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Original Research Article

# Molecular Docking, ADME and SAR Analysis of 383 Phytochemicals in the Quest for Lead Antidiabetic Inhibitors Targeting *α-Amylase* and *α-Glucosidase* Enzymes

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## Abstract

**Purpose:** Diabetes mellitus remains a global health challenge, necessitating the exploration of safe and effective therapeutic agents. The inhibition of *α-amylase* and *α-glucosidase* enzymes plays a crucial role in controlling postprandial hyperglycemia. While synthetic inhibitors exist, they often cause gastrointestinal side effects, prompting the search for novel, naturally derived inhibitors. This study evaluates the molecular interactions of 383 phytochemicals, focusing on alkaloids, terpenes, and flavonoids, for their potential as lead antidiabetic compounds.
**Methods:** Molecular docking studies were performed using AutoDock Vina to assess the binding affinity of selected phytochemicals against human pancreatic *α-amylase* (PDB ID: 5EMY) and *α-glucosidase* (PDB ID: 2QMJ). The physicochemical and pharmacokinetic properties of the top-performing compounds were analyzed using SwissADME, following Lipinski's Rule of Five and Verber's rules. Structure-activity relationship (SAR) analysis was conducted to elucidate key functional groups responsible for enzyme inhibition.
**Results:** Flavonoids exhibited superior inhibitory potential, with binding affinities outperforming the standard inhibitor Acarbose. The most potent compounds, Amentoflavone (-9.5 kcal/mol), Hesperidin (-9.5 kcal/mol), Eriocitrin (-9.5 kcal/mol), and Diosmin (-9.4 kcal/mol), showed strong interactions with key amino acid residues. SAR analysis highlighted the significance of glycosylation and flavone / flavanol moieties in enhancing binding affinity. ADME analysis revealed favorable pharmacokinetic properties, with Amentoflavone demonstrating the highest synthetic accessibility and drug-likeness.
**Conclusion:** This study identifies flavonoids as promising dual inhibitors of *α-amylase* and *α-glucosidase*, with Amentoflavone emerging as a lead candidate for further development as a novel antidiabetic agent, contributing to the search for safer alternatives to conventional therapies.

**Keywords**: *Alpha-amylase*, *Alpha-glucosidase*, Diabetes, Structure-activity relationship, Flavonoids, Amentoflavone.



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## INTRODUCTION

The rising prevalence of Diabetes Mellitus, a syndrome of chronic hyperglycemia characterized by impaired carbohydrate, protein, and fat metabolism, poses global and socioeconomic health concern and therefore underscores the need for safe, innovative and affordable therapeutic strategies[1] particularly those targeting key enzymatic pathways involved in carbohydrate metabolism.

Such glucose level modulation can be achieved by inhibition of the enzymes α-amylase and *α-glucosidase* with the *α-amylase* enzyme being essential for catalyzing the hydrolysis of α-1,4-glycosidic bonds in starch and glycogen to maltose and dextrins while *α-glucosidase* hydrolyses the terminal non-reducing α-D-glucose residues from oligosaccharides and disaccharides, producing free glucose.[2] Inhibition of both enzymes reduces the rate of glucose production and concentration of glucose absorbed by the small intestine thereby preventing rapid spikes in glucose levels post-meal and avoiding high peaks.[3]

FDA approved drugs inhibiting these enzymes include Acarbose, Miglitol and Voglibose. Despite their ability to retard glucose absorption, they are accompanied by undesirable gastrointestinal side effects which impede their application[2] providing a basis for ongoing research and development of new treatments.

Studies have highlighted many bioactive plants' secondary metabolites belonging to classes such as alkaloids, phenols, anthocyanin, flavonoids, saponins, tannins, terpenes and coumarins as having hypoglycemic activity.[4]

In this study, we focus on the Alkaloids, Terpenes, and Flavonoids, being the most naturally abundant of the plant secondary metabolites. The Alkaloids, with over 12,000 identified compounds,[5] are characterized by their nitrogen-containing structures and have shown promise in inhibiting *α-amylase* and *α-glucosidase*. The Terpenes are a large group of over 30,000 compounds of diverse structural framework and bioactivity, many of which are found to have antidiabetic activity.[6] Flavonoids exist naturally as aglycones, glycosides, and methylated derivatives and have the C6–C3–C6 nucleus.[7] They are renowned for their antioxidant properties, and not only aid in reducing oxidative stress but also contribute to the modulation of enzyme activity related to glucose metabolism. So far, more than 10,000 flavonoid compounds have been isolated and identified.[8] A publication by Dirir *et al*.,[2] similarly reported that terpenes and flavonoids represented the largest chemical classes that exhibited inhibitory activities against *α-glucosidase* enzyme.

Molecular docking in recent years has served as an essential drug discovery tool, particularly when investigating the interactions between potential therapeutic compounds and biomolecular targets. This computational methodology employs algorithms to predict the preferred orientation of phytochemicals such as alkaloids, terpenes, and flavonoids, when they bind to protein receptors, thereby providing insights into their potential inhibitory effects against enzymes like *α-amylase* and *α-glucosidase*. *In-silico* screening of compound libraries therefore allows researchers to assess numerous compounds rapidly and at a fraction of the cost of conducting wet lab experiments. The compounds with promising docking scores are then identified for further investigation such as their Absorption, Distribution, Metabolism and Excretion (ADME) profile and "drug likeness". Docking studies also provide valuable insights into binding affinities and the structural characteristics that govern these interactions, which are critical when exploring new drug leads derived from natural sources. In addition, the incorporation of structure-activity relationship (SAR) modeling enhances the understanding of how molecular properties influence biological activity, thereby facilitating the design of more potent antidiabetic agents.

Drug-likeness was assessed using the Lipinski's "Rule of Five" [9] and Verber rules. These set of guidelines use physicochemical parameters such as molecular weight, lipophilicity (LogP), number of hydrogen bond acceptors and number of hydrogen bond donors to predict whether a chemical compound has the properties to be an orally active drug in humans. The Verber rule evaluates a compound's drug-likeness based on its polar surface area and molecular flexibility. It states that compounds with a total polar surface area of 140 or less and 10 or fewer rotatable bonds are likely to have good oral bioavailability.[10]

By employing molecular docking techniques, this study aims to elucidate the interactions between 383 chemically diverse bioactive compounds selected from across the alkaloids, terpenes, and flavonoid class of secondary metabolites in order to assess which class possess better binding scores and therefore present suitable structural moieties for development of novel inhibitory drugs against enzymes *α-amylase* and *α-glucosidase* by performing molecular docking in comparison with reference standard Acarbose.

