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Original Research Article

In Silico Screening and ADMET Profiling of Daidzein and Genistein from Fermented Soybean (*Tempeh*) against Antiangiogenic and Inflammatory Proteins: Potential Antipreeclampsia Agents

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ABSTRACT

Preeclampsia is a pregnancy complication characterized by multiorgan damage and the latest preeclampsia treatment targets oxidative stress and inflammation. The use of fermented natural products such as fermented soybean, which contains the antioxidants Daidzein and Genistein can ameliorate the aforementioned conditions. Therefore, this study aimed to examine the potential of dainzein and genistein from fermented Soybean Extract (STE) as key protein targets against preeclampsia. Different tools were also used, including Protein Data Bank (PDB), SMILES downloaded from PubChem, and AutoDock 1.5.6. Validation was performed using the RSMD method, while ADMET analysis was conducted with the SwissADME and pkCMS applications. The results showed the presence of daidzein and genistein in *tempeh*, these two compounds indicated high interaction with all target molecules by forming hydrogen bonds and active residues. Also, ligand binding with sFlt-1 and NLRP3 showed affinity below that of the original ligand, suggesting the need for further studies on the inhibition process. Similarly, MDA and Gasdermin D showed stable affinity binding with hydrogen bonding media (<4Å). The ADMET profile showed that the two compounds have high intestinal absorption, low toxicity, and good bioavailability. These results show that daidzein and genistein from *tempeh* extract have good predicted druglike-ness property and potential to inhibit the protein targets in preeclampsia pathogenesis, specifically those in oxidative stress and pyroptosis. However, the effectiveness of angiogenic and inflammatory binding needs biological validation for applications as an adjuvant therapy from natural products.

Keywords: ADMET, Angiogenic, Antioxidant, *In Silico* Analysis, Pyroptosis, Preeclampsia

Introduction

Preeclampsia is a multi-organ disorder with clinical characteristics of hypertension and proteinuria in pregnancy of more than 20 weeks.[1] It causes maternal death in 2-8% of cases in the world.[2] This condition is higher in developing countries, including Africa, America, and Asia and it to more than 50,000 deaths each year[3] because complications can cause eclampsia, HELLP (hemolysis, increased liver enzymes, low platelet count) syndrome, and multi-organ failure,[4] resulting to death to if not immediately and properly managed.

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Management of preeclampsia consists of close monitoring, antihypertensives such as labetalol and nifedipine, and seizure prophylaxis with magnesium sulfate (MgSO4).[5] The definitive solution to preeclampsia is currently termination of pregnancy to eliminate the cause of the problem from the placenta.[6] However, this decision has a high risk of neonatal complications, considering the gestational age is not full-term.[7] Interventions for preeclampsia are increasingly being developed while the causes are still being studied. In this line, previous studies have shown that systemic oxidative stress, endothelial dysfunction, and inflammation are the main problems of preeclampsia. Therefore, interventions that address oxidative stress, angiogenic stress, and inflammation are urgently needed to curtail the adverse effect of this condition.[2]

Moreover, promising target biomarkers for preeclampsia treatment include several molecules that play a significant role in antiangiogenic, oxidative stress, and antiinflammation. Among these molecules are soluble Feline McDonough Sarcoma-like tyrosine kinase-1 (sFlt-1), a well-known antiangiogenic factor.[8] in addition, malondialdehyde (MDA), a marker for oxidative stress[9], and inflammation components such as NLRP3 and gasdermin D, which mediates inflammatory cell death through pyroptosis.[10] These biomarkers not only reflect the severity of preeclampsia but can also be an alternative treatment solution by finding antioxidants that can bind to molecules, resulting to their inhibition. Over the years, natural compounds were shown to inhibits oxidative stress and inflammatory associated diseases. These

compounds such as quercetin and resveratrol have been used as antioxidants to abrogate the aforementioned conditions. Natural products intervention came up as a results of setbacks from clinical practice to alleviate preeclampsia.[11,12]

