Annals of Phytomedicine 7(2): 161-169, 2018
DOI: 10.21276/ap.2018.7.2.24; Print ISSN : 2278-9839 and Online ISSN : 2393-9885
Ann. Phytomed., 7(2):161-169 (2018)

Original article

Computational screening of phytochemicals for finding potential inhibitor against C/EBPβ and PPARγ

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Received June 10, 2018: Revised July 30, 2018: Accepted August 3, 2018: Published online December 30, 2018

Abstract

Nowadays, epidemic of obesity become pandemic worldwide and both C/EBPβ and PPARγ played a crucial role in adipogenesis, insulin sensitization, and glucose homeostasis and lipid metabolism. The main objective of this computational study is to identify the drug like molecule, having anti-adipogenesis properties and serve as potential inhibitor against C/EBPβ and PPARγ. In the present study, molecular docking was performed by AutoDock Vina suit. A total of 148 flavonoid compounds were selected for the study and small molecule database created for virtual screening in order to find out new small drug like compound as potential antiadipogenesis agent. The crystal structure of C/EBPβ and PPARγ was retrieved from protein data bank and their active sites were predicted and analyzed. Molecular docking was carried out and results showed that compounds epigallocatechin-3-gallate (EGCG), theaflavine and curcumin had good interaction with both the inhibitors. Further, toxicity analysis had been done and it was found that screened hits did not had any toxic effect, so screened phytochemicals can be used as potent target candidate drugs. The current *in silico* study concludes that flavonoids derivatives can potentially inhibit C/EBPβ and PPARγ inhibitors and further *in vitro* and *in vivo* investigations confirmed its therapeutic potential. Perceptions after this study indicated that these novel phytochemicals could act as potential partial antagonist agents and serve as new antiadipogenesis drug after further investigation.

Key words: *In silico* screening, C/EBPβ, PPARγ, ADMET, adipogenesis, flavonoids

1. Introduction

Obesity is significant risk factor which is responsible for many diseases like cardiovascular diseases, type 2 diabetes, metabolic disbalance, stroke, and many cancers. Individuals are suffering from obese with hypertension and dyslipidemia usually having type 2 diabetes because in both conditions, human body produces insufficient amount of hormonal insulin which is able to covert sugar, starch and food into energy (Al-Goblan *et al*., 2014). Adipose tissue played a major role for energy storage and its sudden increment in terms of size and number (also termed as adipogenesis) will play key role in the development of obesity (Guo *et al*., 2015). The important factors which cause adipogenesis are C/EBPβ family and PPARγ, both are potential transcription factors orchestrate the adipogenic differentiation process. C/EBPβ stimulates the expression of PPARγ, during adipogenesis process, C/EBPβ level become raised due to hormonal inducers which are a combination of insulin, glucocorticoids and agents that elevate cyclic AMP levels. Studies also suggested that PPARγ is molecular target for TZD class of anti-diabetic drugs (Ishibashi *et al.*, 2012). PPARγ and C/EBPβ together regulate adipocyte biology and played an important role in functions of mature adipocytes, insulin sensitivity, and lipid metabolism. During early adipogenesis, both C/EBPβ and δ are expressed with induction of PPARγ. The above mentioned mechanics also revealed that co-operation of C/EBPβ family with PPARγ is necessary for adipocytes optimal differentiation (Lefterova *et al.*, 2008).

The initial stage of adipocyte differentiation was orchestracted by several transcriptional factors, C/EBPβ, PPARγ and C/EBPβ, among these, C/EBPβ expressed during early stage of adipocyte differentiation and then activates the transcription of C/EBPβ and PPARγ which gave rise to adipocyte gene expression (Park *et al.*, 2012). Hence, it is essential and required to identify set of new natural compounds which are able to inhibit adipocyte differentiation and will help to prevent obesity and other metabolic disorder (Valli *et al*., 2018).

Medicinal plants are natural boon for humans and their plant extracts contributing towards effective disease prevention, are termed as "herbal drugs" (Nooreen *et al.*, 2018). Various active compounds of plants have been tested against obesity and they showed specific effects in the inhibition of preadipocyte differentiation and it also induced apoptosis of increased adipocytes in order to decrease their numbers which are helpful to cure the disease. Potential active compounds include flavonoids, phenols and alkaloids which have showed effective inhibition of adipogenesis process (Rajeshwari *et al.*, 2014). Flavonoids contribution towards the antiadipogenic effects and disrupts adipogenesis process during transcription which suppresses the effect of PPARγ expression. Peroxisome proliferator activated receptor (PPARγ) act as key role in adipocyte differentiation (Chien *et al.*, 2005).

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The natural active compounds like epigallocatechin-3-gallate (EGCG), theaflavine, flavnol, curcumin, resveratrol, catechin and apigenin showed very effective results for the inhibition of obesity and down-regulation of adipogenesis and metabolism of lipids (Mukherjee *et al.*, 2015; Drwal *et al.*, 2014).

