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MOLECULAR DOCKING, ADME AND BIOACTIVITY PREDICTION FOR ANTI-ALZHIEMER'S ACTIVITY OF PHYTOCONSTITUENTS

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ABSTRACT

Alzheimer's is the most common form of dementia, a general term for memory loss and other intellectual abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 60 to 80 percent of dementia cases. The β-secretase which is also called as BACE1 (β-site amyloid precursor protein cleaving enzyme 1), is an important enzyme in development of AD pathology. Hence BACE1 has chosen as an target receptor in the study and docked against selected phytoconstituents for studying their interaction. The 12 selected phytoconstituents- Ashwagandhanolide, Proanthocyanidine, Ginsenoside, Glycyrrhizin, Curcumin, Huperzine, Formicacid, Withaferin A, Rosemarinicacid, Resveratrol, Histamine and Caffeicacid were included in the *in silico* analysis to evaluate their Anti-Alzheimer's potential. The adsorbtion, distribution, metabolism, excretion (ADME) properties of these phytochemicals were assessed through Lipinski rule of Five. The Bioactivity properties and Phytoconstituents-likeness of the selective phytoconstituents were calculated using Molinspiration and Molsoft tools and docking of the selected phytoconstituents was carried out using Hex 8.0.0 Interestingly, after application of Lipinski's rule of five, results revealed that among the 12 selected phytoconstituents Ashwagandhanolide, Proanthocyanidine, Ginsenoside and Glycyrrhizin were found to be violatong the Lipinski's rule of five and rest of the phytoconstituents were showing satisfactory results so after comparing binding energy with respect to standard drugs such as diovan and galanthamine ; phytoconstituents withafarin A and Rosemarinic acid had shown

significant results and thus these shall be recommended as safe phytoconstituents for effective treatment of AD though *in vivo* study required in preclinical and clinical phases.

KEYWORDS: Alzheimer's Disease, ADME, Docking.

INTRODUCTION

Alzheimer's disease(AD) is named after German physician Aloes Alzheimer, who first described it in 1906. Alzheimer's disease (AD) is a progressive neurological disease of the brain that affects aging patients in the world.[1] The β-secretase is also called BACE1 (β-site amyloid precursor protein cleaving enzyme 1), which is an important enzyme in development of AD pathology. BACE1 cleaves transmembrane APP between residues 671 and 672, and carboxy-terminal fragment of APP is cleaved by γ-secretase, facilitating intramembrane proteolysis by the presenilin 1 (PSEN1) and presenilin 2 (PSEN2). Subsequently the small 4 kilodalton of amyloid-Aβ1-40 and Aβ1-42 is generated by sequential β and γ-secretase cleavage of APP. Hence, the BACE1 has been recognized as a drug target for curing AD in many studies.[2] Ayurvedic medicinal plants have shown promise in reversing the Alzheimer's disease pathology in the past and hence they may provide useful leads in the discovery of new drugs for AD therapy.[3] Lipinski's rule of five is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity.

MATERIALS AND METHODS

In the present study, the Bioactivity properties and drug-likeness of the above mentioned selected phytoconstituents were calculated using Molinspiration, Molsoft tools.[4]

Validation of phytoconstituents was done by:

a) Literature review based selection of different plants and their respective phytoconstituents used to treat Alzheimer's disease.

b) Obtaining SMILES format for these phytoconstituents using software's.

c) Applying 'Lipinski's rule of five' for each of these phytoconstituents.[4]

Selection of Drugs and Phytoconstituents

Nicardipine, diovan galanthamine drugs and caffeic acid curcumin ginsenoside glycyrrhizin histamine huperzine formic acid withaferin a proanthocyani-dine ashwagandhanolide rosamarinic acid phytoconstituents were selected based on literature review.

The structures were retrieved from Pubchem database, The structure were downloaded in SDF format and was then converted to PDB format and further used for docking studies.

3.2 Ligand optimization

Ligand / Drug molecules was obtained from PubChem Database. Optimization of ligand was carried out using ChemSketch.

3.3 *In silico* ADME

Calculating molecular property and druggability score for phytoconstituents using Molinspiration software and Molsoft tools. Molinspiration tool**,** Molinspiration supports internet chemistry community by offering free on-line cheminformatics services for calculation of important molecular properties (for example logP, polar surface area, number of hydrogen bond donors and acceptors), as well as prediction of bioactivity score for the most important phytoconstituents targets. Molinspiration tools are written in Java, therefore are available practically on any computer platform. Molecular properties and bioactivity of the phytoconstituents showing high affinity predicted using Molinspiration tool. This tool allows physico chemical properties to calculate Log P based on group contributions. The values were obtained by fitting calculated logP with experimental logP. PSA is good descriptor characterizing phytoconstituents absorption, including intestinal absorption, bioavailbility, Caco-2 permeability and Blood brain barrier penetration.