To increase bioavailability, widely available natural products, such as fermented soybeans (*tempeh*), with antioxidant glycoside are considered as alternative intervention for preeclampsia.[13] T*empeh* is one of the fermented soybean products with *Rhizopus oligosporus* fungus, widely consumed by Indonesians.[14] Fermented Soybean allows for better absorption in the body because the antinutrient and phytate content have been removed via fermentation process. This microbial fermentation process, either through bacteria or fungi, degrades these antinutritional factors, thereby increasing the digestibility and bioavailability of protein and minerals. Typical compounds of fermented soybeans are daidzein and genistein, which have shown potent antioxidant and anti-inflammatory activities.[15] Daidzein and genistein, along with derivatives, have been shown to modulate the inflammatory response in various inflammatory diseases. For instance, 8-prenyl daidzein and 8-prenyl genistein effectively suppress the inflammatory response in macrophages by inhibiting NF-κB activation and reducing MAPK pathway activation.[16] Several investigations have shown that both fermented and non-fermented soybeans modulate cytokine signals, oxidative stress, and cell survival and this was attributed to their natural compounds in an *in vitro* studies.[17,18]

The potential of multi-targeted therapy by daidzein and genistein aglycone compounds in preeclampsia cases is still speculative. In the presence study, molecular docking technique and ADMET test was used to predict and investigate interactions in preeclampsia-associated target molecules with daidzein and genistein from fermented soybeans. This approach permits preliminary screening to identify drug similarity, safety, and binding affinity, lowering the demand for costly and extended laboratory studies.

Based on the description above, this study aims to predict molecular interactions and pharmacokinetic properties of daidzein and genistein, in relation to key protein targets associated with preeclampsia, namely MDA, sFlt-1, NLRP3, and Gasdermin D using an in silico study as a potential approach for natural invention against preeclampsia.

Materials and Methods

Tempeh preparation

Soybean tempeh products used were obtained from a local producer "Tempe Sehat" yang affiliated with the Indonesian Tofu and Tempeh Cooperative Primer in Bandar Lampung City, Lampung Province, Indonesia. Fermented soybean was determined used Organoleptik method at Functional Service Unit of Tawangmangu Traditional Health Services, Dr. Sarjito General Hospital, with the number T1.02.04/Dn6/19292.938/2024 dengan Famili Fabaceae, spesies clycine maz (L.) Merr, Sinonim phaeouls max L.

Initially, the *tempeh* was dried in an oven at 40°C for 24 hours to remove moisture, and then ground into a powder sieved through a 50-mesh sieve. The powder was subjected to maceration using 70% ethanol in a 1:10 (w/v) ratio. The mixture was stirred periodically and left to macerate for 72 hours. Subsequently, the fermented soybean filtrate was filtered and concentrated using a rotary evaporator at a temperature of 40ºC until a slurry filtrate was obtained. The evaporated slurry filtrate was then placed in an oven at 40°C until a stable fermented soybean extract was obtained. This procedure was performed at the functional service unit of Tawangmangu Traditional Health Services, Dr. Sarjito General Hospital.

The fermented soybean extract was tested for the flavonoid antioxidant content using Quadrupole Time-of-Flight Mass Spectrometry (QTOF-MS).[19].

Target protein molecule

This study used an ASUS i5 laptop for preparation, docking, and validation. Target proteins, namely sFLT-1, MDA, NLRP3, and Gasdermin, were set, and then the codes were downloaded from the Protein Data Bank (PDB) (https://www.rcsb.org/).[20] The obtained receptors with their ID are MDA (6VJ3), SLFT1 (6JQR), GASDERMIN (5TIB), and NLRP3 (8WSM). The document was saved in pdb format according. The classification used comprises Origin of human species macromolecules, resolution in Å units, and RSMD value with a limit of 2-5 Å. The crystal structure of the protein was prepared by removing water molecules, co-crystal ligands, and ions using the AutoDock Tools 1.5.6 software. Polar hydrogen and Gasteiger were then added before the file was stored in PDBQT format. Three original ligands were redocked on all target molecules to validate the docking results.

