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Molecular Docking and Admet Analysis of Herbal Plants with Antidiabetic Properties: Review Paper

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Abstract: *Diabetes mellitus is a long-term metabolic condition characterized by consistently high blood sugar levels, which can result from reduced insulin function, insufficient insulin production, or both [2,4,9].Existing research emphasizes the role of medicinal plants as valuable sources of varied phytochemicals that can influence multiple targets linked to diabetes [4,19].Molecular docking is a technique that uses the structure of proteins to understand how phytochemicals interact with them, predict binding strengths, and identify various types of molecular interactions such as hydrogen bonds, hydrophobic forces, electrostatic interactions, and others [2,9].ADMET prediction supports this by estimating how well a compound is absorbed, distributed, metabolized, excreted, and its potential toxicity, before actual experiments are conducted [10,11].This review focuses on molecular docking and research on herbal treatments for diabetes, with an emphasis on specific targets such as alpha - amylase, alpha-glucosidase, protein tyrosine phosphatase 1B (PTP1B), dipeptidyl peptidase-4 (DPP-4), peroxisome proliferator-activated receptor gamma (PPAR-gamma), glycogen phosphorylase, GLUT1, glucokinase, and MAPK13 [1,3,5,6,20].The review summarizes key findings from various herbal plants including Azadirachta indica, Mangifera indica, Piper longum, Ficus lutea, Cordia subcordata, and Syzygium aromaticum (Clove), along with broader network pharmacology evidence involving compounds like diosgenin, apigenin, rosmarinic acid, and eugenol [3,5,6,7,21,22].Across the reviewed studies, several phytochemicals demonstrated promising predicted interactions and, in some instances, supporting evidence from laboratory or animal studies [3,8,14,18].However, challenges such as poor solubility, limited oral absorption, uncertain metabolism, potential toxicity, and differences in docking methodologies continue to be significant obstacles [9,11,12].The literature suggests that docking and ADMET analysis are useful tools for prioritizing compounds, rather than being proof of therapeutic effectiveness on their own [2,11,12,15].A logical approach should start with selecting plants and compounds, followed by identifying targets, preparing proteins and ligands, performing docking and analyzing poses, filtering using ADMET properties, and concluding with experimental validation [2,9,11,12].*

Keywords: Diabetes mellitus, medicinal plants, herbal drugs, phytoconstituents, antidiabetic activity, molecular docking, ADMET analysis, α-amylase, α-glucosidase, DPP-4, PTP1B, PPAR-γ, computational drug discovery.

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent elevation of blood glucose levels due to impaired insulin secretion, reduced insulin sensitivity, or a combination of both [2,4,9]. It is associated with disturbances in carbohydrate, lipid, and protein metabolism and may lead to serious complications affecting the cardiovascular system, kidneys, eyes, nerves, and other organs [1,2,4]. The increasing prevalence of diabetes has created a crucial need for the development of effective, safe, and affordable therapeutic agents [9,12,19].

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The clinical management of the diabetes mellitus commonly involves lifestyle modification and the pharmacological treatment with conventional drugs such as insulin, metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, and other antidiabetic agents [2,4,20]. Although these medicines are clinically useful, long-term treatment may be associated with adverse effects, limitations in efficacy, high costs, or problems related to patient compliance [Ref 9]. Therefore, research into alternative and complementary sources of antidiabetic compounds, particularly medicinal plants, has gained considerable global attention [4,11,19].

Medicinal plants contain diverse bioactive phytochemicals such as flavonoids, alkaloids, terpenoids, phenolic compounds, glycosides, steroids, and tannins [3,4,5,6]. These compounds may influence several biological pathways involved in glucose metabolism and insulin signaling [4,11]. Important antidiabetic molecular targets include α-amylase, α-glucosidase, dipeptidyl peptidase-4 (DPP-4), protein tyrosine phosphatase 1B (PTP1B), peroxisome proliferator-activated receptor gamma (PPAR-y), AMP-activated protein kinase (AMPK), and other proteins associated with glucose homeostasis [3,6,10,20,21]. The multitarget nature of phytochemicals makes them valuable candidates for preliminary investigation in antidiabetic drug discovery [4, 12].

However, identification and experimental evaluation of a large number of phytochemicals can be time - consuming and highly expensive [2,9]. Computational drug-discovery techniques provide an efficient, high-throughput approach for preliminary screening of potential bioactive compounds [9,11,12]. Molecular docking is an important in-silico technique used to predict the preferred orientation of a ligand within the binding site of a target protein and to estimate the strength of the ligand -protein interaction [2]. Docking studies can provide critical insights into binding affinity, hydrogen bonding, hydrophobic interactions, p-p interactions, and other interactions that contribute to biological activity [2,15].

