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Tangeretin and its Derivatives: An Integrative Bioinformatic Study of Obesity and Related Immunodeficiency

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Obesity is a complex and major public health concern known to exacerbate many diseases. There are increasing evidences stating the obese people due to adiposity are getting more susceptible to immune deficiency disorders. Tangeretin is a key member of flavonoids reported to have many favourable biological activities. In search of novel leads in ameliorating obesity and related immunodeficiency, the present study is aimed at the *in silico* evaluation of tangeretin derivatives to assess their biological role. Initially tangeretin derivatives are designed by molecular manipulation approach.Drug likeness and bioactivity score prediction was done using Molinspiration web tool. Swiss ADME prediction and toxicological predictions were performed. *In silico* Molecular Docking studies were performed by employing a flexible ligand docking approach using Schrodinger on the protein targets namely leptin, Fat mass and obesity associated protein (FTO), Pancreatic lipase, Peroxisome proliferated receptor (PPARɣ) and NADH oxidase. Further the electronic parameters were computed for the best fitted ligands by DFT analysis. The evaluation of results was made based on Glide (Schrodinger) dock score. Out of 18 screened compounds, some of them showed the best docking scores with the targets when compared with the standard (Lovastatin). Particularly the two ligands (L-13 and L-8) showed the best binding score with all five targets. Moreover, DFT analysis carried out for the tangeretin and best fitted ligands (L13 and L8) substantiated the other *in silico* studies. These findings probably provide excellent lead candidates for the development of therapeutic drugs in combating obesity and related immune deficiency.

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Keywords: Obesity; tangeretin; immune deficiency; molecular docking; DFT analysis.

1. INTRODUCTION

Obesity is a major public health concern all over the world and its prevalence is increasing day by day. It is a major contributor to the global burden of chronic diseases and complications including cardiovascular disorders, diabetes, renal toxicity, inflammation related disorders etc [1]. Less well known is the fact that there is a link between obesity and impaired immune function. There are increasing evidences stating the obese people due to adiposity are getting more susceptible to infectious diseases. Further as per reports of WHO it was clear that of 2.5 million COVID-19 deaths reported in February 2021, 2.2 million were reported in countries where more than half of the population are classified as overweight[2]. Hence there is a dire need to concentrate on the discovery of drugs to combat obesity and also to enhance the immune responses.

Flavonoids have a potential role in combating many disorders including obesity and also play vital role in enhancing immunity[3]. Among various flavonoids tangeretin is a key member of flavonoids having favourable biological activities, which have a prospect to develop as novel leads in drug discovery[4].Presently in the drug discovery process, *in silico* methodologies have become a crucial part and playing an ever-increasing role. These computational strategies can impact the entire drug development trajectory, identifying and discovering new potential drugs with a significant reduction of cost and time [5]. Hence in view of scope to design new derivatives and assess their biological role, the present study is planned to use computational studies in screening some semisynthetic tangeretin derivatives and predict their probability in developing as novel leads in drug discovery to ameliorate obesity and related immunodeficiency.

2. METHODOLOGY

2.1 Prediction of Molecular Properties

Tangeretin derivatives are designed by molecular manipulation approach and the chemical structures for the proposed compounds were drawn using Chem draw software. Lipinski's rule of five was employed to determine drug likeness and also to estimate whether a chemical substance predicted is possessing with some biological activity consists of properties to be orally active [6]. By using Molinspiration, an online server calculation of essential molecular properties like "molecular weight, log P, hydrogen bond acceptor and donor of selected ligands" for selected ligands was performed.

2.2 Calculation of Bioactivity Score

Bioactivity of different selected ligands was determined by determining the activity score of "GPCR ligand, ion channel inhibitor, Kinase inhibitor, nuclear receptor ligand, protease inhibitor, enzyme inhibitor using molinsipartion server".

2.3 ADMET Studies

ADME properties of a compound were estimated using Swiss ADME and PreADMET web tools in which, various physicochemical, pharmacokinetic, drug-likeliness, GI absorption, BBB permeability and skin permeability and toxicity can be predicted [7].

2.3.1 *In silico* molecular docking studies

The tangeretin and its derivatives were docked against five protein targets namely Leptin, Fat mass and obesity associated protein (FTO), Pancreatic lipase, Peroxisome proliferated receptor (PPARɣ) and NADH oxidase (NOX 4) and using Schrodinger Glide software (Version).

2.3.2 Preparation of ligand

The 2D structures of the prepared ligand were downloaded in the SDF format from Pubchem online data base. These molecules were then prepared in Schrodinger Ligprep wizard. In ligand preparation all possible conformations were taken into account. The ligands were then subjected to further predocking preparations where hydrogens were added followed by minimization and optimization of force field and finally in working ligand directory files were created.

2.3.3 Preparation of protein

The protein structure codes for theLeptin (1AX8), Fat mass and obesity associated protein (FTO) (3LFM), Pancreatic lipase (1LPB), Peroxisome proliferated receptor (PPARɣ) (2PRG) and NADH oxidase (NOX 4) (3A1F) were obtained from protein data bank (PDB) online data base

(https://www.rcsb.org/).The proteins were prepared using Schrodinger's protein preparation wizard by removal of crystallographic water molecules and addition of hydrogen atoms, followed by minimization and optimization using force field of Schrodinger.

2.3.4 Grid Preparation and Docking

By applying Maestro search in Glide receptor grid was generated by specifying the binding site residues using site map tool. Upon the preparation of the grid for each protein, ligands were docked to each protein using "Extra precision mode (XP)" and the docked conformers are assessed by employing Glide (G) Score [8].

2.4 DFT Analysis

Density functional theory (DFT) is a computational quantum mechanical modelling method used to examine the electronic structure and also to investigate the interactions involved between the receptors and the ligands. The electronic and structural properties of the two best ligands along with tangeretin were calculated using the Becke3-Lee-Yang-Parr (B3LYP) method with the 6–31G(d,p) basis set aided by Gaussian 09. The computed parameters include the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies, Mulliken charge analysis, and Reactive descriptor values [9].

3. RESULTS

3.1 Prediction of Molecular properties

The proposed tangeretin derivatives with their structures, IUPAC name generated using Chem draw software were mentioned in Table 1. Molecular properties of the selected compounds are read using Molinspiration software to satisfy lipinski's rule of five, which is essential for rational drug design. Most of the selected compounds have number of violations equal to zero. Apart from the standard (L19), L14 and L15 showed high molecular weight and hydrogen bond acceptors. All the other designed compounds obeyed Lipinski's rule of five for drug likeness (Table 2).