Ligand preparation

The two-dimensional structures of daidzein and genistein downloaded along with their SMILES PubChem (https://pubchem.ncbi.nlm.nih.gov/) to confirm their chemical identity.[21] The structure of daidzein ($C_{15}H_{10}O_4$; PubChem CID: 5281708) and genistein ($C_{15}H_{10}O_5$; PubChem CID: 5280961), were made in SDF format, then converted to PDBQT and optimized energy using MMFF94 using PyRx 0.8. The results were decoyed, pasted into the VegaZZ software in the edit-Build-IUPAC column, and saved in pdb format.

Molecular Docking Analysis

Autodock Tool 1.5.6 was used to prepare protein targets. Polar hydrogens were introduced, water molecules were eliminated, Gasteiger charges were allocated, and the proteins were saved in pdbqt format. After cleaning and adding hydrogens along with charges, the ligands used were also saved in the same format [22].

Autogrid 4 was used to create grid boxes centered on each target protein active site. The CMD interface was used to run the grid parameter file (.gdf), which was configured using verified binding coordinates. Autodock4 was used to run docking simulations, and every pair of ligands and protein underwent 100 iterations. Docking logs (.dlg) were created using docking parameter files (.dpl), and validation was performed by redocking native ligands into the crystallographic binding sites of the respective proteins. The protocol was considered valid when the root mean square deviation (RMSD) between native and redocked poses was ≤ 2.0 Å. Docking results were analyzed using AutoDockTools and visualized in BIOVIA Discovery Studio.[23]

ADMET (Absorption, distribution, metabolism, excretion, and toxicity) prediction

SwissADME (http://www.swissadme.ch)[24] was used to predict pharmacokinetic and toxicity properties. ADME parameters included absorption, distribution, metabolism, excretion, toxicity, and drug-likeness evaluation based on Lipinski's rule of five[25,26], using the boiled egg method and radar bioavailability[27]. PkCSM and proTox 3.0[28,29] were used to estimate toxicity class, LD_{50}, and target organ. Lipinski's rule of five does not allow more than one violation[30].

Results and Discussion

The results showed that fermented soybean*t* positively contained Daidzein and genistein. This study focused on evaluating the potential of daidzein and genistein as candidates for the management of preeclampsia agents through an *in silico* approach. *Molecular docking* tests were performed on four primary protein targets that play a role in the pathogenesis of preeclampsia, namely NLRP3 inflammasome, MDA, sFlt-1), and Gasdermin D. Each docking result was validated by re-docking the original ligand to ensure the accuracy of the prediction and the position of the grid box used. The docking simulation was validated by re-docking the original ligand to each target protein using predetermined grid box parameters and coordinate centers. The Root Mean Square Deviation (RMSD) value between the position of the docked ligand and the crystal structure was measured to assess the accuracy of the simulation. Based on international criteria, an RMSD value of ≤2 Å shows that the docking method and parameters used are valid and can be used for docking the test ligand.

Tables 1 and 2 show that both daidzein and genistein from fermented soybean extract have strong affinity binding to target proteins in the

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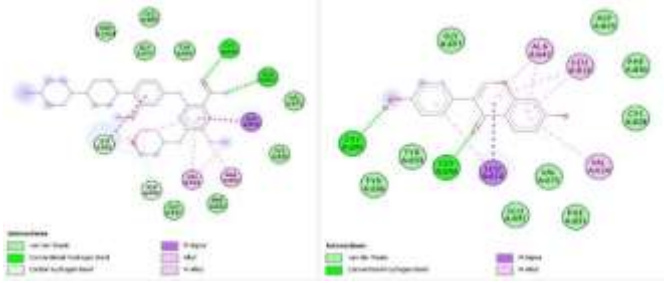
pathophysiology of preeclampsia (sFlt-1, MDA-related protein, NLRP3 inflammasome, and Gasdermin D). Ligand binding to MDA and Gasdermin D is more stable than sFLT-1 and NLRP3. This is because the ligand affinity is lower in MDA and Gasdermin than in targets molecule. Both showed significant antioxidant properties by scavenging free radicals such as superoxide anion, hydroxyl radical, and hydrogen peroxide. In previous research Genistein has been shown showing strong antioxidant capacity.[31]

