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Research Article

In-silico antiobesity activity of *Lagerstroemia speciosa* (L.) bioactive compounds by targeting transcriptional regulators PPAR-γ, C/EBP-α, and FABP-4/ap-2 genes

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Abstract
Obesity has emerged as a major health issue worldwide. Current research mainly focuses on how small bioactive compounds can influence the mechanism of transcription regulatory factors involved in the fat accumulation and weight gain process. *Lagerstroemia speciosa* plant is commonly used in traditional systems of medicine to combat obesity and diabetes. It contains major bioactive compounds, viz. pregnenolone, corosolic acid, fenretidinide, norlargerenol acetate, maslinic acid, olenoic acid and beta-sistosterol. The present study was undertaken to elucidate the role of *L. speciosa* bioactive compounds in obesity control by targeting FABP-4/ap-2, C/EBP-α, and PPAR-γ transcription factors that play a significant role in adipocyte biology and metabolism. The present study screened twenty-nine bioactive compounds against three targets using Autodock Vina, Autodock Tools. Discovery Studio was utilized to visualize the targeted proteins' ligand and amino acid interaction. *In silico* approach showed that screened bioactive compounds downregulate the expression of targeted transcriptional regulatory genes involved in the adipocyte differentiation mechanism. Pregnenolone, a major bioactive compound, scored binding free energy of -6.34, -7.58, and -6.22 kcal/mol with C/EBP-α, PPAR-γ, and FABP-4, respectively, compared to standard drug. Findings showed that these bioactive compounds play a crucial role in regulating adipogenesis and differentiation genes, proving their therapeutic importance as antiobesity agent. Although these findings are encouraging, extensive *in vivo* studies are essential to confirm efficacy, ensure safety, and investigate the therapeutic potential of these compounds for obesity treatment.

Keywords: Bioactive compounds, *In-silico,* Oesity, Transcriptional regulation (ap2/FABP-4, C/EBP-α and PPAR-γ)

INTRODUCTION

The prevalence of obesity and its coinciding disorders has escalated into a global public health emergency, as this condition's pervasiveness has surged dramatically across the world, rendering it a formidable threat to the well-being of populations. This condition arises from an imbalance between excessive caloric intake and insuffi-

cient physical activity, leading to an unhealthy accumulation of body fat (Fatima *et al.,* 2018). The research suggests that obesity raises the risk of noncontagious diseases, such as heart disease, diabetes, chronic respiratory diseases and different types of cancers (Banjare and Bhalerao, 2016). The World Health Organisation (WHO) estimates that 13% of people worldwide have a body mass index (BMI) of 30kg/m^2 or more, which will rise to 20% by 2025. Obesity presents a substantial global health challenge, as it heightens the risk of developing life-threatening cardiometabolic diseases and premature mortality (Sarma *et al.,* 2021). Obesity is a major risk factor that leads to adverse metabolic effects, including high blood pressure (Dzhumayevna, 2024), dyslipidaemia (marked by elevated cholesterol and triglyceride levels) (Khutami *et al.,* 2022), and insulin resistance (Gasmi *et al.,* 2021), potentially causing additional health complications (Rani *et al.,* 2016). Several strategies have been suggested to assist and lessen the negative effects of excessive weight gain, including time-restricted eating, intermittent fasting, and diets that imitate fasting (Waldman *et al.,* 2019).

Plants have been used by humans as medicine for various ailments since ancient times. The field of Phyto-therapeutics has seen a huge amount of research activity in recent decades due to the belief that plants can deliver safe, effective, and economical medicines (Alzahrani *et al.,* 2023). Virtually an endless supply of chemical compounds with a wide range of chemical functions can be found in plants. The chemical compounds of the plant hope for the development of novel medications. Herbal products can be utilized as supplementary and alternative medicine and they also serve as a single molecules for use in allopathic medicine (Balkrishna *et al.,* 2024).

Lagerstroemia speciosa is an ornamental medicinal plant from the Lythraceae family, native to tropical regions of Australia, Malaysia, the Philippines, India, and southern China. It has become a health-promoting tea product in Eastern Asia and the United States. *Lagerstroemia speciosa* fruit and leaf contained a variety of active metabolites, including reducing sugars, tannins, α-amino acids, saponins, glycosides, phenolic compounds, starch, and alkaloids (Al-Snafi, 2019). The plant performs a diverse range of biological activities *viz*. hepatoprotective, nephroprotective, inhibition of TNFα production (Yin *et al.,* 2022), xanthine oxidase inhibition, antimicrobial, antioxidant, anticancer, anti-obesity, hypolipidemic (Yue *et al.,* 2024), analgesic, gastrointestinal (Hussain *et al.,* 2014), diuretic, thrombolytic (Chowdhury *et al.,* 2017), cardiovascular (Sahu *et al.,* 2015), antidiabetic, anticancer (Goyal *et al.,* 2022), anti-hepatic steatosis (Tandrasasmita *et al.,* 2021), anti-ulcerative colitis, treat hypertension, urinary dysfunctions haematuria, and gastrointestinal disturbances (Hussain *et al.,* 2014).

The field of *in-silico* molecular docking is quickly developing to comprehend and forecast potential modes of interaction between a ligand and a target biomolecule. *In-silico* or docking tolls have advanced significant techniques that enable novel drug discovery and identification of potential bioactive compounds present in diverse groups of medicinal and aromatic plants (Chaturvedi *et al.,* 2021). Consequently, the study aimed to perform molecular docking analysis of the major phytochemical constituents present in *Lagerstroemia speciosa* against the target proteins FABP-4 (ap-2), C/EBP-α, and PPAR -γ. This computational approach was undertaken to investigate the potential binding interactions and assess the inhibitory effects of these natural compounds on the key regulators implicated in the development of obesity.

MATERIALS AND METHODS

Macromolecule as target preparation

The 3-D X-ray crystallographic structures of the obesity -relevant targets, PPAR-gamma, C/EBP-alpha, and FABP-4, were obtained from the RCSB (Research Collaboratory for Structural Bioinformatics) in the PDB (Protein Data Bank) format for further analysis (Table 1). After removing water molecules, polar hydrogen atoms were added to the target proteins, and appropriate partial charges were assigned. The three targets, FABP-4/ap-2, C/EBP-α, and PPAR-γ were selected based on their well-established roles in obesity, as reported in the literature (Simu *et al.,* 2019). These macromolecules are implicated in the development of obesity, and identifying potential inhibitors from the natural compounds present in *L. speciosa* could contribute to developing dietary interventions for obesity management.

