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Identification of suitable flavonoids as insulin degrading enzyme inhibitors through *in-silico* approach

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Flavonoids, diabetes, insulin, docking, IDE (insulin degrading enzyme).

ABSTRACT
The present work is aimed to identify the inhibitors for insulin-degrading enzyme (IDE) from plant secondary metabolites through *in-silico* studies. IDE is a protease that cleaves insulin and other bioactive peptides such as amyloid-β. IDE is the important drug target for diabetes because IDE is the principal insulin-degrading protease *in vivo*, IDE inhibitors should enhance insulin signaling and thus have efficacy in relevant animal models of diabetes and also in therapy. The *in-silico* absorption distribution metabolism elimination screening was carried out to find out the drug likeness properties of selected flavonoids. *In-silico* molecular docking simulations have been performed to positional phytoconstituents into the preferred binding site of the protein receptor IDE, to predict the binding modes, the binding affinities and the orientation of all ligands. The docking studies revealed that all compounds showed good docking score. *In-silico* molecular docking simulations have been performed to positional phytoconstituents into the preferred binding site of the protein receptor IDE, to predict the binding modes, the binding affinities and the orientation of all ligands. The docking studies revealed that all compounds showed good docking score. The prediction of the binding affinity of a new compound to an identified target is a significant parameter in the development of a new drug. It is found that the flavonoids **quercetin, genistein, wogonin, isorhamnetin and luteolin** had drug like properties **rutin and Diosmin** are in good bioavailability radar and **diosmin, wogonin and flavilium** elicit a higher binding affinity with IDE.

INTRODUCTION

Diabetes results when the pancreas doesn't really release adequate insulin or if the body does not use the insulin that is released (Figs. 1 and 2). Untreated diabetes may cause long-term harm to a range of biological systems, including blood vessels and neurons. Insulin plays a main role in the metabolism of glucose. Insulin-degrading enzyme (IDE) is a thiol-sensitive zinc-metallopeptidase that has been linked to the development of numerous diseases, including type 2 diabetes. *In vivo*, IDE is the most important insulin-degrading protease, and inhibiting it is a simple way to increase insulin activity, both experimentally and potentially medically. Regardless of the availability of peptide-derived hydroxamic acid inhibitors, there is a problem. Because of its large molecular weight (750 da) and peptidic composition, it is particularly suitable for *in vivo* research (*t*1/2 of 9 minutes in mice). Despite decades of research, there is still a considerable need for powerful, selective, and long-lasting small molecule research compounds that block IDE with target specificity and high potency. While looking for small compounds that inhibit IDEs, we came across a variety of flavonoids with anti-diabetic potential, including Quercetin, Rutin, Diosmin, Isoflavone, Wogonin, Genistein, Flavylium, Luteolin, and Isorhamnetin. Keeping all of the aforementioned perspectives in mind, we discovered an IDE inhibitor from the chosen flavonoids using structure-based *in silico* research (Fig.4).

METHODS AND MATERIALS

Using the SwissADME and PyRx software, experiments were carried out to identify potential flavonoids as IDE inhibitors.

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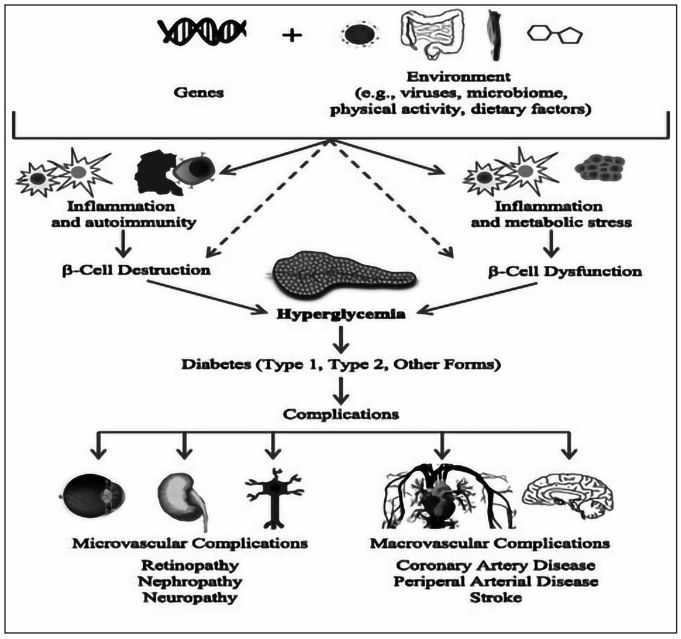


Figure 1. Pathogenesis of diabetes mellitus.

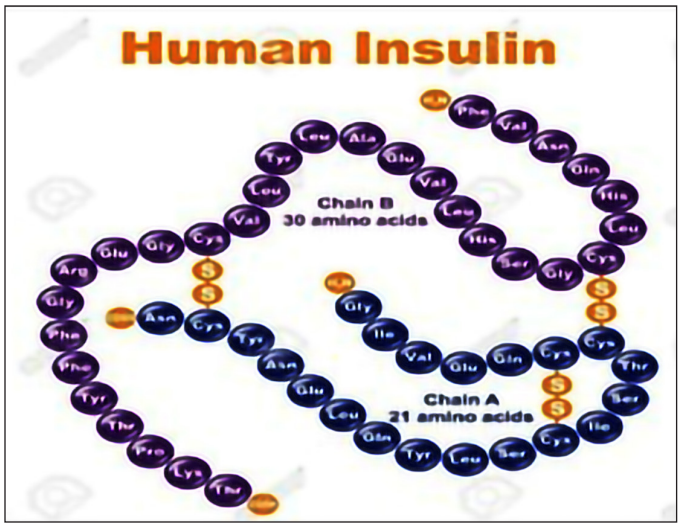


Figure 2. Structure of human insulin.