Table 1: Molecular docking results of *tempeh* extract (daidzein and genistein) against four target proteins

Protein	Compound	ΔG Binding Score (kcal/mol)	Inhibition constant (μM)	RSMD	Interactions of amino acid residues		
					Bond Hydrogen	Bond *Vanderwaals*	Bond other
sFLT-1	Original ligand (C6F)	-7.58 ±0.01	2.78	1.02	Cys694. Glu692	Leu616. Asp698	Val624. Ala642. Leu818
	Daidzein	-6.11 ±0.00	33.11		Cys695. Cys694	-	Leu616. Val624. Ala642. Leu818
	Genistein	-6.71 ±0.00	12.02		Cys695. Cys694. Glu692	-	Val624. Leu818. Ala642. Leu616
MDA	Original ligand (QYA)	-5.84 ±0.02	51.91	0.50	Thr199. Gln92. Gol303. Asn67	His94	Ile91. Leu198. Glu106. Trp209. Phe131. Val121
	Daidzein	-5.94 ±0	43.94		Gln92	-	Ile91. Phe131. Val121. Leu198. His94
	Genistein	-6.02 ±0.0	38.58		Pro201. Thr200. His119. His94. His96	-	Leu198. Pro202
NLRP3	Original ligand (XE3)	-11.33 ±0.03	0.0049	1.57	Gly229. Thr233. Ile234. Thr169	Tyr168. Arg167	Lys232. Pro412. Phe373
	Daidzein	-7.57 ±0	2.83		Arg167. Ile521		Tyr381. Trp416. Leu413
	Genistein	-7.92 ±1.09	2.83		Ile521. Arg167		Leu413. Trp416. Tyr381
Gasdermin D	Original ligand (PRD_900001)	-5.93 ±0.02	44.54	0.02	Asp14. Asn12. Glu111. Lys15. Glu153. Tyr155. Trp62. Asp65. Arg66	-	Trp340
	Daidzein	-7.30 ±0	4.46		Glu111. Lys15. Trp340	-	Tyr155. Glu153. Arg344. Pro154
	Genistein	-6.96 ±0	7.88		Lys15. Glu111. Trp340	-	Tyr155. Arg344. Glu153. Pro154

Table 2: 3D presentation of molecular docking and 2D presentation of binding of components with intermolecular bonds

Binding molecule	3D Visualization	2D presentation binding of components with intermolecular bonds
sFLT-1 with Daidzein		

