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ORIGINAL ARTICLE

Multi-targeted molecular docking, pharmacokinetic analysis, and drug-likeness evaluation of alkaloids for anti-diabetic drug development

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ABSTRACT

Diabetes mellitus is a global health challenge, particularly in low-income regions, leading to severe complications. Plant-derived alkaloids offer potential as alternatives to conventional therapies. This study evaluated 31 alkaloids for antidiabetic drug development through molecular docking, pharmacokinetics, and drug-likeness analyses. Four standard drugs (epalrestat, metformin, acarbose, glibenclamide) and four targets (aldose reductase, adenosine monophosphate-activated protein kinase, α-glucosidase, protein tyrosine phosphatase 1B) were used for computational simulations.

Molecular docking revealed that alkaloids mahanimbine (-11.5 kcal/mol), echinulin (11.3 kcal/mol), coptisine (-10.9 kcal/mol), and groenlandicine (-9.7 kcal/mol) have substantial binding affinities against aldose reductase compared to epalrestat (-9.3 Kcal/mol). In contrast to metformin (-4.8 kcal/mol), coptisine, echinulin, sanguinarine, and groelandicine showed superior binding affinities against adenosine monophosphate-activated protein kinase. In comparison to acarbose (-8.4 Kcal/mol), coptisine (-9.7 Kcal/mol), sanguinarine (-9.3 Kcal/mol), mahanimbine (-8.9 Kcal/mol), and echinulin (-8.9 Kcal/mol) demonstrated better docking scores against α-glucosidase. Jatrorrhizine, coptisine, sanguinarine, mahanimbine and echinuline respectively demonstrated higher binding scores of 8.8, -7.5, -7.5 and -7.2 Kcal/mol against protein tyrosine phosphatase 1B than glibenclamide (-7.0 Kcal/mol). Most alkaloids adhered to Lipinski's rule, except casuarine 6-O-α-glucoside and conophylline. Pharmacokinetics identified pinoline as highly bioavailable and central nervous system penetrant, while conophylline had poor bioavailability.

The study concluded that alkaloids including mahanimbine, echinulin, coptisine, groenlandicine, sanguinarine, and jatrorrhizine show strong binding affinities and favorable pharmacokinetic properties, requiring further *in vitro* and *in vivo* studies for therapeutic validation

Key Words: Diabetes mellitus, molecular docking, alkaloids, pharmacokinetics, antidiabetic therapy

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Introduction

Diabetes mellitus (DM) is a chronic condition characterized by elevated blood glucose levels resulting from either insulin deficiency (Type 1) or insulin resistance (Type 2). DM has become a significant global health issue, affecting approximately 463 million people worldwide in 2019, with numbers expected to rise substantially in the coming decades [1]. The impact is particularly severe in low- and middle-income countries, where a significant portion of adults with diabetes reside [2, 3]. The incidence of diabetes has sharply increased in Africa, where healthcare systems are often overstretched, and the World Health Organization (WHO) has labeled it a "silent killer" [4]. In countries like Ethiopia, diabetes prevalence is also on the rise, exacerbating the challenges for healthcare systems, particularly due to the growing number of untreated cases [5]. Diabetes leads to a wide range of both acute and chronic complications, severely affecting quality of life [6]. Chronic hyperglycemia can result in microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) as well as macrovascular problems, such as cardiovascular disease.

The primary treatment options for DM currently include insulin therapy, oral hypoglycemic drugs such as metformin, sulfonylureas, and thiazolidinediones, as well as newer medications like sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists [7]. While these treatments are effective in controlling blood glucose levels and reducing the risk of complications, they are not without limitations. Prolonged use of insulin and oral hypoglycemics can lead to undesirable side effects, including weight gain, hypoglycemia, and gastrointestinal issues[1]. Additionally, the cost and accessibility of these treatments pose significant challenges, particularly in resource-limited regions like Sub-Saharan Africa, where the prevalence of diabetes is increasing [8].

Diabetes results from β-cell failure and insulin resistance, affecting critical processes like insulin secretion and carbohydrate absorption [9]. Key proteins such as glucokinase, adenosine monophosphate-activated protein kinase (AMPK), and 11β-hydroxysteroid dehydrogenase are involved in diabetes development [10]. While conventional treatments like anti-diabetic drugs and lifestyle changes are available, they often come with side effects and questionable efficacy. As a result, there is growing interest in natural products, particularly plant-derived compounds such as alkaloids, flavonoids, and glycosides, known for their therapeutic potential in managing diabetes [11]. Alkaloids, in particular, have shown promise in improving glucose metabolism, insulin sensitivity, and oxidative stress management [12, 13].