3.2 Calculation of Bioactivity Score

The predicted bioactivity scores of the screened compounds against various types of receptors were found be in the range of -5.0 to 5.0 which indicates that the compounds have ability to possess moderate to good activity towards biological targets (Table 3).

3.3 ADMET Studies

The ADME predicted are summarized in Table 4 and it could be observed that except L15 and L19 all the compounds have shown promising human intestinal percentage absorption and varied cell permeability with Caco2. The compounds skin permeability was also found to be within permissible limits. The computed distribution and metabolic parameters showed the compounds have low BBB permeability. Further, all the compounds were shown to exhibit significantdrug interactions through inhibition of CYP and by toxicity parameters it is observed that there is low to medium risk of hERG inhibition.

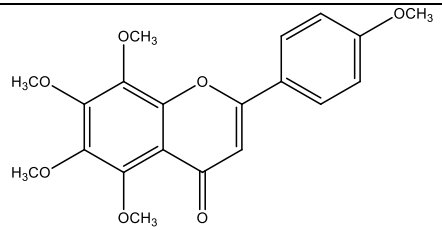
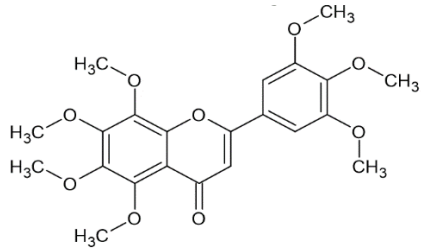
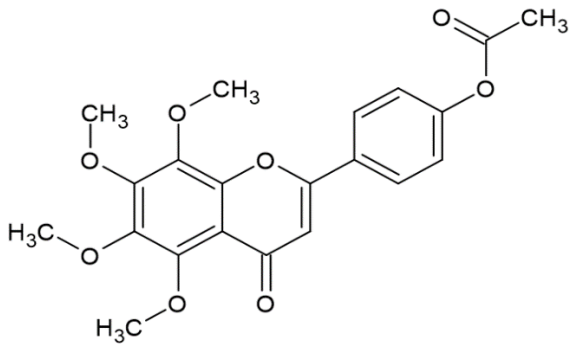
3.4 Molecular Docking Studies

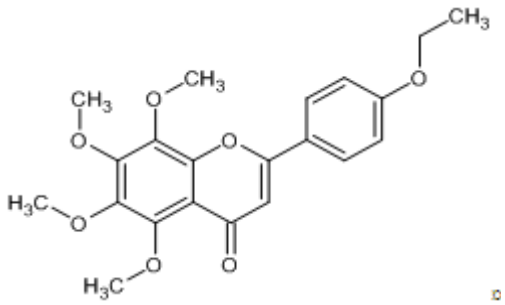
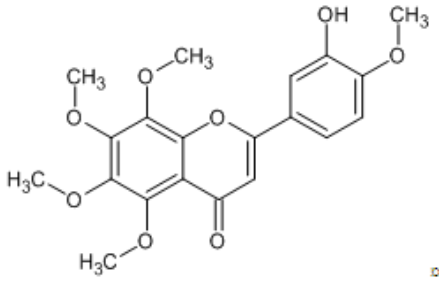
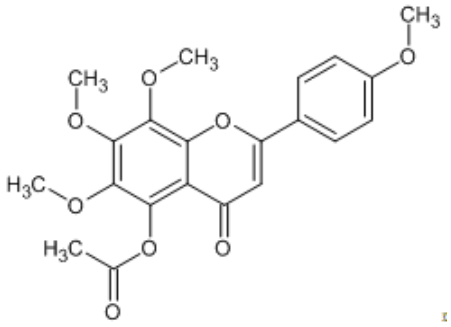
The results were represented in the terms of Glide docking score, Glide energy, H-bonds and nonbonded interactions (van der Waals and Coulombic) and mentioned in Table 5,6,7,8 and 9. The validation of the modelled proteins structures was done using the Ramachandran plot was represented in Fig 1. The ligand interactions are shown in theLigand interaction tool of maestro (Schrodinger) and it was observed that in case of all the targets some of the compounds exhibiting potent score compared with the standard.Most of the compounds showed hydrogen bond interactions and also hydrophobic interactions in the active site of proteins. The more negative values of the glide docking score represent tighter binding to the targets. Among all the compounds L 13 and L8 showed the best G score with all the protein targets[Fig 2&3].

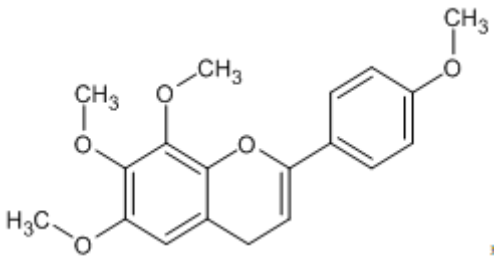
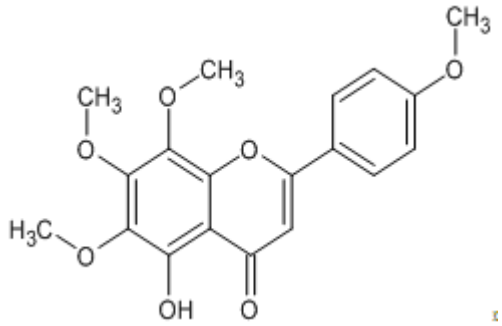
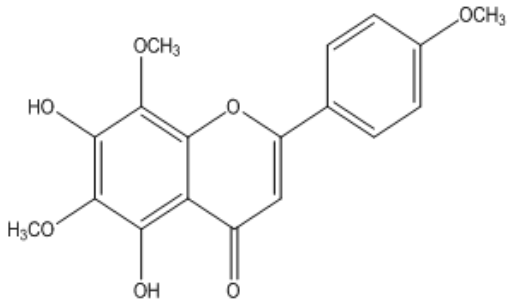
3.5 DFT Analysis