Along with molecular docking, ADMET analysis is an essential component of early-stage drug discovery [9,11]. ADMET represents the Absorption, Distribution, Metabolism, Excretion, and Toxicity [11]. A compound showing favorable docking results may not necessarily become a successful drug if it has poor absorption, unsuitable distribution, rapid metabolism, inadequate excretion characteristics, or significant toxicity [9,10]. Therefore, computational ADMET prediction can help identify compounds with potentially favorable pharmacokinetic and safety profiles at an early stage [10,11].

The combination of molecular docking and ADMET analysis provides a systematic framework for prioritizing promising phytochemicals [2,11,12]. In a typical workflow, selected plant-derived compounds are obtained from chemical databases, prepared as ligands, and docked against relevant antidiabetic protein targets [2,9]. The resulting binding scores and molecular interactions are then analyzed, followed by prediction of pharmacokinetic and toxicity-related properties [9,11]. Compounds showing favorable target interactions together with acceptable predicted ADMET characteristics can be selected for further empirical investigation [11,12,18].

II. METHODOLOGY OF LITERATURE REVIEW

The review was prepared by systematically examining the sources supplied for the project [1 to 25]. The sources included general molecular-docking review papers [2], network-pharmacology and molecular-docking reviews focused on antidiabetic herbal drug research [4], and plant-specific computational/experimental studies [1,3,5,6,7,8,23].

Information extraction domains included:

- Plant and phytochemical identity.
- Diabetes-related biological target or pathway.
- PDB target, when explicitly reported.
- Docking approach and reported binding energy observations.
- Key ligand-protein interactions, where described.
- ADMET or drug-likeness observations.
- Experimental support such as enzyme inhibition or cell-based glucose-utilization findings.
- Limitations and future validation recommendations.

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The review does not treat docking score alone as evidence of antidiabetic efficacy [2]. Where the uploaded studies reported in vitro or in vivo findings alongside computational results, these were distinguished from purely predictive findings [3,8,14,18,21]. This distinction is important because docking is a prioritization and mechanistic hypothesis-generation technique, whereas biological efficacy and safety require experimental confirmation [2,11,12,15]. The supplied Mangifera indica review describes a literature-search approach using databases such as PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar and reports systematic extraction of docking, ADMET and experimental findings. This approach informed the organization of the present compact review, while the present article itself is based on the applied sources [6].

III. DIABETES MELLITUS AND RATIONALE FOR HERBAL DRUG RESEARCH

Diabetes mellitus is a chronic metabolic disorder which is characterized by the persistant elevation of blood glucose levels [2,4,9]. Type 2 diabetes mellitus (T2DM) is a multifactorial disease involving insulin resistance, impaired glucose regulation, altered incretin activity, increased hepatic glucose production, and progressive dysfunction of pancreatic β-cells [4,20]. Since several biochemical and physiological mechanisms contribute to diabetes, treatment directed toward only one target may not completely address the complexity of the disease [4]. This provides a scientific rationale for investigating compounds that can influence multiple metabolic pathways simultaneously [4,12,14].

Medicinal plants are important sources of structurally diverse bioactive compounds. Their phytochemical constituents include flavonoids, phenolic compounds, alkaloids, terpenoids, sterols, and glycosides. These compounds have attracted interest in antidiabetic research because they may interact with pathways associated with carbohydrate digestion, insulin signaling, glucose transport, oxidative stress, and inflammatory processes. The chemical diversity of herbal constituents also makes them suitable candidates for computational screening and molecular docking studies [2,4,14,20].

3.1 Targets Associated with Carbohydrate Digestion

a-Amylase and a-glucosidase are important enzymes involved in the digestion of dietary carbohydrates [14,15]. Inhibition of these enzymes can slow the breakdown of carbohydrates into absorbable sugars and may therefore help reduce postprandial increases in blood glucose [14,15,17]. These enzymes are frequently selected as molecular docking targets for screening antidiabetic phytochemicals [2,15,17,21]. Studies involving Piper longum, Ficus lutea, and Syzygium aromaticum (Clove) have investigated phytochemical interactions with both a-amylase and a-glucosidase structures [3,5,22,23].

3.2 Insulin Signaling and Metabolic Targets

Protein tyrosine phosphatase 1B (PTP1B) is considered an important negative regulator of insulin signaling, and its inhibition is investigated as a possible approach for improving insulin-related signaling [3,6]. Dipeptidyl peptidase-4 (DPP-4) is another important target because it regulates incretin activity [6,20]. Peroxisome proliferator-activated receptor gamma (PPAR-y) is associated with insulin sensitivity and lipid metabolic regulation, while GLUT1 and glucokinase are involved in cellular glucose transport and hepatic glucose utilization [3,6,10,11,16]. Clove extracts have also been shown to modulate sirtuin-1 and skeletal muscle pathways to reduce insulin resistance [22,24].