This chapter provided the resources as well as their working approach (Fig. 3).

Flavonoids selection

An extensive literature search was conducted in order to choose the appropriate flavonoids. Nine flavonoids were chosen and are displayed in Table 1.

Swiss ADME conducts in-silico absorption distribution metabolism elimination (ADME) investigations

Swiss ADME is a free online service that provides access to a variety of powerful and quick estimation techniques for physicochemical properties, medicinal chemistry friendliness, bioavailability radar, pharmacokinetics, and expert techniques

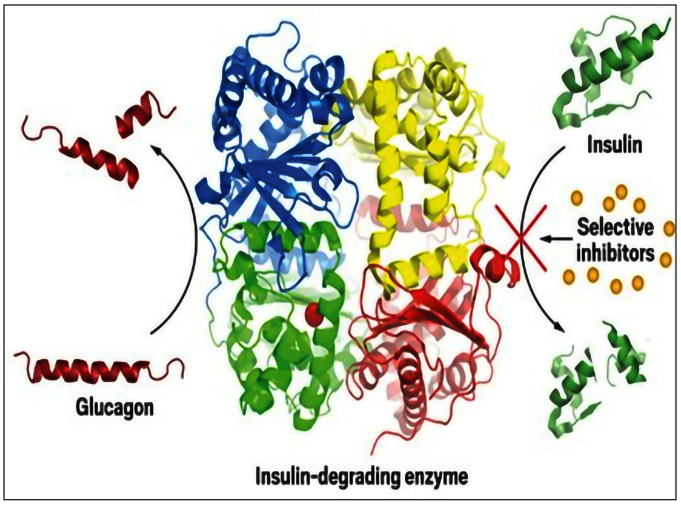


Figure 3. Different domains of IDE.

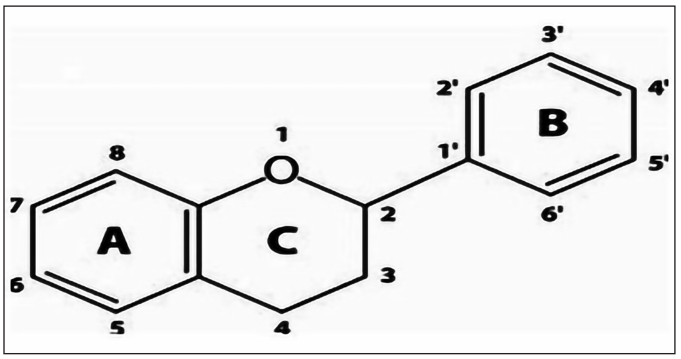


Figure 4. Basic scaffold of flavonoid.

like the ilogP, BOILED-EGG, and drug likeness. It was carried out with the use of a website, http://www.swissadme.ch. The acronym ADME stands for absorption, distribution, metabolism, and elimination (Gleeson *et al*., 2011). The Swiss ADME programme (www.swissadme.ch) produced by the Swiss Institute of Bioinformatics (http://www.sib.swiss) was accessible through a web server, and the Swiss ADME Submission page was shown in Google. It aids in the calculation of flavonoids' individual ADME behaviors. Simplified Molecular Input Line Entry System (SMILES) is used to prepare the list, and the results are provided (Mahanthesh *et al*., 2020; Yi *et al*., 2018) (Table 2).

Radar structure and bioavailability

Bioavailability radar, which gives a first glimpse, may be used to access the drug similarity of desirable compounds. The current study is concerned with many physicochemical characteristics, such as size, flexibility (nrotb flexibility), Polar [topological polar surface area TPSA) polarity], Insolu (Insolubility), Lipo (Lipophilicity), acceptors of H-bonds donors of H-bonds, molecular reactivity, gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeation, CYP2D6 antagonist, Lipinski infractions, Pan-assay interference compounds (PAINS) warnings, flavonoids' synthetic accessibility (Table 4).

Table 1. Selected flavonoids for the *in-silico* study.

