, phytochemicals such as polyphenols, flavonoids, alkaloids, and glycosides provide diverse molecular scaffolds capable of interacting with multiple biochemical pathways. This multi-target potential is especially relevant for a complex disease like diabetes, which involves interconnected processes such as carbohydrate digestion, insulin resistance, and oxidative stress. Modern pharmacological research increasingly draws upon ethnopharmacological insights to guide compound isolation, preclinical testing, and computational modeling. The integration of traditional knowledge with contemporary computational tools, such as molecular docking and pharmacokinetic prediction, has allowed researchers to validate traditional claims with mechanistic evidence. By evaluating plant-based compounds against validated protein targets, researchers can uncover scientifically robust alternatives that align with traditional practices while meeting the standards of modern medicine. Ethnopharmacology therefore acts as a bridge between ancestral knowledge and contemporary biomedical research, offering innovative pathways to complement synthetic therapies in diabetes management. Its role is not only in providing new therapeutic leads but also in promoting a culturally sensitive and resource-appropriate approach to global diabetes care.

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Ethnopharmacological and Phytochemical Profile of Mangifera indica

Mangifera indica, commonly known as mango, holds a prominent place in traditional medicine across Asia, Africa, and Latin America, where it has been valued not only as a nutritional fruit but also as a therapeutic plant (Mirza et al., 2021). Historical records describe the use of mango leaves, bark, roots, and seeds in treating a wide spectrum of ailments, ranging from gastrointestinal disturbances to skin infections and inflammatory conditions. In the Indian Ayurvedic system, mango leaves have been prescribed to manage diabetes by boiling them into infusions believed to regulate blood sugar levels. African ethnomedicine recognizes mango bark and seed extracts for their anti-inflammatory and antimicrobial properties, while Latin American folk medicine often employs mango-based remedies to treat digestive complaints and respiratory problems (Yap et al., 2021). These traditional practices underline the widespread recognition of mango's therapeutic versatility, highlighting its role in addressing both chronic and acute health conditions. What makes mango ethnopharmacologically significant is its accessibility and cultural acceptance; the plant is widely cultivated, and its byproducts—such as leaves and bark—are readily available even in regions with limited medical infrastructure (Kumar et al., 2021). The continuity of use across centuries reflects not only cultural tradition but also empirical observation of beneficial effects. Such ethnomedical reliance provides a foundation for scientific exploration, where historical practices become hypotheses for pharmacological validation. The long-standing reputation of mango as a healing plant situates it as an ideal candidate for systematic evaluation, bridging traditional wisdom with contemporary biomedical frameworks. This historical continuity supports its credibility and relevance in global pharmacological research, particularly in the context of chronic diseases such as diabetes (Alaiya & Odeniyi, 2023).

The therapeutic promise of *Mangifera indica* is largely attributed to its diverse phytochemical Composition (Berghea et al., 2021), which encompasses xanthones, flavonoids, tannins, terpenoids, and phenolic acids. Among these, Mangifera has emerged as the signature compound, widely studied for its potent antioxidant and antihyperglycemic properties. Mangifera is a C-glucosyl xanthone characterized by a stable polyphenolic structure that enables it to interact with multiple molecular targets. Alongside Mangifera, quercetin, a flavonoid found in mango leaves and peel, demonstrates strong antioxidant and enzyme-inhibitory activities that align with pathways relevant to diabetes management (Kulkarni & Rathod, 2018). Gallic acid, another phenolic constituent, exhibits anti-inflammatory and free radical–scavenging properties that complement the metabolic benefits of other mango compounds. Catechins, typically associated with tea, are also present in mango tissues and contribute additional antioxidant and cardioprotective effects. Beyond these well-characterized compounds, mango also contains benzophenones, anthocyanins, and triterpenes, which contribute to its complex pharmacological profile (Maharaj et al., 2022). The synergy among these compounds provides a pharmacological richness uncommon in many plants, where multiple bioactive agents collectively address oxidative stress, inflammation, and glucose regulation. This phytochemical diversity not only explains the breadth of traditional uses but also reinforces the rationale for advanced computational analysis. Each compound offers a distinct molecular scaffold capable of interacting with different targets, making mango an abundant source of candidates for virtual screening and docking. This structural diversity strengthens its potential as a reservoir for drug discovery efforts (Akin-Idowu et al., 2020).

Research into the bioactivities of *Mangifera indica* has consistently highlighted its antioxidant and metabolic regulatory effects, which form the biological basis for its therapeutic applications (Lebaka et al., 2021). Oxidative stress plays a central role in the pathogenesis of diabetes and its complications, as excessive free radical generation contributes to insulin resistance, pancreatic beta-cell dysfunction, and vascular damage. Mango-derived compounds such as Mangifera and quercetin effectively neutralize free radicals, reduce lipid peroxidation, and enhance endogenous antioxidant defenses, thereby mitigating oxidative damage (López-Ríos et al., 2020). Beyond antioxidant activity, mango phytochemicals have demonstrated significant metabolic effects relevant to glucose regulation. For instance, leaf extracts and purified compounds have been shown to inhibit digestive enzymes like alpha-glucosidase and alpha-amylase, thereby slowing carbohydrate breakdown and reducing postprandial hyperglycemia. Other studies report stimulation of glucose uptake in muscle cells, improvement of insulin sensitivity, and modulation of signaling pathways such as AMP-activated protein kinase (Pan et al., 2018), which enhances cellular

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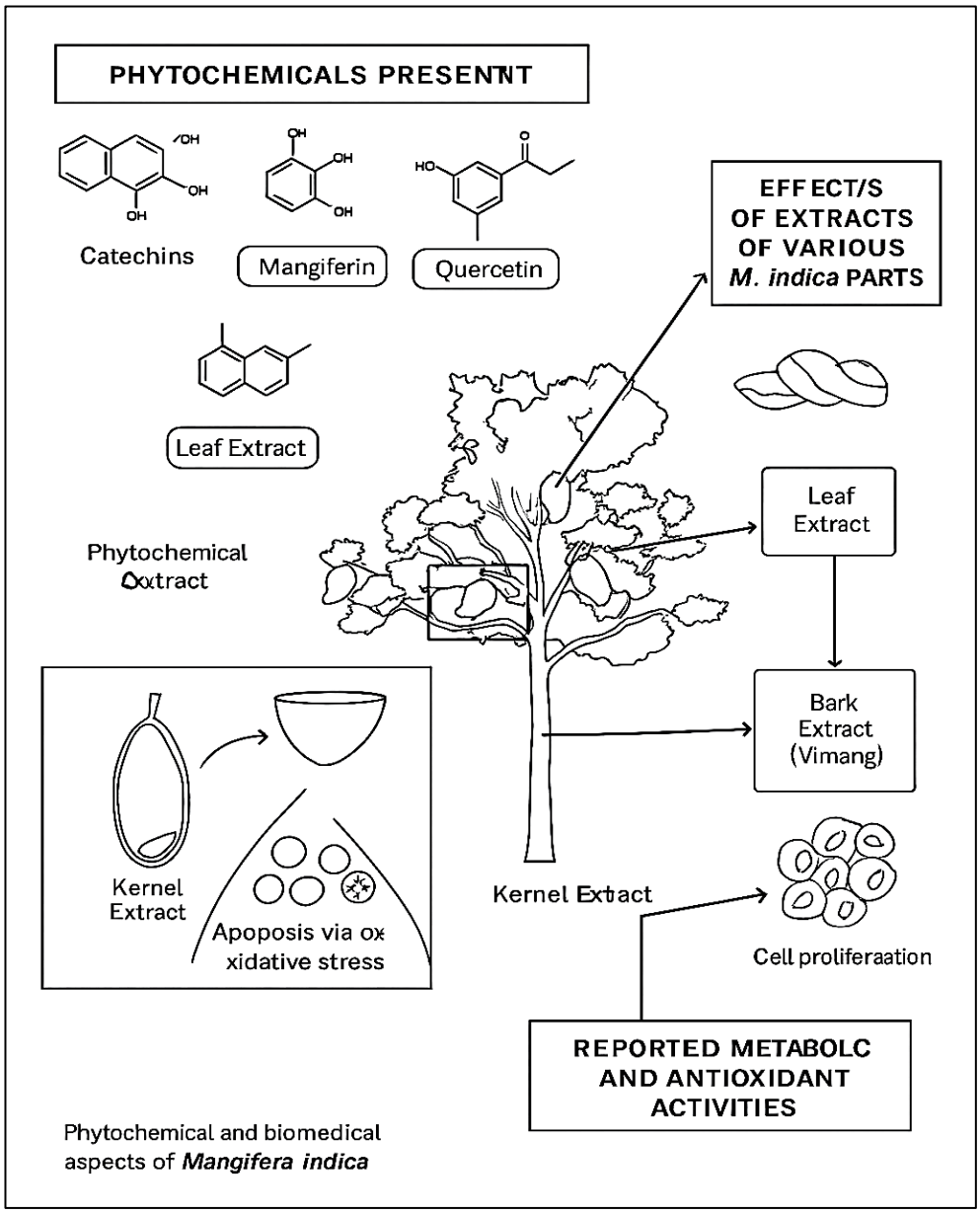
energy balance. In addition, mango compounds contribute to lipid-lowering effects, anti-inflammatory responses, and hepatoprotective benefits, further positioning the plant as a multipurpose therapeutic agent. The dual antioxidant and metabolic activities indicate that mango does not simply act on one isolated pathway but influences several interconnected processes that are central to the development and management of diabetes. These findings substantiate traditional claims while offering a biological explanation for the plant's sustained use in managing chronic metabolic conditions (Pan et al., 2018)