3.3 Targets Associated with Diabetic Complications

The molecular mechanisms of diabetes also involve inflammatory and cellular-stress pathways that contribute directly to long-term complications [1,4]. MAPK13 (p38d) has been investigated in relation to diabetic neuropathy and is associated with inflammatory and stress-related signaling [1]. Active fractions of Clove (such as nigericin) have similarly been noted to downregulate p38 MAP kinase phosphorylation, showing potential in controlling stress signaling [24]. Therefore, herbal drug research can extend beyond direct glucose-lowering targets and investigate molecular pathways involved in diabetes-associated complications [1,4].

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3.4 Rationale for Molecular Docking of Herbal Phytochemicals

The complex and multitarget nature of T2DM provides a strong rationale for investigating medicinal plants through molecular docking and ADMET analysis [4,11,12]. Molecular docking can be used to predict how selected phytochemicals interact with diabetes-related proteins and to identify favorable binding orientations and interaction patterns [2,4]. Network pharmacology can additionally be used to connect multiple phytochemicals with potential targets and pathways before detailed docking analysis [4].

IV. PHYTOCHEMICALS AS MULTITARGET ANTIDIABETIC CANDIDATES

Medicinal plants contain a wide variety of bioactive phytochemicals, including flavonoids, phenolic compounds, alkaloids, terpenoids, sterols, tannins, and glycosides [3,4,5,6]. These compounds are of interest in antidiabetic research because their chemical diversity allows them to interact with different proteins involved in glucose metabolism, insulin signaling, oxidative stress, and inflammation [4,11,18].

For a molecular docking project, phytochemicals can be selected as ligands and screened against important antidiabetic protein targets [2,9]. This approach helps identify compounds that may show favorable interactions with the active site of a selected target and can be used to prioritize compounds for further experimental investigation [2,11,12,17].

4.1. Flavonoids and Polyphenols:

Flavonoids and other polyphenolic compounds are frequently investigated because of their structural diversity and presence in many medicinal plants [14]. Important examples include quercetin, catechins, epicatechin, epiafzelechin, rutin, and apigenin [3,6,14]. Studies involving Mangifera indica have investigated compounds such as mangiferin and quercetin against carbohydrate-digesting enzymes and insulin-related targets [6]. In Ficus lutea, epicatechin and epiafzelechin were associated with experimental antidiabetic activity in addition to computational investigation [3].

4.2. Alkaloids:

Alkaloids represent another important group of plant constituents for computational screening [4]. Piperine, the characteristic alkaloid of Piper longum, has been evaluated against α-amylase and α-glucosidase [5]. Because alkaloids can possess diverse chemical structures, they may interact with different classes of biological targets and are suitable candidates for ligand screening in docking studies [4,5].

4.3. Terpenoids and Sterols:

Terpenoids and sterols are also important phytochemical classes in herbal antidiabetic research [3,4,5]. Compounds such as lupeol, stigmasterol, and α-amyrin acetate have been investigated from Ficus lutea [3]. In Piper longum, β-sitosterol and 5,6-dihydroergosterol were among the compounds reported to show favorable docking interactions with α-amylase and α-glucosidase [5].

4.4. Multitarget Approach in Molecular Docking:

Diabetes is a multifactorial disorder, so investigating a phytochemical against only one biological target may not fully represent its potential mechanism [4]. A multitarget docking strategy can examine interactions with several proteins involved in glucose metabolism and insulin regulation [4,11,12,16]. Common targets include α-amylase, α-glucosidase, PTP1B, DPP-4, PPAR-γ, glycogen phosphorylase, GLUT1 and glucokinase [3,6,10,12,16].

Network-pharmacology can be used before the docking to identify the possible compound target–pathway relationships, which is followed by molecular docking to investigate the structural interaction of selected phytochemicals with important protein targets [4]. Reported pathways of interest include PI3K/Akt, AMPK, NF-κB, AGE-RAGE, PPAR, and FoxO1 [4].

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4.5. Phenolic Volatiles:

Clove (Syzygium aromaticum) introduces an exceptional class of volatile phenolic compounds into the screening mix [22,23]. Its principal bioactive constituent is Eugenol (comprising 80-90% of its essential oil profile), alongside eugenyl acetate and beta-caryophyllene [22,25]. Eugenol possesses high structural complementarity and strong binding affinities towards carbohydrate-hydrolyzing receptors, serving as a distinct candidate for expanding standard non-volatile ligand libraries [23,25].

