

MOLECULAR DOCKING STUDY OF EPIGALLOCATECHIN GALLATE (EGCG) AS A THERAPY FOR TYPE 2 DIABETES MELLITUS

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Received 28 March 2024

Accepted 25 May 2024

Abstract

Epigallocatechin gallate (EGCG) has an effect in reducing sugar levels in the blood by inhibiting α -glucosidase enzyme, which is connected explicitly by hydrogen bonds and modifies the secondary structure and micro-environment of the enzyme reversibly and non-competitive. This study looks at the activity and interaction of EGCG as α -glucosidase inhibitors in the form of binding affinity and compound bonding profiles with receptors, including toxicity predictions and drug-likeness results. The research was performed *in silico* with molecular docking on Autodock Vina that integrated through PyRx, then viewed the compound's binding profile with receptor using Discovery Studio 2021 Client, toxicity prediction using ProTox-II and determination of drug-likeness using SwissADME based on Lipinski's rule of five guidelines. The control drugs used were acarbose and miglitol. The molecular docking results obtained that the binding affinity of EGCG is -8.4 kcal/mol while acarbose and miglitol are -13.8 kcal/mol and -5.3 kcal/mol respectively. There are amino acid residues similar to the drug control with various interactions like electrostatic, hydrophobic, and hydrogen bonds; then it has an inactive target for each toxicity parameter and has a molecular weight of 458.37 g/mol; Log P value of 1.01; H-bond donor of 8; and H-bond acceptor of 11 in the determination of drug-likeness. Based on these results, EGCG has effectiveness as α -glucosidase inhibitors predicted to be non-toxic; however, there are violations in determining drug-likeness.

Keywords: α -glucosidase inhibitors, Autodock vina, drug-likeness, ProTox-II

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by insufficient insulin secretion, sensitivity to insulin action, or both in the pancreas, resulting in high blood sugar levels (DiPiro *et al.*, 2020; Lestari, *et al.*, 2021). Type 2 diabetes mellitus (T2DM), where obesity, lack of activities, or a diet that is not healthy are modifiable risk factors, is the most common form of DM (Baynest, 2015; Galicia-Garcia *et al.*, 2020). According to the International Diabetes Federation (IDF), 537 million persons worldwide, aged 20 to 79, have diabetes. Diabetes also leads to 6.7 million fatalities per year or one every 5 seconds. Indonesia

comes in fifth place, with 19.47 million people living with diabetes. With a population of 179.72 million, the diabetes prevalence in Indonesia is 10.6% (International Diabetes Federation, 2021).

In the management of type 2 diabetes mellitus (T2DM), one pharmacological therapy regimen involves inhibiting the α -glucosidase enzyme, which serves as the primary digestive enzyme within the small intestine, expressed by brush border enterocytes in intestinal villi. This enzyme acts on disaccharides and oligosaccharides, releasing glucose from carbohydrate sources and consequently increasing postprandial blood glucose concentrations (Habtemariam, 2019). α -



glucosidase inhibitors' drugs competitively inhibit the enzyme by converting complex carbohydrates that cannot be absorbed into simple carbohydrates that can be absorbed in the small intestine; this mechanism ultimately results in a reduction in blood glucose levels and consequently leads to a decrease in postprandial insulin levels (Derosa and Maffioli, 2012; Dirir *et al.*, 2022).

Acarbose is one of the drugs belonging to the α -glucosidase inhibitors group where it is known to have a mechanism of action in inhibiting the α -glucosidase enzyme (Derosa and Maffioli, 2012; Dirir *et al.*, 2022). Despite its effectiveness in managing blood glucose levels, the prolonged administration of acarbose can give rise to various undesirable secondary effects, including but not limited to nausea, vomiting, flatulence, severe abdominal pain, diarrhea, bloating, and allergic reactions. Another drug in this group is miglitol, which has the same side effects as acarbose (Kumar *et al.*, 2018; Yuniarto and Selifiana, 2018; Hossain *et al.*, 2020; Liu *et al.*, 2021). These side effects are why new alternative drugs are needed to effectively inhibit the α -glucosidase enzyme and minimize side effects, including catechin compounds derived from the flavonoid compound group.

