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# Natural Remedies for Type 2 Diabetes: Evaluation of Phytochemicals with Bioinformatics and Molecular Approaches/ ADME/T Analysis

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**ABSTRACT**

Diabetes mellitus (DM) is a rapidly spreading chronic disease worldwide, affecting more than 10% of the adult population. Type 2 diabetes (T2DM) accounts for the vast majority of DM cases and can lead to serious health complications. While current treatment options such as α-Glucosidase inhibitors are effective, new alternatives need to be explored due to absorption problems and side effects. In this context, natural compounds have significant potential. The antioxidant, anti-inflammatory and insulin sensitizing effects of phytochemicals offer a promising option in diabetes management. The therapeutic efficacy of phytochemicals can be determined using computational approaches, systems biology and network pharmacology. In this study, the interactions between important diabetes target proteins (1RE1, 5NJK, 5VK1, 5WBL and 6B1E) and phytochemicals (Catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Retusapurpurin_A, Sakuranetin and Thevetiaflavone) were analyzed by molecular docking methods. The highest docking score values of -6.710, -6.173, -5.806 and -5.779 kcal/mol were found between 5VK1/catechine, 5NJK/3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin 6B1E/catechine and 5WBL/catechine, respectively. Furthermore, ADME/T calculations were performed to evaluate the pharmacokinetic properties of these compounds. The findings reveal the potential of natural compounds in the treatment of diabetes and aim at additional contributions of natural products to the treatment in the future.

***Keywords:*** Diabetes mellitus, Phytochemicals, Molecular docking, α-Glucosidase inhibitors, ADME/T analysis.

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## Introduction

DM is a leading cause of death, affecting 530 million people worldwide. This corresponds to a prevalence of 10.5% of adults aged 20-79 years who are caught. Diabetes is a rapidly growing chronic disease affecting more than 10% of adults worldwide and more than 90% of patients with diabetes have T2DM. Without effective intervention, the global prevalence of diabetes is projected to skyrocket to 643 million people by 2030 and 783 million by 2045 [1]. Diabetes mellitus (DM) is a chronic metabolic disease associated with insufficient and/or defective insulin production or insulin resistance [2]. It causes hyperglycemia, which is a high level of glucose in the bloodstream, a condition that, if left untreated, leads to severe damage to various organs such as the kidneys, eyes, blood vessels, heart and nerves [3]. α-Glucosidase inhibitor is a class of drugs clinically approved to help regulate the glycemic index in diabetic patients [4]. The enzyme α-Glucosidase metabolizes disaccharides and oligosaccharides in the gut, resulting in elevated blood glucose levels [5]. Molecules that inhibit α-glucosidase help improve blood glucose levels in type-2 diabetes patients [6]. Deoxynojirimycin, acarbose, voglibos and miglitol are the main drugs used to inhibit α-glucosidase to a large extent; however, these molecules have absorption problems and are associated with many side effects such as cramping, diarrhea and colonic gas production [7]. There is no permanent cure for diabetes, leaving patients dependent on a combination of healthy lifestyle choices and timely medication [8]. In this context, the investigation of natural products as a potential source of antidiabetic drugs holds great promise. Natural compounds have been used for medicinal purposes for thousands of years and offer unique advantages such as easy availability, minimal side effects and compatibility with conventional practices [9].

Recent studies have demonstrated that plant-derived phytochemicals found in fruits, vegetables, and spices offer promising alternatives for diabetes management. These naturally occurring compounds are well recognized for their ability to modulate various biochemical signaling pathways and can be seamlessly integrated into modern therapeutic approaches that target multiple physiological processes with a single drug. Flavonols and steroid saponins, in particular, exhibit antioxidant and anti-inflammatory properties, contribute to glycemic regulation, and enhance insulin sensitivity—key factors in diabetes management. These complex bioactive molecules function through multiple molecular pathways, exerting dual effects in modulating diabetes-related mechanisms [10]. Phytochemicals, particularly those derived from medicinal plants, have demonstrated significant potential in regulating intricate biochemical

networks. Recent research highlights that certain natural compounds, including flavonoids, alkaloids, terpenoids, and saponins, possess antioxidant and anti-inflammatory properties while also enhancing insulin sensitivity. These effects are mediated through direct interactions with protein signaling pathways involved in glucose metabolism. Furthermore, advanced computational techniques such as AI-assisted predictive modeling, systems biology, and network pharmacology facilitate the rapid screening of phytochemicals for their therapeutic potential. The integration of these cutting-edge tools enhances algorithmic performance, enabling a systematic evaluation of phytochemical interactions with key protein targets. This approach aids in the identification and prioritization of small molecules with superior specificity and binding affinity toward crucial drug targets in type 2 diabetes mellitus (T2DM). By merging traditional medicinal plant knowledge with modern diagnostic technologies, a more holistic and sustainable treatment strategy for diabetes can be developed. Such strategies reduce reliance on synthetic drugs, which may cause adverse effects, and contribute to patient-centered, long-term therapeutic solutions.

