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In Silico Evaluation of the Anti-obesity and Hepatoprotective Potential of Epigallocatechin-Gallate (EGCG) and L-Theanine from Green Tea (*Camellia sinensis*)

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Abstract

Background: Obesity is a multifactorial disease characterized by excessive accumulation of body fat. More than 1 billion people worldwide live with obesity, as 1 in 8 deaths of non-communicable diseases are caused by obesity in 2024. The primary objective of obesity management is to improve conditions and reduce the risk of developing comorbidities through lifestyle management combined with pharmacotherapy. The only accepted pharmacological treatment from the Food and Drug Administration (FDA) is orlistat. However, there are popular alternatives by utilizing compounds in green tea (*Camellia sinensis*). **Method:** In silico analysis on EGCG and L-Theanine compounds found in *Camellia sinensis* were conducted to determine the feasibility of both compounds as alternatives pharmaceuticals candidates in managing obesity with hepatoprotective function using molecular docking techniques. **Results:** The molecular docking result demonstrated EGCG's affinity on PPARγ, the target receptor in standard drug orlistat, exhibited higher binding affinity compared to orlistat's affinity on PPARγ. Additionally, docking of L-Theanine compound with PI3K protein showed functional activation of PI3K by L-Theanine as one of the primary hepatoprotective pathways. **Discussion:** Higher binding affinity of EGCG through molecular docking indicates superior anti-obesity activity compared to standard drug orlistat. Hepatotoxicity side effects of EGCG can be mitigated by L-Theanine, which activates PI3K/Akt-NRF2, a hepatoprotective mechanism. **Conclusion:** In silico analysis revealed potential benefits on two compounds in *Camellia sinensis*, EGCG and L-Theanine. Combination of both compounds can be perceived as a new opportunity in development of obesity therapy with better therapeutic effects and safer hepatic protection**.**

Keywords: *EGCG, in silico analysis, L-Theanine, obesity, orlistat*

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1. INTRODUCTION

Obesity is a multifactorial disease characterized by the excessive accumulation of body fat. Globally, more than one billion people are living with obesity, including approximately 200 million men and 300 million women, with its prevalence increasing annually[1]. By 2024, it is estimated that one in eight deaths from non-communicable diseases will be associated with obesity[2]. Diagnosis is generally established based on a Body Mass Index (BMI) greater than 30 kg/m², indicating a significant excess of body weight[3].

Obesity is a major risk factor for non-alcoholic fatty liver disease (NAFLD). Excessive accumulation of adipose tissue leads to an increased flow of free fatty acids to the liver, resulting in triglyceride buildup within hepatocytes[1]. This condition triggers chronic inflammation, which may progress to steatohepatitis, fibrosis, and even cirrhosis[4].

The primary goal of obesity management is to improve the patient's overall health status and reduce the risk of obesity-related comorbidities. Obesity management typically begins with lifestyle modifications, which may be complemented by pharmacotherapy[5]. Lifestyle management of obesity focuses on dietary modifications that create a daily caloric deficit of 500–750 kcal, engagement in aerobic physical activity for at least 30 minutes per day across most days of the week, and behavioral interventions[6].

Orlistat is currently the only pharmacological agent approved by the U.S. Food and Drug Administration (FDA) for the long-term treatment of obesity[7]. The mechanism of action of orlistat involves binding to the active site of the lipase enzyme, thereby inactivating it. As a result, dietary triglycerides are not hydrolyzed into absorbable free fatty acids and monoglycerides, but instead are excreted unchanged in the feces[8]. Based on this mechanism, various studies have shown that orlistat may cause several side effects, including steatorrhea (fatty stools), fecal incontinence, and disturbances in mineral and electrolyte balance. Therefore, its use should be accompanied by supplementation with multivitamins containing vitamins A, D, E, K, and β-carotene[9].

Green tea (*Camellia sinensis*) is a medicinal plant known for its numerous health benefits, one of which is its potential role in promoting weight loss. Currently, green tea supplementation is widely utilized as an adjunctive therapy in the management of obesity. Its antioxidant properties are primarily attributed to its high

content of polyphenols, particularly catechins and flavonols, which are considered the main bioactive compounds responsible for its health benefits[10].