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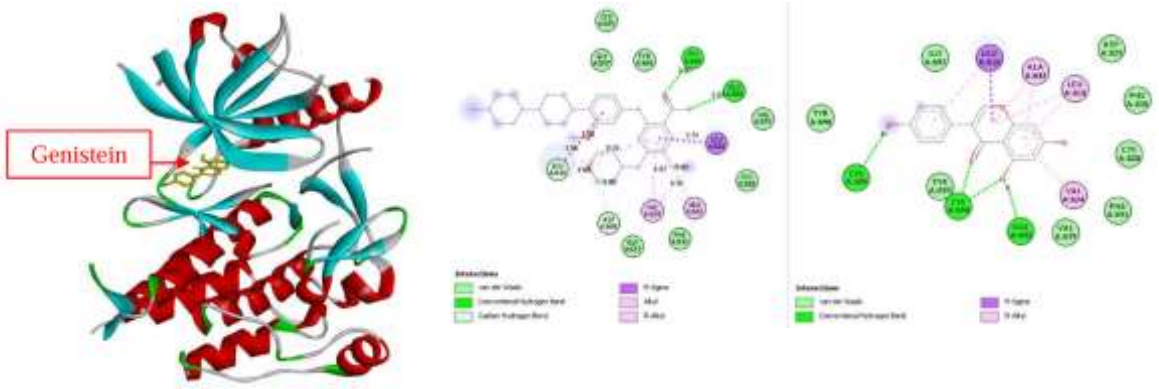
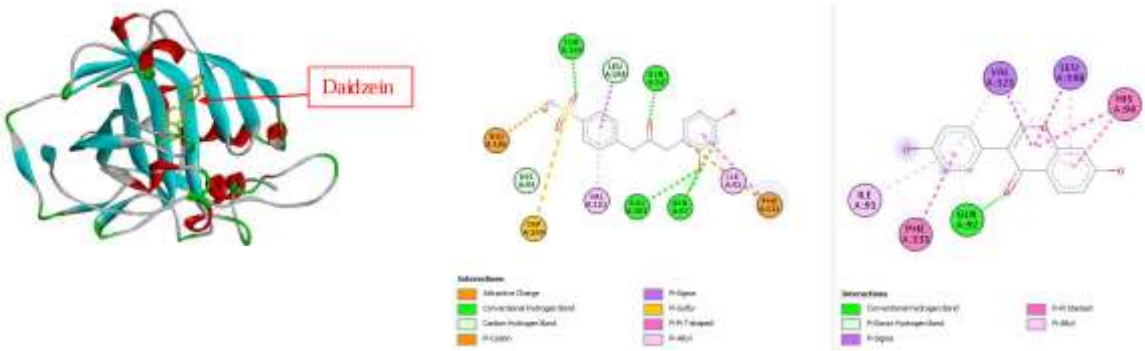
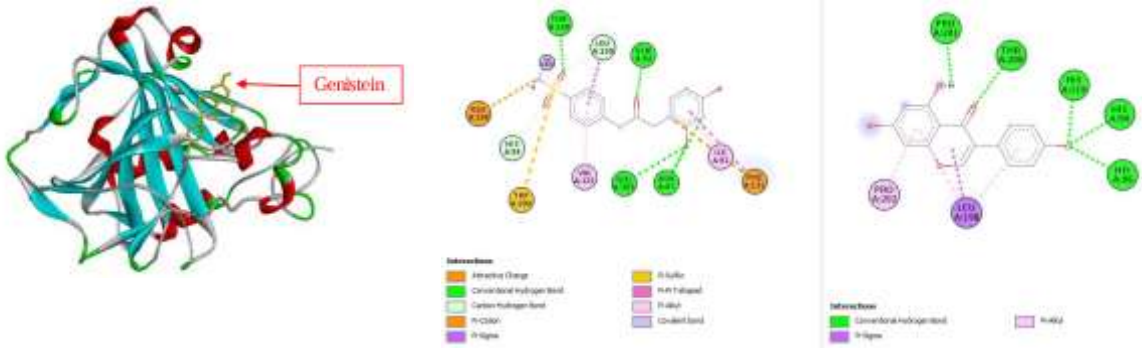
sFLT-1 with Genistein