The search for natural product-derived molecules for diabetes treatment has led to an increasing focus on medicinal plants and their bioactive constituents [14, 15]. Computational drug discovery has become a vital tool in identifying and optimizing small molecules, enabling the prediction of drug-target interactions. These methods are crucial for diabetes management, as they help identify compounds that can regulate blood sugar levels effectively [16]. Molecular modeling and virtual screening techniques have revolutionized drug discovery, making it possible to efficiently evaluate large numbers of compounds for their therapeutic potential [16].

[1] Feingold KR. Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes. [Updated 11.09.2024]. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Accessed on 16.01.2025. https://www.ncbi.nlm.nih.gov/books/NBK279141.

Recent advancements in computational approaches, such as protein-ligand docking and absorption, distribution, metabolism, excretion, and toxicity (ADMET) property prediction, are accelerating drug development. The incorporation of ADMET analysis early in the discovery process helps predict the pharmacokinetic and toxicity profiles of compounds, reducing the risk of clinical failure [17, 18]. This study aims to conduct molecular docking and analyze the pharmacokinetic properties, drug-likeness, and toxicity profiles of selected alkaloids based on their lethal dose (LD50) values and anti-diabetic potential.

Materials and methods

Alkaloids selection

Scientific studies have shown that alkaloids exhibit pharmacological activity against type 2 diabetes mellitus (T2DM) [19]. Alkaloids such as berberine, catharanthine, vindoline, and vindolinine have been reported for their anti-hyperglycemic effects [19, 20]. The selection criteria for molecular docking study against T2DM targets included alkaloids with documented *in vitro* and *in vivo* glucose antidiabetic activity, inhibitory potential against the selected targets, and interactions with other key T2DM-related targets. The antioxidant properties of the compounds were also considered [21]. The alkaloids of plant origin [19, 21-36] selected for the current computational study was indicated below (Fig. 1).

Selection of target proteins and standard drugs

Target proteins and standard drugs were selected based on their established roles in glucose metabolism and diabetes management, as well as their recognition in treatment guidelines. These targets were chosen for their diverse mechanisms of action, allowing for a multifaceted approach to diabetes treatment. AMPK is a key regulator of cellular energy homeostasis, and its activation by metformin, a first-line therapy recommended by the American Diabetes Association and WHO guidelines, promotes enhanced glucose uptake and fatty acid oxidation, improving insulin sensitivity [37]. Aldose reductase, involved in diabetic complications, is targeted by epalrestat to reduce sorbitol accumulation [38]. Alpha-glucosidase is inhibited by acarbose, a drug recommended for its efficacy in slowing carbohydrate absorption and mitigating glucose spikes [39].

Protein preparation

Protein preparations were performed following established protocols [40]. The crystal structures of selected human target proteins were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (https://www.rcsb.org/): aldose reductase (PDB ID: 2R24), alpha glucosidase (PDB ID: 8YIE), AMPK (PDB: 4YEE), and protein tyrosine phosphatase 1B (PDB ID: 7LEO). The 3D crystal structures were imported into Biovia Discovery Studio Visualizer 2021, where water molecules, heteroatoms, and any complexes bound to the receptor molecules were removed. For site-specific molecular docking, ligand groups were selected from the co-crystallized protein structures, defined, and binding sites identified by extracting the x, y, and z coordinates from the structure-based design site spheres. Active sites were determined by analyzing the binding interactions between ligands and receptors with molecular docking performed at the active sites of the prepared proteins. The grid box was created using a docking simulation with dimensions of 40x40x40 Å along the x, y, and z axes, respectively, and a grid point spacing of 0.375 Å. The dimensions of the structure-based design site