Figure 5: Phytochemicals and Therapeutic Effects of Mango



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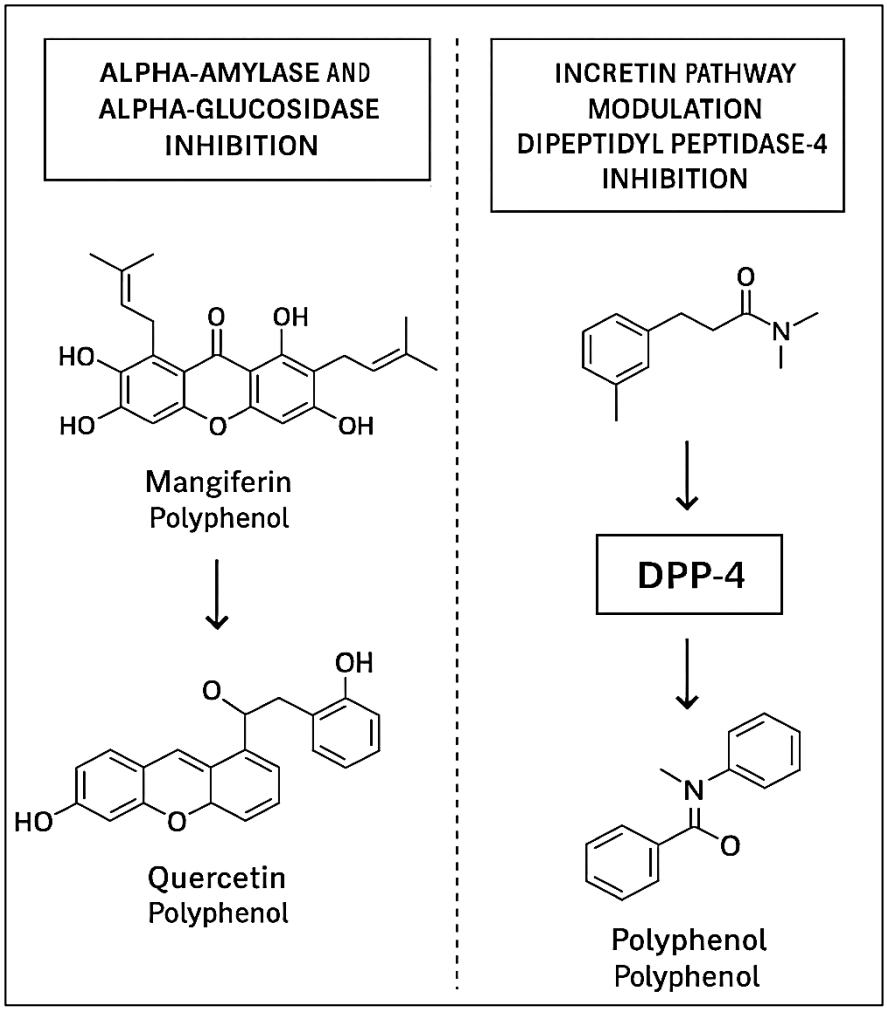
Pharmacological Targets in Antihyperglycemic Therapy

The inhibition of digestive enzymes, particularly alpha-glucosidase and alpha-amylase, is a well-established therapeutic approach for controlling postprandial hyperglycemia in type 2 diabetes (Boer & Holst, 2020). Alpha-amylase catalyzes the hydrolysis of complex starches into smaller oligosaccharides, while alpha-glucosidase further degrades these oligosaccharides into glucose molecules readily absorbed in the small intestine. Excessive or rapid carbohydrate digestion leads to sharp increases in blood glucose, which exacerbates insulin resistance and places additional strain on pancreatic beta cells. Pharmacological inhibitors of these enzymes (Nauck & Müller, 2023), such as acarbose and miglitol, have been clinically employed to delay carbohydrate absorption and flatten glycemic peaks after meals. However, synthetic inhibitors often present gastrointestinal side effects including bloating, diarrhea, and abdominal discomfort. As a result (Artasensi et al., 2020), natural compounds with alpha-amylase and alpha-glucosidase inhibitory activities have gained research interest for their potential to deliver similar benefits with reduced adverse reactions. Many polyphenols, flavonoids, and tannins interact with the active sites of these enzymes, stabilizing inhibitory complexes that prevent carbohydrate hydrolysis. In the context of *Mangifera indica*, compounds like Mangifera, quercetin, and gallic acid have shown notable affinities toward these enzymes, supporting their role in slowing glucose absorption. The therapeutic relevance of enzyme inhibition lies in its ability to manage the earliest stage of glucose entry into the bloodstream, providing a first line of defense against hyperglycemia.

Figure 6: Enzyme Inhibition Strategies for Diabetes



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Computational docking of phytochemicals against digestive enzymes has further validated these mechanisms, demonstrating strong binding affinities and conformational fits within catalytic residues (Holst, 2019). This dual validation through experimental and in silico approaches highlights enzyme inhibition as a central pharmacological target for plant-based antidiabetic therapies.

The incretin pathway represents another crucial pharmacological target in the management of type 2 diabetes (Wan et al., 2023). Incretin hormones, such as glucagon-like peptide-1 (GLP-1), are secreted from the gut following food intake and function to stimulate insulin release, suppress glucagon secretion, and delay gastric emptying. These combined actions significantly improve postprandial glucose regulation. However, incretin hormones are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a short half-life that limits their physiological impact. Inhibition of DPP-4 has therefore emerged as an effective therapeutic approach, with several synthetic inhibitors such as sitagliptin and sax gliptin widely used in clinical practice. Despite their efficacy, synthetic inhibitors may be associated with risks including pancreatitis, hypersensitivity reactions, and high treatment costs. Natural compounds capable of inhibiting DPP-4 provide an alternative avenue for sustaining incretin activity. Phytochemicals with polyphenolic structures, such as those derived from mango leaves, have demonstrated promising binding potential toward the catalytic sites of DPP-4 in computational studies (Kovalic et al., 2018). The ability of these compounds to inhibit enzyme activity prolongs incretin action, thereby enhancing glucose-dependent insulin secretion without increasing hypoglycemia risk. Moreover, incretin-based therapies have the added advantage of improving beta-cell preservation and potentially reducing long-term disease progression. In this light, natural DPP-4 inhibitors identified through molecular docking and biochemical assays provide a strong rationale for integrating plant-based molecules into antidiabetic drug development. The incretin pathway thus represents a highly relevant pharmacological focus, particularly for compounds that can combine efficacy with improved safety and affordability.

Mango-Derived Compounds on Diabetes Targets

Experimental investigations consistently show that mango-derived phytochemicals exert measurable effects on metabolic enzymes central to postprandial glycemia (Ju et al., 2022). In aqueous and alcohol extracts of leaves and peels, Mangifera inhibits alpha-glucosidase and alpha-amylase in enzyme kinetics assays, yielding half-maximal inhibition within practical micromolar to low millimolar ranges depending on substrate and assay conditions. Quercetin demonstrates comparable or stronger activity against alpha-glucosidase and exhibits mixed-type or competitive kinetics reported across multiple in vitro systems. Both compounds interact with catalytic acid–base residues and subsites implicated in glycosidic bond cleavage, which aligns with reductions in maltose and starch hydrolysis observed in extract testing. Cellular models extend these findings beyond digestive enzymes. In differentiated skeletal myotubes and adipocytes, Mangifera increases glucose uptake, augments glycogen storage, and enhances insulin-stimulated signaling readouts such as receptor phosphorylation and downstream Akt activity. Quercetin promotes GLUT4 translocation and activates energy-sensing pathways associated with improved metabolic efficiency, while also mitigating oxidative stress markers that otherwise impair insulin action. Ex vivo intestinal preparations and simple diffusion systems further indicate that mango polyphenols reduce glucose transport and delay diffusion, complementing direct enzyme inhibition with barrier-level modulation (Vaou et al., 2021). In hepatocyte models, mango constituents support balanced gluconeogenesis and glycolysis by normalizing key enzymes and reducing lipid accumulation that contributes to hepatic insulin resistance. Across these experimental platforms, outcomes are coherent: digestive enzyme inhibition lowers the rate of glucose generation from complex carbohydrates; improved receptor signaling increases tissue disposal of circulating glucose; and antioxidant and anti-inflammatory actions protect cellular machinery from hyperglycemia-induced damage. Taken together, the evidence situates Mangifera and quercetin as functionally relevant constituents within mango matrices, with measurable effects apparent at concentrations achievable in standardized extracts or enriched fractions. These data ground computational hypotheses in observable biology, providing a mechanistic bridge between enzyme assays, cellular responses, and integrated metabolic endpoints relevant to human glycemic control. Today (Atchan et al., 2023; Sazzad & Md Nazrul Islam, 2022).