Propolis is a resinous substance collected by bees from plant sources and has various pharmacological uses thanks to its rich flavonoid and phenolic plant content. These products include plants such as Catechin, Thevetiaflavone and 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin. It is important to investigate the lives of these plants on diabetes and to maintain the anti-diabetic potential of propolis [11]. A study in rats induced with streptozotocin diabetes showed that catechin treatment lowered blood glucose levels and alleviated complications associated with diabetes. These effects are attributed to the antioxidant properties of catechin [12]. Although specific studies on thevetiaflavone are limited, it is known that the flavonoids contained in propolis generally exhibit anti-diabetic effects. Propolis supplementation has been shown to improve glycemic control and antioxidant status in patients with type 2 diabetes in randomized controlled trials [13]. Quercetin derivatives are known for their strong antioxidant and anti-inflammatory properties. The positive effects of propolis-derived flavonoids on obesity and diabetes have been demonstrated in cellular and animal models [14]. Catechine, Thevetiaflavone, and 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin were made to better understand the potential therapeutic effects of propolis on diabetes and to elucidate the mechanisms of these compounds. These studies support the role of propolis and its components in diabetes management.

The application of network pharmacology in phytoconstituent research has transformed conventional drug discovery processes, offering a more comprehensive methodology for identifying bioactive compounds. By integrating genetic, proteomic, and metabolomic data, scientists can construct molecular interaction networks that provide insights into protein and RNA interactions with plant-derived compounds or their respective targets within the human system. This systems biology-driven approach enables a deeper understanding of the mechanisms underlying phytochemical functions and their associated therapeutic benefits. Additionally, computational techniques such as molecular docking and dynamic simulations play a crucial role in predicting the binding affinity and stability of plant-derived compounds with target proteins. These technologies significantly enhance the efficiency of identifying lead drug candidates with the highest therapeutic potential [15].

In this study, we analyzed the interactions between key diabetes-related target proteins and crucial regulators of blood glucose levels, including CASP3 (1RE1), MDM2 (5VK1), AKT1 (5WBL), HSP90AA1 (5NJX), and dipeptidyl peptidase IV (PDB ID: 6B1E), alongside alpha-amylase and alpha-glucosidase, using a reference compound [16]. Additionally, ADME/T (Absorption, Distribution, Metabolism, Excretion, and Toxicity) calculations were performed to assess the pharmacokinetic and metabolic interactions of these molecules in the human body. The findings of this study provide valuable insights for the future development of novel antidiabetic drugs.

## Materials and Methods

### *Molecular Docking Calculation*

An important method used to identify molecules with high activity against biological materials is docking. The crystal structures of crystal structure of caspase-3 with a nicotinic acid aldehyde inhibitor (PDB ID: 1RE1, Method: X-ray Diffraction, Resolution: 2.50 Å), Human FKBP51 protein in complex with C-terminal peptide of Human HSP 90-alpha (PDB ID: 5NJX, Method: X-ray Diffraction, Resolution: 2.49 Å), Crystal structure of human MDM4 in complex with a 12-mer lysine-cysteine side chain dithiocarbamate stapled peptide inhibitor PMI (PDB ID: 5VK1, Method: X-ray Diffraction, Resolution: 2.69 Å), Crystal structure of the Arabidopsis thaliana Raptor in complex with the TOS peptide of human PRAS40 alpha (PDB ID: 5WBL, Method: X-ray Diffraction, Resolution: 3.35 Å) and The structure of DPP4 in complex with Vildagliptin (PDB ID: 6B1E, Method: X-ray Diffraction, Resolution: 2.69 Å), were retrieved from the PDB database (http://www.rcsb.org/pdb). Molecular docking calculations were performed with Schrödinger's Maestro Molecular modeling platform. First, the protein preparation module is used to prepare the protein and then the LigPrep module is used to prepare the molecule. The prepared proteins and molecules are also interacted with each other by Glide ligand docking (Schrödinger Release 2022-4).

