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Antidiabetic Potency of Flavonoids Using a Systematic Computer-Aided Drug Design Platform

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Abstract: Diabetic mellitus (DM) is a chronic metabolic disorder, with type 2 diabetes (T2DM) being the most prevalent type globally. Despite the availability of several target-specific drugs, the prevalence rate has remained uncontrollable, prompting a systematic exploration of plant secondary metabolites or phytochemicals for mainstream use. Among all natural resources, citrus fruits like oranges, lemons, grapefruits and limes are rich sources of flavonoids and get more attention due to their higher antioxidant, anti-inflammatory and immunomodulatory effects. Additionally, researchers have employed various strategies to locate the most bioactive and drug-able flavonoids from these herbal extracts for use in managing diabetes. Therefore, the present study selected nine citrus-fruit-derived flavonoids and tested their antidiabetic potency using four target enzymes: α-amylase, AKT Serine/Threonine Kinase 1 (AKT1), dipeptidyl peptidase-4 (DPP-IV), and glucose transporter 1 (GLU1) through molecular docking studies. In addition, we have predicted the physiochemical profile, toxicity, bioavailability, lead-likeness, drug-likeness, and lethal dose of flavonoids, along with five standard antidiabetic drugs, to select the most potential candidates. We used AutoDock 4.2 for the docking study, BIOVID-Discovery Studio for the protein-ligand interaction study, SwissADME, ProTox 3.0 and Molsot tools to predict the drug-likeness profile. Individual and average docking scores indicated that naringin (-11.2 and -10.40 kcal/mol) was the most potent flavonoid, and glimepiride (-11.1 and -10.1 kcal/mol) against AKT1 had the most potential among the five antidiabetic drugs. Naringin had non-toxic profiles, a positive drug-likeness score, and ideal physicochemical profiles, which suggested that it might be the best candidate for further testing. To sum up, the computer-aided drug design platform is an important part of the current drug discovery module to accelerate phyto-based drug discovery within limited time and resources.

Introduction

Diabetic mellitus (DM) is a leading metabolic disorder and the third-most chronic disease with a high prevention rate globally (WHO, 2022; Cloete et al., 2022; Lancet, 2023). Apart from all types, nearly 90% of adults suffer from type 2 diabetes (T2DM), which disproportionately affects low- and middle-income continents like Africa and Asia due to food habits and lifestyles. As per current reports of the World Health Organization (WHO) and the International Diabetic Federation (IDF), the global T2DM cases will cross 560 million by 2045 (WHO, 2022; Cloete et al., 2022; Sarkar et al., 2023; Lancet, 2023; Tyagi et al., 2024). A variety of medications preferable to insulin are available, but the rapid increase in T2DM cases indicates newer potential drugs with new strategies of treatment modalities are urgently required (Grover and Utreja, 2014;

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Padhi et al., 2020; Sur et al., 2023; Biswas et al., 2023). As a polygenic metabolic disorder, the anti-diabetic efficacy of available medicines varies according to disease condition, patient immunity, and daily habits, including their environmental factors (Pramanik, 2018; Jaiswal and Gupta, 2023). For long-term use, drugs produce several minor to severe adverse effects that inherently create several secondary disorders. Therefore, it is crucial to identify alternative regimens to effectively control this debilitating polygenic metabolic disorder.

Natural regimens offer an alternative approach to the treatment of DM, focusing on lifestyle modifications, dietary interventions, and herbal supplements to improve glycaemic control and overall health (Seidel, 2020; Rath et al., 2021; Alam et al., 2022; Mata et al., 2023; Acharya et al., 2023; Vikhe et al., 2024). Herbal supplements for diabetes control commonly include cinnamon, ginseng, fenugreek, and bitter melons, along with several herbal mixes. Natural regimens, while not a replacement for conventional medical treatments, can enhance existing therapies and effectively manage diabetes when used under the proper guidance of healthcare providers to ensure safety and efficacy (Newman and Cragg, 2020; Swain et al., 2021a; Sahoo et al., 2022; Dhakar and Tare, 2023; Pawar et al., 2023). Mechanically, the presence of several bioactive secondary metabolites or phytochemicals belonging to alkaloids, flavonoids, polyphenols, terpenoids, steroids, and glycosides in herbal and natural regimens showed a complementary anti-DM potency from an ethnomedicinal perspective, followed by scientific validation. Apart from other classes of phytochemicals, flavonoids offer distinct advantages and hold considerable promise for antidiabetic drug development (Al-Ishaq et al., 2019; Shamsudin et al., 2022; Aryal et al., 2024).