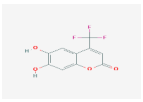
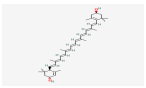
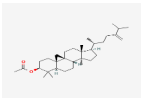
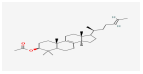
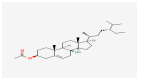
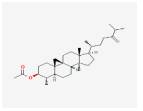
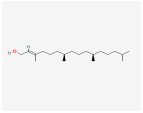
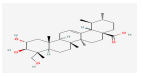
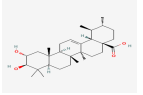
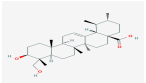
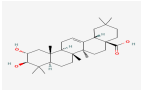
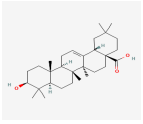
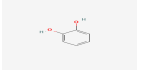
Ligand selection

Through an extensive literature review, various bioactive compounds including phenols, coumarins, flavonoids, alkaloids, and carotenoids, were identified

Table 1. Targets with their PDBID and amino acid chain involved

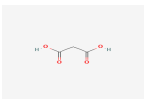
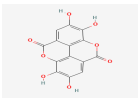
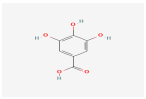
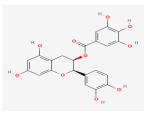
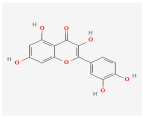
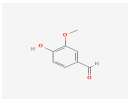
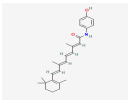
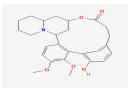
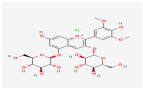
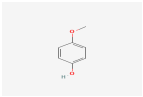
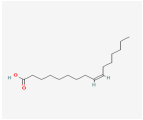
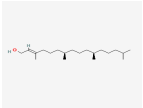
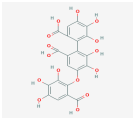
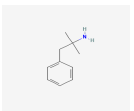
Sr. No.	Target	PDBID	Chain Involved
1	CCAAT-enhancer binding protein-alpha (CEBP-α)	6DCO	A chain
2	Peroxisome proliferator-activated receptor gamma (PPARγ)	2PRG	A chain
3	Fatty-acid binding protein 4 (FABP4)	6LJS	A chain

Table 2. List of selected bioactive ligands with their respective PubChem ID and 2D structure

S. No.	Ligand	PubChem ID	2D structure	Reference
1	6,7-Dihydroxy-4-(trifluoromethyl) coumarin	5393147		(Huang *et al.,* 2013)
2	Lutein	5281243		(Ragasa and Rideout, 2005)
3	24-methylenecycloartenol acetate	13151740		
4	31-norlargerenol acetate	6427336		
5	Beta-sitosterol	5354503		
6	Cycloeucalenol acetate	14282742		
7	Phytol	5280435		
8	Asiatic acid	119034		(Hou *et al.,* 2009)
9	Corosolic acid	6918774		
10	23- hydroxy urosolic acid	14136881		
11	Maslinic acid	73659		
12	Oleanolic acid	10494		
13	Catechol	289		(Sahu *et al.,* 2015)
14	D- limonene	440917		(Zhang and Kang, 2014)

Contd……

Table 2. Contd……

15	Malonic acid	867		(Kolakul and Sripanidkulchai, 2017)
16	Ellagic acid	5281855		
17	Gallic acid	370		
18	Epicatechin gallate	107905		
19	Quercetin	5280343		
20	Vallin	1183		
21	Fenretidinide	5288209		
22	Lagerstroemin	78385190		(Bai *et al.,* 2008)
23	Malvidin	5319251		(Koshio *et al.,* 2012)
24	Mequinol	9015		
25	Palmitoleic acid	445638		(Sirikhansaeng *et al.,* 2017)
26	Pregnenolone	8955		
27	Squalene	638072		
28	Valoneic acid	12444662		(Wei *et al.,* 2022)
29	Standard phentermine	4771		(Faridah *et al.,* 2024)

and selected to evaluate their potential antiobesity properties. The structural files of the identified bioactive compounds were fetched from the ZINC DATABASE and PubChem in SDF (Structure Data File) configuration. These files were then converted into the PDB (Protein Data Bank) format using the OPEN BABLE software, a molecular file conversion tool, to facilitate further computational analysis. Table 2 presents a comprehensive overview of the bioactive molecules under investigation, including their respective molecular types, two-dimensional structural representations, and corresponding PubChem identification numbers. Additionally, the study incorporated phentermine, an FDA-approved antiobesity medication, as a positive control to serve as a reference for comparing and validating the computational analyses (Song *et al.,* 2024).

Molecular docking tools

The "molecular docking" process examines the potential interaction between molecules under topographical restrictions or energy considerations to determine the optimal molecules interaction conformation (Graw *et al.,* 2021). Docking of molecules is the cost-effective and most efficient process to assess the pharmokinetics potential, efficacy and safety profile of identified bioactive compound at clinical and preclinical trial stage (Konappa *et al.,* 2020).

The present examination employed *in-silico* molecular docking analysis using the software Autodock Vina and Autodock Tools. During analysis, the structure of the ligand was kept mouldable while the structure of proteins was kept rigid. AutoDock was used to fabricate grid boxes and prepare PDBQT files for proteins, ligands, and other transitional stages. Docking analysis is performed on the basis of 10 runs of the LGA (Lamarckian Genetic Algorithm). The grid box comprises a total of 2,048,383 grid points having a spacing of 1.0 Å and defined x, y, and z coordinates. The grid box dimensions were set at X=126, Y=126, and Z=126, and the center points of the grid box were defined with the coordinates: X=48.648, Y=59.931 and Z=31.936. The molecular modeling application Discovery Studio Visualizer were used to view, share, and examine the comparative collective data. Top energy scoring docking outcomes were evaluated and analyzed using Biovia Discovery Studio Visualizer, which enables the visual assessment of the predicted protein and ligand connections interactions.

Pharmacokinetics profile

ADME prediction

Therapeutic chemistry and the potential pharmacokinetics of small bioactive compounds are characterized by Absorption, Distribution, Metabolism and Excretion (ADME) studies. Conducting DMPK (Drug Metabolism and Pharmacokinetics) analysis, also known as ADME investigations, represents a key step in developing and discovering novel drugs. SWISSADME and admetSAR are the open-code source tools employed for ADME analysis (Devibala, 2022).

Toxicity examination

The ProTox-II database is utilized to assess toxicity by calculating their LD_{50} value and their respective toxicity class. The LD_{50} value is the lethal dose at which 50% of the resulting population would not survive after administering that dose of bioactive compound (Dearden and Hewitt, 2021). By inputting the SMILES notation from PubChem, the toxicity profile of the specific chemical compound can be studied using the online database pkCSM. The data provide insights such as whether a given substance contains mutagenic potential property based on its Ames positive or negative test. It also estimates the probability of adverse liver function and skin sensitization effect of a specific compound.