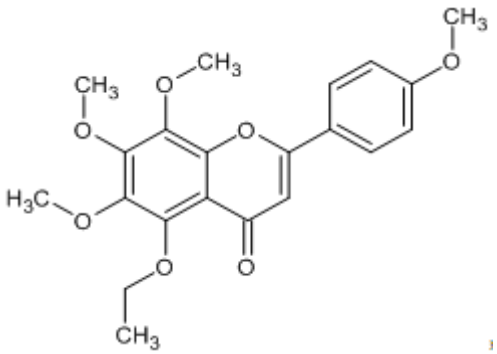
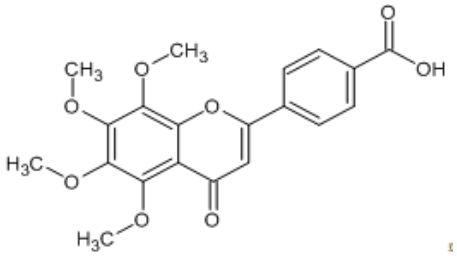
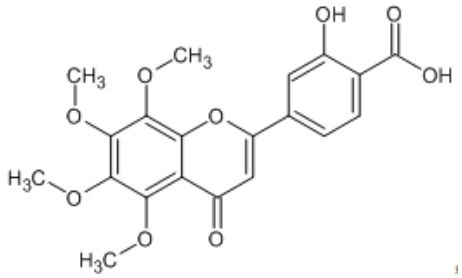
The DFT analysis performed for the tangerertin and selected L13 and L8 compounds showed the energy gap between the LUMO and HOMO (Fig 4). Further Mulliken charge analysis was represented in Table 10. The computed reactive descriptors include ionization potential, electron affinity, chemical potential, chemical hardness, softness, electronegativity and electrophilicity index were represented in Table- 11 clearly supported the ability of the compounds to bind with the receptors and revealed that L 8 and L13 have good chemical reactivity and charge transferability.

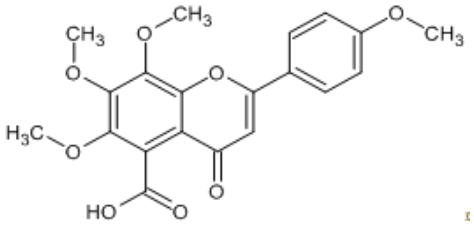
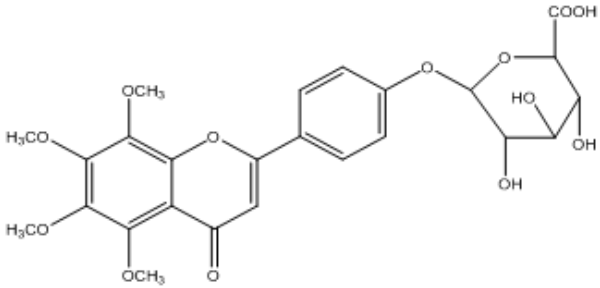
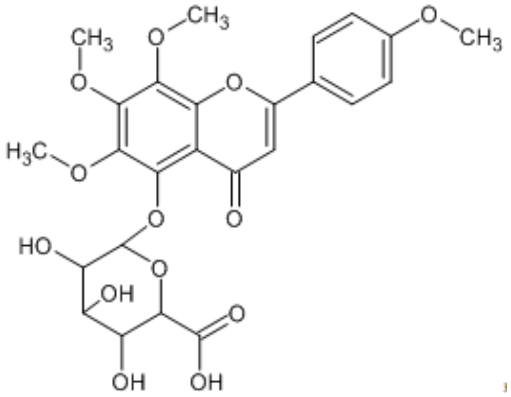
Table 1. List of ligands

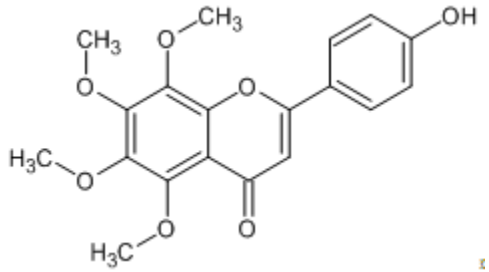
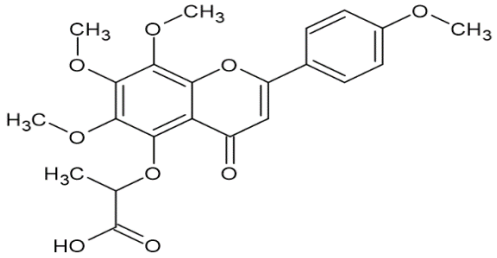
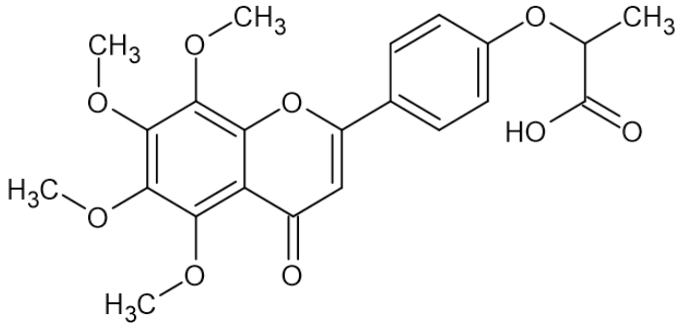
S.no	Compound structure	Name of the compound	IUPAC Name
1.		L-1	5,6,7,8- tetramethoxy-2(4-methoxyphenyl)-4H-chromen-4-one
2.		L-2	5,6,7,8-tetramethoxy-2(3,4,5-trimethoxyphenyl)-4H-chromen-4-one
3		L-3	4-(5,6,7,8-tetramethoxy-4-oxo-4H-chromen-2-yl)phenyl acetate

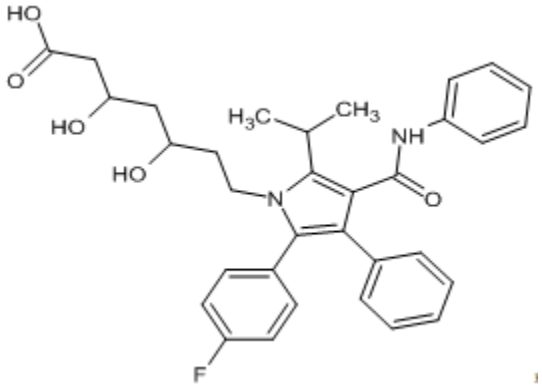
4		L-4	2-(4-ethoxyphenyl)-5,6,7-(tetramethoxy-4H -chromen-4-one
5		L-5	2-(3-hydroxy-4-methoxyphenyl)-5,6,7,8-tetramethoxy-4H-chromen-4-one
6		L-6	6,7,8-trimethoxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-5-yl acetate

7		L-7	6,7,8-trimethoxy-2(4-methoxyphenyl)-4H-chromene
8.		L-8	5-hydroxy-6,7,8-trimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one
9		L-9	5,7-dihydroxy-6,8-dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one

10		L-10	5-ethoxy-6,7,8-trimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one
11		L-11	4-(5,6,7,8-tetramethoxy-4-oxo-4H-chromen-2-yl)benzoic acid
12		L-12	2-hydroxy-4-(5,6,7,8-tetramethoxy-4-oxo-4H-chromen-2-yl)benzoic acid

