Structure-Based Investigation of Chromolaena odorata Compounds Against Key Proteins Implicated in Obesity Using Molecular Docking Approaches

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ABSTRACT

Obesity remains a significant global health burden, contributing to a spectrum of metabolic disorders including cardiovascular diseases, type 2 diabetes, and dyslipidemia. Despite the availability of pharmacological interventions, issues such as adverse effects, high cost, and long-term inefficacy necessitate the search for safer, plant-based alternatives. This study aimed to evaluate the anti-obesity potential of phytochemicals derived from Chromolaena odorata (commonly known as devil weed) through theoretical and molecular docking approaches against two obesity-related protein targets: 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and Fat Mass and Obesity-associated protein (FTO). A total of 68 bioactive compounds were retrieved from literature and docked using PyRx and Discovery Studio. Binding affinities were analyzed, and the molecular interactions were visualized using 2D diagrams to identify key interacting residues. The top compounds—Naringin, Curcumin, Rutin, and Catechin—exhibited higher binding affinities than standard anti-obesity drugs such as Orlistat and Phentermine, with Naringin recording -9.8 kcal/mol against FTO and -9.3 kcal/mol against HMG-CoA reductase. These compounds interacted with critical active site residues such as ARG261, GLU234, TYR108, and HIS231, indicating strong binding potential. Further assessment of pharmacokinetic properties and drug-likeness using ADMETLab 2.0 and Lipinski's rule of five revealed that most lead compounds exhibited favorable oral bioavailability, low toxicity, and acceptable clearance rates. The 2D structural analysis highlighted the importance of hydroxyl-rich polyphenolic and glycosylated frameworks in stabilizing ligand-protein interactions. This study concludes that C. odorata contains promising phytochemical candidates for anti-obesity drug development. The findings provide a scientific foundation for further in vitro and in vivo studies to validate the therapeutic efficacy and safety of these compounds.

Keywords: Chromolaena odorata; obesity; molecular docking; HMG-CoA reductase; FTO protein; phytochemicals; ADMET profiling; bioactive compounds; drug-likeness; in silico screening.

INTRODUCTION

Obesity is one of the most pressing health challenges of the 21st century, with a global rise in prevalence posing significant burdens on healthcare systems, economies, and individual quality of life (World Health Organization, 2020). It is characterized by abnormal or excessive fat accumulation that impairs health, often leading to a range of comorbidities such as type 2 diabetes, hypertension, cardiovascular diseases, non-alcoholic fatty liver disease, and some cancers (Blüher, 2019). Despite numerous interventions, the management of obesity remains a complex issue due to its multifactorial origin encompassing genetic, behavioral, environmental, and metabolic

factors. The conventional treatment options for obesity include lifestyle modifications (diet and physical activity), pharmacotherapy, and bariatric surgery. However, pharmacological treatments such as Orlistat, Phentermine, and Liraglutide are often associated with adverse side effects and limited long-term efficacy (Heck et al., 2000). Moreover, these synthetic agents are often cost-prohibitive in developing nations, emphasizing the need for accessible, safer, and cost-effective alternatives.

In this context, natural products derived from medicinal plants have gained increasing attention as a potential source of novel therapeutic agents for obesity. Among them, Chromolaena odorata commonly referred to as devil weed—has been traditionally used in ethnomedicine for its anti-inflammatory, antimicrobial, antioxidant, and wound-healing properties (Yusuf et al., 2012). However, its role in metabolic regulation, especially in obesity-related mechanisms, remains underexplored. Given the rising interest in plant-derived compounds for metabolic diseases, Chromolaena odorata presents a promising candidate for further scientific investigation.

Advancements in computational biology, particularly molecular docking, have facilitated the high-throughput screening of bioactive compounds against protein targets implicated in disease mechanisms. Molecular docking allows for the prediction of binding affinity and interaction stability between ligands and receptor proteins, serving as a preliminary tool in drug discovery (Kitchen et al., 2004). This theoretical approach significantly reduces the time and cost required in early-stage drug development and provides valuable insights into structure-activity relationships.

In obesity research, two protein targets are of particular interest: HMG-CoA Reductase and the Fat Mass and Obesity-associated protein (FTO). HMG-CoA Reductase is the rate-limiting enzyme in the mevalonate pathway, instrumental in cholesterol biosynthesis (Endo, 2010). Its inhibition is the basis for the action of statins, a well-known class of lipid-lowering agents. On the other hand, the FTO protein regulates energy metabolism through RNA demethylation, and genetic polymorphisms in the FTO gene have been associated with increased body mass index (Zhao et al., 2014). This research employed molecular docking techniques to evaluate the interaction between 68 bioactive compounds from Chromolaena odorata and the aforementioned obesity-related proteins. The goal was to identify compounds with strong binding affinities, favorable ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles, and drug-likeness properties that could serve as lead candidates for anti-obesity drug development.

Preliminary results showed that several compounds—including Naringin, Curcumin, Rutin, and Catechin—demonstrated superior binding affinities when compared with existing anti-obesity drugs like Orlistat and Benzphetamine. This finding not only supports the pharmacological potential of Chromolaena odorata but also underscores the importance of integrating computational tools in natural product research.

Statement of the Problem

Obesity is a global health concern with increasing prevalence and associated economic and medical burdens. Despite the availability of synthetic anti-obesity medications, their efficacy is often limited by side effects, high costs, and contraindications in long-term usage. In many developing countries, these treatments remain inaccessible to the general population. Hence, there is a critical need to discover new therapeutic agents that are effective, safe, affordable, and easily accessible. Medicinal plants, particularly those with documented ethnopharmacological significance, are gaining attention as potential sources of anti-obesity compounds. Chromolaena odorata, commonly referred to as devil weed, is known for its broad spectrum of pharmacological effects, yet its anti-obesity potential remains underexplored. This study addresses the gap in knowledge by applying molecular docking techniques to evaluate the interactions of phytochemicals from C. odorata with obesity-related protein targets.

Aim of the Study

The primary aim of this study is to perform theoretical and molecular docking analysis of bioactive phytocompounds derived from Chromolaena odorata against key proteins implicated in obesity specifically HMG-CoA Reductase and Fat Mass and Obesity-associated protein (FTO). This study also seeks to assess the drug-likeness and pharmacokinetic properties of the selected compounds using ADMET profiling tools. The

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ultimate goal is to identify potential plant-based lead compounds that may serve as novel anti-obesity therapeutics.