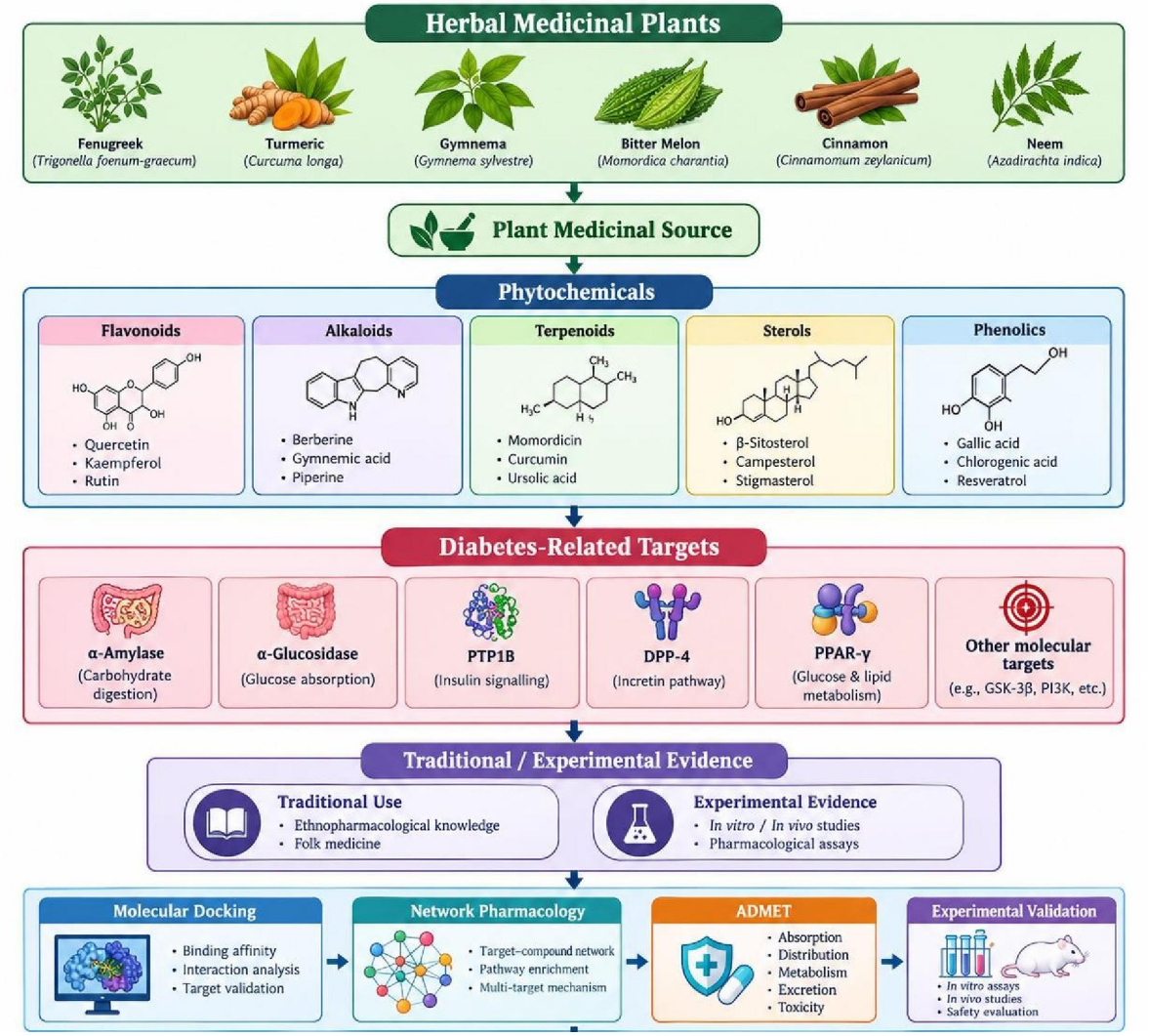


Fig. 1: Phytochemicals as Multitarget antidiabetic candidates

V. MOLECULAR DOCKING: PRINCIPLES AND TYPES

Molecular docking is an in-silico computational technique used to predict the preferred orientation and interaction of a small molecule (ligand) within the binding site of a biological macromolecule such as a protein [2]. It is widely used in computer-aided drug discovery to screen potential drug candidates and investigate their possible interactions with therapeutic targets [2,9,11].

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5.1 Principle of Molecular Docking

The basic principle of molecular docking is based on the recognition and interaction between a ligand and receptor [2]. The ligand is placed within the binding site of the target protein in different possible orientations and conformations [2]. Each ligand–protein pose is evaluated using a scoring function, which estimates the strength or favorability of the interaction [2,9].

A simplified representation is: [2]

Protein target + Ligand → Different binding poses → Scoring → Best-ranked pose

The docking process generally considers: [2,15]

- Shape and structural complementarity between ligand and protein
- Hydrogen-bond interactions
- Hydrophobic interactions
- Electrostatic interactions
- van der Waals interactions
- π–π and other non-covalent interactions
- Ligand flexibility and conformational changes

A more favorable docking score or binding energy generally indicates a stronger predicted interaction within the particular docking protocol. However, docking scores from different studies should not be directly compared unless the same target structure, docking software, scoring function, and parameters are used [2].