13		L-13	6,7,8-trimethoxy-2-(4-methoxyphenyl)-4-oxo-4H-chromene-5-carboxylic acid
14		L-14	(2R,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(4-(5,6,7,8-tetramethoxy-4-oxo-4H-chromen-2-yl)phenoxy)tetrahydro-2H-pyran-2-carboxylic acid
15		L-15	3,4,5-trihydroxy-6-((6,7,8-trimethoxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-5-yl)oxy)tetrahydro-2H-pyran-2-carboxylic acid

16		L-16	5,6,7,8- tetramethoxy-2(4-hydroxyphenyl)-4H-chromen-4-one
17		L-17	2-[[6,7,8-trimethoxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-5-yl)oxy)propanoic acid
18		L-18	2-(4-(5,6,7,8-tetramrthoxy-4-oxo-4H-chromen-2-yl)phenoxy)propanoic acid

19		L-19	7-(2-(4-flurophenyl)-5-isopropyl-3-phenyl-4-9phenylcarbomyl 0-1H-pyrrol-1yl)-3,5-dihydroxyheptanoic acid

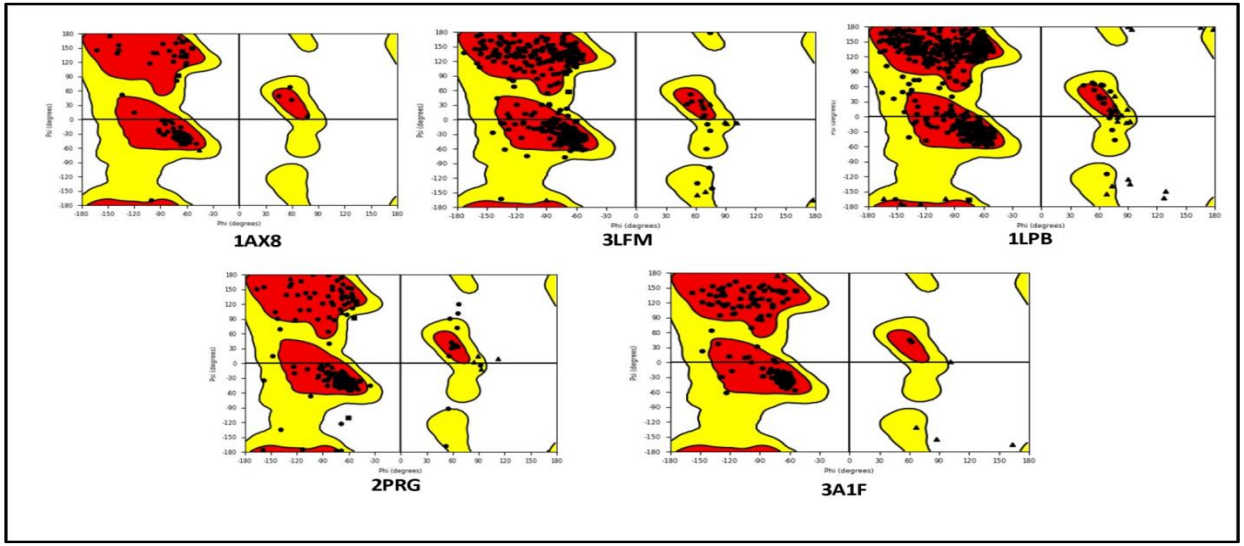


Fig. 1. Ramachandran plot (2D) for the selected proteins

Table 2. Molecular properties of the proposed compounds

Compound	MW	ROB	HBA	HBD	TPSA	Log P	Violation	Volume
L-1	372.37	6	7	0	76.36	3.78	0	327.72
L-2	432.42	8	9	0	94.82	3.35	0	378.81
L-3	400.38	7	8	0	93.43	3.28	0	346.71
L-4	386.4	7	7	0	76.36	4.16	0	344.53
L-5	388.37	6	8	1	96.59	3.06	0	335.74
L-6	400.38	7	8	0	93.43	3.28	0	346.71
L-7	328.36	5	5	0	46.15	3.69	0	300.00
L-8	358.34	5	7	1	87.36	3.50	0	310.20
L-9	344.32	7	7	2	98.36	3.23	0	292.67
L-10	386.4	7	7	0	76.36	4.16	0	344.53
L-11	386.35	8	8	1	104.43	3.63	0	329.18
L-12	402.35	9	9	2	124.66	3.63	0	337.20
L-13	386.35	8	8	1	104.43	3.30	0	329.18
L-14	534.47	8	13	4	183.58	1.33	2	444.50
L-15	534.47	8	13	4	183.58	1.33	2	444.50
L-16	358.34	5	7	1	87.36	3.25	0	310.50
L-17	430.4	8	9	1	113.66	3.39	0	371.55
L-18	430.4	8	9	1	113.66	3.39	0	371.55
L-19	558.64	12	7	4	111.79	5.34	2	513.80

-MiLogP- lipophylicity, TPSA- topological surface area, MW- molecular weight, HBA- Hydrogen Bond Acceptors, HBD- Hydrogen Bond Donars, Violations- no of violations, RTOB- No of rotatable bonds Volume, % ABS – percentage absorption

Table 3. Bioactive scores of proposed compounds

Compound	GPCR ligand	Ion channel inhibitor	Kinase inhibitor	Nuclear receptor	Protease inhibitor	Enzyme inhibitor
L-1	-0.12	-0.04	0.06	0.03	-0.20	0.11
L-2	-0.12	-0.03	0.07	-0.02	-0.21	0.10
L-3	-0.18	-0.07	-0.05	0.06	-0.20	0.09
L-4	-0.18	-0.08	-0.01	0.01	-0.25	0.05
L-5	-0.10	0.00	0.12	0.07	-0.22	0.16
L-6	-0.18	-0.07	-0.05	0.06	-0.20	0.09
L-7	-0.16	-0.28	-0.37	-0.23	-0.24	-0.06
L-8	-0.14	-0.11	0.10	0.04	-0.27	0.13
L-9	-0.16	-0.12	0.12	0.03	-0.28	0.17
L-10	-0.18	-0.08	-0.01	0.01	-0.25	0.05
L-11	-0.10	-0.03	0.02	0.15	-0.16	0.16
L-12	-0.07	-0.01	0.08	0.18	-0.15	0.20
L-13	-0.12	-0.15	-0.05	0.05	-0.22	0.16
L-14	-0.02	-0.09	-0.10	0.16	-0.05	0.30
L-15	-0.02	-0.09	-0.10	0.16	-0.05	0.30
L-16	-0.67	0.03	0.12	0.14	-0.18	0.18
L-17	-0.08	-0.14	-0.08	0.24	-0.17	0.14
L-18	-0.08	-0.14	-0.08	0.24	-0.17	0.14
L-19	-0.20	-0.32	0.13	0.67	0.15	0.40

4. DISCUSSION

In the presentscientific world, *in silico* prediction is a valid alternative to experimental studies and plays a major role in selection of hit molecules from large library in drug discovery process. Because of the wide applications in evaluating bioactive substances and their physicochemical and pharmacokinetic propertiesin the area of research and development these *in silico* studies has been gaining immense importance. This helps to predict numerous failure that arise in the process of new drug development [10].

