

Structure based-molecular modeling and pharmacokinetic investigation of *Caesalpinia sappan* L. against obesity and hypothyroidism

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Abstract: In the present study, an integrated *in silico* approach was employed to investigate phytocompounds from *Caesalpinia sappan* in the context of their predicted interaction with LepR. Molecular docking was performed using a SWISS-MODEL-generated human LepR homology model based on the UniProt sequence (ID: P48357). Among the screened phytocompounds, lupeol exhibited the most favorable predicted docking affinity (−9.4 kcal/mol) and was therefore selected for further computational characterization. The predicted binding mode indicated predominantly hydrophobic/alkyl interactions within the putative LepR binding pocket; however, the observed interactions did not involve the ideal/key residues, and therefore the docking results were interpreted as a predicted ligand–receptor association rather than evidence of receptor modulation. DFT-based frontier molecular orbital analysis yielded a HOMO–LUMO energy gap of 6.998 eV, providing information on the electronic structure and theoretical reactivity of lupeol. SwissADME and pkCSM analyses indicated a mixed drug-likeness and ADMET profile, including high predicted lipophilicity and poor aqueous solubility, as well as model-dependent differences in predicted intestinal absorption. Overall, the findings identify lupeol as a computationally prioritized phytocompound for further investigation in the context of LepR-associated metabolic research. Experimental binding, cellular, and *in vivo* studies are needed to establish the biological relevance of the predicted interaction and assess its potential pharmacological significance in obesity and hypothyroidism.

Keywords: phytomolecules; docking analysis; DFT calculation; bioactive compounds; leptin receptor

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1. Introduction

Obesity and hypothyroidism are two related endocrine-metabolic diseases that have taken epidemic proportions in all countries across the world, becoming a tremendous burden to health systems across the world. Obesity, as an excessive increase in adipose tissue, has been considered a multifactorial disease with complicated causes involving genetic, environmental, and behavioral factors [1]. The World Health Organization reports that the global obesity prevalence has almost tripled since 1975, and there are about 650 million obese adults and more than 1.9 billion overweight adults in the world in 2016 (WHO, 2021). The increasing trend of obesity rates is not slowing down, and by 2030, almost half the adult population of the

United States alone will be obese [2]. At the same time, hypothyroidism is one of the most widespread endocrine diseases, with 5-10 percent prevalence among the world population, where women and the aging population are particularly prone to the disease [3]. Hypothyroidism can be defined as a lack of thyroid hormone production, thyroxine (T4) and triiodothyronine (T3), by the thyroid gland, and it leads to slowing down the metabolic processes in general [4]. The economic impact of these disorders is high, and it includes direct healthcare expenses, loss of productivity, and reduced quality of life for individuals who have these disorders. There is a complex cause-and-effect relationship between hypothyroidism and obesity. The two conditions can be causative of each other. The thyroid hormones are vital in the determination of the basal metabolic rate and lipid and carbohydrate metabolism [5]. In hypothyroidism, the metabolic rate is low, and this fact leads to an elevation of the energy balance and, consequently, an elevation of weight. In addition to that, hypothyroidism is linked with low lipolysis, low biogenesis, and oxidative metabolism of the mitochondrion in adipose tissue and skeletal muscle [6]. Hypothyroidism can also be brought about by obesity. Obesity brings about hypothyroidism in different ways. The pathological changes in adipose tissues, which accompany obesity, result in the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and leptin. These cytokines are produced, and this suppresses the hypothalamic-pituitary-thyroid axis and simultaneously inhibits the manufacture of thyroid hormones [7]. Leptin, a protein produced by the adipose tissue, in its proportion to the mass of adipose tissue, has been determined to be the connection between energy homeostasis and the production of thyroid hormones [8]. The level of leptin goes up in obesity. Leptin disturbs the regular systems of feedback that control the secretion of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). Leptin receptor (LEPR) is one of the cytokine receptors of class I. It is an important part of the biological processes of leptin, which is a 16-kDa hormone that is primarily secreted by adipocytes and is associated with the maintenance of energy balance, food intake, and body weight [9]. LEPR is spliced alternatively, and isoforms of the leptin receptor have been discovered. LEPRb is the isoform of leptin that is essential for the biological activity of leptin. Following the binding of leptin, LEPRb undergoes a conformational change in the course of multiple conformational changes. Those alterations are followed by the activation of the Janus kinase 2 (JAK2), which subsequently causes phosphorylation of the tyrosine residues on the leptin receptor. Such alterations elicit several signaling pathways, such as activation of signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) signaling pathways [10]. The resistance or reduction in leptin sensitivity is a characteristic of common obesity and hypothyroidism. It is linked to elevated leptin concentration in the blood. Several pathways have been suggested as the etiology of leptin resistance. Such mechanisms include reduced leptin transfer across the blood-brain barrier, reduced leptin receptor expression, and impaired leptin intracellular signaling by the action of diverse negative regulators of leptin signaling, such as suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B) [11].

Sappanwood, also called *Caesalpinia sappan* L. (CS), is a flowering tree, a species of the family Fabaceae, and is native to Southeast Asia. [12]. It has also been profoundly embedded in the traditional medicine systems of various Asian cultures, including Ayurveda and Traditional Chinese Medicine, where it has been used for centuries as an analgesic and anti-inflammatory agent in improving blood circulation, wound healing, dysentery, tuberculosis and diabetic complications [13]. Terpenoids are a family of organic compounds