### *ADME Analysis*

ADME analysis of catechin, epicatechin gallate, epigallocatechin gallate, gallic acid, and isoquercitrin was carried out using the Swiss ADME online tool (http://www.swissadme.ch/) and Admetlab (https://admetmesh.scbdd.com/). The canonical SMILES

representations of these compounds were generated using ChemDraw, followed by an assessment of their physicochemical properties. This evaluation included parameters such as lipophilicity, drug-likeness, pharmacokinetics, topological polar surface area (TPSA), the number of rotatable bonds, and compliance with Lipinski's rule of five [17]. Additionally, ADME/T analysis was conducted to investigate how these molecules interact within human metabolism and to assess their pharmacokinetic and toxicological profiles.

## Result and Discussion

Molecular docking calculations are commonly employed to complement experimental studies and to identify the active sites of molecules. Molecular modeling serves as a crucial tool for examining how molecules interact with proteins, providing insights into binding mechanisms through docking simulations [18]. This computational approach evaluates the affinity of molecules for specific protein targets, with stronger interactions typically correlating with higher biological activity. Various parameters are generated as a result of docking analyses, each offering unique insights into the molecular properties under investigation [19, 20]. Among these, the docking score is considered the primary determinant of molecular activity, as it reflects the strength and stability of the molecular-protein interaction. We can say that the lower the docking score value, the stronger the connection [21]. The values between Catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Retusapurpurin_A, Sakuranetin and Thevetiaflavone with docking score values of 1RE1, 5NJK, 5VK1, 5WBL and 6B1E proteins are given in Table 1.

Tablo 1. Catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Retusapurpurin_A, Sakuranetin and Thevetiaflavone with docking score values of 1RE1, 5NJK, 5VK1, 5WBL and 6B1E proteins

| | docking score values (kcal/mol) | | | | |
|---|---|---|---|---|---|
| | 1RE1 | 5NJK | 5VK1 | 5WBL | 6B1E |
| Catechine | -4.991 | -5.352 | -6.710 | -5.779 | -5.806 |
| 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin | -4.160 | -6.173 | -5.731 | -4.993 | -5.841 |
| Retusapurpurin_A | -4.419 | -5.518 | -5.626 | -5.578 | -4.340 |
| Sakuranetin | -4.360 | -5.358 | -5.410 | -4.849 | -5.377 |
| Thevetiaflavone | -4.837 | -5.726 | -6.095 | -5.183 | -5.364 |
| Acarbose | -5.855 | -6.647 | -4.892 | -6.593 | -6.538 |

In this study, the binding affinities of various bioactive compounds (Catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Retusapurpurin_A, Sakuranetin *and* Thevetiaflavone) with different protein targets (1RE1, 5NJK, 5VK1, 5WBL and 6B1E proteins) were examined using molecular docking analysis. Docking scores were calculated in terms of binding free energy (kcal/mol), with negative values indicating higher binding affinity. Docking scores express the binding energy (kcal/mol) of ligands to protein; more negative values indicate stronger binding affinity.

When the results of molecular docking analysis against 1RE1 protein are analyzed; Acarbose shows the strongest interaction with a binding energy of -5.855 kcal/mol. It can be said that Acarbose has a high binding affinity and is a suitable positive control for evaluating the activity of other compounds. Although Catechine (-4.991 kcal/mol) and Thevetiaflavone (-4.837 kcal/mol) have higher binding energy (less negative) compared to Acarbose, they show better binding compared to other compounds. This suggests that Catechine in particular may interact strongly with the 1RE1 protein. Retusapurpurin_A (-4.419 kcal/mol), Sakuranetin (-4.360 kcal/mol) and 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin (-4.160 kcal/mol) have lower binding affinity values. These compounds show weaker interactions than Catechine and Thevetiaflavone. However, binding scores below -4.0 kcal/mol suggest that these compounds may still show some affinity with 1RE1.

When the results of the molecular docking analysis against the 5NJK protein are analyzed; Acarbose (-6.647 kcal/mol) is the compound with the lowest binding energy, i.e. the molecule that shows the strongest interaction with the 5NJK protein. 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin (-6.173 kcal/mol) has the highest binding affinity among the other compounds and gives the best result after Acarbose. Although it has a lower affinity compared to Acarbose, it is thought that this compound may show a significant interaction with the 5NJK protein. Thevetiaflavone (-5.726 kcal/mol) has a high binding energy, suggesting that it could be a potentially effective ligand. Retusapurpurin_A (-5.518 kcal/mol), Sakuranetin (-5.358 kcal/mol) and Catechine (-5.352 kcal/mol) have close binding energies.