Table 4. ADMET properties of proposed compounds

Compound	Caco-2 permeability	GI absorption	Skin permeability	BBB permeability	P-gp Substrate	hERG inhibition Risk	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
L-1	53.6054	High	-3.49	0.027	No	Medium	No	No	Yes	No	Yes
L-2	54.069	High	-3.81	0.038	No	Low	No	No	Yes	No	No
L-3	49.93	High	-3.42	0.0711	No	Medium	No	No	Yes	No	Yes
L-4	49.92	High	-3.85	0.052	No	Medium	No	Yes	Yes	No	Yes
L-5	43.16	High	-3.641	0.012	No	Low	No	No	Yes	No	Yes
L-6	46.99	High	-3.41	0.105	No	Medium	No	No	Yes	No	Yes
L-7	47.77	High	-3.21	0.03	No	Medium	Yes	Yes	Yes	Yes	Yes
L-8	36.48	High	-3.50	0.013	No	Medium	Yes	No	Yes	Yes	Yes
L-9	9.11	High	-3.53	0.030	No	Medium	Yes	No	Yes	Yes	Yes
L-10	52.07	High	-3.386	0.027	No	Medium	No	Yes	Yes	No	Yes
L-11	13.38	High	-3.505	0.079	No	Medium	No	No	Yes	No	Yes
L-12	10.72	High	-3.63	0.021	No	Low	No	No	Yes	No	Yes
L-13	20.144	High	-3.519	0.040	No	Medium	No	No	Yes	No	Yes
L-14	5.777	Low	-3.715	0.0412	Yes	Medium	No	No	No	No	Yes
L-15	8.889	Low	-3.720	0.0378	Yes	High_risk	No	No	No	No	No
L-16	36.493	High	-3.481	0.0131	No	Medium_risk	Yes	No	Yes	Yes	Yes
L-17	35.153	High	-3261	0.0168	No	Medium_risk	No	No	Yes	No	Yes
L-18	41.159	High	-3.261	0.0712	No	Medium_risk	No	No	Yes	No	Yes
L-19	21.709	Low	-2.419	0.673	Yes	Medium_risk	No	Yes	No	Yes	Yes

Caco-2 permeability (Colorectal Adenocarcinoma cells permeability), GI (Gastro intestinal absorption), BBB (Blood Brain Barrier)

Table 5. Molecular docking studies for ligands with Leptin1AX8

Ligand	G Score	G energy	Glide e model	Glide evdw	Glide ecoul
L1	-4.308	-32.546	-39.466	-25.573	-6.973
L2	-4.011	-38.581	-45.538	-33.503	-5.079
L3	-4.72	-35.849	-42.395	-30.355	-5.494
L4	-4.047	-33.023	-37.47	-26.317	-6.706
L5	-4.914	-35.943	-44.801	-23.478	-12.465
L6	-3.962	-35.255	-40.63	-30.081	-5.174
L7	-4.161	-28.654	-34.299	-22.405	-6.249
L8	-4.443	-32.15	-39.546	-24.666	-7.484
L9	-3.894	-29.56	-36.558	-22.168	-7.392
L10	-4.1	-32.842	-38.965	-25.673	-7.169
L11	-5.004	-37.319	-45.183	-26.59	-10.729
L12	-4.292	-41.314	-50.617	-31.276	-10.037
L13	-4.365	-33.894	-43.081	-24.341	-9.553
L14	-5.411	-43.201	-56.014	-19.82	-23.382
L15	-5.041	-42.892	-53.176	-20.03	-22.862
L16	-4.564	-34.166	-44.207	-27.205	-6.961
L17	-4.363	-36.182	-41.337	-25.886	-10.296
L18	-3.838	-34.923	-42.011	-28.576	-6.347
L19	-5.729	-49.205	-62.421	-29.154	-20.051

Table 6. Molecular docking studies for ligands with Fat mass and obesity associated protein-3LFM

Ligand	G Score	G energy	Glide e model	Glide evdw	Glide ecoul
L1	-5.247	-42.358	-52.88	-36.55	-5.808
L2	-5.654	-47.945	-62.869	-42.858	-5.087
L3	-5.654	-47.919	-62.598	-41.825	-6.094
L4	-5.897	-44.787	-57.581	-41.71	-3.078
L5	-5.809	-48.702	-65.445	-40.165	-8.537
L6	-6.504	-49.433	-63.618	-42.896	-6.538
L7	-5.991	-37.499	-49.385	-33.714	-3.785
L8	-6.359	-45.525	-62.696	-42.772	-2.753
L9	-6.508	-45.761	-63.571	-42.138	-3.623
L10	-5.557	-46.871	-61.219	-42.852	-4.019
L11	-6.011	-46.502	-63.351	-39.455	-7.047
L12	-7.06	-50.065	-69.351	-40.424	-9.641
L13	-6.814	-46.783	-64.113	-34.376	-12.407
L14	-5.888	-56.028	-75.846	-47.349	-8.679
L15	-5.798	-50.595	-58.341	-43.635	-6.96
L16	-7.145	-45.513	-60.109	-37.103	-8.409
L17	-5.348	-45.167	-53.71	-39.747	-5.42
L18	-5.714	-51.899	-65.844	-42.037	-9.862
L19	-7.152	-54.352	-70.815	-40.051	-14.301

A drug will be potent when it reaches its active target in the body at sufficient amount and produces biological effect in its active form. About 40% of the candidate compounds not being marketed is due to their poor biopharmaceutical properties (drug likeliness)[11].Prediction of drug likeliness properties like Lipinski's rule of five, bioactivity score and ADME properties has been used immensely to filter out undesirable compounds in early phases of drug discovery[12]. In the current study, tangeretin and its derivatives possess all the drug like properties and these findings come in accordance with the earlier scientific reports of bioactive phytoconstituents and it strongly supports that these can be considered as drug candidates for further studies[13].

Molecular docking was performed to predict the preferred orientation and binding affinity of

molecules to receptor/binding site/an enzyme.Glide was used to calculate the docking score and binding free energy of molecules with proteins. For*in silico* assessment of the ability of compounds in ameliorating obesity and related immunodeficiency the proposed compounds were docked with the five targets Leptin, Fat mass and obesity associated protein (FTO), Peroxisome proliferated receptor (PPARɣ), NADH oxidase (NOX 4) and Pancreatic lipase.