Drug-likeness properties

The chemical drug ability is assessed by using Lipinski's Rule. Lipinski's Rule a refinement of drug-likeness, is used to evaluate whether a chemical compound possesses the pharmacological activity as an orally active drug in humans (Merzoug *et al.,* 2024).

Target prediction

The observed phenotypic effects represent the active potential of small bioactive molecules (metabolites), that modulate cellular function by binding to proteins or other relative macro-molecular targets. Mapping the molecular targets of bioactive small compounds is essential to elucidate the underlying mechanisms behind their bioactivity and to anticipate any potential adverse effects or cross-reactivity (Agamah *et al.,* 2020). In the present analysis, computational methods are employed to identify targets for unexplored chemical compounds or off-targets for recognized molecules. Swiss Target Prediction (http://www.swisstargetprediction.ch/) is an advanced web tool that uses 3D and 2D similarity assessment parameters with known ligands to precisely anticipate the targets of bio-compounds (Gfeller *et al.,* 2014).

RESULTS

Molecular docking

The docking scores exhibit how well the ligands fit or bind into the active site of the precise target, with more negative values indicating the stronger binding affinity of both ligand and target (Rudrapal *et al.,* 2022). In the present study, twenty-nine screened bioactive compounds were docked contrary to the 3 transcriptional regulation targets protein *viz.* CEBP-α (CCAAT-enhancer binding protein-alpha), PPAR-γ (Peroxisome

proliferator-activated receptor gamma), and FABP-4 (Fatty-acid binding protein 4) for obesity. The calculative free binding energy of the screened docked compounds against their C/EBP-α, PPAR-γ and FABP-4/ap-2, transcriptional genes are respectively depicted in Fig. 1A, 2B,2C.

Target I- CCAAT-enhancer binding protein-alpha (CEBP-α)

Selected compounds that were docked counter to the C/EBP-α gene, oleanolic acid, pregnenolone, maslinic acid, and beta-sitosterol, exhibit higher binding energy of -6.52 kcal/mol, -6.34 kcal/mol, -6.32 kcal/mol, -5.98 kcal/mol respectively as compare to standard phentermine i.e. -4.23 kcal mol. The hydrogen bond interaction between the inhibitor bioactive compound molecule and the amino acid residue of the target protein binding site provides the sign of stability of the predicted complex. Maslinic acid formed six hydrogen bonds with the CEBP-α target during docking, and the residual compound formed less than six H-bonds. The amino acids integrated in this bond assembly are Tyr 275, Arg 281, Tyr 282, Arg 298, and Gln 300 with 23.32 µM inhibition constant. Oleanolic acid formed three hydrogen bond formations involving Gly 114, Arg 115, Glu 116, Glu 161, Lys 162, and Phe 164 amino acids with 16.57 µM inhibition constant, whereas pregnenolone formed a bond with Tyr 127, Tyr 134, Ile 135, Ile 146, Val 149 peptide building blocks with 22.64 µM inhibition constant. Beta-sitosterol constrain bond with Ile 135, Ile 146, Val 147, Val 149 protein monomeric residues and 41.36 µM inhibition constant as shown in Table 3.

Target II - Peroxisome proliferator-activated receptor gamma (PPAR-γ)

Screened bioactive compounds that were docked contrary to the transcriptional target PPAR-γ, the compound pregnenolone, fenretidine, corosolic acid, and 31 -norlargerenol acetate showed negative (most favorable) binding energies values of -7.58 kcal/mol, -7.34 kcal/mol, -7.24 kcal/mol, and -7.13 kcal/mol respectively in comparison to selected standard drug phentermine with -4.98 kcal/mol value. The more -ve the value, the greater the stability of the target ligand complex. The pregenolone formed two H-bonds within the pocket domain of the target protein with the peptide residues Glu 259, Ile 262, Arg 280, Ile 281, Arg 288, Ile 341, Ser 342 with 2.79 µM inhibition constant value. Fenretidinide formed only one H-bond with amino acid Ile 262, Leu 270, Arg 280, Ile 281, Gln 283, Phe 287, His 466 with 4.14 µM inhibition constant. Compound corosolic acid also formed two H-bonds with peptide residues Leu 270, Glu 272, Arg 280, Arg 288 with an inhibition constant of 4.90 µM. 31-norlargerenol acetate formed no hydrogen bond with Ile 262, Ile 281, Cys 285, Phe 287, Arg 288, and Ile 341 amino acids with 5.97 µM inhibition constant. All the resultant results values are shown in Table 4.

Target III- fatty-acid binding protein 4 (FABP-4)

In the docking analysis, out of the 29 screened compounds, oleanolic acid, pregnenolone, cycloeucalenol acetate, and 31-norlargerenol acetate showed the highest potential properties of FABP-4 inhibition. Compared to standard phentermine (-3.81 kcal/mol), the oleanolic acid (-6.28 kcal/mol), pregnenolone (-6.22 kcal/mol), cycloeucalenol acetate (-6.14 kcal/mol), and 31-norlargerenol acetate (-5.92 kcal/mol) revealed higher binding energies within the target protein pocket of FABP-4. The oleanolic acid interaction with the target protein chain form two H-bond with the participation of Asn 59, Ile 62, Asp 71, and Val 73 peptide residues and 24.84µM inhibition constant. The pregnenolone also formed one H-bond with Phe 16, Met 20, Ala 75, Asp 76, Arg 78, Val 115, Cys 117, Tyr 128 peptidyl residues with 27.41 µM inhibition constant. Cycloeucalenol acetate binds with the Glu 61 and forms one conventional H-bonds with the target with an inhibition constant of 31.66 µM. The 31-norlargerenol acetate also strongly interacted with the target FABP-4 and form one H-bond with Thr 60, Glu 61, Ile 62, Ile 65, Phe 70, Val 73 peptidyl residues having inhibition constant 45.94 µM as illustrated in Table 5.