Catechin compounds in green tea are composed primarily of Epigallocatechin-Gallate (EGCG), which accounts for approximately 80% of the total catechin content. As the most abundant catechin, EGCG is recognized for its potent anti-obesity effects[10]. Several studies have demonstrated that administration of high-dose EGCG supplements for more than 12 weeks can lead to significant reductions in body weight, waist circumference, and total cholesterol levels[11]. However, long-term administration of high doses of EGCG has been associated with hepatotoxic effects, including increased oxidative stress and elevated liver enzyme levels such as *alanine aminotransferase* (ALT), *aspartate aminotransferase* (AST), and *alkaline phosphatase* (ALP)[12].

L-Theanine is a unique amino acid found in green tea, known for its safety, stability, ease of absorption and utilization, and lack of toxic side effects. Recent studies have demonstrated that L-Theanine possesses antioxidant and hepatoprotective properties[13]. Administration of L-Theanine has been shown to significantly reduce EGCG-induced transaminitis and attenuate oxidative stress caused by high doses of EGCG[14].

This study employed an in silico approach using molecular docking techniques to evaluate the potential of EGCG and L-Theanine from *Camellia sinensis* as anti-obesity drug candidates with hepatoprotective effects. Molecular docking, as part of computational chemistry, allows for the prediction and exploration of interactions between bioactive compounds from herbal sources and their target proteins in a safe and cost-effective manner[15]. Utilizing this computational approach supports the development of safer and more effective herbal-based therapies. Furthermore, research combining two active compounds from a single herbal source that target two receptors simultaneously offers novel value for advancing obesity therapy. Integrating these dual mechanisms presents the potential for developing target-specific drugs with additional protective benefits. Therefore, this study serves as an important first step toward the development of herbal medicine-based obesity treatments.

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2. METHODS

Structure Preparation and Potential Analysis of EGCG and L-Theanine

The compound structures and SMILES (Simplified Molecular Input Line Entry System) of EGCG and L-Theanine were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/), a comprehensive database of chemical compounds, accessed on December 25, 2024. SMILES is a line notation system that represents a molecule's chemical structure. These SMILES data were then used to predict the potential activities of the compounds via PASS Online (Prediction of Activity Spectra for Substances) (https://www.way2drug.com/passonline), which provides Pa (Probability of Activity) and Pi (Probability of Inactivity) values. A Pa value greater than 0.3 indicates that a compound is likely to exhibit significant biological activity.

Protein Ligand Structure Modeling

The target proteins utilized in this study were Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) and Phosphoinositide 3-Kinase–Protein Kinase B/Nuclear Factor Erythroid 2-Related Factor 2 (PI3K-AKT/NRF2). PPARγ was selected as the target receptor for docking with EGCG and orlistat to investigate their potential mechanisms in improving obesity-related metabolic conditions. Meanwhile, the PI3K-AKT/NRF2 pathway was targeted for docking with L-Theanine to evaluate its potential role in preventing hepatocyte apoptosis and promoting hepatoprotective effects.

The target protein sequences were retrieved from the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/) by specifying the protein name in the search field. The three-dimensional (3D) structures of the target proteins were modeled using the SWISS-MODEL web server (https://swissmodel.expasy.org/), which provides automated homology modeling of protein structures. Following structure prediction, validation of the modeled protein structures was conducted using the SAVES v6.0 web server (https://saves.mbi.ucla.edu/). Validation parameters such as the quality factor and Ramachandran plot were assessed to ensure the accuracy and reliability of the generated protein models.

Ligand Binding to Macromolecules

Prior to the molecular docking process, all target proteins were cleaned of water molecules using

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PyMOL software version 2.5. Docking between the ligands and natural compound macromolecules was then performed using PyRx software version 0.9.8. The docking results were expressed as binding affinity values between the target proteins and the natural compounds, as well as with the control ligand (standard drug). Validation of the docking results was conducted based on the Root Mean Square Deviation (RMSD) value, where an RMSD of less than 3 Å indicates that the docking results are acceptable.