that are present in plants and have been proven to possess diverse pharmacological properties, including anti-cancer, anti-inflammatory, and anti-microbial properties. Sappan wood possesses a variety of triterpenoids, such as lupeol, β -amyrin, and cycloartenol [14]. *Caesalpinia sappan* extract and its isolates have demonstrated good hepatoprotective and neuroprotective properties, anti-diabetic properties, and protective properties to the heart, kidney, and gastrointestinal tract [14]. Considering its long ethnomedicinal value and outstanding bioactivity, *Caesalpinia spp.* is an attractive target with regard to conducting additional phytochemical and pharmacological research to come up with new therapeutic products. A popular *in silico* method for assessing the possible binding affinity and interactions between a ligand and a certain protein target is molecular docking. Instead of using leptin (LEP) as the molecular target for docking analysis, the leptin receptor (LEPR/LepR) was used in this investigation. The physiological effects of leptin (LEP), a hormone generated from adipocytes, are mainly achieved via binding to the leptin receptor (LEPR/LepR), which activates downstream signaling pathways such as JAK2/STAT3 and MAPK-related pathways [15]. Consequently, the discovery of putative interactions between phytochemicals and LepR may offer first insights into their potential impact on leptin receptor-mediated signaling; nevertheless, these docking studies do not prove that the phytochemicals and leptin directly bond. The current work used a structure-based *in silico* method to examine whether phytochemicals from *Caesalpinia sappan*, namely lupeol, may interact with the leptin receptor (LepR) and perhaps modify leptin receptor-mediated signaling linked with obesity and hypothyroidism. A homology model was built using the LepR target sequence that was obtained from UniProt. The possible interactions between the chosen phytochemicals and the predicted LepR target were then assessed using molecular docking. Density functional theory (DFT) simulations using the Gaussian software were used to further examine the structural properties of the top-ranked ligand-LepR complex. A mechanistic hypothesis about the putative interaction of *C. sappan* phytochemicals, especially lupeol, with LepR and their potential significance to leptin receptor-mediated signaling was intended to be provided by this integrated computational method. These computational findings should be viewed as predictive, requiring additional *in vitro* and *in vivo* experimental confirmation before any direct receptor contact or functional impact can be proven.

2. Materials and Methods

2.1. Screening of phytomolecules.

The plant *Caesalpinia sappan* contains a diverse array of phytochemicals, as listed in the IMPPAT database (<https://cb.imsc.res.in/imppat/>), [16] each with a unique IMPPAT identifier. The screened ligand includes Tannic acid (IMPHY011741), (+)- α -Phellandrene (IMPHY012076), Myristic acid (IMPHY000060), Lauric acid (IMPHY003016), Decanoic acid (IMPHY003104), Octanoic acid (IMPHY003301), Palmitic acid (IMPHY007327), Triacotane (IMPHY009413), Arachidic acid (IMPHY011394), Oleic acid (IMPHY011797), β -Amyrin (IMPHY012223), Lupeol (IMPHY012473), Linolenic acid (IMPHY012723), β -Sitosterol (IMPHY014836), Stigmasterol (IMPHY014842), Linoleic acid (IMPHY014990), Tetra acetylbrazilin (IMPHY005224), Caesalpin P (IMPHY000537), 1-Octacosanol (IMPHY006972), Caesalpin J (IMPHY009458), 3-DeoxysappanoneB (IMPHY010059), 4-O-methylsappanol (IMPHY010348), (6aS,11bS)-7,11b-dihydro-6H-indeno[2,1-c]chromene-3,6a,9,10-tetrol (IMPHY011233), D-erythro-Pentose, 2-deoxy-

(IMPHY000568), 7-Hydroxy-3-(4-hydroxybenzylidene)chroman-4-one IMPHY001299), (10S)-10-(hydroxymethyl)-8-oxatricyclo [10.4.0.0.2,7] hexadeca 1(16),2(7),3,5,12,14-hexaene-5,10,14,15-tetrol (IMPHY002661), Protosappanin C (IMPHY002662), Sappanone B (IMPHY002681), L-Sorbose (IMPHY003417), Sappanol (IMPHY003575), Episappanol (IMPHY003576), Ombuin (IMPHY004415), Sappanchalcone (IMPHY004448), Quercetin (IMPHY004619), Stearic acid (IMPHY004631), Rhamnetin (IMPHY005543), Norvaline (IMPHY006652), 1-Octacosanol (IMPHY006972), (E)-7-hydroxy-8-methoxy-3-(4-methoxybenzylidene)chroman-4-one (IMPHY007000), (6aS,11bS)-7,11b-dihydro-6H-indeno[2,1-c]chromene-3,6a,9,10-tetrol (IMPHY011233), beta-Lactose (IMPHY011294), alpha-Amyrin (IMPHY011619), Taraxerol (IMPHY011677), D-Galactose (IMPHY012050), D-Glucose (IMPHY014893), Linoleic acid (IMPHY014990), (10S)-10-(hydroxymethyl)-8-oxatricyclo [10.4.0.0.2,7] hexadeca-1(16),2(7),3,5,12,14-hexaene-5,10,14,15-tetrol (IMPHY002661), Caesalpin J (IMPHY009458), Protosappanin A (IMPHY009466), 3-Deoxysappanone B (IMPHY010059), 4-O-Methylepisappanol (IMPHY010380). Further, the structure of these phytochemicals was retrieved from the PubChem database [17].

2.2. Protein target modeling and preparation.

Using accession number P48357, which corresponds to the conventional LepR isoform B (P48357-1), the amino acid sequence of the human leptin receptor (LepR/LEPR) was obtained from the UniProtKB database (<https://www.uniprot.org/>) [18]. The SWISS-MODEL server was used for homology modeling in order to create a three-dimensional structural model of the human LepR. The template was chosen to be the crystal/cryo-EM structure associated with PDB ID 8X85, chain A, which represents the human leptin receptor component of the leptin-LepR complex. Over the aligned area, there was 100% sequence identity between the target and template sequences. The 1,165-residue target sequence's whole C-terminal region was not covered by the chosen template, but it did offer structural coverage for the aligned portion of the LepR sequence. The model-quality metrics offered by SWISS-MODEL were used to evaluate the resulting LepR model's quality. The final model has an appropriate anticipated structural quality for further computational investigation, with a Global Model Quality Estimation (GMQE) score of 0.50 and a QMEANDisCo global score of 0.71 ± 0.05 . MolProbity was used for further stereochemical confirmation. With a collision score of 0.16 and a MolProbity score of 1.38, the model demonstrated high overall stereochemical quality and a low frequency of unfavorable atomic interactions. 91.18% of residues were found in the preferred areas, whereas 0.99% were found in the disallowed or outlier regions, according to Ramachandran plot analysis. The modeled structure of LepR was further visualized using the BIOVIA Discovery Studio 2021 client [19].