Fig 1. Structures of selected alkaloids

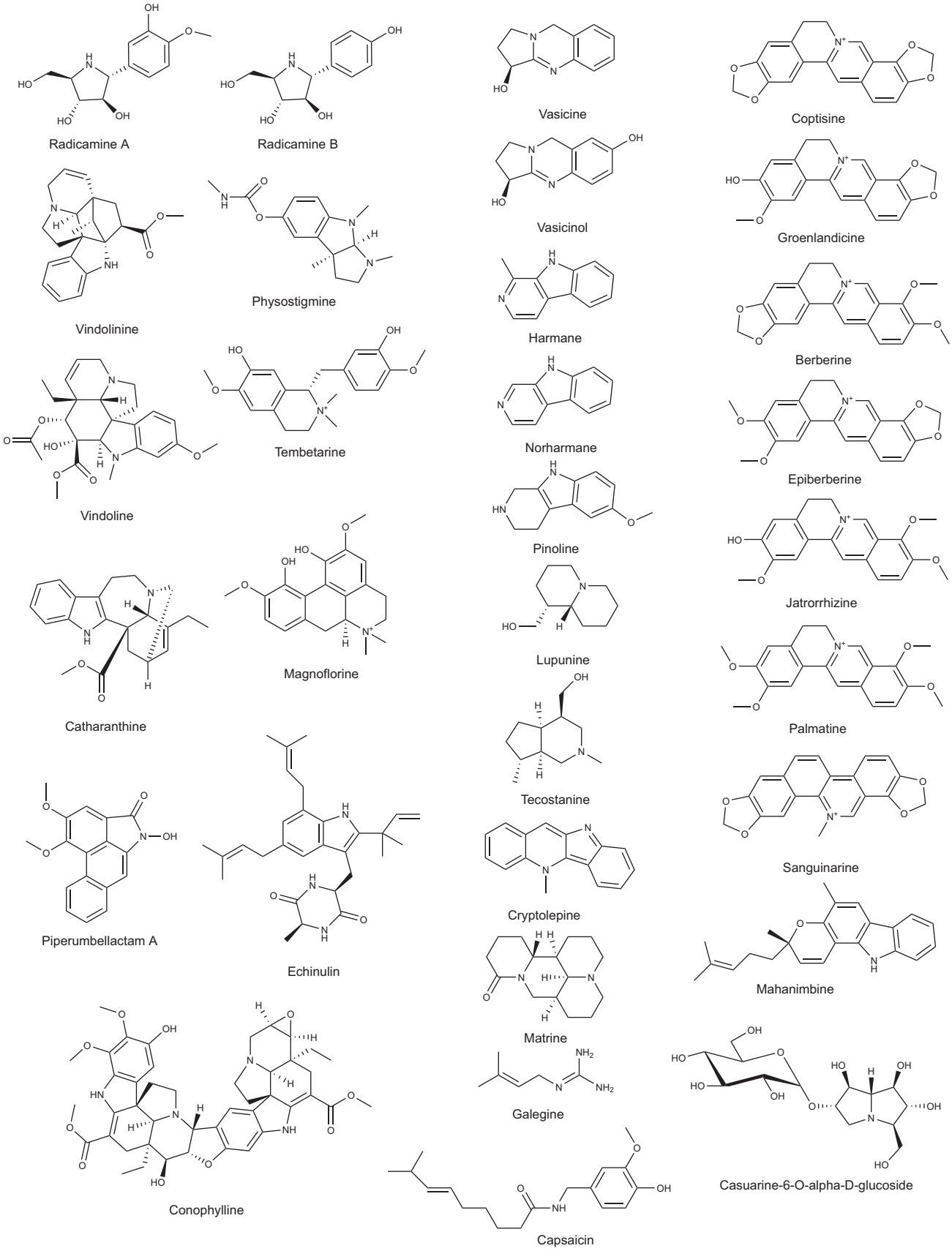


Table. Grid-box coordinates for all targets.

Targets	x-dimension	y-dimension	z-dimension	x-center	y-center	z-center
2R24	40	40	40	16.618583	-7.134417	15.260125
4YEE	40	40	40	80.858534	-5.804455	12.281989
8YIE	40	40	40	-37.153167	32.035500	-4.817833
7LEO	40	40	40	-1.942455	-0.591773	56.110909

sphere for each target protein are listed in Table, with corresponding x, y, and z values. Finally, polar hydrogens were added to ensure proper ionization of the amino acid residues.

Ligand preparation

The 2D chemical structures of selected alkaloids and standard drugs were retrieved from the pubchem database and downloaded in PDB format. Alkaloids whose 2-D structures were not retrieved from the PUBCHEM were generated using the ChemOffice tool (ChemDraw 16.0), and the files were subsequently converted to PDB format using the Open Babel toolbox. These structures were then converted into three-dimensional forms, with polar hydrogens and charges at physiological pH 7.4 added. Energy minimization and optimization were performed using the Merck Molecular Force Field 94 (MMFF94) force field in ChemBio3D Ultra 13.0 (PerkinElmer, 2011) with the molecular modeling algorithm. Additionally, Gasteiger charges were assigned to the three-dimensional ligand structures, and the files were converted to pdbqt format using AutoDock Tools. The energy minimization process was continued until the root mean square deviation (RMSD) gradient reached 0.01 kcal/mol, ensuring that the structures achieved their lowest energy conformations. Once minimized to their lowest energy states, the ligand molecules were saved in PDB format. These minimized ligands were then used as input for AutoDock Vina to perform molecular docking simulations, assessing their binding affinity and interactions with the target proteins [40-42].