Computational screening methodologies are widely recognized as efficient approaches in initial phases of drug discovery. Virtual screening is an emerging and effective approach to computationally analyse the large libraries of compounds which are targeted specific target protein which proceed to find compound which works as lead compound in drug discovery (Savic *et al.*, 2015). In clinical trials, there are more than half drug compounds failed in pharmacokinetics and toxicity issues. Therefore, the computer based screening evaluates the drug-likeness of the molecules (Vyas *et al.*, 2008). Nowadays, computational screening is more successful, in drug discovery of reliable new lead compounds for developing drug against targeted proteins. AutoDock Vina is an efficient bioinformatic tool for virtual screening (Forli *et al.*, 2016).

C/EBPβ and PPARγ are adipogenic transcriptional factors which increase expressions of adipogenic proteins including adipsin D and perilipin (Li *et al.*,2015; Lee *et al.*,2014) and taken as a potential target in this study for inhibition of inflammatory activity and adipocyte synthesis which cause obesity. The current *in silico* study focuses on to screen flavonoids as they showed anti-cancerous, anti-inflammatory and antiobese effect (Drwal *et al.*, 2014). For the examination of molecular and physiological role, ADMET properties analysis is helpful in predicting, assessing efficiency, absorption, react on metabolism and toxicity of drug after its admiration in body.

2. Materials and Methods

2.1 Structure of PPARγ and C/EBPβ

The X-ray crystallographic 3D structure of human protein PPARγ (PDB:4Y29) at 1.98Å resolution composed with 269 amino acids length and C/EBPβ (PDB:2E43) at 2.1Å resolution composed with 78 amino acids length were retrieved from Protein Data Bank (PDB) which used as receptors in this study.

2.2 Phytocompounds selection

From various literature searches, total 148 plant secondary metabolites having antioxidant, antimicrobial and anti-inflammatory properties were selected and taken for virtual screening.

2.3 Binding site prediction

COACH (http://zhanglab.ccmb.med.umich.edu/COACH/) Web server was used for prediction of pockets and cavities present in protein where ligands could bind or dock. It also provides detailed quantitative characterization of interior cavities and surface pockets of proteins, which were prominent concave regions of proteins that frequently associated with binding events.

2.4 Drug-like properties of phytochemicals

Molinspiration (www.molinspiration.com/cgi-bin/) server was used to predict TPSA value, number of rotatable bonds acceptors and hydrogen bond donors. These parameters help in evaluation of drug likeness in light of Lipinski's rule. Lipinski's rule of five as suggested by Christopher A. Lipinski, according to that for any compound to be a good drug candidate, it should had molecular weight (MW) less than 500 Da, H-bond donors (HBD) less than 5, H-bond acceptors (HBA) less than 10, Log P value less or equal to 5 and total rotatable bonds less than 10. For toxicity analysis, PROTOX (http://tox.charite.de/tox) (Drwal *et al.*, 2014) Web server was used for predicting toxicity level of phytochemicals.

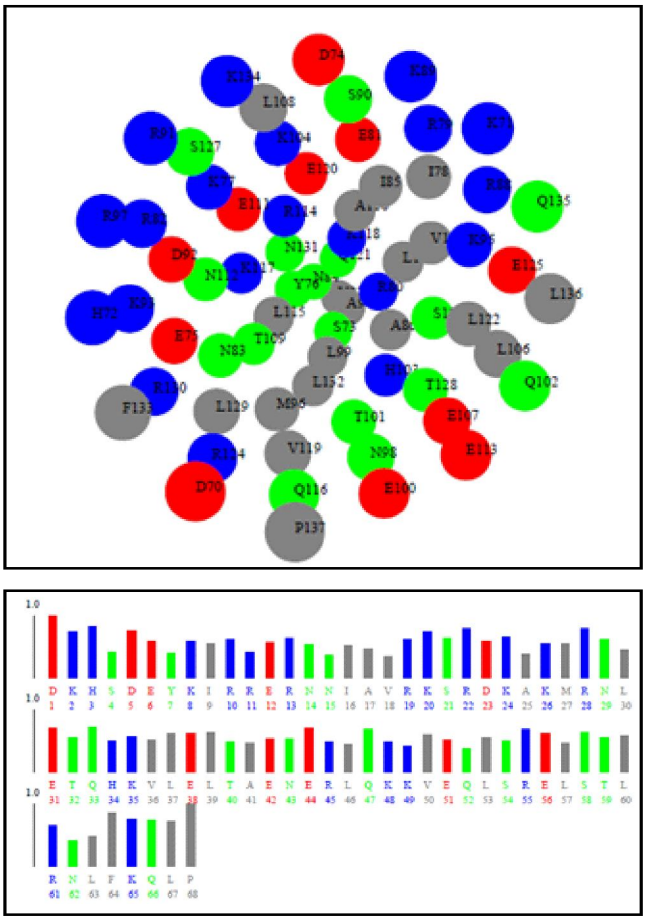
2.5 Virtual screening approach

Virtual screening is well known as well as reliable efficient prototype for filtering lead compounds for drug discovery. In this study, screening of phytocompounds was carried out through using PyRx 0.8 (Dallakyan, 2008). Compounds having good score of drug-likeness were retrieved from ZINC database and saved in SDF format. The SDF file was imported in marvin sketch tool to draw structure of chosen compounds according to PyRx tool and, further energy minimization of all the ligands were performed. Based on the scoring, further ligands were subjected to docking against C/EBPβ and PPARγ protein using AutoDock Vina in PyRx 0.8 (Trott and Olson, 2010).