MATERIALS AND METHODS

Softwares and databases used

The data retrieval and computation of the entire work design utilized Discovery Studio (DS) version 21.1, AutoDock Vina in built in PyRx 0.8, PubChem,RCSB-Protein Data Bank (https://www.rcsb.org/), PubMed Database (https://pubmed.ncbi.nlm.nih.gov/),SwissADME, and ADMETlab 2.0. (Dearsly et al., 2025)

Preparation of the three-dimensional structure of the target proteins

The three-dimensional structures of the human target proteins were retrieved from Research Collaborator for Structural Bioinformatics protein Data Bank (RCSBPDB) and prepared for molecular docking simulation using Discovery Studio (DS v. 21.1).

Preparation of ligands

66 bioactive compounds in structured Data Format (SDF) was derived from **Chromolaena odorata,** they were retrieved from the PubChem database and PubMed Database), the Ligand molecules were further converted to the dockable PDBQT format using AutoDock Tool, Discovery Studio (DS v. 21.1).

Molecular docking

Docking analysis was performed according to (Sharma et al., 2019) protocol. The active binding sites of the protein targets were mapped out. Molecular docking was performed by using AutoDockVina software (Trott and Olson, 1995) in PyRx platform.

2D Molecular interaction post-docking

Determination of the structural interactions of the protein-ligand complex result was performed using Discovery Studio (DS) version 21.1 software.

ADMET analysis

The pharmacokinetics nature of the ligands output was carried out using the adment lab 2.0

Table 1: List of bioactive compounds derived from Chromolaena odorata.

S/N.	Compounds
1	1,8 Cineole
2	2,4 dihydroxy benzoic acid
3	2, 5-bis-(1-dimethyl) Phenol
4	2-Dodecanone
5	3-caffeoyl quinic acid
6	5-caffeoyl quinicacid
7	Alkaloids A
8	Astragalin
9	C15H24 copaene
10	Camphene
11	Carvone
12	Caryophyllene oxide
13	Catechin
14	Citronellyl acetate
15	Curcumin
16	Cymene

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17	Diterpene derive
18	Dodecyl acetate
19	Epicatechin
20	Epihedrine
21	Ethylcaffeate
22	Eugenol
23	Flavan-3-ol
24	Flavone
25	Gallic acid
26	Germacrene D
27	Heptadecene
28	Hexadecanoic acid
29	Hexanoic acid
30	Hyperoside
31	Isopulegol
32	Isosakuranetin
33	Isotrifolin
34	Kaenpferol
35	Kaur-16-ene
36	Lauric Acid
37	Ledol
38	Limonene
39	Linalool
40	Lunamarin
41	Myristic acid
42	Myrtenol
43	Naringenin
44	Naringin
45	Octanoic acid
46	Oxalate
47	Patulein
48	Pentadecanoic acid
49	Quinine
50	Resveratrol
51	Rutin
52	Sapogenin
53	Steroid U
54	Taxifolin
55	Trifolin
56	Undecanal
57	Undecanone
58	Vanillin
59	Viridiflorene
60	Widdrol
61	cis-Linalool oxide (furanoid)
62	cis-Verbenol
63	d-Ribalinidine
64	decanoate ester
65	decanoic acid
66	m-cresol
67	methyl dodecanoate
68	methyl tetradecanoate

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Preparation of protein

The crystal protein structures as presented in Table 2 were retrieved from the Protein Data Bank (https://www.rcsb.org). From the retrieved structures, the native ligands were extracted, and water molecules removed using Autodock version 4.2 programs.

Table 2: Target proteins of obesity

S/N.	Protein	PDB Code	Amino Acid Residues	Reference
1	HMG CoA reductase 3-hydroxy-3-methylglutaryl-coenzymes A reductase	1TO2	ARG261 ALA368 ASN271 LYS267	https://www.rcsb.org/structure/1T02
2	Fat mass of obesity protein (FTO)	3LFM	GLY103 ARG96 TRY295 LEU109 HIS231 ARG322 HIS307 ARG316 MET207 TRY108 GLU234	https://www.rcsb.org/structure/3LFM

RESULTS AND DISCUSSION

Results

Table 3: Molecular docking results

SN	Compounds	HMG CoA Reductase	FTO
1	1,8-Cineole	-5.4	-5.1
2	2,4 dihydroxy benzoic acid	-5.8	-6.2
3	2, 5-bis-(1-dimethyl) Phenol	-6.1	-6
4	2-Dodecanone	-5.1	-5.3
5	3-caffeoyl quinic acid	-7.7	-7.6
6	5-caffeoyl quinic acid	-7.7	-7.6
7	Alkaloids A	-6.4	-7.6
8	Astragalin	-7.6	-8
9	Copaene	-7.4	-6.3
10	Camphene	-5.6	-5.6
11	Carvone	-5.8	-5.7
12	Caryophyllene oxide	-6.8	-6.5
13	Catechin	-7.7	-7.6
14	Citronellyl acetate	-5.5	-5.6
15	Curcumin	-8.2	-7.7
16	Cymene	-5.7	-5.7
17	Diterpene Deriv	-6.4	-7.2
18	Dodecyl acetate	-4.8	-4.9
19	Epicatechin	-7.2	-7.8