Flavonoids have emerged as promising alternative treatment modalities against diabetes, offering several advantages and exhibiting favorable drug-likeness profiles. Fruits, vegetables, and plant-based foods abundantly contain these bioactive compounds. Besides that, citrus fruits like oranges, lemons, grapefruits, and limes contain a lot of flavonoids, such as flavanones (hesperidin and naringenin), flavones (tangeretin), and flavonols (quercetin and kaempferol), etc (Ahangarpour et al., 2019; Shamsudin et al., 2022; Rath et al., 2023). Researchers have extensively studied these flavonoids for their antioxidant, anti-inflammatory, and antidiabetic effects, which collectively enhance diabetic efficacy. Studies have demonstrated that flavonoids enhance insulin sensitivity, facilitate glucose uptake and utilization in peripheral tissues, improve glycaemic control, protect pancreatic cells, maintain adequate insulin secretion, prevent insulin-producing cell dysfunction, and reduce insulin resistance (Shamsudin et al., 2022; Visvanathan and Williamson, 2022; Rath et al., 2023; Gupta et al., 2023). Citrus flavonoids can modulate enzymes involved in glucose metabolism, such as α-glucosidase and glucokinase, thereby regulating blood glucose levels and inhibiting carbohydrate digestion and absorption (Shamsudin et al., 2022; Rath et al., 2023; Aryal et al., 2024). Overall, the diverse bioactive properties of citrus food and derived flavonoids have garnered considerable attention for their potential role in diabetic treatment, prompting several investigations to identify a potential one for mainstream applications (Rath et al., 2023; Gupta et al., 2023; Aryal et al., 2024).

Currently, researchers have used several tools for lead drug candidate selection, where bioinformatics tools are considered a cost-effective and promising platform in modern drug discovery and development. By harnessing the power of computational methods, researchers can efficiently screen vast chemical libraries and predict the pharmacological activities of candidate compounds via systematic analyses to accelerate the drug discovery process and even help reduce experimental costs compared to hit-and-trial methods. Using such a cost-effective and systematic bioinformatics platform, the present study aims to assess the antidiabetic potency of some flavonoids (n = 9) derived from several citrus fruits. In brief, the study employs virtual screening and molecular docking techniques to calculate the binding affinity of flavonoids in comparison with marketed antidiabetic drugs against four key molecular target enzymes involved in diabetes development and progression. In addition, we predicted the physiochemical profiles, toxicity profiles, and drug-ability profiles to select the most potential one for further guidance in subsequent experimental validation studies.

Materials and Methods

Ligand and target structure preparation for docking study

We conducted the entire computational work on a Linux-Ubuntu 16.04 LTS workstation, utilizing several bioinformatics and cheminformatics software and tools (Sahoo et al., 2021; Swain et al., 2022a). According to our hypothesis, selected nine antiobesity and antidiabetic flavonoids chemical structures were retrieved from the PubChem database in individual CIDs: diosmetin (PubChem CID: 5281612), diosmin (PubChem CID: 5281613), hesperidin (PubChem CID: 10621), naringenin (PubChem CID: 439246), naringin (PubChem CID: 442428), nobiletin (PubChem CID: 72344), quercetin (PubChem CID: 5280343), sudachitin (PubChem CID:

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12443122), and tangeretin (PubChem CID: 68077). We also retrieved metformin (PubChem CID: 4091), glimepiride (PubChem CID: 3476), rosiglitazone (PubChem CID: 77999), acarbose (PubChem CID: 41774), and sitagliptin (PubChem CID: 4369359) from the PubChem database for use as standard antidiabetic drugs (Table 1). In addition to the chemical structure, we documented each molecule's Simplified Molecular Input Line Entry System (SMILE) notation for use in further analyses and recorded the physicochemical profiles. All ligand chemical structures were optimized using Avogadro 1.2.0 software and saved in dot-pdb (.pdb) file format for docking studies (Swain et al., 2022a and 2022b).