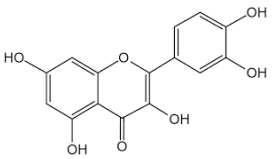
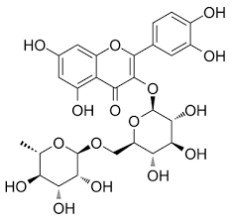
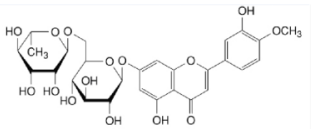
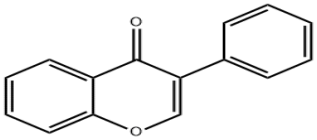
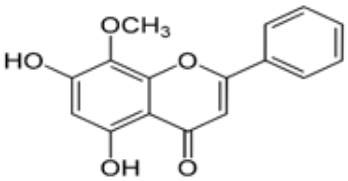
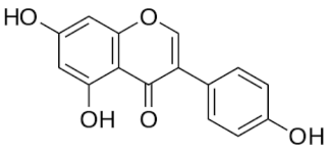
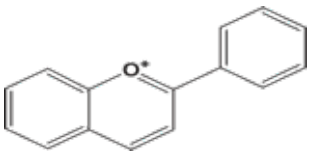
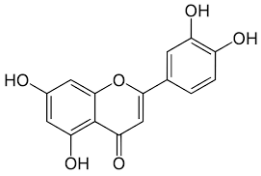
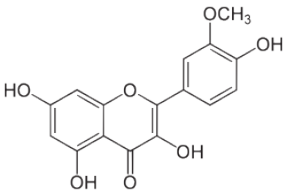
S. No.	Name of the plant	Part of the plant	Name of the compound	Structure	Uses
1.	*Euphorbia guyoniana*	Aerial leaf	Quercetin		a. Antidiabetic b. Inhibit the oxidative stress *in-vitro* and *in-vivo*
2.	*Euphorbia tirucalli*	Aerial leaf	Rutin		a. Antidiabetic b. Antioxidant
3.	*Scrophularia nodosa*	Root	Diosmin		a. Antihypertensive b. Antidiabetic
4.	*Glycine max*	Root and Seeds	Isoflavone		a. Cardiovascular disease b. Antidiabetics
5.	*Scutellaria baicalensis*	Root	Wogonin		a. Anticonvulsant b. Anti-hepatitis
6.	*Genista tinctoria*	Flowering twigs	Genistein		a. Antidiabetics b. Breast cancer
7.	*Vaccinium corymbosum*	Fruits	Flavylium		a. Anti-oxidant
8.	*Euphorbia lunulata*	Whole plant, roots	Luteolin		a. Anti-HBV b. Antidiabetics
9.	*Euphorbia hirta*	Aerial leaf	Isorhamnetin		a. Antiviral b. Oxidative stress

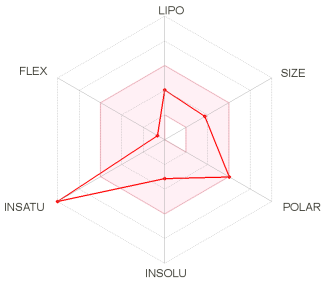
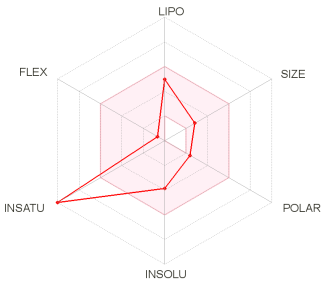
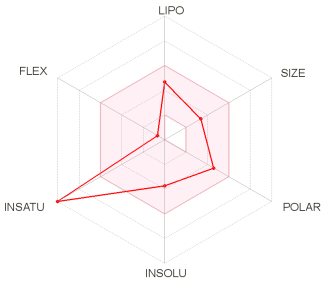
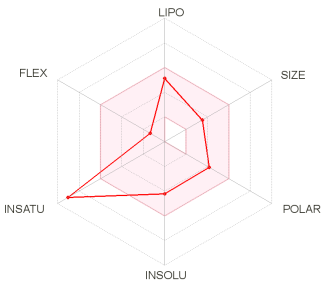
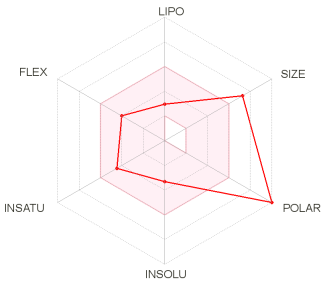
Table 2. Molecular properties of selected flavonoids.

Name of the compound	Canonical SMILES	Formula	Molecular weight	nrtob	H-bond acceptors	H-bond donors	Molar refractivity	TPSA
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)0	$C_{15}H_{10}O_7$	302.24	1	7	5	78.04	131.36
Isoflavone	C1=CC=C(C=C1)C2=COC3=CC=CC=C3C2=O	$C_{15}H_{10}O_2$	224.25	1	2	0	65.5	26.3
Genistein	C1=CC(=CC=C1C2=COC3=CC(=CC(=C3C2=O)O)O)O	$C_{15}H_{10}O_5$	270.24	1	5	3	73.99	90.9
Wogonin	COC1=C(C=C(C2=C1OC(=CC2=O)C3=CC=CC=C3)O)O	$C_{16}H_{12}O_5$	284.26	2	5	2	78.46	79.9
Rutin	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O	$C_{27}H_{32}O_{16}$	610.52	6	16	10	141.38	269.43
Isorhamnetin	COC1=C(C=CC(=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O	$C_{16}H_{12}O_7$	316.26	2	7	4	82.5	120.36
Diosmin	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=CC(=C4C(=C3)OC(=CC4=O)C5=CC(=C(C=C5)OC)O)O)O)O)O)O)O)O	$C_{28}H_{32}O_{15}$	608.54	7	15	8	143.82	238.2
Luteolin	C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O	$C_{15}H_{10}O_6$	286.24	1	6	4	76.01	111.13
Flavylium	C1=CC=C(C=C1)C2=[O+]C3=CC=CC=C3C=C2	$C_{15}H_{11}O^+$	207.25	1	1	0	66.06	13.14
5-Fluro-2-(2-morpholino-5-(morpholinosulfonyl) phenylbenzo[d] isothiazole-3(2H)-one or ML 345	C1COCCN1C2=C(C=C(C=C2)S(=O)(=O)N3CCOCC3)N4C(=O)C5=C(S4)C=CC(=C5)F	$C_{21}H_{22}FN_3O_5S_2$	479.5	4	7	7	126.4	117.7
Limits	--	--	>500	>20	>10	>5	40–130	20–200 A^o

Table 3. Pharmacokinetic properties of selected flavonoids.