2.3. Active site prediction.

The active site is the region of a target protein where a ligand binds and interacts. The target protein's active surface was predicted with the use of the PrankWeb online server (<https://prankweb.cz/>) [20]. This web server assists us in determining the target protein's optimal pockets as well as its active regions. In order to evaluate the optimal zones, the target protein's PDB ID was entered, or in certain situations, the target protein's 3D structures were uploaded in PDB format. Consequently, different pockets were identified, and the pocket with the highest pocket score and probability score was selected [21].

2.4. Molecular docking

Molecular docking is a computational technique frequently utilized in drug design and development. Using PyRx 0.8 software, molecular docking was performed in this investigation [22]. Initially, the screened phytochemicals from *Caesalpinia sappan* were imported into the graphical screen of PyRx, the energies were minimized, and they were converted to PDBQT format. Then the processed structure of the LepR was loaded and converted to macromolecules. The grid box was then structured in the predicted active site region, and docking was carried out. Preparation of the LepR model involved removal of unnecessary water molecules and docking preparation of the receptor, including addition of hydrogen atoms and charge assignment according to the docking workflow that was used. The docking grid was defined as follows: X = 228.001, Y = 211.744, Z = 271.369, size: 83.449 × 58.351 × 212.560 Å. One docking run was done, and nine docking poses (binding modes) were generated. To account for the influence of molecular size on the docking-derived binding energies, ligand efficiency (LE) was calculated for each phytocompound using the standard formula $LE = |\Delta G_{bind}| / N_{heavy}$, where ΔG_{bind} is the binding energy (kcal/mol) obtained from molecular docking, and N_{heavy} is the number of non-hydrogen (heavy) atoms in the ligand, determined from its molecular formula. The best docking mode was chosen among these nine modes according to the predicted docking score and further analyzed with BIOVIA Discovery Studio 2021 Client [19] for analyzing ligand-protein interactions.

2.5. Density functional theory analysis.

The Gaussian 09W computational software was used for the frontier molecular orbital (FMO) study of the top hit molecule, and GaussView 6 was used for orbital analysis and molecular structure visualization. Density Functional Theory (DFT) was used to calculate the energy of the molecule's three-dimensional structure using the B3LYP functional and 6-31G basis set. Using the conversion factor of 1 Hartree = 27.2114 eV, the energies of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) were taken from the output files and converted to electron volts (eV). Koopmans' theorem was then used to determine the HOMO–LUMO energy gap (ΔE). The HOMO–LUMO energy gap (ΔE) was calculated as the difference between the LUMO and HOMO energies. Global chemical reactivity descriptors were estimated using Koopmans' theorem. The ionization potential (I) was obtained from the negative of the HOMO energy, while the electron affinity (A) was obtained from the negative of the LUMO energy. Chemical hardness (η), softness (S), electronegativity (χ), chemical potential (μ), and electrophilicity index (ω) were calculated using the following relationships: $\eta = (I - A)/2$, $S = 1/(2\eta)$, $\chi = (I + A)/2$, $\mu = -\chi$, and $\omega = \mu^2/(2\eta)$, respectively. These parameters were used to describe the calculated electronic structure and theoretical charge-transfer/reactivity characteristics of the top hit molecule. The electrostatic potential distribution was visualized using GaussView 6 and represented using a color scale corresponding to negative, positive, and near-neutral electrostatic potential regions. Negative-potential regions were interpreted as electron-rich areas, whereas positive-potential regions represented relatively electron-deficient regions. The MEP surface was used to identify the spatial distribution of electrostatic potential and the regions of localized polarity around functional groups.

2.6. ADMET and Pharmacokinetic analysis.

The SwissADME web tool, which can be accessed for free (<http://www.swissadme.ch>) [23], was used to predict ADME parameters based on molecular structure. The connection between pharmacokinetic and physicochemical characteristics was outlined by using the SwissADME database. Additionally, the online tool called pkCSM offers a platform for the analysis and optimization of pharmacokinetic and toxicity properties through a freely available web interface (<https://biosig.lab.uq.edu.au/pkcsm/>) [24]. This is a useful tool in medicinal chemistry by striking a balance between pharmacokinetic, safety, and potency properties.

3. Result and Discussion

3.1. Retrieval of phytomolecules from PubChem.

The structure of the screened phytochemicals from PD was retrieved in SDF format for the molecular docking analysis. The retrieved phytochemical's PubChem CID were Tannic acid (CID: 16129778), (+)-alpha-Phellandrene (CID: 7460), Myristic acid (CID: 11005), Lauric acid (CID: 3893), Decanoic acid (CID: 2969), Octanoic acid (CID: 379), Palmitic acid (CID: 985), Triacotane (CID: 12535), Arachidic acid (CID: 10467), Oleic acid (CID: 445639), beta-Amyrin (CID: cc), Lupeol (CID: 259846), Linolenic acid (CID: 5280934), beta-Sitosterol (CID: 222284), Stigmasterol (CID: 5280794), Linoleic acid (CID: 5280450), Tetraacetylbrazilin (CID: 192761), 1-Octacosanol (CID: 68406), Caesalpin J (CID: 127260), 3-Deoxysappanone B (CID: 57391100), 4-O-methylsappanol (CID: 13888973), (6aS,11bS)-7,11b-dihydro-6H-indeno[2,1-c]chromene-3,6a,9,10-tetrol (CID: 222515), beta-Sitosterol (CID: 222284), D-erythro-Pentose, 2-deoxy- (CID: 9828112), 7-Hydroxy-3-(4-hydroxybenzylidene)chroman-4-one (CID: 44443280), (10S)-10-(hydroxymethyl)-8-oxatricyclo[10.4.0.0^{2,7}] hexadeca 1(16),2(7),3,5, 12,14-hexaene-5,10,14,15-tetrol (CID: 13846690), Protosappanin C (CID: 13846692), Sappanone B (CID: 13888976), L-Sorbose (CID: 439192), Sappanol (CID: 13846649), Episappanol (CID: 13846650), Ombuin (CID: 5320287), Sappanchalcone (CID: 5319493), Quercetin (CID: 5280343), Stearic acid (CID: 5281), Rhamnetin (CID: 5281691), Norvaline (CID: 65098), (E)-7-hydroxy-8-methoxy-3-(4-methoxybenzylidene)chroman-4-one (CID: 73353608), Protosappanin A (CID: 128001), 4-O-methylsappanol (CID: 13888973), 4-O-Methylepisappanol (CID: 13888974), (6aS,11bS)-7,11b-dihydro-6H-indeno[2,1-c]chromene-3,6a,9,10-tetrol (CID: 222515), beta-Lactose (CID: 6134), alpha-Amyrin (CID: 73170), Taraxerol (CID: 92097), D-Galactose (CID: 6036), D-Glucose (CID: 5793), (10S)-10-(hydroxymethyl)-8-oxatricyclo[10.4.0.0^{2,7}]hexadeca-1(16),2(7),3,5,12,14-hexaene-5,10,14,15-tetrol (CID: 13846690).