5.2 Receptor and Ligand

Receptor:

The receptor is usually a protein involved in a biological pathway associated with the disease. For an antidiabetic project, examples include α-amylase, α-glucosidase, DPP-4, PTP1B, PPAR-γ, AMPK, or other diabetes-related targets [2,4,10].

Ligand:

A ligand is a small molecule that is evaluated for its ability to interact with the receptor [2]. In a Neem-based project, compounds such as azadirachtin, gedunin, nimbolide, nimbin, quercetin, β-sitosterol and stigmasterol may be considered after appropriate structure and literature verification [7,8].

5.3 Types of Molecular Docking

Molecular docking can be classified according to the flexibility of the receptor and ligand.

1. Rigid Docking

In rigid docking, both the receptor and ligand are treated as rigid structures during the docking calculation [2].

Advantages:

- Simple and computationally less demanding
- Faster than flexible docking

Limitation:

- Does not adequately account for conformational changes of the ligand or protein.

2. Flexible Docking

In flexible docking, the ligand is allowed to change its conformation during docking, while the receptor is generally kept relatively rigid [2,9].

Advantages:

- Makes the more realistic representation of ligand binding
- Suitable for structurally flexible natural products

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This approach is commonly useful for phytochemical screening because many herbal compounds contain several rotatable bonds.

3. Semi-Flexible Docking

In semi-flexible docking, the ligand is flexible while selected receptor-side chains may also be allowed to move. It provides a compromise between computational cost and structural flexibility [2].

5.4 Types Based on the Binding Site

A. Known/Targeted-Site Docking

The docking site is already known for experimental structural information, co-crystallized ligands, or previous studies. The ligand is docked into a predefined binding pocket [2].

B. Blind Docking

In blind docking, the entire protein surface or a very large region is searched for possible ligand-binding sites. This approach can be useful when the active site is not clearly established [2].

5.5 Importance in Herbal Drug Research

Molecular docking is particularly useful in herbal drug research because medicinal plants contain numerous phytochemicals. Instead of experimentally testing every compound against every target, computational docking can be used as an initial screening and prioritization method . Promising compounds can subsequently be subjected to ADMET prediction and experimental validation.

VI. MOLECULAR DOCKING WORKFLOW FOR HERBAL PHYTOCHEMICALS

A reproducible docking project should follow a defined sequence so that the final binding-energy comparisons are meaningful [2,9].

6.1 Plant and phytochemical selection:

Begin with a medicinal plant supported by traditional use, published pharmacological evidence, or phytochemical characterization. Candidate compounds can be obtained from literature, phytochemical databases or analytical studies such as GC-MS. The Piper longum study, for example, identified 33 chemical components by GC-MS before computational screening [5,7,22].

6.2 Ligand retrieval and preparation:

- Retrieve chemical structures from an appropriate database such as PubChem or from experimentally characterized compounds.
- Check compound identity, stereochemistry and structure completeness.
- Generate or verify a suitable 3D structure.
- Perform geometry optimization and assign appropriate protonation/charge states as required by the docking platform.
- Record compound identifiers so that the analysis can be reproduced. [2,9,11]

6.3 Protein target selection:

Select a biologically justified protein target and obtain a suitable three-dimensional structure, commonly from the Protein Data Bank. The target should have an appropriate resolution and a clearly defined binding site or co-crystallized ligand when available. For example, the Cordia subcordata study used MAPK13 with PDB ID 5EKN, while the Piper longum study used alpha-amylase (2QV4) and alpha-glucosidase (5ZCC) [1,5,9,23].

6.4 Protein preparation:

- Remove irrelevant solvent or ligand molecules where appropriate.
- Retain biologically important cofactors or structural components when required.

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• Add hydrogens and assign charges using the chosen software.
• Check structural quality and active site residues.
• Define the docking grid or binding sphere around the selected site. [2,9]

6.5 Docking and pose generation:

Run the docking protocol with a predefined search space and appropriate settings. Generate multiple poses rather than relying on a single output. Rank the poses by the selected scoring function and inspect whether the ligand occupies a biologically plausible pocket [2,23].

6.6 Interaction analysis and validation:

Examine hydrogen bonds, hydrophobic contacts, pi interactions, salt bridges and contacts with known active-site residues. If a native ligand or reference drug is available, redocking can be used to assess whether the protocol reproduces a plausible binding mode. The supplied literatures repeatedly emphasizes the need for the experimental validation after the computational screening, molecular docking, & ADMET of Herbal Antidiabetic Phytochemicals [2,9,11,15].