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20	Epihedrine	-5.4	-5.4
21	Ethyl Caffeate	-7.6	-8.4
22	Eugenol	-5.8	-5.8
23	Flavan-3-ol	-7.5	-7.4
24	Flavone	-8.2	-7.7
25	Gallic acid	-5.8	-6.3
26	Germacrene D	-7.1	-7.1
27	Heptadecene	-4.5	-4.5
28	Hexadecanoic acid	-5.8	-5.1
29	Hexanoic acid	-4.4	-4.4
30	Hyperoside	-8.1	-8.6
31	Isopulegol	-5.6	-5.5
32	Isosakuranetin	-7.4	-7.5
33	Isotrifolin	-7.6	-8.4
34	Kaenpferol	-8.1	-8.3
35	Kaur-16-ene	-7.8	-8.1
36	Lauric Acid	-4.8	-5.7
37	Ledol	-6.8	-6.8
38	Limonene	-5.8	-5.6
39	Linalool	-5.2	-4.7
40	Lunamarin	-7.9	-8.2
41	Myristic acid	-4.9	-5.2
42	Myrtenol	-5.5	-5.2
43	Naringenin	-7.4	-7.6
44	Naringin	-9.3	-9.8
45	Octanoic acid	-4.6	-4.4
46	Oxalate	-4.1	-4.6
47	Patulein	-5.5	-5.8
48	Pentadecanoic acid	-6.1	-5
49	Quinine	-7.7	-7.1
50	Resveratrol	-7.1	-6.8
51	Rutin	-8.4	-8.7
52	Sapogenin	-8.4	-8.4
53	Steroid U	-8.8	-7.9
54	Taxifolin	-7.6	-8.1
55	Trifolin	-7.4	-8.4
56	Undecanal	-4.5	-4.2
57	Undecanone	-4.9	-4.3
58	Vanillin	-5.2	-5.5
59	Viridiflorene	-6.9	-7
60	Widdrol	-6.8	-6.8
61	cis-Linalool oxide (furanoid)	-5.3	-5.3
62	cis-Verbenol	-5.5	-5.4
63	d-Ribalinidine	-7.3	-8
64	decanoate ester	-5.2	-4.7
65	decanoic acid	-4.9	-5.2
66	m-cresol	-4.9	-5.2
67	methyl dodecanoate	-5	-4.9
68	methyl tetradecanoate	-4.6	-4.7

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Dimension for molecular docking of each protein and the ligands

Table 4: Dimension

DESCRIPTION	HMG CoA Reductase
CENTER X	87.7773
CENTER Y	124.7569
CENTER Z	132.5369
DIMENSION X	84.7773
DIMENSION Y	80.5553
DIMENSION Z	14.8287

Table 5: Dimension

DESCRIPTION	FTO
CENTER X	30.9457
CENTER Y	8.7438
CENTER Z	23.4549
DIMENSION X	44.5449
DIMENSION Y	32.7142
DIMENSION Z	24.9472

Docking of selected ligands with high binding affinity

Table 6: Docking results.

S/N	Compounds	HMG CoA Reductase	FTO
1	3-caffeoylquinicacid	-5.4	-8.3
2	Astragalin	-5.2	-7.7
3	Catechin	-5.4	-8.3
4	Curcumin	-5.7	-8.6
5	d-Ribalinidine	-5.2	-8.4
6	Ethyl caffeate	-4.6	-7
7	Hyperoside	-4	-7.4
8	Isosakuranetin	-5.5	-7.8
9	Lunamarine	-5.8	-8.3
10	Naringin	-5.6	-8.2
11	Taxifolin	-5.6	-8.2
S/N	**Drugs Used in Treating Obesity**	**HMG CoA Reductase**	**FTO**
1	Benzphetamine	-3.9	-5.7
2	Orlistat	-4.3	-6.9
3	Setmelanotide	-8.2	-8.1
4	Phentermine	-4.1	-4.8

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Interaction of proteins with selected ligands

Table 7: Table of interaction of top ligands with FTO (3LFM)

FTO 3LFM						
Compounds	**Hydrogen bond interaction (Bond Distance A)**		**Hydrophobic Interaction**		**Other Interaction**	
	No.	**Residues**	**No.**	**Residues**	**No.**	**Residues**
d-Ribalinidine	2	SER229 (2.66) TYR106 (2.05)	3	**TYR108 (4.87)** **TYR108(4.49S)** **LEU109 (4.92)**	3	ASP233 (4.04) **HIS231 (3.82)** **HIS231 (4.48)**
Isosakuranetin	2	SER229 (2.16) **GLU234 (2.28)**	5	TYR106 (4.61) **LEU109 (5.41)** **TYR108 (4.52)** **TYR108 (4.83)** VAL228 (3.91)	1	**HIS231 (3.79)**
Catechin	5	**MET207 (3.03)** **ARG316 (2.87)** **ARG322 (3.06)** **ARG322 (3.02)** TRP270 (3.36)	3	VAL94 (4.49) VAL227 (4.84) VAL309 (4.75) THR320 (3.83)	1	HIS307 (3.26)
Lunamarin	4	SER229 (1.98) **TYR108 (3.54)** **ASP233 (3.64)** **GLU234 (2.75)**	6	VAL228 (3.88) **HIS231 (4.36)** TYR106 (5.31) **TYR108 (4.64)** **LEU109 (4.44)** **LEU109 (4.77)**	1	**HIS231 (4.17)**
Curcumin	7	TYR106 (2.02) **GLU234 (2.29)** TYR295 (2.32) **ARG316 (2.48)** SER318 (2.44) **ASP233 (3.38)** SER229 (3.65)	8	VAL94 (4.67) VAL309 (4.40) VAL309 (5.05) VAL228 (5.18) VAL228 (4.27) **LEU109 (3.52)** HIS321 (4.92) **HIS231 (4.19)**		
Ethyl caffeate	1	**AGR322 (2.96)**	4	**MET207 (4.90)** **ARG316 (4.11)** TRP270 (4.01) VAL228 (5.27)		
Setmelanotide	5	ASN235 (2.07) ASN235 (2.52) LEU236 (3.11) **GLU234 (3.08)** VAL237 (3.03) VAL237 (2.26)	2	HIS232 (5.21) ALA303 (4.79)	5	GLU225 (4.24) ASP238 (4.39) ASP238 (3.06) GLU325 (3.77) GLU325 (4.16)

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2D interactions of ligands interactions with selected receptor

