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In Silico And In Vivo Evaluation Of 5-Ht1b Receptor Agonist In High Fat Diet-Induced Obese Rats

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ABSTRACT

Aim of the study:

To find out 5HT1B receptor agonist with better binding affinity by molecular docking method for anti-obesity activity in rat model of high fat diet induced obesity.

Materials and Methods:

Molecular docking is a computational method employed to predict the binding mode of a small molecule, such as a ligand or a drug, to a protein or enzyme. In present study, 5 HT1B receptor agonists have been reported to reduce hunger, food intake. Therefore molecular docking of Dihydroergotamine (protein bound), CP94253 (agonist), atorvastatin (standard drug), eletriptan (test drug), almotriptan, rizatriptan, frovatriptan and naratriptan was done by selecting UCSF-Chimera© (version 1.13) software.

Results:

The docking outcomes showed better binding affinity of the atorvastatin and eletriptanthan other 5HT1Breceptor agonists for antiobesity activity by utilizing high fat diet-induced obesity model.

Keywords: *5HT1 Breceptor agonist, Molecular docking, Eletriptan,obesity,Atorvastatin.*

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1. INTRODUCTION

Molecular docking aims to find Predominant orientation of ligands when they bind to protein with known three-dimensional structures.(1)It allows researchers to screen large libraries of compounds quickly, identifying potential candidates for further testing. (2)This approach simulates actual docking process by computing interaction energies among ligand and protein allowing for a more detailed understanding of binding affinities.(3)Understanding drug-receptor interaction using molecular docking has been a common practice in contemporary drug design. To anticipate the affinity and activity of small molecules, molecular docking is employed to predict binding orientation of small molecule drug candidates to their target protein. It also yields valuable information regarding drug-receptor interactions.

For the treatment of obesity, several key agents have been created. (5, 6) The biogenic amine function was altered by these substances to induce their effects. According to research (4,7), the 5-HT1B receptor has a complementary role in the regulation of eating. By blocking neuronal activity, activation of this receptor on arcuate NPY/Agrp cells derepresses the inhibitory GABAergic transmission from NPY/Agrpneurones to nearby POMC (pro-opiomelanocotin) neurones. POMC cells are thus indirectly stimulated by 5-HT1B activation, which supplements the 5-HT2C receptor's direct activation of these same neurones.A combined 5-HT2C/1B receptor agonist should strongly promote catabolic melanocortin pathways in the hypothalamus, according to the clinical implications of these findings. This action would occur downstream of at least some of the levels at which leptin resistance associated with obesity arises.

Experimental:

Material Methods:

We employed molecular docking to better understand the molecular mechanism. “UCSF-Chimera© (version 1.13)” is a software program employed for molecular docking calculations and protein target preparation for docking. After docking, protein-ligand complexes were produced with “PyMol Molecular Graphic System version 2.4.1”, and protein-ligand complexes as well as interactions were visualized in two dimensions employing Discovery Studio 2016. Since 5HT-1B receptor agonists were shown to decrease appetite and food intake, they are a significant factor in the decline of obesity [1, 8]. Thus, using the resolution 2.80A° criteria, 5HT-1B receptor’s 3D structurehave been obtained from the protein data bank (PDB ID: 4IAQ). The Dock preparation device of the “UCSF-Chimera© (version 1.13)” program has been employed to select and clean protein receptors from hetero atoms after importing the PDBs into Chimera. The UCSF-Chimera software's AMBER force field was applied to minimize the receptors, with conjugated gradient set to 10 & steepest gradient100. To confirm the accuracy and reliability of the docking results, the docking methodology was validated. The goal of the current in silico investigations is to accurately replicate binding model along with co-crystallized ligand’s molecular interaction of experimentally crystallized protein structures.

As a result, the natural ligands of all X-ray proteins have been separated fromprotein to make it ready for docking using UCSF-Chimera. The Auto Dock Vina module was then used to dock the ligands back into receptors' active regions [2, 9]. ByPyMOL molecular visualizer, docked complexes have been aligned with Xrayed resolved crystals of proteins that contained the co-crystallized ligand to generate root mean square deviation (RMSD) value. Except for the grid box, which was modified based on each protein molecule's active sites; all other parameters remained at their default settings. The receptor became stiff because all of the ligand's links were free to rotate. Ten configurations were produced for every protein-ligand combination after the molecular docking studies were finished. The ideal docking stance was thought to be the one with the lowest BE (binding energy, kcal/mol) and RMSD. In order to obtain more reliable and precise results, an exhaustiveness of Ten was chosen for docking as well as number of modes was set at ten throughout this in silico experiment. Py MOL and Discovery Studio 2016 were then used to construct, display, and analyze the ligand-protein interaction.

In silico molecular docking studies:

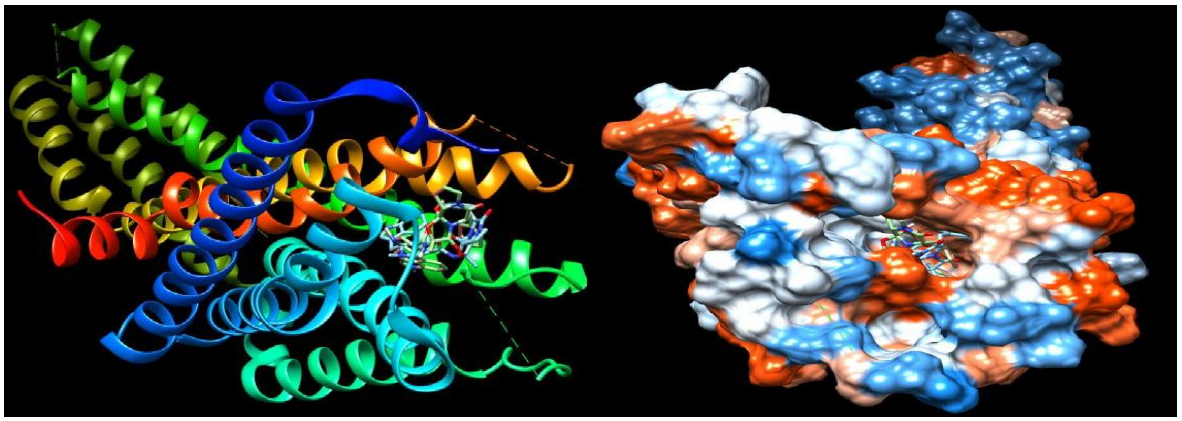

Figure1.Optimisation for docking of bound ligand(dihydroergotamine)with5HT1B receptor protein (PDB:4IAQ).