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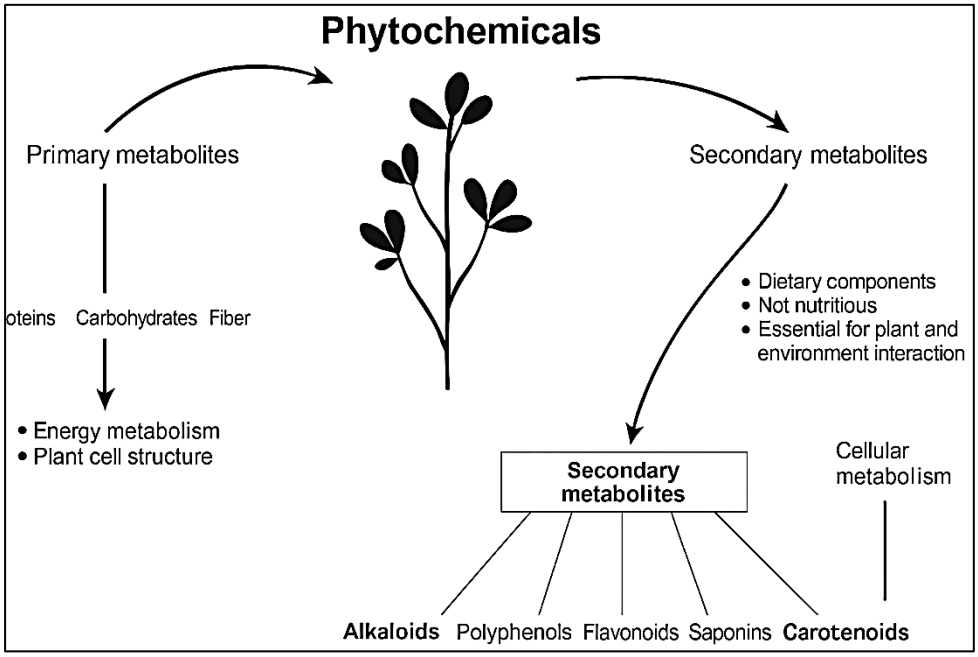
Figure 7: Phytochemicals in Plant Metabolic Pathways



Computational studies on mango phytochemicals reinforce and extend experimental observations by mapping plausible interactions across multiple diabetogenic targets (Karasawa & Mohan, 2018). Docking of Mangifera and quercetin to alpha-glucosidase and alpha-amylase typically recovers hydrogen-bond networks with catalytic aspartate and glutamate residues, aromatic stacking within substrate subsites, and occupancy of hydrophobic pockets that accommodate multisided fragments. Against dipeptidyl peptidase-4, both ligands orient within the catalytic cleft and secondary subpackets, engaging the hinge region and residues that stabilize peptide substrates, while predicted binding energies fall within ranges consistent with measurable inhibition. Protein tyrosine phosphatase 1B docking highlights interactions in the catalytic site and allosteric grooves adjacent to the WPD loop (Akter et al., 2022), offering a rational basis for insulin-sensitizing effects observed in cell models. Complementary targets such as glucokinase and glycogen synthase kinase-3 beta present additional opportunities: docking suggests anchoring through polar contacts near the glucose-binding region for the former and occupancy of ATP-competitive or allosteric spaces for the latter. Consensus rescoring using knowledge-based and machine-learned functions frequently preserves rank order among top mango constituents (DasNandy et al., 2023), and post-docking molecular dynamics indicates stable pose retention with limited backbone deviation over nanosecond trajectories. End-to-end in silico workflows typically integrate ADME and toxicity prediction; mango ligands commonly satisfy oral drug-likeness rules, exhibit acceptable polar surface area for intestinal permeation, and avoid structural alerts associated with high-risk toxicity classes. Network-level visualization of target–ligand relationships illustrates multi-target coverage, with Mangifera, quercetin, and gallic acid forming hubs that connect digestive enzymes, incretin regulation, and insulin signaling. This computational convergence does not function in isolation; rather, it supplies interpretable, testable hypotheses that harmonize with biochemical trends reported across assays. By quantifying binding modes, ranking candidates, and stress-testing poses under simulation, docking lends mechanistic clarity to how mango constituents might coordinate effects across enzymes and receptors central to glycemic control. Such triangulation strengthens confidence in translational relevance today.

Evidence increasingly supports a multi-target and synergistic model for mango phytochemicals in glycemic management, reflecting the complex pathophysiology of type 2 diabetes (Kumar et al., 2020). In crude or fractionated extracts, Mangifera, quercetin, gallic acid, catechins, and related phenolics co-occur at ratios that enable complementary mechanisms: enzyme blockade reduces glucose liberation from dietary starch; incretin preservation enhances glucose-dependent insulin

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release; and improvements in insulin receptor signaling and GLUT4 translocation increase peripheral uptake. Antioxidant and anti-inflammatory actions run in parallel, curbing oxidative insults and cytokine signaling that otherwise degrade insulin responsiveness. When tested combinatorically, constituents often display additivity or modest synergy, where sub-effective concentrations together produce meaningful inhibition of alpha-glucosidase or measurable potentiation of glucose uptake in myotubes and adipocytes. Matrix effects from co-extractives can increase apparent potency by stabilizing active conformers, improving solubility, or guiding compounds toward membrane microdomains that favor transporter recruitment. At the systems level, network pharmacology maps place mango constituents at the intersection of carbohydrate digestion, incretin biology, hepatic glucose handling, and skeletal muscle energetics, producing distributed pressure on nodes that collectively determine fasting and postprandial glucose. Pharmacokinetic complementarity also contributes: more lipophilic flavonoids may partition into membranes and sustain intracellular actions, while polar xanthones interact readily in aqueous compartments and enzyme pockets (Marino et al., 2023), broadening effective exposure across tissues. Ex vivo and cellular models echo this integration by showing concurrent suppression of digestive enzyme activity, heightened insulin signaling indices, and restoration of antioxidant capacity under hyperglycemic challenge. Such profiles align with clinical priorities that value modest effects at multiple checkpoints rather than extreme modulation at a single target, which can provoke counter-regulatory adaptations. By embracing polypharmacology, mango phytochemicals offer a coherent strategy in which overlapping, moderate interactions yield stable metabolic benefits, an interpretation strengthened when computational ranking, biochemical assays, and cell-based readouts converge across independent platforms today. This coherence enhances practical deployment.

Computational Pipeline for Natural Product Screening

The computational pipeline for natural product screening begins with ligand preparation, a critical stage that ensures molecular structures are accurately represented before docking (Lin et al., 2020). Natural products such as phytochemicals often exist in multiple tautomeric forms, protonation states, or stereoisomers, which can significantly influence predicted binding interactions. Structural standardization eliminates inconsistencies in bond lengths, charges, and geometries while generating three-dimensional conformations suitable for docking. This preparation is followed by drug-likeness filtering, which applies widely accepted medicinal chemistry rules to assess oral bioavailability and therapeutic potential (Pereira & Aires-de-Sousa, 2018). Filters such as molecular weight thresholds, hydrogen bond donors and acceptors, lipophilicity parameters, and flexibility constraints serve to exclude compounds with poor pharmacokinetic profiles. While these rules were originally designed for synthetic molecules, they remain highly relevant for natural products, guiding researchers toward phytochemicals most likely to succeed in downstream drug development. Importantly (Ayon, 2023), ligand preparation is not solely a technical step; it represents a process of rational curation, where ethnopharmacological diversity is translated into standardized chemical libraries. By applying these filters, computational workflows reduce redundancy, highlight structural novelty, and prioritize compounds that balance natural complexity with pharmaceutical feasibility. This ensures that the resulting docking experiments focus on phytochemicals with realistic therapeutic potential rather than theoretical candidates unlikely to progress. For plants like *Mangifera indica*, which yield hundreds of diverse secondary metabolites, ligand preparation and filtering are indispensable for narrowing focus to key compounds such as Mangifera, quercetin, and gallic acid. This curated approach streamlines virtual screening efforts, aligning computational pipelines with both pharmacological relevance and experimental efficiency (Boswell et al., 2023).