2D Molecular interaction post-docking of FTO and ligands complexes

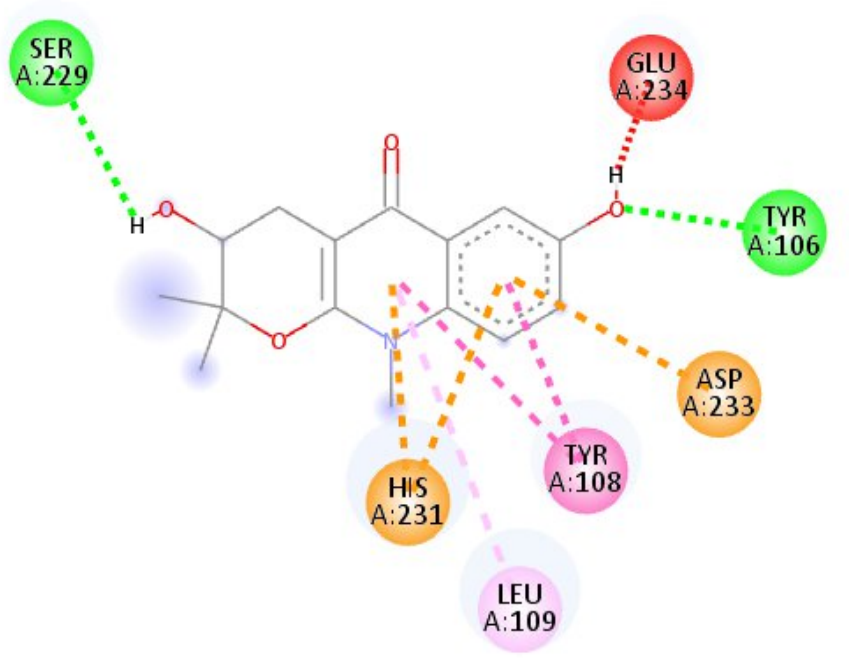

Figure 1: 2D molecular docking complexes of FTO and d-Ribalinidine

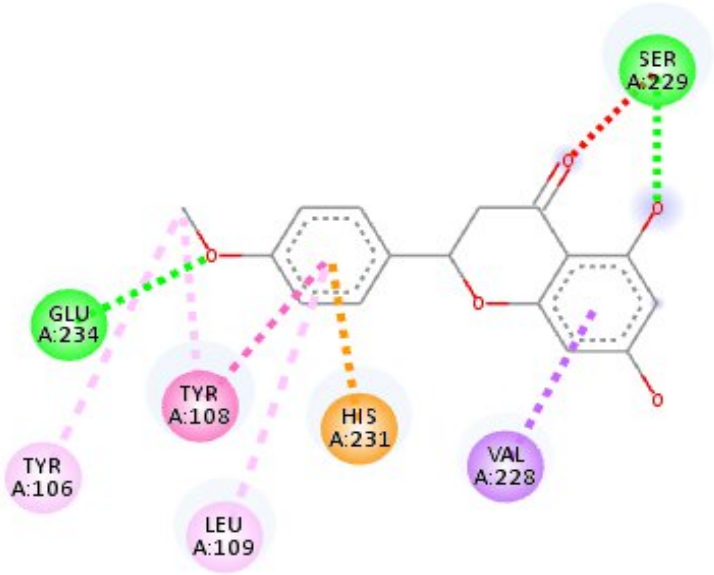

Figure 2: 2D molecular docking complexes of FTO and Isosakuranetin

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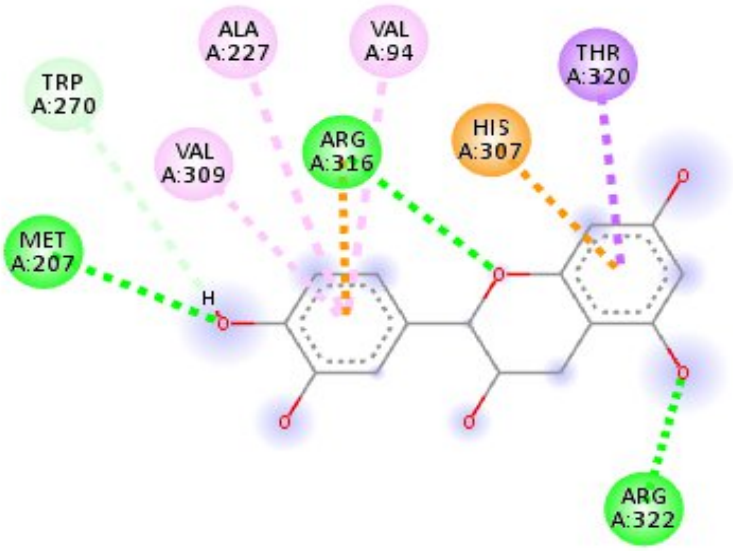

Figure 3: 2D molecular docking complexes of FTO and Catechin

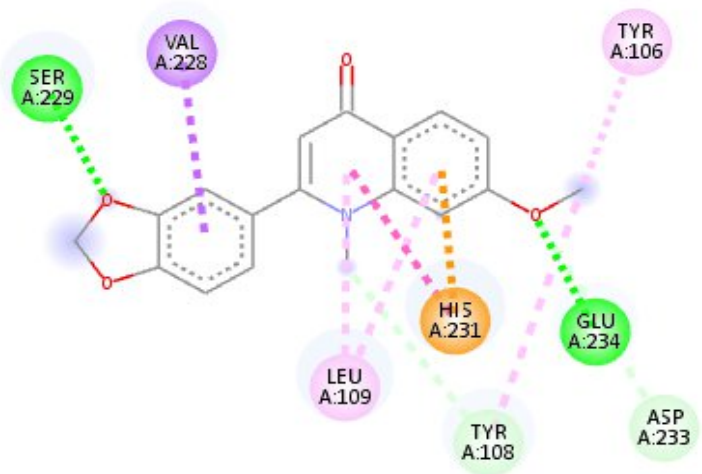

Figure 4: 2D molecular docking complexes of FTO and Lunamarine

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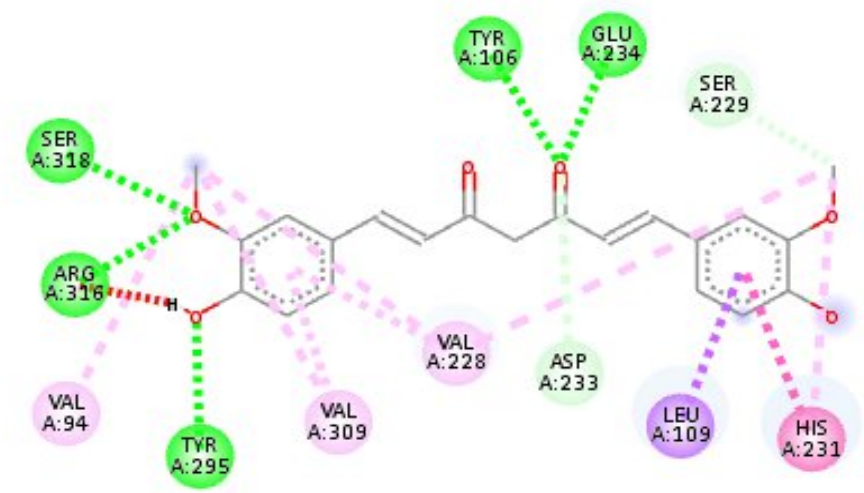