To our knowledge, no prior research on this area has been published and this study will answer the question of which secondary metabolites have

greater inhibitory effect against *α-amylase* and *α-glucosidase* enzymes and the binding site interactions thus presenting a framework for identifying novel drug leads.
Additionally, structure-activity relationship (SAR) modeling based on docking scores will further enhance our understanding of the structural characteristics that underpin the efficacy of these ligands, thereby contributing to the holistic advancement of therapeutic options in antidiabetic treatment.

## MATERIALS AND METHODS

### Sample size determination

The population sample size was calculated with 95% confidence, and a margin of error of 5%. The population proportion was assumed to be 0.5, and of unlimited population size. Z for a 95% confidence level is 1.96.

Unlimited population: $N = \frac{Z^2 \hat{p}(1-\hat{p})}{\varepsilon^2}$….Equation 1

Where; Z is the z-score, ε is the margin of error, N is the population size and $\hat{p}$ is the population proportion.[11]

### Retrieval and Preparation of Proteins

The 3D structures of human pancreatic *α-amylase* (PDB ID: 5EMY) and human maltase-glucoamylase (PDB ID: 2QMJ), an *α-glucosidase* enzyme that belongs to glycoside hydrolase family 31[12] were retrieved from the Protein Data Bank (http://www.rcsb.org)[13] as PDB files. Native ligands, water molecules and co-crystallized structures were removed. The missing hydrogen atoms were added using Biovia Discovery Studio. Kollman charges were assigned to atoms, and the proteins were saved as PDBQT format using AutoDock Vina prior to docking simulations.

### Ligand Preparation

Literature studies was conducted for bioactive compounds with antidiabetic activity using Google Scholar and PubMed search sites. The 3D structures of the selected 383 bioactive compounds were then retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) [14] as SDF format.
The structures were then converted to PDB format using Open Babel tool version 2.4.1 [15], with polar hydrogens added, Gasteiger charges assigned and Ligand torsions set. The ligands were then converted to PDBQT format using AutoDockTools for docking simulations.

### Molecular Docking Studies

Molecular docking was conducted using AutoDock Vina (version 4.2.6) [16] to assess the binding affinity of the bioactive compounds and reference inhibitors. The grid box parameters for 5EMY were (X = -7.665, Y = -16.067, and Z = 0.393) and (X = -20.807, Y = -6.586, and Z = -5.073) for 2QMJ. The same grid dimensions was used for both enzymes (Angstrom, X = 40.00, Y= 40.00, and Z= 40.00). The docking validation was performed by redocking Acarbose into the active sites of *α-amylase* and *α-glucosidase*. The docking results were analyzed, and the docked complexes visualized using PyMOL [17] and Discovery Studio Visualizer.[18]

### ADME and Physiochemical Properties

The physicochemical properties of the six bioactive compound with the lowest binding energies were assessed using the SwissADME online server http://www.swissadme.ch/index.php.[19]

### Statistical Analysis

Data were analysed using one way ANOVA. $p < 0.05$ were considered statistically significant. GraphPad Prism (version 10.4.0) was used for statistical analysis.

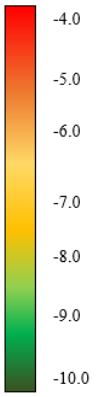
## RESULT AND DISCUSSION

The increasing search for novel antidiabetic agents has led researchers to explore bioactive compounds from medicinal plants as potential leads. The control of postprandial hyperglycemia has been judged a viable prophylactic treatment approach for type 2 diabetes mellitus[3] by the inhibition of the enzymes *α-amylase* and *α-glucosidase*.
In order to gain insights into the antidiabetic mode of action of secondary metabolites such as alkaloids, flavonoids and terpenes, molecular docking study was performed and the results obtained were analyzed.
The population sample size was calculated to be 383 using the Cochran's Sample Size formula[11] with the binding affinities against the enzymes *α-amylase* (5EMY) and *α-glucosidase* (2QMJ) shown in Table 1 below.

