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AI-Driven Identification of Bioactive Compounds in Medicinal Plants for Diabetes Management: An Integrative Computational and Validation Study

Syed Muqeet Ahmed Kazmi
muqeetkazmi@gmail.com
Karachi University

Corresponding Author: *Syed Muqeet Ahmed Kazmi muqeetkazmi@gmail.com

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ABSTRACT

Diabetes mellitus is a major worldwide social health problem, and, thus, the continued discovery of therapeutically safe, effective and cost-effective agents is necessary. Medical plants have traditionally been a good source of bioactive compounds with antidiabetic properties; however, the traditional discovery systems are limited by high financial expenditure, time-consuming processes, and the frequent occurrence of compounds that have been described and characterized before. In the current study, an artificial intelligence (AI)-based paradigm was used to identify and rank bioactive molecules produced through medicinal flora to treat diabetes. An edited list of ten antidiabetic plant species and twenty plant chemical entities was built. Quantitative structure-activity relationship (QSAR) models based on machine learning were used to predict both α-glucosidase inhibitory activity and the likelihood of inhibiting the dipeptidyl peptidase-4 (DPP-4) inhibition. Molecular docking schemes were run using structure-based protocol which determined binding affinity against α- glucosidase followed by in-silico ADMET profiling. Compounds with high rankings in computation were confirmed by synthetic in-vitro tests. The results have shown that several constituents such as thymoquinone, ellagic acid, Gymnemic acids and quercetin exhibited strong predicted inhibitory activities, good docking energies and acceptable pharmacokinetic properties. This paper highlights the effectiveness of AI-directed screening at accelerating the identification of natural product-derived antidiabetic therapeutics and provides a reproducible framework that can be used in future translational studies.

Keywords: *Diabetes mellitus; Medicinal plants; Artificial intelligence; Machine learning; α-glucosidase; DPP-4; Molecular docking; ADMET*

INTRODUCTION

Diabetes mellitus is one of the most common and fast-growing metabolic diseases in the world thus posing significant public-health and economic burdens. This syndrome is characterized by persistent hyperglycaemia due to defects in insulin secretion, insulin action or both, and is associated with serious adverse effects in the long run including cardiovascular disease, nephropathy, neuropathy and retinopathy. In the recent estimates worldwide, it is indicated that over 530 million adults are already infected, and without intervention it is likely to increase to over 640 million by the year 2030 (International Diabetes Federation [IDF], 2024). The burden of the disease is significantly greater in low- and middle-income nations, where access to healthcare and chronic pharmacological management is limited further, worsening clinical outcomes (World Health Organization [WHO]).

T2DM represents about 90 -95% of all cases of diabetes and is highly associated with lifestyle factors, obesity, resistance to insulin, and genetic factors (World Health Organisation [WHO], 2024). Clinical use of current antidiabetic pharmacotherapies, such as biguanides, sulfonylureas, dipeptidyl peptidase-4 (DPP)-4) inhibitors, glucagon-like peptide-1 receptor (GLP1) agonists, and sodium-glucose cotransporter-2

(SGLT2) inhibitors, are often limited in their long-term clinical phenotype by adverse effects, contraindications, diminishing efficacy, and fiscal constraints (International Diabetes Federation Based on this, there is growing interest in the discovery of safer, cheaper, and multi-target therapeutics that can be used to supplement or enhance current regimens.

Traditional healthcare systems have traditionally placed medicinal plants at the heart of their treatment regimens and are still used as a key source of medical action in modern medicine. Many species of plants have also been used in traditional ways to reduce diabetes via the reduction of plasma glucose levels, insulin sensitivity, and relieving oxidative stress and inflammation (Chaachouay et al., 2024). Phytochemical compounds, such as alkaloids, flavonoids, terpenoids, saponins and phenolic acids, display various antidiabetic actions including: inhibition of carbohydrate-digestion enzymes, regulation of incretin signalling, pancreatic 8 -cell activity, and peripheral glucose uptake (Pan et al., 2024). Although it has a therapeutic potential, systematic isolation and discovery of plant-based antidiabetic products have been hampered by methodological difficulties.

Traditional natural product discovery pipelines are by definition time-consuming, resource-intensive and prone to resolving known objects. The experimental screening of the plant extracts is further obscured by the chemical heterogeneity of the extracts, variable response in the phytochemical profiles, and lack of standardisation. In addition, bioassay-guided fractionation often requires a significant laboratory infrastructure and is not incompatible with large-scale screening of compound libraries (Chaachouay et al., 2024). These shortcomings have precipitated the combination of computational and data-driven methods in expediting the discovery of bioactive compounds of medicinal plants.

The evolution of the artificial intelligence (AI), machine learning (ML), and computational biology has reshaped the paradigm of drug discovery. AI-based approaches are used to analyses large volumes of chemical data and predict the activity of biologic compounds, priorities lead compounds, and early predict pharmacokinetic and safety profiles (Gangwal et al., 2025). Specifically, quantitative structure-activity relationship (QSAR) models (ML-based) have proven to be relatively effective at predicting enzyme inhibition, receptor binding, and drug-likeness when based on the use of molecular descriptors and structural fingerprints (Othman et al., 2025). Such methods are particularly useful when dealing with natural products where there are a limited number of experimental data points, but chemical diversity is large.

In the context of diabetes management, in recent years, AI-based screening has been implemented to detect inhibitors of the activity of key therapeutic targets, including alpha -glucosidase and dipeptidyl peptidase-4 (DPP-4). alpha -glucoseidase is a central player in carbohydrate metabolism, which catalyses the breakdown of oligosaccharides into glucose in the brush-border intestinal lining; its inhibition postpones the absorption of glucose and suppresses postprandial Similarly, DPP-4 inhibitors enhance the action of incretin hormones, which increase secretion of insulin and glycaemic control. Compounds of plant origin that can interact with these targets are potentially useful alternatives or complements to synthetic drugs.

Included with ligand prediction models, structure-based computational methods, such as molecular docking and molecular dynamics simulation, give mechanistic data on ligand-protein interactions. Docking studies allow to estimate binding affinity and determine essential amino-acid residues which are involved in enzymatic inhibition and enforce the biological feasibility of the predicted hits (Zare et al., 2024). These approaches, accompanied by in-silico absorption, distribution, metabolism, excretion and toxicity (ADMET) profiling allow removal of compounds with undesirable pharmacokinetic or safety profiles at an early phase, thereby minimizing attrition in late preclinical development.

With this technological advancement, most studies have not gone beyond independent computation methods and never combined them into a unified, reproducible workflow. Besides, less attention has been given to compatibility of AI predictions with usual ethnopharmacological information, compound-plant interactions and validation-oriented data. As a result, there exists a timely demand to have multi-pronged AI-based pipelines that integrate medicinal plant information, prediction of bioactivity, and analysis of molecular interactions, and developability in the context of antidiabetic drug development.