Name of the compound	XLOGP3	ESOL Class	GI absorption	BBB Permeation	CYP2D6 inhibitor	Lipinski violations	PAINS alert	Synthetic accessibility
Quercetin	1.54	Soluble	High	No	No	0	1	3.23
Isoflavone	3.07	Soluble	High	Yes	No	0	0	2.86
Genistein	2.67	Soluble	High	No	No	0	0	2.87
Wogonin	3.49	Moderate Soluble	High	No	No	0	0	3.15
Rutin	−0.33	Soluble	Low	No	No	3	1	6.52
Isorhamnetin	1.87	Soluble	High	No	No	0	0	3.26
Diosmin	0.14	Soluble	Low	No	No	3	0	6.48
Luteolin	2.53	Soluble	High	No	No	0	1	3.02
Flavylium	3.39	Soluble	High	Yes	No	0	0	2.78
5-Fluro-2-(2-morpholino-5-(morpholinosulfonyl) phenylbenzo[d]isothiazole-3(2H)-one or ML 345	1.64	Soluble	High	No	No	0	0	3.79
Limits	−0.7 to 5	--	--	--	--	0 to 1		0 to 10

Table 4. Results of biological radar for selected flavonoids.

SI. No.	Name of the compound	Biological radar
1.	Quercetin	
2.	Isoflavone	
3.	Genistein	
4.	Wogonin	
5.	Rutin	

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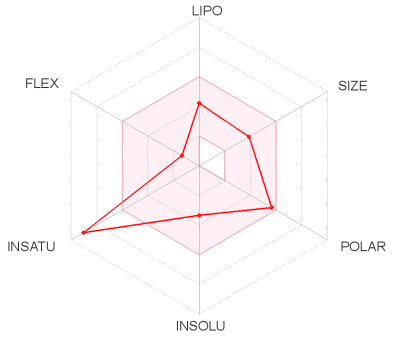
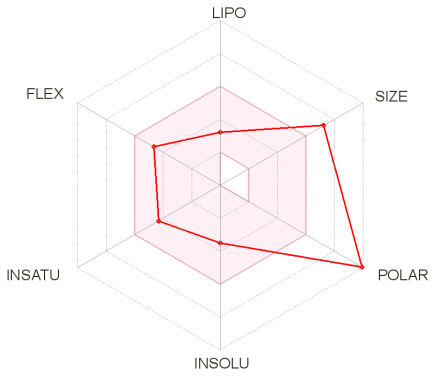
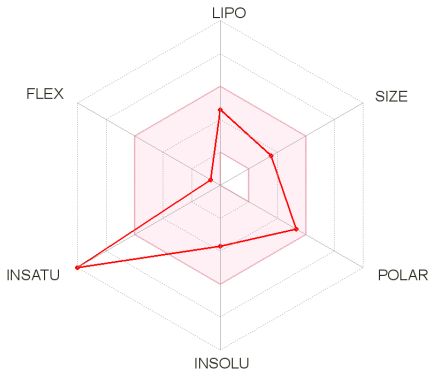
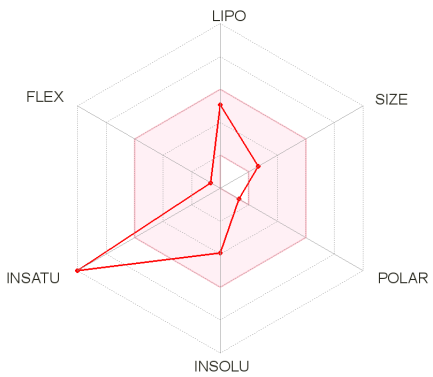
SI. No.	Name of the compound	Biological radar
6.	Isorhamnetin	
7.	Diosmin	
8.	Luteolin	
9.	Flavylium	

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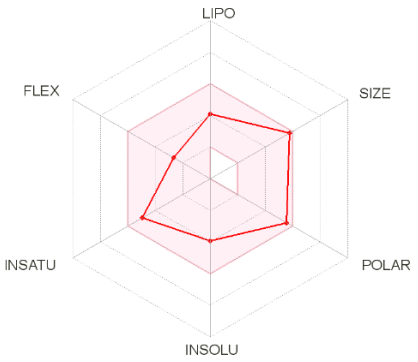
SI. No.	Name of the compound	Biological radar
10	5-Fluro-2-(2-morpholino-5-(morpholinosulfonyl) phenylbenzo[d]isothiazole-3(2H)-one or ML 345	

Spectrum of qualifications

Lipophilicity: XLOGP3 ranging from −0.7 to +5.0
MW ranges between 150 and 500 g/mol.
Polarity: TPSA of 20–130.0,
Solubility: log S less than 6 and
Flexibility: a maximum of nine rotatable bonds (Daina *et al*., 2017).

