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Discovery of Potential DPP-4 Inhibitors from *Cassia auriculata* Through Dual Molecular Docking with GNINA and PLANTS

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Abstract

Cassia auriculata is a medicinal plant recognized for its rich phytochemical composition and potential antidiabetic properties. However, the reliability of virtual screening is often influenced by the choice of docking algorithm and scoring function, leading to variations in compound prioritization. This study aimed to identify potential dipeptidyl peptidase-4 (DPP-4) inhibitors from *C. auriculata* phytochemicals using a consensus molecular docking strategy integrating GNINA and PLANTS. A total of 96 phytochemicals were docked against the DPP-4 crystal structure (PDB ID: 5Y7H), followed by Min–Max normalization of docking scores, consensus score calculation, Pearson and Spearman correlation analyses, and Venn analysis. GNINA and PLANTS produced significantly correlated normalized docking scores (Pearson $r = 0.5829$, $p < 0.001$; Spearman $\rho = 0.5684$, $p < 0.001$), indicating a moderate level of agreement despite their distinct scoring functions and search algorithms. Venn analysis identified 13 consensus compounds among the top-ranked candidates, while consensus scoring further prioritized Gambiriin A3, Asparanin B, Hordatine A, Albanol A, Isoorientin 7-glucoside, Epicatechin gallate, Campesteryl p-coumarate, Catechin, Orcein, and Auriculine, with Gambiriin A3 achieving the highest consensus score. Structural comparison revealed that the highest-ranked compounds predominantly possessed polyphenolic scaffolds characterized by multiple hydroxyl groups and aromatic ring systems, features commonly associated with favorable ligand–protein recognition. The integration of GNINA and PLANTS through score normalization and consensus ranking provides a systematic and reliable strategy for prioritizing potential natural DPP-4 inhibitors and identifies several promising phytochemicals from Cassia auriculata for subsequent experimental validation.

Keywords: *Cassia auriculata*, DPP-4, Molecular docking, Consensus scoring, Virtual screening

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders and remains a major global public health challenge. According to the International Diabetes Federation (IDF) Diabetes Atlas 11th edition, approximately 589 million adults aged 20–79 years were living with diabetes worldwide in 2024, representing 11.1% of the global adult population. This number is projected to increase to 853 million by 2050, indicating a continuing rise in the global burden of diabetes (Genitsaridi et al. 2026). More than 90% of all diabetes cases are classified as T2DM (Gregg and Bracco 2019). T2DM is a multifactorial metabolic disorder characterized by insulin resistance and progressive pancreatic β-cell dysfunction, resulting in chronic hyperglycemia (Accili, Deng, and Liu 2025; Khin, Lee, and Jun 2023). Recent advances in pharmacological therapy have expanded the treatment options

for T2DM through the development of antihyperglycemic agents with distinct mechanisms of action, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors (Abolfazli et al. 2025).

Among the available antihyperglycemic agents, DPP-4 inhibitors have become an established therapeutic option for the management of T2DM owing to their efficacy, good tolerability, and low risk of hypoglycemia (Ling et al. 2019). DPP-4 inhibitors prevent the enzymatic degradation of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thereby enhancing glucose-dependent insulin secretion while suppressing glucagon release (Deacon 2020). Consequently, DPP-4 inhibition improves both fasting and postprandial glycemic control and reduces glycated hemoglobin (HbA1c) by approximately 0.5-1.0% (Gallwitz 2019). Furthermore, their glucose-dependent mechanism minimizes the risk of hypoglycemia, and they are generally considered weight-neutral, making them suitable for long-term glycemic management (Chen et al. 2015; Naim 2024). Several synthetic DPP-4 inhibitors, including sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin, have been successfully introduced into clinical practice. Although sitagliptin is an effective and widely used DPP-4 inhibitor, it has some limitations, including the need for dose adjustment in patients with renal impairment and the occurrence of adverse effects in some patients. Therefore, the discovery of new DPP-4 inhibitors with improved efficacy, safety, and pharmacokinetic properties remains important. Natural products may provide promising sources of structurally diverse compounds for the development of new DPP-4 inhibitor (Standl, Erbach, and Schnell 2014). Nevertheless, the discovery of novel DPP-4 inhibitors remains an active area of research, particularly from natural products, which continue to provide structurally diverse scaffolds and valuable lead compounds for antidiabetic drug discovery (Singla et al. 2019).