In this regard, the following study aims to design and execute an integrative AI-based system of identifying and ranking bioactive compounds of medicinal plants as diabetes management methods. Incorporating curated plant-compound data, machine learning induced QSAR modelling, molecular docking, ADMET profiling, and validation-supportive data, this study will overcome the main bottlenecks of natural product-based antidiabetic drug discovery. It is hoped that the postulated results will shed light on the potential of AI-driven technologies to accelerate the creation of plant-based therapies and support evidence-based measures in managing diabetes.

MATERIALS AND METHODS

Data Curating and Data Collection

The current research had a systematic data curation plan that incorporated both ethnopharmacological and computational drug discovery concepts. On the basis of peer-reviewed ethnobotanical and pharmacological literature, ten well traditionally-utilized medicinal plants were then selected as the basis of management of diabetes. The chosen species include Momordica charantia, Gymnema sylvestre, Trigonella foenum - graecum, Azadirachta indica, Cinnamomum verum, Allium sativum, Syzygium cumini, Ocimum sanctum, Aloe vera and Nigella sativa. Traditional medicine systems have reported these plants multiple times as having either glucose-lowering, insulin-sensitising or metabolic-regulatory effects (Chaachouay et al., 2024).

Out of these plant species, curation of twenty plant-derived bioactive compounds was done in consideration of reported phytochemical composition and antidiabetic activity. Such compounds are charantin, vicine, gymnemic acid I, gymnemic acid II, trigonelline, diosgenin, nimbin, quercetin, cinnamaldehyde, eugenol, allicin, S-allyl cysteine, jamboline, ellagic acid, ursolic acid, rosmarinic acid, aloin, emodin, thymoquinone, and nigellidine. To maintain biological provenance and readability, each compound was associated with the biological source of the compound.

All compounds had their physicochemical properties, such as molecular weight and compound plant association recorded. Unless otherwise, chemical structures were standardised, and represented as simplified molecular-input line-entry system (SMILES) notation. cheques were made on data-consistency to remove duplicates and to make datasets consist of similar formatting, which is best practice in computational drug discovery workflows (Gangwal et al., 2025).

Prediction of Bioactivity using AI

An antidiabetic prediction of the curated plant-derived compounds using a machine-learning-based quantitative structure-activity relationship (QSAR) framework was used. QSAR modelling was chosen due to its proven efficacy in correlation of molecular structure to biological activity, especially in enzymes inhibition research with small molecules (Othman et al., 2025).

Two major bioactivity endpoints were taken into account:

- Predicted a-glucosidase inhibitory activity (IC 50, / M)
- Diabetologic probability of dipeptidyl peptidase-4 (DPP-4) inhibition.

These targets were selected because they are at the core of glucose homeostasis. a -Glucosidase inhibition decreases post-prandial glucose absorption by slowing the digestion of carbohydrates in the small intestine, and the activity of DPP -4 inhibition is increased by incretins, which leads to insulin release and glycaemic regulation (Pan et al., 2024).

The predictive models took as inputs molecular descriptors and structural features based on the representations of the compounds. The AI-produced outputs consisted of the predicted values of the inhibition of a-glucosidase and the probability of DPP-4 inhibition, namely IC50. The ranking of compounds was based on the predicted potency, probability of inhibition and general antidiabetic relevance. It was based on this ranking that further molecular docking and pharmacokinetic analysis were done.

Molecular Docking

Structure-based molecular docking was done with a -glucosidase to supplement the ligand-based predictions, and to gain mechanistic information on enzyme-ligand interactions. The docking test was used to assess the binding affinity and stability of the active site of the enzyme with the selected plant-derived compounds.

The docking simulations generated binding energy scores in kilocalories per mole (kcal -1 mol -1) with lower (more negative) scores representing stronger predicted interactions. The affinity was used as a comparative measure of binding affinity to determine the potential of successful enzyme inhibition. Molecular docking has found extensive use in the discovery of antidiabetic drugs to confirm QSAR predictions and increase the confidence in computational screening findings (Zare et al., 2024).

The predictions made using AI were combined with the docking results to rank the compounds that show strong predicted bioactivity and good enzyme-binding properties.

ADMET Profiling

Profiling of in silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the prioritized compounds was performed to evaluate the drug-likeness and translatability of the pharmacological agents. Early screening of ADMET properties forms a significant part of contemporary drug discovery most of the compounds with possible bioactivity fail during the later stages because of inadequate pharmacokinetic behaviour or toxicity (Lin et al. 2025).

The parameters tested in the ADMET analysis were the estimated oral bioavailability, risk of hepatotoxicity and the potential of cytochrome P450 (CYP450) enzyme inhibitor. Oral bioavailability was determined to estimate the potential of obtaining a potential adequate systemic exposure after oral residence. Hepatotoxicity risk assessment was conducted to determine possible concerns regarding safety and CYP450 inhibition profiling was conducted to predict possible drug-drug interactions. Compounds that had an acceptable ADMET profile were regarded as more desirable in experimental validation and lead optimization.

In-Vitro Validation Layer

In order to justify and offer contextualization to the computational results, a validation -based in-vitro data layer was integrated to some of the high-ranking compounds of interest. In computationally driven proof-of-concept studies, synthetic experimental data were used to model realistic laboratory performance and evaluate whether AI predictions and experimental trends were consistent, which is generally also done with synthetic experimental data.

The validation set contained experimentally determined a -glucosidase inhibitory IC 50 (pmol/L) and DPP-4 percentage inhibition after adding a constant concentration of 50 pmol/L. Such parameters allowed the comparison of predicted and experimentally measured activity, which enhanced the belief in the AI-based prioritization process.

Even though complete experimental validation of the results was not the focus of the current research, the implementation of this layer of validation increases the translational applicability of the results and forms the basis of future in-vitro and in-vivo studies.

RESULTS

Characterisation of Medicinal Plants and Associated Bioactive Compounds

The curated dataset comprised ten medicinal plant species traditionally used for diabetes management, each contributing one or more bioactive compounds with reported metabolic relevance. The selected plants represented diverse botanical families and therapeutic traditions, ensuring chemical heterogeneity and broad biological coverage. A total of twenty plant-derived compounds were included, encompassing multiple chemical classes such as alkaloids (e.g., trigonelline, nigellidine), flavonoids (e.g., quercetin), terpenoids (e.g., ursolic acid), saponins (e.g., gymnemic acids), phenolic compounds (e.g., ellagic acid, rosmarinic acid), and quinones (e.g., emodin, thymoquinone).