Table 3. Molecular docking analysis of the predicted target protein CEBP-α (6DCO)

Sr. No.	Ligand	Binding energy (-3.81 kcal/mol)	Inhibition constant	Amino Acid involved	Hydrogen bond
1	Pregnenolone	-7.58	2.79 uM	Glu 259, Ile 262, arg 280, Ile 281, Arg 288, Ile 341, Ser 342	2
2	Fenretidinide	-7.34	4.14 uM	Ile 262, Leu 270, Arg 280, Ile 281, Gln 283, Phe 287, His 466	1
3	Corosolic acid	-7.24	4.9 uM	Leu 270, Glu 272, Arg 280, Arg 288	2
4	31-norlargerenol acetate	-7.13	5.97 uM	Ile 262, Ile 281, Cys 285, Phe 287, Arg 288, Ile 341	0
5	Standard Phentermine	-4.98	222.15 uM	Leu 270, Glu 272	1

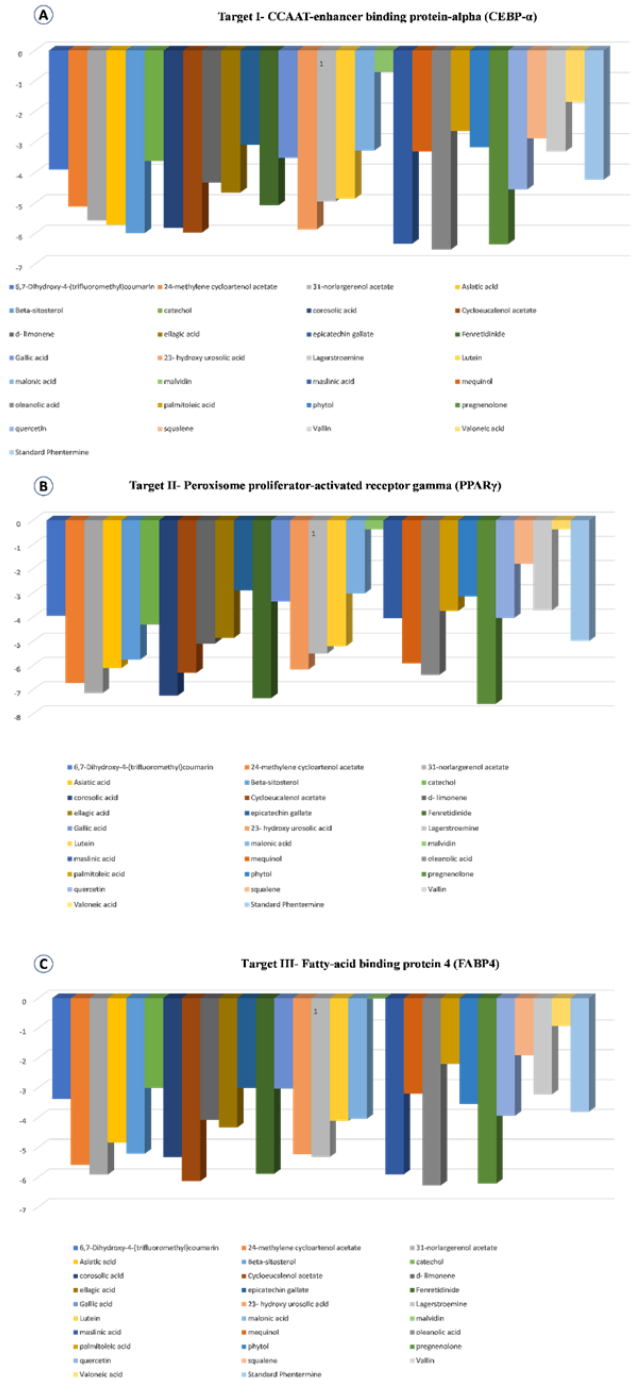


Fig. 1. *Calculated binding free energy of the bioactive compounds against target protein- (1a) CCAAT/-enhancer binding protein-alpha (CEBP-α), (1b) Peroxisome proliferator-activated receptor gamma (PPAR-γ), (1c) Fatty-acid binding protein 4 (FABP4)*

Pharmacokinetics studies

SWISSADME and pkCSM are used to analyse the biochemical characteristics, drug-like nature and medicinal chemistry of a compound as well as its absorption, distribution, metabolism, excretion and toxicity (ADMET) profile (Daina *et al.,* 2017).

Their solubility and stability also direct the body's potential to assimilate bioactive substances due to critical pH levels in the stomach and microbial metabolism in the intestine.

Topological Polar Surface Area is an extensively used molecular descriptor in studying drug transport attributes, including intestinal absorption. Compounds exhibiting TPSA values less than 70 Å are considered to have favourable brain permeability, while compounds with TPSA less than 140 Å exhibit efficient intestinal absorption characteristics (Rashid, 2021). According to the findings, the bioactive compound pregnenolone has TPSA value < 70 Å, suggesting that it might be an excellent brain penetration compound (Table 6a).

The rule of five, proposed by Lipinski's has widely accepted guidelines or criteria that help in physiochemical entities analysis of bioactive compounds by providing desirable adequate absorption and pharmacokinetics profile upon oral administration in the human body (Redka *et al.,* 2023).

The canonical SMILES from the PubChem database were used to identify Lipinski's properties. Pregnenolone exhibited characteristics of a medication since it satisfied the criteria outlined by Lipinski rule. Table 4 demonstrates that pregnenolone exhibits an acute oral toxicity dosage of 1.91 mol/kg and an upper limit tolerated dose of 0.453 log mg/kg/day when administered orally.A bioactive compound (Pregnenolone) was further examined to determine whether it may act as an inhibitory agent for obesity.

Physiochemical properties

According to the physical attributes, pregnenolone has a molecular weight of 316.47 g/mol. Their sp^3 hybridization contain 23 heavy atoms, 0.2 carbon atoms, one rotatable, two H-bond acceptors, and one H-bond donor. The determined topological polar surface area was 37.3 Aº, and the molar refractivity was 94.97 (Table 6a). Octanol water coefficient (log P) range suggests favorable lipophilic potential of the compound. The log Po/w (log P) is 3.25, the log Po/w (Xlog P3) is 4.22, the log Po/w (Wlog P) is 4.52, the log Po/w (MlogP) is 4.05, the log Po/w (SILICOS-IT) is 3.9. Collective log P values indicate that the compound exhibited good lipophilic properties, which are desirable characteristics for drug