Catechins are natural flavonoid polyphenol compounds that have inhibitory activity on the α -glucosidase enzyme; one of them is epigallocatechin gallate (EGCG), which is derived from catechin compounds (Wen *et al.*, 2022). EGCG has an effect as an α -glucosidase inhibitor due to its acyl gallate on the C3 carbon hydroxyl group and hydroxyl structure on the B-ring (Wen *et al.*, 2022). Hydroxyl may contribute to distributing the electrons to stabilize free radicals and inhibit enzymes (Kumar and Pandey, 2013). EGCG distinctively connects to the α -glucosidase enzyme via hydrogen bonding and modifies the secondary

structure and micro-environment of the α -glucosidase enzyme in a reversible and non-competitive way, ultimately reducing its activity (Wen *et al.*, 2022). EGCG compounds have potential as a drug therapy regimen in treating T2DM, especially in inhibiting the α -glucosidase enzyme. Previously, a molecular docking research has been conducted by Nguyen *et al.* (2012) where the researchers used the same receptor also in this study which was 2QMJ with EGCG and EGCG glucoside (EGCG-G1) as their ligand compounds but with different molecular docking applications named Autodock 3.05 with the binding affinity value of -14.20 kcal/mol (EGCG). Therefore, the importance of this research is to find antidiabetic drugs with preliminary studies are carried out *in silico* through molecular docking studies because if it's done in the laboratory, it requires expensive costs. In addition, the *in silico* study of EGCG as an antidiabetic using PyRx has never been done so that for this reason the research is important.

This study was conducted *in silico* with chemical computation, i.e., molecular docking, by assessing compounds' binding affinity and interaction profile against a receptor. Molecular docking is a structure-based *in silico* method often used in drug development because it has a relatively short research period, is cheap and can save energy (Suharyani *et al.*, 2022). Determination of drug-likeness and toxicity prediction are also done in developing new drugs. Determination of drug-likeness is done to qualitatively assess the chances of a molecule to become an oral drug concerning bioavailability (Daina *et al.*, 2017), while toxicity prediction is used to provide information or knowledge about the harmful activity of a compound; hence, its unfavorable impacts on health and the environment can be evaluated effectively (Gupta *et al.*, 2022). This context led to the use of molecular docking *in silico* study to assess EGCG's binding affinity

and interaction profile with the α -glucosidase enzyme receptor, as well as the results of toxicity and drug-likeness predictions.

Research Methods

Instruments

The instrument used in this research is an ASUS A416EPO-VIPS554 computer set with an Intel CORE i5 processor, 8GB RAM, 512GB SSD storage, and Windows 11 (64-bit). The software used are Protein Data Bank (RCSB PDB), PubChem database, Autodock Tools v1.5.6 (Morris *et al.*, 2009), Discovery Studio Visualizer (DSV) 2021 Client v21.1.0.20298 (BIOVIA, 2021), Open Babel and Vina Wizard integrated in PyRx 0.8 software (Dallakyan and Olson, 2015), SwissADME server page (Daina,

Michielin and Zoete, 2017), and ProTox-II server page (Banerjee *et al.*, 2018).

Materials

The materials used in this research are crystal structure of 2QMJ (N-terminal Subunit of Human Maltase-Glucoamylase in Complex with Acarbose) that bound to several ligands named alpha_acarbose (native ligand), 2-acetamido-2-deoxy-beta-D-glucopyranose, sulfate ion, and glycerol (Sim *et al.*, 2008). This receptor was downloaded in "pdb" format from Protein Data Bank (<http://www.rcsb.org/pdb/>). The ligand compounds: acarbose, miglitol (control drugs), and epigallocatechin gallate (EGCG) were downloaded from the PubChem database with 3D structures in "sdf" format.