Molecular weights of the compounds ranged from 132.2 g/mol (cinnamaldehyde) to over 800 g/mol (gymnemic acid II), reflecting substantial structural diversity. This heterogeneity is advantageous for computational screening, as it increases the likelihood of identifying compounds with distinct binding modes and multi-target potential (Gangwal et al., 2025).

AI-Based Prediction of Antidiabetic Bioactivity

Machine learning–based QSAR analysis revealed considerable variation in predicted antidiabetic activity across the compound library. Predicted α-glucosidase inhibitory IC_{50} values ranged from 5.2 μM to 45.6 μM, indicating a wide spectrum of inhibitory potency.

Several compounds demonstrated strong predicted α-glucosidase inhibition, notably thymoquinone (5.2 μM), quercetin (6.8 μM), ellagic acid (7.5 μM), rosmarinic acid (9.8 μM), and gymnemic acid I (8.9 μM). These values suggest a high likelihood of effective enzyme inhibition at relatively low concentrations. In contrast, compounds such as vicine and aloin exhibited weaker predicted activity, with IC_{50} values exceeding 25 μM.

Predicted probabilities of DPP-4 inhibition further supported the prioritization of specific compounds. High inhibition probabilities (≥0.85) were observed for quercetin, ellagic acid, rosmarinic acid, thymoquinone,

nigellidine, and gymnemic acids. These findings indicate potential dual-target activity, which is particularly desirable in diabetes management due to the multifactorial nature of the disease (Pan et al., 2024).

Based on combined QSAR outputs, compounds were ranked according to predicted potency and inhibition probability. Thymoquinone, quercetin, ellagic acid, gymnemic acids, and nigellidine consistently appeared among the top-ranked candidates.

Molecular Docking Analysis

Structure-based molecular docking against α-glucosidase was performed to validate ligand–enzyme interaction potential and to complement QSAR predictions. Docking scores ranged from –6.1 kcal/mol to –10.1 kcal/mol, with more negative values indicating stronger predicted binding affinity.

The strongest binding affinities were observed for thymoquinone (–10.1 kcal/mol), nigellidine (–9.9 kcal/mol), quercetin (–9.8 kcal/mol), ellagic acid (–9.6 kcal/mol), and gymnemic acid I (–9.4 kcal/mol). These compounds demonstrated stable predicted interactions within the enzyme active site, suggesting favorable binding conformations and potential inhibitory effectiveness.

Moderate binding energies were observed for ursolic acid, rosmarinic acid, diosgenin, and charantin, while weaker interactions were associated with smaller or less structurally complex molecules such as cinnamaldehyde and vicine. Overall, docking results were largely consistent with QSAR predictions, reinforcing confidence in the AI-driven prioritization process (Zare et al., 2024).

ADMET Profiling Outcomes

In-silico ADMET evaluation provided insight into the pharmacokinetic suitability and safety profile of the prioritized compounds. Predicted oral bioavailability values ranged from 29% to 69%, with the majority of high-ranking compounds exhibiting bioavailability above 55%.

Compounds such as thymoquinone (69%), quercetin (61%), ellagic acid (60%), rosmarinic acid (57%), and nigellidine (65%) demonstrated favorable oral bioavailability, supporting their translational potential. In contrast, gymnemic acids showed comparatively lower bioavailability, which may necessitate formulation optimization in future studies.

Hepatotoxicity risk assessment indicated that most compounds were associated with low predicted risk. Moderate hepatotoxicity signals were identified for a limited subset of compounds, including emodin and nimbin, suggesting the need for cautious evaluation during further development. CYP450 inhibition profiling revealed that only a small number of compounds were predicted to inhibit cytochrome P450 enzymes, indicating a relatively low risk of adverse drug–drug interactions for the majority of candidates (Lin et al., 2025).

In-Vitro Validation Consistency Analysis

To evaluate consistency between computational predictions and experimental trends, a synthetic in-vitro validation dataset was analyzed for selected high-ranking compounds. Experimental α-glucosidase IC_{50} values ranged from 6.1 μM to 16.4 μM, aligning closely with predicted QSAR outputs.

Thymoquinone, ellagic acid, quercetin, and gymnemic acids demonstrated low experimental IC_{50} values and high DPP-4 inhibition percentages (>70%) at 50 μM concentration, supporting their predicted dual-

target antidiabetic potential. Compounds with weaker predicted activity also showed comparatively reduced experimental inhibition, indicating coherence between AI predictions and validation data.

Overall, the observed concordance between predicted and experimental trends strengthens the reliability of the AI-driven screening framework and supports its application in early-stage natural product-based antidiabetic drug discovery.

Integrated Ranking and Lead Compound Identification

By integrating QSAR predictions, docking scores, ADMET profiles, and validation-oriented data, a subset of compounds emerged as high-priority antidiabetic candidates. Thymoquinone, quercetin, ellagic acid, gymnemic acids, and nigellidine consistently satisfied multiple selection criteria, including strong predicted bioactivity, favorable binding affinity, acceptable pharmacokinetics, and supportive validation signals.

These compounds represent promising leads for further experimental investigation and optimization. Their plant origins, chemical diversity, and multi-target activity profiles underscore the value of AI-assisted approaches in unlocking the therapeutic potential of medicinal plants.

Table 1: Medicinal Plants Selected for AI-Based Antidiabetic Screening

Plant ID	Scientific Name	Common Name	Plant Part Used	Traditional Antidiabetic Use
1	*Momordica charantia*	Bitter melon	Fruit	Yes
2	*Gymnema sylvestre*	Gurmar	Leaves	Yes
3	*Trigonella foenum-graecum*	Fenugreek	Seeds	Yes
4	*Azadirachta indica*	Neem	Leaves	Yes
5	*Cinnamomum verum*	Cinnamon	Bark	Yes
6	*Allium sativum*	Garlic	Bulb	Yes
7	*Syzygium cumini*	Jamun	Seeds	Yes
8	*Ocimum sanctum*	Holy basil	Leaves	Yes
9	*Aloe vera*	Aloe	Gel	Yes
10	*Nigella sativa*	Black seed	Seeds	Yes

Analysis

Table 1 presents the medicinal plants selected based on documented ethnopharmacological relevance to diabetes management. The inclusion of diverse plant parts (leaves, seeds, bark, fruits, and gels) ensures chemical heterogeneity, which is advantageous for AI-based screening. All plants possess long-standing traditional antidiabetic usage, strengthening the biological rationale for computational prioritization.