Molecular weight

It is the area that a molecule takes up in 3D space. The volume of any mass is the amount of space it takes up in 3D space. The molecular weight of the drug-like molecule is 200–600 g/mol (Wildman and Crippen, 1999).

Number of rotatable bonds—flexibility

The number of rotating bonds is the number of bonds that can freely rotate around each other. Bonds attached to a non-terminal heavy atom that is not part of a ring like amides, C–N bonds are excluded from the count due to their high rotation barrier. The drug-like structure has a total of 15 rotatable linkages (Egan *et al*., 2000).

Polarity (TPSA)

Polarity is the separation of electrical charge that results in an electric dipole moment with an oppositely charged end. Reduced TPSA corresponds to a higher permeation rate. The TPSA of the drug-like compound is 150 (Lombardo *et al*., 2003).

Solubility

The solubility is determined by the solvent employed and also by the ambient pressure and temperature. When a medicine's maximum dose is soluble in 250 ml or less of aqueous media with a pH range of 1–7.5, then it is extremely soluble (Cheng, 2007; Yalkowsky and Valvani, 1980).

The Swiss ADME includes the following methodologies for predicting water solubility: Each value that is predicted is calculated using the log of molar solubility in water (log S). In addition, Swiss ADME provides solubility in mg/ml and mol/l units as well as qualitative solubility classes (Lipinski *et al*., 2001).

Lipophilicity

Lipophilicity has a major role in drug discovery and design and may be measured experimentally as partition coefficients (log P) or distribution coefficients (log D). Log P represents the partition equilibrium of a unionized solute in the presence of an immiscible organic solvent and water. The bigger the log *p* values, the stronger the lipophilicity (Moriguchi *et al*., 1994).

The five models supplied by Swiss ADME to obtain the lipophilicity character in a chemical are as follows: XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP.

XLOGP3. It is an atomistic approach that includes remedial measures and a knowledge-based library. The XLOGP of the drug-like molecule ranges between 2 and 5.

WLOGP. It involves the use of a purely atomistic technique based on a fragmentary system.

MLOGP. It is a topological approach archetypal based on a linear connection with 13 molecular descriptors incorporated.

SILICOS-IT. It is a haphazard technique based on 27 pieces and 7 topological descriptors.

ILOGP. It is a physics-based technique that relies on solvation-free energies in n-octanol and water derived using the generalized-born and solvent-accessible surface area model. The mean value anticipated by the five recommended approaches is log P o/w (Darvas *et al*., 2002).

Acceptors of H bonds and donors of H bonds

Hydrogen bonds form when a hydrogen atom is connected to a tiny, extremely electronegative atom and another small, very electronegative atom with an unshared electron pair. Aliphatic fluorine, oxygen, and nitrogen are examples of H-bond acceptors, while all nitrogens and oxygens with at least one hydrogen are examples of H-bond donors. The drug-like molecule has a 10 H-bond acceptor and a 5 H-bond donor (Di *et al*., 2012).

Molecular reactivity

It is a measure of the overall polarizability of a substance that is impacted by the index of refraction, temperature, and pressure. The drug-like molecule's molar refractivity ranges from 40 to 130 (Brito Sanchez *et al*., 2015).

Absorption in the GI tract

Drugs are absorbed from the GI tract via active transport or passive transport. The most important mechanism is passive diffusion, which involves transporting drugs from the mucosa to the circulation along a concentration gradient. The rate of transfer is influenced by the concentration gradient, molecular-weight lipid solubility, molecular weight, and permeability. The epithelial cells act as a lipid barrier, allowing lipid-soluble molecules through but blocking highly ionized, water-soluble compounds.

Permeation of the BBB

BBB penetration is a statistic for determining if a drug crosses the BBB. Most drugs must not cross the BBB if the goal is unrelated to the neurological system.

CYP2D6 antagonist

One of the most significant enzymes responsible for the breakdown of xenobiotics in the system is CYP2D6, a component of the cytochrome P450 blended oxidase system. It converts and eliminates roughly 25% of medically used drugs by adding or removing functional groups such as demethylation, hydroxylation, and decarboxylation. CYP2D6 also activates a number of prodrugs. CYP2D6 in the brain and liver metabolizes and converts endogenous chemicals such as neurosteroids, hydroxytryptamines, and both m- and p-tyramine into dopamine (Ogu and Maxa, 2000).

Lipinski infractions

Lipinski's rule of five (RO5) is a thumb rule for identifying whether a chemical compound with a certain pharmacological or biological activity has the chemical and physical qualities to be an orally active medication in humans. It is also known as Pfizer's RO5. According to the rule, most "drug-like" molecules contain a molecular weight of 500, 5 hydrogen bonds, log p = 5, and 10 hydrogen bond acceptors and donors. Molecules that breach more than one of these parameters may have bioavailability issues. Because the boundary values are 5, 500, 2 × 5, and 5, the rule is known as the "Rule of 5" (Lipinski *et al*., 1997).

PAINS warnings

PAINs are chemical substances that often produce false positives in high-throughput screening. Instead of affecting a specific target, PAIN frequently responds non-specifically to a broad spectrum of biological targets (Baell and Holloway, 2010).