3.2. Prediction of active site region in Leptin receptor structure.

A protein's active site is an essential area with substantial biological and biochemical significance. It is essential to the function of the protein since it is the precise location where ligands attach, and chemical reactions take place. The target LepR protein's active binding area was identified using the PrankWeb web server. The ligand of interest will be able to bind at the optimal pockets in the target protein's receptor region with the aid of the predicted active areas. PrankWeb's output showed the quantity of optimal pockets and optimal chains present in the target protein. Based on the PrankWeb output, it was predicted that the target protein LepR from UniProt ID P48357 has 14 pockets, from which the best ideal pocket is selected based on

the probability score and pocket score. For the best pocket, the predicted probability score is 0.535, and the pocket score is 9.12, which is considered a high value when compared with other pockets. Figure 1 represents the active site region of the target protein, the leptin receptor.

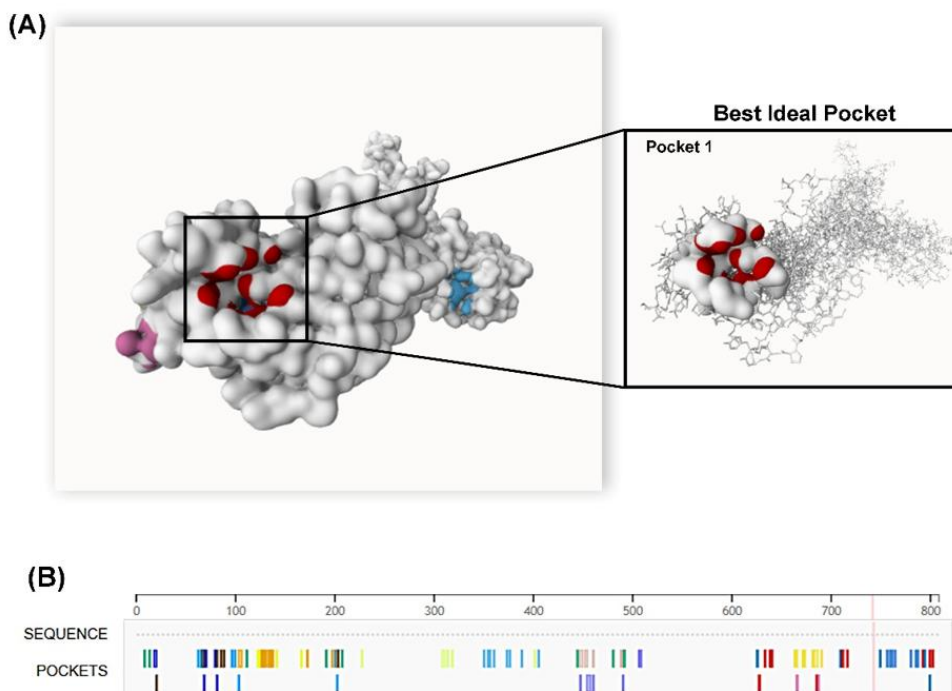


Figure 1. Active site prediction of the target protein LepR using the PrankWeb tool. **(A)** Three-dimensional surface representation of the LepR showing the predicted binding pocket, with Pocket 1 (red color) highlighted as the best-ranked potential binding site and enlarged to illustrate the pocket architecture and surrounding residues. **(B)** Linear sequence-based distribution of the predicted binding pockets along the LepR sequence, indicating the positions of the identified pockets and their corresponding residue locations.

In the predicted active regions, a total of sixteen amino acid residues were observed in chain A. The predicted amino residues were A_647, A_648, A_649, A_653, A_658, A_660, A_705, A_731, A_732, A_733, A_736, A_737, A_812, A_819, A_820 and A_822, respectively. In the process of molecular docking, active-site residues were predicted. The unique shape and the chemistry of the active site allow a particular binding of ligands due to the complementary shape and electrostatic interactions. This ensures that only the right molecules get bound. This binding affinity is dependent on the strength of the interaction, and the highest binding affinity results in improved biological activity. The binding capacity of these active regions through the docking of ligands increases their interaction and affinity [25].

3.3. Molecular docking analysis.

The binding energies of retrieved phytochemicals with the target protein LepR from the UniProt ID P48357 were assessed using molecular docking experiments [26]. The docking results presented in Table 1 correspond to the best-scoring binding modes obtained from the docking analysis. Among all phytocompounds, Lupeol showed the highest binding affinity (-9.4 kcal/mol), suggesting strong interaction potential for the leptin receptor (UniProt ID P48357). Other pentacyclic triterpenoids such as α -amyrin (-9.2 kcal/mol), Taraxerol (-8.6 kcal/mol), and β -amyrin (-8.6 kcal/mol) also exhibited favorable binding energies, ranking close to the top. The Phytosterol Phytocompounds Stigmasterol (-8.3 kcal/mol) and β -sitosterol (-8 kcal/mol) have further reinforced the strong binding profile of PD phytochemicals. The