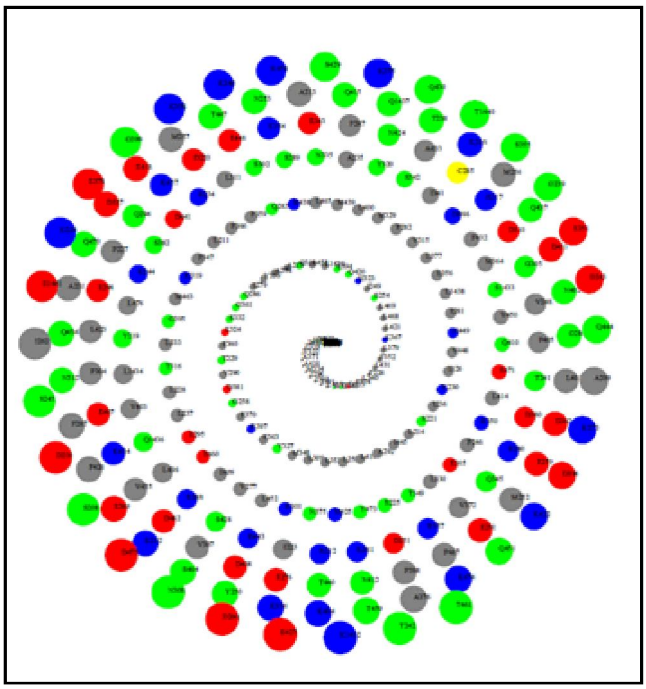
3. Result and Discussion

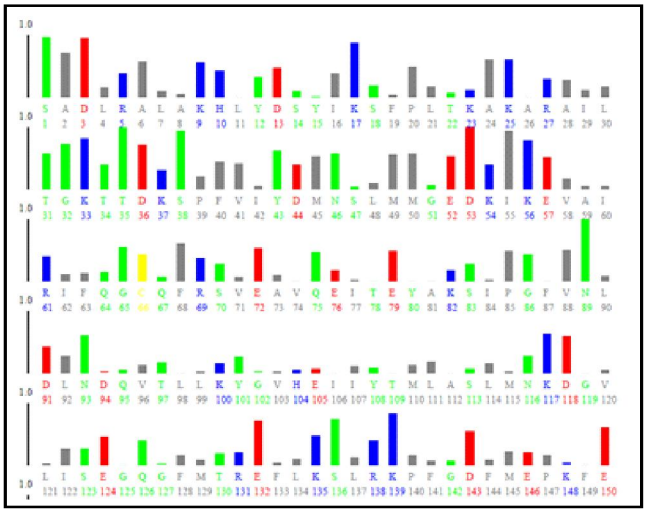
3.1 Surface analysis

Prediction of accessible surface area (ASA) of C/EBPβ and PPARγ was carried out by ASA view (http://www.abren.net/asaview/) (Ahmad *et al.*, 2004). The server provides graphical representation of solvent accessibility of amino acid residues in proteins (Figure.1)



(A)





(B)

Figure 1: (A) Shown surface area analysis of 2E43 protein and (B) shown surface area of 4Y29 protein where radius of spiral plot of amino acids arranged according to solvent accessibilities of the residues in which green color indicated polar residues, grey colour represents non-polar residues, red colour presented negative charges, blue color indicated positive charges and yellow colour represented cystein residues. Radius of the solid circles representing these residues corresponds to the relative solvent accessibility. Bar view of residues arranged in organized order in which length of bar represents the ASA in units relative to extended state ASA of that residue.

3.2 Protein binding sites

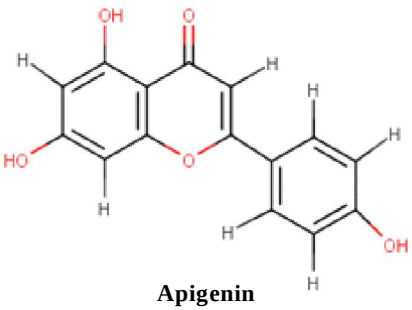
The active sites of the receptor C/EBPβ (PDB ID: 2E43) and PPARγ (PDB ID: 4Y29) determined by using COACH server. Detail description of active sitearranged in Table 1.