Figure 5: 2D molecular docking complexes of FTO and Curcumin

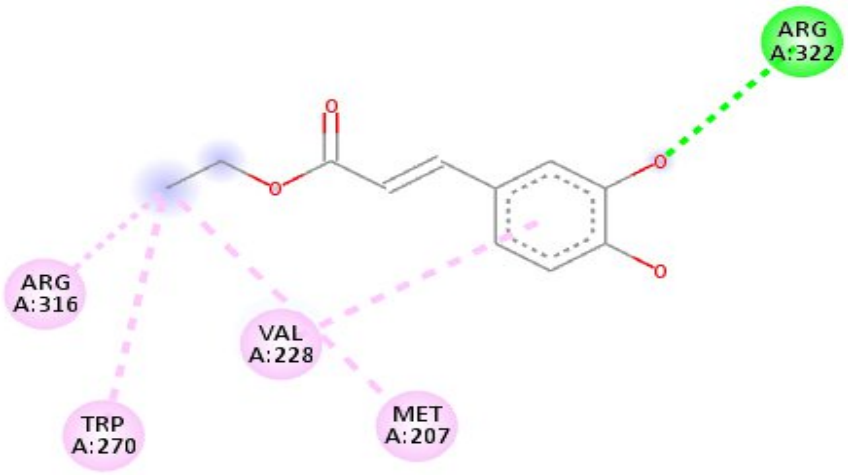

Figure 6: 2D molecular docking complexes of FTO and Ethyl caffeate

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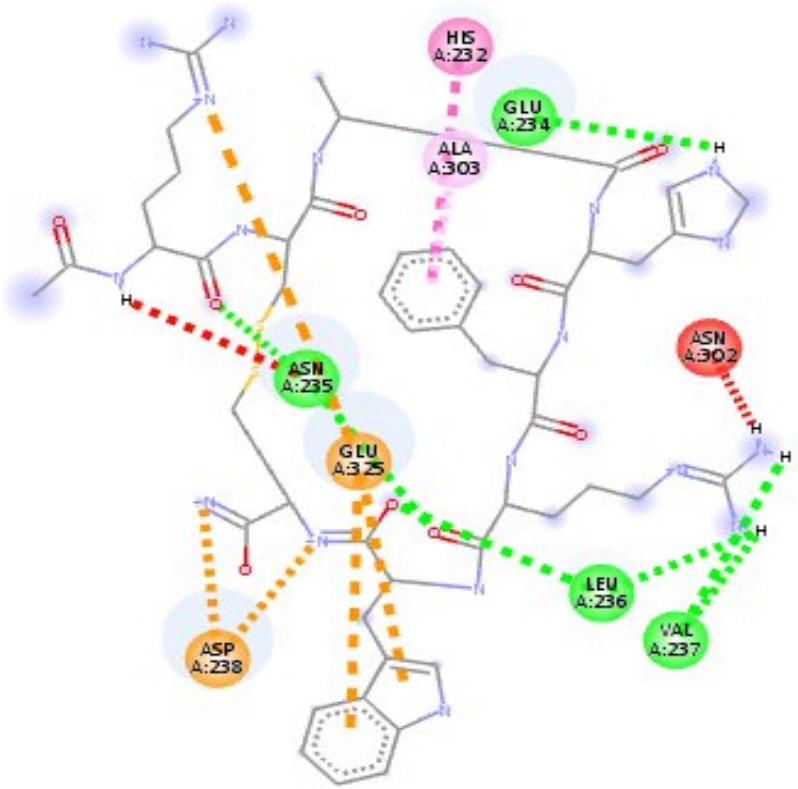

Figure 7: 2D molecular docking complexes of FTO and Setmelanotide

Table 8: Most promising compounds

	Compounds
1	d-Ribalinidine
2	Isosakuranetin
3	Catechin
4	Lunamarine
5	Curcumin
6	Ethyl caffeate

Drug likeness test of selected ligands

Table 9: Drug likeness results of compounds with high binding interaction with target proteins

Compounds	Lipinski	Ghose	Veber	Egan	Muegge	Reference
d-Ribalinidine	Yes	Yes	Yes	Yes	Yes	Passed
Isosakuranetin	Yes	Yes	Yes	Yes	Yes	Passed
Catechin	Yes	Yes	Yes	Yes	Yes	Passed
Lunamarine	Yes	Yes	Yes	Yes	Yes	Passed
Curcumin	Yes	Yes	Yes	Yes	Yes	Passed
Ethyl caffeate	Yes	Yes	Yes	Yes	Yes	Passed

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ADMET analysis result of FTO with top selected compounds

	d-Ribalinidine	Isosakuranetin	Catechin	Curcumin	Ethyl caffeate
Properties	**Value**	**Value**	**Value**	**Value**	**Value**
water solubility	-2.91	-3.70	-2.22	-3.94	-2.78
HIA	0.005	0.008	0.096	0.06	0.009
BBB	0.009	0.048	0.025	0.103	0.197
CYP1A2 Inhibitor	0.476	0.094	0.219	0.593	0.964
CYP2C19 Inhibitor	0.074	0.948	0.037	0.287	0.513
CYP2C9 Inhibitor	0.024	0.887	0.218	0.661	0.612
CYP2D6 Inhibitor	0.655	0.825	0.173	0.037	0.424
CYP2D6 Substrate	0.7	0.882	0.41	0.895	0.671
CYP3A4 inhibitor	0.027	0.827	0.315	0.674	0.457
Hepatotoxicity	0.104	0.117	0.071	0.475	0.1
Ames Mutagenesis	0.01	0.474	0.522	0.234	0.285
Carcinogenicity	0.71	0.652	0.09	0.706	0.54
Acute Oral Toxicity	0.938	0.576	0.467	0.896	0.741
Excretion	7.735	13.625	17.911	13.839	15.766