Molsoft Software

Molsoft is a California based software company that is a primary source of new breakthrough technologies in: Molecular graphics and visualization, Molecular modeling, Docking and Virtual screening, computational biology and Cheminformatics. All molecular property predictors are calculated using fragment-based contributions. It developed an original method for splitting a molecule into a set of linear or non-linear fragments of different length and representation levels and counting the number of occurrences of each chemical pattern found. A Partial Least Squares (PLS) regression model was built and optimized for a particular property using a leave-50%-out cross-validation calculation. The method is very robust and fast (about 5K of compounds per second).

3.4 Selection of Target

The Kyoto Encyclopedia of Genes and Genome pathway database (KEGG) was the source of metabolic pathway information. It was found that different proteins were responsible for

cause of Alzheimer's disease. The PDB structure was available for BACE1 (PDB ID:4PJE). Which was downloaded for the study.

3.5 Receptor optimization

The crystal structure of BACE1 was taken from PDB database (PDB code: 4JPE) [55]; the missing atoms and loops were corrected by *Prepare Protein module* under Accelrys Discovery Studio 4 (DS 4) [56]; residues of BACE1 were protonated in pH 7.4 condition.

3.6 Computational docking studies

The docking of selected protein with ligand molecules were performed by using Hex 8.0.0. Hex is an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex can also calculate protein- ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes. In Hex 's docking calculations, each molecule is modelled using 3D expansions of real orthogonal spherical polar basis functions to encode both surface shape and electrostatic charge and potential distributions. Essentially, this allows each property to be represented by a vector of coefficients (which are the components of the basis functions). Hex represents the surface shapes of proteins using a two-term surface skin plus van der Waals steric density model, whereas the electrostatic model is derived from classical electrostatic theory. By writing expressions for the overlap of pairs of parametric functions, one can obtain an over- all docking score as a function of the six degrees of freedom in a rigid body docking search. With suitable scaling factors, this docking score can be interpreted as an interaction energy,which we seek to minimise. Due to the special orthogonality property of the basis functions, the correlation (or overlap as a function of translation/rotation operations) between a pair of 3D functions can be calculated using expressions which involve only the original expansion coefficients. In many respects, this approach is similar to conventional fast Fourier transform (FFT) docking methods which use Cartesian grid representations of protein shape and other properties, and which then use translational FFTs to perform the docking correlations. However, the Cartesian grid approach only accelerates a docking search in three translational degrees of freedom whereas the SPF approach allows the effect of rotations and translations to be calculated directly from the original expansion coefficients.

Even though the FFT part of a docking search may be fast, the overall speed of calculation still depends very much on the initial "set-up" costs and the final "post-processing costs" of

filtering and perhaps clustering the results. Hex is fast because it uses FFT correlations as much as possible, and because the "set-up" costs are much lower in the SPF approach than in Cartesian grid-based approaches. It also turns out that the FFT part of the calculation maps very well to the GPU hardware. Thus, further speed-ups can be expected if you have a suitable graphics card.

Although it is not always easy to compare the performance of different docking algorithms because a lot depends on the size of the translational or rotation steps used, for example, Hex is also very easy to use. However, to use Hex most effectively, it can sometimes require some thought when setting up the calculation, especially when setting up the starting orientations of the proteins to be docked.

In the spherical polar approach, it is natural to assign the six rigid body degrees of freedom as five Euler rotation angles and an intermolecular separation. Thus, in complete contrast to Cartesian based FFT approaches, the rotational part of a docking search is the “easy bit” and modelling translations becomes the “hard part.” Fortunately, however, only a few translations (typically about 40 steps of 0.75 °Angstrom) are required to complete a six dimensional docking search. One advantage of the spherical polar approach is that it is easy to constrain the docking search to one or both binding sites, when this knowledge is available, simply by constraining one or two of the angular degrees of freedom. This can reduce docking times to a matter of minutes on a modern workstation.

The Hex version 8.0.0 includes several bug fixes since 6.3 and 6.12. Behind the scenes, the code has been re-structured quite considerably.