Table 1: Contains binding sites of the receptor 4Y29 and 2E43 detected by COACH server, digits showed the location of amino acid residues

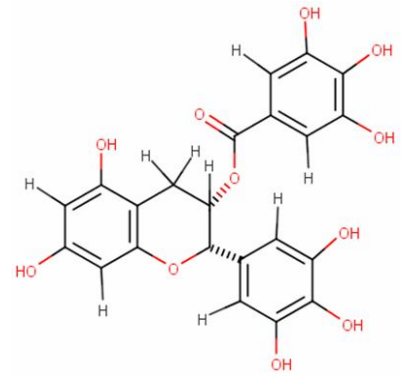
Protein ID	Binding sites
4Y29	Ile237, Leu234, Arg69, Met145, Leu246, Glu124, Pro149, Tyr254, Met110, Lys148, Ser123, Leu101, His220, Leu114, Phe63, Cys66, Pro140, Gly125, Tyr108, Leu111.
2E43	Val18, Ala17, Lys24, Arg22, Lys26, Asn15, Tyr7, Ser21, Arg11, Arg18, Arg19, Asn14, Arg28.

3.3 Ligand preparation for screening

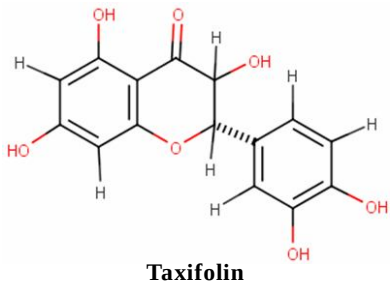
Chemical structures of phytocompounds which used as ligands were retrieved from the ZINC database (Figure.2) and molecules file was prepared in PDBQT format as AutoDock Vina tool used the PDBQT molecular structure file format for molecular docking (Trott and Olson, 2010). The completion of the docking search, the final compound pose was located by evaluating Auto Dock empirical scoring function in which the conformation with the lowest docked energy value was chosen as the best ligand. The docking model and hydrogen bonds were predicted and visualized by ADT and PyMol software. Selected phytocompounds were docked with PPARγ and C/EBPβ protein, responsible for adipogenesis reaction around its important binding site residues in PPARγ Lys148, Met145, Pro149, Lys148, Ser123, Leu114, Pro140and in C/EBPβ Ala17, Arg22, Lys26, Arg18.