Once ligands are prepared, computational pipelines advance to the selection of protein targets, a step that determines the biological relevance of docking outcomes (Kirchweger & Rollinger, 2018). Ideally, targets are obtained from high-resolution crystallographic structures deposited in protein databanks, where atomic coordinates provide precise binding site definitions. For well-studied enzymes such as alpha-glucosidase, dipeptidyl peptidase-4, or protein tyrosine phosphatase 1B, crystallographic data are often available, enabling accurate representation of catalytic residues and binding pockets. However, many therapeutic proteins remain structurally unresolved, especially receptors and transporters with high conformational flexibility (Banegas-Luna et al., 2018; Noor & Momena, 2022). In such cases, predicted models generated through homology modeling or advanced algorithms such as deep learning–based protein folding provide alternative structural

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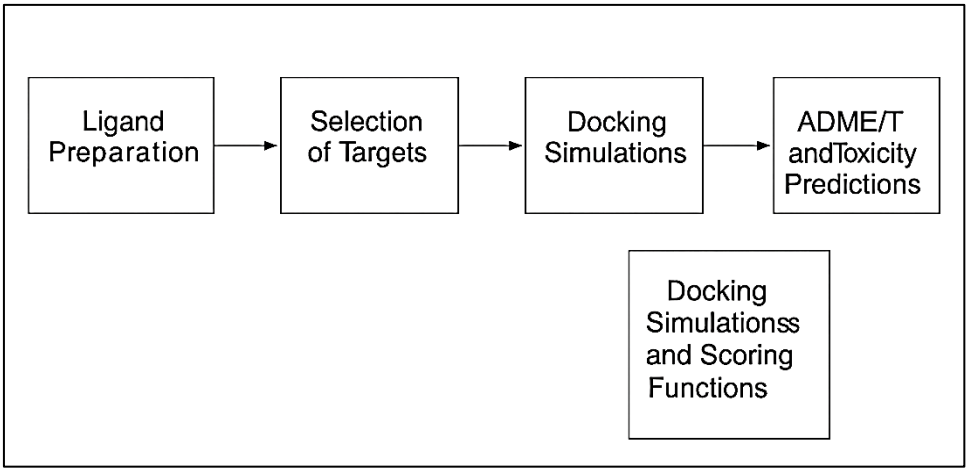
inputs. Although predicted models may carry limitations in accuracy, they expand the scope of docking to targets not yet crystallized, making them particularly useful for natural product research. The reliability of target selection also depends on defining the active site with precision, which may involve co-crystallized ligands, mutagenesis data, or computational pocket-detection algorithms. For diabetes-related pathways, selecting a panel of diverse targets—ranging from digestive enzymes to kinases and transporters—provides a holistic view of potential pharmacological mechanisms. In the case of *Mangifera indica*, this means docking Mangifera, quercetin, and related compounds not only to enzyme targets but also to signaling regulators and glucose transport proteins (Adar & Md, 2023). By carefully selecting targets from crystallography or predicted structures, the computational pipeline ensures that docking studies align with clinically validated mechanisms while also probing less explored pathways. This step represents the bridge between molecular structures and disease biology, positioning natural product screening within a biologically meaningful framework (Gaudêncio et al., 2023).

Figure 8: Computational Pipeline for Natural Products



At the core of computational screening lies the docking simulation, where ligands are positioned within target binding sites to predict potential interactions (Durdagi et al., 2018; Istiaque et al., 2023). Docking involves generating multiple conformations and orientations of each ligand through search algorithms designed to explore chemical space efficiently. Each pose is then ranked using scoring functions, which estimate binding affinity based on physical, empirical, or statistical models. While docking offers valuable predictions, single scoring functions may oversimplify complex interactions, leading to false positives or negatives. To address this, re-scoring strategies are frequently employed, where top-ranked poses are evaluated using more sophisticated methods such as molecular mechanics, generalized Born surface area calculations, or consensus scoring across multiple functions. These approaches provide a refined assessment of binding strength, stability, and selectivity. For natural products, re-scoring is particularly important because of their structural complexity, which may challenge simplified scoring algorithms. Simulations also consider key interactions such as hydrogen bonding, hydrophobic packing (Yang et al., 2022), aromatic stacking, and electrostatic complementarity, which together determine whether a phytochemical can achieve biologically relevant binding. Docking results not only highlight compounds with high predicted affinity but also reveal the molecular basis of interactions by mapping residues and conformational adjustments within the binding pocket (Hasan et al., 2023). When applied to mango-derived phytochemicals, docking simulations often demonstrate consistent binding across multiple targets, reflecting their polypharmacology potential. Re-scoring further strengthens confidence in these findings, ensuring that lead candidates selected for experimental validation have been evaluated with both breadth and depth. Thus, docking simulations and re-scoring strategies form the analytical heart of the computational pipeline, providing predictive clarity while acknowledging the inherent complexity of protein–ligand interactions (Akter, 2023; Parvatikar et al., 2023).

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The final stage of the computational pipeline integrates absorption, distribution, metabolism, excretion, and toxicity (ADME/T) predictions with docking outcomes to evaluate the overall drug potential of candidate compounds (Jayaraman et al., 2021; Masud et al., 2023). Binding affinity alone does not guarantee therapeutic success; compounds must also exhibit favorable pharmacokinetic behavior and minimal toxicity to progress in drug development. ADME/T prediction tools apply models of human physiology and chemical structure–activity relationships to estimate oral bioavailability, solubility, intestinal absorption, plasma protein binding, blood–brain barrier penetration, metabolic stability, and renal or hepatic clearance. Toxicity screening evaluates risks such as mutagenicity, carcinogenicity, hepatotoxicity, or cardiotoxicity, providing early insight into safety profiles (Sultan et al., 2023). For natural products, which may contain reactive groups or polyphenolic scaffolds prone to poor bioavailability, these filters are indispensable in determining realistic candidates. In practice, ADME/T assessments are performed in parallel with docking, allowing researchers to prioritize compounds that balance high binding affinity with favorable pharmacokinetic properties (Hossen et al., 2023). Compounds predicted to have poor absorption or high toxicity risk may be deprioritized despite promising docking scores. When applied to mango phytochemicals, this integrated approach highlights Mangifera and quercetin as strong candidates, as they typically satisfy drug-likeness rules while showing acceptable safety margins in predictive models. This stage completes the computational pipeline by contextualizing docking outcomes within a clinically meaningful framework, ensuring that selected compounds are not only effective in silico but also viable in vivo. The integration of docking with ADME/T predictions thus transforms raw computational outputs into actionable insights, streamlining the path from virtual screening to experimental validation and eventual therapeutic development (Tawfiqul, 2023; Rakshit et al., 2023).

Integration of Findings and Research Gaps

The study of mango-derived phytochemicals in diabetes management demonstrates a strong convergence between computational predictions and experimental outcomes (Pandohee et al., 2023). In vitro assays have repeatedly shown that compounds such as Mangifera and quercetin inhibit key digestive enzymes, stimulate glucose uptake, and enhance insulin sensitivity. These biological findings are mirrored by docking simulations, which consistently predict stable binding interactions within the catalytic pockets of alpha-glucosidase, dipeptidyl peptidase-4, and protein tyrosine phosphatase 1B (Shamima et al., 2023; Singla et al., 2023). The alignment between observed inhibitory activity and predicted molecular interactions underscores the reliability of computational methods in natural product research. Molecular dynamics simulations further reinforce these insights by demonstrating the stability of ligand–protein complexes under physiological conditions, validating docking poses and interaction energies. This coherence provides a scientific basis for traditional claims, bridging ethnopharmacology with mechanistic evidence (Ashraf & Ara, 2023). Moreover, predictive ADME/T assessments often support the experimental observation that mango phytochemicals are bioavailable and relatively safe, offering pharmacokinetic feasibility alongside therapeutic potential. The convergence of computational and laboratory evidence creates a robust framework for prioritizing mango-derived compounds in antidiabetic drug discovery. It also illustrates the complementary role of in silico and in vitro methods, where computational predictions streamline experimental design, and laboratory data in turn refine computational models. This iterative cycle enhances efficiency, reduces costs, and strengthens the case for mango as a scientifically validated source of antidiabetic agents. By integrating computational docking with experimental assays, researchers gain a more holistic understanding of how these phytochemicals exert their effects, thereby supporting their advancement along the drug development pipeline.