When the results of molecular docking analysis against 5VK1 protein are analyzed; Acarbose (-4.892 kcal/mol) is the compound with the weakest binding energy in this study. While it is generally expected to be the strongest binding compound, the compounds tested in this study appear to have higher binding affinity than Acarbose. This result suggests that some of the compounds may have stronger inhibitory potential than Acarbose. Catechine (-6.710 kcal/mol) has the lowest binding energy and shows the highest affinity for the 5VK1 protein. Thevetiaflavone

(-6.095 kcal/mol) also shows strong binding and ranks second. Catechine is the compound showing the strongest binding for the 5VK1 protein and can be considered as the best inhibitor candidate. Thevetiaflavone is the compound with the second highest binding affinity and could be a strong alternative inhibitor. Acarbose has the weakest binding energy, indicating that the tested compounds may be more effective inhibitors for the 5VK1 protein.

When the results of the molecular docking analysis against the 5WBL protein are analyzed; Acarbose (-6.593 kcal/mol) is the compound with the lowest binding energy and the molecule showing the strongest binding. The other compounds tested have higher binding energies and show lower affinities compared to Acarbose. Catechine (-5.779 kcal/mol) is the compound with the lowest binding energy and has the best binding affinity after Acarbose. Retusapurpurin_A (-5.578 kcal/mol) shows a similarly strong binding. These two compounds show better interaction with the 5WBL protein than the other compounds and can be considered as potential inhibitor candidates.

When the results of the molecular docking analysis against the 6B1E protein are analyzed; Acarbose (-6.538 kcal/mol) is the compound with the lowest binding energy and is the reference point as the compound showing the highest affinity for the 6B1E protein. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin (-5.841 kcal/mol) and Catechine (-5.806 kcal/mol) have the best binding affinity among the other compounds. These two compounds, although not as strong as Acarbose, can be considered as potential inhibitor candidates due to their high binding affinity. Sakuranetine (-5.377 kcal/mol) and Thevetiaflavone (-5.364 kcal/mol) have very close binding energies and show moderate binding affinity. Although these two compounds have lower binding energies compared to Acarbose and the strongest binding compounds, they may still have some inhibitory potential.

When the binding energies of molecular docking analyses with five different proteins (1RE1, 5NJK, 5VK1, 5WBL, 6B1E) are evaluated together; Acarbose has the lowest binding energy overall in terms of docking scores and shows the strongest binding with 5NJK (-7.012 kcal/mol) and 5WBL (-6.593 kcal/mol) proteins. It has the weakest binding affinity with the 5VK1 protein (-4.892 kcal/mol), meaning that for this protein the binding strength of other compounds is higher than Acarbose. These results suggest that Acarbose may be a potent inhibitor for 5NJK and 5WBL proteins, but may show lower inhibitory activity for 5VK1. Catechine shows the strongest binding with the 5VK1 protein (-6.710 kcal/mol) and binds much better than Acarbose. We can say that there is a strong binding between Catechine and 6B1E (-5.806 kcal/mol) and 5WBL (-5.779 kcal/mol) proteins. Catechine may be a better inhibitor than Acarbose, especially for the 5VK1 protein. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin has the lowest binding energy with 5NJK protein (-6.173 kcal/mol) and can be considered as a strong inhibitor for this protein. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin has variable binding affinity depending on the protein type. For the protein 5VK1 (-6.095 kcal/mol), Thevetiaflavone showed a relatively strong binding.

Acarbose has the strongest binding affinity with most proteins. Catechine and Thevetiaflavone have the best binding energy among the natural compounds tested and can be considered as potential inhibitor candidates. However, Catechine has stronger binding affinity for the 5VK1 protein. This suggests that Catechine may be a better inhibitor for this protein than Acarbose. Catechine has better binding affinity than other compounds in general. It has a higher inhibitory potential than Acarbose, especially for the 5VK1 protein and binds well with other proteins. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin showed high binding with 5NJK and 6B1E proteins, indicating that it may have inhibitory potential for these proteins. These findings should be supported by biological activity tests and ADMET assays. Especially the biological activity of Catechine and 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin should be tested experimentally.

Thevetiaflavone interacts with the target protein 1RE1 by forming one hydrogen bonds with the backbone residues Arg341. The hydroxyl (OH) group probably acts as a hydrogen bond donor and interacts with polar amino acids.

The carbonyl (C=O) group acts as a bond acceptor and provides bonds with polar groups in the protein. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin interacts with the target protein 5NJK by forming two hydrogen bonds and one Pi bonds with the backbone residues Arg53, Lys113 and Phe162. Catechine interacts with the target protein 5VK1 by forming five hydrogen bonds with the backbone residues Gln58, Gln71, Hıe54. Different OH groups Gln58 and Gln71 made two hydrogen bonds each. Catechine interacts with the target protein 5WBL by forming five hydrogen bonds with the backbone residues Asp352, Arg379, Asn334, Gln333, respectively. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin interacts with the target protein 6B1E by forming four hydrogen bonds and one pi bağı with the backbone residues Hıs 740, Asp709, Lys122, Lys 554 and Trp627, respectively. All 2D and 3D interactions are shown in Figures 1 and 2.