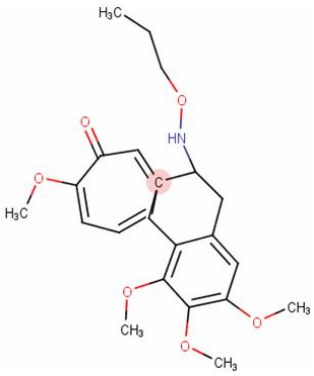
Apigenin



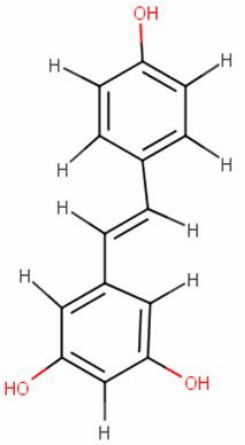
EpigalocatechinGallate



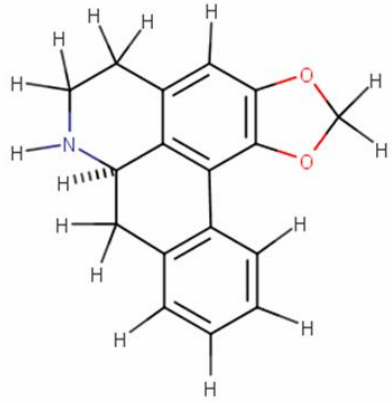
Taxifolin



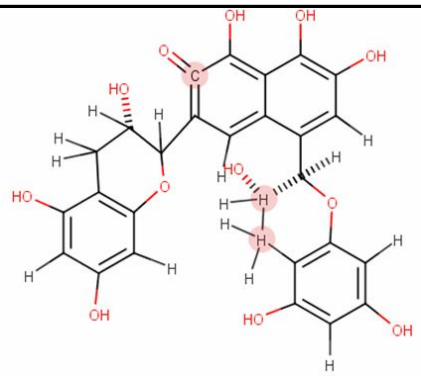
Epicatechin



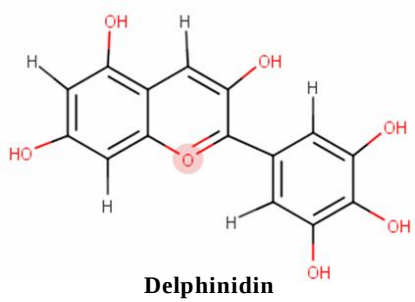
Resveratol



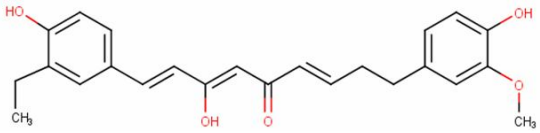
Anonain



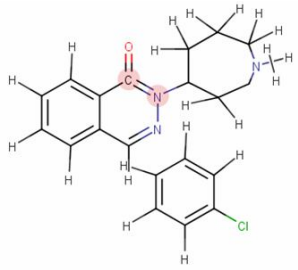
Theaflavine



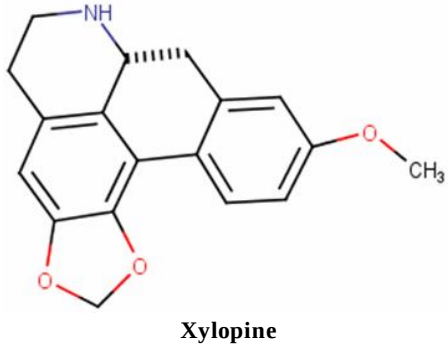
Delphinidin



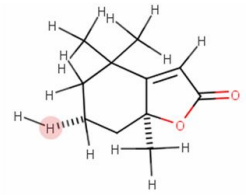
Curcumin



Azelastine



Xylopine



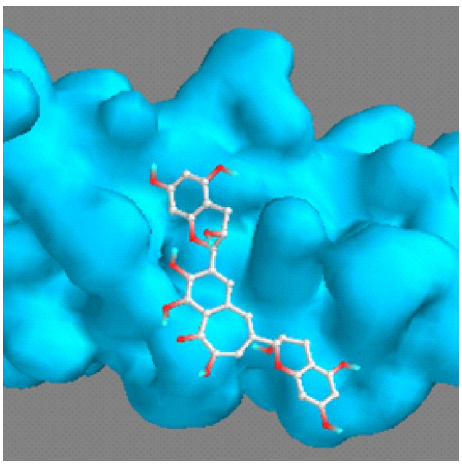
Loliolide

Figure 2: Chemical structures of phytochemical compounds which are intracting with 2E43 and 4Y29 proteins and showed good binding affinity with the receptor proteins, derived from various natural resources having anti-cancerous and anti-adiposegenesis properties.

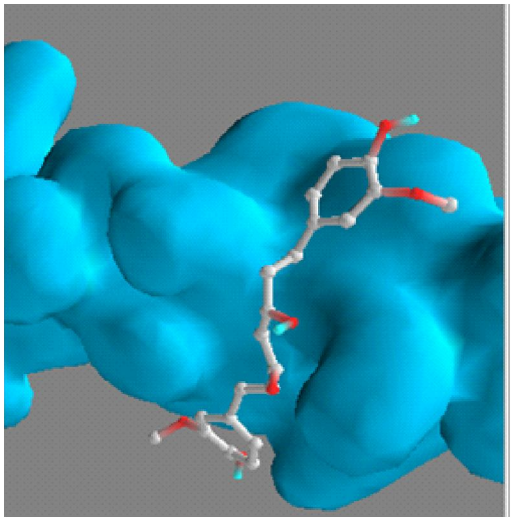
3.4 Protein preparation for molecular docking

In the present study, PyRx 0.8 tool was used for screening lead molecules against C/EBPβ and PPARγ protein for finding a new compound which act as partial antagonist for adipogenesis and obesity. C/EBPβ (PDB ID: 2E43) and PPARγ (PDB ID: 4Y29) were used as receptors to screen 148 drug-like compounds (plants secondary metabolites). These compounds were selected based on Lipinski rule. AutoDock Vina suit in PyRx 0.8 was employed to screen all ligands; the tool generates nine different poses of each ligand. Further, evaluation of results of docking were based on the hydrogen bonds interaction with active sites residues of C/EBPβ and PPARγ, the best docking pose for each ligand was selected.

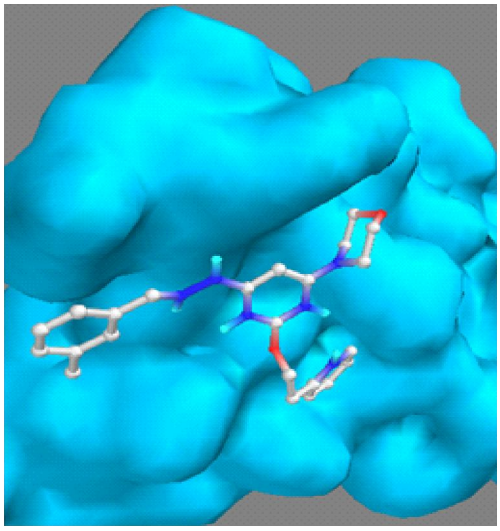
Molecular docking of 2E43 was carried out by the help of PyRx 0.8 and selecting AutoDock Vina as docking software. Vinagrid coordinated were set as x=35.39, y=89.11, z=12.48 and dimensions of search space were set as x =26.24, y=38.73, z=25.0. Molecular docking of PPARγ (PDB ID: 4Y29) was carried out with the help of PyRx 0.8 and selecting AutoDock Vina as docking software. Vina search space coordinated was set as x= 8.89, y= 1.97, z = 13.29, dimensions ands search space were set as x =25.0, y=26.54, z=25.0 and exhaustiveness was set at 5. All docked poses were saved in PDB format for further analysis on PyMol version 1.7.4.5 Edu. In different docking poses red dash dots showed the hydrogen bonding interactions with corresponding amino acids residues (Figures 2, 3). Among all, the compounds having good docking score were selected and showing in Table 1. Docking poses of PPARγ and C/EBPβ protein with theaflavine, apigenine, epigallocatechin gallate, curcumine and taxifoline having good RDMS value and binding affinity score are shown in Figure 2 and Figure 3.