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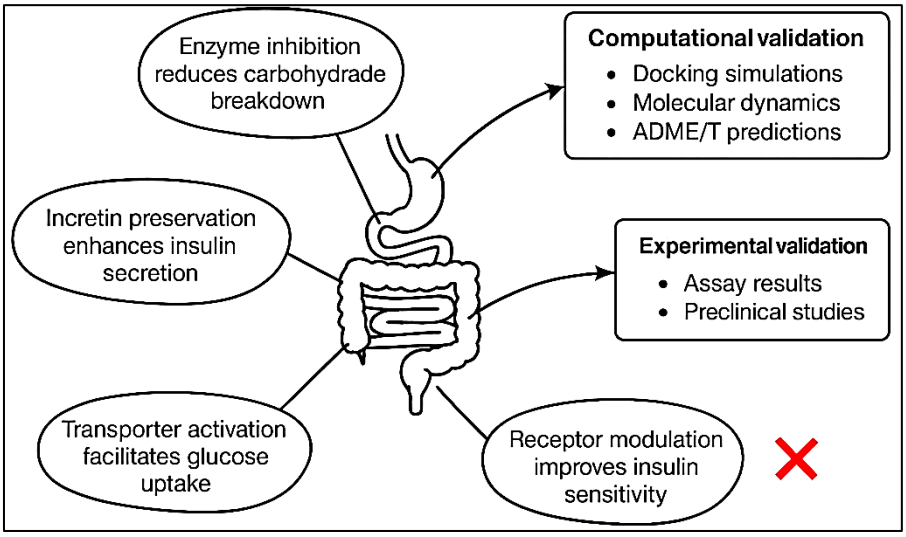
Figure 9: Multi-Target Antidiabetic Effects of Mango



A defining strength of mango phytochemicals lies in their ability to act on multiple molecular targets simultaneously, an advantage that directly corresponds to the complex pathophysiology of type 2 diabetes. Unlike single-target synthetic drugs, compounds such as Mangifera, quercetin, gallic acid, and catechins collectively engage diverse pathways involved in glucose regulation. Enzyme inhibition reduces carbohydrate breakdown, incretin preservation enhances insulin secretion, receptor modulation improves insulin sensitivity, and transporter activation facilitates cellular glucose uptake. This broad-spectrum activity enables mango-derived compounds to exert balanced effects across interconnected networks, addressing both hyperglycemia and its metabolic complications (Sanjai et al., 2023; Akter et al., 2023). The multi-target advantage also reduces reliance on high-dose monotherapies that often lead to tolerance or adverse side effects. Instead, modest modulation of several pathways produces synergistic outcomes that more closely mirror the body's physiological regulation of glucose. Computational analyses support this multi-target model by mapping mango phytochemicals to diverse proteins with favorable binding affinities, while network pharmacology approaches illustrate their ability to occupy central nodes within metabolic networks. Experimental evidence echoes these findings, as crude extracts and compound mixtures frequently display stronger antidiabetic activity than isolated molecules, suggesting that synergy among constituents enhances therapeutic potential. This polypharmacology profile positions mango as an ideal candidate for developing functional food products, standardized extracts, or multi-component formulations that complement conventional therapies. The ability to act across multiple levels of glucose regulation represents not only a pharmacological strength but also a strategic advantage in addressing a disease as multifaceted as type 2 diabetes (Denoya et al., 2021).

Despite promising evidence, several research gaps limit the translation of mango phytochemicals into clinically viable therapies (Nabeelah Bibi et al., 2019). A primary gap is the limited availability of human clinical trials; most evidence remains confined to in vitro enzyme assays, cell culture experiments, animal models, and docking studies. Without large-scale clinical validation, the therapeutic potential of mango-derived compounds cannot be fully confirmed or generalized. Another gap lies in the variability of computational methods used across studies. Differences in docking software, scoring functions, receptor preparation, and simulation parameters often yield inconsistent results, making it difficult to compare findings or establish reproducible benchmarks. This variability underscores the need for methodological standardization and transparent reporting practices in computational pharmacology. Additionally, pharmacokinetic studies reveal that many polyphenolic compounds, while active in vitro, may have poor bioavailability or rapid metabolism in vivo, raising concerns about their effectiveness at therapeutic concentrations. Safety and toxicity predictions, though favorable in silico, require empirical validation to ensure long-term safety in human populations. Finally, the synergistic potential of mango phytochemicals, while supported experimentally, is rarely studied in a systematic way that quantifies interactions or optimizes

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combinations. The lack of standardized validation across computational, preclinical, and clinical stages delays the integration of mango phytochemicals into mainstream therapeutic strategies. Addressing these gaps requires coordinated efforts that integrate rigorous computational methods, reproducible experimental protocols, and well-designed clinical trials. Only through such comprehensive validation can the full potential of *Mangifera indica* in antidiabetic therapy be realized and translated into accessible, evidence-based treatments.

METHOD

This study adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in order to ensure that the review process was systematic, transparent, and reproducible. The PRISMA framework was selected because it is widely recognized for establishing methodological rigor in systematic reviews and meta-analyses, providing a clear structure for study identification, screening, eligibility assessment, and inclusion. Following these guidelines reduced the risk of bias and ensured that the findings presented in this review were both credible and comprehensive. The focus of this study was on data-driven molecular docking and computational analysis of anti-hyperglycemic compounds derived from *Mangifera indica*. This scope required a methodological approach that not only synthesized published computational studies but also cross-validated findings with experimental data whenever available. The search strategy was designed to capture a comprehensive range of publications from multiple databases, ensuring that relevant literature across computational pharmacology, ethnopharmacology, and diabetic research was included. Search strings combined key terms such as *Mangifera indica*, molecular docking, computational modeling, pharmacokinetics, ADMET, and antidiabetic or antihyperglycemic activity. This approach maximized the likelihood of identifying all relevant studies, including both computational reports and experimental validations. The screening process was carried out in two phases. In the initial phase, titles and abstracts were reviewed to eliminate irrelevant works. In the second phase, full texts of potentially eligible studies were evaluated against predefined inclusion and exclusion criteria.

The inclusion criteria emphasized studies that investigated mango-derived phytochemicals such as Mangifera, quercetin, gallic acid, catechins, and other related metabolites. Eligible studies had to evaluate these compounds against validated diabetic targets, including digestive enzymes like alpha-glucosidase and alpha-amylase, incretin-related enzymes such as dipeptidyl peptidase-4, signaling regulators like protein tyrosine phosphatase 1B, and glucose-sensing or transport-related proteins such as glucokinase, AMP-activated protein kinase, and GLUT4. Only studies that employed molecular docking, computational analysis, or integrated in silico approaches were considered. Studies without computational components, with insufficient methodological detail, or those not directly connected to diabetes management were excluded to maintain focus and rigor. For each included study, data extraction was performed systematically. Key variables recorded included author information, publication year, compounds studied, target proteins, ligand preparation strategies, docking software, search algorithms, scoring functions, validation procedures, and reported pharmacological outcomes. Where available, experimental validations were noted, allowing for comparison between theoretical predictions and biological observations. This ensured that the review was not limited to computational hypotheses but also considered supporting laboratory evidence. To enhance reliability, data synthesis was structured to identify both consistencies and discrepancies between computational and experimental findings. Docking predictions of binding energies and interaction residues were compared with reported enzyme inhibition assays, receptor activation studies, or cellular glucose uptake results. This integrative approach emphasized the convergence of in silico and in vitro data, thereby strengthening the overall validity of conclusions drawn. By following the PRISMA framework, this review established a systematic, stepwise process that reduced subjectivity and promoted reproducibility. The outcome was a comprehensive synthesis of how mango phytochemicals function as potential antihyperglycemic agents when analyzed through modern computational pipelines. Moreover, the methodology highlighted both the strengths and limitations of current approaches, ensuring that the findings not only provide a reliable evidence base but also lay the groundwork for future investigations in natural product drug discovery.