Molecular docking

Molecular docking predicts the binding affinity of ligand molecules by assessing protein-ligand interactions and estimating the scoring function based on geometry. Computational molecular docking studies were performed to investigate the binding patterns of selected alkaloids (Figure 1), along with the crystal structures of the chosen target proteins. The crystal structures of the human target proteins – aldose reductase (PDB ID: 2R24), alpha glucosidase (PDB ID: 8YIE), AMPK (PDB: 4YEE), and protein tyrosine phosphatase 1B (PDB ID: 7LEO) – were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/). Using AutoDock Vina 4.2.6 (MGLTools 1.5.7), a software suite in the Discovery Studio 2021 Client (a program for interactive visualization and analysis of molecular structures and related data), the interactions and binding affinities of the ligands with the selected target proteins were evaluated. Binding affinity was explored using the View Dock tool. The final results were analyzed and visualized using Discovery Studio 2021 Client, with bound ligands as the standard. Visualization of protein-ligand interactions reveals the number of interactions and the active residues responsible for significant binding at the active sites of the selected targets [42]. Epalrestat, glibenclamide, metformin, and acarbose were used as standards.

Drug-likeness and ADMET prediction

SwissADME (http://www.swissadme.ch/) web servers were used to predict the drug-likeness and ADME profiles of the selected alkaloids, while toxicity analysis was conducted using the ProTox-II web server (http://tox.charite.de/protox_II). The predicted drug-likeness and ADMET profiles of the compounds were obtained by uploading the simplified molecular-input line-entry system formats of each alkaloid's structure to the respective web servers [43-45].

Results and Discussion

Drug likeness properties and ADMET

The failure rate in drug development across preclinical to clinical stages exceeds 90%. Even among drug candidates that successfully complete clinical trials, approximately 90% face failure in later stages [46]. Contributing factors to clinical trial failures include suboptimal pharmacokinetic profiles, lack of clinical efficacy, unmanaged toxicity, and poor drug-like properties. Among these, the most critical issue arises from the failure of investigational drugs in late-stage clinical development. Therefore, it is essential to evaluate the ADMET properties early in the drug development process to mitigate these risks [47]. Currently, numerous available *in silico* drug-likeness and ADMET prediction tools supplement experimental data and are becoming increasingly indispensable in the context of efforts to minimize animal testing [48, 49].

Physicochemical properties are critical parameters that influence both the pharmacodynamics and pharmacokinetic profiles of drug candidates. In this study, Lipinski's and Veber's rules were employed to evaluate the drug-likeness properties of the selected alkaloids. According to this rule, a molecule is considered drug-like if its molecular weight (MW) is < 500 Da, the number of hydrogen bond donors (HBD) is <5, the number of hydrogen bond acceptors (HBA) is <10, and the octanol-water partition coefficient (Log P) is <5. Compounds that do not violate more than two of these parameters are deemed to possess drug-like properties [50]. Molecules that violate fewer than two criteria are expected to demonstrate favorable gastrointestinal absorption. In this study, casuarine 6-O-α-glucoside and conophylline, violate Lipinski's Rule of Five. It is important to note that Lipinski's rule is not applicable to amino acids and sugars. Although casuarine 6-O-α-glucoside does not adhere to Lipinski's Rule of Five, it contains a sugar moiety, which facilitates its absorption upon oral administration. This underscores that the Lipinski Rule of Five is not an absolute criterion, and drug discovery should extend beyond these parameters [51, 52]. One of the key molecular descriptors in Lipinski's Rule is molecular weight. According to the rule, compounds with a molecular weight greater than 500 Da are less likely to traverse the paracellular pores of the intestinal epithelium. All alkaloids, except for conophylline (MW = 794.89 Da), possess an acceptable molecular weight for potential bioavailability.

Lipophilicity is a crucial physicochemical parameter in the development of new drug entities, as it significantly influences drug-likeness properties and the pharmacokinetic profile. It is one of the key factors in Lipinski's Rule of Five [53]. All alkaloids included in this study exhibit optimal MlogP values (less than 4.5) or ClogP values below 5, indicating that these compounds possess favorable lipophilicity. Furthermore, lipophilicity plays a significant role in the binding affinity of these alkaloids to receptors at the drug's target site, as many receptors are inherently lipophilic [54].

While lipophilicity plays a critical role in the pharmacokinetic profile of a drug, it is essential that a new drug entity does not exhibit excessive

lipophilicity. Highly lipophilic compounds may have poor solubility in the gastrointestinal tract (GIT), thus hindering absorption [55]. An ideal drug entity demonstrates optimal absorption when there is a balanced hydrophilic-lipophilic balance, meaning the compound should possess sufficient lipophilicity to permeate biological membranes while remaining polar enough to dissolve in the GIT.