Medicinal plants remain an important source of structurally diverse bioactive compounds for the discovery of novel antidiabetic agents (Tran, Pham, and Le 2020). Among these, *Cassia auriculata* Linn. has garnered considerable attention due to its long-standing use in traditional medicine for managing diabetes and other metabolic disorders (Tietel et al. 2024; Wadekar et al. 2008). Treatment of diabetic rats with oral administration of *Cassia auriculata* at a dose of 120 mg/kg body weight for 15 days resulted in significant alterations compared with the diabetic control group (Kalaivani et al. 2008). In addition, its extracts have been reported to inhibit carbohydrate-hydrolyzing enzymes, including α-amylase and α-glucosidase (Nagarajaperumal et al. 2018), suggesting their potential to improve postprandial glycemic control. Phytochemical analysis demonstrated that *C. auriculata* is rich in polyphenolic compounds, with flavonoids being the predominant constituents in the leaves (4204 µg/g DW) and benzoic acids predominating in the flowers (3924 µg/g DW) (Ananth et al. 2021). These findings support the reported medicinal and antidiabetic potential of *C. auriculata* and suggest that its phytochemicals may serve as promising candidates for the discovery of novel DPP-4 inhibitors.

The DPP-4 inhibitory potential of phytochemicals from C. auriculata has not yet been systematically investigated. Molecular docking is a widely used computational approach in

early-stage drug discovery. It enables the prediction of ligand–protein binding modes and binding affinities, thereby facilitating the identification of potential bioactive compounds (Makambwa et al. 2025). As different docking platforms employ distinct search algorithms and scoring functions, the use of complementary approaches can provide a more reliable assessment of ligand–protein interactions. However, each docking method has its own advantages and limitations due to differences in search algorithms and scoring functions (Illahi and Candra 2026). Therefore, the use of complementary docking approaches can provide a more reliable assessment of ligand–protein interactions. In this study, PLANTS and GNINA were employed as complementary docking methods. PLANTS uses the CHEMPLP scoring function with an ant colony optimization algorithm, whereas GNINA incorporates a convolutional neural network (CNN)-based scoring function (Korb, Stützle, and Exner 2006; McNutt et al. 2025). The combination of these approaches may improve confidence in prioritizing *C. auriculata* phytochemicals as potential DPP-4 inhibitors.

Therefore, this study aimed to systematically investigate the potential of phytochemicals from *C. auriculata* as DPP-4 inhibitors using PLANTS and GNINA. The docking performance of the phytochemicals was compared with the native ligand and the clinically used inhibitor sitagliptin. The results from both docking methods were further compared to identify compounds with consistently favorable docking scores. This dual-docking strategy was expected to provide greater confidence in prioritizing promising *C. auriculata* phytochemicals for further experimental investigation.

METHOD

Phytochemical Dataset Preparation

A total of 96 phytochemicals reported from *Cassia auriculata* were collected from published literature (Rajagopal and Rajakannu 2022; Ramakrishnan, Kalakandan, and Pakkirisamy 2018; Tejaswini et al. 2024). Chemical information, including compound names, PubChem Compound Identifiers (CID), and canonical SMILES, was retrieved programmatically from the PubChem database using the PubChemPy Python library. For compounds that were unavailable in PubChem, chemical structures and corresponding SMILES were manually curated from the literature (Kim et al. 2025).