The presence of different groups in the catechine, epicatechin gallate, epigallocatechin gallate gallic acid and isoquercitrin may enhance their activity by modifying their physicochemical properties and pharmacokinetic parameters to increase their bioavailability and metabolic stability as well as their binding affinity to receptors.

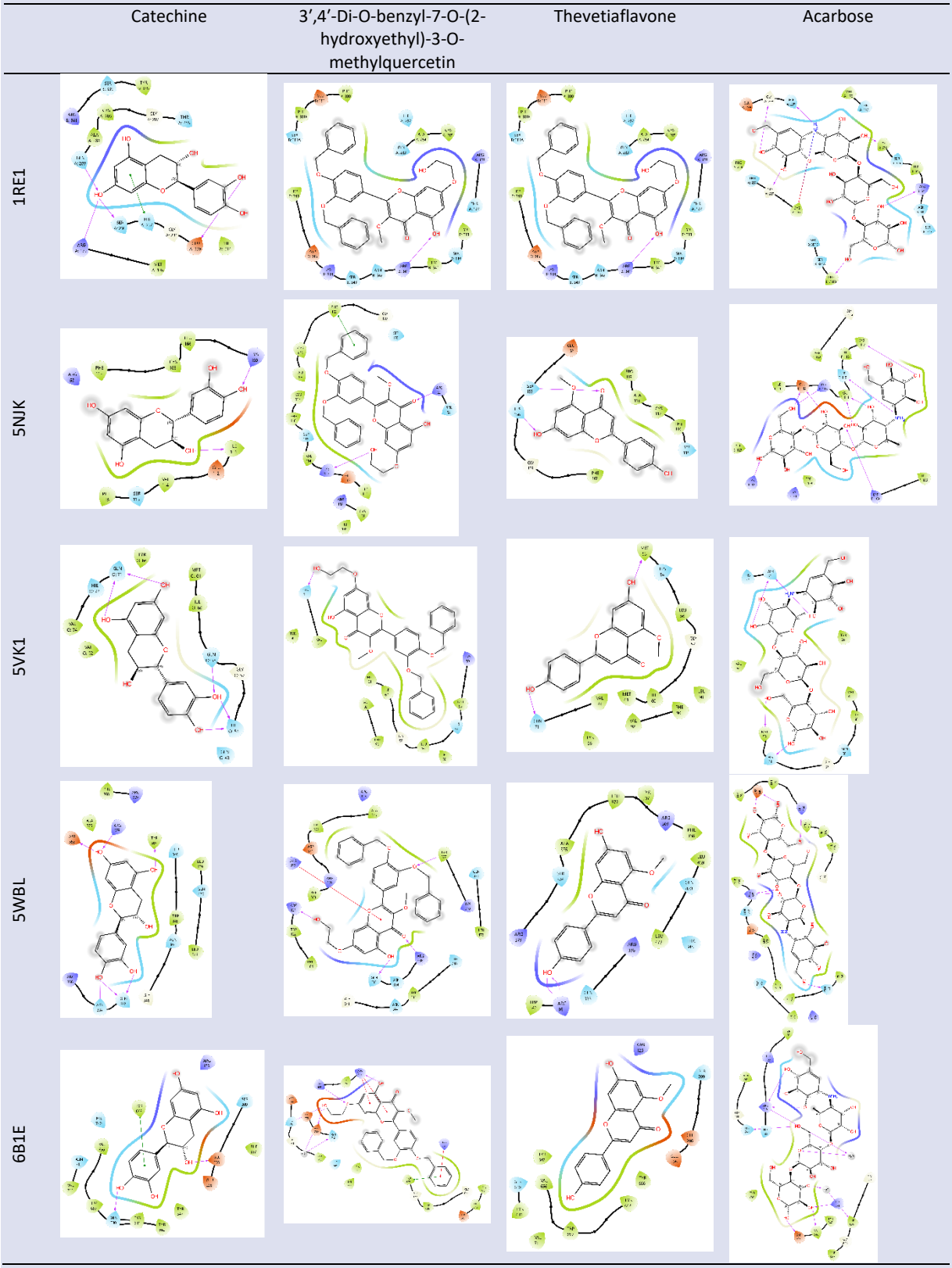



Figure 1. 2D bond interactions of catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Thevetiaflavone and Acarbose