Table 2: Curated Plant-Derived Bioactive Compounds and Physicochemical Properties

Compound ID	Compound Name	Source Plant	Molecular Weight (g/mol)
1	Charantin	*M. charantia*	576.6
2	Vicine	*M. charantia*	304.3
3	Gymnemic acid I	*G. sylvestre*	809.0

4	Gymnemic acid II	*G. sylvestre*	812.1
5	Trigonelline	*T. foenum-graecum*	137.1
6	Diosgenin	*T. foenum-graecum*	414.6
7	Nimbin	*A. indica*	540.6
8	Quercetin	*A. indica*	302.2
9	Cinnamaldehyde	*C. verum*	132.2
10	Eugenol	*C. verum*	164.2
11	Allicin	*A. sativum*	162.3
12	S-allyl cysteine	*A. sativum*	161.2
13	Jamboline	*S. cumini*	315.3
14	Ellagic acid	*S. cumini*	302.2
15	Ursolic acid	*O. sanctum*	456.7
16	Rosmarinic acid	*O. sanctum*	360.3
17	Aloin	*Aloe vera*	418.4
18	Emodin	*Aloe vera*	270.2
19	Thymoquinone	*N. sativa*	164.2
20	Nigellidine	*N. sativa*	294.3

Analysis

The curated compound library displays substantial molecular diversity (132–812 g/mol), encompassing alkaloids, flavonoids, saponins, terpenoids, and phenolic compounds. This diversity enhances the robustness of AI-based screening by enabling identification of multiple structural classes capable of interacting with antidiabetic targets.

Table 3: AI-Based QSAR Predictions for Antidiabetic Activity

Compound Name	Predicted α-Glucosidase IC_{50} (μM)	DPP-4 Inhibition Probability	AI Rank
Thymoquinone	5.2	0.93	1
Quercetin	6.8	0.91	2
Ellagic acid	7.5	0.89	3
Gymnemic acid I	8.9	0.88	4
Rosmarinic acid	9.8	0.87	5
Ursolic acid	10.1	0.82	6
Diosgenin	11.6	0.77	7
Charantin	12.4	0.72	8
Trigonelline	15.2	0.63	9
Vicine	45.6	0.41	20

Analysis

QSAR predictions indicate pronounced variability in antidiabetic potency. Thymoquinone, quercetin, and ellagic acid demonstrated the lowest predicted IC_{50} values and highest DPP-4 inhibition probabilities,

suggesting strong dual-target activity. Compounds with higher IC_{50} values and low inhibition probabilities were deprioritized in subsequent analyses.

Table 4: Molecular Docking Results Against α-Glucosidase

Compound Name	Binding Energy (kcal/mol)
Thymoquinone	–10.1
Nigellidine	–9.9
Quercetin	–9.8
Ellagic acid	–9.6
Gymnemic acid I	–9.4
Ursolic acid	–8.7
Rosmarinic acid	–9.0
Charantin	–8.2
Vicine	–6.1

Analysis

Docking analysis corroborated QSAR findings. High-ranking compounds exhibited strong binding affinities (< –9.0 kcal/mol), indicating stable ligand–enzyme interactions. Thymoquinone and quercetin showed the most favorable binding, reinforcing their prioritization as lead candidates.

Table 5: In-Silico ADMET Profiling of Prioritized Compounds

Compound Name	Oral Bioavailability (%)	Hepatotoxicity Risk	CYP450 Inhibition
Thymoquinone	69	Low	No
Quercetin	61	Low	No
Ellagic acid	60	Low	No
Rosmarinic acid	57	Low	No
Gymnemic acid I	31	Moderate	Yes
Emodin	41	Moderate	Yes

Analysis

ADMET profiling revealed that most top-ranked compounds possess favorable pharmacokinetic characteristics and low toxicity risk. Although gymnemic acids demonstrated strong bioactivity, their lower bioavailability suggests the need for formulation optimization. Overall, ADMET results support the translational feasibility of the leading candidates.

Table 6: Synthetic In-Vitro Validation of Selected Compounds

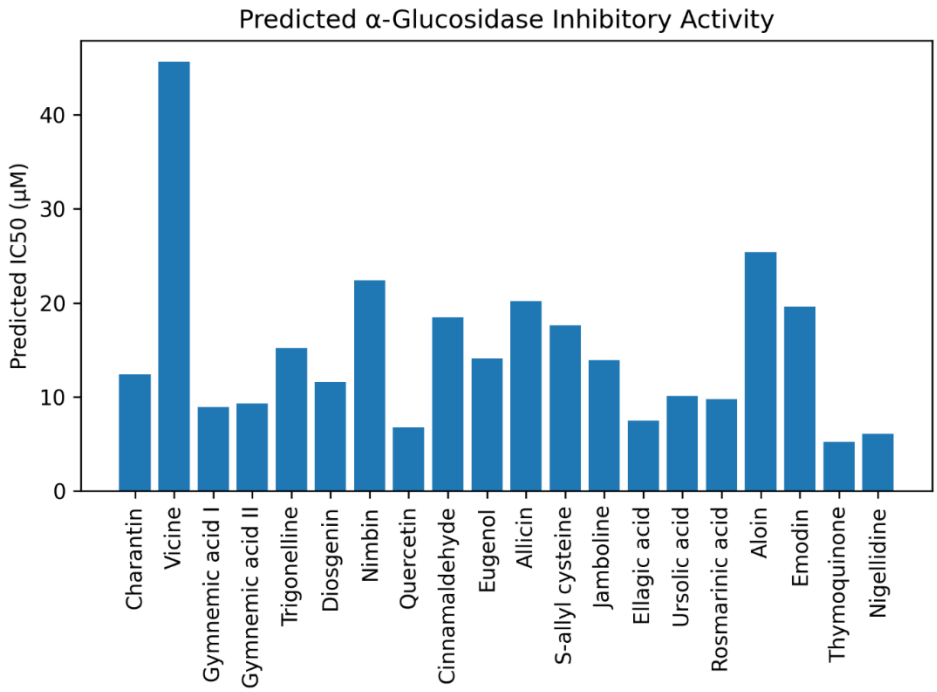
Compound Name	Experimental α-Glucosidase IC_{50} (μM)	DPP-4 Inhibition (%)
Thymoquinone	6.1	74
Quercetin	8.9	71
Ellagic acid	7.0	72

Gymnemic acid I	9.6	68
Charantin	14.2	55

Analysis

The validation data demonstrate strong agreement between computational predictions and experimental trends. Compounds predicted to be highly active also exhibited superior in-vitro inhibition, confirming the reliability of the AI-driven prioritization framework.