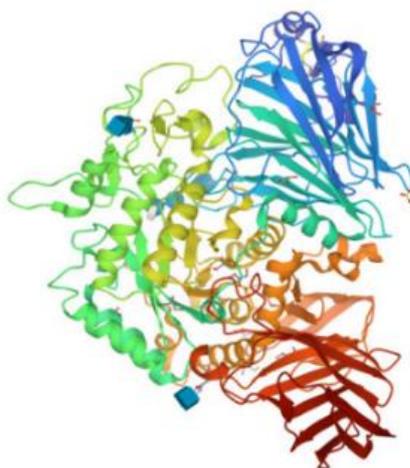


Figure 1. 3D structure of the α -glucosidase enzyme (Maltase-Glucoamylase)

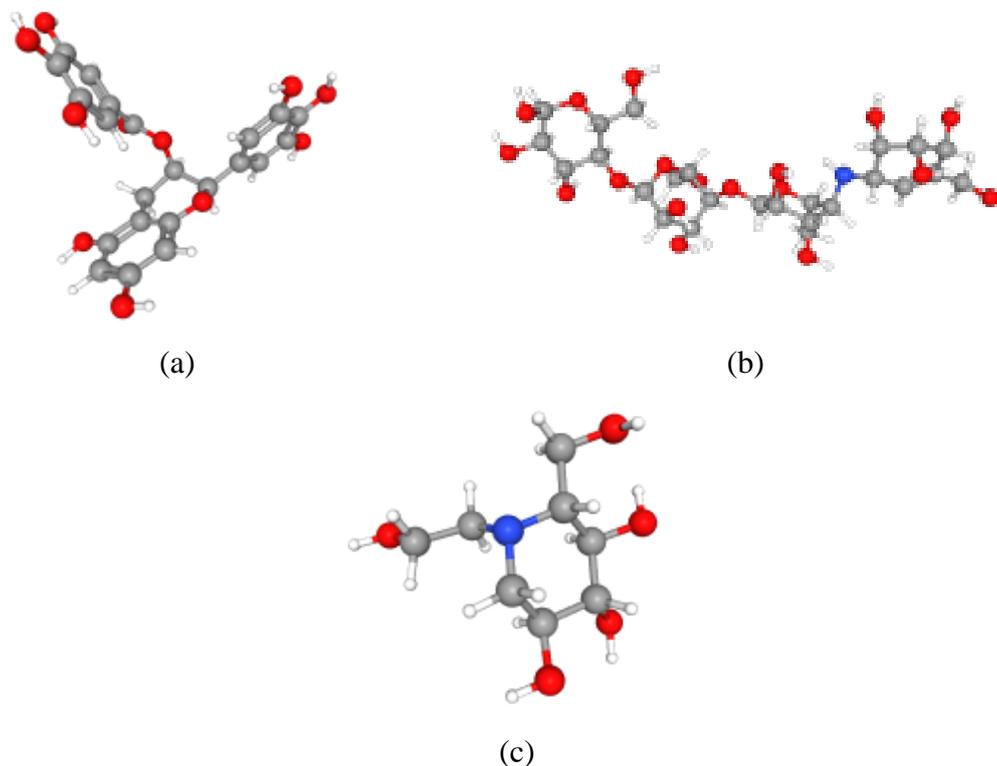


Figure 2. 3D structure of (a) EGCG, (b) Acarbose and, (c) Miglitol

Procedure

1) Preparation of receptor and native ligand

The α -glucosidase enzyme receptor was prepared using Discovery Studio Visualizer (DSV) 2021 Client to remove water residues, the atomic chain side of the protein data, and the native ligand bound to the protein. To present the location and coordinate point of the active site, Autodock Tools v1.5.6 was utilized for their determination. The gridbox dimension size is $40 \times 40 \times 44$ and the receptor's gridbox position shows x center = -21.727; y center = -6.323; z center = -5.281. After that, polar properties were added to the protein to be tested. The native ligand was obtained by separating it from the receptor and all unused molecules, then used as method validation. The receptor and native ligand were saved in "pdb" file format (Sari *et al.*, 2020; Dyas *et al.*, 2023; Irawan *et al.*, 2023).

2) Ligand preparation

The structure of Epigallocatechin Gallate (EGCG) and the control drugs acarbose and miglitol were prepared through OpenBabel integrated through PyRx by minimizing the energy of each ligand compound. Due to the existence of the conjugate gradient algorithm, energy minimization was accomplished using the universal force field (UFF). The compound files were converted into "pdbqt" format for further analysis (Aissouq *et al.*, 2021).