cassane-type diterpenoid, Caesalpin P, has (-7.8 kcal/mol). The polyphenolic tetraacetylbrazilin has (-7.5kcal/mol). Homoisoflavonoid, 3-Deoxysappanone B has (-7.5kcal/mol). (6aS,11bS)-7,11b-dihydro-6H-indeno[2,1-c] chromene-3,6a,9,10-tetrol, 7-Hydroxy-3-(4-hydroxybenzylidene) chroman-4-one, and Quercetin have shown moderate affinity (-7.4 to -7.2 kcal/mol). Overall, pentacyclic triterpenoids emerged as the most promising class, especially lupeol [20]. To account for the potential influence of molecular size and hydrophobicity on docking scores, the phytochemicals were assessed by considering ligand efficiency (LE), and results were tabulated in Table 1. Lupeol, with the highest docking score, exhibited an LE of 0.303 and 31 heavy atoms. Other structurally related triterpenoids such as α -amyrin, taraxerol, and β -amyrin, which showed favorable docking scores, exhibited LE values ranging from 0.277 to 0.297. Notably, several smaller compounds displayed higher ligand efficiencies despite having less favorable absolute docking scores. For example, 7-hydroxy-3-(4-hydroxybenzylidene)chroman-4-one, 3-deoxysappanone B, and the related chroman derivative exhibited LE values of 0.360, 0.357, and 0.352, respectively. Thus, ligand efficiency provides complementary information to the absolute docking score and highlights the importance of considering molecular size when prioritizing compounds. In this screening, we selected lupeol for further DFT analysis based on its most favorable absolute docking affinity, while recognizing that the docking score should not be interpreted independently of molecular size and physicochemical characteristics.

Table 1. Binding affinity of retrieved phytochemicals from *Caesalpinia sappan* with LepR retrieved from UniProt.

Phytochemicals	PubChem CID	Binding affinity (kcal/mol)	Heavy atoms	LE
Lupeol	259846	-9.4	31	0.303226
alpha-Amyrin	73170	-9.2	31	0.296774
Taraxerol	92097	-8.6	31	0.277419
beta-Amyrin	73145	-8.6	31	0.277419
Stigmasterol	5280794	-8.3	30	0.276667
beta-Sitosterol	222284	-8	30	0.266667
Tetraacetylbrazilin	192761	-7.5	33	0.227273
3-Deoxysappanone B	57391100	-7.5	21	0.357143
(6aS,11bS)-7,11b-dihydro-6H-indeno[2,1-c]chromene-3,6a,9,10-tetrol	222515	-7.4	21	0.352381
7-Hydroxy-3-(4-hydroxybenzylidene)chroman-4-one	44443280	-7.2	20	0.36
Quercetin	5280343	-7.2	22	0.327273
Sappanone B	13888976	-7.1	22	0.322727
Sappanchalcone	5319493	-7.1	21	0.338095
Ombuin	5320287	-6.9	24	0.2875
Sappanol	13846649	-6.8	22	0.309091
Rhamnetin	5281691	-6.8	23	0.295652
(E)-7-hydroxy-8-methoxy-3-(4-methoxybenzylidene) chroman-4-one	73353608	-6.8	23	0.295652
Protosappanin A	128001	-6.8	20	0.34
(10S)-10-(hydroxymethyl)-8-oxatricyclo[10.4.0.0 ^{2,7}]hexadeca-1(16),2(7),3,5,12,14-hexaene-5,10,14,15-tetrol	13846690	-6.6	22	0.3
Episappanol	13846650	-6.6	22	0.3
Caesalpin J	127260	-6.4	23	0.278261
4-O-methylsappanol	13888973	-6.4	23	0.278261
4-O-Methylepisappanol	13888974	-6.2	23	0.269565
beta-Lactose	6134	-5.6	23	0.243478
(+)-alpha-Phellandrene	7460	-5.6	10	0.56
Linoleic acid	5280450	-5.5	20	0.275
D-Glucose	5793	-5.4	12	0.45
Oleic acid	445639	-5.4	20	0.27
Linolenic acid	5280934	-5.3	20	0.265

Phytochemicals	PubChem CID	Binding affinity (kcal/mol)	Heavy atoms	LE
D-Galactose	6036	-5.2	12	0.433333
Lauric acid	3893	-5	14	0.357143
Octanoic acid	379	-5	10	0.5
L-Sorbose	439192	-5	12	0.416667
1-Octacosanol	68406	-4.8	29	0.165517
Decanoic acid	2969	-4.6	12	0.383333
Palmitic acid	985	-4.6	18	0.255556
Arachidic acid	10467	-4.5	22	0.204545
Stearic acid	5281	-4.4	20	0.22
Norvaline	65098	-4.3	8	0.5375
Triacotane	12535	-4.3	30	0.143333
D-erythro-Pentose, 2-deoxy-	9828112	-4.1	9	0.455556
Myristic acid	11005	-4	16	0.25

3.4. Interaction of Lupeol with LepR.

To investigate the predicted binding mode of the selected phytochemical lupeol within the putative binding pocket of the leptin receptor (LepR), molecular docking analysis was performed. As shown in Figures 2 and 3, lupeol was positioned within the predicted binding pocket of LepR and exhibited predominantly hydrophobic/alkyl contacts with residues including LEU261 and ILE318.

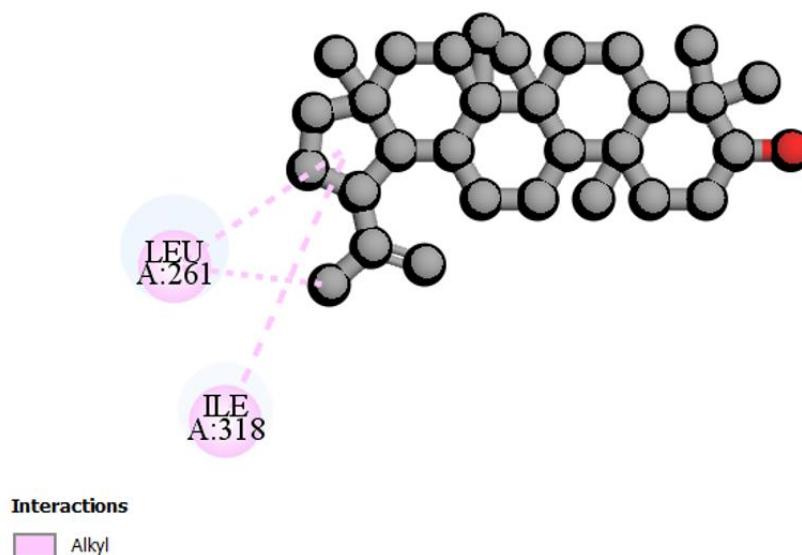


Figure 2. Two-dimensional interaction analysis of Lupeol with amino acid residues of the Leptin Receptor showing hydrophobic interactions.