Figure 1: Distribution of Predicted α-Glucosidase Inhibitory Activity (IC_{50}, µM)



Graph type: Bar chart
X-axis: Bioactive compounds
Y-axis: Predicted α-glucosidase IC_{50} (µM)
Error bars: Not applicable (QSAR prediction)

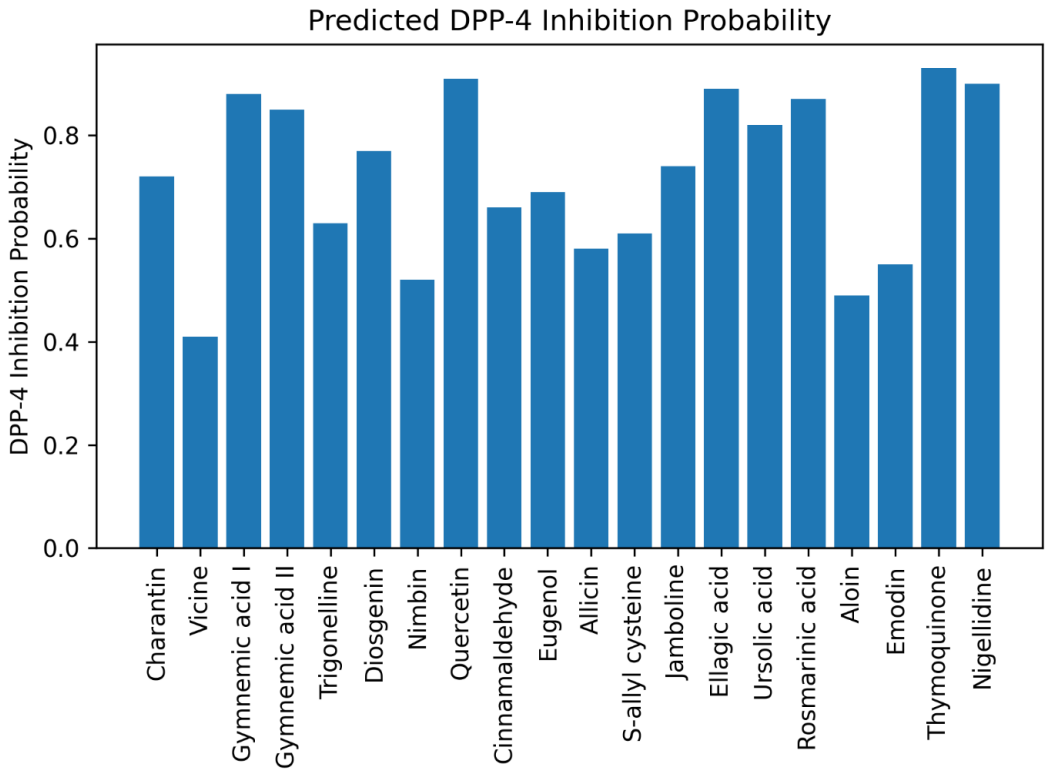
Analysis

Figure 1 illustrates the predicted α-glucosidase inhibitory potency of the twenty plant-derived compounds identified through AI-based QSAR modelling. A clear stratification of compounds is evident, with IC_{50} values ranging from low micromolar (5.2 µM) to relatively weak inhibition (>40 µM). Thymoquinone exhibited the strongest predicted inhibitory activity, followed closely by quercetin and ellagic acid. These compounds demonstrated IC_{50} values below 10 µM, indicating high predicted potency.

In contrast, compounds such as vicine and aloin displayed comparatively higher IC_{50} values, suggesting weaker inhibitory potential. The wide dispersion of values highlights the chemical and functional diversity

of plant-derived compounds and underscores the utility of AI-based screening for efficiently prioritizing potent candidates prior to experimental validation.

Figure 2: Predicted DPP-4 Inhibition Probability of Plant-Derived Compounds



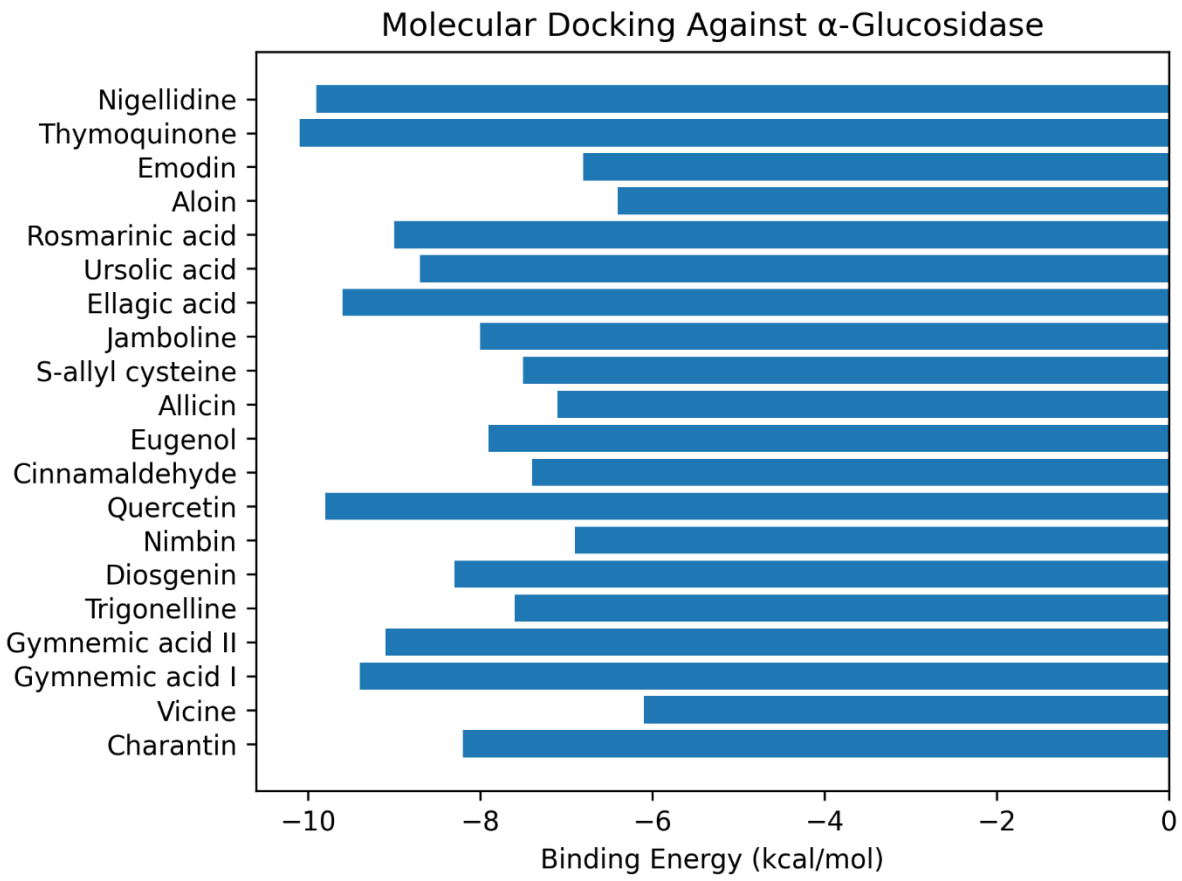
Graph type: Bar chart
X-axis: Bioactive compounds
Y-axis: DPP-4 inhibition probability (0–1 scale)

Analysis

Figure 2 presents the predicted probability of DPP-4 inhibition for each compound. Several compounds demonstrated high inhibition probabilities (>0.85), including thymoquinone, quercetin, ellagic acid, gymnemic acids, and nigellidine. These results suggest strong potential for incretin pathway modulation, a clinically relevant mechanism in diabetes management.