**Table 1:** Molecular Docking Scores using AutoDock Vina

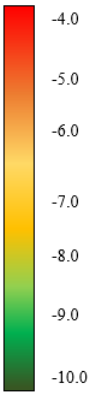
| Alkaloids | Affinity (kcal/mol) | | Flavonoids | Affinity (kcal/mol) | | Terpenes | Affinity (kcal/mol) | |
|---|---|---|---|---|---|---|---|---|
| | 5EMY | 2QMJ | | 5EMY | 2QMJ | | 5EMY | 2QMJ |
| 13A Hydroxylupanine | -7.2 | -5.9 | 2-Hydroxyflavone | -6.9 | -7.9 | 1,4-Cineole | -5.7 | -6.2 |
| 13 Hydroxylupanine | -6.5 | -5.5 | 3,5,7,3,4-pentahydroxyflavone | -8.2 | -7.5 | 3-Carene | -5.2 | -5.7 |
| 15β Hydroxy-17-oxolupanine | -7.5 | -6.0 | 3-Hydroxyflavone | -6.8 | -7.2 | 5-hydroxy ferulic acid | -6.5 | -6.0 |
| 17-oxolupanine | -7.1 | -6.4 | 5,4-Dihydroxyflavone | -7.2 | -7.2 | Achilleol A | -6.0 | -6.0 |
| 1-deoxynojirimycin | -4.9 | -5.8 | 5-Hydroxyflavone | -7.0 | -7.2 | Alpha Amyrin | -8.3 | -8.9 |
| 7-Hydroxymitragynine | -6.1 | -6.8 | Acacetin | -7.2 | -7.3 | Alpha Bisabolol | -5.6 | -6.9 |
| Aconine | -6.8 | -6.0 | Amentoflavone | -9.3 | -9.5 | Alpha Cadinene | -6.6 | -6.7 |
| Aconitine | -6.4 | -6.8 | Apigenin | -7.2 | -7.5 | Alpha Cubebene | -6.5 | -6.7 |
| Aegeline | -6.7 | -7.2 | Apigetrin | -8.6 | -7.9 | Alpha Farnesene | -5.3 | -6.5 |
| Ageladine A | -6.8 | -6.4 | Astragalin | -8.4 | -7.6 | Alpha Patchoulene | -5.5 | -5.3 |
| Ajmalicine | -7.8 | -7.0 | Aureusidin | -7.6 | -7.7 | Alpha Phellandrene | -5.7 | -5.8 |
| Ajmaline | -7.4 | -6.4 | Aurone | -6.7 | -7.0 | Alpha Pinene | -5.3 | -5.7 |
| Akuammine | -7.1 | -6.6 | Baicalein | -7.5 | -7.2 | Alpha Santalene | -5.4 | -6.5 |
| Alstonidine | -7.7 | -7.1 | Baicalin | -8.4 | -8.2 | Alpha Selinene | -6.3 | -6.3 |
| Alstonine | -8.2 | -7.1 | Beta_Citronellol | -5.2 | -5.7 | Andrastin A | -6.8 | -6.7 |
| Ammothamnine | -6.6 | -6.2 | Biochanin A | -7.1 | -7.2 | Angelic acid | -4.2 | -4.7 |
| Anhalonidine | -6.2 | -5.3 | Butein | -7.5 | -7.6 | Aromadendrene | -6.9 | -6.0 |
| Anisotine | -7.7 | -7.5 | Caffeic acid | -6.3 | -6.3 | Artemisinin | -6.9 | -6.6 |
| Arborine | -6.9 | -7.1 | Caflanone | -7.8 | -8.1 | Ar-Artemisene | -5.3 | -6.7 |
| arestrictin_B | -7.2 | -8.4 | Carlinoside | -8.6 | -7.9 | Ar-Turmerone | -6.4 | -6.5 |
| Aricine | -8.6 | -7.3 | Chalcone | -6.4 | -7.2 | Bacosine | -8.2 | -6.9 |
| Berberine | -7.3 | -7.2 | Chlorogenic acid | -8.0 | -7.2 | Bassic acid | -8.7 | -7.3 |
| Bufotenin | -6.0 | -5.8 | Chrysin-6-C-glucoside | -7.6 | -7.7 | Bergamotene | -6.1 | -6.3 |
| Bupropion | -5.6 | -6.0 | Chrysin | -7.2 | -7.4 | Betacurcumene | -5.5 | -6.3 |
| Caffeine | -6.1 | -4.6 | Chrysoeriol | -7.4 | -7.3 | Beta amyrin | -8.2 | -8.0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Calpurnine | -8.2 | -7.0 | Cianidanol | -7.2 | -7.4 | Beta Bisabolol | -5.5 | -6.2 |
| Calystegine B2 | -5.5 | -6.2 | Cinnamic_Acid | -5.8 | -6.9 | Beta Cadinene | -6.4 | -6.5 |
| Calystegine | -5.5 | -6.1 | Curcumin | -7.3 | -6.9 | Beta Carotene | -7.2 | -7.3 |
| Canadine | -7.2 | -7.3 | Cyanidin-3-O-glucoside | -8.7 | -7.5 | Beta Citronellol | -5.3 | -6.0 |
| Capsaicin | -5.4 | -7.0 | Cyanidin-3-sophoroside | -8.0 | -7.7 | Beta Farnesene | -4.6 | -6.0 |
| Cathinone | -5.9 | -6.1 | Cyanidin | -7.3 | -7.2 | Beta Ocimene | -5.5 | -6.0 |
| Cephalotaxine | -7.6 | -6.9 | Daidzein | -6.9 | -7.0 | Beta Pinene | -4.9 | -4.2 |
| Cicutoxin | -5.7 | -5.7 | Delphinidin | -7.5 | -7.4 | Beta Santalol | -6.1 | -6.6 |
| Cinchonidine | -7.6 | -6.9 | Delta Cadinene | -6.5 | -6.8 | Beta Terpinene | -5.6 | -5.8 |
| Colchicine | -6.9 | -6.8 | Dihydromyricetin | -7.9 | -7.4 | Betulinic acid | -8.2 | -7.6 |
| Coniine | -4.9 | -5.8 | Dihydroquercetin | -7.3 | -7.6 | Betulin | -8.6 | -6.9 |
| Coptisine | -7.7 | -8.0 | Dihydro_quercetin | -7.9 | -7.8 | Bicyclogermacrene | -5.4 | -6.3 |
| Corynanthine | -7.5 | -7.7 | Diosmin | -9.4 | -9.2 | Bisabolol | -5.6 | -6.8 |
| Cryptolepine | -7.0 | -7.6 | Ellagic acid | -8.1 | -6.8 | Bisacurone | -6.1 | -6.7 |
| Cryptopine | -7.6 | -7.4 | Epicatechin | -7.3 | -7.3 | Borneol | -4.7 | -4.9 |
| Cyclopamine | -8.7 | -8.5 | Equol | -6.9 | -6.9 | Cadalene | -6.7 | -6.2 |
| Dehydroevidiamine | -8.1 | -8.2 | Eriocitrin | -9.5 | -8.6 | Cafestol | -7.6 | -7.1 |
| Dehydronuciferine | -7.0 | -6.3 | Eriodictyol | -7.8 | -7.6 | Camphene | -5.4 | -4.2 |
| Dictamnine | -6.4 | -6.7 | Eupatilin | -7.1 | -7.2 | Camphor | -4.7 | -4.5 |
| Dihydroberberine | -7.3 | -7.3 | Fastigenin | -7.3 | -7.2 | Carvacrol | -5.9 | -7.2 |
| Dihydrocodeine | -7.9 | -6.2 | Ferulic acid | -6.5 | -6.1 | Caryophyllene | -5.6 | -5.9 |
| Echinulin | -7.7 | -8.9 | Fisetinidol | -7.2 | -7.2 | Chrysin-6-C-glucoside | -7.6 | -7.7 |
| Emetine | -8.3 | -7.2 | Fisetin 3-O-rutinoside | -8.3 | -7.3 | Cinnamaldehyde | -5.2 | -6.3 |
| Ephedrine | -5.8 | -6.4 | Fisetin-8-C-glucoside | -8.7 | -6.9 | Citral | -4.9 | -5.5 |
| Evodiamine | -8.5 | -8.3 | Fisetin | -7.2 | -7.5 | Citronellal | -5.1 | -5.6 |
| Fangchinoline | -8.2 | -8.2 | flavopiridol | -7.5 | -8.4 | Cucurbitacin | -8.7 | -8.3 |
| Gelsemine | -7.6 | -6.7 | Formononetin | -6.6 | -7.2 | Danshenol | -7.5 | -7.5 |
| Gentianine | -6.0 | -5.4 | Galangin | -6.9 | -7.2 | Dihydromyrcene | -5.1 | -5.2 |
| Harmaline | -6.5 | -6.8 | Gallic Acid | -5.7 | -5.9 | Dihydromyrcenol | -5.2 | -5.6 |