3) Validation docking method

The docking method must be validated to establish the proper position and docking procedure. The validity of the molecular docking approach is demonstrated by redocking the native ligand to the target protein that has been prepared (Shah *et al.*, 2019; Susanti *et al.*, 2019; Budiarto *et al.*, 2023). The target protein was α -glucosidase enzyme (Maltase-Glucoamylase) with PDB ID 2QMJ, which has a native ligand

named alpha_acarbose then see the RMSD value by using DSV 2021 Client.

4) Protocol docking and visualization of ligand compound

The molecular docking process was performed using Vina Wizard integrated in PyRx with an exhaustiveness value of 64 and a dimension size on the active site of 20 x 20 x 20 Å. The results were obtained by the binding affinity value (ΔG_{Bind}) and the binding of the ligand to the receptor target. The resulting complex compound was then analyzed for the visual mechanism between compound molecules and receptors. Visualization of the bond between the ligand and the receptor was observed through Discovery Studio Visualizer 2021 Client by displaying the type of bond between the receptor and ligand, followed by data analysis. (Sari *et al.*, 2020).

5) Drug-likeness and toxicity analysis of ligand compounds

The SwissADME server page (<http://www.swissadme.ch/index.php>) was used to view the drug-likeness of the investigated compounds. The canonical SMILES code of each tested compound was copied from PubChem and then entered into the SwissADME server. In toxicity, the ProTox-II

server page (https://tox-new.charite.de/prottox_II/) was used. Then, the canonical SMILES code of the compound test from PubChem, after which it was entered into the ProTox-II server with parameters such as LD₅₀ (Lethal Dose), toxicity class, and toxicity classification, namely organ toxicity and toxicity endpoints, Tox21-Nuclear receptor signaling pathways, and Tox21-Stress response pathways.

Results and Discussion

Validation of docking method

The results of redocking of receptor ligands showed the Root Median Square Deviation (RMSD) was 0.7522 Å. This RMSD value indicates that the receptor (2QMJ) is valid and can be used for further molecular docking studies. The visualization of the original and counterpart ligand positions can be seen in Figure 2 as overlapping. The magnitude of the RMSD value shows the accuracy of the calculation, where if the RMSD value < 2 Å, then the smaller the calculation error, so it is said to be a more accurate calculation value. If the RMSD value is > 2 Å, the deviation of the calculation results is getting bigger/invalid (Ferwadi *et al.*, 2017; Sari *et al.*, 2020).

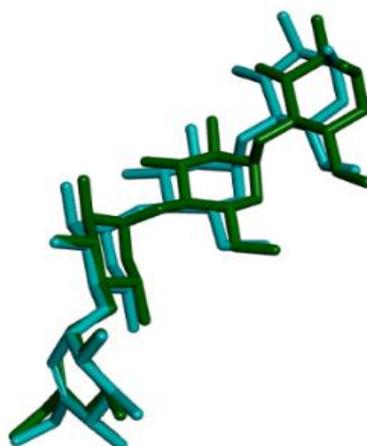


Figure 3. Overlay of native ligand (light blue) and test ligand (dark green) position

Molecular docking and visualization of ligand compound bonding with receptor

The results in Table 1 show that EGCG as a ligand test compound has a lower affinity value (-8.4 kcal/mol) compared to the control drug miglitol (-5.3 kcal/mol) but still higher than acarbose (-13.8 kcal/mol), which is a native ligand as well as the control drug at the α -glucosidase enzyme receptor stating that the native ligand has a stronger bond than EGCG.

Even so, EGCG is still said to be able to form a bond with the α -glucosidase enzyme because the low-affinity value means that the compound requires less energy when it binds, so it can be said that the compound has more significant potential to interact and form a strong bond with the target protein (Perumal *et al.*, 2017; Wijianto *et al.*, 2020; Wijianto *et al.*, 2020; Rena *et al.*, 2022).