- The CUDA version now is built using CUDA 5.0.
- Fixed a nasty bug in CUDA for non-standard SPF expansion orders.
- Now uses FTGL for better fonts in the graphics window.
- The maximum correlation order has been increased to N=36.
- More of the translation matrix code is multi-threaded.
- A non-graphical version is available for headless workstations or clusters.[24]

RESULT AND DISCUSSION

4.1 ASSESEMENT OF ADME PROPERTIES OF THE PHYTOCONSTITUENTS

TABLE No. 1 Assesment of phytoconstituents for Lipinksy rule of five

S.No	Phytoconstituent	Molecular formula	Molecular weight	HBA (>10)	HBD (>5)	MolLogP (>5)	MOLPSA	MolVol	No. of stereo centers	No. of rotatable bonds
1	Caffeic acid	C9 H8 O4	180.04	4	3	1.69	61.72 A^2	174.88 A^3	0	2
2	Curcumin	C21 H20 O6	368.13	6	2	3.41	73.83 A^2	393.60 A^3	0	8
3	Ginsenoside	C42 H72 O13	784.50 (> 500)	13 (> 10)	9 (> 5)	2.94	175.10 A^2	841.38 A^3	20	10
4	Glycyrrhizin	C42 H62 O16	822.40 (> 500)	16 (> 10)	8 (> 5)	2.06	206.93 A^2	862.79 A^3	19	7
5	Histamine	C5 H9 N3	111.08	2	3	-1.01	43.19 A^2	109.50 A^3	0	2
6	Huperzine	C15 H18 N2 O	242.14	2	3	2.71	45.34 A^2	338.23 A^3	2	0
7	Formic acid	C H2 O2	46.01	2	1	-0.34	29.25 A^2	36.86 A^3	0	0
8	Withaferin A	C28 H38 O6	470.27	6	2	3.21	75.66 A^2	564.08 A^3	11	3
9	Proanthocyani-dine	C31 H28 O12	592.16 (> 500)	12	9	3.63	171.13 A^2	538.08 A^3	5	4
10	Ashwagandhanolide	C56 H78 O12 S	974.52 (> 500)	13	6	5.23	163.82 A^2	1130.51 A^3	22	8
11	Rosamarinic acid	C18 H16 O8	360.08	8	5	2.44	114.28 A^2	339.44 A^3	1	7
12	Resveratrol	C14 H12 O3	228.08	3	3	3.65	52.82 A^2	224.35 A^3	0	2

BIOACTIVITY VALUES FOR THE PHTOCONSTITUENTS

Table 4.2 Bioactivity of the selected Phytoconstituents

Phytoconstituent	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Withaferin A	0.08	0.14	-0.49	0.76	0.15	0.94
Rosemarinicacid	0.17	-0.08	-0.18	0.57	0.15	0.24
Huperzine	-0.06	0.16	-0.41	-0.32	-0.36	1.13

DOCKING SCORE FOR THE LIGAND MOLECULES

Table 4. 3Total Binding Energy Of The Ligand Molecules

Serial No.	Name Of Ligand	Total Binding Energy
1	Curcumin	-249.45
2	Caffeic acid	-165.08
3	Diovan	-265.84
4	Huperzine	-209.03
5	Galanthamine	-199.48
6	Formic acid	-99.79
7	Hydralazine	-133.14
8	Propranolol	-231.89
9	Tacrine	-153.18
10	Withaferin A	-286.55
11	Resveratrol	-195.90
12	Rivastigimine	-189.82
13	Histamine	-118.49
14	Rosemarinic acid	-240.43