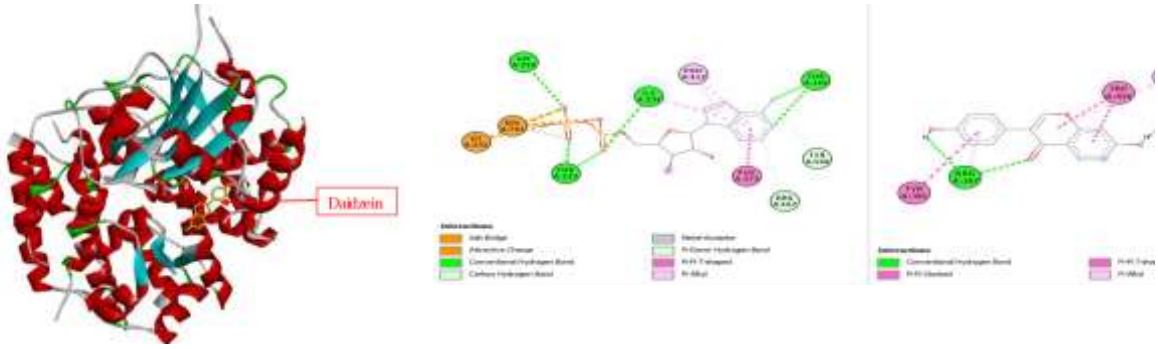
MDA with Daidzein



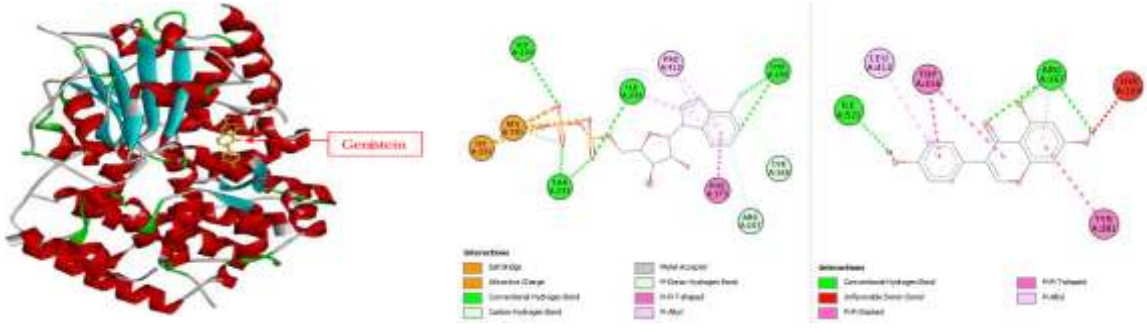
MDA with Genistein



NLRP3 with Daidzein



NLRP3 with Genistein



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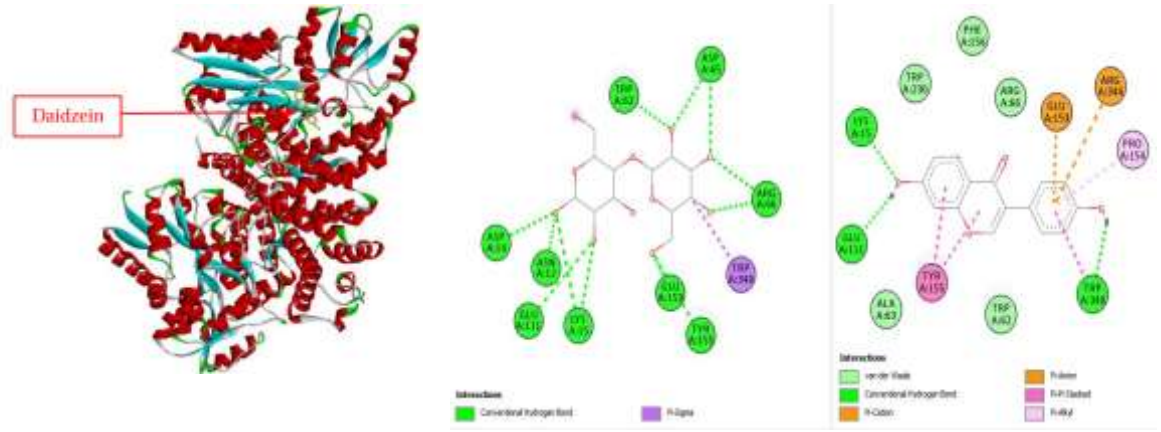
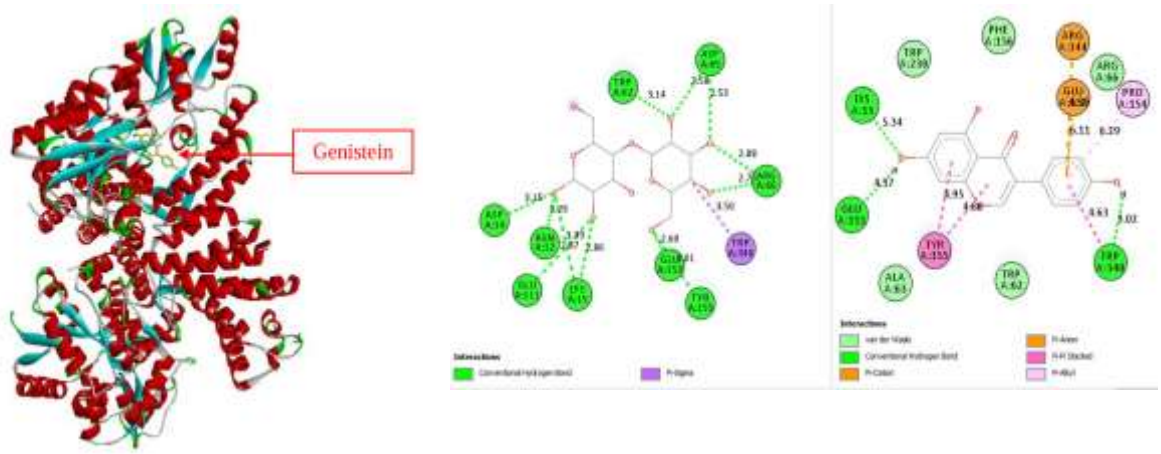
Gasdermin with Daidzein