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Harmine | -6.6 | -6.3 | Galloylquinic acid | -7.6 | -7.0 | Dithymoquinone | -7.4 | -6.5 |
| Heliotrine | -6.5 | -6.4 | Garcinia biflavonoid 1 | -8.6 | -8.8 | DL-alpha-Tocopherol | -5.7 | -7.0 |
| Hordenine | -5.3 | -5.5 | Genistein | -7.0 | -7.1 | Eucalyptol | -5.0 | -4.7 |
| Huperzine A | -7.1 | -6.7 | Genistin | -8.3 | -7.8 | Eudesmol | -6.1 | -6.1 |
| Hydroxyevodiamine | -8.5 | -8.3 | Glycitein | -6.8 | -7.0 | Eugenol | -5.7 | -6.2 |
| Hyoscyamine | -6.3 | -6.6 | Hesperetin | -7.6 | -7.3 | Farnesol | -5.1 | -5.8 |
| Isoboldine | -7.6 | -7.0 | Hesperidin | -9.3 | -9.5 | Fenchol | -5.9 | -5.5 |
| Isocorydine | -7.2 | -6.7 | Hesperidin methyl chalcone | -8.2 | -7.9 | Fenchone | -5.0 | -4.7 |
| Isolobinine | -6.3 | -6.9 | Hispidulin | -7.2 | -7.1 | Gamma Terpinene | -5.6 | -6.7 |
| Jacquilenin | -7.7 | -6.5 | Homoorientin | -8.2 | -7.8 | Geraniol | -5.4 | -5.5 |
| Jatrorrhizine | -7.3 | -7.1 | Humulone | -6.3 | -7.5 | Geranyl Linalool | -5.2 | -6.6 |
| Nuciferine | -7.0 | -6.4 | Isobavachin | -7.5 | -8.0 | Germacrene_A | -6.1 | -6.2 |
| Koenigicine | -7.1 | -6.8 | Isoferulic acid | -6.3 | -5.9 | Germacrene B | -5.6 | -5.4 |
| Lactucin | -7.7 | -6.2 | Isoquercetin | -8.9 | -7.7 | Germacrene D | -6.5 | -6.3 |
| Lepidine | -6.1 | -5.7 | Isorhamnetin | -7.2 | -7.4 | Guaiazulene | -7.2 | -7.2 |
| Lobelanidine | -7.2 | -8.0 | Isovitexin | -7.7 | -7.6 | Guaiol | -6.3 | -6.6 |
| Lobelanine | -6.9 | -8.2 | Kaempferol-3-xylosylglucoside | -8.7 | -8.0 | Gymnemagenin | -8.3 | -7.6 |
| Lobeline | -7.3 | -8.2 | Kaempferol | -7.1 | -7.4 | Hinokitiol | -6.1 | -5.5 |
| Loperamide | -7.7 | -7.9 | Kempferol-3-O-rutinoside | -8.9 | -8.9 | Humulene | -5.6 | -5.8 |
| Lupanine | -7.0 | -6.0 | Licochalcone A | -7.1 | -6.8 | Isoborneol | -4.9 | -4.8 |
| L_Hyoscyamine | -6.4 | -6.7 | Licochalcone B | -6.9 | -7.7 | Isocaryophyllene | -5.7 | -6.1 |
| Magnoflorine | -7.5 | -7.4 | Licochalcone C | -7.1 | -7.7 | Isovaleric acid | -4.2 | -4.8 |
| Mescaline | -5.4 | -4.8 | Licochalcone D | -7.4 | -7.5 | Kempferol-3-O-rutinoside | -8.9 | -9.0 |
| Methadone | -5.9 | -6.3 | Licochalcone E | -6.7 | -7.7 | Kessane | -6.8 | -6.1 |
| Methscopolamine | -6.7 | -7.0 | Licochalcone G | -7.1 | -7.5 | Limonene | -5.4 | -6.3 |
| Mimosine | -6.1 | -5.7 | Luteolin-4-O-glucoside | -8.5 | -7.5 | Linalool | -5.2 | -5.4 |
| Mitragynine | -6.5 | -6.4 | Luteolin-7-O-glucoside | -8.8 | -8.1 | Loganin | -7.0 | -6.8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Momordicin | -7.9 | -8.2 | Luteolin | -7.9 | -7.6 | Longifolenaldehyde | -5.7 | -5.1 |
| Momordicin II | -8.2 | -7.1 | Malvidin | -7.3 | -6.6 | Longifolene | -5.8 | -5.3 |
| Muscimol | -5.0 | -5.2 | Mangiferin | -8.1 | -7.8 | Lupane | -8.2 | -8.1 |
| Nandinine | -7.9 | -6.7 | Morin | -7.1 | -7.3 | Lupeol | -8.7 | -7.3 |
| Neferine | -7.9 | -7.0 | Myrciacitrin | -8.8 | -8.5 | Menthol | -5.6 | -5.7 |
| Nicotine | -5.8 | -6.5 | Myricetin-3-galactoside | -8.5 | -6.9 | Methyl Eugenol | -5.4 | -5.5 |
| Oriciacridone F | -9.1 | -8.3 | Myricetin | -7.9 | -7.6 | Momordicin IV | -7.6 | -7.5 |
| Methylmurrayamine_A | -7.1 | -7.3 | Naringenin chalcone | -7.2 | -6.8 | Myrcene | -5.0 | -5.1 |
| Nornuciferine | -6.9 | -6.8 | Naringenin | -7.2 | -7.6 | Myricetin | -7.9 | -7.6 |
| Dimethylmagnoflorine | -6.5 | -6.5 | Naringin | -8.2 | -8.1 | Myrtenol | -5.7 | -6.0 |
| Palmatine | -6.7 | -6.3 | Nobelitin | -6.5 | -6.8 | Oleanolic acid | -8.3 | -7.5 |
| Papaverine | -7.3 | -7.2 | Ornithine | -4.7 | -5.3 | Palbinonet | -8.3 | -7.1 |
| Picrasidine C | -7.8 | -9.0 | Pelargonidin | -7.0 | -7.0 | Phytol | -4.6 | -5.8 |
| Picrasidine I | -6.8 | -6.5 | Phloretin | -6.9 | -6.9 | Pinocarveol | -5.1 | -4.9 |
| Picrasidine L | -7.4 | -6.6 | Pierotin B | -8.1 | -8.3 | Piperitone | -5.8 | -4.7 |
| Picrasidine N | -10.0 | -8.1 | Pinoquercetin | -7.3 | -7.6 | Pulegone | -5.9 | -6.0 |
| Picrasidine Q | -7.2 | -6.6 | Ponciriin | -8.3 | -8.3 | p-Cymene | -5.6 | -6.9 |
| Piperine | -6.8 | -7.3 | Protocatechuic acid | -5.5 | -6.4 | Quercetin | -7.1 | -7.5 |
| Pseudoephedrine | -5.6 | -5.6 | Prunetin | -6.8 | -7.0 | Rosmaridiphenol | -7.5 | -9.3 |
| Pseudopunicine | -4.9 | -4.3 | Pseudocyphellarin A | -7.1 | -6.6 | r-Terpinene | -7.1 | -7.3 |
| Quassine | -7.8 | -7.1 | Quercetin-3-rhamnoside | -8.2 | -7.8 | Sabinene | -5.2 | -5.7 |
| Quinidine | -7.2 | -6.5 | Quercetin | -7.1 | -7.5 | Santalene | -5.4 | -6.0 |
| Quinine | -7.4 | -6.4 | Resveratrol | -6.5 | -7.1 | Sclarenet | -6.1 | -7.1 |
| Raubasine | -7.8 | -7.4 | Rhamnazin | -7.2 | -7.4 | Sclareol | -6.7 | -6.8 |
| Rauwolscine | -8.3 | -7.0 | Rhamnetin | -7.8 | -7.5 | Scopadulcic acid B | -8.2 | -8.2 |
| Reserpine | -8.5 | -6.9 | Rhamnocitrin | -7.1 | -7.4 | Scoparic acid A | -7.4 | -7.8 |
| Retrosine | -7.7 | -7.0 | Robinetinidol | -7.6 | -7.5 | Squalene | -5.3 | -6.5 |
| Salsolinol | -5.8 | -6.0 | Rosmarinic acid | -8.2 | -7.6 | Taxadiene | -6.4 | -6.5 |