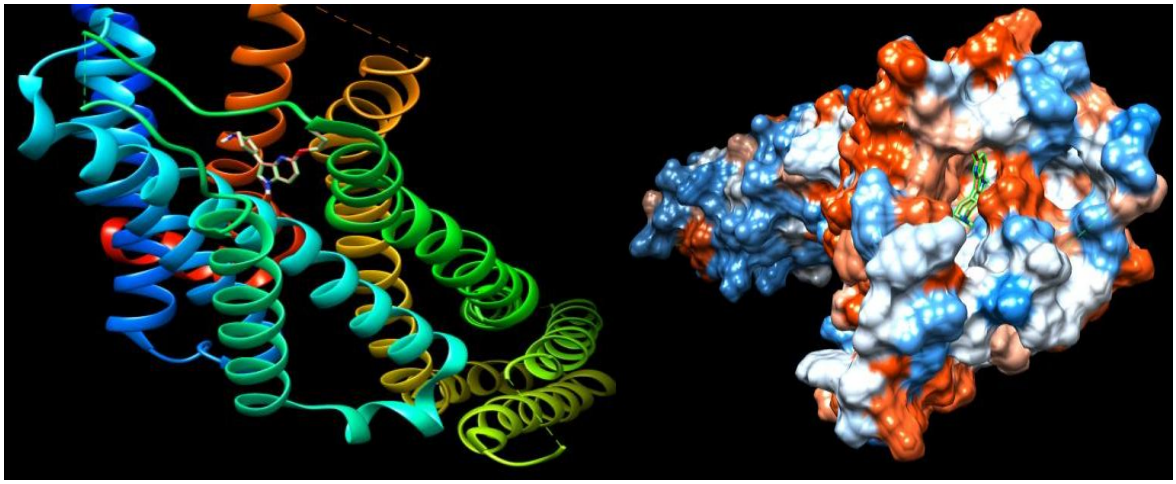

Figure2.Docking of CP94253 with 5HT1B receptor protein.

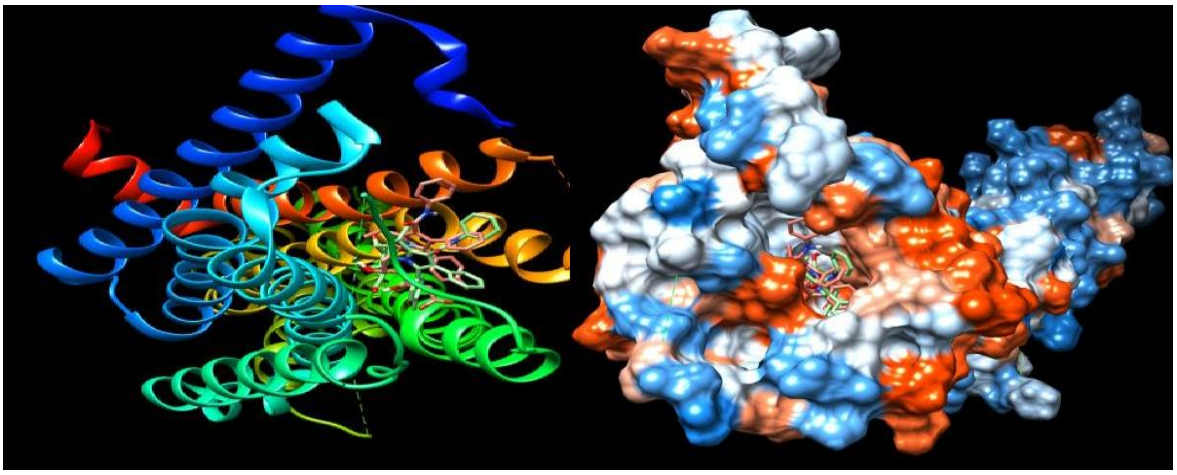

Figure3.Docking of atorvastatin with 5HT1Breceptor protein.

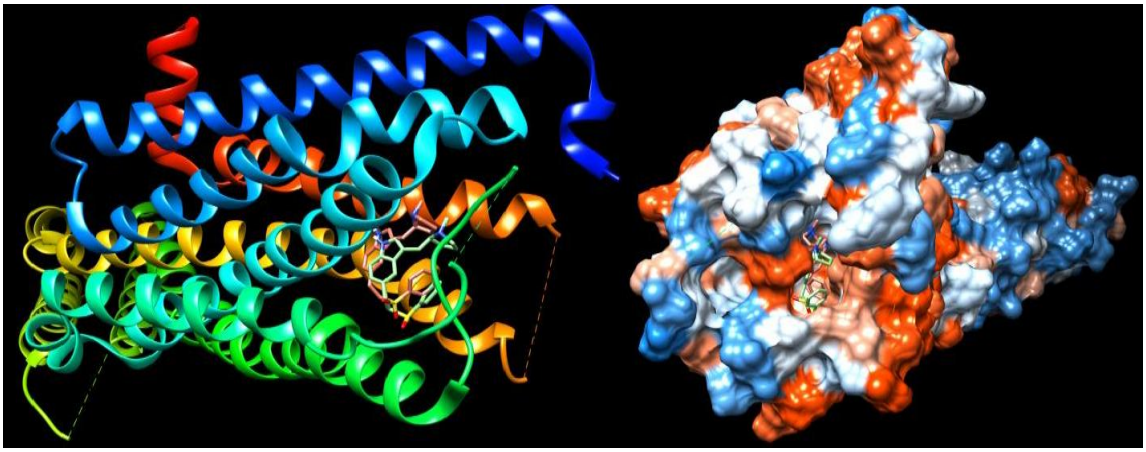

Figure4.Docking of Eletriptan with5HT1B receptor protein.