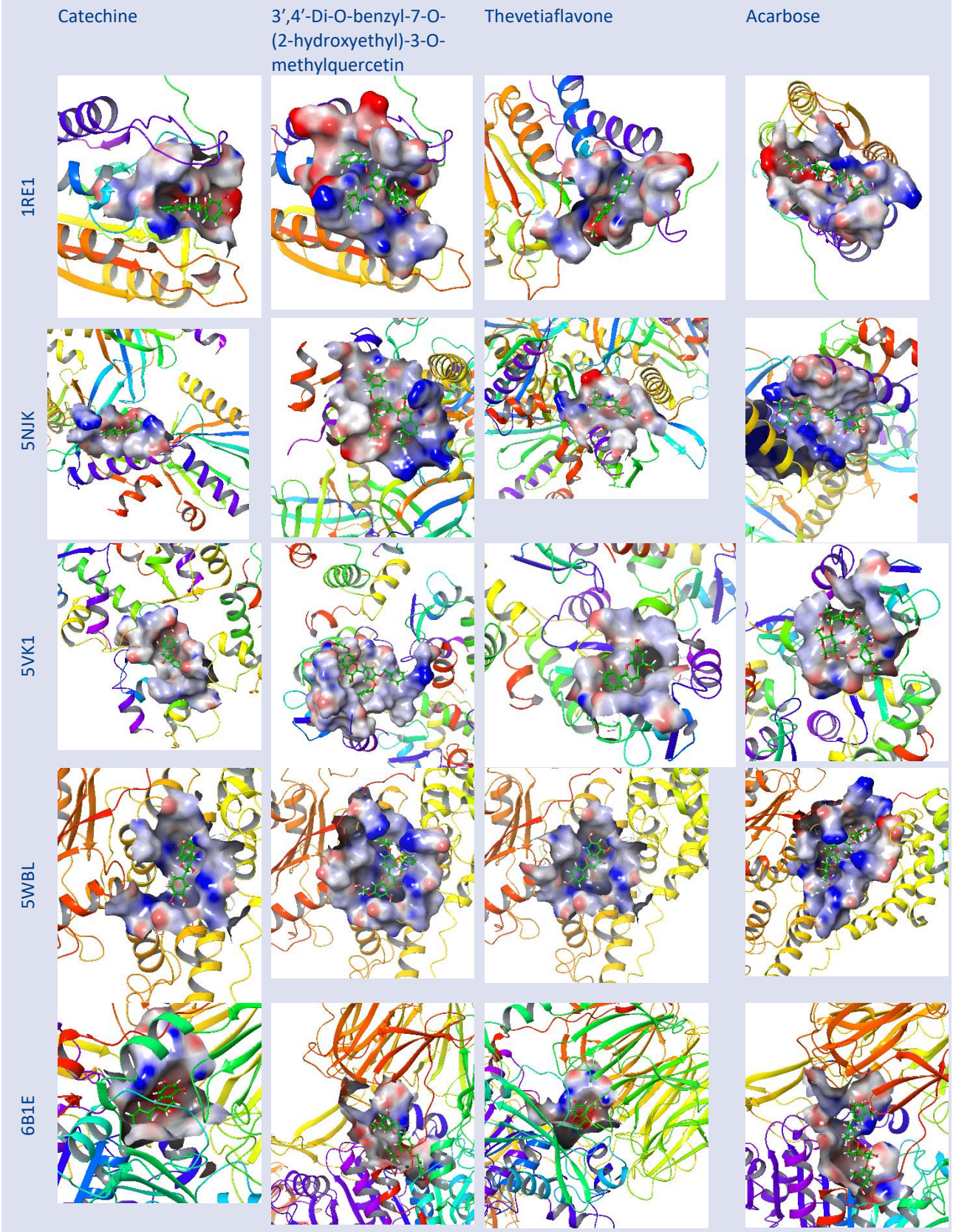



Figure 2. 3D bond interactions of catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Thevetiaflavone and Acarbose