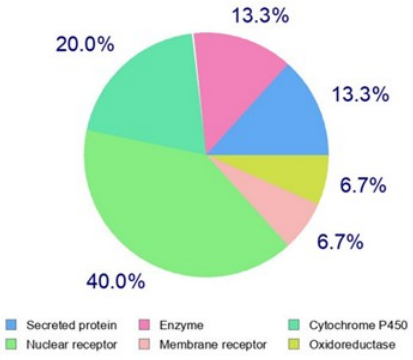


Fig. 2. *Target prediction of pregnenolone*

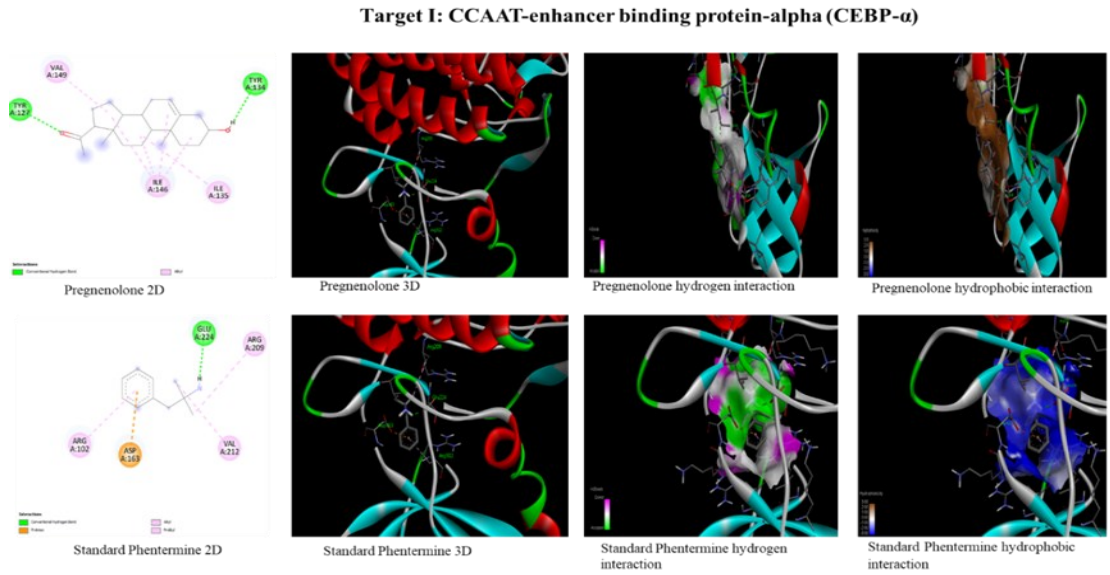


Fig. 3. *Visualisation of binding interaction, formation of hydrogen and hydrophobic bonds between pregnenolone and Target I CCAAT-enhancer binding protein-alpha (C/EBP-α) with their positive control*

molecules. A log S (ESOL) value of -4.39 shows that the chemo entity belongs to the moderately water-soluble category that was applied to investigate the substance's water solubility (Table 6a).

Compounds exhibit tremendous drug-like properties by scoring bioavailability of 0 through conforming to the Lipinski, Veber and Egan guidelines. Swiss ADME Synthetic Accessibility score calculation relies on the principle that the molecular segment is frequently observed in fast synthesizable molecules, which indicates greater synthetic accessibility. The fragmental contribution to SA score is designed to reward the favorable chemical moieties and diminish the unfavorable moieties. The synthetic accessibility score value was recorded to be 4.97, meaning the synthesis of the molecule would not be challenging. The absence of PAINS alert implies that the bio-compound has quite desirable specificity in nature (Table 6a).

Pharmacokinetics profiles

Absorption

The investigated pharmacokinetic profile of pregnenolone showed blood-brain permeability of 0.092 log BB, and its estimated diffusivity to the CNS is -2.373 log PS; both values indicate a low propensity of CNS adverse effects. According to its admetSAR data value, the compound has a low probability of acting Pgp (P-glycoprotein) inhibitor. It is considered to have a low potential for medication interactions. Score value closer to 1 indicates strong inhibitor potential, while near 0 reveals a non-inhibitor. This scoring number output reveals the potential that the compound is Pgp non-suppressor. The score value 0.6312 suggests a diminished propensity for being a Pgp substrate. Pgp substrate acquires a score of 1, while a non-substrate obtains a score of 0 (Table 6b).

Distribution

To investigate the distribution parameters of the compound, the liberated fraction in plasma (Fu), blood-brain barrier (BBB) permeability and volume of distribution (VD) were admitted to consideration (Table 6b,c). The esteemed volume of distribution (VD) was determined to be 0.251 L/kg. The cover span of 0.04 to 20 L/kg is ideal for VD. The score of 0.9424 shows that pregnenolone has a higher expected occurrence of blood-brain barrier permeability. Calculations highlighted that the plasma's free fraction (Fu) was 0.06. That means

Table 5. Molecular docking analysis of the predicted target protein FABP-4 (6LJ3)

Sr. No.	Ligand	Binding energy (kcal/mol)	Inhibition constant	Amino Acid involved	Hydrogen bond
1	Oleanolic acid	-6.28	24.84uM	Asn59, Ile62, Asp71, Val73	2
2	Pregnenolone	-6.22	27.41uM	Phe16, Met20, Ala75, Asp76, Arg 78, Val115, Cys 117, Tyr 128	1
3	Cycloeucalenol acetate	-6.14	31.66uM	Glu 61	1
4	31-norlargerenol acetate	-5.92	45.49uM	Thr60, Glu61, Ile62, Ile65, Phe 70, Val73	1
5	Standard Phentermine	-3.81	1.6mM	Cys1, Asp47, Ile65, Leu66	0

Table 6a. Physiochemical properties of pregnenolone

Molecule	Pregnenolone 8955
Ali Class	Moderately soluble
Ali Log S	-4.71
Aromatic heavy atoms	0
Bioavailability Score	0.55
Brenk alerts	1
Canonical SMILES	OC1CCC2(C(=CCC3C2CCC2(C3CCC2C(=O)C)C)C1)C
Consensus Log P	3.99
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Egan violations	0
ESOL Class	Moderately soluble
ESOL Log S	-4.39
ESOL Solubility (mg/ml)	1.28E-02
ESOL Solubility (mol/l)	4.03E-05
Formula	C21H32O2
Fraction Csp3	0.86
Ghose violations	0
Hydrogen-bond acceptors	2
Hydrogen-bond donors	1
Heavy atoms	23
iLOGP	3.25
LD_{50} value	>200 mg/kg (mouse)
Leadlikeness violations	1
Lipinski #violations	0
log Kp (cm/s)	-5.23
MLOGP	4.05
MR	94.97
Muegge violations	0
MW	316.48
PAINS alerts	0
Pgp substrate	No
Rotatable bonds	1
Silicos-IT class	Soluble
Silicos-IT Log P	3.9
Silicos-IT LogSw	-3.69
Silicos-IT Solubility (mg/ml)	6.51E-02
Silicos-IT Solubility (mol/l)	2.06E-04
Synthetic Accessibility	4.97
Toxicity class	Class III (GHS system)
TPSA	37.3
Veber violations	0
WLOGP	4.52
XLOGP3	4.22

more free plasma fractions are present for pharmacological potential (Table 6b).