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Samandarine | -7.6 | -6.9 | Rutin | -9.3 | -8.8 | Terpinolene | -5.7 | -5.8 |
| Sanguinarine | -8.3 | -7.6 | Sakuranetin | -7.3 | -7.5 | Tetrahydrolinalool | -4.9 | -4.7 |
| Sarcolobine | -8.2 | -7.1 | Schizandrin | -6.1 | -5.6 | Thujone | -5.4 | -5.8 |
| Spilanthol | -5.5 | -6.1 | Scutellarein | -7.9 | -7.3 | Thujopsene | -5.8 | -5.4 |
| Strophanthidin | -8.9 | -7.0 | Silybin | -8.8 | -7.9 | Thymol | -5.9 | -6.8 |
| Strychnine | -8.1 | -7.6 | Silymarin | -8.7 | -8.4 | Thymoquinone | -5.9 | -5.4 |
| Swerchirin | -7.0 | -6.6 | Syringic acid | -5.8 | -5.1 | Tiglic acid | -4.2 | -4.9 |
| Tembetarine | -6.7 | -7.5 | Tangeretin | -6.5 | -6.5 | Trans Nerolidol | -5.3 | -5.7 |
| Tetrahydroalstonine | -8.5 | -7.5 | Taxifolin | -7.3 | -7.6 | Umbellulone | -5.5 | -6.2 |
| Tetrandrine | -7.9 | -8.1 | Trans Stilbene | -6.0 | -6.7 | Ursolic acid | -8.7 | -7.5 |
| Thalifoline | -6.3 | -5.4 | Tricetin | -7.9 | -7.7 | Valencene | -5.9 | -7.2 |
| Theobromine | -6.1 | -4.9 | Umbelliferone | -6.3 | -6.1 | Valerianol | -6.2 | -6.1 |
| Theophylline | -5.9 | -5.2 | Urolithin A-3-O-glucuronide | -8.3 | -8.9 | Valerophenone | -5.7 | -5.8 |
| Trigonelline | -5.2 | -5.1 | Urolithin A | -7.9 | -6.9 | Vanillin | -5.1 | -5.1 |
| Vasicinone | -6.5 | -6.0 | Urolithin B | -7.1 | -7.0 | Vernodalin | -7.2 | -6.8 |
| Vindolinine | -7.1 | -7.2 | Urolithin C | -7.1 | -6.5 | Vernodalol | -6.9 | -6.4 |
| Yohimbine | -7.5 | -7.3 | Xanthohumol | -7.3 | -7.7 | Vernolide B | -6.9 | -7.4 |
| | | | Zingerone | -5.9 | -6.0 | Vetivazulene | -7.1 | -6.7 |
| | | | | | | Zingiberene | -5.6 | -6.3 |
| | | | | | | Z-3-Nonenal | -4.3 | -5.1 |
| | | | | | | Z-Alpha-Santalol | -6.0 | -5.9 |
| Acarbose | -8.0 | -7.5 | Acarbose | -8.0 | -7.5 | Acarbose | -8.0 | -7.5 |
| Miglitol | -5.4 | -5.6 | Miglitol | -5.4 | -5.6 | Miglitol | -5.4 | -5.6 |
| Voglibose | -6.0 | -6.1 | Voglibose | -6.0 | -6.1 | Voglibose | -6.0 | -6.1 |

The box plot shown in Figure 1 below compared the binding affinities (kcal/mol) of the three classes of secondary metabolites - alkaloids, flavonoids, and terpenes - to *α-amylase* (5EMY) and *α-glucosidase* (2QMJ).

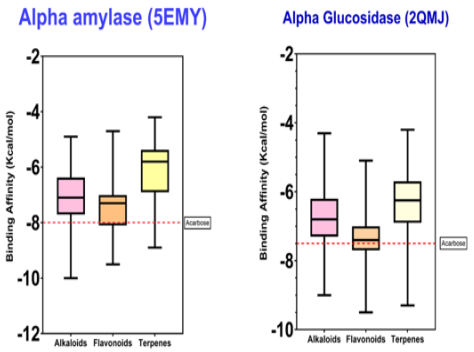



**Figure 1:** Box Plot comparing the binding affinities of Alkaloids, Flavonoids and Terpenes against *alpha amylase* and *alpha glucosidase*

The binding affinity of Acarbose, a known inhibitor, is represented by the red dashed line at -8.0 Kcal/mol for *α-amylase* (5EMY) and at -7.5 Kcal/mol for *α-glucosidase* (2QMJ), serving as reference for comparison.

The Alkaloids exhibited binding affinities ranging from -4.0 to -10.0 Kcal/mol, with a median of -7.1 Kcal/mol for the enzyme *α-amylase* (5EMY) while flavonoids demonstrated affinities spanning -4.7 to -9.5 Kcal/mol, with a median of approximately -7.3 Kcal/mol. In contrast, terpenes showed a weaker binding profile, with a median affinity of about -5.7 Kcal/mol and a range from -4.2 to -8.9 Kcal/mol. This suggests that the majority of terpenes have a lower inhibitory activity compared to Acarbose.