Simultaneously, we selected four well-known target proteins of diabetes through an extensive literature search for our study: α-amylase (α-1,4-glucan-4-glucanohydrolase), AKT Serine/Threonine Kinase 1 (AKT1), dipeptidyl peptidase-4 (DPP-IV), and glucose transporter 1 (GLU1). For the molecular docking study, we used the X-ray crystal structures of four target enzymes: alpha-amylase (PDB ID: 4X9Y), AKT1 (PDB ID: 3O96), DPP-IV (PDB ID: 5T4E), and GLU1 (PDB ID: 5EQI) from the protein data bank. After that, we removed attached heteroatoms, ligands, and chains from the retrieved protein structure and saved it in.pdb format for the docking study. The molecular docking study was done with AutoDock 4.2 software, with the default settings and a grid box that was already set up within the active side residues (Swain et al., 2018; Swain et al., 2022b; Sahoo et al., 2022b). Each ligand generated ten docking poses (kcal/mol.) against each target, and we selected the best pose (the one with the lowest binding energy) against the respective target enzyme. We primarily determine the antidiabetic potency of selected flavonoids by comparing their binding efficacy or docking score to standard drugs. Using the software BIOVIA-DSV-2019 (Swain et al., 2022a; Sahoo et al., 2022b), we also saw the 3-D and 2-D molecular interactions between the proteins and their targets.

Physicochemical profile analyses and toxicity prediction

Experts suggest that the Lipinski rule (RO5) and physicochemical profiles are one of the approach/ method for selecting active oral candidates. These profiles are based on molecular weight, XlogP, the number of hydrogen bond acceptors and donors, and tPSA profiles. So, we have analysed the RO5 profiles of each flavonoid and antidiabetic drug using the SwissADME (http://www.swissadme.ch/) tool with reference to the PubChem database (Sahoo et al., 2022b; Swain et al., 2022b). After biological activity, the toxicity profile is another crucial parameter to consider when selecting any lead drug candidate. Higher toxicity often led to the withdrawal of active candidates from clinical trials, despite their higher therapeutic value. In the past, researchers have used different *in vitro* and *in vivo* models to study toxicity profiles, but now advanced computational tools can predict different toxicity profiles based on chemical structure by comparing them with a training set dataset (Sahoo et al., 2021; Swain and Hussain, 2022). Therefore, we predicted the possible toxicity profiles—hepatotoxicity (HT), neurotoxicity (NT), respiratory toxicity (RT), cardiotoxicity (CD), carcinogenicity (CG), immunotoxicity (IT), cytotoxicity (CT), ecotoxicity (EC), and toxicity class (TC) of all nine flavonoids and five anti-diabetic drugs using the ProTox 3.0 tool (https://tox.charite.de/protox3/).

Overall drug-likeness profile prediction

Drug-ability is defined as the ideal characteristics of parameters (physiochemical, toxicity, pharmacokinetic, etc.) that determine whether a chemical has the potential to be an ideal drug. Using a computational platform, we can also predict this potential parameter to identify drug-able candidates from a large pool of chemicals for further study and increased clinical success. We used the MolSoft tool (https://www.molsoft.com/) to predict the overall drug-likeness score. Overall, the results help to get some prior information to select some desired candidates to accelerate the drug-development process (Swain et al., 2022a; Swain and Hussain, 2022). We used the ProTox 3.0 tool(https://tox.charite.de/protox3/index.php?site=compound_input) to determine the bioavailability (BA), lead likeness (LL), and fifty percent lethal dose (LD_{50} in mg/kg) of all nine flavonoids and five anti-diabetic drugs.

Results

Molecular docking results

The individual docking score was recorded in Table 2 and indicates that except for GLUT1 (-10.7 kcal/mol.), naringin was the most potential one against α-amylase (-10.6), AKT1 (-11.2 kcal/mol.), and DPP-4 (-9.1 kcal/mol.). Particularly, diosmin and hesperidin (-11.1 kcal/mol.) showed comparatively stronger binding affinity against GLUT1 than naringin. Even so, naringin (-10.40 kcal/mol.) and hesperidin (-10.25 kcal/mol.), which have the lowest average docking scores against four target enzymes, are thought to be the most promising of the nine flavonoids. Similarly, the docking scores of

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Table 1. Physicochemical profiles with PubChem IDs of selected flavonoids and drugs