Metabolism

Drug metabolism is crucial for determining drug concentration levels in the blood plasma. The data repository classified ligands as either non-inhibitor (category 0) or inhibitor (category 1), based on the properties to inhibit the enzyme or not. Additionally, a score of 1 represents the probability of acting as a substrate for an enzyme, while 0 scores suggest a lower probability of serving as an enzyme substrate. The molecule falls under category 1 substrate while a category 0 non-substrate of the enzyme. Because of the pregnenolone assigned score (0.917), the prediction indicates a low probability of acting as an inhibitor of CYP1A2. The feasibility of CYP2C19 inhibition is 0.90. Moreover, there is no valid evidence of CYP2D6 substrate or inhibitor. Pregnenolone is likely to be a substrate of CYP3A4 (Table 6b).

Excretion

Analysis revealed that pregnenolone exhibits a relatively low excretion rate of 0.677 mL/min/kg, represented in clearance (CL) data values (Table 6b). A molecule/compound is regarded as having a high CL rate if it scores > 15 mL/min/kg, a moderate scale rate if the value ranges between 5–15 mL/min/kg and 5 mL/min/kg if it has a low clearance rate. Renal organic cation transporters (ROCTs) are facilitated diffusion transporters that mediate the directional transport of various physiological compounds, xenobiotics, and drugs across the kidney, liver, and placenta cells in mammals, playing a crucial role in their absorption and elimination. Concluding analysis reveals that pregnenolone did not inhibit the Renal OCT2 transporter or act as a substrate for this transporter (Table 6b).

Toxicity

The toxicity parameters include rat oral acute toxicity, human hepatotoxicity, carcinogenicity, skin sensitization, AMES toxicity, hepatotoxicity and hERG inhibiting. In accordance with the ADMET test, pregnenolone was non-AMES chemically and was not believed to be carcinogenic. There is a low probability that pregnenolone causes skin corrosive effects. The potassium ion channel that anticipates the cardiac normal repolarization function is encoded by the human hERG. With a projected probability value of 0.517 for hERG inhibition, all the kinetic profiling factors (absorption, distribution, metabolism, and excretion) are summarized in Table 6b.

Target prediction

The examined phenotypic effects result from the activity of small bioactive molecules, such as metabolites, which modulate the active potential of protein or essen-

Table 6b. ADMET prediction using SwissADME and admetSAR

Absorption	Water solubility	-4.628 log mol/L
	Caco2 permeability	1.048(log Papp in 10^{-6} cm/s
	Intestinal absorption (human)	95.631%
	P-glycoprotein substrate	No
	P-glycoprotein I inhibitor	Yes
	P-glycoprotein II inhibitor	No
Distribution	VDss (human)	0.251 log L/kg
	Fraction unbound (human)	0.06 Fu
	BBB permeability	0.092 log BB
	CNS permeability	-2.373 log PS
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP1A2 inhibitior	No
	CYP2D6 inhibitior	No
Excretion	Total Clearance	0.677 log ml/min/kg
	Renal OCT2 substrate	No
Toxicity	AMES toxicity	No
	Max. tolerated dose (human)	-0.453 log mg/kg/day
	hERG I inhibitor	No
	hERG II inhibitor	Yes
	Oral Rat Acute Toxicity (LD_{50})	1.91 mol/kg
	Oral Rat Chronic Toxicity (LOAEL)	1.777 log mg/kg_bw/day
	Nephrotoxicity	No
	Skin Sensitisation	No
	T. Pyriformis toxicity	0.905(log ug/L)
	Minnow toxicity	0.586 log mM

tial macromolecules due to their binding affinities. It is crucial to outline their targets to elucidate the molecular functionality of bioactive small compounds and predict any adverse reaction or off-targeting interactions (Kapoor *et al.,* 2016). Through *in-silico* approach, new targets can be predicted for uncharacterized biomolecular compounds or off-targeting interactions for recognized bioactive molecules. Swiss Target Prediction is an advanced web tool that serves as a comprehensive set of 3D and 2D similarity algorithms with known ligands to precisely determine/project the targets of bioactive compounds (Shaikh *et al.,* 2021). Five different organisms can be used to carry out predictions, and mapping presumptions by genetic similarity within and between species is possible for near paralogs and orthologs. The pregnenolone of the closely related receptors was calculated using ChEMBL-ID, UniProt ID, likelihood score, target class and known active compounds through 2D/3D structural similarity algorithm against database of closely related receptors. The results predicted the potential target class of pregnenolone as follow: 20% cytochrome P_{450}, 40.0% nuclear receptor, 13.3% secreted protein, and 6.7% other cytochrome P_{450} enzymes. Prediction also suggests that pregnenolone may target other proteins (Fig. 2).

DISCUSSION

Carrying excess weight is a major health concern for individuals of both age groups, including adults and children. Diet, exercise, medication, and surgery are the main approaches employed for the management of obesity, although each approach has drawbacks and potential adverse consequences (Zolotarjova *et al.,* 2018). Consequently, a series of research have looked for potential bioactive ingredients in food. Rich array of bioactive compounds, which are utilized as food additives, agrochemicals, flavors, perfumes, colors, and biopesticides, are obtained from plants (Nxumalo, 2023).

C/EBP-α, PPAR-γ, and FABP4 are central regulators of adipogenesis, lipid and glucose metabolism, and obesity-related inflammation. Their roles in fat cell development, energy balance, and insulin sensitivity make them strategic targets for assessing the potential anti-obesity effects of bioactive compounds (Kumari *et al.,* 2025). During adipogenesis, FABP4, C/EBP-α, and PPAR-γ work together to drive preadipocyte commitment, differentiation, and maturation. PPAR-γ and C/EBP-α are activated early, with FABP4 upregulated later, as C/EBP-α enhances both its own and PPAR-γ's expression. Together, they promote mature adipocyte formation and lipid storage (Moseti *et al.,*2016). Their dysregulation can lead to excessive fat accumulation and metabolic disturbances, contributing to the development and progression of obesity and related comorbid conditions (Shen *et al.,* 2019).

Present *in-silico* approach investigated novel bioactive compounds as an inhibitor from *Lagerstroemia speciosa* against transcriptional regulator CEBP-α (CCAAT-enhancer binding protein-alpha), PPARγ (Peroxisome proliferator-activated receptor gamma), Fatty-acid binding protein 4 (FABP4). A structure-based *in-silico* screening method called molecular docking was employed to identify the active inhibitors based on the binding interaction with their corresponding transcriptional regulatory targets. The most favorable binding docking poses are investigated for protein-ligand complexes with low energy conformation (Rudrapal *et al.,* 2022).