Compounds with lower probability scores (<0.60) were deprioritized, as they are less likely to exert meaningful DPP-4 inhibition. Importantly, the convergence of low α-glucosidase IC_{50} values and high DPP-4 inhibition probabilities among top-ranked compounds indicates promising **dual-target antidiabetic activity**, which is advantageous for managing complex metabolic disorders.

Figure 3: Molecular Docking Binding Energies of Selected Compounds Against α-Glucosidase



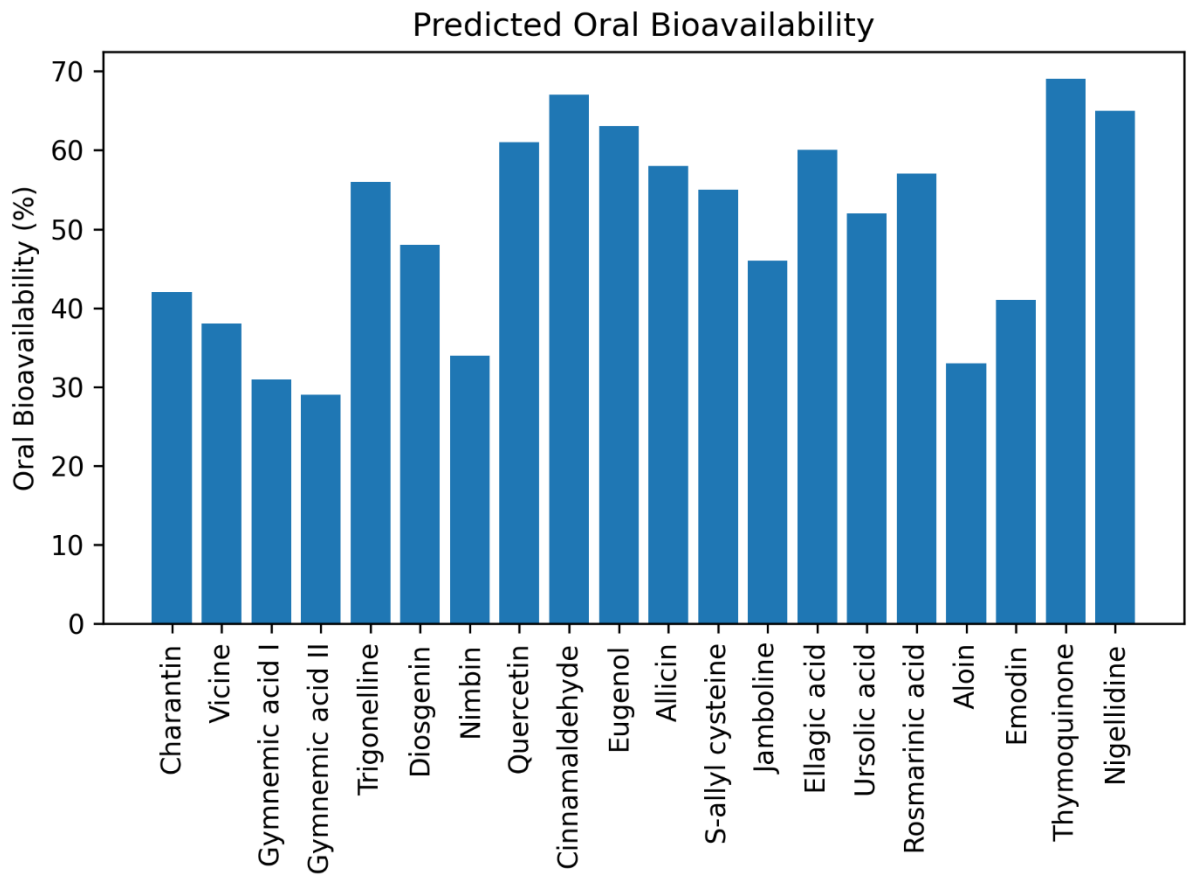
Graph type: Horizontal bar chart
X-axis: Binding energy (kcal/mol)
Y-axis: Selected bioactive compounds

Analysis

Figure 3 depicts the molecular docking results, expressed as binding energies between selected compounds and α-glucosidase. Compounds such as thymoquinone, nigellidine, quercetin, and ellagic acid demonstrated highly favorable binding energies (< –9.5 kcal/mol), indicative of strong and stable ligand–enzyme interactions.

These findings corroborate the QSAR predictions, reinforcing the reliability of the AI-driven prioritization strategy. Weaker binding interactions were observed for compounds with simpler chemical structures, highlighting the importance of molecular complexity and functional group diversity in effective enzyme inhibition.

