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IN SILICO ANTIUROLITHIATIC SCREENING OF *Luffa acutangula* (L) ROXB ISOLATED CONSTITUENTS

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ABSTRACT

The bioactive compounds from ethanloic extract of *Luffa acutangula* L using gas chromatography–mass spectrometry and their inhibition potential against the enzyme 5FBH were studied. The research work focuses on the molecular simulations of bioactive compounds against the enzymes that acts as a potential drug target and support the drug discovery process. Eleven active compounds and their interactions with 5FBH were studied in this research work. The compounds were docked against the enzyme with the help of AutoDock vina software. Gallic acid showed the highest binding affinity values such as -7.6 with 5FBH. Protein-ligand Interaction and Visualization by Discovery studio 2020 client showed that the selected lead molecules exhibited the best interaction with the following amino acids viz. ARG A:69, THR A:406, THR A:412, TYR A:411, PRO A:407, ARG A:415,ALA A:321with 5FBH.

Keywords: Luffa acutangula, 5FBH, AutoDock vina, Gallic acid.

INTRODUCTION

Medicinal plants are major part of traditional system in developing countries .Herbal medicine is defined as the branch of science in which plant used formulations are used to alleviate the diseases. It is also known as botanical medicine or phytomedicine. Many infectious diseases are known to be treated with herbal remedies throughout the history of mankind. Even today plant materials continue to play a major role in primary healthcare as therapeutic remedies in many developing countries [1-2]. A medicinal plant which forms the backbone of traditional medicine has in the last few decades have been the subject of very intense pharmacological studies.

Molecular docking is one of the in silico method which is more efficient compared to in vitro and in vivo method for its capability of finding the active compound in medicinal plants. A three dimensional structure becomes very important in the molecular docking methods that depicts the compound [3-5].

Luffa acutangula (L) Roxb belongs to the family cucurbitaceace, commonly known as Ridge gourd is a large monoecious, annual climber used as vegetable in Asian countries. India is considered as a centre of its origin. The different parts of Luffa acutangula (Leaves, seeds, fruits, stem) have both medicinal and ethano botanical significance. The phytochemical studies have resulted in isolation and identification of approximately 50 compounds, such as flavonoids, antraquinones, proteins, fatty acid, saponins, triterpene, volatile components, and other phytoconstituents. The present paper deals with the utility of compound isolated from Luffa acutangula L (Roxb) leaf extract by molecular docking to assess its antiurolithiatic property [6].

MATERIALS AND METHODS

Bioactive compounds obtained from gas chromatography– mass spectrometry (GC-MS) analysis of *Luffa acutangula* L

The information about the bioactive compounds, such as IUPAC name, structure, and chemical formula, were retrieved from PubChem database. The bioactive compounds mentioned in Table 1 were used for molecular docking against the enzyme. The two-dimensional (2D) chemical structures of the ligands were sketched using

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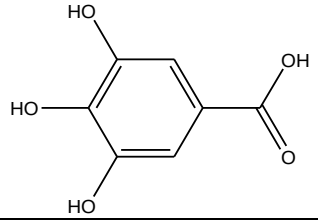
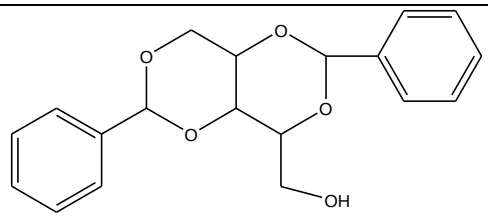
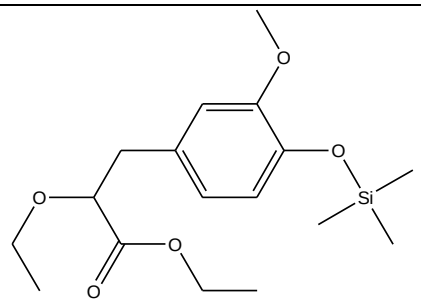
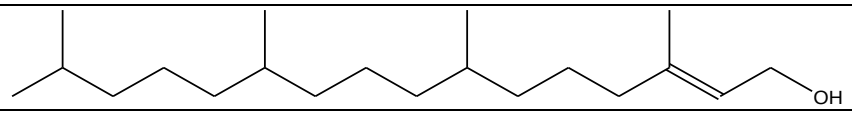
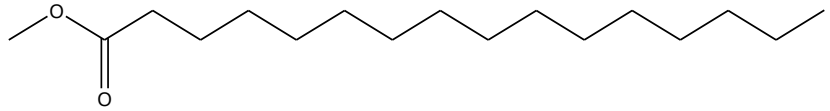
ChemDraw Ultra 2008, and the energy minimizations of the prepared ligands were carried out with Chem3D Ultra and were saved in pdb format.