Table 7. Molecular docking studies for ligands with pancreatic lipase-1LPB

Ligand	G Score	G energy	Glide e model	Glide evdw	Glide ecoul
L1	-7.519	-42.677	-59.193	-39.381	-3.296
L2	-5.989	-44.882	-60.076	-42.291	-2.591
L3	-6.907	-43.355	-56.966	-38.726	-4.629
L4	-7.179	-43.388	-60.1	-39.033	-4.355
L5	-6.177	-39.663	-54.4	-36.192	-3.471
L6	-6.544	-39.314	-50.238	-39.182	-0.133
L7	-6.159	-36.433	-49.164	-35.809	-0.624
L8	-7.578	-43.507	-60.357	-39.679	-3.828
L9	-7.126	-40.408	-57.236	-35.66	-4.748
L10	-7.206	-40.7	-56.284	-38.417	-2.282
L11	-5.553	-39.782	-50.752	-32.671	-7.111
L12	-6.273	-42.717	-57.73	-38.919	-3.798
L13	-8.061	-45.848	-64.581	-40.142	-5.706
L14	-7.077	-48.936	-65.569	-39.352	-9.585
L15	-6.154	-49.002	-65.026	-41.559	-7.443
L16	-7.454	-41.601	-58.484	-38.386	-3.215
L17	-6.814	-46.869	-65.272	-41.031	-5.838
L18	-5.967	-43.445	-54.767	-37.839	-5.606
L19	-5.779	-43.343	-50.986	-39.05	-4.293

Table 8. Molecular docking studies for ligands with ppargamma- 2PRG

Ligand	G Score	G energy	Glide e model	Glide evdw	Glide ecoul
L1	-7.543	-43.839	-60.481	-38.243	-5.596
L2	-7.523	-44.253	-62.253	-41.45	-2.802
L3	-6.016	-48.769	-65.822	-45.466	-3.303
L4	-7.661	-44.913	-61.241	-40.503	-4.411
L5	-7.806	-46.498	-65.701	-39.952	-6.546
L6	-6.521	-46.661	-59.777	-44.228	-2.433
L7	-6.878	-37.329	-52.867	-35.805	-1.524
L8	-7.235	-44.168	-60.951	-37.667	-6.501
L9	-5.896	-42.242	-57.522	-41.092	-1.15
L10	-7.356	-45.125	-62.659	-38.03	-7.096
L11	-7.78	-49.502	-71.31	-40.522	-8.98
L12	-6.626	-50.804	-69.922	-41.931	-8.873
L13	-8.664	-53.182	-74.665	-41.332	-11.85
L14	-7.293	-52.771	-61.229	-42.641	-10.131
L15	-7.386	-59.071	-79.996	-45.737	-13.334
L16	-7.026	-45.596	-62.871	-38.752	-6.843
L17	-6.951	-46.025	-59.533	-41.305	-4.72
L18	-8.57	-51.726	-68.346	-38.967	-12.759
L19	-6.193	-50.562	-65.757	-52.084	1.522

Table 9. Molecular docking studies for ligands with NADH Oxidase (NOX 4)- 3A1F

Ligand	G Score	G energy	Docking score	Glide e model	Glide evdw	Glide ecoul
L1	-3.636	-28.908	-3.636	-35.914	-21.349	-7.559
L2	-3.422	-32.67	-3.422	-38.522	-29.069	-3.6
L3	-3.495	-31.175	-3.495	-36.784	-23.297	-7.879
L4	-3.296	-32.402	-3.296	-38.55	-28.766	-3.636
L5	-3.649	-30.699	-3.649	-38.008	-22.527	-8.172
L6	-3.326	-31.054	-3.326	-36.247	-25.88	-5.174
L7	-3.797	-29.434	-3.797	-35.289	-27.859	-1.575
L8	-4.444	-31.202	-4.444	-36.507	-19.268	-11.934
L9	-5.298	-34.206	-5.298	-41.498	-27.824	-6.382
L10	-3.448	-29.151	-3.448	-36.033	-21.663	-7.487
L11	-4.424	-34.945	-4.424	-43.177	-25.826	-9.12
L12	-3.799	-31.774	-3.799	-39.947	-22.234	-9.54
L13	-3.785	-33.909	-3.785	-40.643	-26.955	-6.955
L14	-1.823	-26.507	-1.823	-24.826	-21.738	-4.768
L15	-3.958	-40.355	-3.958	-47.624	-25.321	-15.034
L16	-3.674	-29.633	-3.674	-34.914	-23.396	-6.238
L17	-3.417	-34.225	-3.417	-40.304	-26.976	-7.249
L18	-4.278	-36.797	-4.278	-46.222	-25.318	-11.479
L19	-3.625	-42.784	-3.625	-52.088	-34.51	-8.274

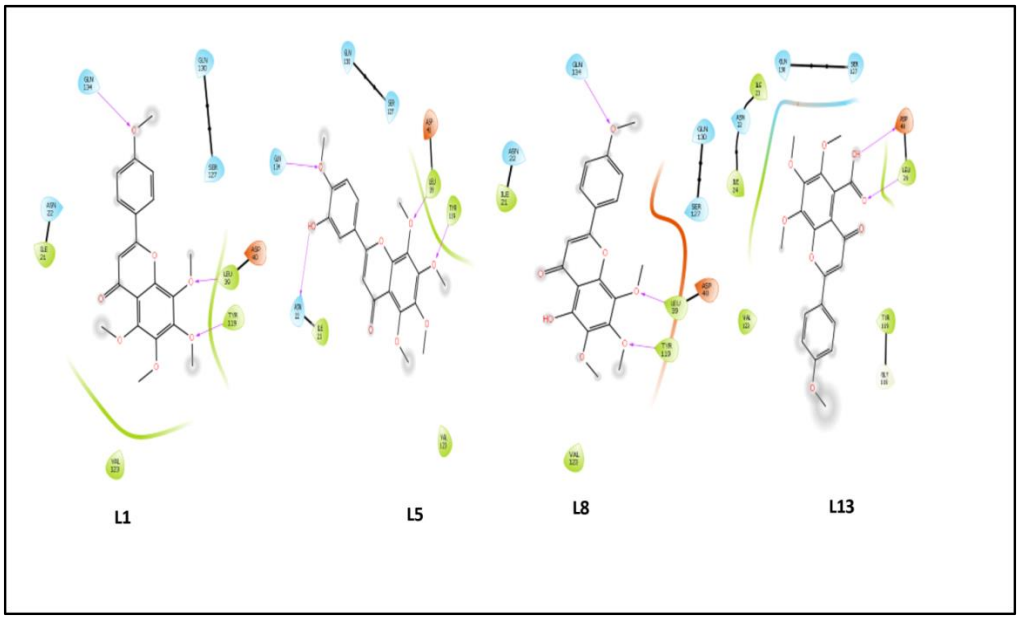


Fig. 2. Binding interactions (2D) of Ligands with Leptin – 1AX8

The leptin receptor is crucial for energy homeostasis and regulation of food uptake. The rational design of leptin agonists/antagonists could be an appealing challenge in the battle against obesity[14]. Many of the ligands like L5, L8, L11and L13showed good Glide score near to that of standard and it was observed that these ligands had made prominent hydrophobic interactions with the Asp 40 and Leu 39 of Leptin. These findings come in accordance with the earlier findings on computational studies of other phytoconstituents which played a potential role in combating obesity[15].