In-silico molecular docking research

Materials and devices

In modern drug design molecular scenarios, molecular docking is used to investigate the connections between target components by detecting the relationship between the target lead molecules and ligand binding with its protein. *In silico* research was carried out using bioinformatics approaches. Offline programming tools are employed: the Marvin sketch, the Protein Data Bank (PDB) (www.rcsb.org/pdb), and the PubChem database. The molecular docking studies are done with PyRx 0.9, which may be found at https://pyrx.sourceforge.io/.

Protein preparation

The offline software PDB was used to get the human IDE inhibitor complex (PDB: 3E4A) with a resolution of 2.60 AO, and Swiss PDB Viewer was used to save energy (Fig. 5).

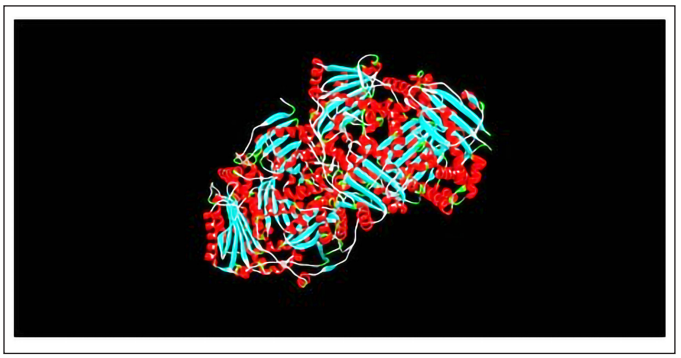
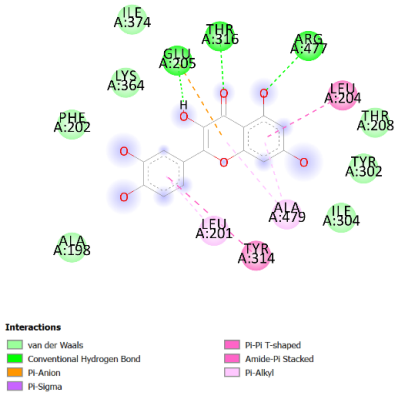
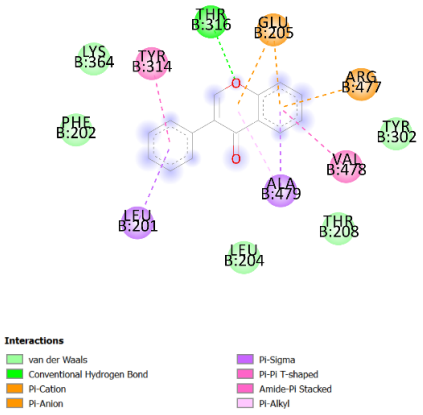
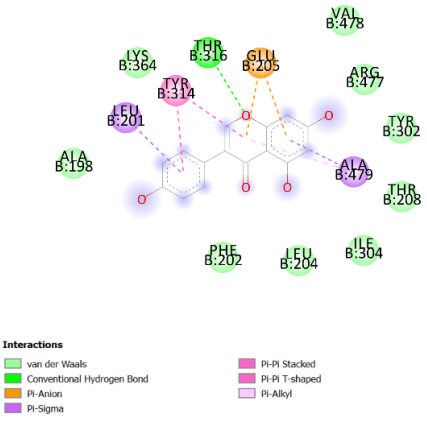


Figure 5. 3D structure of protein.

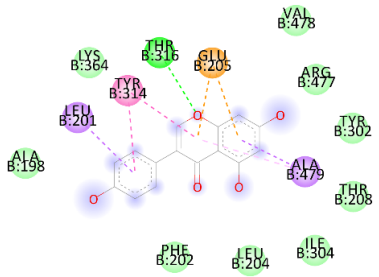
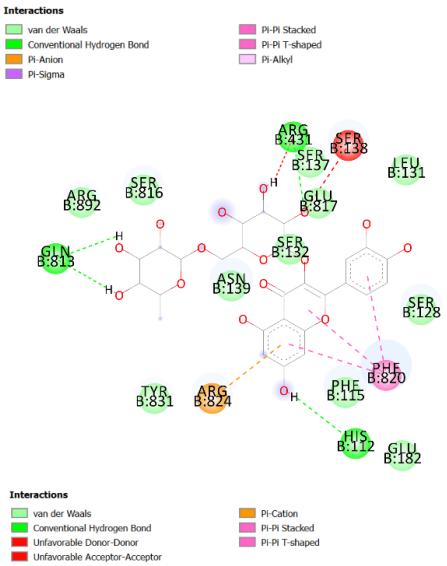
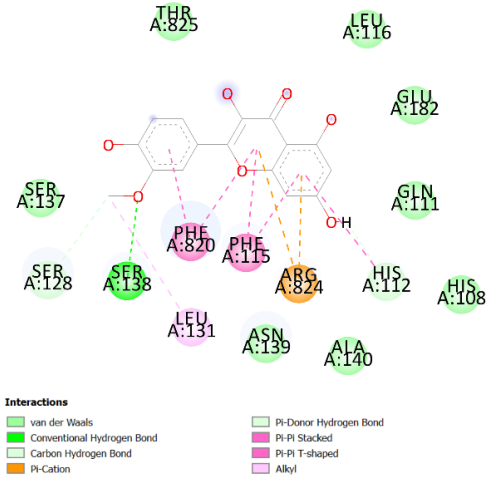
Table 5. Binding energies of selected flavonoids.