Gasdermin with Genistein



Isoflavones are included in the flavonoid category, which has structural and biosynthetic similarities with flavonols, flavanones, and anthocyanins.[32] Structural similarities allow daidzein and genistein to engage the active site of proteins that play a role in angiogenesis, oxidative stress, inflammation, and cell death through pyroptosis, as evidenced by the competitive binding affinity (ΔG) values relative to the native ligand for each target. The affinity values of daidzein and genistein were comparable to or slightly lower than those of the native ligands, showing significant inhibitory potential. The binding energies (ΔG) of daidzein and genistein compounds with the sFlt-1 and NLRP3 receptors were higher than those of the native ligands, showing that the energy required for ligand-receptor interaction is increased, resulting in a less stable binding. In contrast, the binding energies observed in docking with the MDA receptor and Gasdermin D were lower (ΔG more negative) compared to those of the native ligands, showing a more stable association between the ligand and receptor.[33] Similar studies have reported that ligands with more negative binding energy tend to show stronger and more stable interactions.[34] Inhibition of Gasdermin D-mediated pyroptosis by compounds such as disulfiram ligands is associated with reduced inflammatory responses, emphasizing the importance of binding energy in therapeutic applications.[35]

Docking confirmation by calculating RMSD values showed that re-docking of native ligands on NLRP3, MDA, sFlt-1, and Gasdermin D resulted in RMSD values of less than 2 Å, indicating the validity of the method used to evaluate ligand-protein interactions.[36] The formation of hydrogen bonds between daidzein and genistein with essential amino acid residues in target protein active site is a critical element that affects the strength and selectivity of the interaction.

Docking data showed that daidzein forms up to four hydrogen bonds with Gasdermin D (Ser257, Glu242, Arg236, and Gln244; distance 2.19–3.62 Å), while genistein primarily forms hydrogen bonds with Asp381, Gly329, and Phe506 in NLRP3 (distance 2.18–3.95 Å). Daidzein and genistein form multiple hydrogen bonds with residues, including Cys694, Val624, Ala642, and Gly621 in sFlt-1. In MDA-related proteins, both isoflavones form hydrogen bonds with Ser38 and Asn64 at an optimal distance of less than 4 Å.