Data Analysis

Molecular docking results are presented as binding energy values, which indicate the strength of the interaction between a compound and its target protein. A lower (more negative) binding energy value reflects a stronger and more stable interaction, suggesting higher affinity between the ligand and the protein's binding site.

Druglikeness and Toxicity Prediction

he prediction of druglikeness was conducted based on Lipinski's Rule of Five, which evaluates a compound's potential as an orally active drug in humans. The criteria include: fewer than 5 hydrogen bond donors, fewer than 10 hydrogen bond acceptors, a molecular weight of less than 500 g/mol, a log P value below 5, and molar refractivity in the range of 40–130. These parameters are used to assess the physicochemical properties and lipophilicity of candidate compounds. The prediction was performed using the SwissADME web server (http://www.swissadme.ch/).

Following the assessment of druglikeness, toxicity prediction was carried out using the ProTox-III platform (https://tox.charite.de). The objective of this analysis is to determine the LD_{50} (lethal dose 50) value, which represents the dose required to cause death in 50% of test organisms and serves as an important parameter in evaluating the compound's safety profile.

3. RESEARCH RESULTS

3.1 Structure and Potential Analysis of EGCG and L-Theanine

The molecular structures of EGCG and L-Theanine retrieved from the PubChem database, along with the potential activity prediction results obtained using PASS Online, are presented in Figure 1 and Table 1.

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Figure 1. Molecular structures of (A) EGCG and (B) L-Theanine retrieved from the PubChem database

Tabel 1. Predicted biological activities of EGCG and L-Theanine based on PASS Online analysis

Compounds	Potency	Potential Value	
		Pa	***Pi***
EGCG	Lipid peroxidase inhibitor	0,946	0,002
L-Theanine	Antitoxic	0,758	0,004

3.2 Protein Target Structures

The protein structures obtained form the NCBI Protein database are shown in Figure 2.

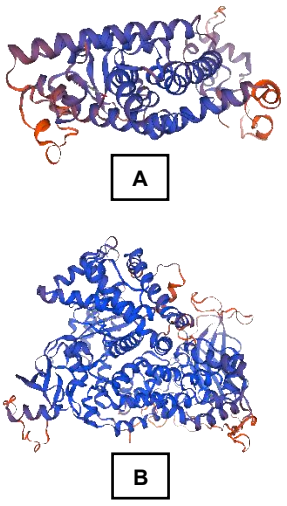


Figure 2. Target protein structures used for molecular docking: (A) PPARγ for EGCG, and (B) PI3K-AKT/Nrf2 for L-Theanine

The validation test results using the SAVES Webserver showed that the quality factor value of the PPARγ protein was 98.1627, and that of the PI3K protein was 94.5593. These values indicate that both protein structures are of high quality and valid, as the scores are close to the maximum value of 100[16].

In addition, the validation of the obtained protein structures was performed using Ramachandran plots for both models.

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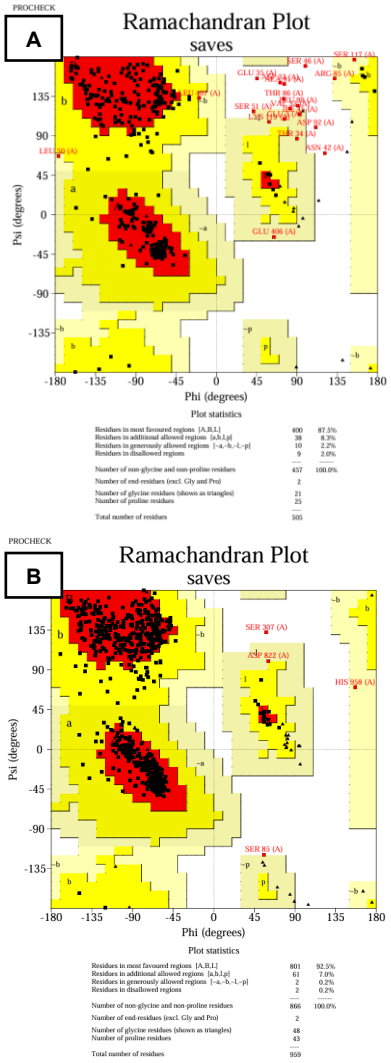
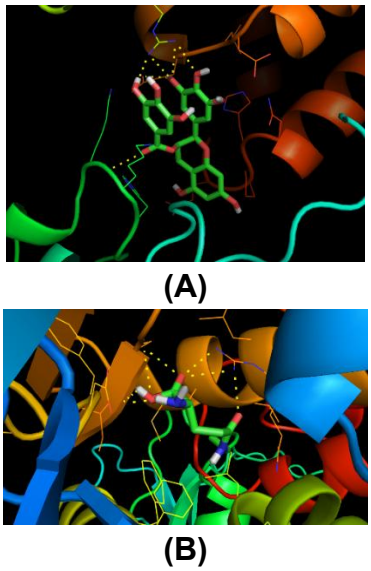