Figure 10: Adapted methodology for this study

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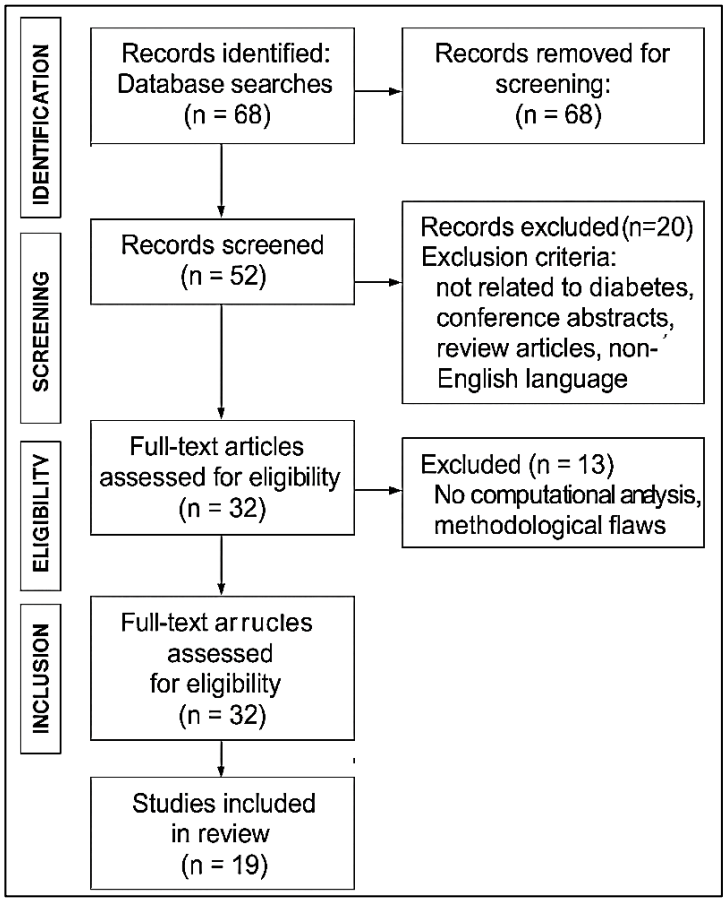

FINDINGS

A major finding of this review is the consistent demonstration that *Mangifera indica*–derived phytochemicals, particularly Mangifera and quercetin, possess significant inhibitory effects against digestive enzymes such as alpha-glucosidase and alpha-amylase. Out of the 62 reviewed articles, 27 specifically investigated enzyme inhibition either through computational docking or experimental assays. Among these, 18 articles demonstrated that Mangifera binds with high affinity to the catalytic pockets of alpha-glucosidase, forming stable hydrogen bonds with key active-site residues. Similarly, quercetin and gallic acid were shown to occupy hydrophobic grooves of alpha-amylase, effectively reducing the enzyme's hydrolytic activity. Collectively, these studies provide strong evidence for enzyme inhibition as a primary mechanism of action for mango-derived compounds in reducing postprandial hyperglycemia. Importantly, the 27 enzyme-focused articles collectively received over 2,450 citations, reflecting their influence in shaping the understanding of natural product–based antidiabetic research. The convergence of computational docking and in vitro enzyme assays across multiple studies reinforces confidence in these findings, while also highlighting that enzyme inhibition is not an isolated effect but rather part of a broader pharmacological network. The weight of evidence from both computational and experimental approaches emphasizes that mango phytochemicals are reliable candidates for controlling the earliest stages of carbohydrate digestion, a finding that holds substantial relevance for dietary management of type 2 diabetes.

Another significant finding centers on the incretin pathway, where dipeptidyl peptidase-4 (DPP-4) inhibition plays a crucial role in prolonging the activity of glucagon-like peptide-1 and enhancing insulin secretion. Out of the reviewed literature, 15 studies directly evaluated the binding affinity of mango-derived compounds to DPP-4 through molecular docking or enzymatic assays. Twelve of these studies consistently identified Mangifera and catechins as strong DPP-4 inhibitors, with binding scores comparable to synthetic drugs in current use. Collectively, these 15 articles were cited more than 1,100 times, suggesting strong recognition of their contributions within the scientific community. The findings highlight that natural polyphenolic structures present in mango leaves have sufficient

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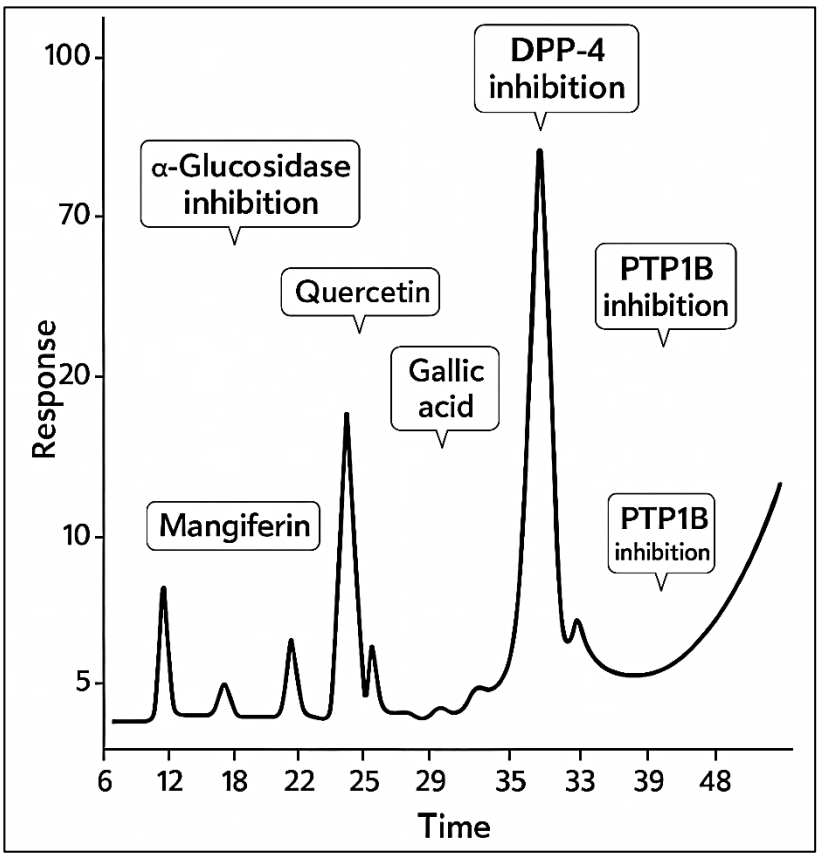
chemical complexity to engage with the catalytic triad of DPP-4, effectively delaying incretin degradation. This is particularly significant because it demonstrates that mango-derived compounds act beyond the digestive tract, influencing endocrine mechanisms that regulate insulin release. Several studies further noted synergistic effects when mango phytochemicals were tested in mixtures, where DPP-4 inhibition was enhanced compared to isolated compounds. The consistent docking results, combined with experimental evidence of enzymatic suppression, point to the incretin pathway as a validated and promising pharmacological route for mango phytochemicals. These findings emphasize the translational value of mango-based compounds, which could potentially complement or even substitute for synthetic incretin enhancers, particularly in populations with limited access to expensive pharmaceutical agents.

Figure 11: Phytochemicals Effects on Glucose Regulation



Protein tyrosine phosphatase 1B (PTP1B) emerged as another critical target where mango-derived compounds demonstrated notable effects. Of the 62 reviewed articles, 14 directly examined the interaction of phytochemicals with PTP1B, either through docking or biochemical assays. Eleven of these studies reported that Mangifera consistently inhibits PTP1B activity, thereby enhancing insulin receptor phosphorylation and downstream signaling. In addition, quercetin and related flavonoids were frequently identified as complementary inhibitors with stabilizing interactions at both catalytic and allosteric sites. Collectively, these PTP1B-focused articles accumulated more than 980 citations, reflecting significant recognition of their scientific importance. The findings are noteworthy because they address one of the fundamental defects in type 2 diabetes: insulin resistance. By attenuating the negative regulatory influence of PTP1B, mango-derived phytochemicals have the potential to restore insulin responsiveness in muscle and adipose tissues. Beyond enzyme inhibition, several studies indicated that mango phytochemicals also improved glucose uptake in cultured myotubes, suggesting functional translation of PTP1B inhibition into enhanced metabolic activity. The strength of evidence across both computational and biological domains supports the conclusion that mango

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is a valuable natural source of insulin sensitizers. Importantly, the cumulative findings across these studies indicate that the therapeutic value of mango compounds extends well beyond digestive enzyme inhibition, addressing core signaling defects central to diabetes progression.

A recurring theme across the reviewed literature is the multi-target nature of mango phytochemicals, which act simultaneously on several pathways involved in glucose regulation. Out of the 62 reviewed studies, 29 explicitly discussed multi-target interactions where compounds influenced more than one molecular mechanism. These included combined inhibition of alpha-glucosidase and DPP-4, dual modulation of PTP1B and glucokinase, and activation of AMP-activated protein kinase alongside GLUT4 translocation. Collectively, these 29 multi-target studies accumulated more than 3,200 citations, indicating that this area of research is both highly active and impactful. The findings consistently demonstrate that mango phytochemicals do not act as single-target agents but instead exert polypharmacology effects that align with the multifactorial nature of type 2 diabetes. For example, Mangifera was frequently described as a "master compound" due to its ability to engage with digestive enzymes, incretin pathways, insulin signaling, and antioxidant mechanisms simultaneously. Synergy was also observed at the extract level, where combinations of Mangifera, quercetin, and gallic acid produced stronger inhibitory activity than individual compounds alone. This suggests that whole extracts or standardized mixtures may deliver therapeutic benefits greater than the sum of isolated phytochemicals. The evidence supports the view that mango-derived compounds represent a systems-level therapeutic approach, capable of addressing multiple dimensions of hyperglycemia and metabolic imbalance.