Name of the compound	Binding energy (kcal/mol)
Quercetin	−9.1
Isoflavone	−9.1
Genistein	−9.1
Wogonin	−9.6
Rutin	−8.8
Isorhamnetin	−8.8
Diosmin	−10.3
Luteolin	−8.9
Flavylium	−9.3
5-Fluoro-2-(2-morpholino-5(morpholinosulfonyl)phenyl)benzo[d]isothiazol-3(2H)-one or ML 345 (std)	−9.2

Table 6. 2D interactions of selected flavonoids.

SI. No.	Name of the compound	2D Interaction
1.	Quercetin	
2.	Isoflavone	
3.	Genistein	

Continued

SI. No.	Name of the compound	2D Interaction
3.	Genistein	
4.	Rutin	
5.	Isorhamnetin	

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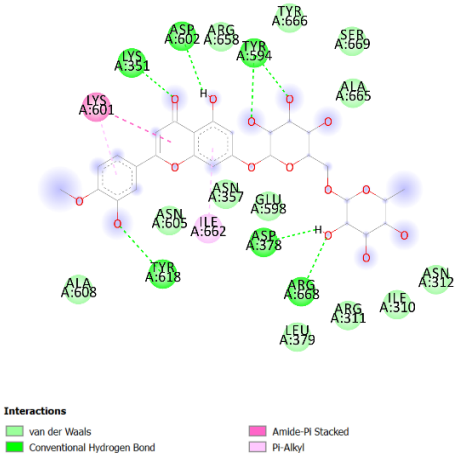
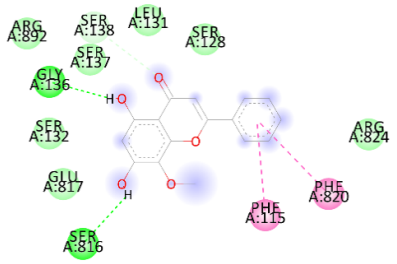
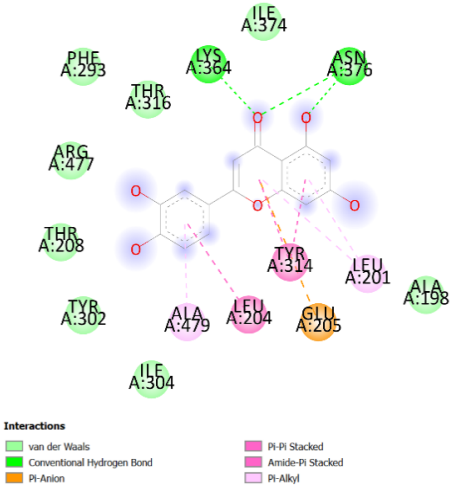
SI. No.	Name of the compound	2D Interaction
6.	Diosmin	
7.	Wogonin	
8.	Luteolin	

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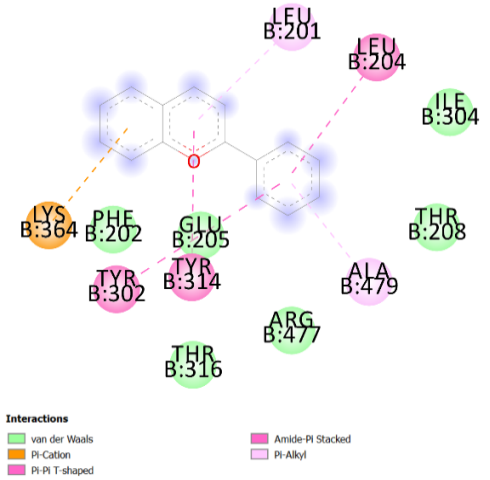
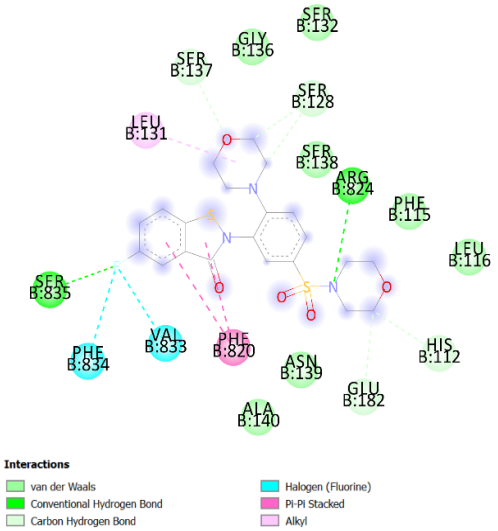
SI. No.	Name of the compound	2D Interaction
9.	Flavylium	
10.	5-Fluoro-2-(2-morpholino-5-(morpholinosulfonyl)phenyl) benzo[d]isothiazol-3(2H)-one or ML 345	

Active site identification

Protein–Ligand Interaction Profile https://plip-tool.biotec.tu-dresden.de/plipweb/plip/index A Google offline tool is used to determine the presence of active amino acids in a protein. As a consequence, we find the active amino acid in the protein.

Ligand preparation

Using the Marvin sketch approach, the molecules are represented in 2D and 3D. After designing the molecule, the structure was optimized in 3D in Marvin Sketch and saved as a PDB file.