A transcription factor called CCAAT-enhancer binding protein-alpha (C/EBP-α) is an important key regulator in

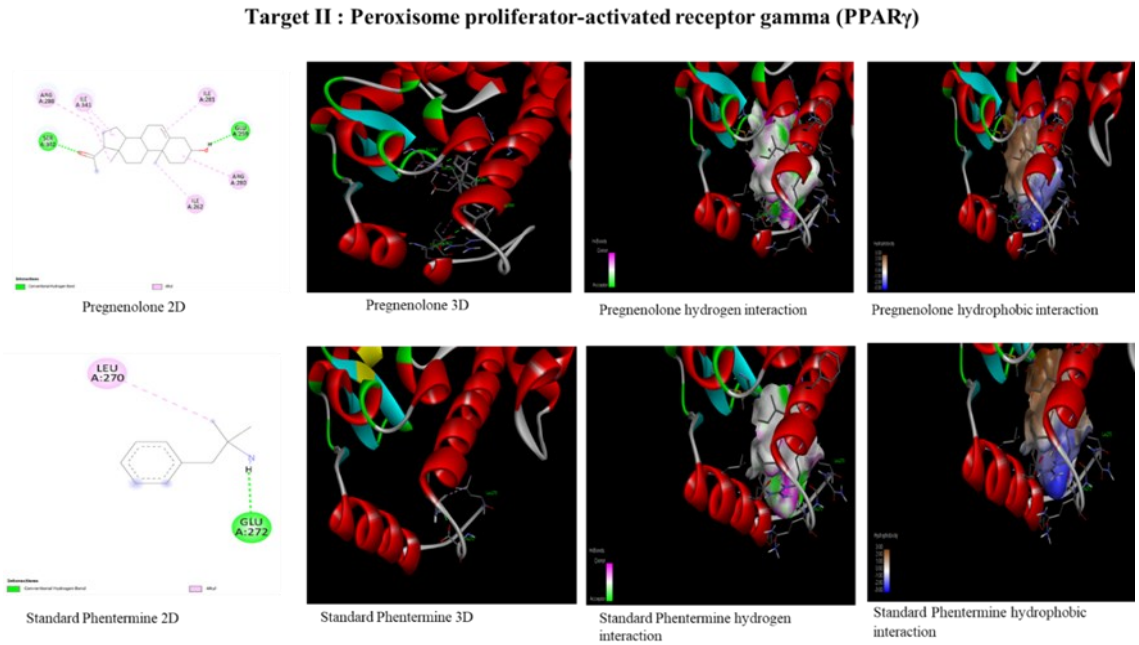


Fig. 4. *Visualisation of binding interaction, formation of hydrogen and hydrophobic bonds between pregnenolone and Target II Fatty acid-binding protein 4 (FABP-4) with their positive control*

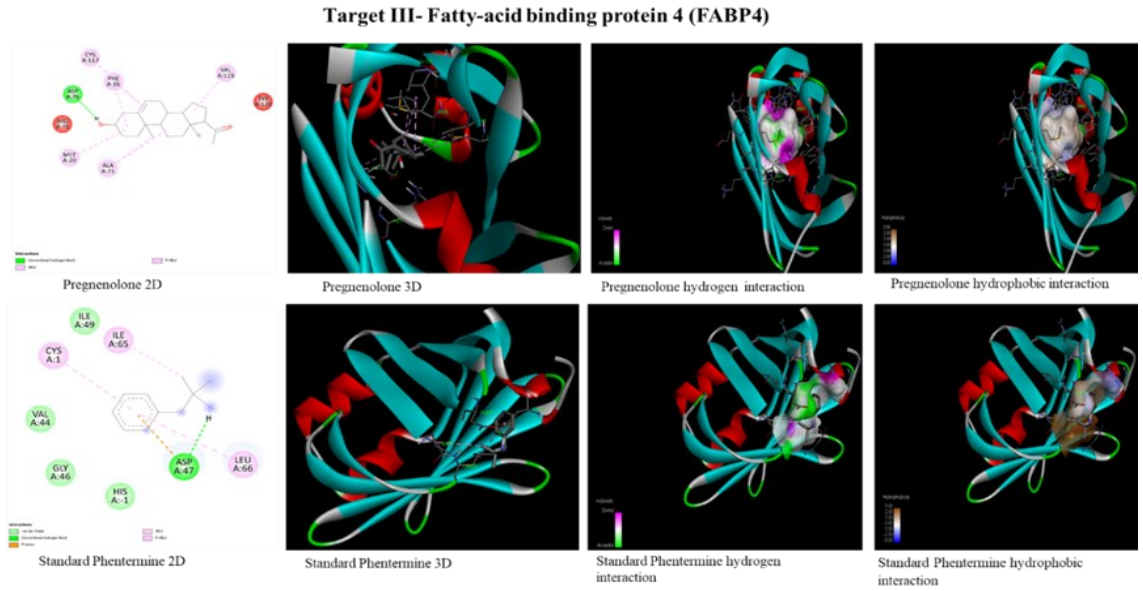


Fig. 5. *Visualization of binding interaction, formation of hydrogen and hydrophobic bonds between pregnenolone and Target III Peroxisome proliferator-activated receptor gamma (PPAR-γ) with their positive control*

controlling the process of adipogenesis, in which precursor preadipocyte cells develop into mature or differentiated adipocytes (fat cells) (Lee *et al.,* 2020). In mature adipocytes, C/EBP-α controls the expression of genes related to lipid metabolism and glucose homeostasis, which are the defining features of metabolic diseases associated with obesity (Pant *et al.,* 2021). It prevents ectopic lipid buildup in non-adipose tissues, such as the liver and muscle, which can result in insulin resistance and metabolic syndrome (Zaiou *et al.,* 2018). It facilitates the intake of free fatty acids and their storage as triglyceride content forms within the cells (Balakrishnan *et al.,* 2018). Chronic low-grade inflammation in adipose tissue is directly linked with obesity, insulin resistance and metabolic dysfunction (Castro *et al.,* 2017). The control of inflammatory gene expression in adipocytes has been linked to C/EBP-α, and adequate functioning of this protein may help reduce inflammation linked to obesity (Boughanem *et al.,* 2019).