Sl. No	Flavonoids/ standard drugs	PubChem CID	Molecular formula	MW (≤ 500)	XLogP (≤ 5)	HBD (≤ 5)	HBA (≤ 10)	tPSA (≤ 142 Å)
1	Diosmetin	5281612	$C_{16}H_{12}O_6$	300.26	1.7	3	6	96.2
2	Diosmin	5281613	$C_{28}H_{32}O_{15}$	608.5	-0.8	8	15	234
3	Hesperidin	10621	$C_{28}H_{34}O_{15}$	610.6	-1.1	8	15	234
4	Naringenin	439246	$C_{15}H_{12}O_5$	272.25	2.4	3	5	87
5	Naringin	442428	$C_{27}H_{32}O_{14}$	580.5	-0.5	8	14	225
6	Nobiletin	72344	$C_{21}H_{22}O_8$	402.4	3	0	8	81.7
7	Quercetin	5280343	$C_{15}H_{10}O_7$	302.23	1.5	5	7	127
8	Sudachitin	12443122	$C_{18}H_{16}O_8$	360.3	2.6	3	8	115
9	Tangeretin	68077	$C_{20}H_{20}O_7$	372.4	3	0	7	72.4
10	Metformin*	4091	$C_4H_{11}N_5$	129.16	-1.3	3	1	91.5
11	Glimepiride*	3476	$C_{24}H_{34}N_4O_5S$	490.6	3.9	3	5	133
12	Rosiglitazone*	77999	$C_{18}H_{19}N_3O_3S$	357.4	3.1	1	6	96.8
13	Acarbose*	41774	$C_{25}H_{43}NO_{18}$	645.6	-8.5	14	19	321
14	Sitagliptin*	4369359	$C_{16}H_{15}F_6N_5O$	407.31	0.7	1	10	77

Standard antidiabetic drugs; ***MW, molecular weight; ***HBD,*** hydrogen bond donor; ***HBA,*** hydrogen bond acceptor, ***tPSA,*** topological polar surface area.

Table 2. Molecular docking scores against four target enzymes along with drug-likeness profiles of selected flavonoids and standard antidiabetic drugs

Sl. No.	Flavonoids/ standard drugs	Docking score (kcal/mol.)				Drug-ability profiles			
		α-Amylase	AKT1	DPP-4	GLUT1	BA	LL	DL	LD50
1	Diosmetin	-8.5	-9.4	-8.1	-8.5	0.55	Yes	0.06	3919
2	Diosmin	-9.7	-8.9	-9.1	-11.1	0.17	No	0.70	5000
3	Hesperidin	-9.6	-11.2	-9.1	-11.1	0.17	No	0.94	12000
4	Naringenin	-9.3	-9.5	-7.8	-8.2	0.55	Yes	0.82	2000
5	Naringin	-10.6	-11.2	-9.1	-10.7	0.17	No	1.05	2300
6	Nobiletin	-7.6	-8.7	-7.0	-8.3	0.55	No	-0.23	5000
7	Quercetin	-9.4	-9.7	-8.9	-8.8	0.55	Yes	0.52	159
8	Sudachitin	-8.3	-9.4	-7.7	-8.4	0.55	No	0.04	3919
9	Tangeretin	-7.4	-8.9	-7.0	-8.3	0.55	No	-0.56	5000
10	Metformin*	-5.0	-5.3	-5.2	-8.2	0.55	No	-0.82	680
11	Glimepiride*	-9.4	-11.1	-9.1	-10.8	0.55	No	1.25	4000
12	Rosiglitazone*	-7.6	-9.1	-7.8	-7.6	0.55	No	1.06	1000
13	Acarbose*	-8.2	-7.8	-7.9	-8.9	0.17	No	0.40	24000
14	Sitagliptin*	-9.5	-10.1	-8.3	-8.9	0.55	No	0.52	2500

standard drugs; ***α-amylase, α-1,4-glucan-4-glucanohydrolase; ***AKT1***, AKT Serine/Threonine Kinase 1; ***DPP-IV***, dipeptidyl peptidase-4; ***GLU1***, Glucose transporter 1; ***BA***, bioavailability; ***LL***, Lead likeness; ***DL***, drug-likeness, ***LD_{50}***, fifty percent lethal dose (mg/kg).

five antidiabetic drugs indicate that glimepiride has the potential to be a single individual (-9.4, -11.1, -9.1, and -10.8 kcal/mol), as well as an average docking score of -10.1 kcal/mol. Further, the protein-ligand interactions of docking complexes indicated that naringin formed a number of h-hydrogen bonds, pi-pi interactions, and van der Waal interactions against all target enzymes (Figure 1), and due to this higher number of bindings, it expressed a strong docking binding affinity especially AKT1.

Physicochemical profile analyses and toxicity prediction

The physicochemical profiles shown in Table 1 showed that some flavonoids had molecular weights between 310 and 611 g/mol. Quercetin had the lowest (302.23 g/mol.), and hesperidin had the highest (610.6 g/mol.) molecular weight ligand or candidate from the list. On the standard drug side, except acarbose (645.6), all have an ideal molecular weight range (≤ 500).

