RESEARCH PAPER

# In Silico Molecular Interactions and Admet Profiling of Cow Milk-Derived Polyphenols Reveals Promising, Obesity Inhibitors by Blocking Autoimmune Recognition of Plin1 Gene

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**ABSTRACT:**
Obesity is a major chronic non-communicable disease affecting millions worldwide. Although diet, exercise, and pharmacological therapies are used for its management, maintaining long-term weight loss remains challenging. Perilipin 1 (PLIN1), a lipid droplet-associated protein in adipocytes, regulates lipid storage and lipolysis. Loss or degradation of PLIN1 has been linked to reduced fat accumulation and a lean phenotype, making it a promising target for obesity treatment. The aim of this study is to use in silico screening of anti- Obesity potential polyphenols from the cow milk by targeting Perilipin 1 (PLIN1) as a potential inhibitor to be used as treatment of obesity. The predicted 3D structure of perilipin 1 had a high confidence score reflecting the reliability of the obtained structure. Gardenin B (-7.2 kcal/mol) showed a high reliable docking score suggesting its potential action as perilipin 1 inhibitor. In conclusion This study shows that Gardenin B, O-Desmethylangolensin, and Equol and compounds can be evaluated its preclinical as an inhibitor for perilipin 1 and a potential treatment for obesity.
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## INTRODUCTION:

Dairy cows with ketosis displayed lipid metabolic disorder and high inflammatory levels. Adipose tissue is an active lipid metabolism and endocrine tissue and is closely related to lipid metabolism homeostasis and inflammation (Noureldein *et al*. 2014, Zhang *et al*. 2018; Mondal *et al*. 2024). Perilipin 1 (PLIN1), an adipocyte-specific lipid-coated protein, may be involved in the above physiological function. Perilipin 1 (PLIN1) is a critical protein found on the surface of lipid droplets in adipocytes (fat cells), where it acts as a gatekeeper regulating storage and hydrolysis of neutral lipids. It protects stored fat from basal lipase activity and is phosphorylated by PKA during lipolysis to mobilize energy. Deficiencies in PLIN1 can lead to lipodystrophy, severe metabolic issues, and inflammation (Desgrouas *et al*. 2024; Skinner *et al*. 2013, Sohn *et al*. 2018).

*In silico* studies offer several advantages over the traditional methods which includes rapid screening of large datasets with reduced costs and time with the ability to predict drug properties and toxicity, eventually accelerating drug discovery and development. Computational docking is applied to structure-based drug design and can be utilized to predict binding for small molecule ligands to macromolecular targets. It is widely used for the study of biomolecular interactions and mechanisms. Docking analysis was accomplished to have a better understanding about the inhibitory mechanisms as well as the mode of interactions (Skariyachan *et al*, 2018).
Phenolic structures there are more than 8000 different types in plants. These structures serve as UV or pathogen defence in plants. In food products, phenolic compounds are responsible for colour, astringency, or bitterness, among others. All of the phenolic

compounds in plants originate from phenylalanine or shikimic acid. There is a wide range of classification for phenolic compounds, the most selective of which depend on the number of phenolic rings and the structural component linking the rings. Consuming a polyphenol-rich diet has been linked with a reduced risk for chronic diseases based on the results of various epidemiological studies. There are several different ways in which polyphenols may affect glycemia, including by the inhibition of glucose absorption in the gut or by the inhibition of glucose uptake in the peripheral tissues (Pandey *et al*. 2009).

Milk can be enriched with polyphenols from manipulation of cow's diet. Metabolic disorders of obesity can be ameliorated with intake of whole milk or milk enriched with polyphenols (Santos *et al*. 2017). Dietary phenols are also known to reduce the allergy caused by β- lactoglobulin, which is a milk protein (Zhang *et al.* 2024). It was observed that the polyphenols have effect on mammary gland function, promoting milk production (Kelleher *et al*. 2024).

The unhealthy lifestyles and prolonged exposure to the different risk factors lead to the development of chronic degenerative diseases (de Paulo Farias *et al*. 2021). The diabetes and hypertension are one such conditions where deficiency of insulin secretion, hyperglycaemia or both are responsible for changes in the metabolism leading to death of the individual, whereas hypertension is associated with the cardiovascular disease, myocardial infraction, stroke and heart failure (FitzGerald *et al*. 2004). Globally it is estimated that more than 430 million individuals are going to be affected with diabetes by 2030 (Yoshimura *et al*. 2018). The aim of this study is in silico evaluation and pharmacological study of anti- Obesity potential polyphenols from the cow milk.