These interactions are consistent with the hydrophobic nature of the pentacyclic triterpenoid scaffold of lupeol and indicate its accommodation within the nonpolar region of the predicted binding site. However, the observed interactions did not involve the previously identified key or ideal amino-acid residues associated with the functional recognition of LepR; therefore, the present docking results should be interpreted as evidence of a predicted ligand–receptor interaction rather than confirmation of specific receptor modulation. Furthermore, the docking analysis alone cannot establish binding stability, altered receptor dynamics, downstream leptin signaling, or effects on appetite, energy expenditure, obesity, or hypothyroidism. Accordingly, the present findings provide a structural basis for considering lupeol–LepR interaction as a computationally predicted association that requires further validation through molecular dynamics simulations and appropriate biochemical or cellular experiments.

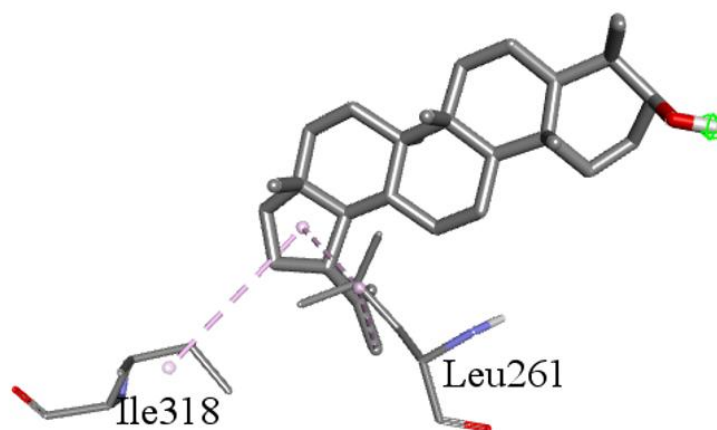


Figure 3. Three-dimensional interaction analysis of Lupeol with amino acid residues of the leptin receptor.

3.5. Frontier molecular orbital analysis.

The frontier molecular orbital (FMO) analysis was performed to characterize the electronic properties and theoretical reactivity of lupeol, and the results are presented in Figures 4 and 5. The structure was optimized at the DFT/B3LYP/6-31G level of theory, yielding HOMO and LUMO energies of -6.192 and 0.806 eV, respectively. The calculated HOMO-LUMO energy gap (ΔE) was 6.998 eV, representing the energy separation between the frontier molecular orbitals. A relatively large HOMO-LUMO gap is generally associated with lower electronic excitation propensity and comparatively lower intrinsic chemical reactivity within the framework of frontier-orbital theory.

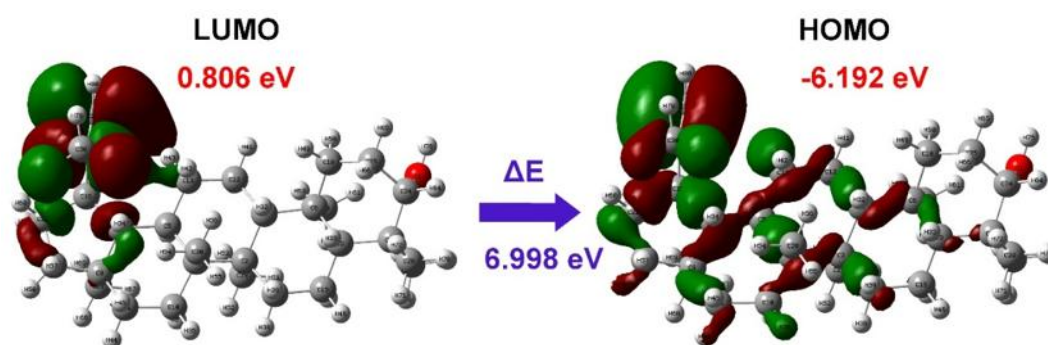


Figure 4. Generated map of the LUMO and HOMO regions of the lupeol molecule.

The calculated chemical hardness (η) of 3.499 eV and softness (S) of 0.143 eV⁻¹ further describe the relatively hard electronic character of lupeol. The electronegativity (χ) and chemical potential (μ) were calculated as 2.693 and -2.693 eV, respectively, while the electrophilicity index (ω) was 1.04 eV. These descriptors provide information on the theoretical electron-donating, electron-accepting, and charge-transfer characteristics of lupeol based on its calculated electronic structure. The negative HOMO energy and positive LUMO energy further characterize the respective occupied and unoccupied frontier orbitals of the molecule. Overall, the FMO results describe the intrinsic electronic properties and theoretical reactivity profile of isolated lupeol under the applied computational conditions. These electronic descriptors should be considered as computational indicators of molecular electronic structure and should not be interpreted as direct evidence of receptor binding, biological activity, pharmacological mechanisms, or therapeutic efficacy.

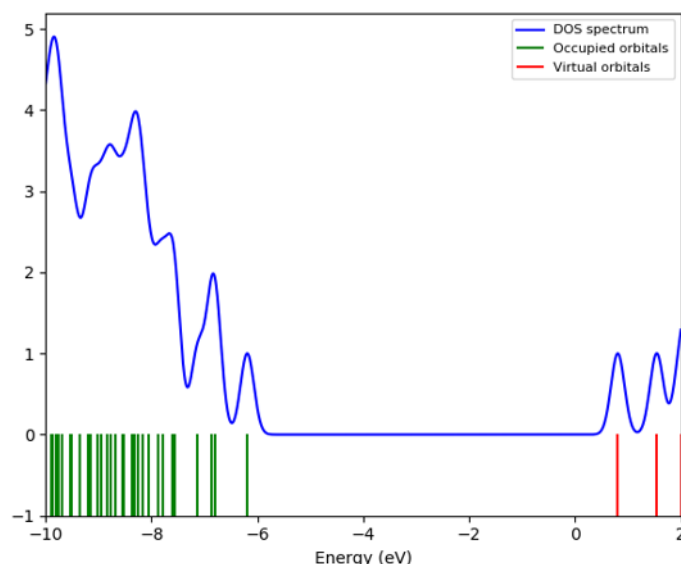


Figure 5. Graphical representation of the DOS spectrum along with virtual and occupied orbitals.