Table 1. Docking results and amino acid residues that bound to α -glucosidase enzyme receptor

| Compounds | Binding Affinity (kcal/mol) | Hydrogen Bond Residues | Other Bonds/Interactions Residues |
|---------------------------------|-----------------------------|--|-----------------------------------|
| Epigallocatechin Gallate (EGCG) | -8.4 | Thr205, Tyr299, Arg526, Asp327, Asp542, Gln603 | Asp542, Tyr299, Phe575 |
| Miglitol (Control Drug) | -5.3 | Arg526, His600, Asp542 | Asp443 |
| Acarbose (Control Drug) | -13.8 | Asn207, Arg526, Thr544, Asp203, Met444, Asp542, His600, Asp327 | Thr205, Asp542, Asp443, Tyr299 |

Note: The **color-coded** amino acid residues have a similar mechanism as the native ligand

Amino acid residues describe the active sides of the 2QMJ receptor as antidiabetic activity. 2QMJ is a receptor of human maltase-glucoamylase where the active side is on residues Asn207, Arg526, Thr544, Asp203, Met444, Asp542, His600, Asp327. The amino acid residues obtained from the molecular docking process on the EGCG test compound are not entirely similar to the native ligand acarbose (Table 1). EGCG binds to amino acids **Arg526**, **Asp327**, and **Asp542** in the α -glucosidase enzyme protein, where these residues are similar to the native ligand. This result corresponds to previously study (Sim *et*

al., 2008), where the amino acids bound to the α -glucosidase enzyme protein, especially in acarbose, are bound explicitly by hydrogen bonds to the amino acids **Asp327**, **Arg526**, **Asp542**, and **His600**. This result may imply that the docking results are appropriate, so it can be said that EGCG affects the treatment of T2DM even though the amino acid residues are not entirely similar. The types of interactions that can be seen are hydrogen, electrostatic (π -anion), and hydrophobic (π - π T-shaped) (Wijianto *et al.*, 2020; Kurniawan *et al.*, 2023) (Figure 3).