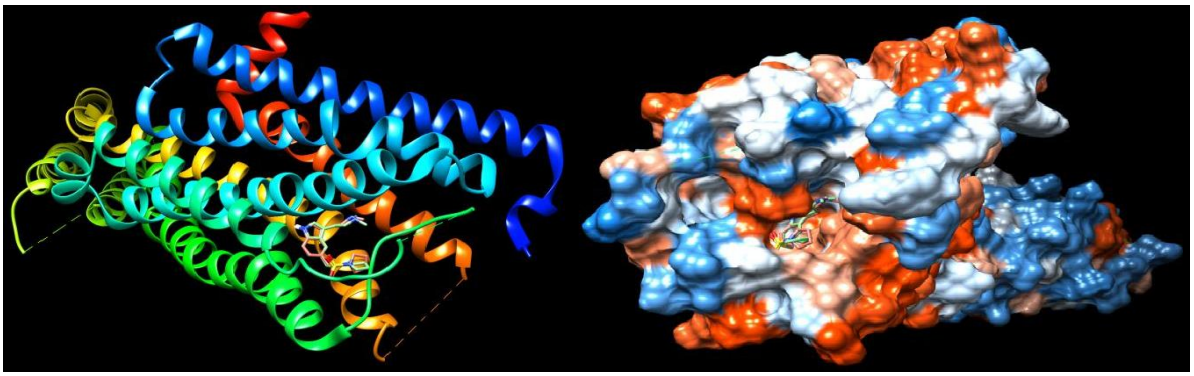

Figure5.Docking of Almotriptan with 5HT1Breceptor protein

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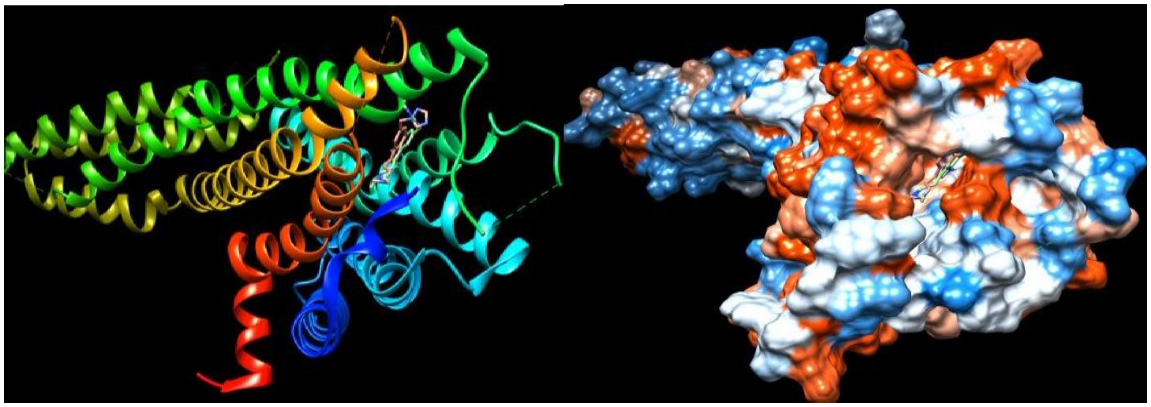

Figure6.Docking of Rizatriptan with5HT1Breceptor protein.

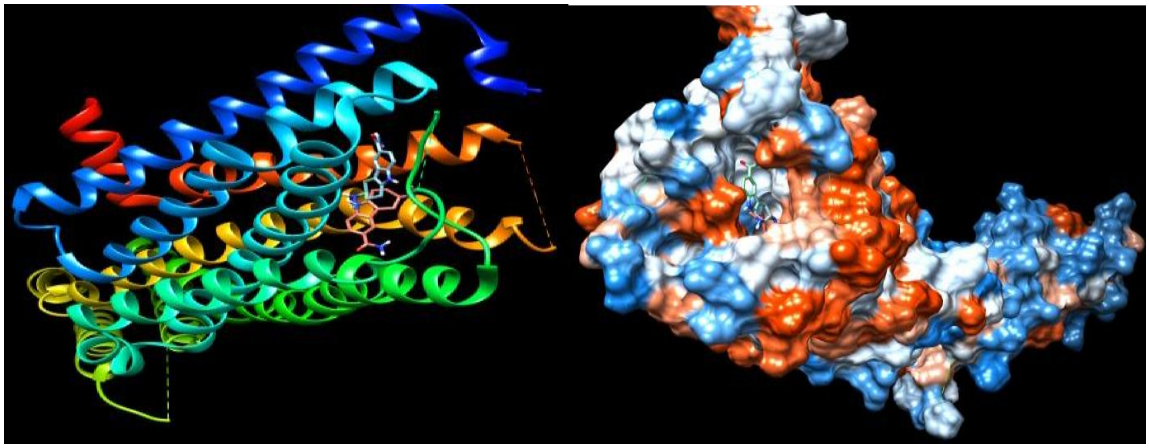

Figure7.Docking of Frovatriptan with5HT1Breceptor protein.

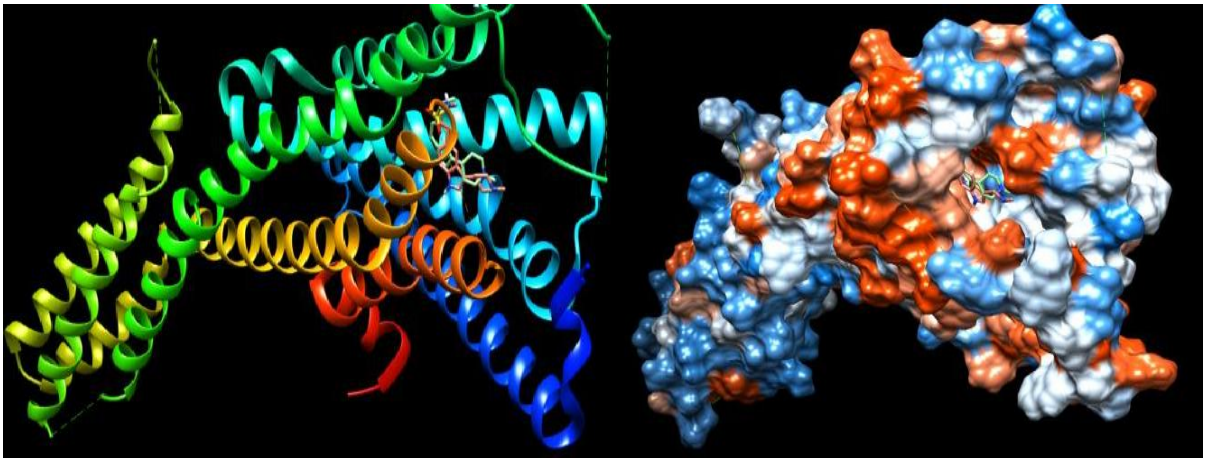

Figure8.Docking of Naratriptan with5HT1Breceptor protein.