Target Preparation and Validation of Docking Method

The three dimensional structure of protein was obtained from Brook haven protein databank (PDB ID: 5FBH). The docking study was started with the definition of a binding site, in general a restricted region of the protein. The size and location of this binding site was visualized in PyMOL. The protein targets were further validated with AutoDock Vina in PyRx 0.8 by RMSD value determination 8.

Molecular Docking Analysis Binding mode and interaction of Protein (5FBH) with individual chemical constituent of *Luffa acutangula* L, was performed using AutoDock Vina software. Docking was performed to obtain a population of possible conformations and orientations for the ligand at the binding site. The protein was loaded in PyRx software, creating a PDBQT file that contains a protein structure with hydrogens in all polar residues. All bonds of ligands were set to be rotatable. All calculations for protein-fixed ligand-flexible docking were done using the Lamarckian Genetic Algorithm (LGA) method. The docking site on protein target was defined by establishing a grid box with the dimensions of X: 38.0729 Y: 33.3208 Z: 25.0000 Å, with a grid spacing of 0.375 Å, centered on X: 20.2892 Y: 10.3219 Z: 32.3218 Å. The best conformation was chosen with the lowest docked energy, after the docking search was completed. Ten runs with AutoDock Vina were performed in all cases per each ligand structure, and for each run the best pose was saved. The average affinity for best poses was taken as the final affinity value. The interactions of complex protein-ligand conformations, including hydrogen bonds and the bond lengths were analyzed using PyMol [7-10].

Table 1. Molecular structure of identified compounds from the ethanolic leaf extract of Luffa acutangula

S. No	Name of the compound	Molecular structure
01	Gallic acid	
02	Ribitol, 1,3:2,4-di-O-benzylidene	
03	Ethylethoxy (3methoxy4[(trimethylsilyl)oxy]phenyl) acetate	
04	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	
05	Hexadecanoic acid, methyl ester	