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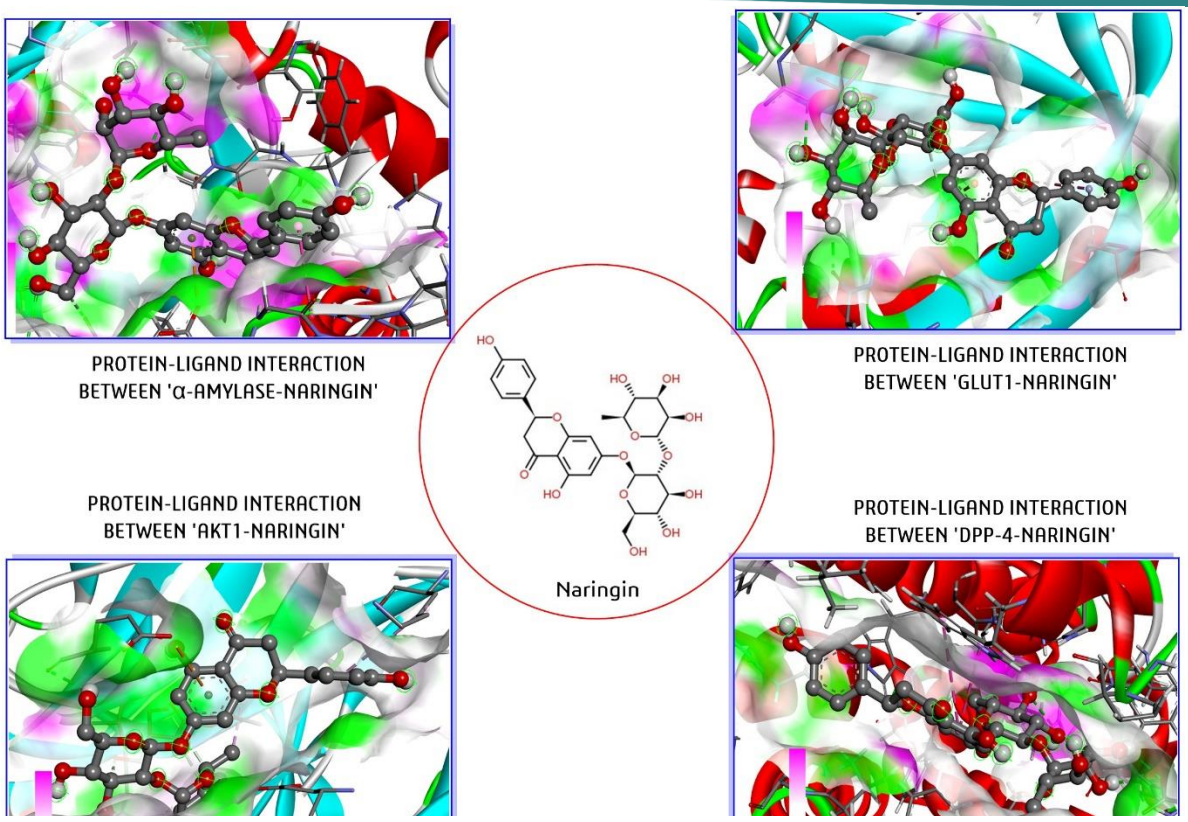

Figure 1. Protein-ligand interactions of the most potential ligand, naringin, with four target enzymes during molecular docking studies. The interaction analyses were visualized by BIOVIA-Discovery Studio and presented by ChemDraw 20.0 software

The recorded XlogP profiles show that hesperidin had a higher affinity for water or higher aqueous solubility (-1.1), which is similar to the metformin profile (-1.3). The records also show that acarbose was the fastest-solving candidate (-8.5). Other physicochemical profiles, such as the presence of h-bond donors, acceptors, and tPSA profiles of flavonoids, are within an ideal range comparable to standard drugs (Table 1). The current drug screening platform uses RO5, which is the best approach to choosing active oral candidates based on their physicochemical profiles, where flavonoids have a higher drug-ability profile to be used as potential drug candidates for use as oral anti-diabetic drugs. In the current drug development module, the RO5 is a crucial platform to select the most bioactive candidates with a higher chance of success in experiments, but it does not always work as some of the existing drugs do not follow the RO5 (Chen et al., 2020; Sahoo et al., 2022b).