Fat mass and obesity associated protein is mainly associated with energy and body weight regulation. Inhibition of FTO is a main target in controlling obesity and in the current study L8, L9, L13and L16 showed high glide score nearly to that of standard and it was revealed that they

show prominent pi-pi stacking with HIS 231 and TYR 108 and hydrogen bonding interactions with ASP 233, GLU 234 and ARG 96. These studies were in harmony with the previous findings on molecular docking studies on FTO protein for flavonoids like quercetin, Kaempferol which proved to be used in attenuating obesity [16].

Pancreatic lipase is an essential enzyme recognized for the digestion and absorption of lipids and reported to be a promising drug target towards the future development of antiobesity therapeutics in the cure of obesity disorders[17].In present investigation many of the compounds showed better Glide score than that of standard. L13 and L8 showed the best glide score by exhibiting pi-pi staking with HIS 263 and TYR 114 and hydrogen bonding and hydrophobic interactions with ASP79 and PHE77. These findings are in line with earlier scientific reports on various bioactive phytoconstituents which binds to the pancreatic lipase enzyme and interrupt the conformational changes required for the fat hydrolysis [18].

PPARγ plays an important role in regulating lipid metabolism, insulin sensitivity, and glucose homeostasis and their agonist are used in treating hyperlipidemia. Interestingly PPARγ is prominently involved in maturation and function of various immune system-related cell types[19]. In the present study, the molecular docking studies result in high glide score for most of the proposed compounds mainly L13, L18 and L8 exhibited prominent binding interactions with the receptor by forming hydrophobic interactions with ARG 288, GLU343, TYR 327 sites. These studies are in accordance with the earlier reports which revealed that some phytoconstituents like flavonoids and other phenolic derivatives possess both anti obesity and immunity enhancing capability[20].

NADH oxidase (NOX4) is an enzyme that exhibits vital role in free radical scavenging which inturn leads to the importance in controlling adipogenesis and regulating immune deficiency disorders [21]. The docking studies in the current screening revealed that L8 had showed the best glide score followed by L18, L11 and L13 by forming strong hydrophobic interactions with GLU 156 and GLH 104. These observations come in harmony with various previous scientific reports on phytocompounds possessing both antioxidant and antihyperlipidemic potential [22].

Upon Molecular docking analysis of all the proposed compounds with different targets it is clearly evident that L8 and L13 exhibited efficient docking score with all proteins. This may be due to the modification of OCH3 group at the fifth position of tangeretinwith polar groups OH and COOH groups in L8 and L13 respectively.

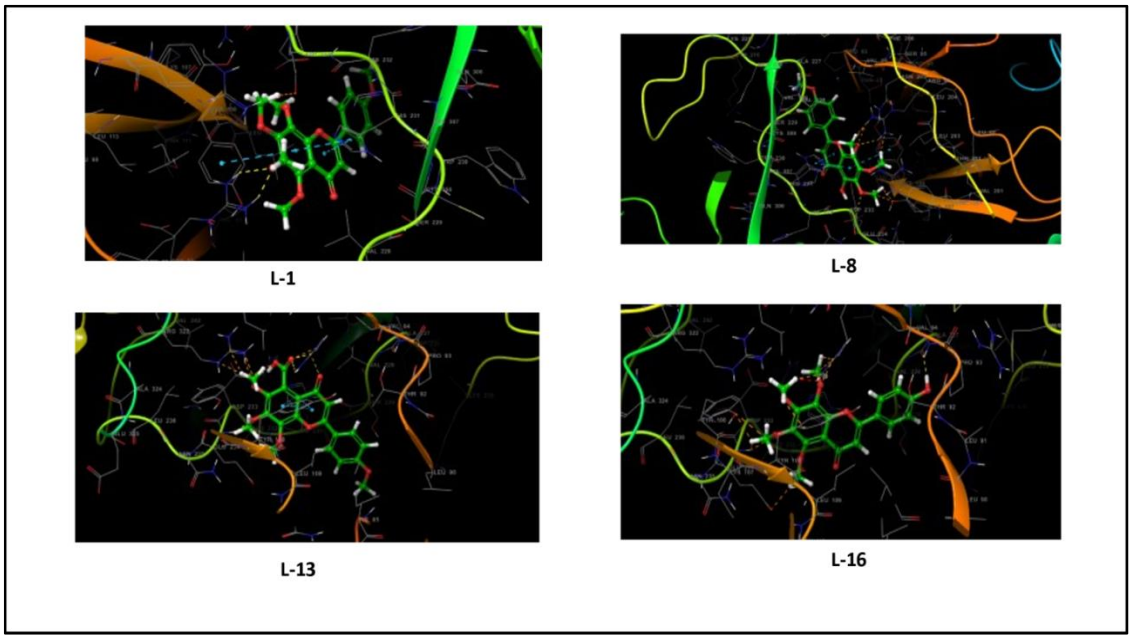


Fig. 3. Binding interactions (3D) of Ligands with Fat Mass and Obesity Associated Protein – 3LFM

Table 10. Mulliken charge analysis of Selected Compounds by B3LYP/6-31G(d,p)