Solubility characteristics are classified as insoluble when the value is more negative than -10. The solubility ranges from poorly soluble to highly soluble, with values between -10 and 0 indicating varying degrees of solubility. Poorly soluble compounds exhibit values between -10 and -6, moderately soluble compounds range from -6 to -4, soluble compounds fall between -4 and -2, very soluble compounds are in the range of -2 to 0, and highly soluble compounds have values greater than 0. In this study, all alkaloids exhibit acceptable solubility, with the exception of mahanimbine, echinulin, and conophylline, which display poor water solubility. To further evaluate drug-likeness and oral bioavailability, Veber's Rule is employed. This rule predicts the drug-likeness and oral bioavailability of new drug entities by considering the number of rotatable bonds and topological polar surface area (TPSA) as key determinants.

With respect to TPSA, Veber and colleagues suggest that for optimal oral bioavailability, compounds should have a TPSA of ≤140 $Å^2$ [56]. Molecules exceeding this threshold are generally considered less favorable as drug candidates due to poor absorption and distribution characteristics. The TPSA values of most alkaloids in this study fall within the acceptable range, indicating their druggability. However, three compounds – cryptolepine (17.82 $Å^2$), casuarine 6-O-α-glucoside (183.54 $Å^2$), and conophylline (163.82 $Å^2$) violate Veber's rule with respect to this molecular descriptor. The presence of polar functional groups plays a crucial role, not only in determining the pharmacokinetic profile but also in influencing the pharmacodynamic properties of drug-like molecules. These polar functional groups interact with receptor residues, which are critical for effective binding [57].

The second key variable in Veber's rule is the number of rotatable bonds (NRB), which reflects a compound's flexibility. A compound is predicted to have favorable oral bioavailability if its NRB does not exceed 10, as excessive flexibility may hinder absorption [56]. All selected alkaloids possess fewer than 10 rotatable bonds, suggesting favorable bioavailability. As the number of rotatable bonds increases, however, toxicity risks also rise as excessive flexibility allows a compound to adopt multiple conformations, increasing its potential to bind with various receptors [56, 58].

Molecular Docking

Molecular docking analysis of various alkaloids against aldose reductase (PDB: 2R24) revealed a range of binding affinities and represented in Supplement A (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-a). The most promising candidates, mahanimbine and echinulin, exhibited strong docking scores of -11.5 kcal/mol and -11.3 kcal/mol, respectively, suggesting that these alkaloids form stable interactions with this enzyme and are potential inhibitors of it. Coptisine (-10.9 kcal/mol) and berberine (-9.5 kcal/mol) also demonstrated potent binding affinities, aligning with their previously reported bioactivity against aldose reductase, making them suitable for further exploration as therapeutic agents. Moderate binding affinity was observed for standard medication epalrestat (-9.3 kcal/mol) and alkaloids harmane (-9.3 kcal/mol) and sanguinarine (-8.8 kcal/mol), suggesting potential aldose reductase inhibitors with less potency, potentially contributing to therapeutic strategies. Weaker docking scores

were recorded for alkaloids such as galegine (-5.8 kcal/mol), vindoline (-5.8 kcal/mol), and lupinine (-5.8 kcal/mol), which showed the least favorable interactions with aldose reductase. Despite their lower binding affinity, these compounds could still hold therapeutic potential, possibly in combination therapies or as adjuncts to more potent inhibitors. Overall, the study highlights the diverse binding profiles of alkaloids, with mahanimbine, echinulin, and coptisine being the most promising candidates for further investigation as aldose reductase inhibitors, while moderate and weaker binders may still be valuable in specific therapeutic contexts.

The molecular docking analysis of various ligands against AMPK (PDB: 4YEE), represented in Supplement B (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-b), revealed a range of binding affinities, suggesting differences in their potential to interact with the enzyme's active site. Among the most promising compounds, coptisine exhibited the highest docking score of -10.1 kcal/mol, indicating a strong binding affinity to AMPK. Other notable high-affinity ligands included sanguinarine (-9.5 kcal/mol), groenlandicine (-9.4 kcal/mol), and echinulin (-9.7 kcal/mol), which also showed robust binding interactions, positioning them as potential candidates for further investigation in the development of AMPK-targeted therapies.