For *α-glucosidase* (2QMJ), Alkaloids exhibited binding affinities ranging from -4.3 Kcal/mol to -9.0 Kcal/mol with a median of -6.8 Kcal/mol, flavonoids had a slightly narrower binding affinity range from -5.0 Kcal/mol to -9.5 Kcal/mol with median at -7.4 Kcal/mol while terpenes had binding affinities ranging from -4.2 Kcal/mol to -9.3 Kcal/mol with a median of -6.2 Kcal/mol.

We observed the flavonoids displayed a narrow interquartile range (IQR) of -7.0 to -8.0 Kcal/mol for 5EMY and -7.0 Kcal/mol to -7.7 Kcal/mol for 2QMJ, indicating consistent binding affinity within this class. The strongest binding affinity was observed among flavonoids at -9.5 Kcal/mol. The differences amongst the Alkaloids, Flavonoids and Terpenes using the one-way ANOVA Bartlett's test was statistically significant ($p = 0.0072$ for 2QMJ and $p = 0.0259$) suggesting key structural differences that could serve as scaffolds for novel antidiabetic agents.

It is important to note that all three compound classes demonstrated binding energies comparable to Acarbose for both *α-amylase* and *α-glucosidase*. However, the boxplots reveal considerable variation within each class, as evidenced by the whisker lengths with the trend being Flavonoids > Alkaloids > Terpenes. These findings suggest that representatives from all three secondary metabolite classes, particularly alkaloids and flavonoids, could potentially serve as promising dual *α-amylase* and *α-glucosidase* inhibitors with binding strengths comparable to the established inhibitor Acarbose.

Following the molecular docking, four Flavonoids with the highest inhibitory activities were selected for ADME, SAR and binding site analysis. For 5EMY: Eriocitrin (-9.5 kcal/mol) and Diosmin (-9.4 kcal/mol) while for 2QMJ they were Hesperidin (-9.5 kcal/mol) and Amentoflavone (-9.5 kcal/mol). Our findings are in line with findings by Ogunwa and Swargiary *et al.*, who reported that Amentoflavone showed the strongest binding affinity with *α-glucosidase* in a pool of 155 flavonoids, and a much more potent inhibition than reference Acarbose.[20, 21]

The structure activity relationship for flavonoids indicated that the flavanone, flavonol or chalcone moiety is essential for binding.

In Figure 2, the biflavonoid, Amentoflavone having two flavonol moieties showed a better binding affinity compared with Apigenin which lacked a flavanone moiety on C8. The presence of more aromatic rings and hydroxyl and carbonyl groups therefore allow for hydrogen bond formation at the enzyme binding site. This is in accordance with the findings by Shamsudin *et al*., in which the dimerization of flavonoids was found to be responsible for stronger inhibition of *α-glucosidase.*[7]

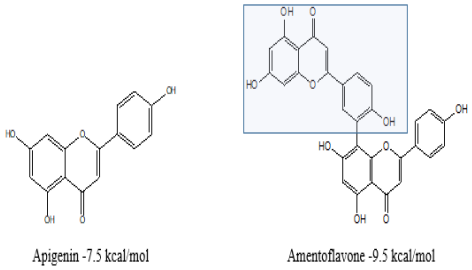



**Figure 2:** Structural and binding affinity of Apigenin and Amentoflavone

It was observed that the presence of two glycosyl moieties attached to a chalcone or flavone moiety at position 4′ significantly improved binding affinity. This is exemplified in Figure 3, where there was an improved binding score from Chalcone with binding affinity -6.4 kcal/mol, to -8.2 kcal/mol of Hesperidin methyl chalcone which has two glycosyl moieties. The presence of other functional groups such as hydroxyl groups or ether linkage further improved the binding affinity.

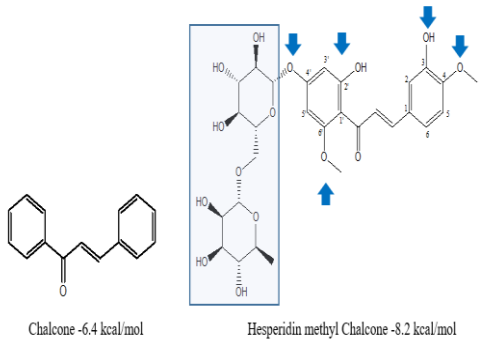



**Figure 3:** Structural and binding Affinity of Chalcone and Hesperidin methyl Chalcone

In Figure 4, we again see the impact of the presence of two glycosyl moieties attached to the flavanone moiety of Hesperidin leading to an improved binding score of -9.3 kcal/mol compared to Hesperetin -7.6 kcal/mol.
This trend is also seen with Kaempferol with binding affinity of -7.1 kcal/mol in which the presence of two glycosyl moieties leads to a higher binding affinity as seen with Kaempferol-3-O-rutinoside with -8.9 kcal/mol binding affinity.
These observations indicate that the presence of the glycosyl moiety is essential for binding at the enzyme binding site and is in line with findings by Ortega *et al.*, [22] which showed that glycosylated derivatives of quercetin and myricetin possessed higher antiviral activities than the aglycones.

In figure 5, the conversion of the ether linkage in Diosmin to a hydroxyl group and the loss of double bond between C2 and C3 as seen in Eriocitrin did not lead to significant increase in binding affinity indicating that these functional groups do not play a key role at the enzyme binding site.

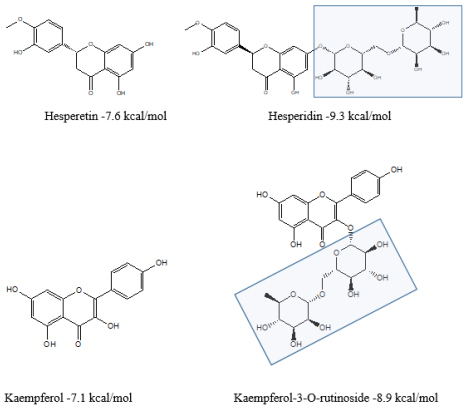



**Figure 4:** Structural and binding Affinity comparing Hesperetin with Hesperidin and Kaempferol with Kaempferol -3-O-rutinoside

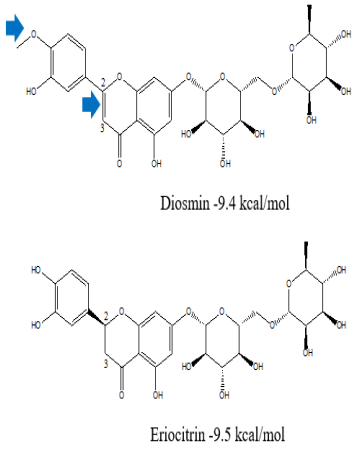



**Figure 5:** Structural and binding Affinity of Diosmin and Eriocitrin

The ADME profile for Eriocitrin, Amentoflavone, Hesperidin, and Diosmin in comparison with Acarbose is depicted in Table 2 below.