Figure 3. Ramachandran Plot of Protein Structure (A) PPARγ, and (B) PI3K-AKT/Nrf2 for L-Theanine

3.3 *Molecular Docking* Results

The optimized compounds, EGCG and L-Theanine, were docked to the PPARγ and PI3K proteins, respectively, using PyRx software. The docking process generated nine binding conformations for each compound–target protein pair: EGCG with PPARγ and L-Theanine with PI3K. The conformation with the lowest binding energy was selected for further analysis. Among the generated conformations, the one with the most negative binding energy was selected, indicating the most stable interaction. The visualizations of the docking interactions between EGCG and PPARγ, as well as L-Theanine and PI3K, are presented in Figure 3.



(A)

(B)

Figure 3. Visualization of molecular docking interactions showing the binding poses of (A) EGCG with PPARγ and (B) L-Theanine with PI3K, as generated by PyRx and visualized using PyMol

To evaluate the binding affinity of the EGCG compound to PPARγ, a comparative analysis was conducted using Orlistat as the standard drug control. A compound exhibiting a lower binding energy than the control ligand is considered to form a stronger and more

stable interaction with the target protein.

The validity of molecular docking is assessed based on the Root Mean Square Deviation (RMSD) value of each binding conformation. RMSD measures the deviation between the predicted binding position and the actual or reference position. A higher RMSD value indicates a greater deviation in binding accuracy. A comparison of docking interaction results and RMSD values is presented in Table 2. An RMSD value below 3.0 Å is generally considered acceptable for valid docking predictions

Table 2. Comparative analysis of molecular docking results, including binding energy values and RMSD scores, for EGCG, L-Theanine, and orlistat with their respective target proteins

Ligand	Macromolekul	Binding Energy (kcal/mol)	RMSD (Å)	Interaction type
Orlistat	PPARγ	-6,1	1,687	Hydrogen bond
EGCG	PPARγ	-7,5	2,378	Hydrogen bond
L-Theanine	PI3K	-5,6	2,930	Hydrogen bond

3.4 Drug-Likeness and Toxicity Prediction Results

Table 3 presents the outcomes of the drug-likeness prediction analysis, highlighting the pharmacokinetic feasibility of EGCG and L-Theanine as potential drug candidates.

Table 3. Drug-Likeness Evaluation of EGCG and L-Theanine Based on Lipinski's Rule of Five

No	Compounds	*Lipinski's Rule of Five* Criteria Components				
		H^+ atom donor	H^+ acceptor	Molecular weight	Log P	Molar refractivity
1	EGCG	8	11	458,37	0,95	112,06
2	L-Theanine	3	4	174,20	-1,42	43,24

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Based on the data presented in Table 3, EGCG fulfills three of Lipinski's Rule of Five criteria, while L-Theanine meets all of the criteria. The number of hydrogen bond donors exceeding five and hydrogen bond acceptors exceeding ten in EGCG indicates its low oral absorption, bioavailability, and water solubility. Meanwhile, the results of the toxicity prediction for EGCG and L-Theanine are presented in Table 4. Both compounds are classified under toxicity class IV, suggesting that careful dose optimization is required. As potential candidates for combination therapy in obesity treatment with hepatoprotective properties, EGCG and L-Theanine may be co-administered at doses below their respective lethal dose 50 (LD_{50}) values.