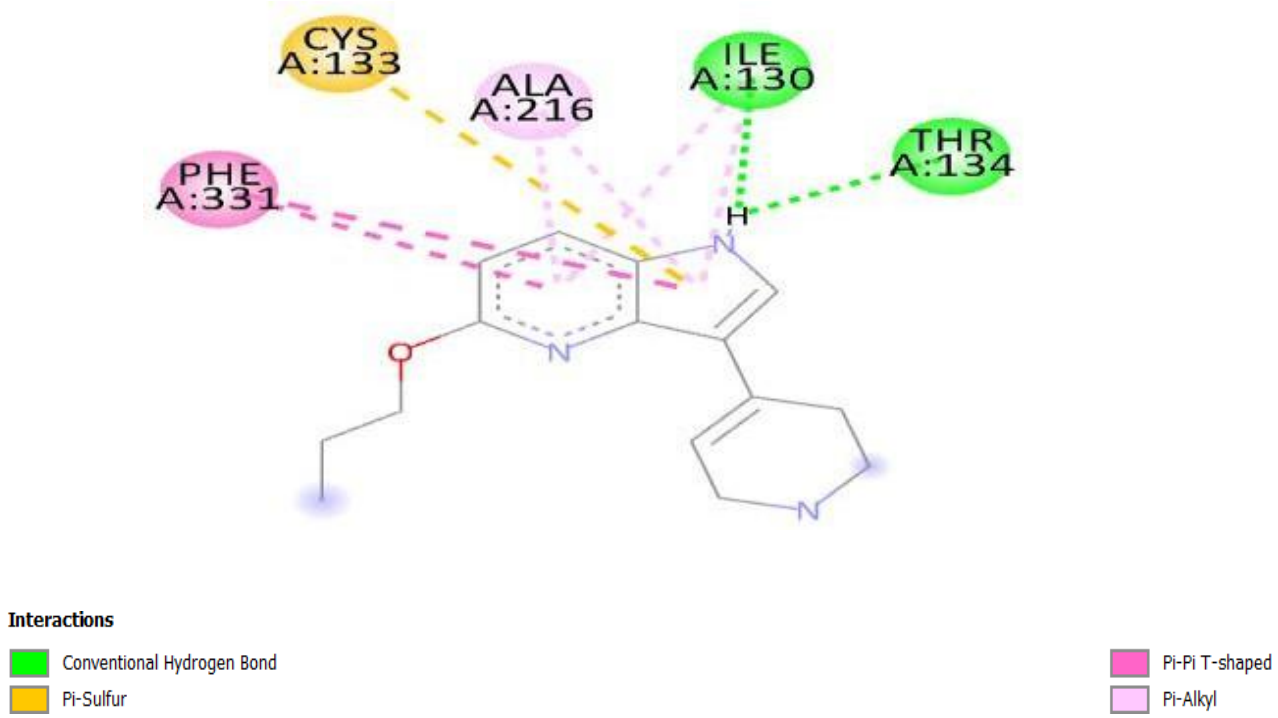

Figure9. Molecular interactions of CP94253with5HT1Breceptor protein

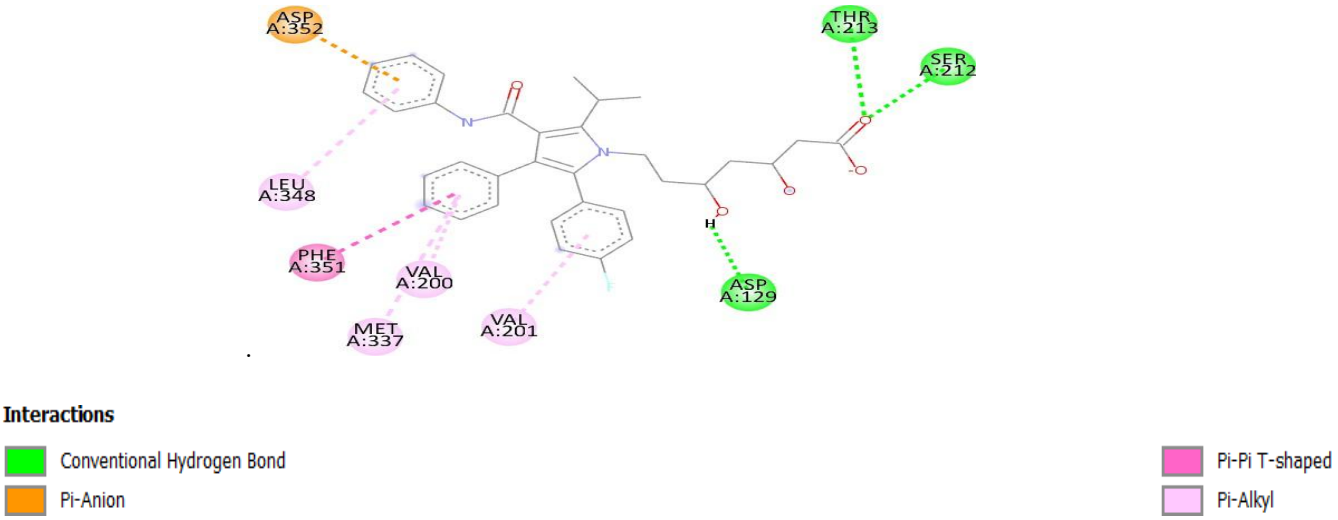

Figure10.Molecular interactions of atorvastatinwith5HT1B receptor protein.

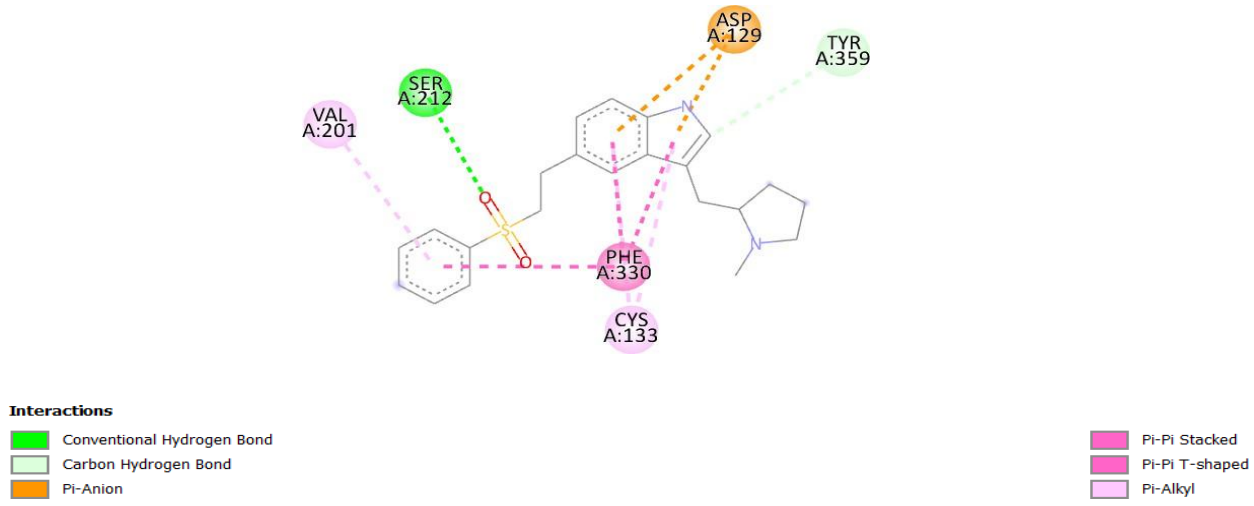

Figure11.Molecular interactions of Eletriptan with 5HT1B receptor protein.