Ligand and Protein Preparation

Canonical SMILES of all phytochemicals were converted into three-dimensional (3D) molecular structures using RDKit. Hydrogen atoms were added using the AddHs() function, while the formal charges and stereochemical information encoded in the input SMILES were retained. Three-dimensional conformations were generated using the ETKDG method. The resulting structures were subjected to geometry optimization using the Merck Molecular Force Field (MMFF). The optimized ligands were then saved in PDB format for subsequent molecular docking analysis. The crystal structure of human DPP-4 (PDB ID: 5Y7H) was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (Lee et al. 2017). Prior to molecular docking, the co-crystallized ligand, crystallographic water molecules, and other non-essential heteroatoms were removed from the protein structure. The

prepared protein was subsequently used as the receptor for molecular docking (Illahi et al. 2024).

Molecular Docking Data Analysis

Molecular docking was performed using two complementary docking platforms, GNINA and PLANTS, to evaluate the binding interactions between *C. auriculata* phytochemicals and DPP-4. GNINA employs a convolutional neural network (CNN)-based scoring function to improve docking pose evaluation (McNutt et al. 2025), whereas PLANTS utilizes the CHEMPLP scoring function combined with the Ant Colony Optimization (ACO) search algorithm (Korb, Stützle, and Exner 2006). The docking search space was centered at x = 66.2477, y = 49.6386, and z = 91.9574, corresponding to the active site of the co-crystallized ligand in the DPP-4 structure (PDB ID: 5Y7H) (Jakubec et al. 2022). A 40 × 40 × 40 Å search box was used for GNINA, while a binding site radius of 20 Å was used for PLANTS, with both approaches centered on the same active site. Docking scores, predicted binding poses, and ligand–protein interactions obtained from both platforms were compared to identify potential DPP-4 inhibitory phytochemicals (Triadisti et al. 2025).

To enable direct comparison between the two docking platforms, the docking scores were normalized using the Min–Max normalization method, which transforms the values to a range of 0 to 1 according to Equation (1). Since lower docking scores indicate stronger binding affinity, the normalized values were inverted so that a value of 1 represented the highest predicted binding affinity (Wallach et al. 2011). Pearson and Spearman correlation analyses were subsequently performed to evaluate the agreement between the normalized docking scores generated by GNINA and PLANTS.

$$Normalized\ Score = \frac{x - x_{min}}{x_{max} - x_{min}} \quad (1)$$

The compounds were ranked according to their normalized scores, and the top 20 compounds from each docking platform were selected for comparative analysis. The overlap between the two ranked compound sets was evaluated using a Venn analysis to identify consensus candidates consistently prioritized by both docking approaches. The detailed computational workflow, including data preparation, protein and ligand preprocessing, molecular docking protocols using GNINA and PLANTS, and post-docking analyses, is publicly available in the GitHub repository at https://github.com/adhadastuilahi/dpp4-cassiaauriculata-docking to facilitate transparency, reproducibility, and reuse of the computational procedures.

RESULTS AND DISCUSSION

The molecular docking results obtained from GNINA and PLANTS revealed distinct score distributions, reflecting the differences in the scoring functions and search algorithms implemented by the two docking platforms. The docking results showed distinct score distributions between the two platforms, reflecting differences in their scoring functions and search algorithms. GNINA generated docking scores ranging from −11.71 to −4.53 kcal/mol (mean ± SD: −7.50 ± 1.78 kcal/mol), whereas PLANTS produced CHEMPLP scores ranging from −119.11 to −44.30 (mean ± SD: −78.91 ± 12.65). The differences in score ranges between GNINA and PLANTS reflect the distinct scoring functions implemented by each

docking platform rather than differences in binding affinity itself (Korb, Stützle, and Exner 2006; McNutt et al. 2025).