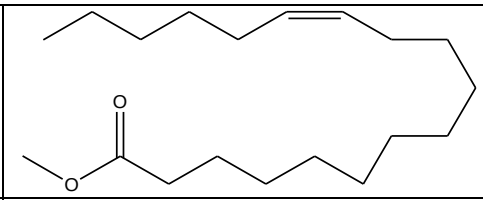
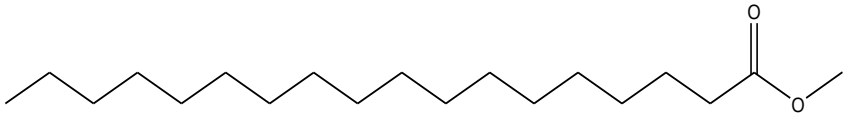
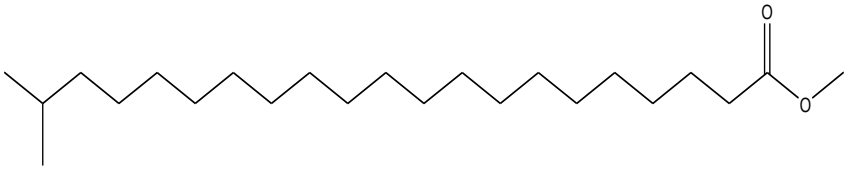
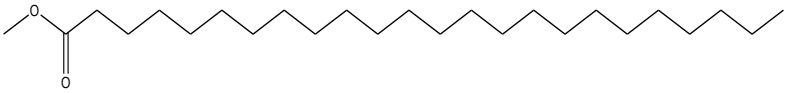
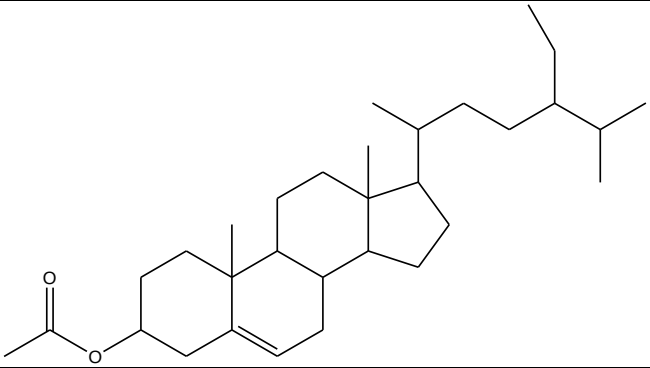
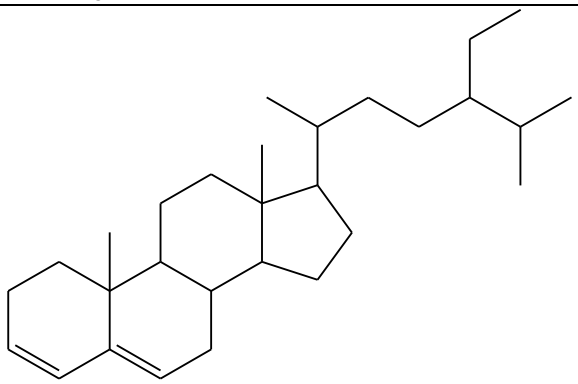
06	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	
07	Octadecanoic acid, methyl ester	
08	Methyl 20-methyl-heneicosanoate	
09	Tetracosanoic acid, methyl ester	
10	β-Sitosterol acetate	
11	Stigmastan-3,5-diene	

