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(RESEARCH ARTICLE)

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# Multiple flavonoid docking studies for checking the anti-diabetic activity of *Annona species*

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## Abstract

*Diabetes mellitus* (T2DM) is one of the world's most prevalent metabolic disorders with a huge demand for both affordable and effective drugs. Apart from conventional drugs a large number of plant products and their secondary metabolites have been found to possess anti-diabetic properties; among these flavonoids have been reported by recent scientific studies to be one of the main functional compounds against T2DM. Hence our main area of interest was exploring the anti-diabetic potential of various flavonoids present in *Annona species* using multiple flavonoid docking. Flavonoids predominant in the plant were chosen as the ligands to be docked with the receptors (T2DM targets) that were identified to have major influence on the treatment of type 2 diabetes. The interactions between the flavonoids and the targets were studied using PyRx, a virtual screening software for computational drug discovery. The results were compared with that of a commonly used anti-diabetic drug- glibenclamide to prove that these flavonoids have better interactions with the targets and hence, more efficient than the conventional drug. This was achieved by analogizing the binding energies of the flavonoid dockings to that of the drug with the respective targets. The flavonoids chosen would produce minimal side effects to that of conventional drugs and can act as potential substitutes for T2DM treatment.

**Keywords:** Glycogen phosphorylase; α-glucosidase; Potassium sensitive ATP channels (KATP); Flavonoids; *Annona species*; Multiple flavonoid docking; T2DM

## 1. Introduction

Type 2 diabetes is a metabolic impairment in the way the body controls and uses sugar (glucose) as a source of energy. This chronic condition leads to high sugar levels circulating within the bloodstream, which eventually results in disorders of the circulatory, nervous and immune systems. In type 2 diabetes, there are primarily two problems - the pancreas does not produce enough insulin (a hormone that regulates the movement of sugar into the cells) and causes cells to respond poorly to it, resulting in less sugar uptake. At present, there is no cure for type 2 diabetes, but weight loss, healthy eating habits and proper exercise can help manage the disorder. Apart from these, people can also opt for anti-diabetic medications or insulin therapy if required [https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/symptoms-causes/syc-20351193] [1].

There are many drugs which are being used for T2DM treatment, examples of which include Metformin, Glibenclamide, GLP1 agonists and DPP4 inhibitors. Side effects of such drugs include low blood glucose levels (hypoglycaemia) characterized by dizziness, sweating, palpitations, hunger pangs, dry mouth, taste change, nausea, diarrhea, abdominal or stomach pain, sore throat, headaches and upper respiratory tract infections [https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/in-depth/diabetes-treatment/art-20051004] [2].

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If the plant extracts were given instead of these drugs, it would be more suitable to the body as it will have minimal side effects and no known adverse effects [3].