The docking performance of the screened phytochemicals was further evaluated by comparison with the co-crystallized native ligand and the reference DPP-4 inhibitor, sitagliptin. Using GNINA, the native ligand and sitagliptin exhibited docking scores of −8.24 kcal/mol and −9.02 kcal/mol, respectively. Of the 96 screened phytochemicals, 36 compounds (37.50%) showed more favorable docking scores than the native ligand, while 25 compounds (26.04%) outperformed sitagliptin. In contrast, PLANTS predicted CHEMPLP scores of −72.77 for the native ligand and −90.69 for sitagliptin. Based on the PLANTS results, 65 compounds (67.71%) exhibited more favorable docking scores than the native ligand, whereas 15 compounds (15.63%) achieved better scores than sitagliptin. The more favorable docking score of sitagliptin relative to the native ligand in both docking platforms is consistent with its established binding affinity toward DPP-4. The complete docking results, including the docking scores of all screened compounds and their comparisons with the reference ligands, are publicly available in the GitHub repository accompanying this study (Paggi, Pandit, and Dror 2024).

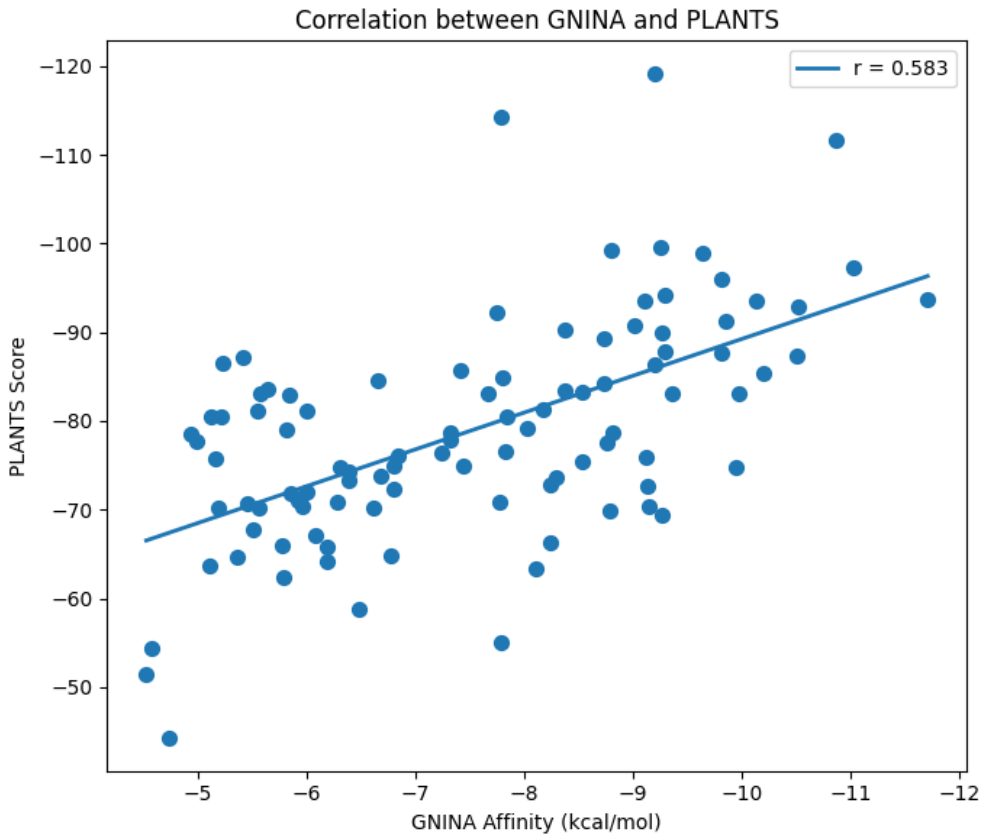

Figure 1. Correlation between GNINA binding affinity and PLANTS docking score for the screened phytochemicals.

The relationship between the molecular docking scores generated by GNINA and PLANTS is presented in Figure 1. Overall, both docking platforms exhibited a similar trend in