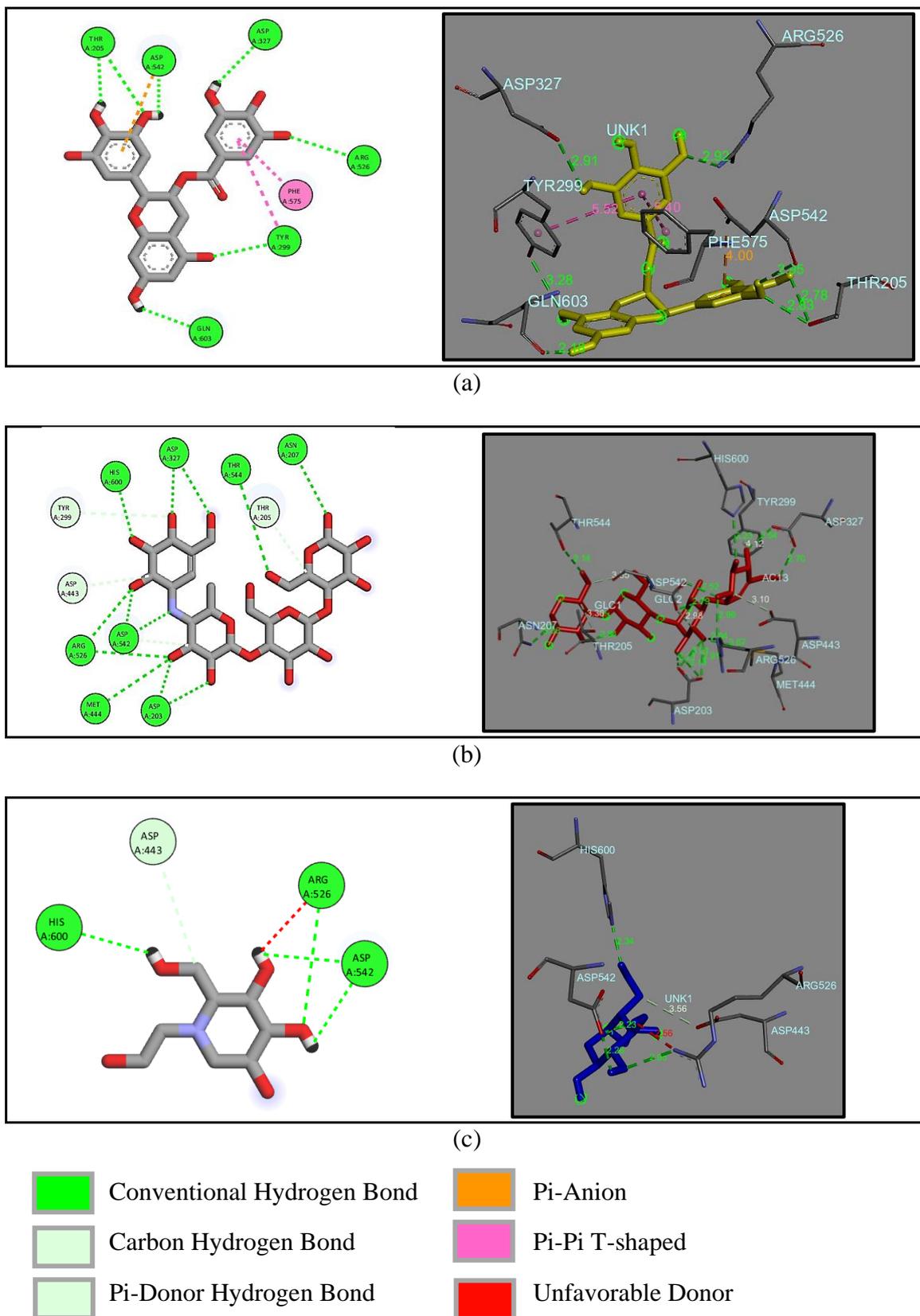


Figure 4. Interaction ligand-receptor of (a) EGCG; (b) Acarbose; and (c) Miglitol with 2QMJ receptor

Drug-likeness of ligand compounds

The meaning of "drug-like" depends on the drug's administration mode. RO5 (rule of five) initially addressed orally active compounds and then defined simple physicochemical parameters such as molecular weight ≤ 500 g/mol, log P value ≤ 5 , H-bond donor ≤ 5 , and H-bond acceptor ≤ 10 . These parameters

correspond to 90% of orally active drugs that have reached clinical phase II (Lipinski, 2004). The results in Table 2 state that EGCG violates two criteria of Lipinski's rule of five (H-bond donor and acceptor) and acarbose violates three criteria (molecular weight, H-bond donor, and acceptor), while miglitol fulfills all criteria.

Table 2. Drug-likeness results based on Lipinski's Rule of Five

| Compound | Molecular Formula | Molecular Weight (g/mol) | Parameter | | | Eligibility |
|---------------------------------|--|--------------------------|-----------|--------------|-----------------|-----------------------|
| | | | Log P | H-Bond Donor | H-Bond Acceptor | |
| Epigallocatechin Gallate (EGCG) | C ₂₂ H ₁₈ O ₁₁ | 458.37 | 1.01 | 8 | 11 | No (2 violations) |
| Acarbose | C ₂₅ H ₄₃ NO ₁₈ | 645.6 | -6.22 | 14 | 19 | No (3 violations) |
| Miglitol | C ₈ H ₁₇ NO ₅ | 207.22 | -1.95 | 5 | 6 | Yes (0 violations) |

Note: **Bolded** numbers indicate violations in Lipinski's Rule of Five

The physicochemical properties of a compound are seen from its characteristics in the form of molecular weight, log P value, H-bond donor, and H-bond acceptor, according to Lipinski. Molecular weight < 500 g/mol allows it to enter and penetrate the cell membrane quickly; compounds that are more than the determination cannot diffuse into cells. Log P value < 5 allows selective binding to target proteins; the lower the Log P value, the better and more accessible to dissolve in water. The compound will be hydrophobic when it has a higher Log P value. The higher the hydrophobic properties, the tendency to have higher toxic properties and less selective binding to target proteins/enzymes because these compounds will be stored longer and distributed more widely in the lipid bilayer. More energy is needed for the absorption process the higher the hydrogen bonding capacity, as demonstrated by the amount of hydrogen bond donors and acceptors (Syahputra et al., 2014; Sukmawaty et al., 2021).