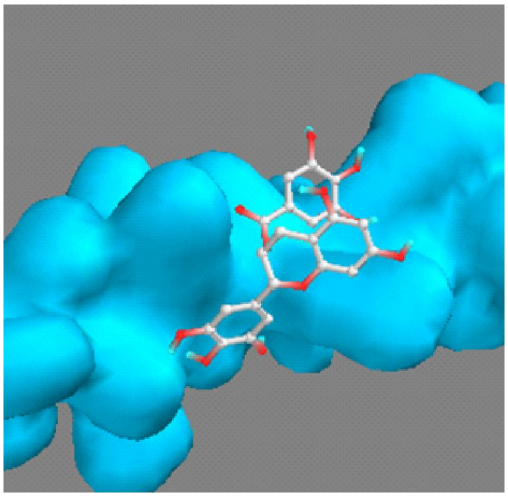
(A)



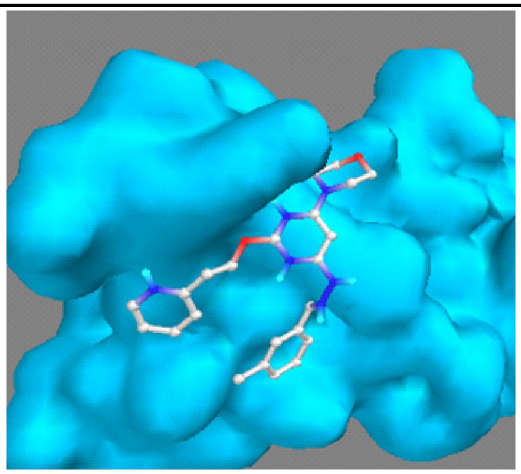
(B)



(C)

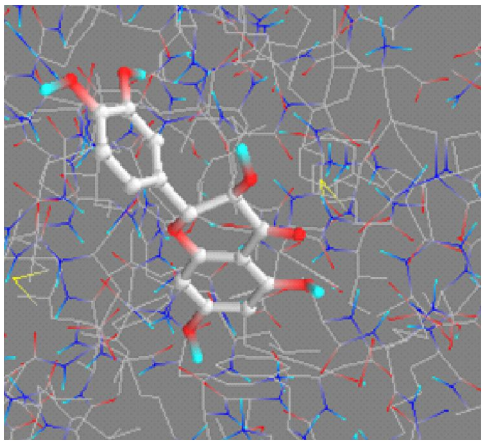


(D)

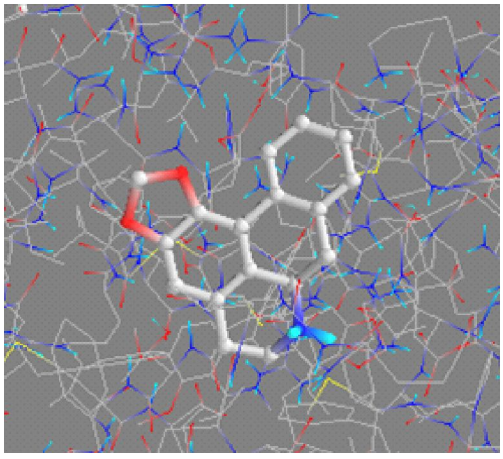


(E)

Figure 3: Ligand receptor docking complex structure of best 10 lead compounds and known inhibitor of 2E43 along with hydrogen bonds bond ligands are: (A) ZINC33963966, (B) ZINC100067274, (C) ZINC11726230, (D) ZINC3870412 and (E) ZINC105086 where red dashed lines indicated hydrogen bonds which are interacted with the corresponding amino acid residues.



(A)



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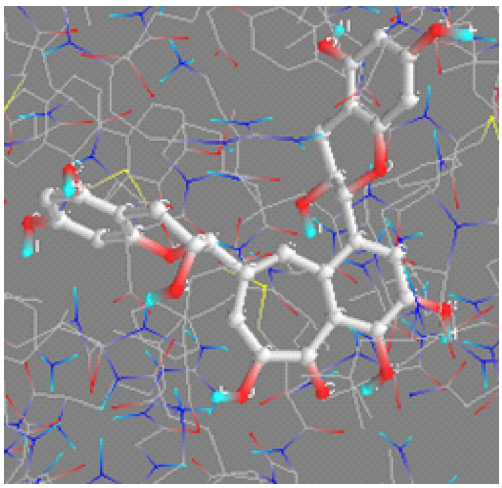


(C)

Figure 4: Ligand receptor docking complex structure of best lead compounds and known inhibitor of 4Y29 along with hydrogen bonds bond ligands are: (A) ZINC105086, (B) ZINC898396 and (C) ZINC33963966 where red dashed lines indicate hydrogen bonds which interacted with the corresponding amino acid residues.