DISCUSSION

Obesity is a multifactorial metabolic disorder characterized by excessive fat accumulation and is associated with numerous comorbidities such as type 2 diabetes, cardiovascular disease, and certain forms of cancer (World Health Organization, 2020). In recent years, the search for alternative therapies has intensified, particularly those derived from natural sources with fewer side effects compared to synthetic drugs (Newman & Cragg, 2020). This study explores the molecular docking and pharmacokinetic potential of bioactive phytochemicals from Chromolaena odorata against two key obesity-related proteins: HMG-CoA Reductase and the Fat Mass and Obesity-associated protein (FTO). This study employed PyRx and Discovery Studio to dock 68 bioactive compounds from Chromolaena odorata against two key obesity-associated targets: HMG-CoA Reductase (1TO2) and Fat Mass and Obesity-associated protein (FTO; 3LFM). Binding affinities were analyzed to predict the strength and stability of ligand-protein complexes and to infer the inhibitory potential of the phytochemicals. Among the tested ligands, Naringin exhibited the strongest binding affinity toward both FTO (-9.8 kcal/mol) and HMG-CoA Reductase (-9.3 kcal/mol), indicating a strong molecular interaction and potential dual inhibition of metabolic pathways contributing to obesity. This is significant because Naringin has previously been associated with anti-inflammatory and lipid-lowering effects, further reinforcing its potential for repurposing as an anti-obesity agent. Several other compounds followed closely in binding performance. Rutin (-8.4 with HMG-CoA Reductase, -8.7 with FTO), Sapogenin (-8.4 with both targets), and Steroid U (-8.8 with HMG-CoA Reductase, -7.9 with FTO) also demonstrated strong affinities. These values were significantly lower (more favorable) than standard drugs such as Benzphetamine (-3.9), Phentermine (-4.1), and Orlistat (-4.3), which served as positive controls.

To better understand the structural relevance of these interactions, the ligand-binding domains of each target protein were studied. The residues engaged by top-performing compounds in FTO included TYR108, ARG316, MET207, and GLU234, which are critical for catalytic activity and have been implicated in previous mutagenesis studies. For HMG-CoA Reductase, residues like ARG261, ALA368, and LYS267 were consistently involved in stable interactions with multiple ligands. It is noteworthy that most of these phytochemicals possess polyphenolic, flavonoid, or glycosidic structures, which facilitate extensive hydrogen bonding and pi-stacking interactions within the binding pocket. This structural advantage may explain their stronger affinities relative to synthetic drugs, which are typically smaller and less complex.

Furthermore, the docking analysis also considered the number and type of bonds involved. For instance, Curcumin and Catechin formed between 5 to 7 hydrogen bonds with FTO, increasing their binding specificity and potential inhibitory effect. Such interactions were visualized through 2D docking interaction diagrams and confirmed with post-docking analysis using Discovery Studio. The docking data provides strong evidence for

the therapeutic potential of several phytochemicals from Chromolaena odorata. Their dual-target affinity, structural complexity, and consistent hydrogen bonding patterns suggest that they may function as lead compounds for the development of novel anti-obesity therapeutics. These findings highlight the promise of natural product libraries in identifying multi-target ligands for complex metabolic disorders such as obesity.

Structural Features and 2D Ligand Interaction Profiles

Beyond the analysis of binding affinity scores, evaluating the 2D chemical structures of docked ligands provides deeper insight into the specific molecular features responsible for strong protein-ligand interactions. The visualized 2D structures and interaction diagrams generated through Discovery Studio revealed distinct functional groups and stereochemical arrangements that contribute significantly to the docking stability of key compounds derived from Chromolaena odorata.

Phytocompounds such as Naringin, Curcumin, Rutin, Catechin, and Isosakuranetin share structural similarities that correlated with high docking scores. Most notably, these compounds possessed polyphenolic frameworks, hydroxyl groups, carbonyl functionalities, and in some cases, glycosidic attachments, all of which are known to enhance hydrogen bonding and increase ligand polarity—critical features for interacting with hydrophilic pockets in protein active sites (Gschwend et al., 1996). For example, Curcumin is characterized by two methoxyphenol rings connected by a heptadienone chain, containing diketone and hydroxyl groups that facilitated strong hydrogen bonding and π–π stacking interactions within the FTO protein's binding domain. The presence of both donor and acceptor atoms enabled Curcumin to form stable interactions with amino acids such as ARG316, GLU234, and HIS231, aligning with previously reported binding behaviors (Aggarwal & Harikumar, 2009). Similarly, Rutin, a flavonol glycoside with multiple hydroxyl groups and a sugar moiety, exhibited a high degree of interaction with residues in HMG-CoA Reductase through hydrogen bonds and van der Waals forces. The 2D ligand interaction diagrams displayed strong polar contacts with catalytic residues such as ALA368, ASN271, and ARG261, indicating that the spatial orientation of functional groups plays a decisive role in binding (Morris & Lim-Wilby, 2008).

Naringin's high affinity can be attributed to its C-ring flavanone structure and rhamnoglucoside group, which enhance both water solubility and electrostatic interactions with active site residues. The sugar units are particularly important, as they increase molecular surface area and allow for additional anchoring to polar residues in both targets (Li et al., 2012).

The 2D interaction diagrams further clarified how these compounds aligned within the enzyme cavities. Visualization features included Green dashed lines representing hydrogen bonds, Aromatic ring arcs indicating π-π interactions with phenylalanine and tyrosine residues, Hydrophobic contact regions shown as brown circles/arcs, and Electrostatic interactions marked near charged amino acids. These diagrams helped confirm that most ligands not only fit sterically within the binding sites but also formed multiple stabilizing interactions—a critical consideration in ligand efficacy (Meng et al., 2011). The repeated appearance of structural motifs such as catechol groups, conjugated aromatic systems, and glycoside linkages across top-scoring ligands suggests that these features may form the basis for structure-activity relationship (SAR) modeling and potential optimization. The 2D structure-based analysis highlights the chemical rationale behind the high docking performance of several C. odorata phytochemicals. This structural insight complements binding energy data and supports the hypothesis that these compounds possess favorable pharmacophores for anti-obesity drug development.