Acarbose, proven to violate Lipinski's rule of five, is still used in clinical treatment therapy because it works locally on the surface of enterocytes in the digestive tract. Hence, the Lipinski parameters violated by acarbose are not significant. For EGCG, previous studies have overcome this by changing the drug delivery system such as nanoliposome and self-double-emulsifying drug delivery system (SDEDDS) (Schmeltz and Metzger, 2007; Furniturewalla and Barve, 2022).

Toxicity prediction

Toxicity prediction attempts to estimate a substance's toxicity level in the human body. This section was carried out using the ProTox-II website. The parameters tested were LD₅₀ (Lethal Dose), toxicity class and toxicity classification, i.e., organ toxicity involving hepatotoxicity; toxicity endpoints consisting of carcinogenicity, mutagenicity, immunotoxicity, and cytotoxicity; nuclear receptor signaling pathways representing AhR, AR, AR-

LBD, ER, ER-LBD, and PPRA-Gamma; and stress response pathways representing nrf2/ARE, HSE, MMP, p53, and ATAD5. The toxicity class is classified based on the Globally Harmonized System (GHS), where the toxicity class is divided into six classes based on the LD₅₀ value range (El-Din *et al.*, 2016) (Table 3 and 4).

In Table 3, EGCG has an LD₅₀ of 1000 mg/kg body with a toxicity class 4 (harmful if swallowed). When considering the predicted toxicity effects, EGCG is safe to consume at doses < 1000

mg/kg body. Table 4 shows that EGCG has no toxicity in each parameter tested with its probability value. The probability value in ProTox-II only indicates a prediction on each target toxicity parameter tested. Probability values with confidence below 70% (0.7) are usually omitted, indicating they are "Below Threshold." This can be seen with EGCG, which has a probability value for carcinogenicity of 0.54. This means that EGCG does not have carcinogenic properties by about 54%.

Table 3. Results of acute toxicity prediction of EGCG

| Parameter Classification | Target Parameter | Prediction Results |
|--------------------------|------------------------------------|--------------------|
| | | EGCG |
| Acute Toxicity | LD ₅₀ Toxicity class | 1000 mg/kg 4 |

Table 4. Results of organ toxicity, endpoints, and Tox-21 prediction of EGCG

| Parameter Classification | Target Parameter | Prediction Results | |
|--|---|--------------------|-------------|
| | | EGCG | Probability |
| Organ Toxicity | Hepatotoxicity | Inactive | 0.7 |
| | Carcinogenicity | Inactive | 0.54 |
| Toxicity End Points | Immunotoxicity | Inactive | 0.89 |
| | Mutagenicity | Inactive | 0.7 |
| | Cytotoxicity | Inactive | 0.82 |
| | Aryl hydrocarbon Receptor (AhR) | Inactive | 0.85 |
| Tox-21 Nuclear Receptor Signaling Pathways | Androgen Receptor (AR) | Inactive | 0.96 |
| | Androgen Receptor Ligand Binding Domain (AR-LBD) | Inactive | 0.95 |
| | Aromatase | Inactive | 0.98 |
| | Estrogen Receptor Alpha (ER) | Inactive | 0.87 |
| | Estrogen Receptor Ligand Binding Domain (ER-LBD) | Inactive | 0.89 |
| | Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma) | Inactive | 0.92 |
| | Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE) | Inactive | 0.98 |
| Tox-21 Stress Response Pathways | Heat shock factor response element (HSE) | Inactive | 0.98 |
| | Mitochondrial Membrane Potential (MMP) | Inactive | 0.79 |

| | | |
|---|----------|------|
| Phosphoprotein (Tumor Suppressor) (p53) | Inactive | 0.93 |
| ATPase family AAA domain-containing protein 5 (ATAD5) | Inactive | 0.97 |

Conclusions

EGCG has the potential as an α -glucosidase inhibitor in the therapy regimen of T2DM and has an inactive result for each toxicity parameter, which can be concluded that EGCG is safe to be used.

Acknowledgment

The authors thank the Pharmacy Study Program, Faculty of Medicine, Universitas Tanjungpura for supporting this research.

Conflict of Interest

The authors have no conflict of interest.

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