All four compounds showed a comparable ADME profile with reference standard Acarbose with Amentoflavone having the lowest synthetic accessibility score, lower violations with either the Lipinski or Verber Rules and absence of CYP450 enzyme interactions indicating that Amentoflavone could serve as a potential lead antidiabetic agent due to its ease of synthesis compared with Acarbose.

**Table 2:** ADME analysis of Eriocitrin, Amentoflavone, Hesperidin, and Diosmin in comparison with Acarbose

| Property | Eriocitrin | Amentoflavone | Hesperidin | Diosmin | Acarbose |
|---|---|---|---|---|---|
| **Molecular weight (g/mol)** | 596.53 | 538.46 | 610.56 | 608.17 | 645.60 |
| **Consensus Log Po/w** | -1.28 | 3.62 | -1.09 | -0.52 | -6.06 |
| **nHAcc** | 15 | 10 | 15 | 15 | 19 |
| **nHdon** | 9 | 6 | 8 | 8 | 14 |
| **Synth** | 6.21 | 4.27 | 6.34 | 6.48 | 7.34 |
| **TPSA ( Å²)** | 245.29 | 181.80 | 234.29 | 238.20 | 321.17 |
| **Lipinski Rule** | 3.0 Violations | 2.0 Violations | 3.0 Violations | 3.0 Violations | 3.0 Violations |
| **Verber Rule** | 1.0 Violation | 1.0 Violation | 1.0 Violation | 1.0 Violation | 1.0 Violation |
| **GI Absorption** | Low | Low | Low | Low | Low |
| **BBB Permeant** | No | No | No | No | No |
| **BA Score** | 0.17 | 0.17 | 0.17 | 0.17 | 0.17 |
| **CYP1A2** | No | No | No | No | No |
| **CYP2C19** | No | No | No | No | No |
| **CYP2C9** | No | No | No | No | No |
| **CYP2D6** | No | No | No | No | No |
| **CYP3A4** | No | No | No | No | No |

Consensus Log Po/w= Average of log P values of n-octanol / water coefficient at pH = 7.4, nHAcc = Num. H-bond acceptors, nHdon = Num. H-bond donors, Synth = Synthetic accessibility, GI Absorption = Gastro-intestinal absorption, BBB Permeant = Blood Brain Barrier Permeation, BA Score = Bioavailability Score.

The partition coefficient between n-octanol and water (log $P_{o/w}$) is an important physicochemical parameter for drug discovery, design, and development.[23, 24] The ideal lipophilicity range is between 1.35–1.8 and is the ability to cross through cell membranes.[25] This cell permeation could be decreased when lipophilicity is too low, whereas compounds with high hydrophilicity are not able to passively diffuse through the membranes.[26] SwissADME computes five values of this descriptor using different models. In this work, we used the descriptor Consensus $LogP_{o/w}$, which is the arithmetic mean of the values predicted by the five proposed methods. In this study Amentoflavone had a Consensus LOGP value of 3.06 suggesting it may not be able to easily partition into aqueous compartments in the body, therefore further modifications of physicochemical features of Amentoflavone may be necessary.

Figure 6 below shows the 2-dimentional and 3-dimentional interactions between Eriocitrin and Amentoflavone with *α-amylase* (5EMY) and *α-glucosidase* (2QMJ) amino acid residues. The flavanone B ring moiety in Eriocitrin formed *pi*-Alkyl, *pi-pi* T-shaped interaction at distance of 4.75Å with PRO 332 residue and a *pi*-cation interaction with HIS 331 at 6.71Å. Eriocitrin formed 1 Van der Waals interaction with THR 11 at 5.63Å. There are 2 unfavorable donor–donor and acceptor-acceptor interactions with HIS 331, GLU 282, PRO 332, GLY 9 and ARG 421 residues. The formation of unfavorable interactions indicates presence of repulsive forces between ligand and target which can adversely influence ligand-target complex stability.[27] One Carbon-Hydrogen interaction between the hydroxyl group and ASP 402. Two conventional hydrogen bonds between the hydroxyl groups and amino acids residues TRP 280 at 6.35Å and GLN 7 at 6.36Å.

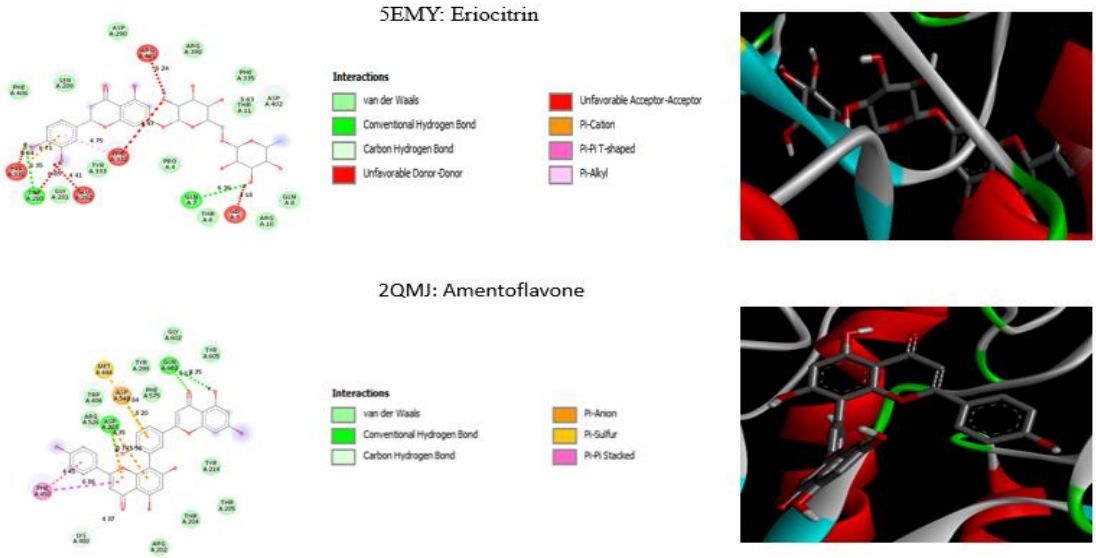



**Figure 6:** 2-D and 3-D binding interactions of Eriocitrin and Amentoflavone with *alpha amylase* and *alpha glucosidase* amino acid residues

For Amentoflavone, the flavone ring moiety formed two *pi-pi* stacked interaction at 4.45Å and 6.86Å with PHE 450, a *pi*-sulphur interaction between MET 444 at 7.84Å and a *pi*-Anion interaction with ASP 542 at 6.20Å. Amentoflavone formed 1 Van der Waals interaction between the carbonyl functional group and LYS 480 at 4.37Å. There were three conventional hydrogen bond interactions between the hydroxyl and carbonyl functional groups and ASP 203 at 6.35Å and GLN 603 at 2.35Å and 4.13Å respectively.