prioritizing compounds with favorable predicted binding affinities toward DPP-4. Pearson correlation analysis revealed a moderate positive correlation between the normalized docking scores ($r = 0.5829$, $p < 0.001$), while Spearman rank correlation analysis also demonstrated a moderate positive association ($\rho = 0.5684$, $p < 0.001$). These statistically significant correlations indicate that compounds receiving favorable docking scores in one platform generally tended to receive favorable scores in the other (Thirumalai, Chandhini, and Vaishnavi 2017). The moderate correlation observed in this study is expected because GNINA and PLANTS employ fundamentally different docking strategies. GNINA incorporates a CNN-based scoring function to improve docking pose evaluation, whereas PLANTS utilizes the empirical CHEMPLP scoring function together with the ACO search algorithm . Consequently, each platform evaluates ligand binding using different scoring criteria, which may lead to differences in docking scores and compound rankings despite targeting the same binding pocket (Khamis and Gomaa 2015). Although the rankings were not identical, the significant positive correlations indicate that both docking platforms consistently identified a subset of compounds with favorable predicted binding affinities. Therefore, compounds that were independently prioritized by both GNINA and PLANTS were considered more reliable candidates than those identified by only a single docking platform. Based on this rationale, a consensus analysis was subsequently performed using the top-ranked compounds from both docking platforms to identify the most promising DPP-4 inhibitor candidates.

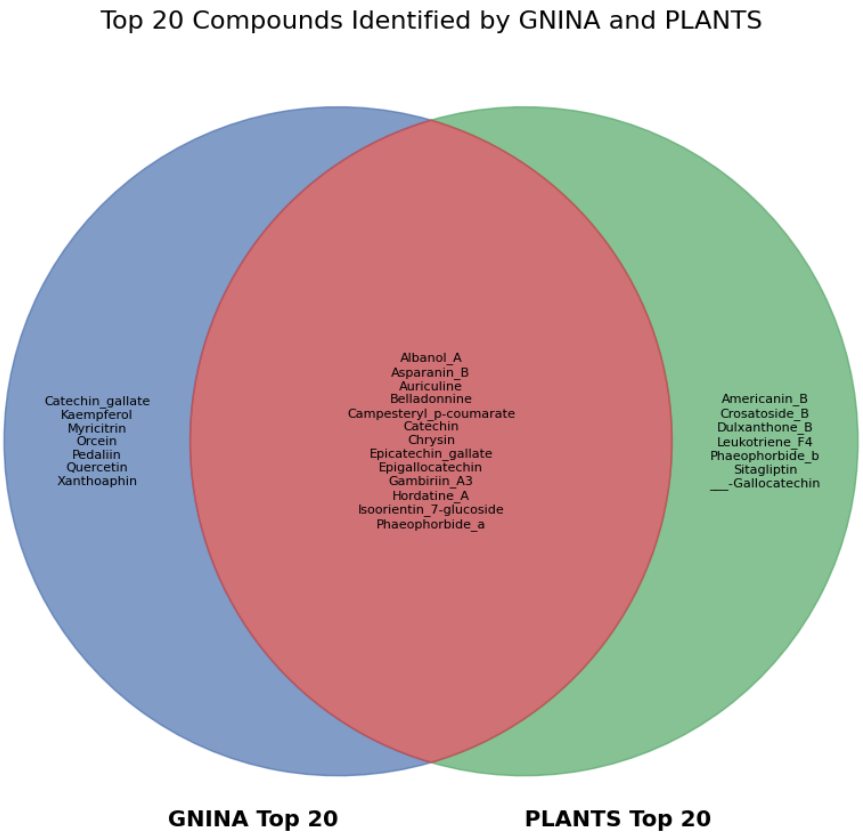

Figure 2. Identification of consensus phytochemical hits based on the overlap between GNINA and PLANTS docking results.

To further improve the reliability of candidate selection, the top 20 ranked compounds obtained from GNINA and PLANTS were compared using a Venn analysis (Figure 2). Despite employing different scoring functions and search algorithms, the two docking platforms identified 13 common compounds, representing 65% of the top-ranked candidates. The shared compounds were Albanol A, Asparanin B, Auriculine, Belladonnine, Campesteryl *p*-coumarate, Catechin, Chrysin, Epicatechin gallate, Epigallocatechin, Gambiriin A3, Hordatine A, Isoorientin 7-glucoside, and Phaeophorbide *a*. The substantial overlap between the two docking platforms demonstrates a high level of agreement in prioritizing compounds with favorable predicted binding affinities toward DPP-4, despite the moderate correlation observed in the overall docking scores. This finding suggests that these consensus compounds are less likely to represent algorithm-specific predictions and are more likely to constitute robust candidate DPP-4 inhibitors. Consequently, the shared compounds identified by both GNINA and PLANTS were considered high-confidence candidates for subsequent analyses and literature-based biological interpretation.