Simulation of molecular docking

PyRx software was used to conduct molecular docking experiments, yielding accurate predictions and conformations for ligands and their target receptor proteins, as well as the complexes that formed. PDB ID: 3E4A for human IDE inhibitor complex with a resolution of 2.60 A0 was obtained. The docking stimulations are carried out in accordance with the docking procedure, which includes the following steps: Create the binding site and binding pocket in a Molecule Project, dock ligands in a molecular table, and analyze the docking data. To guarantee the authenticity of ligand orientations and sites derived from molecular docking research, redocking was utilized to check the docking procedures and parameters employed. Hydrogen bonds established with amino acids via group interaction atoms and docking scores are used to predict the affinities, interaction modes, and location of docked flavone derivatives in the protein-receptor active site. PyRx 0.9 was used for the docking investigation. PyRx is a Python programming language that can run on anything from a PC to a supercomputer. PyRx is used for molecular docking and determining the affinity of ligands and proteins. PyRx, a docking programme based on structure, was employed to detect all nine flavonoids for IDE (PDB: 3E4A). Furthermore, energy-saving ligands form beneficial interactions. The mmff94 force field was used to do the minimization in 200 steps with an root mean square gradient of 0.1, and the ligands were changed to Protein Data Bank, partial charge (Q) and atom type (T) format. selecting the

"macromolecule" that will establish the protein's binding location. Using bound ligand binding sites, the docking active site was generated. Using a molecular window, all generated ligands were virtually tested on the chosen active site. The PyRx score was used to categorize each ligand's binding affinity.

RESULTS

ADME simulations *in silico*

The drug likenesses of selected phytoconstituents were determined by analyzing their physicochemical and pharmacokinetic characteristics using Swiss ADME and tabulating the findings in Table 1. The water solubility of the medicine is regarded as the most essential criterion when assessing its bioavailability. The chosen flavonoids were soluble, except for wogonin, which is moderately soluble. XlogP3 calculates a molecule's lipophilicity and shows partition co-efficient values (logarithms) of compounds in an n-octanol/water system. It is a critical parameter that influences drug bioavailability, membrane permeability, distribution, and clearance routes. This characteristic is also important in the pharmacological and toxicological aspects of medicines. All of the produced compounds had XlogP3 values that were less than five. The polar surface area of the chemical has an inverse association with human intestinal absorption, and all of the chosen flavonoids, with the exception of rutin, had values less than 200, indicating strong absorption. If the goal is not connected to the neurological system, most medications must not cross the BBB. The chosen flavonoids, with the exception of isoflavone and flavone, would not cross the BBB. The total number of rotatable bonds is 1–7, demonstrating the versatility of all of the flavonoids chosen. Except for rutin and diosmin, all of the compounds followed the Lipinsky RO5.

Radar for chemical structure and bioavailability

The bioavailability radar quickly assesses drug-likeness. The six physicochemical properties evaluated are lipophilicity, solubility, size, polarity, flexibility, and saturation. A physicochemical range was set on each axis using descriptors derived from references and presented as a pink zone where the molecule's radar plot must fall entirely to be deemed drug-like in Table 3. The pink zone denotes the optimal range for each property. All of the compounds, with the exception of rutin and diosmin, have a high bioavailability.

Molecular docking research

Binding affinity characteristics were used in PyRx to choose the optimal "HITS" and compared to the known inhibitor, curcumin. The energy of the interaction between the protein and the ligand is referred to as "PyRx binding energy." This number clearly shows the amount to which proteins and ligands interact. The binding energies of diosmin, wogonin, and flavilium (−10.3 to 9.6 and −9.3 kcal/mol, respectively) were lower than those of the reference compound ML-345 (−9.1 kcal/mol), showing that these three compounds had a stronger affinity for IDEs (Table 5). The energies of the other compounds were likewise close to those of the reference compound, ML-345. The comparative investigation of receptor-ligand interactions with the active amino acid residues of IDE validated the enhanced binding energies of all drugs. The primary non-bonded interactions of these two compounds, such as hydrophilic, hydrophobic, and pi-pi interactions, were examined and compared to the standard reference ML-345. The findings are shown in Tables 6–8.

CONCLUSION

IDE is a protease that degrades insulin as well as other bioactive peptides, including amyloid. IDE has been related to Alzheimer's disease and type 2 diabetes in knockout and genetic investigations. As the most important insulin-degrading protease, IDE is a potential therapeutic target in diabetes.

As we all know, the first step of drug development is the characterization of the compounds being investigated as possible therapeutic candidates' ADME, and toxicity (T). Building mathematical models, known as "*in silico* screens," to predict ADMET properties simply from molecular structure is important to this attempt to reduce costs and development cycle time. ADME screening is used to determine the drug-like characteristics of chosen compounds.

To anticipate the binding modalities, binding affinities, and orientation of all ligands, *in-silico* molecular docking simulations were used to insert phytoconstituents into the preferential binding site of the protein receptor IDE. All compounds had an excellent docking score, according to the docking studies. The research reported in this publication demonstrates the importance of molecular docking techniques in the design and development of novel drugs with biological activity. The prediction of a novel compound's (a ligand's) binding affinity to a specified target (protein or enzyme) is an important metric in the development of a new medicine. Drug-like effects were found in the flavonoids quercetin, genistein, wogonin, isorhamnetin, and luteolin. Except for rutin and diosmin, all flavonoids have high bioavailability. The flavonoids diosmin, wogonin, and flavilium have a greater affinity for IDE.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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