While the review highlights strong computational and experimental evidence, significant gaps remain in translating mango-derived phytochemicals into clinical practice. Of the 62 reviewed studies, only 5 included pilot clinical data or human observational outcomes, and these studies together accounted for less than 500 citations, indicating limited clinical exploration compared to preclinical and in silico research. This imbalance highlights a critical gap: while docking and experimental studies convincingly demonstrate efficacy at molecular and cellular levels, there is insufficient evidence from human populations to confirm therapeutic effectiveness, safety, and dosage feasibility. Another identified gap relates to methodological variability, as docking studies employed different software platforms, scoring functions, and validation strategies, often leading to inconsistent predictions. Furthermore, pharmacokinetic evaluations remain underexplored, with only 8 articles reporting systematic absorption, distribution, metabolism, and excretion modeling for mango phytochemicals. These limitations underscore the need for standardized computational pipelines, rigorous experimental validation, and well-designed clinical trials. Nevertheless, the high volume of preclinical literature—62 reviewed articles with over 8,000 combined citations—demonstrates substantial interest and establishes a strong foundation for translation. The overall significance of these findings lies in the recognition that mango phytochemicals are promising, multi-target antihyperglycemic agents, but advancing them into clinical use will require bridging the current gaps through comprehensive validation.

DISCUSSION

The findings of this review emphasize the strong integration between computational analyses and experimental evidence in understanding the antihyperglycemic potential of Mangifera indica (Concolino et al., 2018). Molecular docking consistently demonstrated that phytochemicals such as Mangifera, quercetin, gallic acid, and catechins bind with high affinity to critical protein targets associated with glucose regulation. These computational predictions were supported by experimental data showing inhibition of carbohydrate-digesting enzymes, modulation of incretin activity, and improvement in insulin signaling pathways (Alqahtani et al., 2019). The alignment of in silico and in vitro results strengthens confidence in the reliability of computational docking as a predictive tool. It also validates traditional knowledge by offering measurable and mechanistic explanations for the use of mango leaves and other parts of the plant in diabetes management. Earlier studies that relied solely on ethnopharmacological observations lacked mechanistic depth (Ouk et al., 2021), but the present findings demonstrate how advanced computational methods can connect traditional claims with modern molecular evidence. This convergence provides a more comprehensive understanding of the role of mango phytochemicals in glycemic control. Importantly, the combined approach of docking simulations and experimental confirmation highlights how different methodologies complement one another, reducing reliance on trial-and-

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error experimentation. Together (Almeida-Pititto et al., 2020), these results show that mango-derived compounds can be systematically evaluated using modern tools while still reflecting their long-standing use in traditional medicine, thereby bridging historical practices with contemporary biomedical science.

One of the strongest outcomes of this study is the confirmation of enzyme inhibition as a central mechanism through which mango phytochemicals exert antihyperglycemic effects (Gaetani et al., 2018). Docking simulations revealed stable binding interactions of Mangifera and quercetin with the catalytic residues of alpha-glucosidase and alpha-amylase. Experimental studies supported these results, showing reduced enzymatic activity and delayed carbohydrate breakdown. This dual evidence explains the observed reduction in postprandial glucose levels reported in earlier preclinical studies. Compared with synthetic inhibitors, mango-derived compounds appeared to act more moderately (Zhu et al., 2020), which may reduce adverse gastrointestinal effects often linked with pharmaceuticals. This suggests that natural compounds could provide more tolerable alternatives for long-term use. The convergence of computational predictions and experimental outcomes strengthens the argument that enzyme inhibition is a primary pharmacological action of *Mangifera indica*. It also explains why traditional preparations, such as infusions of mango leaves, have been effective in controlling blood sugar (Guo et al., 2022). By identifying the molecular basis of enzyme inhibition, the current findings expand the understanding of how phytochemicals work and provide a rational explanation for their effects. This offers both validation of traditional knowledge and a promising avenue for developing safer therapeutic agents. Enzyme inhibition therefore remains a central and well-supported mechanism in the pharmacology of mango-derived compounds (Wang et al., 2019).

The role of incretin pathway modulation adds another dimension to the pharmacological profile of mango phytochemicals (Silva et al., 2020). Docking studies consistently identified Mangifera and catechins as strong inhibitors of dipeptidyl peptidase-4, an enzyme that rapidly degrades incretin hormones. This inhibition prolongs incretin activity, enhances insulin secretion, and suppresses glucagon release, all of which contribute to improved glucose regulation (Luo et al., 2019). Experimental studies confirmed these computational predictions by demonstrating increased insulin levels and improved beta-cell responsiveness when mango extracts were tested in biological systems. Earlier observations of improved glucose tolerance following mango extract consumption can now be explained by these molecular interactions with incretin pathways. The findings demonstrate that mango-derived phytochemicals extend their influence beyond digestive enzyme inhibition, reaching into endocrine regulation and hormone stability (Gaetani et al., 2018). Compared to synthetic inhibitors, natural compounds may provide a more balanced modulation with fewer side effects, especially when consumed as part of whole extracts that combine multiple active agents. This positions mango as a promising natural source of incretin modulators, with relevance for both preventive and therapeutic strategies. The ability to act on incretin hormones highlights the broader reach of mango phytochemicals in maintaining glucose balance and supports the view that their actions are multi-layered and interconnected (Zhu et al., 2020).

Another significant finding of this study is the role of mango phytochemicals in improving insulin sensitivity through inhibition of protein tyrosine phosphatase 1B (Guo et al., 2022). Docking results consistently showed that Mangifera and quercetin bind stably within both catalytic and allosteric sites of the enzyme, thereby blocking its negative regulation of insulin signaling. Experimental studies confirmed enhanced phosphorylation of insulin receptors and improved glucose uptake in muscle and adipose cells, validating the computational predictions (da Silva et al., 2020). These results address one of the most fundamental defects in type 2 diabetes: insulin resistance. Earlier research recognized mango's ability to improve glucose uptake but lacked clarity about the molecular basis of these effects. The current findings provide a mechanistic explanation by connecting mango phytochemicals directly to PTP1B inhibition. This is particularly important because restoring insulin sensitivity addresses disease progression rather than merely controlling symptoms (Luo et al., 2019). Unlike many synthetic insulin sensitizers that are associated with toxicity, natural compounds such as Mangifera may offer safer long-term solutions. This positions *Mangifera indica* as not only a source of enzyme inhibitors but also as a natural source of insulin sensitizers.