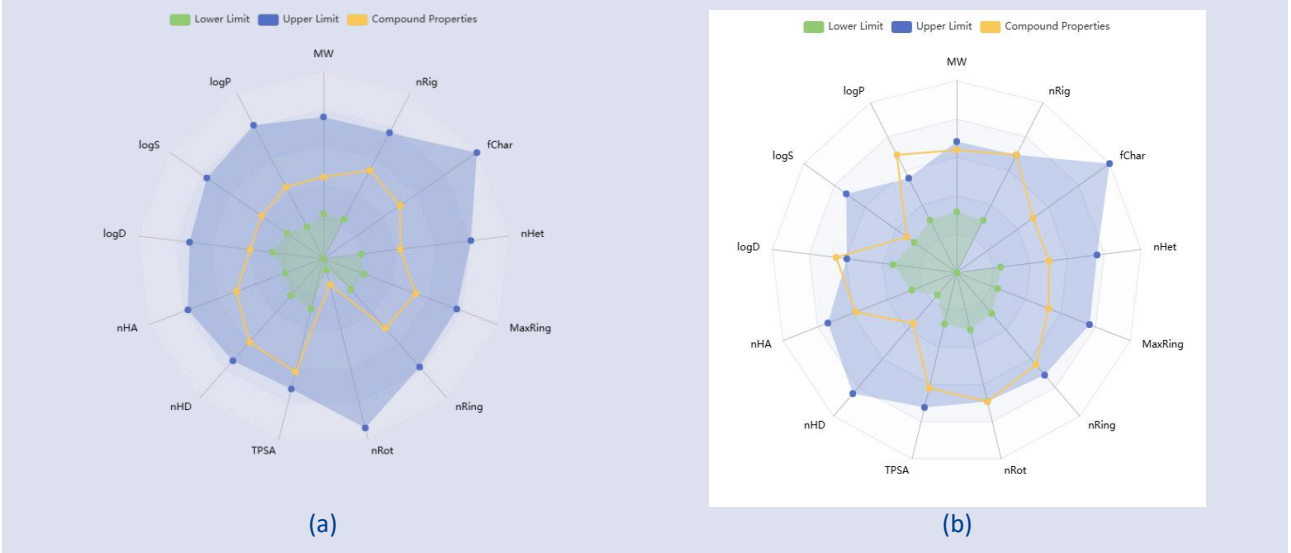
To evaluate the effects and interactions of the studied molecules within human metabolism, an ADME/T (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was conducted. This analysis provided insights into how these molecules are absorbed, distributed, metabolized, and eventually eliminated from the body, along with an assessment of their potential toxicity. By examining these parameters, a comprehensive understanding of the molecules' pharmacokinetic and toxicological properties was obtained. Many parameters that analyze the chemical properties of molecules are calculated, such as mol_MW (molar mass of molecules), Molecular Weight (MW), Volume (molecular volume), LogP (The degree of lipophilicity of the molecule), TPSA (Total Polar Surface Area, Refers to the polar surface area of the molecule, affects bioavailability), nRot (Number of rotationally free bonds), LogS (Degree of water solubility), nHA and nHD (Refers to the number of atoms that accept and give hydrogen bonds). The physicochemical and ADME properties of the catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Thevetiaflavone and Acarbose are given in Table 2.

The molecular weights of all compounds are in the range of 100-600 Da, within the accepted limits for drug-like molecules. Although the number of atoms capable of hydrogen bonding generally complies with Lipinski's rules, it exceeds the limit values in some compounds. In particular, catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Thevetiaflavone and Acarbose (nHA=12, nHD=8) may violate Lipinski rules due to its high hydrogen bonding capacity.

Table 2. Physicochemical and ADME properties of catechine, 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Thevetiaflavone and Acarbose

| | Catechine | 3',4'-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin | Thevetiaflavone | Acarbose | Optimal |
|---|---|---|---|---|---|
| Molecular Weight (MW) | 290.08 | 540.18 | 284.07 | 645.25 | 100-600 |
| Volume | 279.249 | 552.657 | 282.482 | 573.315 | |
| Density | 1.039 | 0. 977 | 1.006 | 1.125 | |
| nHA | 6 | 8 | 5 | 19 | 0-12 |
| nHD | 5 | 2 | 2 | 14 | 0-7 |
| nRot | 1 | 11 | 2 | 9 | 0-11 |
| nRing | 3 | 5 | 3 | | 0-6 |
| MaxRing | 10 | 10 | 10 | 4 | 0-18 |
| nHet | 6 | 8 | 5 | 6 | 1-15 |
| fChar | 0 | 0 | 00 | 0 | -1 |
| nRig | 17 | 30 | 18 | 24 | 0-30 |
| Flexibility | 0.059 | 0.367 | 0.11 | 0.375 | |
| Stereo Centers | 2 | 0 | 0 | 19 | <2 |
| TPSA | 110.38 | 107.59 | 79.9 | 321.17 | 0-140 |
| logS | -2.581 | -3.512 | -3.889 | 0.533 | |
| logP | 1.173 | 4.651 | 2.507 | -4.808 | 0-3 |
| logD7.4 | 1.537 | 3.465 | 2.45 | -3.652 | 1-3 |
| Lipinski Rule | ** | ** | ** | * | |
| Pfizer Rule | ** | ** | ** | ** | |
| GSK Rule | ** | * | ** | * | |