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a prime target for antiobesity medications due to their regulatory adipocyte impact on lipid metabolism, insulin sensitivity, inflammation, and energy balance (Jakab *et al.,* 2021). PPAR-γ activation encourages preadipocyte differentiation into mature adipo-

cytes (fat storage cells), fatty acid intake, synthesis, and storage in adipocytes (Montaigne *et al.,* 2021). Insulin resistance and metabolic syndrome are consequently linked to PPAR-γ activated adipose tissue. It also prevents lipo-toxicity and ectopic lipid buildup in other tissues (Atal *et al.,* 2022). Fatty acid-binding protein 4 (FABP-4), often referred to as adipocyte protein 2 (ap 2) is a cytoplasmic protein that is mostly expressed in macrophages and adipocytes (Catalioto *et al.,* 2009). It significantly impacts the process of lipid metabolism, adipocyte regulation, insulin sensitivity, energy homeostasis, and inflammation, which are factors strongly linked to obesity and its associated consequence complications. FABP-4 plays a major role in fatty acid transport within macrophages and adipocyte tissue of the body (Furuhashi, 2019). It attaches to the fatty acids, especially with long-chain and facilitates their movement to different cells for use or storage purposes (Michler *et al.,* 2024).

FABP-4 may aid in preventing the buildup of extra lipids in non-adipogenic tissues, including the liver and muscle, which may result in insulin resistance and metabolic dysfunction by encountering the process of fatty acid trafficking. It could be involved in controlling lipolysis, the process by which triglycerides are broken down into fatty acids and glycerol (Hotamisligil and Bernlohr, 2015). FABP-4 can affect the release of fatty acids into the bloodstream and their subsequent uptake by other tissues for energy generation by regulating lipolytic activity in adipocytes (Ha and Bauer, 2018). An *in-silico* approach revealed that the binding energy suggested a more robust and long-lasting bond between the ligand and the target molecule. The lower (more negative) binding energy shows stronger target ligand complex formation in the interaction pocket (Chaturvedi *et al.,* 2021). Pregnenolone emerged as the most versatile bioactive compound, successfully docking against all three targets and forming stable complexes with each. The Globally Harmonised System of Classification and Labelling of Chemicals (GHS) describes the six classes of toxicity classifications, out of which LD_{50} can quantify acute toxicity. Present results reveal that pregnenolone was categorized into class III, according to the GHS system. The compound showed no Ames toxicity and no nephrotoxicity. The pregnenolone follows Lipinski's rule of five. The interaction between the pregnenolone and targets against the positive control is shown in Fig. 3-5.

Targeting multiple transcriptional regulators such as PPAR-γ, C/EBP-α, and FABP-4 enhances the potential effectiveness of pregnenolone as an antiobesity agent by simultaneously modulating various critical pathways involved in adipocyte differentiation, lipid metabolism, and inflammation. The *in-silico* findings revealed that pregnenolone exhibits strong binding affinities with all three targets, suggesting its ability to inhibit multiple mechanisms that promote obesity.

The bioactive compounds corosolic acid, pregnenolone, fenretinide, maslinic acid, norlargerenol acetate, oleanolic acid, beta-sitosterol are widely accepted for their therapeutic potential and reported in various plant species. Pregnenolone, a precursor steroid growth hormone known for its tremendous neuroprotective effects, has functional similarities with certain plant sterols. New evidence indicates that pregnenolone may influence lipid metabolism via nuclear receptors such as PPAR-γ (Żulińska *et al.,* 2024). The primary source of corosolic acid, which is believed to possess PPAR-γ agonist and insulin-sensitizing properties, is the leaves of *Lagerstroemia speciosa* (Banaba), though it can also be found in other medicinal plants such as *Centella asiatica* (Alam *et al.,* 2022). Maslinic acid, derived from olives (*Olea europaea*), shows potent antidiabetic and anti-inflammatory effects, often through PPAR-γ modulation. Stone fruits and grapes may also contain related chemicals (Claro-Cala *et al.,* 2022). Chinese privet (*Ligustrum lucidum*) and self-heal (*Prunella vulgaris*) are two examples of traditional medicinal herbs that contain oleanolic acid, which has hepatoprotective and metabolic effects and is structurally and functionally comparable to maslinic acid. Less often researched norlargerenol acetate is consistent with the bioactivity of phytoestrogens and lignans, which are present in plants like flaxseed and sesame and are known to have anti-inflammatory and anticancer effects (Al-Snafi, 2019). Nuts, seeds, and oils contain beta-sitosterol, a phytosterol that interacts with molecular targets such as PPAR-γ, C/EBP-α, and FABP-4/ap-2 to control inflammation, adipogenesis, and lipid metabolism. It influences C/EBP-α to promote healthy adipocyte development and activates PPAR-γ, which improves insulin sensitivity and glucose uptake. Beta-sitosterol decreases lipotoxicity and enhances fatty acid transport by modifying FABP-4. Because of these qualities, it is a promising option for treating inflammation, metabolic problems, and associated illnesses (Dini, 2018). Its medicinal promise is increased by its widespread presence in plants and its potential for broad sourcing through phytochemical research.

Incorporating corosolic acid, pregnenolone, fenretinide, maslinic acid, norlargerenol acetate, oleanolic acid, beta-sitosterol bioactive compounds into food products or supplements could provide a natural approach to obesity management and related metabolic disorders. This research thus paves the way for designing functional foods enriched with these potent phytochemicals, emphasizing their safety, efficacy, and health benefits, which are crucial for nutraceutical formulations. Docking studies reveal potential compound–protein interactions but do not account for biological factors like me-

tabolism, toxicity, or pharmacokinetics. While promising, these *in-silico* results need validation by *in-vivo* and clinical studies to confirm safety and effectiveness.

Conclusion

The holistic or naturopathic treatment of obesity is of significant interest as it seeks to develop effective natural pharmacological approaches to addressing obesity with no or minimal toxicity and side effects. Present research proved the antihyperlipidemic potential of *Lagerstroemia speciosa* through *in-silico* approach by targeting transcriptional regulators genes PPAR-γ, C/EBP-α, and FABP-4/ap-2. It was found that pregnenolone and oleanolic acid with target protein FABP-4, pregnenolone, corosolic acid, fenretidinide, norlargerenol acetate with PPAR-γ, pregnenolone, maslinic acid, olenoic acid, beta-sistosterol with C/EBP-α show highest binding (more negative) energy as compared to standard drug. The present screening findings concluded that pregnenolone exhibits the strongest inhibitory action potential against all three targets, suggesting its efficacy as an antiobesity agent. Results recommend further investigation of pregnenolone for developing a novel *L. speciosa* derived drug due to its multitarget inhibitor potential in obesity-related metabolic pathways. However, further research is needed to evaluate the toxicological effects of each bioactive compound before the recommended human trials are performed to determine the *L. speciosa* antiobesity agent plant.

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Conflict of interest

The authors declare that they have no conflict of interest

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