3.5 *In silico* assessment of drug likeness

Molinspiration Web server was used for analyzing absorption, distribution, metabolism and excretion properties of top 10 virtual screening hits. ADMET properties of top successive hits were checked in optimal descriptors in pH=7.4. Moreover, oral toxicity was analyzed by PROTOX (http://tox.charite.de/tox/) Web server (Figure 6). The server allows checking of probable accessorial human protein targets for every successive hit.

Drug ability of compounds was assessed based on physiochemical properties and Lipinski rule include TPSA value, number of rotatable bonds, hydrogen bond donors and acceptors of phytocompounds represents in Figure 5.

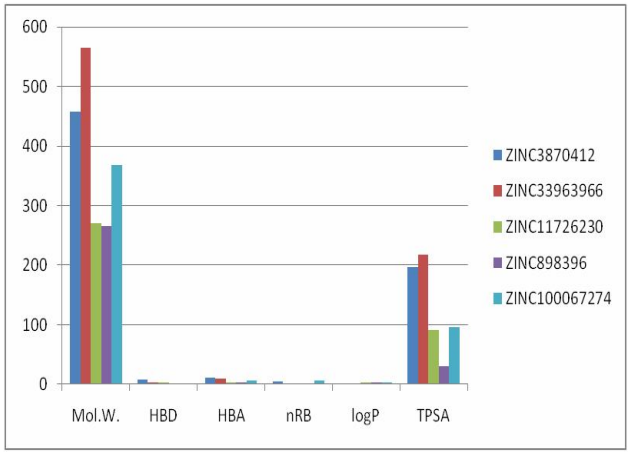
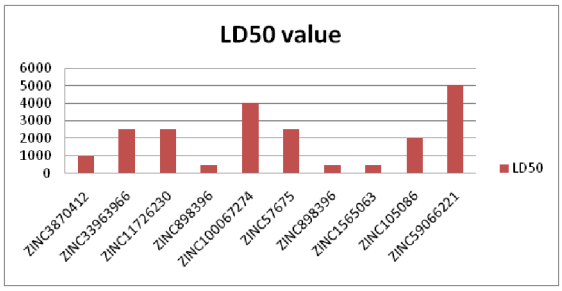
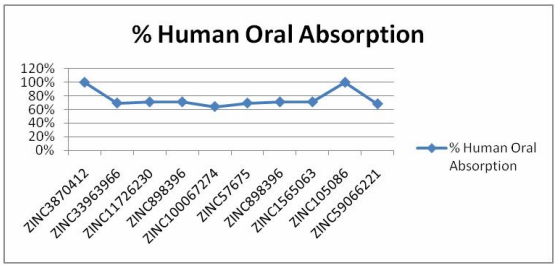


Figure 5: Physiochemical properties of phytocompounds.



(A)



(B)

Figure 6: (A) Showed LD50 values of selected compounds in graphical view and (B) graphical presentation of percentage human oral absorption of phytochemicals. Both LD50 and oral absorption % indicated the toxicity level in compounds.

Drug likeness properties of screened compounds scored on the basis on Lipinski rules given in Table 2. It indicated that the screened compounds were fulfilling all the criteria of Lipinski's rule of five. Compound epigallocatechin gallate have maximum number of hydrogen bonds acceptor and hydrogen bond donor properties (Table 2). Topological polar surface area (TPSA) was calculated for selected compounds. It should be ≤ 140.5b of molecules which well interrelated with the passive molecular transport through membranes which showed high blood brain permeability score and all the compounds are within the range. The drug-likeness data of selected compounds suggested that flavonoids could be used as drug for the treatment of obesity. Calculated LD50 (Lethal Dose 50%) values from PROTOX server results represented in Figure 6 which indicates ZINC59066221, ZINC100067274 and ZINC339 63966 had low toxic values. Flavonoids like maysin, curcumin, delphinidin, theaflavine, apigenin, flavonol and dihydroflavonol were found to be non-toxic as they possess low LD_{50} value are mentioned in Table 2 and could be used oral drug compound.

Among all phytochemicals phytosterols, polyphenols and alkaloids active compounds showed antiobesity effects as well as treating metabolic disorders. According to previous research work, genistein had been shown inhibition properties for both PPARγ and C/EBPβ in Wnt/catenin pathway fighting against obesity (Feng *et al.*, 2016). The calculated molecular properties of phytocompounds and PROTOX results indicated that the carcinogenicity and oral toxicity (LD_{50}) parameters of compounds theaflavin and curcumin compounds might be a more promising lead candidate than ECG. In summary, the present study provides potential inhibitory effects of theaflavin and curcumin against deposition of adiopose tissues causing obesity. It also provides an overview of the structural interactions between phytocompounds and C/EBPβ and PPARγ, in which theaflavin, epigallocatechin-3-gallate (EGCG) and curcumin may be useful in the identification of other inhibitors against these proteins. Theaflavine extracted from *Camellia sinensis* plant, the previous studies showed theaflavine shown inhibitory effects in fat digestion and absorption (Glisan *et al.*, 2017). Curcumin polyphenol compound extracted from turmeric, previous studies shown that in Wnt/β catenin pathway curcumin suppressed adipocytes tissues and inhibit the activity of C/EBPβ, C/EBPβ and PPARγ and fatty acid synthase (FAS) in adipocytes (Aggarwal, 2010). Hence, the conducted computational screening of phytochemicals will be crucial for experimental biologists for the future development of an effective anti-adipogenesis drug molecule against obesity.