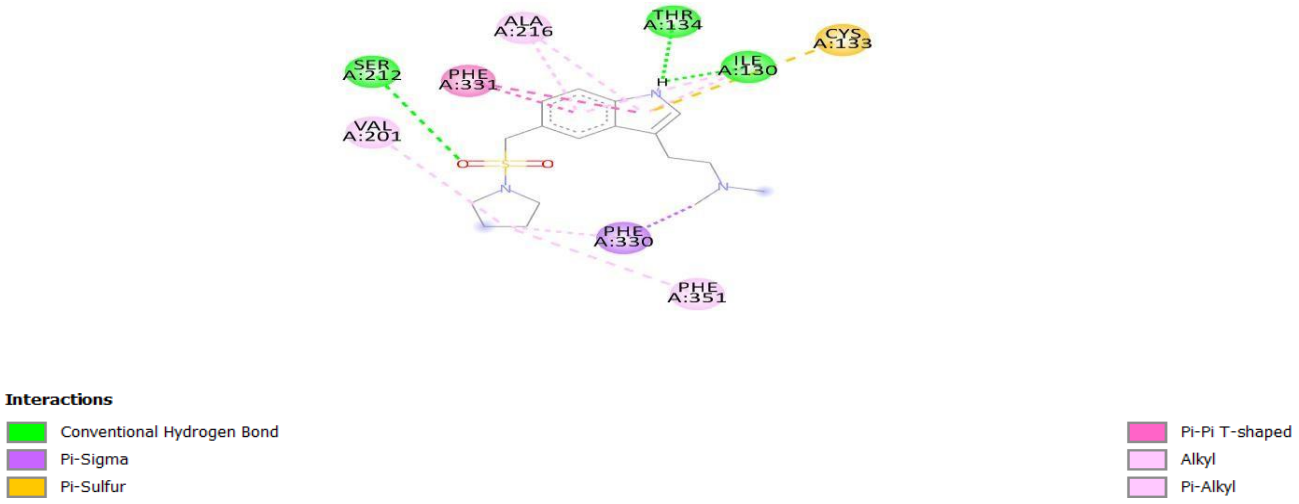

Figure12.Molecular interactions of Almotriptan with 5HT1B receptor protein.

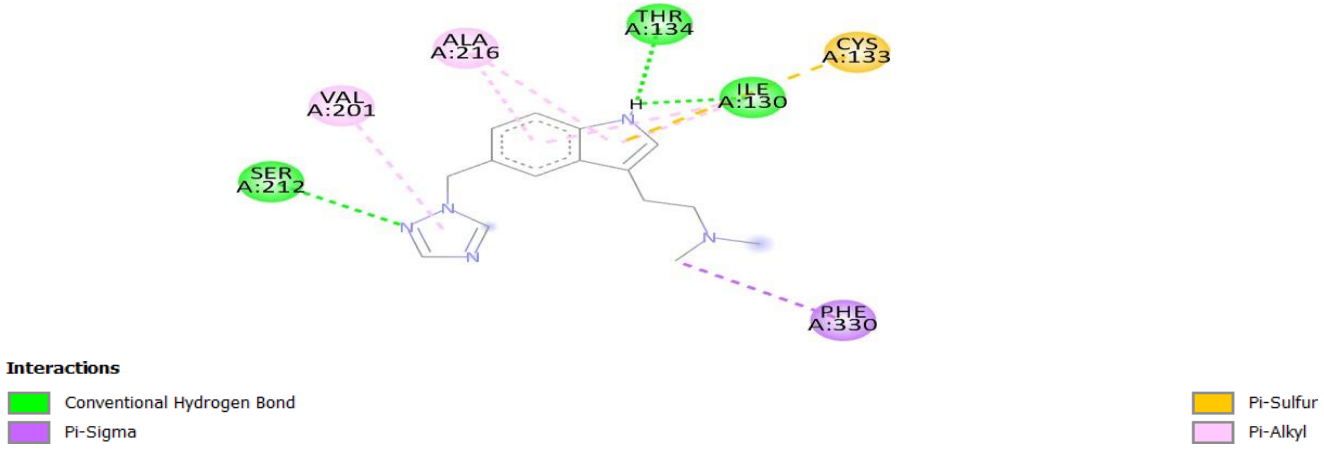

Figure13.Molecular interactions of Rizatriptanwith5HT1Breceptor protein.

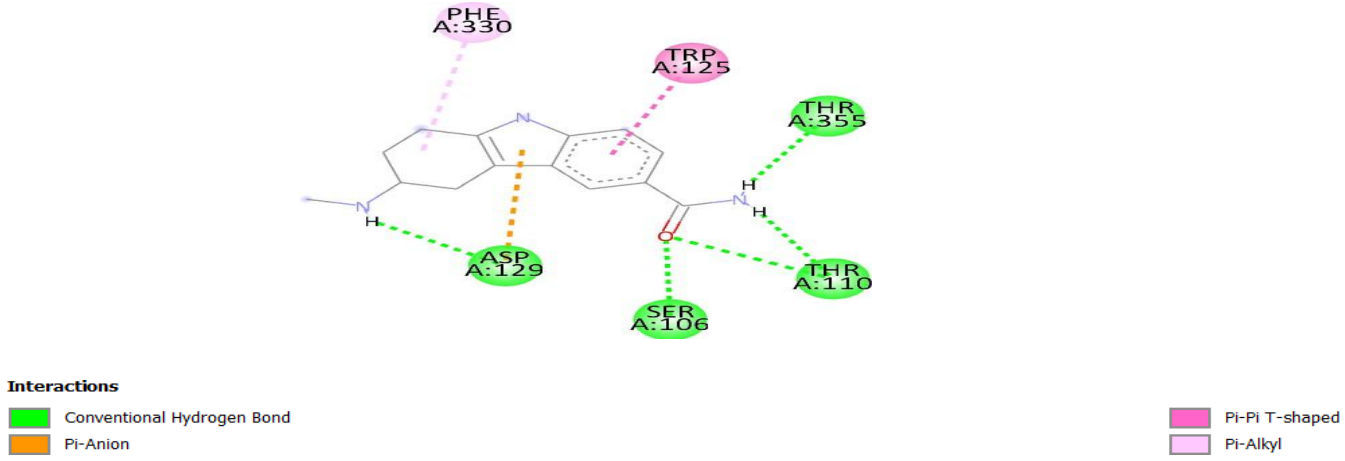

Figure14. Molecular interactions of Frovatriptan with 5HT1B receptor protein.