HMG-CoA Reductase Interactions

HMG-CoA Reductase is a critical enzyme in the mevalonate pathway, catalyzing the rate-limiting step in cholesterol biosynthesis by converting HMG-CoA to mevalonate (Endo, 2010). This makes it a strategic target for anti-obesity and lipid-lowering therapies. The inhibition of this enzyme not only reduces intracellular cholesterol levels but also influences lipid metabolism and adipocyte function. In this study, multiple phytocompounds derived from Chromolaena odorata demonstrated notable binding affinities with HMG-CoA Reductase. Among these, Steroid U exhibited the most potent interaction with a binding affinity of -8.8 kcal/mol, followed closely by Rutin (-8.4 kcal/mol), Curcumin (-8.2 kcal/mol), and Sapogenin (-8.4 kcal/mol). These compounds outperformed the reference anti-obesity drugs Orlistat (-4.3 kcal/mol) and Phentermine (-4.1

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kcal/mol) in terms of binding affinity, suggesting a potentially stronger and more stable enzyme-ligand interaction.

The docking analysis revealed that these ligands consistently interacted with key active site residues including ARG261, ALA368, ASN271, and LYS267. These residues are well-documented as essential for the catalytic mechanism of HMG-CoA Reductase, with ARG261 and LYS267 known to stabilize substrate orientation, and ASN271 participated in the coordination of enzymatic transformation. The interaction of multiple ligands with these residues suggests that the phytocompounds may competitively inhibit the enzyme's activity by occupying or obstructing the catalytic site. Curcumin, a diarylheptanoid polyphenol, not only demonstrated strong binding affinity but also formed multiple hydrogen bonds and hydrophobic contacts within the enzyme's binding cavity. Previous literature supports Curcumin's capacity to suppress cholesterol synthesis via SREBP-1c downregulation (Aggarwal & Harikumar, 2009), indicating its multi-modal action at both the transcriptional and enzymatic levels. This dual mechanism may enhance its potency as a therapeutic agent.

Rutin, a glycosylated flavonoid, is widely recognized for its antioxidant properties. Its interaction with the catalytic pocket may enhance its role in modulating cholesterol homeostasis by reducing oxidative stress-induced lipid peroxidation, a contributing factor in obesity-related dyslipidemia. The stabilization of Rutin within the binding site, evidenced by its low docking score and orientation toward the active residues, suggests a strong inhibitory profile. Steroid U and Sapogenin, both exhibiting steroidal backbones, mimicked the orientation of endogenous substrates and showed significant overlap with the natural ligand site. This structural mimicry may contribute to high binding efficiency and potential reversible competitive inhibition. In summary, the high binding affinities and specific residue interactions of Chromolaena odorata compounds with HMG-CoA Reductase support their potential as effective inhibitors. These findings reinforce the utility of natural products in targeting lipid metabolism, with applications in developing novel therapeutics for hyperlipidemia and obesity.

FTO Protein Interactions

The Fat Mass and Obesity-associated protein (FTO) is an Fe(II)- and 2-oxoglutarate-dependent demethylase that catalyzes the demethylation of N6-methyladenosine (m6A) in RNA. This activity plays a critical role in regulating energy intake, adipogenesis, and systemic metabolism (Zhao et al., 2014). Dysregulation of FTO expression and activity has been consistently linked to increased adiposity and metabolic disorders, positioning it as a high-value target in anti-obesity drug development. In this study, several bioactive compounds from Chromolaena odorata displayed strong binding affinities with the FTO protein. Naringin exhibited the highest binding energy (-9.8 kcal/mol), followed by Hyperoside (-8.6 kcal/mol), Curcumin (-8.6 kcal/mol), Isotrifolin (-8.4 kcal/mol), and Lunamarin (-8.3 kcal/mol). These values significantly exceed the docking scores of standard drugs such as Setmelanotide (-8.1 kcal/mol), Benzphetamine (-5.7 kcal/mol), and Phentermine (-4.8 kcal/mol), indicating more stable and possibly more effective protein-ligand interactions.

Molecular interaction analysis highlighted the involvement of key active site residues, including TYR108, GLU234, ARG316, HIS231, and MET207. These residues are crucial in maintaining the demethylation function of FTO and serve as primary anchoring points for ligand interaction. For example, Curcumin formed seven hydrogen bonds with residues such as TYR106, GLU234, ARG316, and ASP233, along with extensive hydrophobic contacts involving VAL228 and HIS231. This comprehensive interaction profile mimics that of Setmelanotide and supports the compound's potential to act as a competitive FTO inhibitor.

Naringin, a flavanone glycoside commonly found in citrus fruits, not only demonstrated the highest affinity but also exhibited multiple hydrogen bonds with residues like SER229 and TYR108, and hydrophobic interactions with LEU109 and TYR295. Its strong binding energy and robust interaction map suggest that Naringin could effectively inhibit FTO activity and consequently regulate appetite and energy metabolism. Hyperoside and Isotrifolin, both glycosylated flavonoids, also demonstrated extensive interaction profiles, including hydrogen bonding with SER229 and GLU234 and hydrophobic interactions with key aromatic and aliphatic residues. Their complex structures likely contribute to the stabilization of the FTO-inhibitor complex and enhance binding selectivity. Lunamarin, another potent binder, formed both polar and nonpolar interactions with residues like HIS231, TYR108, and ASP233. The diversity of interactions underscores its potential as a flexible ligand capable of adjusting to the conformational dynamics of the binding pocket.

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The consistent interaction of these phytochemicals with essential residues, their low docking energies, and multi-point anchoring patterns suggest that they could disrupt the enzymatic function of FTO. This could lead to reduced m6A demethylation, thereby altering gene expression patterns linked to energy balance and fat accumulation. Collectively, the evidence indicates that these naturally occurring compounds could act as modulators of FTO activity. Their strong docking profiles, diverse interaction patterns, and prior literature supporting their metabolic effects make them promising candidates for further development as anti-obesity therapeutics. Future experimental validation, including FTO enzyme inhibition assays and adipocyte differentiation studies, will be critical to confirm their functional relevance.

Comparative Analysis with Standard Drugs

A critical aspect of this study is the comparison between natural phytocompounds and standard anti-obesity drugs. Orlistat, a pancreatic lipase inhibitor, had relatively low docking scores (-4.3 with HMG-CoA Reductase and -6.9 with FTO), suggesting weaker interactions (Heck et al., 2000). Benzphetamine and Phentermine, central nervous system stimulants, also showed modest binding affinities. In contrast, compounds like Rutin, Naringin, Curcumin, and Catechin not only outperformed these drugs in binding energy but also displayed favorable interaction profiles. This suggests that these phytocompounds could be optimized to develop potent multi-target anti-obesity agents.