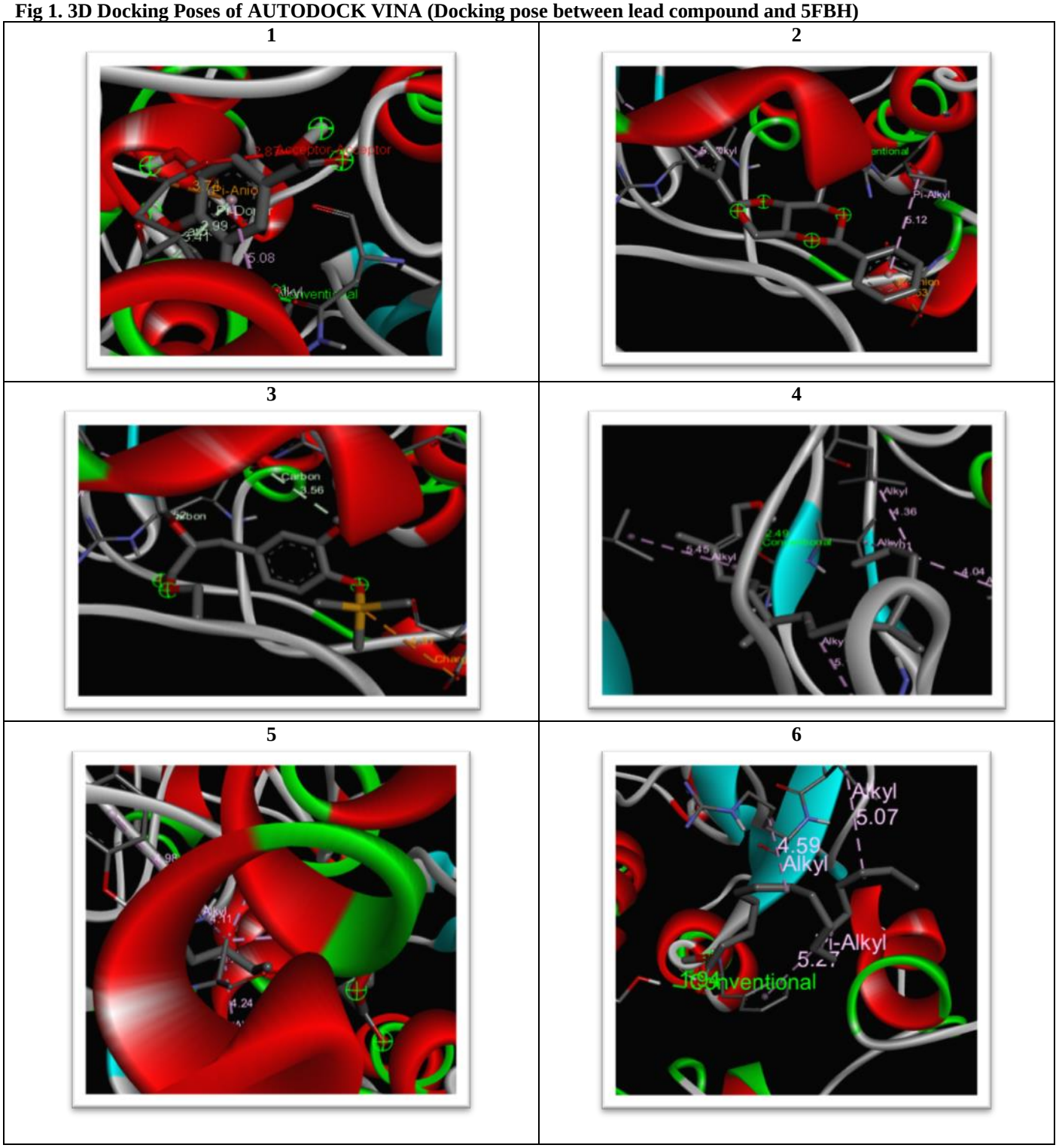
Table 2. The interaction energies (kcal mol-1) of 5FBH and ligands obtained from the molecular docking with AutoDock vina with PyRx.

Comp code	Auto dock vina	H-Bonds	Vander waal forces	Pi-alkyl	Pi-anion	RMSD
	PyRx	Residues	Residues	Residues	Residues	Residues
1	-7.6	ARG A:69	THR A:406, THR A:412, TYR A:411	PRO A:407, ARG A:415, ALA A:321	ASP A:410	0.0
2	-5.8	ARG A:66, ARG A:415,	PHE A:505, ILE A:492, ALA A:300, GLU A:297, ARG A:69, PRO A:407	ILE A:492, ALA A:321,		0.0