Alkaloids such as vindolinine (-7.6 kcal/mol), physostigmine (-7.3 kcal/mol), harmane (-7.5 kcal/mol), and jatrorrhizine (-8.8 kcal/mol) exhibited binding affinity, suggesting they may be useful in modulating AMPK activity. Pinoline (-6.7 kcal/mol) and berberine (-8.3 kcal/mol) also demonstrated moderate affinity, indicating that these compounds may still have potential as AMPK modulators, potentially in combination with other agents to enhance therapeutic outcomes. These findings highlight the broader potential of these alkaloids in regulating AMPK activity and warrant further investigation.

Metformin exhibited a docking score of -4.8 kcal/Mol, which is lower than the tested alkaloids though metformin has been extensively studied and demonstrated to activate AMPK *in vivo* through mechanisms not solely reliant on direct binding affinity. The modest docking score reflects the complexity of metformin's action, which involves multiple pathways, including inhibition of mitochondrial complex I and alteration of cellular energy status, rather than a direct, strong binding interaction with the AMPK active site. Therefore, despite the lower docking score, metformin remains a valuable therapeutic agent, and its clinical efficacy in AMPK activation supports its continued use and exploration in metabolic disease management. Overall, this study identified coptisine, sanguinarine, and echinulin as the most promising candidates for AMPK modulation, while metformin's weaker binding score does not diminish its established therapeutic relevance in clinical practice.

Molecular docking analysis of various ligands against alpha-glucosidase (PDB: 8YIE), represented in Supplement C (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-c), revealed a broad spectrum of binding affinities, reflecting the potential of different compounds as inhibitors of this enzyme. Among the alkaloids studied, coptisine exhibited the highest docking score of -9.7 kcal/mol. Conophylline (-9.5 kcal/mol), sanguinarine (-9.3 kcal/mol), mahanimbine (-8.9 kcal/mol), and echinulin (-8.9 kcal/mol), showed promising docking scores.

Other alkaloids demonstrated moderate binding affinities to alpha-glucosidase, with docking scores ranging from -7.0 to -8.7 kcal/mol. These include radicamine A (-8.7 kcal/mol), acarbose (-8.4 kcal/mol), groenlandicine (-8.6 kcal/mol), berberine (-8.5 kcal/mol), and piperumbel-

latm A (-8.5 kcal/mol). These compounds exhibited favorable binding, indicating their potential as moderate alpha-glucosidase inhibitors. Acarbose, a known alpha-glucosidase inhibitor used in clinical practice, shows a docking score of -8.4 kcal/mol, which aligns with its established therapeutic effect, validating the docking results.

Some compounds showed weaker docking scores, suggesting less effective binding to alpha-glucosidase. These include radicamine B (-5.5 kcal/mol), galegine (-4.9 kcal/mol), and lupinine (-5.3 kcal/mol), which demonstrated the least favorable interactions with the enzyme. Although these compounds exhibited weaker binding, their potential utility might lie in other therapeutic contexts or in combination therapies with stronger inhibitors. Additionally, the lower binding affinities observed in these compounds may be attributed to factors such as weaker molecular interactions or alternative mechanisms of action that were not captured by the docking analysis alone.