## METHODOLOGY:

**Accession of Cow Milk Polyphenolic Compounds and Anti - Obesity Target Proteins:** The three-dimensional structure of anti - Obesity target protein like perilipin-1 is critical for lipid accumulation in adipocytes sequence downloaded from uniport (Uniport ID: O60240). And 3D structure was predicted by using AlphaFold Server. The predicted protein was used for further docking analysis. Chemical structures of cow milk polyphenolic used in the study were identified and reported by Rocchetti *et al*. 2022 and the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was used for accession of each chemical structure into SDF format from to study the possible molecular binding mechanism of the chosen polyphenolic chemical compounds as potential inhibitors of target proteins as anti-obesity therapeutics (Rocchetti *et al*. 2022).

**Molecular Docking:** Molecular docking was performed to study the binding interactions between the polyphenolic compounds as a inhibitor of perilipin-1 as potential anti-obesity target proteins. 6 cow milk phenolic compounds' ligands were subjected to molecular docking analysis with target proteins inhibitors using cavity detection-guided blind docking (CB-Dock) (Yang *et al*., 2022). The docked complex results were visualized using PyMol Viewer software. Docking provides information about binding affinity and possible interactions that contribute to the inhibition and act as a potential anti-diabetic activity (Burranboina *et al*. 2022).

**ADMET analysis:** ADMET analysis was carried out by using pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) and ProTox 3.0 online tools for prediction of toxicities of small molecules (Banerjee et al. 2024).

## RESULTS AND DISCUSSION:

**Alphafold Prediction of Perilipin-1 (PLIN1):** The AlphaFold prediction of Perilipin-1 (PLIN1) indicates that the protein has a mixed structural organization. A well-defined central α-helical core (high confidence) that likely forms the functional scaffold responsible for lipid droplet binding and stability. Extended terminal and loop regions with low confidence, suggesting they are intrinsically disordered and flexible, which is typical for regulatory proteins. The PAE plot supports this, showing High confidence within the core domain. Low confidence between distant regions, indicating flexible domain arrangement Figure 1.

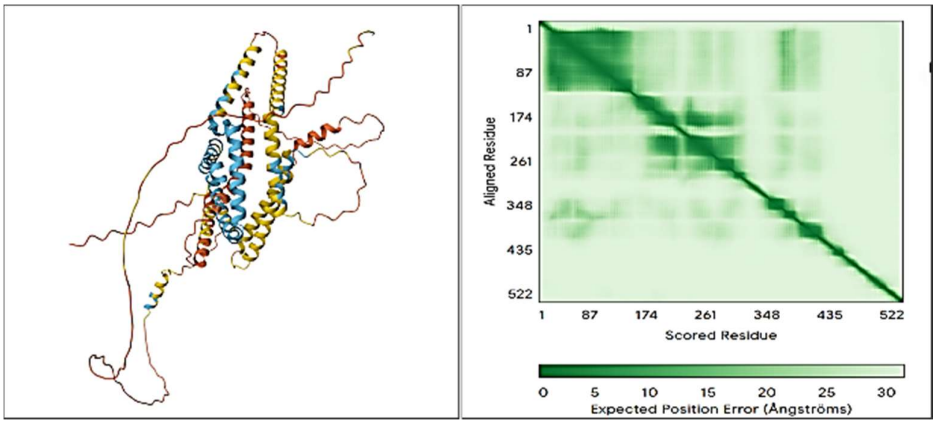

**Figure 1: Predicted 3D structure of Perilipin 1 (PLIN1) protein.**

**Molecular docking and pharmacological study of polyphenolic compounds:**

A compound is more likely to have good oral bioavailability HBA (Hydrogen Bond Acceptors) ≤ 10, HBD (Hydrogen Bond Donors) ≤ 5, Molecular Weight (MW) ≤ 500 Da, logP (lipophilicity) ≤ 5 the detailed passed compounds were showed in table 1. All selected compounds exhibit promising drug-likeness characteristics and can be considered suitable candidates for further pharmacological or biological evaluation. However, additional studies (ADMET, toxicity, and efficacy) are necessary to confirm their therapeutic potential.