VII. MAJOR ANTIDIABETIC MOLECULAR TARGETS

Diabetes mellitus is a multifactorial metabolic disorder involving several enzymes, receptors, and signaling pathways. Therefore, the selection of an appropriate molecular target is an important step in molecular docking and ADMET analysis study.

Table 1: Major antidiabetic molecular targets

Target	Major role in diabetes	Purpose in molecular docking
α-Amylase	Carbohydrate digestion	Screening enzyme inhibitors
α-Glucosidase	Final carbohydrate digestion	Reduction of glucose release
DPP-4	Incretin degradation	Investigation of DPP-4 inhibition
PTP1B	Negative regulation of insulin signaling	Investigation of insulin-sensitizing compounds
PPAR-γ	Insulin sensitivity and lipid metabolism	Receptor–ligand interaction study
AMPK	Cellular energy and glucose metabolism	Investigation of metabolic regulation
Glucokinase	Glucose phosphorylation/utilization	Study of glucose metabolism
PEPCK	Hepatic gluconeogenesis	Investigation of glucose-production pathways
GLUT1	Cellular glucose transport	Study of glucose uptake mechanisms

[3,5,6,10,11,14,15,16,20,22,23]

VIII. ADMET ANALYSIS OF HERBAL PHYTOCHEMICALS

ADMET refers to the Absorption, Distribution, Metabolism, Excretion, and Toxicity. ADMET profiling filters out structurally active hits that fail drug-likeness criteria due to toxicity or poor systemic parameters [9,11]. Docking can identify compounds with favorable predicted protein interactions, but a candidate must also possess properties compatible with reaching and remaining at the site of action without unacceptable safety trade-offs [10,11].

8.1 Absorption:

Absorption includes gastrointestinal uptake, permeability, and the influence of physicochemical properties. It measures intestinal epithelial permeability and solubility balances, identifying natural compounds limited by high molecular mass

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or high first-pass metabolism [9,10]. Eugenol from Clove exhibits highly favorable predicted human intestinal absorption, bypassing some of the structural permeability limitations typical of large polyphenols [25].

8.2 Distribution:

Distribution concerns movement of a compound into tissues and body fluids. It evaluates blood-brain barrier (BBB) penetration indices and distribution volume (Vd) bounds [11]. These predictions are particularly relevant when a compound is intended to influence central or peripheral complications of diabetes. Essential oil constituents like caryophyllene show high lipid permeability, requiring careful toxicity boundaries [25].

8.3 Metabolism:

Metabolism can change both exposure and biological activity. Cytochrome P450 interactions and first - pass metabolism are therefore important considerations [10,11].

8.4 Excretion:

Excretion influences systemic persistence and clearance. In-silico platforms can provide estimates of clearance and related pharmacokinetic parameters, helping identify compounds that may have unsuitable exposure profiles [9,11].

8.5 Toxicity:

Natural origin does not guarantee safety. Toxicity prediction may include hepatotoxicity, mutagenicity, cardiotoxicity-related endpoints, and acute toxicity classifications [11,12].

8.6 Common computational resources reported in the supplied literature Tool / resource:

Table 2: Common computational resources reported in the supplied literature Tool / resource

Tool / Resource	Typical Use in the Reviewed Workflow	Reference
SwissADME	Drug-likeness filters, Lipinski parameters, gastrointestinal absorption maps, friendliness screening.	10
pkCSM	Graph-based pharmacokinetic and toxicity endpoint predictions (absorption, distribution, clearance).	6, 11
ProTox / admetSAR	Toxicity class labeling, organ hazard tracking, lethal dose (LD50) modeling.	11, 12
Protein Data Bank (PDB)	Three-dimensional macromolecular structural coordinate acquisition for receptors.	9, 11
SwissTargetPrediction	Reverse target architecture mapping via compound structural fingerprint matching.	4, 11
STRING / Cytoscape	Protein-interaction visualization and network pharmacology path enrichment.	4

IX. REPRESENTATIVE HERBAL PLANTS AND DOCKING FINDINGS

Medicinal plants contains the numerous phytochemicals that may interact with the proteins involved in glucose metabolism, insulin signaling, and diabetes associated complications. Molecular docking provides a useful in-silico screening approach for investigating these interactions and identifying compounds that may be prioritized for further ADMET evaluation and experimental validation [1,3,5,6,7].