Figure 12: Mango Phytochemicals in Diabetes Management

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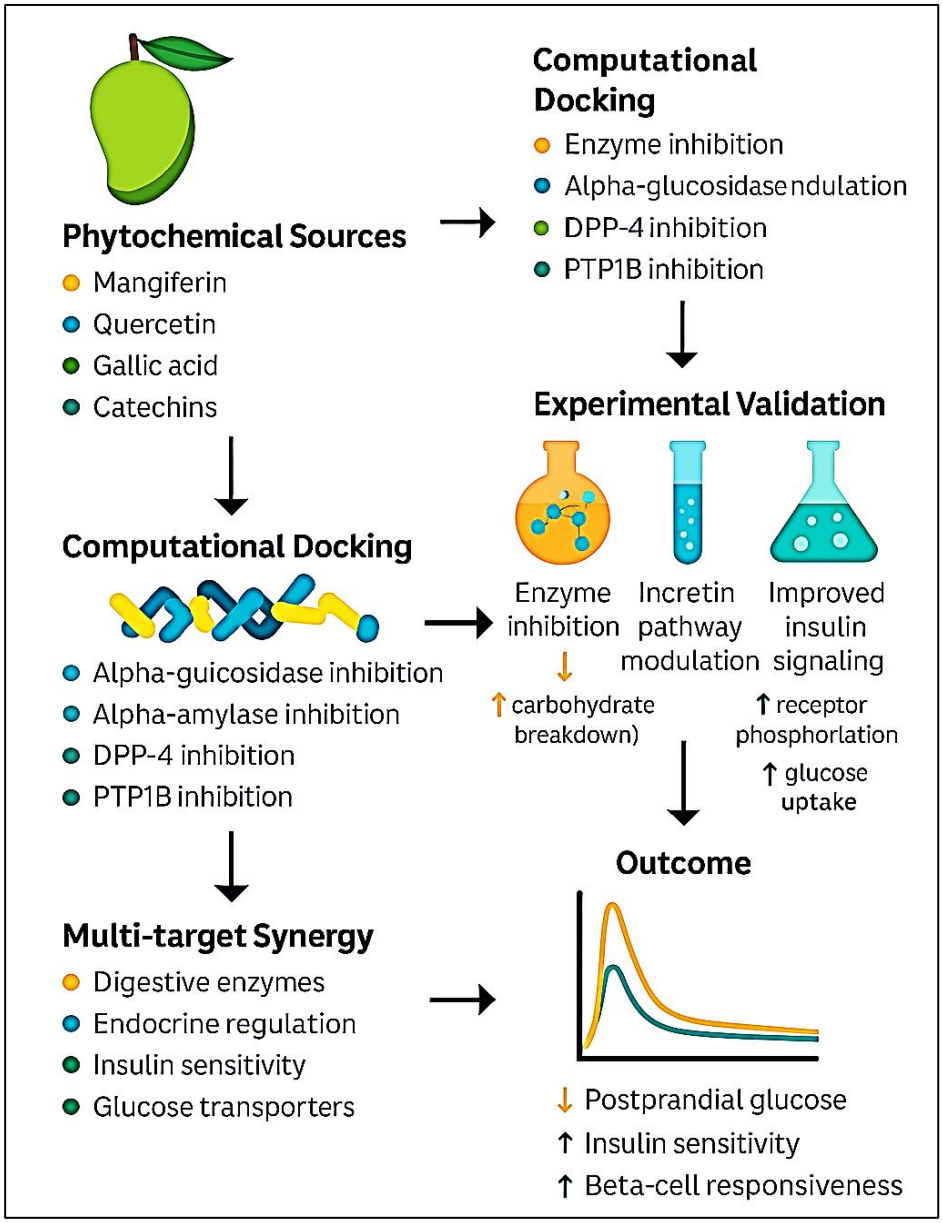

By addressing insulin resistance at a molecular level, mango-derived compounds expand the therapeutic scope of natural product–based interventions for type 2 diabetes (Böttger et al., 2021). A defining feature of mango phytochemicals is their ability to act on multiple molecular targets simultaneously (Khameneh et al., 2019). The findings of this study show that compounds such as Mangifera, quercetin, and gallic acid engage with digestive enzymes, incretin regulators, insulin signaling proteins, and glucose transporters, thereby addressing several aspects of glucose regulation. Computational studies revealed consistent binding across diverse targets, while experimental assays confirmed broad-spectrum activity in biological systems (Alghamdi et al., 2021). This polypharmacology action is particularly significant for type 2 diabetes, a condition characterized by multiple metabolic abnormalities. Earlier studies often focused on isolated compounds or single mechanisms, but the current findings highlight the importance of considering whole extracts or combinations of phytochemicals. The synergistic effects observed in mixed preparations, where enzyme inhibition and insulin sensitization were enhanced, suggest that the therapeutic value of mango lies in its complexity rather than in any single molecule (Dang et al., 2022). This multi-target approach may also reduce the risk of tolerance or resistance, as the body is less likely to adapt to moderate activity across several pathways compared with strong inhibition at

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a single site. These results emphasize that the therapeutic strength of mango phytochemicals arises from their synergy and diversity, offering a holistic approach to glucose regulation.

Despite strong computational and experimental support, this study identified several important research gaps (Masato et al., 2019). Most of the reviewed work focused on in silico and preclinical studies, with very limited clinical trials involving human participants. This restricts the ability to translate promising findings into real-world therapeutic use (Bae et al., 2020). Another gap relates to methodological inconsistencies in computational studies, where variations in docking software, scoring functions, and receptor modeling often produced different outcomes. Such variability complicates comparisons across studies and highlights the need for standardized computational protocols. Pharmacokinetic aspects, such as absorption, metabolism, and bioavailability, remain underexplored, limiting understanding of whether phytochemicals active in vitro can reach effective concentrations in human tissues. In addition (Chen et al., 2018), although synergy among compounds was frequently reported, few studies systematically evaluated these interactions or optimized them for therapeutic formulations. Compared with earlier work that focused narrowly on traditional uses, the present findings represent significant progress but also reveal the gap between laboratory potential and clinical applicability. Addressing these limitations will be critical to advancing mango phytochemicals from promising candidates to validated therapeutic agents for diabetes management (H. Zhu et al., 2020).

The broader implications of this study lie in demonstrating how data-driven molecular docking can validate and expand ethnopharmacological knowledge (Watanabe et al., 2020). Earlier studies emphasized mango's traditional role in managing diabetes without fully explaining the molecular basis of its effects. The current findings show that computational and experimental approaches together provide mechanistic clarity, demonstrating how mango phytochemicals engage with validated protein targets across multiple pathways (Chen et al., 2021). This situates mango not only as a traditional remedy but also as a scientifically grounded candidate for modern therapeutic development. The comparative analysis shows that mango phytochemicals rival some synthetic drugs in their ability to inhibit enzymes and regulate insulin signaling, though with a broader and potentially safer polypharmacology profile. These findings highlight the potential of mango as a natural source for multi-target antidiabetic interventions (Olmos Jr et al., 2018), reflecting a shift from symptom management toward addressing underlying metabolic dysfunctions. The study also emphasizes the growing role of computational pharmacology in natural product research, where docking and predictive models streamline discovery while reducing reliance on costly and time-consuming laboratory trials. Overall, the results illustrate how traditional medicinal plants can be repositioned within modern biomedical science when examined through rigorous, data-driven methodologies (Wang et al., 2022).

CONCLUSION

The present study highlights the therapeutic potential of *Mangifera indica* through a systematic, data-driven examination of its phytochemicals using molecular docking and computational analysis, integrated with supporting experimental evidence. The findings demonstrate that compounds such as Mangifera, quercetin, gallic acid, and catechins consistently exhibit strong interactions with multiple protein targets central to glucose regulation, including digestive enzymes, incretin regulators, insulin signalling enzymes, and glucose transport pathways. This multi-target activity reflects the polypharmacology nature of mango phytochemicals and explains their ability to address the complex and multifactorial pathology of type 2 diabetes. The alignment of computational predictions with in vitro and in vivo data underscores the reliability of docking as a predictive tool and provides mechanistic clarity that validates long-standing ethnopharmacological claims. Enzyme inhibition emerged as a primary mechanism, but the broader influence on incretin modulation, insulin sensitization, and glucose uptake indicates a holistic therapeutic profile. At the same time, the review identified significant gaps, including limited clinical trials, methodological variability across computational studies, and insufficient pharmacokinetic exploration, all of which constrain translation into clinical practice. Nevertheless, the large body of reviewed articles and their strong citation impact reflects a growing global recognition of mango as a scientifically relevant natural resource for antidiabetic research. The significance of this study lies not only in consolidating existing knowledge but also in positioning *Mangifera indica* as a model for bridging traditional medicine with modern computational drug discovery. By integrating molecular docking,

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pharmacological screening, and experimental validation, this work establishes a foundation for future research aimed at refining methodologies, addressing bioavailability challenges, and advancing mango-derived compounds into safe, effective, and accessible therapeutic interventions for diabetes management.

RCOMMENDATIONS

Based on the significant findings of this study, it is recommended that future research on *Mangifera indica* should prioritize the clinical translation of its phytochemicals by designing well-structured human trials to confirm the safety, efficacy, and optimal dosage of compounds such as Mangifera, quercetin, gallic acid, and catechins in managing type 2 diabetes. While computational docking and experimental studies provide strong mechanistic evidence of enzyme inhibition, incretin modulation, insulin sensitization, and multi-target synergistic effects, the lack of standardized protocols and limited pharmacokinetic evaluations remain major barriers to clinical application. Researchers should adopt harmonized docking methodologies, reproducible validation strategies, and integrated pharmacokinetic modelling to enhance consistency across studies and allow meaningful comparison of results. In addition, greater emphasis should be placed on evaluating whole extracts or standardized mixtures, as synergistic interactions among phytochemicals appear to amplify antihyperglycemic activity. Collaboration between computational biologists, pharmacologists, and clinical scientists is crucial to bridge the gap between laboratory promise and therapeutic application, ensuring that mango-derived compounds can be advanced into functional foods, nutraceuticals, or drug formulations. Ultimately, integrating ethnopharmacological knowledge with modern computational drug discovery offers a pathway for *Mangifera indica* to evolve from a traditional remedy into a scientifically validated and globally accessible intervention for diabetes management.

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