		SER A:301				
3	-6.0	GLN A:476	ASN A:471, THR A:186, LEU A:322, ASN A:419, ASN A:488, GLU A:475, VAL A:486, TYR A:418, GLY A:487, THR A:478, TYR A:514	LEU A:422, LEU A:485, VAL A:477, LYS A:323, VAL A:513	GLU A:475	0.0
4	-5.8	THR A:355, PHE A:65, SER A:303, LEU A:304, PHE A:42, LYS A:281, PRO A:278, TYR A:246, ALA A:46, ALA A:45, GLY A:43, ILE A:61	ASN A:471, THR A:186, LEU A:322, ASN A:419, ASN A:488, GLU A:475, VAL A:486, GLY A:487, TYR A:514, THR A:;478	LEU A:422, LEU A:485, VAL A:477, LYS A:323, VAL A:513		0.0
5	-4.1	SER A:303	LEU A:304, PHE A:42, ASN A:64, TYR A:63, ASN A:357, ARG A:66, GLU A:354	ARG A:62, ILE A:61, PHE A:65		
6	-5.3		ASN A:419, TYR A:418, LYS A:323, LEU A:422, PRO A:188, THR A:186, ILE A:187, ASN A:471, GLU A:475, GLY A:487, VAL A:486, TYR A:514, GLN A:476	LEU A:485, LEU A:322, VAL A:477, VAL A:513		
7	-3.9		GLU A:277, ARG A:62, GLU A:282, GLU A:249, GLN A:245, ILE A:252, TYR A:246, SER A:247, GLY A:253, ASP A:248, ALA A:46	LYS A:281, PRO A:278		
8	-3.7	THR A:263	ARG A:205, ASN A:207, TRP A:208, VAL A:209, VAL A:537, ILE A:292, PRO A:538, GLY A:290, THR A:289	TRPN A:206, ALA A:264, LYS A:265, TRP A:530		
9	-6.1		ALA A:45, ARG A:62, VAL A:44, GLY A:43, ALA A:46, GLN A:245, TYR A:246, SER A:247, ASP A:248, LYS A:281, GLU A:282, GLN A:253, GLU A:249	ILE A:61, PRO A:278		
10	-7.4		TYR A:411, ARG A:69, PRO A:407, ASP A:410, SER A:502, VAL A:504, ILE A:503, ASP	PHE A:505, ALA A:321, ILE A:492		

			A:500, THR A:412, SER A:301, ARG A:415, ALA A:300			
11	-5.7	ASN A:102	THR A:103,GLN A:245, SER A:272, GLY A:148, ASP A:216, VAL A:149, SER A:147	PRO A:274	ASP A:275	0.0

Fig 1. 3D Docking Poses of AUTODOCK VINA (Docking pose between lead compound and 5FBH)



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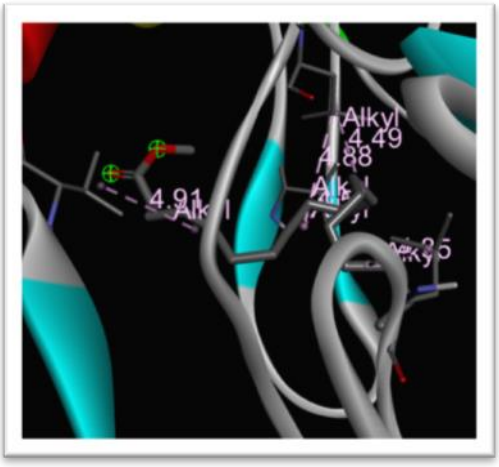

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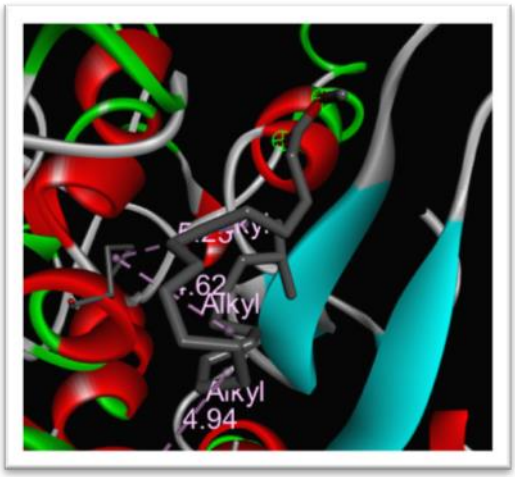

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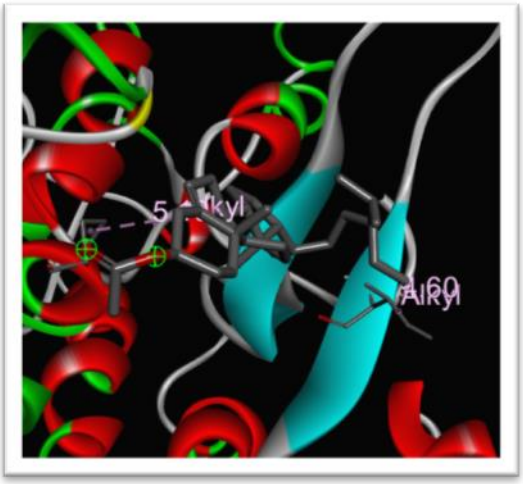