3.6. Molecular electrostatic potential (MEP) analysis.

Lupeol's Molecular Electrostatic Potential (MEP) surface showed an electrostatic potential range of -5.380×10^{-2} to $+5.380 \times 10^{-2}$ a.u. when calculated at the DFT/B3LYP/6-31G level of theory, and the generated MEP surface was shown in Figure 6.

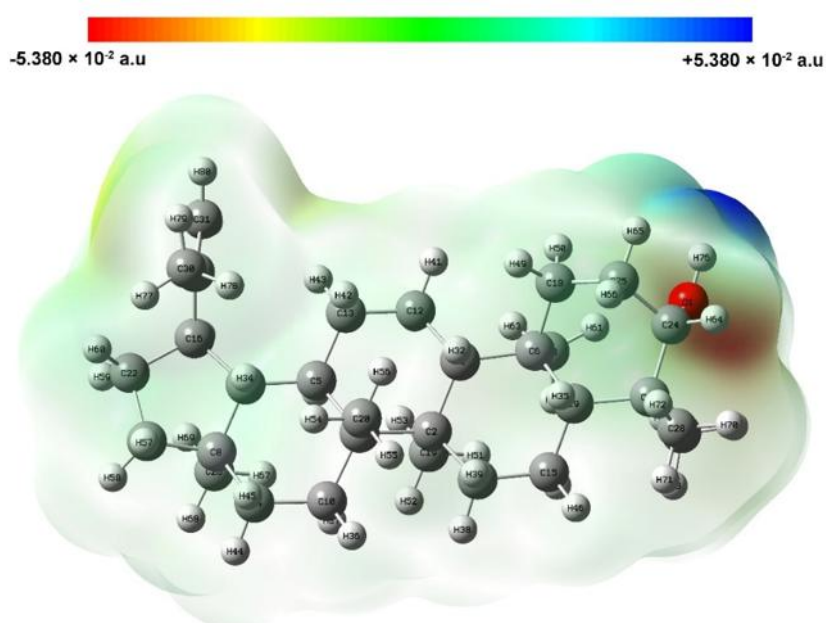


Figure 6. Mapped MEP regions of Lupeol structure.

The region surrounding the hydroxyl oxygen (O1) exhibited relatively negative electrostatic potential, whereas the hydrogen attached to the hydroxyl group was associated with a relatively positive potential region. These features indicate the distribution of electrostatic potential around the hydroxyl functionality and are consistent with its potential hydrogen-bond accepting and donating characteristics, respectively. The remaining carbon-rich pentacyclic framework displayed predominantly neutral to weakly varying electrostatic potential, consistent with its largely nonpolar character. Thus, the MEP analysis identifies the hydroxyl group as the principal region of localized electrostatic variation in the lupeol

molecule. However, these MEP features represent theoretical electrostatic properties of the isolated molecule and cannot, by themselves, establish specific intermolecular interactions, receptor binding, pharmacological mechanisms, or therapeutic effects [27].

3.7. SwissADME analysis of lupeol.

According to the SwissADME evaluation, lupeol displayed a mixed drug-likeness profile, with several physicochemical characteristics falling within commonly applied drug-likeness criteria, while its high lipophilicity represented an important limitation. The predicted SwissADME results were tabulated in Table 2. The molecular weight (426.72 g/mol), hydrogen-bond donors (1), hydrogen-bond acceptors (1), and rotatable bonds (1) were within the ranges generally considered favorable by conventional drug-likeness filters. However, the predicted LogP of 7.27 indicated pronounced lipophilicity, which may be associated with poor aqueous solubility and may influence oral absorption. The low topological polar surface area (20.23 Å²) is consistent with a predominantly nonpolar molecular character. CYP1A2 and other key CYP450 isoforms (2C19, 2C9, 2D6, and 3A4) are not inhibited by lupeol, indicating a low risk of metabolic drug-drug interactions. Lupeol had a bioavailability score of 0.55, no PAINS alerts, and a single Brenk alert for an isolated alkene. Although several drug-likeness filters were satisfied, violations associated with high lipophilicity, low heteroatom content, and elevated molar refractivity were also observed. Therefore, the SwissADME results indicate a mixed physicochemical and drug-likeness profile rather than unequivocal suitability for oral drug development [28].

Table 2. Predicted physicochemical and drug-likeness properties of Lupeol using SwissADME.

Parameter	Predicted values
Molecular Weight	426.72 g/mol
Lipinski Violations	1 (MLOGP > 4.15)
Log P (Consensus)	7.27
Topological Polar Surface Area (TPSA)	20.23 Å ²
H-bond Donors (HBD)	1
H-bond Acceptors (HBA)	1
Rotatable Bonds	1
GI Absorption	Low
CYP1A2 Inhibition	No
Other CYP Inhibition	No (2C19, 2C9, 2D6, 3A4)
Bioavailability Score	0.55
PAINS Alerts	0
Brenk Alerts	1 (isolated alkene)
Synthetic Accessibility	5.49

3.8. Pharmacokinetic analysis for lupeol.

The predicted ADMET characteristics obtained from pkCSM are presented in Table 3. In contrast to the SwissADME prediction, pkCSM estimated high intestinal absorption for lupeol (97.88%) and favorable Caco-2 permeability (1.248 log Papp in 10⁻⁶ cm/s). However, this prediction was accompanied by poor predicted water solubility (log mol/L = -5.922), indicating that the high intestinal absorption estimate should be interpreted cautiously. Importantly, the discrepancy between the two computational platforms, with SwissADME predicting low GI absorption whereas pkCSM predicts approximately 97.9% intestinal absorption, demonstrates model-dependent uncertainty in the estimation of oral absorption. Such differences can arise from the distinct algorithms, molecular descriptors, training datasets, and prediction endpoints employed by the respective platforms. Therefore, neither prediction was definitive, and we did not interpret the favorable pkCSM absorption estimate

independently of the low-solubility prediction and the unfavorable lipophilicity identified by SwissADME. The remaining pkCSM predictions also indicated a mixed ADMET profile. Lupeol was predicted to have a fraction unbound close to zero, suggesting extensive plasma protein binding, while the predicted volume of distribution was 0.023 log L/kg. It was predicted to be a CYP3A4 substrate but not a CYP2D6 substrate and showed no predicted inhibition of the major CYP450 isoforms evaluated. The predicted CNS permeability (log PS = -1.7) and BBB permeability (log BB = 0.747) suggest potential central distribution according to the model; however, these predictions should not be regarded as experimental evidence of CNS exposure. Similarly, the predicted low total clearance (0.153 log mL/min/kg) and absence of OCT2 substrate activity provide computational estimates rather than experimentally confirmed pharmacokinetic behavior.