4. Conclusion

In the present study, *in silico* screening of active compounds was carried out by, using molecular docking approach and analyze against PPARγ and C/EBPβ proteins. Among all compounds, the most effective compounds are theaflavine (ZINC33963966) and curcumin (ZINC100067274) which have shown highest binding affinity as -6.2 kcal/mol and-4.6 kcal/mol and they also possess good ADMET property score as well. Docking interaction analysis also identifies few similar active site residues in PPARγ and C/EBPβ which inhibit adipogenesis. Based on their binding affinities in docking and ADMET properties, both ZINC33963966 and ZINC100067274 compounds inhibit the adpogenesis activity of both PPARγ and C/EBPβ proteins and could be used as potential anti-adipogenesis drug molecules. Observations are made in this study might be extended an assuring platform for developing *in silico* approach to identify new compounds which are capable of inhibiting adipogenesis.

Table 2: Top five compounds binding affinity and RMSD value of upper as well as lower bonds with C/EBPβ and PPARγ

Protein	Compounds	Binding affinity	RMSD lower bond	RMSD upper bond
2E43	Theaflavine (ZINC33963966)	-6.2	0.79	6.57
	Curcumin (ZINC100067274)	-5.8	0.82	1.22
	Apigenin (ZINC11726230)	-5.6	1.72	2.72
	EpigallocatechinGallate (ZINC3870412)	-4.9	0.048	2.04
	Anonain (ZINC898396)	-4.6	1.23	2.91
4Y29	Anonain (ZINC898396)	-6.9	1.50	2.92
	Theaflavine (ZINC33963966)	-6.6	1.7	4.5
	Curcumin (ZINC100067274)	-6.2	0.42	1.61
	Epicatechin (ZINC119983)	-6.4	1.36	2.43
	Resveratol (ZINC000100067274)	-5.7	0.94	1.9

Table 3: Contains calculated ADMET properties of compounds which includes molocular weight, hydrogen bond donar, hydrogen bond acceptor, log p value, topological polar surface analysis value, % human oral absorption and LD_{50} value for toxicity check of compounds

In silico ADMET screening for phytocompounds								
Compounds	Mol.W.	HBD	HBA	nRB	logP	TPSA	% Human oral absorption	LD_{50}
Epigallocatechin Gallate (ZINC3870412)	458.375	8	11	4	2.25	197.36	100%	1000 mg/kg
Theaflavine (ZINC33963966)	564.49	3	9	2	2.213	217.59	69.26%	2500 mg/kg
Apigenin (ZINC11726230)	270.24	2	3	1	2.577	90.89	70.97%	2500 mg/kg
Maysin (ZINC59066221)	576.51	3	8	4	-0.28	213.81	68.07%	5000 mg/kg
Anonain (ZINC898396)	265.31	1	2	0	2.825	30.50	70.97%	450 mg/kg
Curcumin (ZINC100067274)	368.385	2	6	7	3.05	96.22	64.05%	4000 mg/kg
Doxycycline (ZINC16052277)	444.44	4	8	2	0.702	182.60	68.07%	2240 mg/kg
Procynidine (ZINC4098620)	578.52	3	10	3	2.99	202.75	69.26%	1000 mg/kg
Xylopine (ZINC1565063)	295.33	1	3	1	2.834	39.73	70.97%	450 mg/kg
Taxifolin (ZINC105086)	304.25	5	7	1	1.186	127.44	100%	2000 mg/kg
Catechin (ZINC119983)	290.27	5	6	1	1.546	110.37	100%	10000 mg/kg
Flavonol (ZINC57675)	238.24	1	3	1	3.166	50.44	69.26%	2500 mg/kg
Dihydroflavonol (ZINC95004884)	240.25	2	3	1	2.364	46.53	69.26%	2647 mg/kg
Delphinidin (ZINC3777403)	303.24	5	7	2	2.614	132.54	69.26%	5000 mg/kg
Epicatechin (ZINC119988)	288.25	4	6	1	2.216	110.37	72.9%	6 mg/kg
Loliolide (ZINC1565391)	196.24	1	3	2	1.409	46.53	70.97%	34 mg/kg

Acknowledgements

We would like to put on record our sincere thanks to all staff members of Bioinformatics Infrastructure Centre at Zoology Department, D.G. P.G. College, Kanpur. We also thank our Centre authorities for providing all necessary facilities to carry out this work.

Conflict of interest

We declare that we have no conflict of interest.

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