Analysis of amino acid residue similarities in docking results of MDA, sFlt-1, Gasdermin D, and NLRP3 receptors with test ligands shows a variety of amino acid congruencies that contribute to the formation of hydrogen bonds and other interactions. The effective hydrogen bond distance (<4 Å) serves as a major predictor of ligand-protein complex stability.[37] The number, position, and proximity of these hydrogen bonds are critical to maintaining ligand orientation at the binding site, enhancing affinity, and facilitating effective suppression of target protein activity[38], as evidenced in almost all interactions between daidzein, genistein, and target proteins. Studies have shown the importance, strength, and occurrence of hydrogen bonds between specific amino acid residues and ligand functional groups, which can be mapped to predict binding affinity and selectivity, offering a new approach to drug design.[39]

ADMET results showed that daidzein and genistein have good pharmacokinetic characteristics and are relatively safe (Table 3). Both compounds showed molecular weights consistent with Lipinski criteria. The number of hydrogen acceptors and donors complied with the ideal threshold, and the log Po values remained within the safe range. Daidzein violated one saturation parameter, while genistein did not. Intestinal absorption of both compounds was significant, with daidzein able to cross the Blood-Brain Barrier (BBB), while Genistein did not. Neither is a substrate for glycoprotein-P, and not showed potential hepatotoxicity. The high LD_{50} values show that both compounds have moderate toxicity, with potential target organs being the kidneys and lungs. The bioavailability of Genistein was considered optimal in six SwissADME measures, while daidzein was optimal in five parameters. Both isoflavones derived from *tempeh* deserve further investigation as viable options for safe, natural pharmacological agents. Daidzein and genistein have the potential to be developed as effective and safe natural multi-targeted therapies against preeclampsia. However, additional in vitro and in vivo validation is needed to confirm clinical efficacy and safety.

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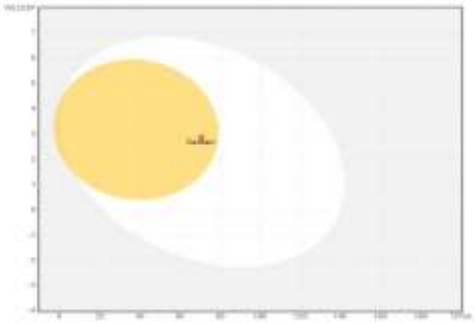
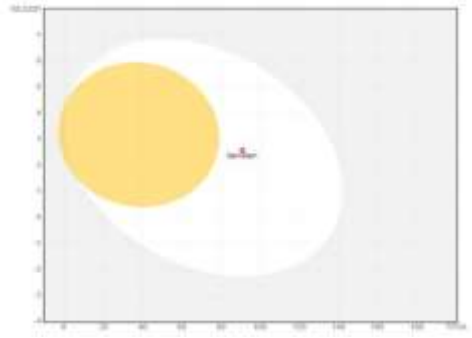
Table 3: ADMET analysis and pharmacokinetic properties

Properties	Molecule	
	Daidzein	**Genistein**
MW (g/mol)	254.24	270.24
H-bond acceptors (≤10)	4	5
H-bond donors (≤5)	2	3
Log Po/w (≤5)	2.47	2.67
Violation (≤1)	1 (saturation)	0
GI absorption	High	High
BBB permeant	Yes	No
P-gp substrate	No	No
Hepatotoxicity	No	No
LD_{50} (mg/kg)	2430	2500
Organ toxicity	Kidney, lung	Kidney, lung
Bioavailability	5/6 optimal	6/6 optimal
Toxicity class	5	5

Table 4: Illustrative table of boiled egg diagram and radar bioavailability of daizein and genistein compounds

Compound		
Daidzein		
Genistein		

Conclusion

In conclusion, daidzein and genistein, derived from fermented soybean extract, showed promising potential for inhibiting critical molecular target that play a role in the pathophysiology of preeclampsia, particularly those related to pyroptosis and oxidative stress. However, additional *in vitro* and *in vivo*validation is necessary to ascertain the binding affinity to inflammatory and angiogenic target. These compounds may facilitate the development of multitarget strategies for managing preeclampsia in the future by serving as potential adjuvant therapies based on natural products.

Conflict Of Interest

The authors declare no conflict of interest

Author's Declaration

The authors hereby declares that the work presented in this article is original and all responsibility for claims related to the content will be borne by them.

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