**Table 1: Lipinski rule 5 passed polyphenolic compounds**

| Sl.No | Pubchem id | Compound name | HBA | HBD | logP | MR | MW | TPSA |
|---|---|---|---|---|---|---|---|---|
| 1 | 464 | Hippuric acid | 4 | 2 | 0.9 | 46 | 179.2 | 66.4 |
| 2 | 7139 | Dimethoxyphenyl)acetic acid | 4 | 1 | 1.3 | 51 | 196.2 | 55.8 |
| 3 | 8468 | Vanillic Acid | 4 | 2 | 1.1 | 41.9 | 168.1 | 66.8 |
| 4 | 89472 | Desmethylangolensin | 4 | 3 | 2.8 | 72 | 258.3 | 77.8 |
| 5 | 91469 | Equol | 3 | 2 | 2.8 | 69.1 | 242.3 | 49.7 |
| 6 | 96539 | Gardenin B | 7 | 1 | 3.2 | 95.9 | 358.3 | 87.4 |

**Molecular Docking analysis:**

Molecular interactions of Lipinskirule5 passed compounds against Perilipin 1 (PLIN1) protein. Among the studied compounds, Gardenin B exhibited the highest binding affinity (-7.2 kcal/mol), followed by O-Desmethylangolensin and Equol, indicating strong interactions with key active site residues. These compounds may serve as promising leads for further drug development studies, while the remaining ligands showed comparatively lower binding potential Table 2 and figure 2.

**Table 2: Molecular interactions of Lipinskirule5 passed compounds against Perilipin 1 (PLIN1) protein**

| ***Compound name*** | **Energy value (Kcal/mol)** | **Amino acid interactions** |
|---|---|---|
| *Hippuric acid* | -5.7 | CYS34 PHE37 GLN38 TYR41 THR44 VAL51 CYS55 TYR58 |
| *Dimethoxyphenyl)acetic acid* | -5.4 | ALA238 ARG239 ALA240 LEU241 GLU242 |
| *Vanillic Acid* | -5.2 | GLN17 GLU18 ASN19 VAL20 LEU21 GLN22 VAL77 |
| *Desmethylangolensin* | -7 | LEU25 THR33 CYS34 GLU35 PHE37 GLN38 TYR41 |
| *Equol* | -6.7 | THR33 CYS34 PHE37 GLN38 THR40 TYR41 THR42 |
| *Gardenin B* | -7.2 | GLN17 GLU18 ASN19 VAL20 LEU21 |

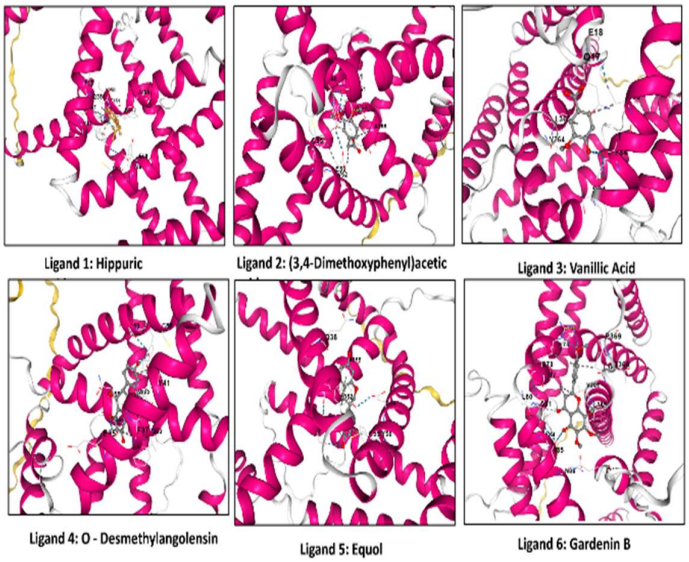


**Figure 2: Molecular interactions of Lipinskirule5 passed compounds against Perilipin 1 (PLIN1) protein.**

**ADME-TOXICITY ANALYSIS:**

The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile of O-Desmethylangolensin, Equol, and Gardenin B indicates that all three compounds possess generally favorable pharmacokinetic and safety characteristics. Overall, these compounds exhibit acceptable pharmacokinetic and toxicological profiles, supporting their further investigation as potential therapeutic or nutraceutical candidates Table 3.