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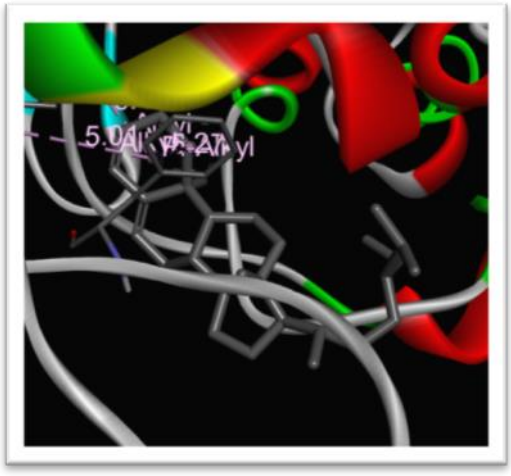

RESULTS AND DISCUSSION

Docking of small molecule compounds into the binding site of a receptor and estimating the binding affinity of the complex is an important part of the structure based drug design process. AutoDock Vina is a open-source program for drug discovery, molecular docking and

virtual screening, offering multicore capability, high performance and enhanced accuracy and ease to of use.

Docking of 5FBH protein with 11 isolated plant compounds were done by AUTODOCK VINA software and dock scores of these molecules were represented in (Table 2, Fig 1), with their binding affinity and types of bonds with which different amino acids bonded to the ligand's different functional groups. Binding affinity of the protein-ligand interactions are important to describe how fit the drug binds to the target macromolecules. In the present study, the results generated by AutoDock Vina revealed that binding energies of the protein-ligand (drug) interactions are important to describe how fit the drug binds to the target macromolecule. The Ligands (i) Gallic acid (-7.6); (ii) Ribitol, 1,3:2,4-di-O-benzylidene (-5.8); (iii)Ethylethoxy(3-methoxy-4[(trimethylsilyl)oxy]phenyl) acetate (-6.0); (iv) 3,7,11,15-Tetramethyl-2-hexadecen-1-ol (-5.8); (v) 16-Octadecenoic acid, methyl ester (-4.1); (vi) 9,12-Octadecadienoic acid (Z,Z)-, methyl ester (-5.3); (vii) Octadecanoic acid, methyl ester (-3.9); (viii) Methyl 20-methyl-heneicosanoate (-3.7); (ix) Tetracosanoic acid, methyl ester (-6.1); (x) β-Sitosterol acetate (-7.4); (xi) Stigmastan-3,5-diene (-5.7)), docks into good the binding pockets of 5FBH protein

Gallic acid showed the highest binding affinity values such as -7.6 with 5FBH. Protein-ligand Interaction and Visualization by Discovery studio 2020 client showed that the selected lead molecules exhibited the best interaction with the following amino acids viz. ARG A:69, THR A:406, THR A:412, TYR A:411, PRO A:407, ARG A:415,ALA A:321with 5FBH.

However Gallic acid showed the highest binding affinity value (-7.6) with 5FBH. Similarly, Sitosterol acetate showed highest binding affinity (-7.4) with the 5FBH.

CONCLUSION

Virtual screening methods are extensively used in drug discovery process to reduce the time spent on the research as well as expenditure. The approach utilized in this study resulted in identifying compound Gallic acid with high binding affinity towards 5FBH. The docked pose of compound Gallic acid revealed more number of H-bond interactions than the cocrystallized ligand. Therefore, this study states the importance of small molecules from various plant sources as docking agents. This approach to screen compounds from plants depends on various parameters such as size and shape of the compound and pharmacophoric groups attached on the compounds, among others. Further, work can be extended to study the receptor-ligand interactions experimentally and evaluation of their biological activity would help in specific isolation and effective treatment of diseases.

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