The eight different toxicity profiles with toxicity classes are summarized in Table 3. According to the report, most flavonoids were non-toxic in nature except for respiratory toxicity. All the flavonoids exhibited safe hepatotoxicity, neurotoxicity, carcinogenecity and cytotoxicity profiles, but diosmetin and sudachitin showed a high risk of cardiotoxicity, while diosmin and sudachitin demonstrated a high risk of immunotoxicity. On the other hand, most of the candidates showed a moderate risk of ecotoxicity. On the drug side, except for respiratory, glimepiride and metformin were presented as safe candidates, whereas rosiglitazone, acarbose, and sitagliptin showed moderate to high risk of neurotoxicity and cardiotoxicity profiles. From a toxicity class point of view, except quercetin, all drugs and flavonoids are in classes IV to VI. Overall, flavonoids could be used as non-toxic or negligible-toxicity bioactive lead candidates for further study. Generally, researchers find it challenging to measure different types of toxicity in various *in vitro* and *in vivo* models (Kim et al., 2021; Casser et al., 2012; Gao and Shen et al., 2021). However, a computational prediction report can assist in obtaining potential toxicity profiles without the need for experiments, thereby facilitating the selection of non-toxic candidates for further study (Swain et al., 2022b; Swain and Hussain, 2022).

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Table 3. Predicted different toxicity profiles of selected flavonoids and standard drugs using bioinformatics tool.

Sl. No.	Flavonoids/ standard	HT	NT	RT	CD	CG	IT	CT	EC	TC
1	Diosmetin	IA(0.72)	IA(0.88)	A(0.85)	A(0.82)	IA(0.68)	IA(0.61)	IA(0.95)	IA(0.55)	V
2	Diosmin	IA(0.81)	IA(0.87)	A(0.66)	IA(0.53)	IA(0.93)	A(0.99)	IA(0.52)	IA(0.58)	V
3	Hesperidin	IA(0.89)	IA(0.88)	A(0.73)	IA(0.87)	IA(0.67)	IA(061.)	IA(0.69)	IA(0.65)	VI
4	Naringenin	IA(0.67)	IA(0.84)	A(0.82)	IA(0.79)	IA(0.62)	IA(0.88)	A(0.59)	A(0.51)	IV
5	Naringin	IA(0.81)	IA(0.78)	A(0.58)	IA(0.54)	IA(0.90)	A(0.99)	IA(0.69)	A(0.58)	V
6	Nobiletin	IA(0.69)	IA(0.74)	A(0.57)	IA(0.71)	IA(0.53)	A(0.51)	IA(0.82)	A(0.68)	V
7	Quercetin	IA(0.69)	IA(0.89)	A(0.83)	IA(0.99)	IA(0.68)	IA(0.87)	IA(0.99)	IA(0.53)	III
8	Sudachitin	IA(0.70)	IA(0.85)	A(0.79)	A(0.71)	IA(0.69)	A(0.96)	IA(0.75)	A(0.50)	V
9	Tangeretin	IA(0.69)	IA(0.74)	A(0.57)	IA(0.71)	IA(0.53)	IA(0.80)	IA(0.82)	A(0.68)	V
10	Metformin*	IA(0.74)	IA(0.84)	IA(0.60)	IA(0.56)	IA(0.68)	IA(0.99)	IA(0.69)	A(0.58)	IV
11	Glimepiride*	IA(0.71)	IA(0.70)	A(0.91)	IA(0.70)	IA(0.72)	IA(0.99)	IA(0.64)	IA(0.75)	V
12	Rosiglitazone*	IA(0.59)	A(0.92)	A(0.95)	IA(0.76)	IA(0.52)	A(0.75)	IA(0.62)	IA(0.61)	IV
13	Acarbose*	A(0.65)	IA(0.60)	A(0.55)	A(0.60)	IA(0.84)	A(0.99)	IA(0.70)	IA(0.66)	VI
14	Sitagliptin*	IA(0.60)	A(0.97)	A(0.97)	IA(0.90)	IA(0.50)	IA(0.82)	IA(0.73)	A(0.63)	V

*standard drugs; ***HT,*** Hepatotoxicity; ***NT,*** Neurotoxicity; ***RT,*** Respiratory toxicity; ***CD,*** Cardiotoxicity; ***CG,*** Carcinogenicity; ***IT,*** Immunotoxicity; ***CT,*** Cytotoxicity; ***EC,*** Ecotoxicity; ***TC,*** toxicity class.