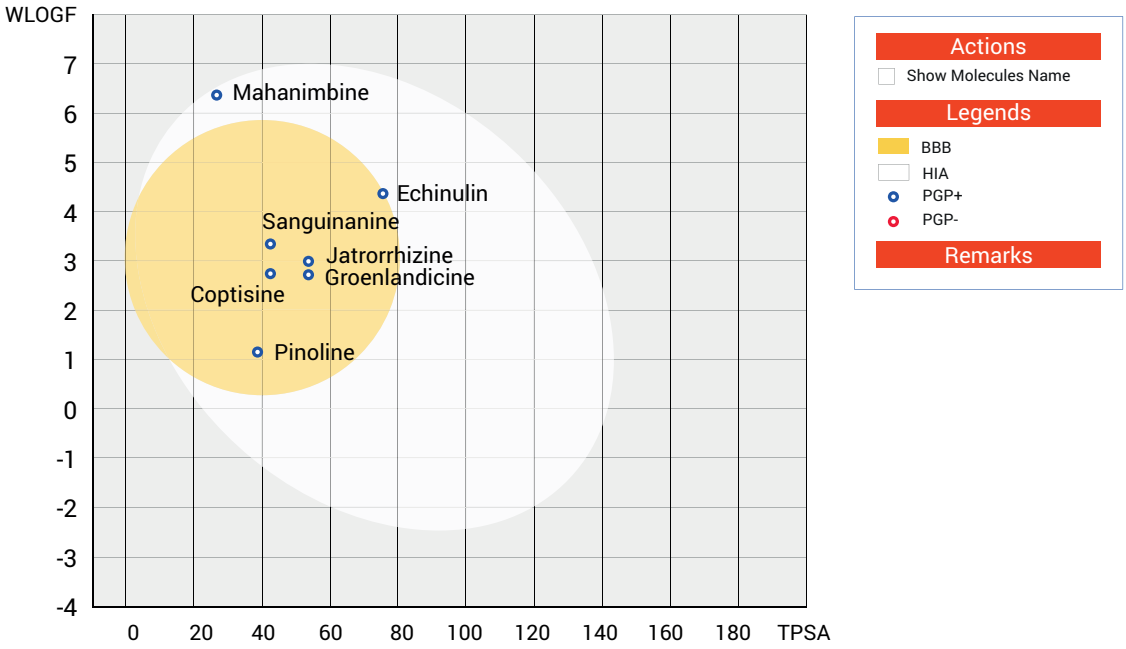
Molecular docking of various ligands against protein tyrosine phosphatase 1B (PDB:7LEO), represented in Supplement D (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-d), revealed varying degrees of binding affinity. Jatrorrhizine, coptisine, sanguinarine, mahanimbine, and echinulin, all with strong binding properties, are promising alkaloids for further investigation in managing type 2 diabetes. They may offer valuable therapeutic potential in regulating postprandial glucose levels through protein tyrosine phosphatase 1B inhibition. The alkaloids radicamine A (-6.6 kcal/mol), radicamine B (-5.5 kcal/mol), vindolinine (-6.3 kcal/mol), and groenlandicine (-6.8 kcal/mol) displayed moderate binding, suggesting potential in combination therapies or glucose regulation adjuncts. Weaker docking scores were observed for galegine, tecostanine, and capsaicin, indicating less favorable interactions with this protein.

Comprehensive analysis of the drug likeness and ADMET prediction 31 alkaloids, represented in Supplement E https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-e), revealed favorable characteristics for drug development among which coptisine, sanguinarine, and jatrorrhizine exhibited promising drug-like properties, including optimal molecular weight, moderate lipophilicity, and strong hydrogen bonding potential. These compounds are well-suited for further development as alpha-glucosidase inhibitors. The bioavailability score of all alkaloids, represented in Supplement F (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-f), except casuarine 6-O-α-glucoside and conophyline, was consistently 0.55, suggesting moderate systemic availability [59].

Cryptolepine, jatrorrhizine, and epiberberine have been identified as CYP450 inhibitors, particularly targeting CYP3A4 and CYP1A2, which may influence the metabolism of co-administered drugs. In contrast, compounds such as palmatine, pinoline, and radicamine A were found to exhibit minimal interactions with major cytochrome P450 enzymes, making them favorable in terms of lower drug-drug interaction risks. The blood-brain barrier (BBB) permeant data suggested that harmane and sanguinarine can cross BBB. Although for antidiabetic applications, this may not be relevant unless central nervous system (CNS) effects are desired. Alkaloids with high gastrointestinal absorption, moderate lipophilicity, and minimal metabolic interference such as vindolinine, coptisine, and sanguinarine present the most promise.

Gastrointestinal absorption and brain access are two pharmacokinetic behaviors crucial to estimate at various stages of the drug discovery processes. To this end, the Brain Or IntestinaL Estimate D permeation

Fig 2. Boiled egg model of selected alkaloids.



method (BOILED-Egg) is proposed as an accurate predictive model that works by computing the lipophilicity and polarity of small molecules. In this study, seven alkaloids were selected based on their binding affinity and pharmacokinetic property. Mahanimbine, found at the border of the egg white (white eclipse), is likely hydrophilic, which suggests limited BBB penetration. This positioning indicates that mahanimbine may exert its effects peripherally. Echinulin, positioned at the boundary between the yolk and the egg white (yolk eclipse), appears to have a dual solubility profile, allowing it to interact with both aqueous and lipid environments. This suggests that echinulin may have the potential to cross the BBB due to its ability to interact with lipid-rich membranes. Sanguinarine, jatrorhizine, groenlandicine, coptisine, and pinoline, located predominantly in the lipid-rich yolk are lipophilic, are able to cross BBB and GIT. Their lipophilic nature positions them as promising agents for both central and peripheral therapeutic effects in the management of diabetes (Fig. 2).