In Figure 7, we illustrate the 2-dimentional and 3-dimentional interactions between Diosmin and Hesperidin with *α-amylase* (5EMY) and *α-glucosidase* (2QMJ).
The flavone B ring moiety in Diosmin formed a *pi*-Alkyl interaction with PRO332. Diosmin formed 1 Van der Waals interaction between the carbonyl functional group and LYS 480 at 4.37Å. The two glycosyl groups contributed majority of the eight conventional hydrogen bond interactions observed between the hydroxyl functional groups and TRP 280, PRO 332, GLY 9, GLN 7, ARG 10, THR 6, ASP 402, and ARG 398.
While for Hesperidin, The flavanone B ring moiety in Hesperidin formed a *pi*-Sigma interaction with LEU473 at 5.69Å and a *pi*-Anion interaction withASP203 at 5.46Å. Hesperidin formed a total of 15 van der Waals interactions and 3 conventional hydrogen bond interactions between the epoxy functional groups and ASN 209 at 3.89Å, THR 205 at 3.90Å and ARG 526 at 6.08Å. Four conventional hydrogen bond interactions between the hydroxyl functional groups and THR 205, ASP 327, ASP 443 and TRP 406.
The *pi*-Alkyl interactions occur in the *pi*-electron cloud of the ligand aromatic groups and electron groups of amino acid residues[28] and play a key role in defining the stability and conformation of 3D

structures. *Pi*-cation interactions are strong attractive forces between positively charged entities and the $\pi$-electron cloud of aromatic groups and enhance the binding affinity, specificity, selectivity, lipophilicity, bioavailability, and metabolic stability.[29]

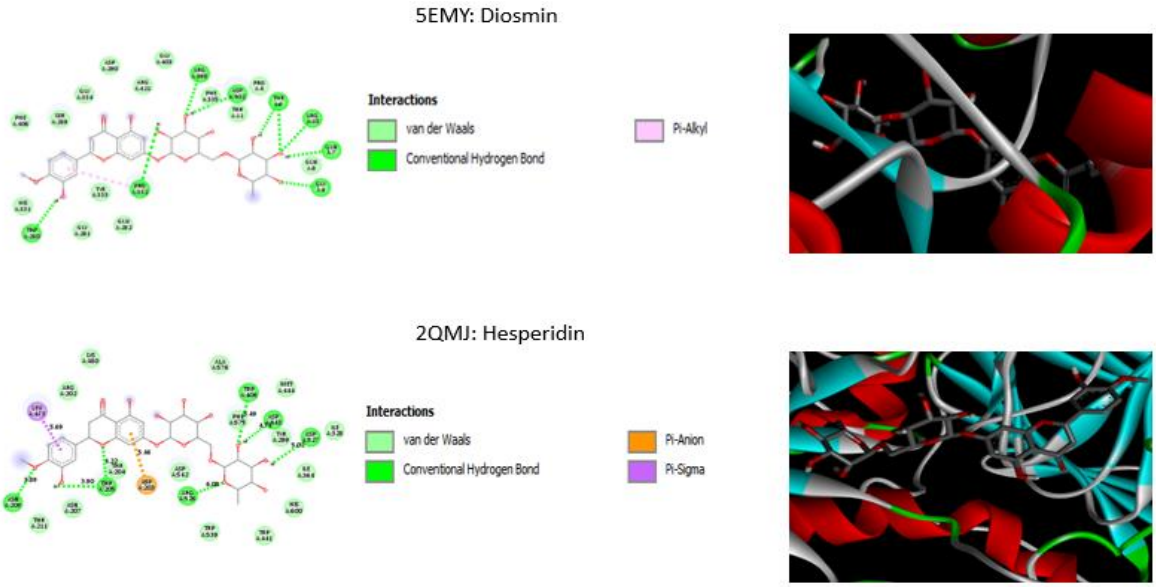



**Figure 7:** 2-D and 3-D binding interactions of Diosmin and Hesperidin with *alpha amylase* and *alpha glucosidase* amino acid residues

The *pi-pi* T-shaped interaction are non-covalent, pH sensitive interactions formed between the ligand and aromatic groups containing $\pi$ bonds and play a key role in conferring lipophilicity.[26] Hydrogen bonds occurring between hydrogen atoms and electronegative oxygen atoms of the proteins and ligands facilitate the binding. *Pi*-Sigma bonds contribute to the stability of ligand-protein complexes and usually occur along with other interactions, such as hydrogen bonds, alkyl, *pi-pi* stacked, and *pi*-sulfur bonds.[30] The Van der Waals forces are attractive forces between neutral atoms or groups which are generally weaker than covalent bonds. The play critical role in stabilizing the drug-receptor interaction.[31]

## CONCLUSION

This study showed that Flavonoids had a superior inhibitory activity against *α-amylase* (5EMY) and *α-glucosidase* (2QMJ) with the trend being Flavonoids > Alkaloids > Terpenes based on superior binding affinities outperforming the known inhibitor Acarbose following molecular docking of 383 secondary metabolites. Detailed SAR analysis revealed that structural features, such as glycosylation and presence of the flavone / flavanol moiety enhanced binding affinity. Amentoflavone emerged as a lead compound with high binding affinity, favorable ADME properties, and synthetic accessibility, indicating its strong potential as a novel antidiabetic agent.

The interactions of selected flavonoids with key amino acids in the binding sites of 5EMY and 2QMJ provided insights into their inhibitory mechanisms, emphasizing the role of functional groups like hydroxyl, glycosyl, and flavonoid ring systems in enhancing binding and activityfor patients with chronic medical conditions.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHORS DECLARATION

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

## ACKNOWLEDGMENT

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