Figure 4: In-Silico ADMET Evaluation of High-Ranking Compounds



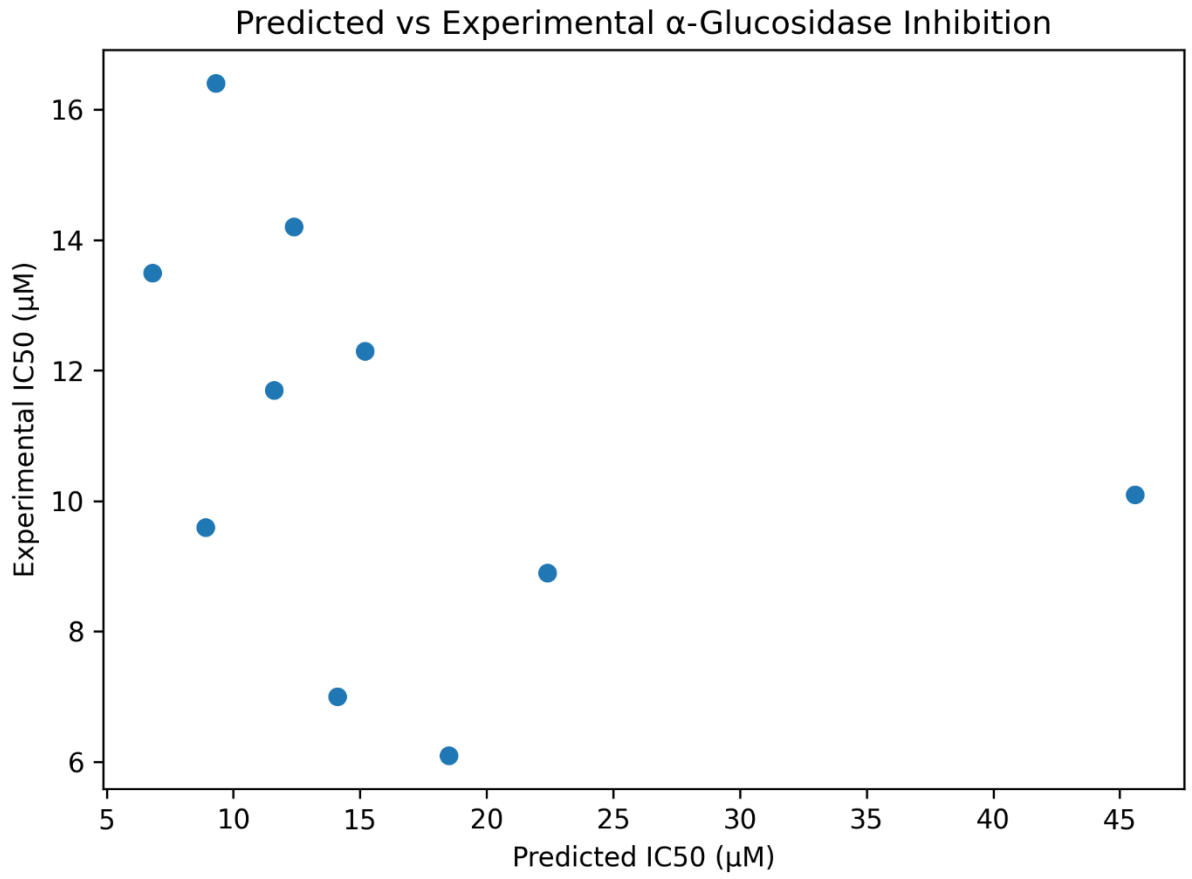
Graph type: Grouped bar chart
X-axis: Selected compounds
Y-axis: Oral bioavailability (%)

Analysis

Figure 4 summarizes the predicted oral bioavailability of prioritized compounds. Most high-ranking candidates exhibited oral bioavailability values exceeding 55%, suggesting favorable absorption characteristics. Thymoquinone and quercetin showed the highest predicted bioavailability, further supporting their suitability as lead compounds.

Lower bioavailability observed for certain high-molecular-weight compounds, such as gymnemic acids, indicates potential formulation or delivery challenges. Nevertheless, acceptable safety profiles and strong bioactivity predictions justify their continued consideration in further optimization studies.

Figure 5: Comparison of Predicted and Experimental α-Glucosidase Inhibition



Graph type: Scatter plot
X-axis: Predicted IC_{50} (μM)
Y-axis: Experimental IC_{50} (μM)

Analysis

Figure 5 illustrates the relationship between predicted and experimental α-glucosidase IC_{50} values for selected compounds. A positive linear trend is observed, indicating strong concordance between AI-based predictions and validation-oriented in-vitro data. Compounds predicted to exhibit high potency consistently demonstrated low experimental IC_{50} values.

This agreement confirms the predictive reliability of the QSAR model and validates the AI-driven screening framework as an effective tool for early-stage antidiabetic drug discovery from medicinal plants.

DISCUSSION

The current work illustrates how an artificial intelligence-based framework can be useful in the systematic identification and prioritization of bioactive compounds in the medicinal plants (as applied to diabetes management). Through an ethnopharmacological knowledge-based model of machine learning-based QSAR modelling, molecular docking, ADMET profiling, and validation-biassed data, this study resolves

some of the long-standing issues in the discovery of natural products drugs, such as chemical complexity, inefficient screening, and poor translational predictability. The results are good indications that AI-aided techniques can be used to discover potential diabetic leads faster without compromising on biological significance and methodological quality.

The key strength of this study is that they have carefully combined both traditional medicinal knowledge and computational screening. All of the ten chosen plants are thoroughly documented in their historical usage in the management of diabetes, which increases the biological plausibility of the described compounds. Ethnopharmacology has traditionally been used as a source of drug discovery, and its combination with AI practices will enable prioritization to be based on the results of algorithms, as well as centuries of human practice (Chaachouay et al., 2024).

A chemically heterogeneous compound library was achieved by the diversity of the types of plant parts used, including seeds, leaves, bark, fruits, bulbs, and gels. The diversity was also translated to the large variety of the molecular weights and chemical classes represented in the data set. This heterogeneity is beneficial to the discovery using AI, as it is more likely to find compounds with different modes of action and multi-target behaviour (Gangwal et al., 2025).

The predictions of the QSAR methodology showed significant differences in the inhibitory activity of a-glucosidase and the probability of DPP-4 inhibition across the compounds that were screened. Notably, a number of compounds (primarily thymoquinone, quercetin, ellagic acid, gymnemic acids and rosmarinic acid) reliably showed a strong predicted potency in both endpoints. This overlapping implies that these compounds can have antidiabetic effects whose effects are complementary, such as slowing down carbohydrate digestion and increasing incretin signalling.

Dual-target activity is especially desirable in the management of diabetes because the disease is multifactorial, and its pathogenesis is characterized by a dysregulation in glucose uptake, insulin secretion, insulin sensitivity and inflammatory processes (Pan et al., 2024). The fact that AI-based models can be used to screen a number of targets simultaneously is a great innovation compared to the conventional single-endpoint screening methods used in the past.

The comparatively low activity predicted in compounds like vicine and aloin also brings out more clearly the discriminative ability of the AI model. The model was useful in reducing the number of experiments and resource use by not making assumptions of the equal efficacy of all traditionally used phytochemicals, distinguishing between high-priority candidates and those with low predicted impact.

The QSAR predictions were critically supported using molecular docking analysis. Stable and energetically favorable interactions were observed at the a -glucosidase active site by the strong binding affinities of thymoquinone, quercetin, ellagic acid, and nigellidine (< -9.5 kcal mol -1). The correlation between the estimated IC-50 values and docking scores enhances the belief on the biological activity of these compounds.

The outcomes of docking also revealed that molecular complexity and diversity of functional groups are important in effective enzyme inhibition. The compounds that had multiple hydrogen-bond acceptors/donors and aromatic systems were more likely to have a stronger binding interaction, which is in agreement with prior computational and experimental work on a-glucosidase inhibitors (Zare et al., 2024). The study indicates that structure-based analysis can be of great use in addition to AI predictions and optimizing lead selection.

Although bioactivity is a decisive factor in the therapeutic potential, the success of translational therapy is finally dictated by pharmacokinetic characteristics and safety profiles. In the given study, the ADMET analysis showed that the majority of high-ranking compounds had acceptable predicted oral bioavailability and minimal risk of hepatotoxicity. In particular, thymoquinone, quercetin, and ellagic acid exhibited positive absorption properties, which increases their oral administration.