Drug-Likeness Evaluation

Drug-likeness is a qualitative assessment of a compound's potential to become an oral drug based on its physicochemical properties. The study evaluated compounds using Lipinski's Rule of Five and additional filters like Ghose, Veber, Egan, and Muegge (Lipinski et al., 2001). All selected top ligands passed these drug-likeness criteria. For instance, Catechin, Curcumin, Isosakuranetin, and Ethyl Caffeate exhibited molecular weights below 500 Da, acceptable hydrogen bond donors/acceptors, and suitable logP values. This increases their likelihood of oral bioavailability and metabolic stability.

ADMET Profiling

ADMET analysis covering Absorption, Distribution, Metabolism, Excretion, and Toxicity—is a critical step in the drug discovery process. It ensures that selected lead compounds not only exhibit strong pharmacological activity but are also safe and pharmacokinetically viable in biological systems. In this study, the top-performing phytocompounds from Chromolaena odorata (e.g., Curcumin, Catechin, Isosakuranetin, d-Ribalinidine, Lunamarin, Ethyl caffeate) were subjected to in silico ADMET analysis using ADMETLab 2.0 (Xiong et al., 2021).

Absorption and Water Solubility Human intestinal absorption (HIA) is vital for oral drug efficacy. Catechin (HIA: 0.096), Curcumin (0.06), and d-Ribalinidine (0.005) demonstrated varying levels of intestinal absorption, suggesting that although some compounds have moderate absorption, others may require formulation optimization to enhance bioavailability. Water solubility, an important factor for oral delivery, ranged from moderate to low: Catechin (-2.22 log mol/L) and d-Ribalinidine (-2.91) were reasonably soluble, whereas Curcumin (-3.94) and Isosakuranetin (-3.70) showed lower solubility, which may limit absorption unless solubilizing agents or drug delivery systems are applied.

Distribution: Blood-Brain Barrier (BBB) Permeability Most compounds demonstrated low BBB permeability. For instance, d-Ribalinidine (0.009), Isosakuranetin (0.048), and Catechin (0.025) indicated minimal likelihood of crossing into the central nervous system (CNS), reducing the potential for CNS-related side effects. This low permeability is advantageous for obesity-targeting drugs, which act on peripheral rather than central pathways.

Metabolism: Cytochrome P450 Enzyme Interaction Interactions with cytochrome P450 enzymes are pivotal in predicting drug-drug interactions and metabolic fate. Several compounds inhibited key CYP isoforms: Isosakuranetin inhibited CYP2C19 (0.948), CYP2C9 (0.887), and CYP3A4 (0.827). Curcumin strongly inhibited CYP1A2 (0.593), CYP2C9 (0.661), and CYP3A4 (0.674). These profiles suggest potential modulation of hepatic enzymes, which could be either beneficial or detrimental depending on co-administered drugs. Catechin showed minimal inhibition, making it a safer candidate regarding metabolic interactions.

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Toxicity Assessment Toxicological predictions are critical to determine the safety margins of drug candidates. The hepatotoxicity of all top compounds scored below 0.5, indicating low potential for liver toxicity. Curcumin scored 0.475, which is higher but still within acceptable limits. Mutagenicity (Ames Test) ranged from low to moderate across compounds. d-Ribalinidine (0.01) and Catechin (0.522) demonstrated minimal mutagenic risks.

Carcinogenicity: d-Ribalinidine (0.71) and Curcumin (0.706) had higher predicted carcinogenicity scores and would require in-depth long-term toxicity studies. Acute oral toxicity scores ranged from 0.467 (Catechin) to 0.938 (d-Ribalinidine), implying varying risk levels. However, most were within manageable thresholds for early-stage development.

Excretion Clearance values indicated how quickly the body might eliminate these compounds. Catechin (17.91 mL/min/kg) and Ethyl caffeate (15.77) showed high excretion rates, reducing the risk of bioaccumulation and associated toxicity. Curcumin and Isosakuranetin had moderate excretion profiles, indicating the possibility of sustained therapeutic activity without prolonged retention.

Overall, most of the top ligands satisfied the basic criteria for oral drugs, with acceptable ADMET properties. While some like Catechin and Ethyl caffeate displayed the most favorable ADMET profiles across all parameters, others such as Curcumin and d-Ribalinidine showed promise but may require structural optimization to reduce toxicity and improve solubility. These insights support the continued exploration of these phytocompounds, albeit with a tailored development strategy based on their individual pharmacokinetic and safety profiles.

CONCLUSION

This study successfully explored the anti-obesity potential of phytochemicals derived from Chromolaena odorata through theoretical and molecular docking approaches targeting two key obesity-related proteins: HMG-CoA Reductase and Fat Mass and Obesity-associated protein (FTO). Utilizing computational tools such as PyRx, Discovery Studio, and ADMETLab 2.0, 68 bioactive compounds were screened for binding affinity, drug-likeness, and pharmacokinetic profiles. The results revealed that several compounds particularly Naringin, Curcumin, Rutin, and Catechin exhibited strong binding affinities with both target proteins, outperforming known synthetic anti-obesity drugs like Orlistat and Phentermine. Detailed interaction analyses showed that these phytochemicals formed stable and specific hydrogen bonds and hydrophobic interactions with essential catalytic residues in the active sites of both HMG-CoA Reductase and FTO, suggesting their potential to modulate lipid metabolism and energy homeostasis. Furthermore, ADMET profiling confirmed that most top ligands had favorable absorption, low toxicity, acceptable metabolic profiles, and minimal predicted side effects, highlighting their suitability for oral administration and long-term therapeutic application. The structural analysis of 2D ligand interaction diagrams further reinforced the importance of hydroxyl groups, glycosidic linkages, and aromatic scaffolds in driving strong protein-ligand interactions. This project provides compelling computational evidence that Chromolaena odorata harbors promising phytochemicals that can serve as lead compounds in the development of novel, safe, and cost-effective anti-obesity therapeutics. These findings lay a robust foundation for future experimental validation through in vitro enzyme inhibition assays, cell-based metabolic studies, and in vivo pharmacological testing to translate these theoretical insights into practical clinical applications.

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