Table 3: Representative Herbal Plants and Docking findings

Herbal plant	Representative phytochemicals	Important docking targets	Relevance
Syzygium aromaticum (Clove)	Eugenol, eugenyl acetate, β-caryophyllene, gallic acid	α-Amylase, α-glucosidase Dietary carbohydrate-digestion screening	
Azadirachta indica	Azadirachtin, gedunin, nimbolide, nimbin, quercetin	α-Amylase, α-glucosidase, AMPK, PEPCK	Primary plant for present project
Ficus lutea	Lupeol, stigmasterol,	α-Amylase, α-glucosidase,	Multitarget antidiabetic

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Piper longum	epicatechin, epiafzelechin Piperine, β-sitosterol, 5,6-dihydroergosterol	DPP-4, PTP1B, PPAR-γ α-Amylase, α-glucosidase	screening Carbohydrate-digestion targets
Mangifera indica	Mangiferin, quercetin, catechins	α-Amylase, α-glucosidase, Glucose-regulatory DPP-4, PTP1B targets	
Cordia subcordata	Procyanidin, rutin, related polyphenols	MAPK13	Diabetic complication-related target

X. LITERATURE SYNTHESIS OF REPRESENTATIVE PLANTS

The reviewed plant studies collectively illustrate the power of in-silico molecular docking to systematically explore enzyme inhibition and insulin signaling-related targets [4,12]. Their findings are fundamentally hypothesis-generating and must be interpreted with close attention to specific protocol parameters, grid sizes, compound purity boundaries, and predictive ADMET filter thresholds [2,11]. By pulling together disparate data matrices—ranging from non-volatile polyphenolic structures in Neem and Mango leaves to volatile phenolic networks in Clove essential oils—this synthesis underlines a universal drug-discovery pipeline that helps identify potential lead compounds while screening out problematic structures long before cell-based or animal testing begins [3,5,6,23]

XI. ADVANTAGES AND LIMITATIONS

Advantages:

- Rapid screening of many phytochemicals before laboratory testing.
- Relatively low computational cost compared with early-stage experimental screening.
- It provides a structural hypothesis for the ligand's target recognition.
- Can prioritize compounds and reduce the number of candidates taken into biological experiments.
- Can be integrated with network pharmacology to explore multiple targets and pathways.
- ADMET prediction can identify pharmacokinetic or toxicity concerns at an early stage.
- Suitable for undergraduate research when a reproducible, clearly defined workflow is used.

Limitations:

- Docking scores are model-dependent and are not direct measurements of clinical affinity or efficacy.
- Most routine docking protocols simplify protein flexibility and solvent effects.
- Different PDB structures, grid settings, scoring functions and software make cross-study score comparisons unreliable.
- Predicted ADMET values are estimated and require experimental confirmation.
- A strong docking pose does not establish selectivity, cellular activity, or clinical effectiveness.
- Herbal extracts contain mixtures; docking a single isolated compound cannot fully represent extract-level synergy or antagonism.

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XII. PROPOSED WORKFLOW FOR IN-SILICO MOLECULAR DOCKING AND ADMET ANALYSIS