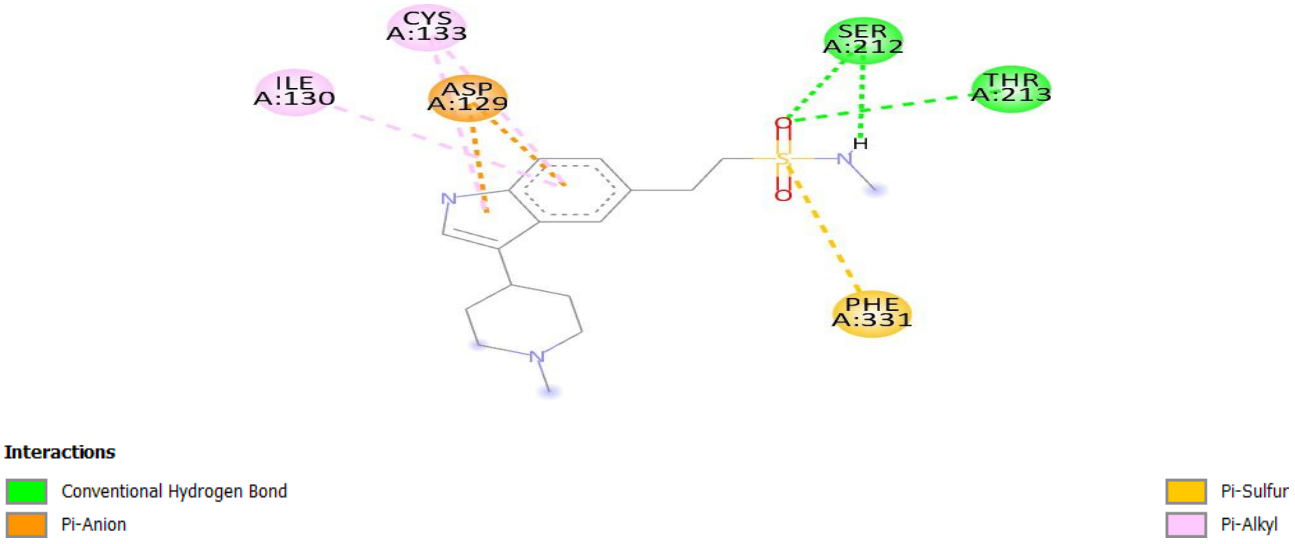

Figure15.Molecular interactions of Naratriptan with 5HT1B receptor protein.

2. RESULTS AND DISCUSSIONS:

Docking studies: The comparative *in silico* docking studies were performed on the synthesized molecules and bound ligand (dihydroergotamine) on 5HT1B receptor protein(**Fig. 1-15**), which was evaluated in obesity as 5HT1B agonists.Dihydroergotamine(protein bound), CP94253 (agonist), atorvastatin(standard drug), Eletriptan(test drug),almotriptan,rizatriptin, frovatriptan and naratriptan exhibited a docking score of -14.2, -8.6, -10.2, -9.5, -8.7, -8.0, -8.7 and -8.8Kcal/mol respectively with Chimera USF software at zero deviation pose. A molecule's binding affinity is determined by its negative docking score; a higher negative score indicates a higher binding affinity. According to the docking data, atorvastatin and eletriptan had higher binding affinities than other 5HT receptor agonists **(Table 1).**All themolecules werefound to possess binding affinity towards chains receptor protein and showed different types of molecular interactions with 5HT1B (**Fig. 9-15**). Atorvastatin and Eletriptan were found to form H bonding interactions with Thr213, Ser212, and Asp129 and Ser 212 amino acids of receptor. The hydrophobic interactions were observed with Leu348, Phe351, Val200, Met337, and Val201 in atorvastatin and with Val201, Phe330 and Cys133 in Eletriptan at the binding site of the protein as shown in **Fig.10 and 11**. These interactions contributed significantly to the stability of the ligand-receptor complex.Based on the in silico results, Atorvastatin and Eletriptanwas found to possess the significant binding affinity/docking score on selected 5HT1B receptor protein and may act as agonists to reduce obesity and may

beused as an anti – obesity agents.

Table1: Binding affinity/Dockingscoreofvarious5-HT1B agonists.

SNO.	DOCKSCORES	5-HT1BAGONISTS
1.	-14.2kcal/mol	Dihydroergotamine
2.	-8.6kcal/mol	CP94253
3.	-10.2kcal/mol	Atorvastatin
4.	-9.5kcal/mol	Eletriptan
5.	-8.7kcal/mol	Almotriptan
6.	-8.0kcal/mol	Rizatriptan
7.	-8.7kcal/mol	Frovatriptan
8.	-8.8kcal/mol	Naratriptan

High Fat Diet-induced Obesity:

Procedure: To produce experimental obesity, rats have been fed a high-fat diet(HFD) consisting of 365g of powdered normal chow(NC), 310g of lard, 250g of casein, 250g of cholesterol, 60g of vitamin mix along with mineral mix, 03g of dl-methionine, 01g of yeast powder, and 01g of sodium chloride(NaCl) to create a 1.0 kg diet (10). Whereas the typical chow has 3.80 kcal/gm, HFDhas 5.33kcal/gm. In contrast to conventional chow, which offers 65% of energy as carbohydrates, 20percent as protein, as well as 4% as fat, this diet causes rats to become obese by providing 68percent energy as carbohydrates, 20percent as protein, plus 12percent as fat (11).

Animal Treatment: The Institute's animal facility (G H G Khalsa College of Pharmacy) provided male Wistar rats that were 7-8 weeks old. The animals were kept in cages made of polypropylene, with two rats per cage, and were kept at a controlled ambient temperature of 25±2°C with a light and dark cycle of 12:12hrs. Research has been conductedby the rules of the Govt. of India's Committee for Control and Supervision of Experiments on Animals (CPCSEA), and prior authorization has been obtained from institutional animal ethics committee (approvedno.GHG/2024/IAEC/P01/M05). For eight weeks, the animals were fed either a HFDor NC.The animals were split up into groups, 6 animals per group. Animals fed NC were assigned to group 1 and kept on the same diet for an additional eight weeks.

Animals fed anHFD were randomly assigned to six groups (groups 2–6) based on their body weight, and these groups were kept on the diet for an additional eight weeks. Group 2 was designated as the HFD control and received no therapy. Group 3 was designated as vehicle control and administered DMSO 1mlkg-1 day-1, i.p. (12). Group 4 was designated as the standard control and administered atorvastatin five mg/kg day-1, p.o. (13) to them. Eletriptan5mg/kg day-1,.p.o., was administered to Group 5 (14).Every day, the animals were examined, and they all had unrestricted access to water. Body weight as well as food consumption were recorded twice a week.