The *in silico* toxicity analysis of the selected compounds, represented in Supplement G (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-g), provided valuable insights into their potential toxicological risks, highlighting critical safety considerations for their future applications. The data included predicted LD_{50} values, identifying various toxicity targets, such as enzymes, receptors, and physiological systems. Physostigmine and capsaicin, categorized as class 1 and class 2, respectively, exhibited low LD_{50} values (2 mg/kg and 47 mg/kg), indicating high toxicity and posing significant risks at low doses. These compounds require careful consideration when exploring therapeutic applications, particularly in populations with sensitivities to neurotoxic or respiratory effects. In contrast, catharanthine and casuarine, classified as class 5, exhibited much higher LD_{50} values (2100 mg/kg and 3500 mg/kg), which suggest a relatively safer profile, although other toxicological endpoints should still be examined.

One of the most significant findings from the analysis was the extensive prediction of interactions with specific toxicity targets, which helped to identify potential risks associated with the compounds. Cryptolepine, vindolinine, and harman exhibited high probabilities for neurotoxicity, respiratory toxicity, and immunotoxicity suggesting that these compounds could adversely affect the nervous system, respiratory function, and immune response. Cryptolepine (Class 4, LD_{50}=1190 mg/kg) showed high probabilities for respiratory toxicity (0.98) and neurotoxicity (0.87), underscoring its potential to cause organ damage at elevated doses.

Neurotoxicity was a common concern across several compounds such as vindolinine, palmatine, and groenlandicine where interactions with neural pathways were predicted with high probabilities. The potential for CNS toxicity emphasizes the need for careful evaluation of these compounds in neurological contexts. Further research is needed to investigate these compounds' CNS effects and their ability to cross the BBB, as indicated by high BBB penetration probabilities.

High probability for mutagenicity for harmane and norharmane suggest these compounds may cause genetic damage, which could potentially lead to cancerous growths. The long-term use of such compounds should be approached cautiously, particularly if they are to be considered for therapeutic purposes. Sanguinarine and capsaicin, with interactions at the estrogen receptor ligand binding domain and aromatase suggest the potential for disrupting hormone signaling pathways, which could lead to adverse effects in both male and female reproductive systems. Cryptolepine, vindolinine, and magnoflorine were predicted to affect environmental organisms with moderate to high probabilities. Given their potential to enter the ecosystem, either through waste, runoff, or environmental contamination, the environmental risks posed by these compounds should not be underestimated. Further studies are necessary to assess their biodegradability, persistence in the environment, and potential to accumulate in non-target organisms.

In silico toxicity profiling of the alkaloids, has provided valuable predictive information regarding their safety and potential risks. While some compounds showed promising safety profiles with higher LD_{50} values and lower toxicity target probabilities, others displayed significant toxicity risks that require further experimental validation. This analysis underscores the importance of combining computational toxicity predictions with *in vivo* studies to obtain a more comprehensive understanding of the risks associated with these compounds.

Conclusion and recommendation

The docking study indicated mahanimbine, echinulin, and coptisine inhibit aldose reductase, and coptisine, sanguinarine, and echinulin significantly modulate AMPK activity, regulate blood glucose levels. Similarly, the alkaloids coptisine, sanguinarine, and mahanimbine exhibited favorable binding against α-glucosidase and jatrorrhizine showing high binding affinity for tyrosine phosphatase 1B. Pharmacokinetic evaluations also uncovered most alkaloids conformed to Lipinski's Rule of Five, indicating favorable oral bioavailability, with some showing optimal lipophilicity. However, some alkaloids, mahanimbine, echinulin, and conophylline, showed poor water solubility, which may limit their clinical applicability and warrants further optimization. Most compounds had favorable TPSA values.

The pharmacokinetic evaluation indicated that pinoline exhibited excellent oral bioavailability and CNS penetration, while conophylline demonstrated poor bioavailability. Toxicity analysis identified cryptolepine

and vindolinine as high-risk compounds for neurotoxicity and hepatotoxicity, necessitating further investigation. Despite these concerns, several alkaloids demonstrated favorable ADMET profiles, positioning them as promising drug leads for diabetes treatment. Sanguinarine, jatrorhizine, groenlandicine, coptisine, and pinoline, located predominantly in the lipid-rich yolk part of the boiled egg model, suggesting these alkaloids are lipophilic, making them ideal candidates for BBB penetration and efficient GI absorption.

Thus, further studies are recommended that mahanimbine, echinulin, coptisine, groenlandicine, sanguinarine, and jatrorrhizine be prioritized for further experimental studies, including *in vitro* and *in vivo* testing. These compounds demonstrated strong binding to key diabetes-related targets and exhibited favorable pharmacokinetic properties, making them viable candidates for antidiabetic drug development. The promising drug-like properties of these alkaloids suggest that they could serve as the foundation for developing novel anti-diabetic therapies, offering alternative treatment options for managing diabetes and its associated complications.

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