The predicted LD50 analysis indicates that most of the evaluated compounds exhibit low to moderate toxicity levels. Among the tested metabolites, Equol showed the highest toxicity with the lowest LD50 value (500 mg/kg), whereas Gardenin B demonstrated the lowest toxicity with the highest LD50 value (4000 mg/kg). Hippuric acid, Vanillic Acid, and O-Desmethylangolensin displayed relatively safer toxicity profiles with higher LD50 values ranging from 2000–2500 mg/kg. Overall, the findings suggest that most compounds possess acceptable safety margins for further pharmacological and nutraceutical investigations, although additional in vivo and clinical toxicity studies are required for confirmation figure 3.

**Table 3: ADMET Properties of Selected O-Desmethylangolensin, Equol, Gardenin B**

| Model Name | Desmethylangolensin | Equol | Gardenin B | Unit |
|---|---|---|---|---|
| **Absorption** | | | | |
| Water solubility | -3.368 | -3.24 | -4.103 | Numeric (log mol/L) |
| Caco2 permeability | 1.058 | 1.218 | 1.148 | Numeric (log Papp in 10-6 cm/s) |
| Intestinal absorption (human) | 92.705 | 94.189 | 96.145 | Numeric (% Absorbed) |
| Skin Permeability | -2.74 | -2.858 | -2.738 | Numeric (log Kp) |
| P-glycoprotein substrate | Yes | Yes | Yes | Categorical (Yes/No) |
| P-glycoprotein I inhibitor | No | No | Yes | Categorical (Yes/No) |
| P-glycoprotein II inhibitor | No | No | Yes | Categorical (Yes/No) |
| **Distribution** | | | | |
| VDss (human) | 0.506 | 0.42 | -0.217 | Numeric (log L/kg) |
| Fraction unbound (human) | 0.166 | 0.085 | 0.127 | Numeric (Fu) |
| BBB permeability | -0.793 | 0.324 | -0.909 | Numeric (log BB) |
| CNS permeability | -2.266 | -1.99 | -3.069 | Numeric (log PS) |
| **Metabolism** | | | | |
| CYP2D6 substrate | No | No | No | Categorical (Yes/No) |
| CYP3A4 substrate | No | Yes | Yes | Categorical (Yes/No) |
| CYP1A2 inhibitior | Yes | Yes | Yes | Categorical (Yes/No) |

| | | | | |
|---|---|---|---|---|
| CYP2C19 inhibitior | Yes | Yes | Yes | Categorical (Yes/No) |
| CYP2C9 inhibitior | Yes | No | No | Categorical (Yes/No) |
| CYP2D6 inhibitior | No | No | No | Categorical (Yes/No) |
| CYP3A4 inhibitior | No | No | Yes | Categorical (Yes/No) |
| **Excretion** | | | | |
| Total Clearance | 0.156 | 0.154 | 0.69 | Numeric (log ml/min/kg) |
| Renal OCT2 substrate | No | No | Yes | Categorical (Yes/No) |
| **Toxicity** | | | | |
| AMES toxicity | No | No | No | Categorical (Yes/No) |
| Max. tolerated dose (human) | 0.033 | -0.497 | 0.247 | Numeric (log mg/kg/day) |
| hERG I inhibitor | No | No | No | Categorical (Yes/No) |
| hERG II inhibitor | No | No | No | Categorical (Yes/No) |
| Oral Rat Acute Toxicity (LD50) | 2.396 | 2.384 | 2.344 | Numeric (mol/kg) |
| Oral Rat Chronic Toxicity (LOAEL) | 1.677 | 1.924 | 1.171 | Numeric (log mg/kg_bw/day) |
| Hepatotoxicity | No | No | No | Categorical (Yes/No) |
| Skin Sensitisation | No | No | No | Categorical (Yes/No) |
| T.Pyriformis toxicity | 0.881 | 0.849 | 0.388 | Numeric (log ug/L) |
| Minnow toxicity | 1.646 | 1.76 | 1.3 | Numeric (log mM) |