Overall drug-likeness profile prediction

The drug-ability profiles are the overall profiles of pharmacokinetics, toxicity, pharmacokinetics, bioavailability, etc., and mainly depend on chemical structure. In this study, we predicted the bioavailability, lead likeness, drug-likeness, and 50% lethal dose to look at the drug-ability profile of flavonoids and common drugs (Table 2). Because of the slightly higher molecular weight (> 500 g/mol.), only two of the nine showed lead-likeness profiles. The bioavailability is similar to that of standard drugs, being within 0.17 to 0.55. Except for nobiletin (-0.23) and tangeretin (-0.56), all had a positive drug-likeness score, with naringin (1.05) having the most potential. Similarly, on the drug side, all but metformin (-0.82) showed a positive score, while glimepiride was the lead drug (1.25). The predicted LD_{50} (mg/kg) indicated that, except quercetin (159 mg/kg), all were > 2000 mg/kg (Figure 2). Similarly, except for metformin (680 mg/kg), all showed LD_{50} values > 1000 mg/kg. In general, the results made it clear that small changes in the flavonoid core moiety's functional attachment caused variations in activity and profiles. Currently, such a computational platform helps to elucidate these profiles and saves resources compared to a hit-and-trial experimental study.

Discussion

At present, DM is a chronic metabolic disorder with significant rise in global prevalence and its associated complications underscore the urgent need for effective therapeutic interventions (WHO, 2022; Cloete et al., 2022; Lancet, 2023). In this perspective, phytochemical benefits in modern drug discovery entail leveraging the known therapeutic properties of plant-derived compounds to develop new treatments for a variety of diseases. This approach capitalizes on the extensive historical use of phytochemicals in traditional medicine, along with modern scientific advancements, to streamline the drug development process (Al-Ishaq et al., 2019; Shamsudin et al., 2022; Aryal et al., 2024).

In this study, we employed the CADD platform to evaluate the antidiabetic potency of flavonoids, a class of natural compounds with well-documented bioactive properties. One of the best things about our method is that we used molecular docking to figure out how well flavonoids would bind to key molecular targets involved in the development of diabetes (Sahoo et al., 2021; Swain et al., 2022a; Swain and Hussain, 2022). The docking studies showed that some flavonoids have strong binding affinity and good interactions with these molecular targets, especially AKT1. This suggests that they could be useful as effective anti-DM agents, and a newer target might be

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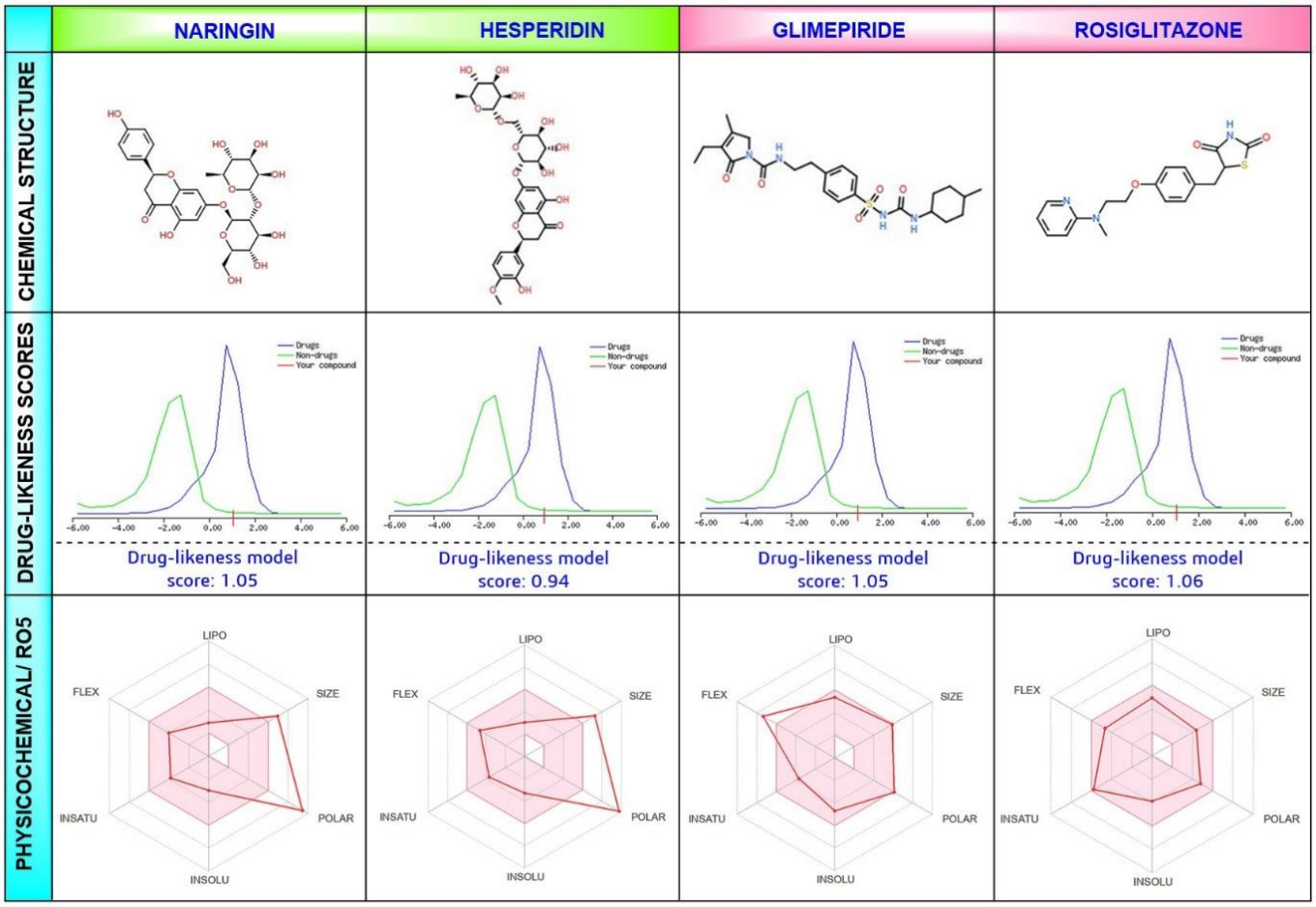