* Rejected **Accepted



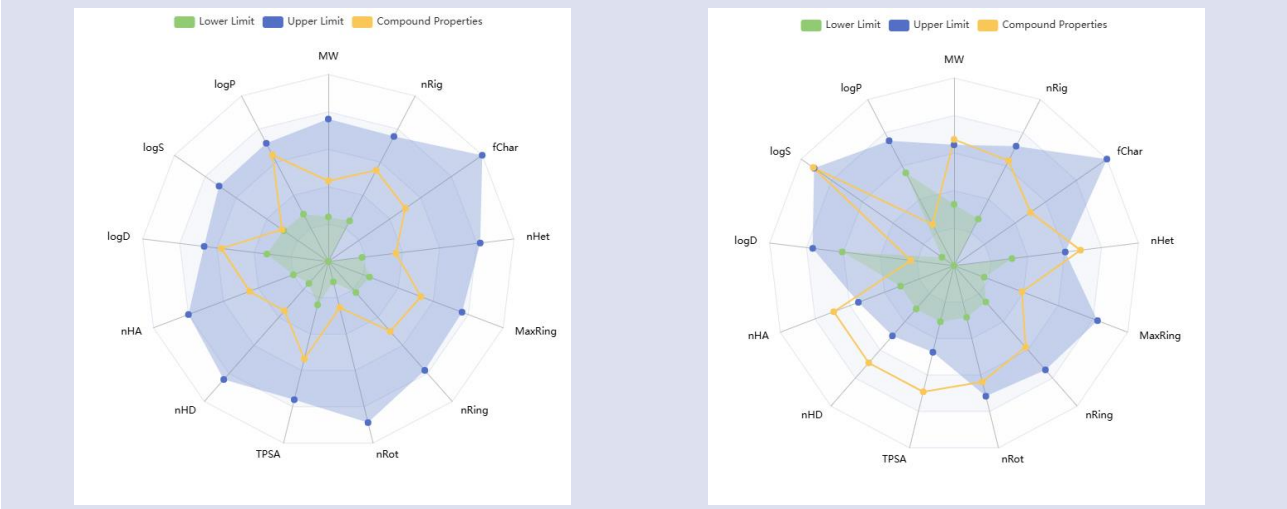



Figure 3. Radar graph showing the chemical structure and physicochemical properties of of catechine (A), 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin (B), Thevetiaflavone (C) and Acarbose (D)

Catechine (290.08 Da), Thevetiaflavone (284.07 Da) and 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin (540.18 Da) fall within this range. Acarbose (645.25 Da) exceeds the optimal limit and may be disadvantageous in terms of absorption due to the large molecular weight. The TPSA values for Catechine, 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Thevetiaflavone and Acarbose were 110.38, 107.59, 79.9 and 321.17, respectively. Acarbose (321.17 Å) may be difficult to pass through the cell membrane by passive diffusion due to its high TPSA value. The logP values of the compounds are in the range of 0-3 and are at acceptable levels in terms of drug design. This indicates that the lipophilic properties of the compounds are sufficient and membrane permeability may be appropriate. Although the water solubility (logS) of the compounds is relatively low for catechine (-2.581), 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin (-3.512), Thevetiaflavone (-3.889) and Acarbose 0.533) it is critical in terms of bioavailability. Catechine and Thevetiaflavone stand out as the most favorable compounds in terms of their pharmacokinetic properties. 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin can be considered even though its logP value is high.

## Conclusion

This study investigated the molecular docking interactions of various bioactive compounds, including Catechine, 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin, Retusapurpurin_A, Sakuranetin, and Thevetiaflavone, with five different protein targets (1RE1, 5NJK, 5VK1, 5WBL, and 6B1E). Acarbose served as a positive control due to its strong binding affinity. The results demonstrated that Catechine exhibited the highest binding affinity for the 5VK1 protein (-6.710 kcal/mol), indicating its potential as a strong inhibitor. Thevetiaflavone also displayed strong interactions with 5VK1, while 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin showed high affinity for 5NJK and 6B1E proteins. These findings suggest that these natural compounds could serve as promising inhibitors for their respective targets.

Hydrogen bonding and π interactions played a key role in stabilizing ligand-protein complexes, with Catechine forming multiple hydrogen bonds with 5VK1 and 5WBL. The results highlight the importance of structural features such as hydroxyl and carbonyl groups in enhancing binding affinity. However, to confirm these computational findings, biological activity assays and ADMET studies are necessary. In particular, Catechine and 3’,4’-Di-O-benzyl-7-O-(2-hydroxyethyl)-3-O-methylquercetin should be further evaluated for their potential inhibitory effects. These findings provide valuable insights into the development of natural inhibitors, contributing to future research in drug discovery and biotechnological applications.

## Conflicts of interest

The authors report no conflicts of interesr in this work

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