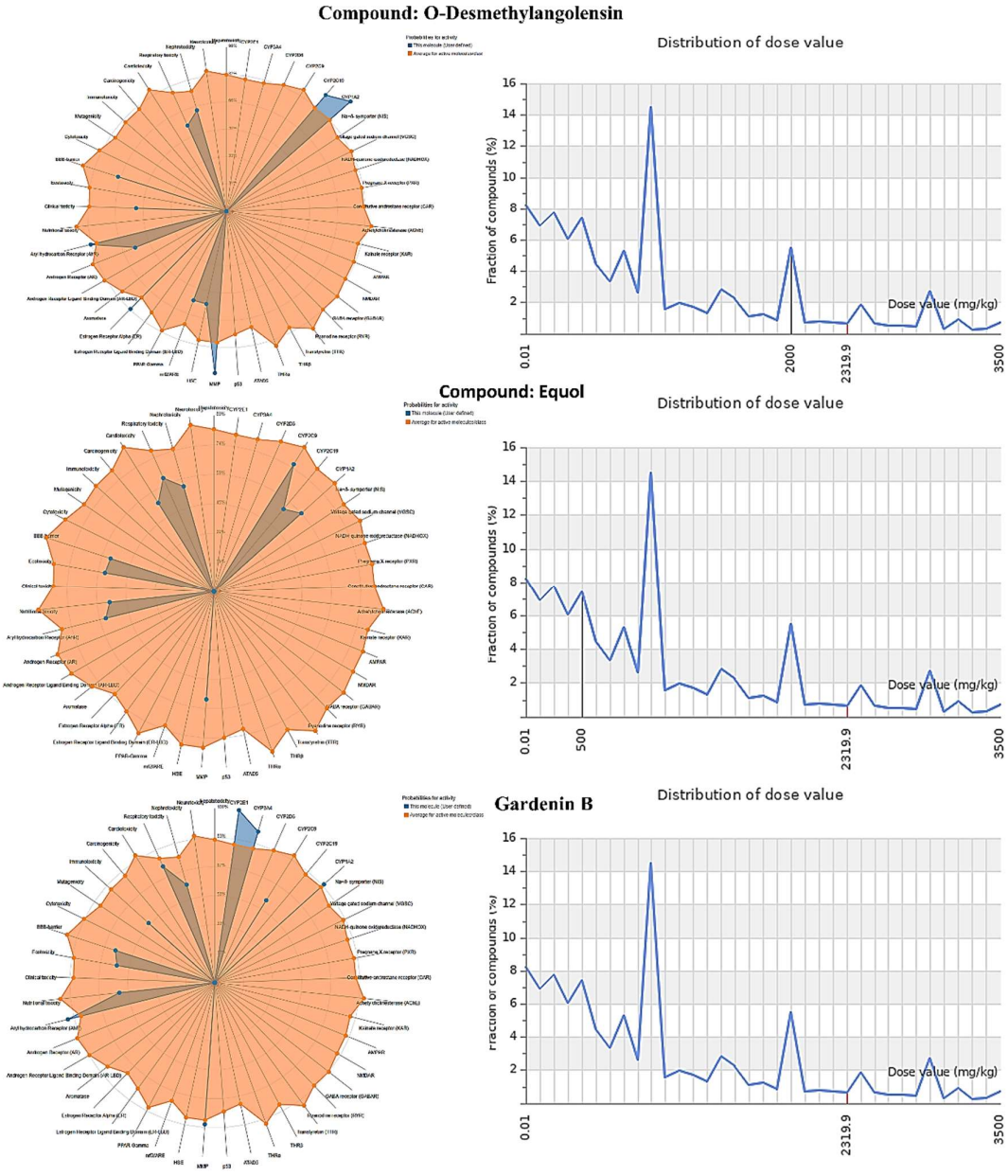


**Figure 3: Toxicity radar chart and Distribution dose value of selected high interactive molecules**

**Conclusion:** In conclusion in silico analysis revealed that milk-derived polyphenols, particularly Gardenin B, O-Desmethylangolensin, and Equol, exhibit significant binding affinity toward the selected obesity-related target protein. Their compliance with Lipinski's Rule of Five further supports their drug-likeness and oral bioavailability. These findings suggest that such compounds may serve as promising candidates for the development of anti-obesity therapeutics, warranting further in vitro and in vivo validation.

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**Author Contributions:**
NMR and BKK Conceptualization, methodology, investigation, data curation, formal analysis, writing and original draft preparation. VSM and SSM Supervision, validation, writing review and editing, correspondence and GNM Literature survey, data collection, manuscript editing.

**Conflicts of Interest:** The author declared that there is conflict of interest of this research work.

**Ethical approval:** Not applicable

**Data availability**: All the data included in the manuscript.

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