Tangeretin L1		L8		L13	
Atom Position	**Mulliken charge**	**Atom Position**	**Mulliken charge**	**Atom Position**	**Mulliken charge**
C1	0.3250	C1	0.32078	C1	0.3237
C2	-0.1886	C2	-0.19285	C2	-0.1870
C3	0.4146	C3	0.41656	C3	0.4173
C4	0.0433	C4	0.02463	C4	0.0403
C5	0.2499	C5	0.25537	C5	0.0053
C6	0.2934	C6	0.25850	C6	0.2897
C7	0.2860	C7	0.30191	C7	0.3041
C8	0.2613	C8	0.24829	C8	0.2675
C9	0.2307	C9	0.25019	C9	0.2446
O10	-0.5395	O10	-0.54474	O10	-0.5390
O11	-0.5249	O11	-0.50536	C11	0.5308
C12	0.0377	C12	0.04070	O12	-0.4587
C13	-0.1192	C13	-0.10962	O13	-0.4625
C14	-0.1384	C14	-0.12090	O14	-0.5288
C15	0.3615	C15	0.36089	C15	0.0377
C16	-0.1265	C16	-0.14349	C16	-0.1075
C17	-0.1096	C17	-0.11993	C17	-0.1205
O18	-0.5137	O18	-0.51427	C18	0.3626
C19	-0.0827	C19	-0.08259	C19	-0.1435
O20	-0.5382	O20	-0.54279	C20	-0.1187
C21	-0.0820	C21	-0.07946	O21	-0.5128
O22	-0.5370	O22	-0.54515	C22	-0.0837
C23	-0.0844	C23	-0.08683	O23	-0.5371
O24	-0.5395	O24	-0.56402	C24	-0.0866
C25	-0.0806	C25	-0.08922	O25	-0.5397
O26	-0.5275	O26	-0.52875	C26	-0.0871
C27	-0.0735	H27	0.10316	O27	-0.5444
H28	0.1046	H28	0.11977	C28	-0.0913
H29	0.1234	H29	0.09996	H29	0.1069
H30	0.0917	H30	0.09220	H30	0.3230
H31	0.1026	H31	0.10031	H31	0.1228
H32	0.1005	H32	0.12928	H32	0.1024
H33	0.1298	H33	0.11605	H33	0.0940
H34	0.1171	H34	0.11692	H34	0.1009
H35	0.1163	H35	0.11795	H35	0.1310
H36	0.1159	H36	0.11769	H36	0.1174
H37	0.1286	H37	0.11299	H37	0.1179
H38	0.1064	H38	0.11906	H38	0.1209
H39	0.1180	H39	0.13409	H39	0.1324
H40	0.1125	H40	0.11684	H40	0.1099
H41	0.1332	H41	0.12101	H41	0.1207
H42	0.1153	H42	0.11050	H42	0.1169
H43	0.1323	H43	0.13826	H43	0.1357
H44	0.1074	H44	0.32612	H44	0.1191
H45	0.1148	--	--	H45	0.1403
H46	0.0994	--	--	H46	0.1130
H47	0.1326	--	--	--	--

Table 11. Reactive descriptors energy values of selected compounds in gas phase by B3LYP/6-31G (d,p)

Parameter	L1(Tangeretin)	L13	L8
E_{HOMO} (ev)	-5.820	-5.99	-5.620
E_{LUMO} (ev)	-1.510	-1.69	-1.370
$E_{LUMO} - E_{HOMO}$ (ev)	4.31	4.30	4.250
Ionization Potential (ev)	5.820	5.99	5.620
Electron Affinity (ev)	1.510	1.69	1.370
Chemical potential(μ)	-3.665	-3.84	-3.495
Chemical hardness (η)	2.155	2.15	2.125
Chemical Softness (s)	0.2421	0.232	0.2352
Electronegativity(χ)	3.665	3.84	3.495
Electrophilicity index (ω)	3.1165	3.429	2.8741

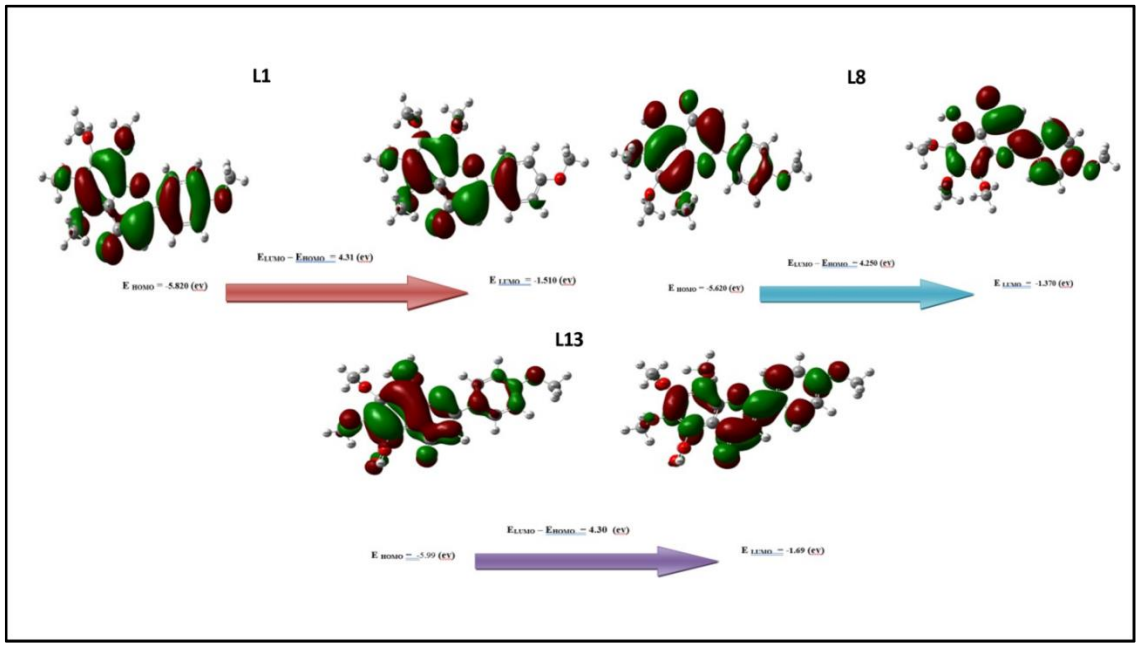


Fig. 4. Energies for the HOMO and LUMO of Selected compounds

Further DFT analysis carried out for the selected potent Ligands and tangeretin substantiated the molecular docking and other *in silico* predictions. The higher HOMO value states that molecule with a good electron donor, whereas a lower value indicates a weak electron acceptor. Moreover, a smaller energy gap between the LUMO and HOMO energies has a considerable influence on the intermolecular charge transfer and bioactivity of molecules [23]. In the current study the tangeretin and its derivatives L8 and L13 were found to possess less energy gap which supports their ability to binding with receptors. The reactive descriptors like chemical potential (μ) indicate negative values for all the compounds, which implies good stability, and the formation of a stable complex with the receptor. The other reactive descriptors also clearly indicated that the analysed compounds possess better bioactivity and chemical reactivity with considerable intra-molecular charge transfer between electron-donor to electron-acceptor groups which comes in accordance with previous *in silico* studies on biologically active phytocompounds [24].

5. CONCLUSION

In the current computational study, it is evident that proposed tangeretinderivatives have marked binding ability with obesity and associated immune related targets. Hence, the present bioinformatic findings probably provide excellent lead candidates for the development of therapeutic drugs in combating the obesity and related immune deficiency.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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