Table 1. Consensus molecular docking results of the top-ranked phytochemicals obtained from GNINA and PLANTS.

Compund	GNINA Affinity (kcal/mol)	GNINA Norm	PLANTS Score	PLANTS Norm	Consensus Score
Native Ligand	-8.24	0.52	-72.77	0.38	0.45
Sitagliptin	-9.02	0.63	-90.69	0.62	0.62
Gambiriin A3	-10.87	0.88	-111.66	0.90	0.89
Asparanin B	-11.71	1.00	-93.76	0.66	0.83
Hordatine A	-9.2	0.65	-119.11	1.00	0.83
Albanol A	-11.03	0.91	-97.30	0.71	0.81
Isoorientin 7-glucoside	-10.52	0.83	-92.89	0.65	0.74
Epicatechin gallate	-9.64	0.71	-98.87	0.73	0.72
Campesteryl p-coumarate	-10.14	0.78	-93.62	0.66	0.72
Catechin	-9.81	0.74	-95.91	0.69	0.71
Orcein	-10.51	0.83	-87.42	0.58	0.70
Auriculine	-9.25	0.66	-99.51	0.74	0.70

To further prioritize the consensus candidates, the normalized docking scores obtained from GNINA and PLANTS were averaged to generate a consensus score for each compound. Unlike the Venn analysis, which identifies compounds consistently appearing among the top-ranked candidates in both docking platforms, the consensus score integrates the relative docking performance of each compound across both methods. Based on this approach, the top 10 consensus compounds are presented in Table 1, comprising Gambiriin A3, Asparanin B, Hordatine A, Albanol A, Isoorientin 7-glucoside, Epicatechin gallate, Campesteryl *p*-coumarate, Catechin, Orcein, and Auriculine. Most of these compounds were also identified in the Venn analysis, demonstrating consistent prioritization by both docking platforms. Interestingly, Orcein emerged among the top consensus candidates despite not being included in the overlapping compounds identified by the Venn analysis, indicating that its overall normalized docking performance across both docking platforms was superior to several compounds identified solely by the overlap analysis. These findings demonstrate that consensus scoring provides a more balanced ranking by integrating the relative performance of compounds across multiple docking algorithms rather than relying solely on overlapping rankings (Ravitz, Zsoldos, and Simon 2011).