The toxicity predictions were also mixed. Negative predictions for AMES mutagenicity, hepatotoxicity, and skin sensitization indicate lower predicted risk for these endpoints, whereas predicted hERG II inhibition and a low maximum tolerated dose warrant further attention. The predicted acute oral LD50 and chronic LOAEL values should likewise be considered as model-derived estimates rather than definitive evidence of safety. Overall, the combined SwissADME and pkCSM analyses provide a heterogeneous ADMET profile for lupeol. The contrasting intestinal absorption predictions particularly emphasize the uncertainty associated with in silico ADMET models. Therefore, these computational results should be considered hypothesis-generating and require experimental confirmation of solubility, intestinal permeability, plasma protein binding, metabolic stability, and safety before drawing conclusions about lupeol's pharmacokinetic or therapeutic suitability [29].

Table 3. The ADMET profiling of lupeol using the pkCSM tool.

Property	Model Name	Predicted Value
Absorption	Water solubility (log mol/L)	-5.922
	Caco2 permeability (log Papp in 10 ⁻⁶ cm/s)	1.248
	Intestinal absorption (human) (% Absorbed)	97.882
	Skin Permeability (log Kp)	-2.747
	P-glycoprotein substrate	No
	P-glycoprotein I inhibitor	Yes
Distribution	P-glycoprotein II inhibitor	Yes
	VDss (human) (log L/kg)	0.023
	Fraction unbound (human) (Fu)	0
	BBB permeability (log BB)	0.747
Metabolism	CNS permeability (log PS)	-1.781
	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP1A2 inhibitor	No
	CYP2C19 inhibitor	No
	CYP2C9 inhibitor	No
Excretion	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
	Total Clearance (log ml/min/kg)	0.153
Toxicity	Renal OCT2 substrate	No
	AMES toxicity	No
	Max. tolerated dose (human) (log mg/kg/day)	-0.303
	hERG I inhibitor	No
	hERG II inhibitor	Yes
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.594
	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	0.917
	Hepatotoxicity	No
	Skin Sensitisation	No
	<i>T.Pyriformis</i> toxicity (log ug/L)	0.318
	Minnow toxicity (log mM)	-1.973

4. Conclusion

This integrative *in silico* study identified lupeol from *Caesalpinia sappan* as a computationally prioritized phytocompound for further investigation in the context of leptin receptor (LepR)-associated metabolic research. Molecular docking using the SWISS-MODEL-generated human LepR homology model (UniProt ID: P48357) predicted a favorable binding affinity for lupeol, with the ligand accommodated within a predominantly hydrophobic region of the predicted binding pocket and interacting mainly through hydrophobic/alkyl contacts. However, the predicted interactions did not involve the ideal or previously characterized key residues of LepR; therefore, the docking findings should be interpreted as a predicted ligand–receptor association rather than evidence of specific receptor modulation or functional activity. The FMO analysis further characterized the intrinsic electronic properties of lupeol, including a HOMO–LUMO energy gap of 6.998 eV, while the MEP analysis indicated localized electrostatic potential around its hydroxyl group. These computational descriptors provide information on the electronic structure and theoretical reactivity of lupeol but do not independently establish receptor binding, signaling modulation, or pharmacological efficacy. The SwissADME and pkCSM analyses also revealed a mixed ADMET profile, including high predicted lipophilicity and poor aqueous solubility, together with model-dependent differences in predicted intestinal absorption. Collectively, the findings support lupeol as a computationally prioritized molecule for further mechanistic investigation rather than as an established LepR-targeting therapeutic candidate. Experimental studies, including direct binding assays, receptor-dependent cellular studies, metabolic functional assays, and appropriate *in vivo* investigations, are required to determine whether the predicted lupeol–LepR association has measurable biological consequences and to clarify its pharmacological relevance.

Author Contributions

Conceptualization: J.K.; Methodology: P.R.A.; Software: P.R.A. and A.Z.; Validation: P.R.A. and J.K.; Formal analysis: P.R.A. and J.K.; Investigation: P.R.A., A.Z. and J.K.; Resources: J.K.; Data curation: P.R.A.; Writing—original draft preparation: P.R.A.; writing—review and editing: J.K. and A.Z.; Visualization: P.R.A.; Supervision: J.K.; Project administration: J.K. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

Artificial Intelligence Disclosure

The online tool QuillBot, an AI-powered writing assistant, was used to check grammatical accuracy and language clarity in this manuscript. No AI-generated content was used in the conceptualization, analysis, or interpretation of the study results.

Abbreviations

Abbreviation	Definition
WHO	World Health Organization
DFT	Density Functional Theory
ADMET	Adsorption, Distribution, Metabolism, Excretion and Toxicity
TNF	Tumor Necrosis Factor
IL-6	Interleukin-6
TRH	Thyrotropin-releasing hormone
TSH	Thyroid Stimulating Hormone
LEPR	Leptin receptor
JAK2	Janus Kinase 2
STAT3	Signal Transducer and Activator of Transcription 3
MAPK	Mitogen-Activated Protein Kinase
SOCS3	Suppressor of Cytokine Signaling 3
PTP1B	Protein Tyrosine Phosphatase 1B
CS	<i>Caesalpinia sappan</i>
FMO	Frontier Molecular Orbital
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
IMPPAT	Indian Medicinal Plants, Phytochemistry and Therapeutics
PDB	Protein Data Bank
MEP	Molecular Electrostatic Potential
RMSD	Root Mean Square Deviation
B3LYP	Becke, 3-parameter, Lee-Yang-Parr

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