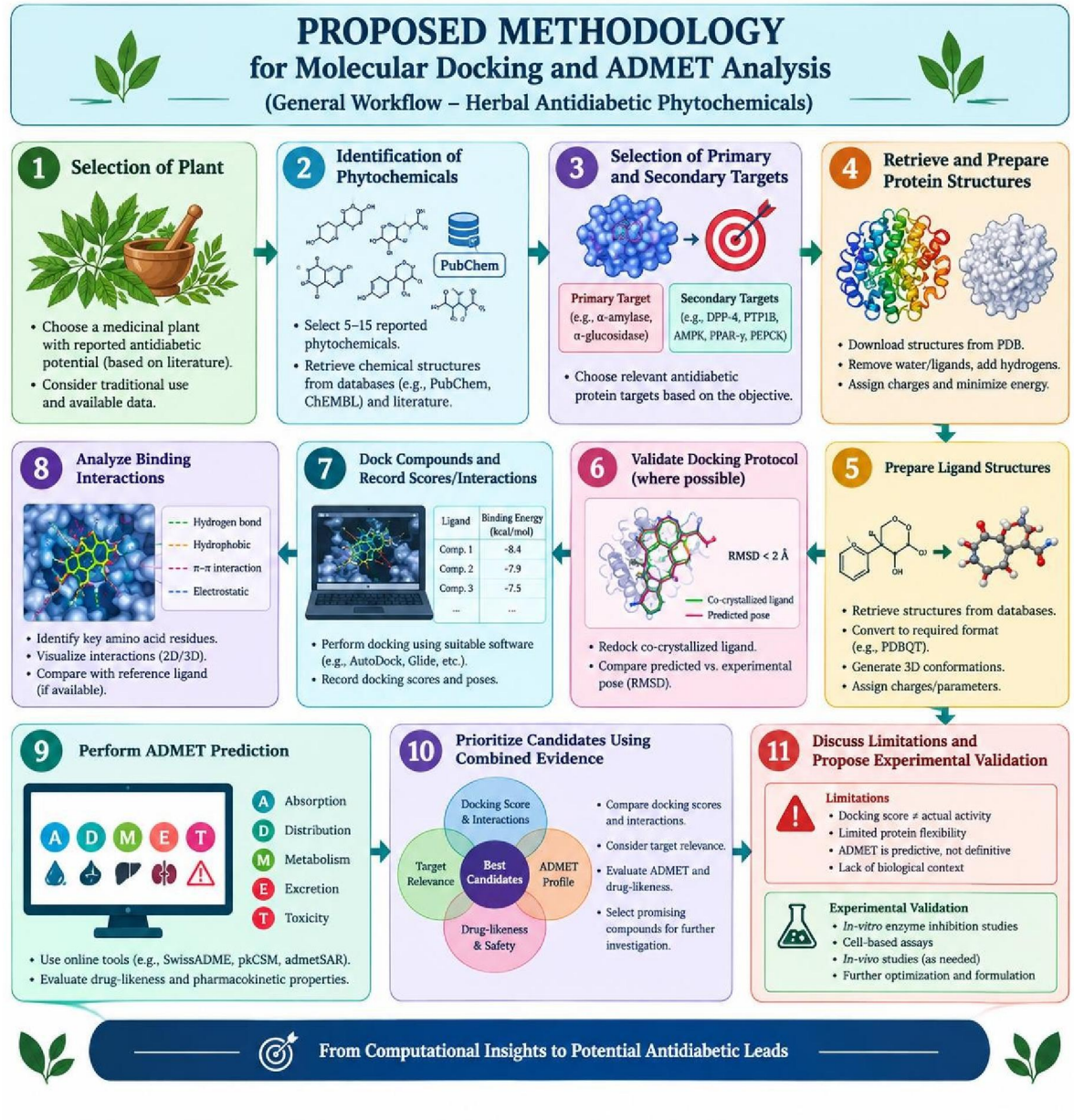


Fig. 2: Proposed workflow for In-silico molecular docking and ADMET analysis

XIII. FUTURE PERSPECTIVES

Molecular docking and ADMET analysis provide useful computational approaches for the preliminary investigation of herbal phytochemicals with potential antidiabetic activity. These approaches can help identify promising compounds and their possible interactions with diabetes-related molecular targets. However, further research is required to establish their actual biological activity and therapeutic potential.

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13.1 Experimental Validation

High-scoring hits must transition into empirical bench assays (e.g., spectrophotometric enzyme inhibition runs) followed by cell-based glucose uptake assays to confirm functional activity [3,8,14,21].

13.2 Advanced Computational Studies:

Transitioning from static structures to dynamic models over time via Molecular Dynamics (MD) simulations and tracking explicit binding balances through free-energy calculations (MM-PBSA/GBSA) [9,11,12].

13.3 Expanded ADMET Evaluation:

Refining safety profiling via specialized cardiotoxicity limits (hERG channel), plasma protein binding (PPB) margins, and comprehensive cytochrome isoform inhibition matrices [9,11].

13.4 Multitarget and Synergy Modeling:

Designing unified network pharmacology structures mapping out complex multi-target signaling networks to assess how crude mixture fractions (such as Clove's complex eugenol/acetyleugenol mix) interact simultaneously [4,12,23].

13.5 Improved Computational Accuracy:

Validating docking outputs through mandatory positive controls and standardized reference drug benchmarks to align structural comparisons [2,9].

XIV. CONCLUSION

Molecular docking and ADMET analysis provide the valuable in-silico approaches for the preliminary investigation of herbal phytochemicals with potential antidiabetic activity. Diabetes mellitus is a complex metabolic disorder involving multiple enzymes, receptors and signaling pathways; therefore, investigation of phytochemicals against relevant molecular targets can provide useful insights into their possible mechanisms of action.

Here, reported phytochemicals from medicinal plants can be screened against selected antidiabetic protein targets using molecular docking. The analysis of docking scores, binding poses, and protein–ligand interactions can help identify compounds with favorable predicted interactions. Subsequent ADMET analysis provides preliminary information regarding their absorption, distribution, metabolism, excretion, and toxicity, along with drug-likeness characteristics.

An integrated assessment of target relevance, docking results, binding interactions and ADMET properties can be used to prioritize promising phytochemicals for further investigation. This approach can reduce the initial screening burden and provide a rational basis for selecting compounds for experimental studies.

However, molecular docking and ADMET prediction are computational methods, and their results should not be considered direct evidence of therapeutic efficacy or safety. In-vitro enzyme inhibition studies, cellular studies, and appropriate in-vivo investigations are required to validate the computational findings.

Overall, the combination of herbal phytochemical screening, molecular docking, and ADMET analysis represents a useful preliminary strategy for identifying potential antidiabetic lead compounds and supporting future natural-product drug discovery.

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