Figure 2. Graphical presentation of the drug-likeness and physicochemical profiles of two potential phytochemicals and two anti-diabetic drugs using computational tools

better for controlling DM. In addition to the prediction of physicochemical profiles, toxicity, bioavailability, and drug-likeness profiles, they describe the possible flavonoids, especially naringin, that can be studied further with a better chance of success in experiments (Sahoo et al., 2021; Swain et al., 2022a; Swain and Hussain, 2022). Future studies should focus on the experimental validation of the lead compounds identified in this study, as well as the elucidation of their mechanisms of action and therapeutic efficacy in preclinical and clinical settings. By bridging the gap between computational predictions and experimental outcomes, we can advance our understanding of flavonoid-based interventions for diabetes and ultimately improve patient outcomes in this global health epidemic.

Overall, the integration of bioinformatics tools holds tremendous potential for the discovery of novel antidiabetic flavonoids, offering a rational and cost-effective approach to identifying lead compounds for preclinical and clinical development. However, before formulating any computational-based hypotheses, researchers must first understand the advantages and disadvantages of each tool and be hands-on with programming and coding knowledge to get more reliable results (Sahoo et al., 2021; Swain et al., 2022a; Swain and Hussain, 2022). By leveraging computational methods to screen, prioritize, and optimize candidate molecules, researchers can accelerate the translation of promising flavonoids from bench to bedside, ultimately improving therapeutic outcomes for patients with diabetes.

Conclusion

This systematic CADD-based investigation highlights the considerable potential of flavonoids, particularly naringin, to serve as effective antidiabetic agents. After evaluating the docking or binding affinity of each target flavonoid and standard antidiabetic drugs against four target enzymes, we revealed that naringin exhibited the potential as per the docking scores: -10.6, -11.2, -9.1, -10.7 kcal/mol., with a drug-likeness score of 1.05 among the nine flavonoids, while glimepiride, with docking scores of -9.4, -11.1, -9.1, -10.8 kcal/mol., with a drug-likeness score of 1.25, emerged as the most promising antidiabetic drug among the five, indicating its potential for use in target-specific treatment. The inclusion of drug-ability profiles further reinforced the notion that flavonoids possess favorable drug-ability profiles for mainstream use. However, the computational study needs to be validated in

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in vitro and in vivo models individually, and it could be used ingeniously as a synergetic approach for a better treatment option. The CADD platform may be considered a cost-effective platform for accelerating modern drug discovery by locating bioactive candidates at the preliminary stage, thereby improving DM management through natural products.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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