Table 4. Predicted Toxicological Classification and LD_{50} Values of EGCG and L-Theanine Based on In Silico Analysis

No	Compounds	LD_{50}	Toxicity Class
1	EGCG	1000 mg/kg	IV
2	L-Theanine	1750 mg/kg	IV

4. DISCUSSION

The activity prediction of EGCG using PASS Online showed a Pa value of 0.946 (Pa > 0.3), indicating strong potential as a lipid peroxidase inhibitor. This activity may contribute to inhibiting the lipid peroxidation process often associated with obesity. Meanwhile, L-Theanine exhibited a Pa value of 0.758 and was predicted to possess antitoxic properties. The combination of these two compounds appears promising, as the potential hepatotoxic risk of EGCG could be mitigated by the protective effects of L-Theanine.

Protein structure validation was performed to ensure the suitability of the models before the molecular docking process. Ramachandran plot analysis revealed that the PPARγ model had 87.5% of residues in the most favored regions, 8.3% in additional allowed regions, 2.2% in generously allowed regions, and only 2.0% in disallowed regions, indicating that more than 95% of the residues were within acceptable regions, validating the structure for in silico studies. In comparison, the PI3K model demonstrated higher quality, with 92.5% of residues in the most favored regions and only 0.2% in disallowed regions, resulting in more than 99% of residues being within acceptable regions. According to the criteria of Laskowski et al. (1993)[17], a protein model is considered to have adequate stereochemical quality if ≥90% of the residues are

in the most favored regions and <5% are in disallowed regions. Therefore, both structures were deemed suitable for molecular docking analysis[18].

Based on the validated protein structures, molecular docking was performed to evaluate the potential interactions between EGCG and L-Theanine with the target proteins PPARγ and PI3K. The analysis showed that EGCG exhibited a lower binding energy value than the reference ligand, orlistat, suggesting a potentially higher affinity for the PPARγ receptor. However, it is important to emphasize that these findings are computational predictions and must be further verified through in vitro and in vivo studies before biological confirmation can be made.

Meanwhile, docking of L-Theanine with the PI3K protein suggested potential activation of a hepatoprotective pathway involved in regulating antioxidant gene expression, which could theoretically reduce the risk of oxidative damage to liver cells, including damage potentially induced by EGCG at certain doses. Additionally, RMSD values below 3 Å for both docking results further support the reliability of the ligand orientation within the protein's active site, confirming that the models meet the quality standards required for in silico ligand–protein interaction analysis.

Peroxisome Proliferator-Activated Receptors (PPARs), particularly PPARγ, are ligand-activated nuclear receptors that respond to fatty acids and their metabolites. Upon ligand binding, PPARγ forms a heterodimer with the retinoid X receptor (RXR), and this complex subsequently regulates the transcription and expression of target genes[19]. This receptor is expressed in various body tissues, including white and brown adipose tissue, liver, colon, and muscle. In general, PPARγ functions as a target receptor for its agonists, regulating the expression of genes involved in glucose and lipid metabolism[20]. Several therapeutic approaches for obesity and diabetes employ PPARγ agonists, as they are capable of regulating insulin-sensitive adipocyte differentiation in subcutaneous fat while simultaneoisly reducing visceral fat mass. In addition, PPARγ agonists enhance insulin sensitivity in skeletal muscle and the liver[21].

In addition to being activated by endogenous ligands such as fatty acids, PPARγ can also be activated by various natural compounds found in medicinal plants and spices, including flavonoids, alkaloids, natural acids (e.g., arachidonic acid, hydroxypentanoic acid, taurine),

terpenoids, and phenolic acids. Several of these bioactive compounds have demonstrated therapeutic potential in improving conditions such as atherosclerosis, dyslipidemia, and obesity[22]. Natural compounds that act as PPARγ ligands tend to exhibit more favorable drug-like properties compared to synthetic compounds. They often possess-superior physicochemical characteristics, better bioavailability, and demonstrate high affinity and selectivity toward their molecular targets[23].