After the allotted time had passed, the animals had been slaughtered by cervical dislocation, and blood had been drawn for some biochemical markers using a retro-orbital puncture performed under light ether anaesthesia. On same day that blood has been drawn into tubes, the serum was separated and examined the outcomes. For histological examination, the white adipose tissue(WAT) fromepididymis, mesenterium, as well as retroperitoneum was weighed, dissected, washed, as well as preserved in a 10percent buffered formalin solution. After experiment, Lee index (16), which measures obesity, was computed as follows: (Body Weightingms) $1/3^{rd}$(ano-nasal length[cm]).

Histological Analysis and Morphometry: After being preserved in 10% formalin, the epididymal adipose tissue was paraffin-embedded. On microscope slides, tissue sections (10µm) were cut and adhered. They were allowed to air dry before being stained with hematoxylin as well as eosin and is captured on 100X magnification camera. To measure adipocyte size, at least 2 fields/slice as well as6slices/fat mass have been examined.

Measurements: Commercially available kits were used to measure the concentrations of serum glucose, triglycerides, total cholesterol(TC), as well as HDL cholesterol.

Statistical Analysis: The mean ± standard deviation (STDEV) is used to express all values. Using the Graph Pad Prism 4 program, a one-way ANOVA&Tukey's multiple range tests have been used to estimate the significantvariationamong means of the different groups. p-value<0.05 hasbeen estimated statistically significant.

3. RESULTS:

Effect of Eletriptan and SB-224289 on body weight, fat depots weight and lee index in further eight-weekhigh-fat diet treated obese rats:

Rats on a high-calorie diet for sixteen weeks had body weight as well as total fat content that were significantly higher than those of NC(Normal Control) rats of the same age. In addition, these animals' Lee index was significantly higher than that of control rats. However, the weight of the body, fat pad's weight, as well as Lee index were all reduced after nine to sixteen weeks of therapy with Eletriptan (5mg/kg). Additionally, administering SB-224289 (5mg/kg) from nine to sixteen weeks did not reduce body weight, obesity index, or fat pad weight caused by a high-calorie diet. When atorvastatin (5mg/kg) was administered to obese rats between weeks nine and sixteen, the weight of their fat pads, lee index, and enlarged body weight drastically decreased.

Effect of Eletriptan and SB-224289 on lipid profile in furthereight-weekhigh-fatdiet-treated obese rats: Rats on a high-calorie diet for 16 weeks showed elevated levels of triglycerides, glucose, as well asTC compared to NC rats ofsame age.

Eletriptan (5mg/kg) treatment, however, reduced hyperglycemia, hypertriglyceridemia, and hypercholesterolemia brought on by a high-calorie diet from nine to sixteen weeks. This treatment increased HDL. Furthermore, administering SB-224289 (5mg/kg) from 9-16weeks did not reduce hyperglycemia, hypertriglyceridemia, or hypercholesterolemia brought on by a high-calorie diet. The levels of glucose, triglycerides, as well asTC in obese rats were significantly reduced when atorvastatin (5mg/kg)—a common treatment for obesity—was administered to them between weeks nine and sixteen (Table 2).

Effect of Eletriptan and SB-224289 on adipocyte size in further eight-weekhigh-fat diet-treated obese rats: Microscopic analysis of adipose tissue showed that rats fed a high-calorie diet for eight weeks had adipose cells that were considerably larger than those fed a regular diet.In comparison to rats fed a high-calorie diet, rats treated with Eletriptan (5mg/kg) and Atorvastatin (5mg/kg) showed a discernible reduction in fat cell size. In contrast to HFD rats, SB-224289 (5mg/kg) did not change the size of the adipose tissue.

3.1.4. Effect of Eletriptan and SB-224289 on intake(Kcal) of daily feed in further eight-weekhighfatdietreated obese rats: Compared to rats fed regular chow, a sharp increase in feed consumption (Kcal) has been observed in the high-calorie diet model. In comparison to rats fed anHFD, the usual control in this study, atorvastatin (5mg/kg), dramatically reduces feed consumption. From nine to sixteen weeks, the administration of Eletriptan (5mg/kg) resulted in a considerable reduction in food intake. However, compared to HFD rats, the treatment of SB-224289 (5mg/kg) enhanced food intake from 9 to 16 weeks (Table 2).

Table 2: Effect of 5-HT1B receptor agonist Eletriptan (5mg/kg) and 5-HT1B receptor antagonist SB224289(5mg/kg) on various parameters in 16-week high fat diet treated.

obese rats.

Parameters	NC	OHFD-C	Vehicle Control (10%v/v DMSO, 1ml/kg)	Atorvastatin (5mg/kg,p.o)	Eletriptan (5mg/kg,p.o)	SB-224289 (5mg/kg,p.o)
Initial body wt(g)	221 ± 8.3	230±6.1	231± 9.7	236±10	229±1.0	232±1.1
Finalbodywt (g)	272 ± 16.8	398 ± 15.2[a]	396± 12[a]	299±11.6[b]	319±7.4[b]	399±1.1[b]
Leeindex	347 ± 8.1	388 ± 15.7[a]	393.18± 13[a]	360±12.4[b]	354±4.2[b]	390±1.2[b]
Feed intake Kcalday^{-}	92± 2.1	112 ± 7.6[a]	111 ± 10.2[a]	86±12[b]	97±6.0[b]	115 ±3.1[b]

Epididymal fat	1.72 ± 0.21	5.22 ± 0.91[a]	5.24 ±0.8[a]	1.80±0.30[b]	1.87±0.1[b]	5.5±0.1[b]
Retroperitonealfat	1.50 ± 0.27	5.6 ± 0.81[a]	5.5 ± 0.73[a]	1.86±0.20[b]	1.92±0.1[b]	5.8±0.7[b]
Mesentricfat	2.6 ± 0.17	5.4 ± 0.92[a]	5.70 ± 0.73[a]	2.5±0.30[b]	2.54±0.3[b]	5.9±0.12[b]
Glucose(mg/dL)	95± 5.1	151.5 ± 5.41[a]	147.6 ± 10.2[a]	96.1±4.01[b]	97 ±2.1[b]	154 ±0.5[b]
TG(mgdL^{-1})	65.7 ± 4.2	145.5± 10.61[a]	144.2 ±10.1[a]	71.1±5.12[b]	72 .1±1.8[b]	147.1±2.1[b]
TC(mgdL^{-1})	94.9 ±4.0	162 ±11.61[a]	161.8 ± 11.8[a]	94.2±4.19[b]	95.6±1.1[b]	165±1.13[b]
LDL(mg/dL)	48.7 ± 4.7	110.2 ±12.50[a]	110.8 ±10.5[a]	49±7.01[b]	50 ±1.2[b]	109.1±3.0[b]
VLDL(mg/dL)	13.1±0.87	28.3±2.11[a]	28.1±2[a]	14.1±1.03[b]	14.71±0.5[b]	29.5±1.0[b]
HDL(mg dL^{-1})	32.4±2.10	23.1±2.90[a]	22.5±1.45[a]	31.1±2.45[b]	31.4±1.1[b]	23 ±1.7[b]

Data are presented as STDEV (Mean±Standard deviation), assessed with 1-way ANOVA with Tukey-Kramer method, n=6. TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoproteins,VLDL:Very low density lipoproteins,HDL: High-density lipoproteins. [a] =p less than 0.05versus NormalControl(NC), [b]=p lessthan0.05 versus Obese high-fat diet control (OHFD-C).