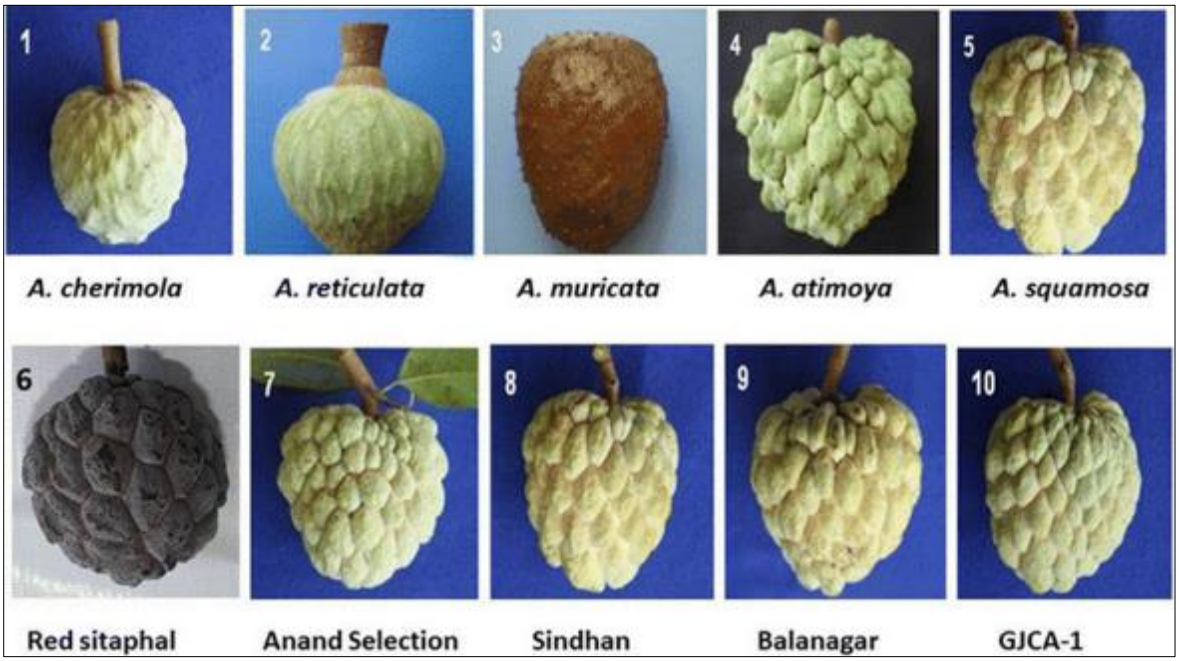


**Figure 1** Different *Annona species* [courtesy: ResearchGate]

*Annona* is a genus of flowering plants in the sugar apple family, *Annona*ceae. It is the second largest genus in the family after *Guatteria*, containing approximately 166 species of mostly Neotropical and Afrotropical trees and shrubs. *Annona species* are taproots, evergreen or semi deciduous, tropical trees or shrubs. The plants grow in areas where air temperature does not drop below 28 °F (−2 °C), especially Cuba, Jamaica, Central America, India, the Philippines, Calabria and in certain parts of the Andes mountains in South America and Florida [Wikipedia: *Annona*, https://en.wikipedia.org/wiki/*Annona*] [4].

*Annona species* are known to possess anti-bacterial, anti-cancer, anti-inflammatory and anti-diabetic properties [5]. The objective was to explore the anti-diabetic properties of this species, especially against T2DM, which can be attributed to the presence of flavonoids in this plant [6], and to compare the results with that of a commonly used anti-diabetic drug- glibenclamide [Glibenclamide: Uses and Side effects, https://www.apollopharmacy.in/salt/GLIBENCLAMIDE] [7] to prove that these flavonoids are more efficient than the conventional drug.

## 2. Material and methods

Flavonoids are polyphenolic molecules (a group of plant metabolites) thought to provide health benefits through cell signaling pathways and antioxidant effects. Examples of some flavonoids include kaempferol, quercetin, myricetin and fisetin. Some of the flavonoids identified in *Annona* are quercetin, kaempferol, luteolin, rutin, catechin, epicatechin, trifolin, cynaroside, quercetin-3-O-β-D-glucoside and biorobin [8].

The objective was carried out using docking studies performed with the selected flavonoids and evaluating the binding efficiency of these secondary metabolites with the reference ligand (glibenclamide). The receptors that were docked with the flavonoids include α-glucosidase, KATP channels and glycogen phosphorylase, which were identified to be some of the main proteins associated with diabetes [9-11].

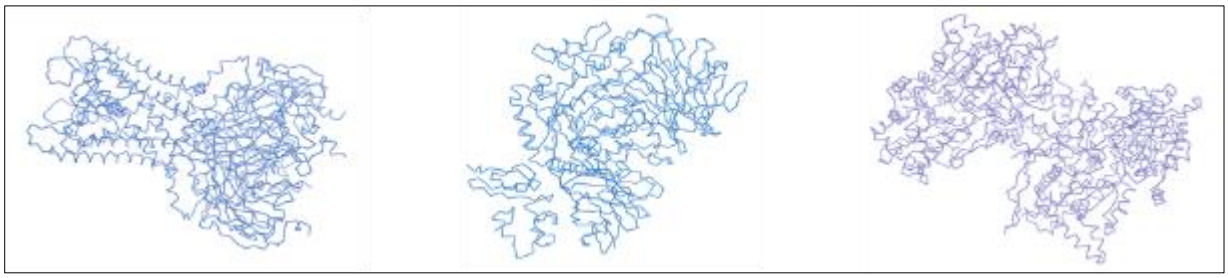

**Figure 2** Structures of KATP (PDB ID:7S5T), α-glucosidase (PDB ID:8D43) and glycogen phosphorylase (PDB ID:1FC0) respectively [courtesy: RCSB-PDB and PyMOL]

The flavonoids were docked with the above mentioned receptors using PyRx [PyRx: Virtual Screening Tool, Welcome to the PyRx Website (sourceforge.io)] [12].