In green tea (*Camellia sinensis*), EGCG is classified as a catechin compound and represents its main active component. EGCG is found in higher concentrations in young leaves compared to mature ones. This compound significantly contributes to the characteristic taste of green tea, particularly its bitterness and astringency[10]. Research conducted by Li et al. (2018) demonstrated that administration of EGCG to experimental animals with obesity models effectively reduced weight gain and adipose tissue accumulation[24]. Other studies involving human subjects have also evaluated the effectiveness of green tea as a therapeutic agent for obesity. Green tea, either in its original form or in capsule preparations containing its full constituents, has been shown to significantly contribute to weight loss in individuals with obesity. This effect is associated with mechanisms such as adipocyte size reduction, enhanced lipolysis, and the prevention of fatty acid peroxidation in the body[25].

Meanwhile, other studies have reported hepatotoxic side effects associated with EGCG. High concentrations of EGCG, such as those found in green tea extract equivalent to the consumption of six cups per day as an anti-obesity therapy, have been shown to increase serum alanine aminotransferase (ALT) levels. This effect is linked to the metabolism of green tea polyphenols in the liver[12]. The metabolic byproducts of EGCG can develop into reactive oxygen species (ROS), which may cause damage to hepatocytes[12].

The PI3K/Akt-NRF2 signaling pathway is one of the intracellular mechanisms activated in response to oxidative damage in liver cells to maintain cellular homeostasis. This pathway is also considered a therapeutic target for Non-Alcoholic Fatty Liver Disease (NAFLD), hepatitis, and liver fibrosis due to its role in sustaining intracellular stability [26,27].

L-Theanine is one of the bioactive compounds in green tea that may act as a hepatoprotective agent, particularly when co-administered

with EGCG. In vivo studies have demonstrated that L-Theanine can attenuate EGCG-induced elevations in liver enzymes (ALT, AST), inflammation, and hepatocyte necrosis. This protective effect is associated with enhanced activity of antioxidant enzymes such as glutathione, superoxide dismutase (SOD), and malondialdehyde (MDA), which are regulated through the Nrf2 signaling pathway, a key mechanism for cellular defense against oxidative stress and inflammation[14].

Based on the results of molecular docking, L-Theanine demonstrated a negative binding energy with PI3K as its receptor protein and fulfilled all the criteria of Lipinski's Rule of Five, indicating good drug-likeness. The isolation of EGCG and L-Theanine from green tea (Camellia sinensis) shows promising potential as a combination therapy targeting obesity through specific molecular pathways. To improve the pharmacokinetic properties and bioavailability of these compounds, the use of nanoparticle-based drug delivery systems can be considered. Previous studies have shown that EGCG encapsulated in lipid-based nanoparticles exhibits enhanced stability and pharmacokinetic profiles[28]. The application of such nanotechnology may complement in silico predictions by providing a more comprehensive insight into the compounds mechanisms of action and their potential effectiveness as therapeutic agents.

5. CONCLUSION

This in silico analysis demonstrates the potential of EGCG from *Camellia sinensis* as an anti-obesity therapeutic candidate. Molecular docking modeling predicts the compound can act as a PPARγ agonist. The co-occurrence of L-Theanine in the same plant is predicted to mitigate the potential hepatotoxic side effects. Although predictive in nature, these findings suggest that the EGCG and L-Theanine combination represents a promising and innovative approach for developing obesity therapies with an improved safety profile.

6. SUGGESTION

To strengthen the initial findings from this in silico analysis, further validation is required. Before proceeding to more complex biological studies, it is recommended to conduct additional in silico analyses, including Molecular Dynamics (MD) Simulation, ADME and Toxicity prediction, Pathway Enrichment Analysis, and QSAR modeling. These analyses will improve the validity of the observed compound interactions.

Once the supplementary in silico data provides stronger validation, further research on the pharmacokinetics of both compounds can be performed to determine their interactions and potential synergy, and to optimize the combination dosage. This study can then serve as a crucial initial step for subsequent drug development studies.

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