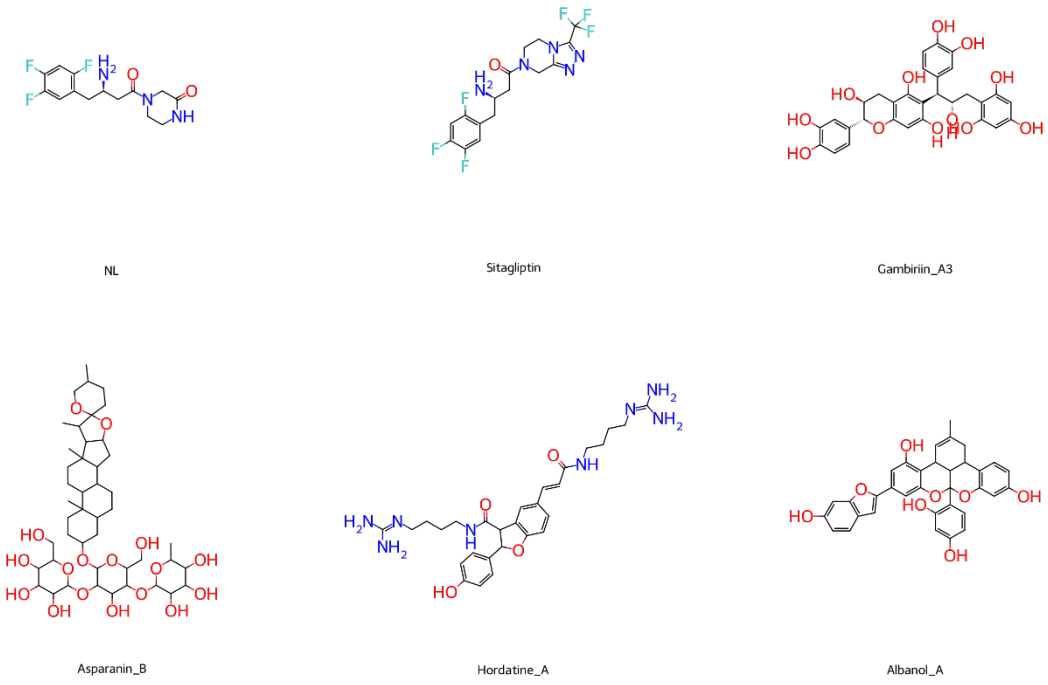

Figure 3. Chemical structures of the native ligand and the top 3 phytochemicals selected by consensus docking

The chemical structures of the four highest-ranked consensus compounds, together with the native ligand and sitagliptin, are presented in Figure 3. Although these compounds belong to different chemical classes, several common structural features can be observed. Sitagliptin and

the native ligand contain fluorinated aromatic moieties, including ortho- and meta-fluorine substitutions, which have been reported to enhance hydrophobic interactions and improve binding affinity toward the DPP-4 active site (Mathur et al. 2023). In contrast, the four selected phytochemicals are predominantly characterized by multiple hydroxyl (–OH) groups attached to aromatic rings, reflecting their polyphenolic nature. These hydroxyl groups may facilitate the formation of hydrogen bonds with amino acid residues within the DPP-4 binding pocket, whereas the aromatic ring systems provide hydrophobic and π-related interactions. Despite their distinct molecular scaffolds, all selected compounds possess multiple aromatic ring systems, suggesting that aromaticity represents a common structural feature that may contribute to their predicted affinity toward DPP-4.

CONCLUSION

This study demonstrated that the combined use of GNINA and PLANTS, together with Min–Max normalization and consensus scoring, can be used to prioritize *Cassia auriculata* phytochemicals for further investigation as potential DPP-4 inhibitors. Although the two docking platforms employ different scoring functions and algorithms, both showed significant moderate positive correlations, indicating a degree of consistency between the two docking approaches. Integration of the normalized docking scores identified Gambiriin A3, Asparanin B, Hordatine A, Albanol A, Isoorientin 7-glucoside, Epicatechin gallate, Campesteryl *p*-coumarate, Catechin, Orcein, and Auriculine as the top-ranked consensus candidates, with Gambiriin A3 showing the highest consensus score. Structural analysis revealed that these compounds contain aromatic frameworks and hydroxyl-rich functionalities, which may contribute to their predicted interactions with DPP-4. However, these findings are based solely on molecular docking predictions and do not confirm DPP-4 inhibitory activity. Therefore, the identified compounds should be considered prioritized candidates for further experimental validation, including enzymatic and biological assays.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

AI USE STATEMENT

The authors used LLM to assist with language editing, grammar improvement, and manuscript refinement. All scientific content, data analysis, interpretation of the results, and final responsibility for the manuscript remain with the authors.

AUTHOR CONTRIBUTIONS

Adha Dastu Illahi: Conceptualization, Methodology, Software, Formal analysis, Data curation, Visualization, Writing – Original Draft, Project administration. Tifany Maulida Candra: Data curation, Validation, Writing – Original Draft. Imam Lukmanul Hakim: Validation, Formal analysis, Writing – Review & Editing. Delila Eliza: Validation, Writing – Review & Editing. Mabrurotul Mustafidah: Writing – Review & Editing. Ezekiel Makambwa:

Validation, Methodology, Writing – Review & Editing. All authors have read and approved the final version of the manuscript.

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