**Table 1** List of predominant flavonoids in *Annona species* [courtesy: PubChem]

| Flavonoid | PubChem ID |
|---|---|
| Cynaroside | 5280637 |
| Rutin | 5280805 |
| Biorobin | 15944778 |
| Quercetin-3-O-beta-D-glucoside | 25203368 |
| Trifolin | 5282149 |
| Luteolin | 5280445 |
| Quercetin | 5280343 |
| Epicatechin | 72276 |
| Catechin | 9064 |
| Kaempferol | 5280863 |

Materials included softwares like PyRx and Biovia Discovery Studio [PyRx Tutorial https://youtu.be/UIk6ISuS5Lk] [13] and databases such as RCSB -PDB (for obtaining protein structures) [RCSB-PDB, https://www.rcsb.org/] [14] and PubChem (for obtaining ligand structures) [PubChem, https://pubchem.ncbi.nlm.nih.gov/] [15].

Potassium sensitive ATP channels, α-glucosidase and glycogen phosphorylase receptors were identified as potential T2DM targets through scientific studies and their structural information was taken from RCSB PDB- Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) [16].

The structures of the predominant ligands: Cynaroside, Rutin, Biorobin, Quercetin-3-O-beta-D-glucoside, Trifolin, Luteolin, Quercetin, Epicatechin, Catechin and Kaempferol were downloaded from the PubChem database; and using the Biovia Discovery Studio software they were prepared for binding to the protein targets to carry out docking studies. These docking studies were performed for each receptor using PyRx software and the binding energies were analyzed.

**Table 2** Physiochemical properties of antidiabetic drug glibenclamide [courtesy: PubChem]

| Compound name | Molecular formula | Molecular Weight (g/mol) | XlogP3 | H-bond donor | H-bond acceptor |
|---|---|---|---|---|---|
| Glibenclamide | $C_{23}H_{28}ClN_3O_5S$ | 494.0 | 4.8 | 3 | 5 |

**Table 3** Physiochemical properties of compounds from *Annona species* [courtesy: PubChem]

| Compound name | Molecular formula | Molecular Weight (g/mol) | XlogP3 | H-bond donor | H-bond acceptor |
|---|---|---|---|---|---|
| Cynaroside | $C_{21}H_{20}O_{11}$ | 448.4 | 0.5 | 7 | 11 |
| Rutin | $C_{27}H_{30}O_{16}$ | 610.5 | -1.3 | 10 | 16 |
| Biorobin | $C_{27}H_{30}O_{15}$ | 594.5 | -0.9 | 9 | 15 |
| Quercetin-3-O-beta-D-glucoside | $C_{21}H_{19}O_{12}$ | 463.4 | 1 | 7 | 12 |
| Trifolin | $C_{21}H_{20}O_{11}$ | 448.4 | 0.7 | 7 | 11 |
| Luteolin | $C_{15}H_{10}O_6$ | 286.24 | 1.4 | 4 | 6 |
| Quercetin | $C_{15}H_{10}O_7$ | 302.23 | 1.5 | 5 | 7 |
| Epicatechin | $C_{15}H_{14}O_6$ | 290.27 | 0.4 | 5 | 6 |
| Catechin | $C_{15}H_{14}O_6$ | 290.27 | 0.4 | 5 | 6 |
| Kaempferol | $C_{15}H_{10}O_6$ | 286.24 | 1.9 | 4 | 6 |

The physicochemical properties of flavonoids in *Annona species* were studied. The molecular formula, molecular weight, and XlogP3 values were identified. It was also analyzed that most of the compounds have many hydrogen bond acceptors.