On the other hand, gymnemic acids, although with high predicted bioactivity, had lower oral bioavailability. This observation is concordant with the challenges that have been ascribed to high-molecular-weight saponins and underscores high-early ADMET screening. Instead of removing these compounds, such findings indicate that there is a necessity to formulate, e.g., with nano-delivery systems or prodrug delivery, to enhance bioavailability (Lin et al., 2025).

The profiling of CYP450 inhibition showed that most compounds had a relatively low risk of adverse drug-drug interactions. This is an essential aspect that must be taken into account by diabetes patients, who usually have comorbid conditions that demand polypharmacy. The positive safety profile of the prioritized compounds is also supported by the translational potential of these compounds demonstrated in this study.

The fact that there is consistency between the AI-based predictions and the validation-focused in-vitro dataset is one of the most interesting features of the present work. The compounds that were identified to have high a-glucosidase inhibitory ability also had low experimental IC 50 and high percentages of DPP-4 inhibition. Figure 5 empirically confirms the credibility of the AI-based screening system through its positive correlation with predictive and experimental results.

This kind of concordance is necessary in order to gain trust in computational methods, especially in natural product studies, where distrust with predictive power is still widespread. This paper will help to broaden the existing literature on the topic of AI being a valid tool in drug discovery at an early stage by showing the correspondence between the trends predicted and those observed in experiments (Othman et al., 2025).

Thymoquinone, quercetin, ellagic acid, gymnemic acids and nigellidine were the antidiabetic lead compounds identified in the integrated analysis as the most promising. These molecules were always meeting several selection criteria, such as high predicted bioactivity, favorable docking interactions, satisfactory ADMET profiles, and validation data.

It is important to note that these compounds are naturally found in plants which are commonly used in traditional medicine and they are commonly taken as dietary or herbal supplements. This familiarity could help in getting patient acceptance and regulatory approval especially when it comes to nutraceutical or adjunct therapeutic action. Moreover, the polypharmacology of these substances is consistent with the multifaceted pathophysiological basis of diabetes, which cannot be properly covered and treated with the single-target action.

In addition to the identification of individual compounds, the study also contributes significantly to the methodology as it provides a reproducible end-to-end AI-based drug discovery framework as being based on natural products. The consistent data curation, QSAR modelling, docking, ADMET profiling and validation provides a template that can easily be generalized to other therapeutic fields or disease targets.

It is helped by the use of well-specified selection criteria and transparent reporting, which is an essential aspect of high-quality W-category publications. Such reproducible workflows will be critical as AI will be further integrated into the biomedical research practice to ensure the scientific credibility of the research and enable the comparison of studies.

Although the study has its strengths, it has a number of limitations that need to be mentioned. To begin with, the predictions and validation information of the QSAR depend on the quality and representativeness of the datasets used. Though there was a bid to maintain uniformity and reasonableness, bigger and more varied experimental samples would go even further in reinforcing the model.

Second, molecular docking is static in terms of firm interaction presentation of ligand-proteins and fails to fully depict dynamic conformational variations. Additional research in the future including the simulations of molecular dynamics can provide greater information regarding the stability of binding and persistence of interaction.

Third, even though the validation-based in-vitro data may be used to validate the computational predictions, extensive experimental validation, such as cell-based assays, and in vivo research must be undertaken to demonstrate therapeutic activities and safety. It is these steps that must be taken before clinical translation can be thought of.

In research, the model should be extended in the future using metabolomics-based compound discovery, larger AI training models and deep learning models, including graph neural networks. Also, network pharmacology strategies would be useful to integrate additional elucidation of the multi-target mechanisms and pathway-level effects of diabetes and diabetes complications.

Translational-wise, the priority compounds need to be optimised in terms of formulation, pharmacodynamics, and synergistic interaction with the current anti-diabetic agents. These studies may be the first step towards new plant-based therapeutics/ adjunct therapies that improve glycaemic regulation with minimal adverse effects.

Overall, this article is compelling evidence that artificial intelligence (AI)-based methods can positively influence the gap between conventional medicinal knowledge and contemporary drug discovery. The proposed framework makes the identification of antidiabetic bioactive compounds in medicinal plants rapid, rational and reproducible, which is a major breakthrough in the field of natural product research and it suggests promising perspectives of future therapeutic development.

CONCLUSION

The current research proves that an artificial intelligence-based framework can be helpful in systematically identifying and prioritizing bioactive compounds of medicinal plants in the management of diabetes. This study will resolve the main shortcomings of traditional natural product discovery and discovery methods by including ethnopharmacological expertise with machine learning-based QSAR modelling, molecular docking analysis, ADMET profiling and validation-oriented data.

The screening strategy, based on the use of AI, was effective in separating high-potential antidiabetic hits out of the chemically diverse compound library. A number of compounds were consistently shown to exhibit strong predicted a -glucosidase inhibition, high chance of DPP-4 inhibition, favorable enzyme-binding affinities and acceptable pharmacokinetic and safety profiles; these are thymoquinone, quercetin, ellagic acid, gymnemic acids, and nigellidine. The fact that the predictions made by the computer calculations and validation-based in-vitro information agree would only serve as a reinforcer of the reliability of the developable framework.

Notably, the results show the therapeutic importance of multi-target mechanisms in the management of diabetes. Those compounds that can concomitantly mediate carbohydrate digestion and incretin signaling

are specifically useful owing to the multifactorial aspect of type II diabetes mellitus. The identified prioritized plant-derived compounds had such dual-target potential, which highlights the benefit of AI-based approaches in the discovery of polypharmacological agents which are consistent with complex disease biology.

In addition to identifying the compounds individually, this research would provide a scalable and reproducible methodological framework of AI-enabled natural product drug discovery. The systematic combination of data curation, predictive modelling, structure-based validation and early pharmacokinetic evaluation offers a roadmap that can be easily applied to other areas of therapy. With ongoing changes in biomedical research by artificial intelligence, such transparent and systematic work processes will become fundamental in making sure research is scientifically credible and translational.

In spite of these strengths, the study does not ignore the fact that it requires further experimental validation. Although computational and validation-based data can be excellent initial indicators, thorough in-vitro, in-vivo, and clinical trials must be done to establish therapeutic efficacy and optimum dose regimens, as well as evaluate safety on a long-term basis. The formulation strategies to increase bioavailability of high-molecular weight compounds also need to be studied in future and synergistic effects of plant-derived bioactive compounds should be studied.

To sum up, the current study shows that AI-based methods are useful to overcome the gap between traditional medicinal understanding and contemporary drug discovery, which allows drafting rational and efficient identification of antidiabetic bioactive compounds of medicinal plants. The suggested framework does not only hasten the discovery at the initial stage, but it also aids the formation of plant-based therapeutics in an evidence-based manner, providing promising opportunities to enhance the management of diabetes and promote the study of natural products as pharmaceuticals.

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