4. DISCUSSION:

Before treatment started, absence of significant difference among the animals' body weights across various treatment groups; nevertheless, when compared to age-matched normal control rats, the animals' body weight increased significantly ($p < 0.05$) after receiving HFD for 8 weeks (Table 2).

Impact of Different Pharmacological Treatments on Lee Index, Adipose Tissue Weight, and Body Weight: Following HFD feeding of 16week, the body weight as well as total fat content of obese rats were considerably higher than those of age-matched normal control rats. Rats who were obese had a much higher Lee index than rats who were not obese.

However, HFD-induced increases in body weight, adipose pad weight, as well as lee index were mitigated by treatment with Eletriptan from 9–16 weeks.

Adipose pad weight, Lee index, and body weight increase were significantly reduced in obese rats given the conventional medication atorvastatin for 9–16 weeks.

The current study, however, demonstrates that SB-224289, a specific 5-HT1B antagonist, did not reduce body weight, obesity index, or fat pad weight in response to an HFD. When atorvastatin (5 mg/kg), a common treatment for obesity, was administered to obese rats between weeks nine and sixteen, the weight of their fat pads, lee index, and enlarged body weight drastically decreased (17).

5. CONCLUSION:

Eletriptan and atorvastatin were discovered to have a considerable docking score and binding affinity on a specific 5HT1B receptor protein, suggesting that they could function as agonists of this receptor to lower obesity. The 5-HT1B receptor

may have a part in controlling body weight based on the findings of in silico research and anti-obesity action. Eletriptan reduced the rise in visceral adipose pad weights, body weight, serum TC, lee index, TG, as well as glucose levels brought on by anHFD. According to the current findings, a 5-HT1B receptor agonist may be a novel treatment option for obesity. These results provide

compelling evidence that the 5-HT1B receptor has a major part in obesity. Conversely, HFD-induced body weight, obesity index, and fat pad weight were not reduced by SB-224289, a specific 5-HT1B antagonist.

From the explanation above, it can be inferred that brain neurotransmitters play a part in controlling body weight. The different parameters of experimental obesity are changed when the 5-HT1B receptor is modulated by its receptor agonist or antagonist.Eletriptan decreased the rise in visceral adipose pad weights,TG, body weight, serum TC, lee index, as well as glucose levels brought on by HFD. According to the current findings, a 5-HT1B receptor agonist might be a novel treatment option for obesity.

Ethical Approval:

The research was conducted by the rules of the Government of India's Committee for Control and Supervision of Experiments with Animals (CPCSEA), and prior authorization was obtained from the institutional animal ethics committee (approvedno. GHG/2024/IAEC/P01/M05)..

REFERENCES

[1] Morris GM, Wilby ML. Molecular docking. Methods Molecular Biology.2008; 443:365-82.

[2] PaggiJM,PanditAandDrorRO.TheArtandScienceofMolecularDocking.

[3] Torres PHM,Sodero ACR,JofilyP, Silva-Jr FP. KeyTopics inMolecular Docking for Drug Design.International Journal of Molecular Sciences. 2019 Sep 15; 20(18):4574.

[4] Bray GA, Greenway FL. Pharmacological, treatment of the overweight patient. PharmacologyReviews. 2007; 59:151–84.

[5] Clapham JC, Arch JRS, Tadayyon M. Anti-obesity drugs: a criticalreview of current therapies and future opportunities. Pharmacology & Therapeutics. 2001; 89: 81–121.

[6] CliftonPG, Kennett GA. Monoamine receptorsin the regulationoffeeding behaviour and energy balance. CNS &Neurological Disorders- Drug Targets 2006; 5: 293–312.

[7] McIntyre AM. Burden of illness review of obesity are the true costs realized.Journal of Royal Society of Health. 1998; 118: 76-84.

[8] Bouwknecht JA, vander GugtenJ,HijzenTH,MaesRA, HenR, Olivier B. Male and female 5-HT1B receptor knockout mice have higher body weights than wildtypes. Physiology &behavior. 2001 Nov 12; 74(4-5):507-16.

[9] Umar HI, SirajB, Ajayi A, JimohTO, Chukwuemeka PO. Molecular docking studies of some selected gallic acid derivatives against five non-structural proteins of novel coronavirus. Journal of Genetic Engineering and Biotechnology. 2021 Dec1;19(1):16.

[10] Qian, C., Zhu, C., Jiang, C. W., Yu, & Zhang, F. (2015). High-fat diet/low-dose streptozotocin-induced type 2 diabetes inrats impactsosteogenesis and Wnt signaling in bone marrow stromal cells. PLoS ONE, 10, 1-15.

[11] Malik, Z., & Sharma, P. L. (2011). An ethanolic extract from licorice (Glycyrrhiza glabra) exhibits anti-obesity effects by decreasing dietary fat absorption in a high-fat diet-induced obesity rat model. International Journal of Pharmaceutical Sciences and Research, 2, 3010-3018.

[12] Chung, S., Ivy, G. O., & Reid, S. G. (2006). GABA-mediated neurotransmission in thenucleusofthesolitarytractaltersresting ventilationfollowingexposuretochronic hypoxia in conscious rats. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 291, R1449–R1456.

[13] Patricia, G. S., & Georgina, R. L. A. (2006). Convulsant bicuculline modifies CNS muscarinic receptor affinity. BMC Neuroscience, 7, 1-8.

[14] Garabadu, D., & Krishnamurthy, S. (2014). Diazepam potentiates the antidiabetic, antistress, and anxiolytic activities of metformin in type-2 diabetes mellitus with co- occurring stress in experimental animals. BioMed Research International, 1-15.

[15] Verma, A., Goyal, A., Kaur, R., Kamboj, A., & Jain, U. K. (2016). Beneficial effect of vitamin D on high-fat diet-induced obesity in Wistar rats. Asian Journal of Pharmaceutical and Clinical Research, 9, 337-340.

[16] Selkirk,J.V., Scott,C., Ho,M., Burton,M.J., Watson,J., Gaster,L.M.,Collin,L., Jones,B.J., DN Middlemiss,D.N., Price G.W.(1998).SB-224289--a novel selective (human) 5-HT1B receptor antagonist with negative intrinsic activity. British Journal Pharmacology, 1,202.