## 3. Results and discussion

**Table 4** Docking results with the compounds and their binding energies

| Compound name | Binding energy (kcal/mol) | | | | | |
|---|---|---|---|---|---|---|
| | With glycogen phosphorylase | | With KATP | | With α-glucosidase | |
| | Max. | Min. | Max. | Min. | Max. | Min. |
| Cynaroside | -10.3 | -8.8 | -8.5 | -8.2 | -9.2 | -7.9 |
| Rutin | -9.7 | -9 | -8.8 | -8.4 | -9 | -8.1 |
| Biorobin | -9.6 | -8.7 | -7.2 | -6.7 | -8.5 | -7.5 |
| Quercetin-3-O-beta-D- glucoside | -9.3 | -8.4 | -8.1 | -7.9 | -7.6 | -6.6 |
| Trifolin | -8.7 | -8.2 | -8.4 | -8.2 | -7.6 | -6.8 |
| Luteolin | -8.7 | -7.6 | -8.1 | -7.0 | -7.8 | -7.1 |
| Quercetin | -8.6 | -7.5 | -7.2 | -7.1 | -8.2 | -6.8 |
| Epicatechin | -8 | -7.3 | -8.4 | -8.1 | -7.8 | -6.9 |
| Catechin | -8.6 | -7.5 | -8.1 | -7.0 | -7.9 | -6.9 |
| Kaempferol | -7.9 | -6.9 | -7.8 | -6.9 | -8 | -6.4 |

From the table, it was inferred that rutin had the most negative binding energy (-8.8) with KATP, cynaroside had the most negative binding energies with alpha glucosidase (-9.2) and glycogen phosphorylase (-10.3).

A molecular docking was also performed between the antidiabetic drug glibenclamide and the KATP channels; and a highly negative value of -8.7 was obtained, indicating spontaneous binding of the drug to the protein receptor. The mechanism of action of the drug consists of blocking the KATP channels causing cell depolarization and thereby leading to insulin secretion by the pancreatic cells.

On comparison of the binding energies it was found that rutin had a slightly more negative binding energy (-8.8) than glibenclamide (-8.7) with the KATP channels.

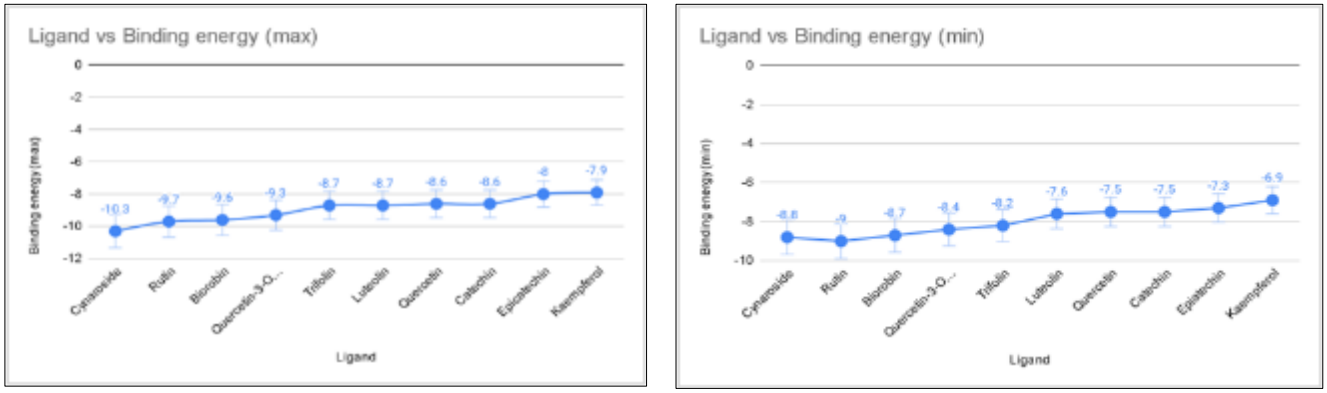


**Figure 3** Maximum and minimum binding energies of ligands to glycogen phosphorylase

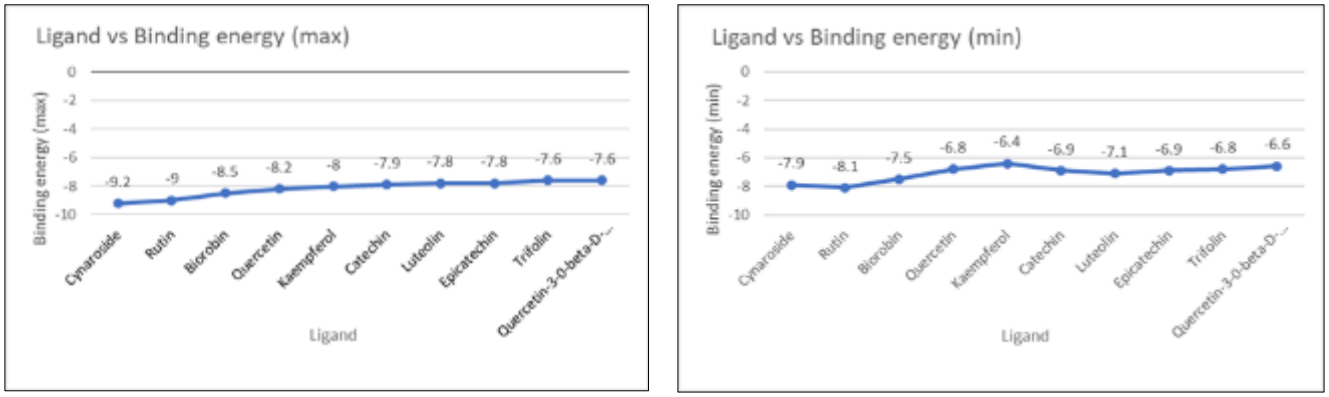


**Figure 4** Maximum and minimum binding energies of ligands to alpha glucosidase

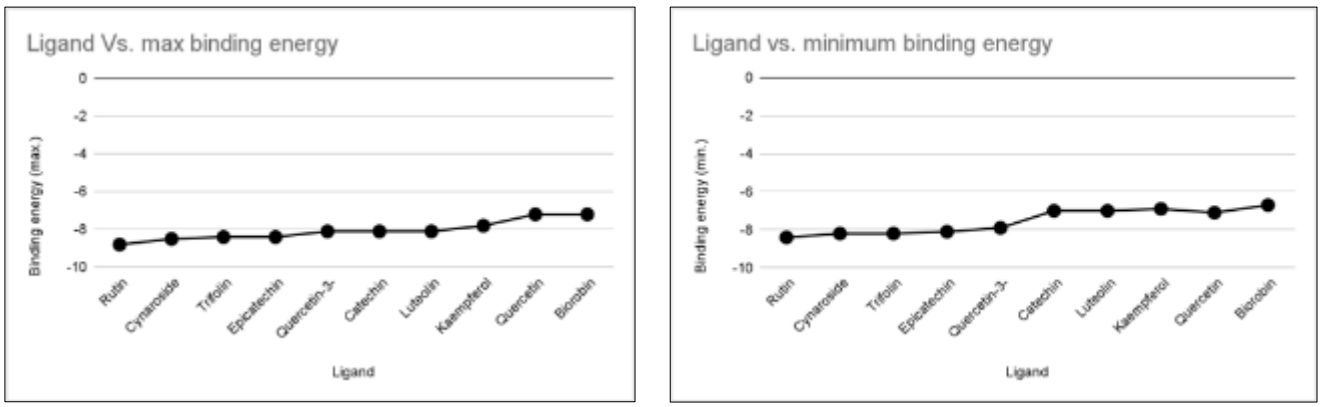


**Figure 5** Maximum and minimum binding energies of ligands to KATP

## 4. Conclusion

From the results, it was inferred that rutin had the most negative binding energy (-8.8) with KATP; cynaroside had the most negative binding energies with alpha glucosidase (-9.2) and glycogen phosphorylase (-10.3). This shows that these flavonoids have good binding affinities for their corresponding targets. Scientific journals validated that the flavonoid rutin would decrease hyperglycemia by working in a manner similar to that of oral antidiabetic drugs [17] and from the molecular docking studies, it was inferred that the flavonoid cynaroside has the highest potential to inhibit the activity of alpha glucosidase and glycogen phosphorylase and decrease glucose synthesis (based on the binding energy values).

It was also inferred that flavonoids would be more suitable to the body as it will have synergic effects by working through multiple mechanisms and have minimal toxic effects compared to conventional drugs like glibenclamide or metformin. Wet lab studies would be required for the in-depth analysis of the anti-diabetic properties of flavonoids.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Authors contribution*

Authors 1, 2 and 3 had equal participation in the concept and designing of this paper and in drafting it. Author 4 was involved in the analysis and interpretation of data and also in the critical revision of the manuscript.

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