4.2. DRUG LIKENESS GRAPH FOR PHYTOCONSTITUENTS

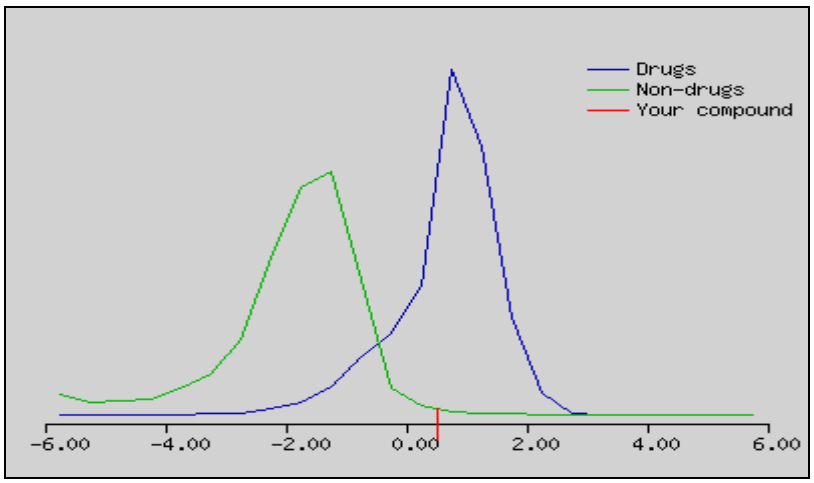

Figure 1. Ashwagandhanolide: Druglikeness model score: 0.53

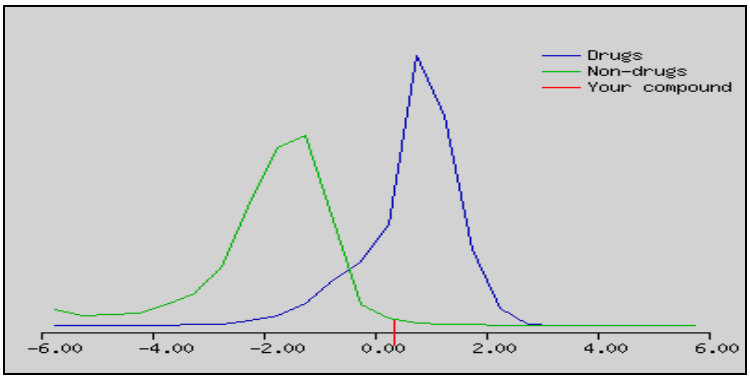

Figure 2. Withafirin A: Druglikeness model score: 0.36

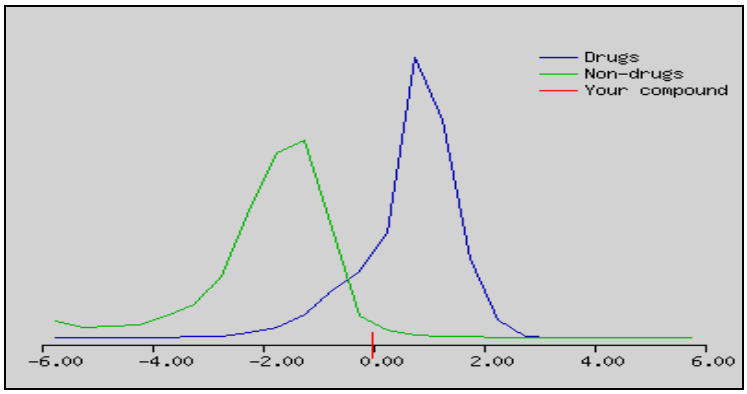

Figure 3. Caffeic acid: Druglikeness model score:-0.02

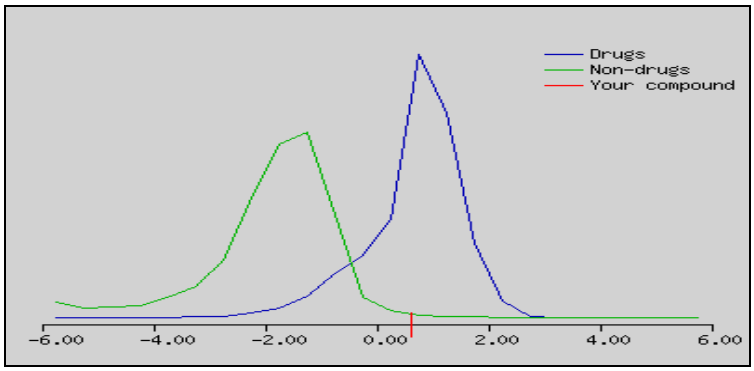

Figure 4.Rosemarinic acid: Druglikeness model score:0.63

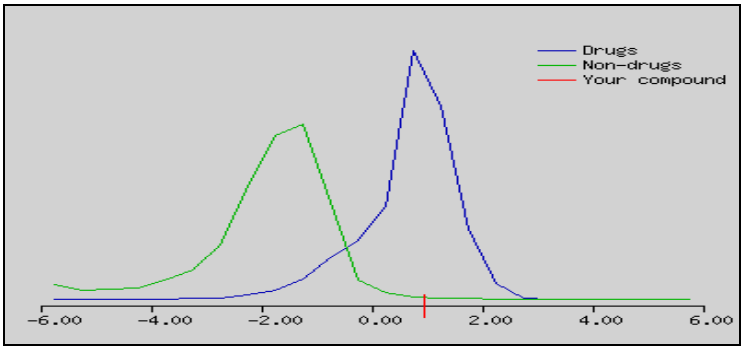

Figure 5. Proanthocyanidine: Druglikeness model score:0.94

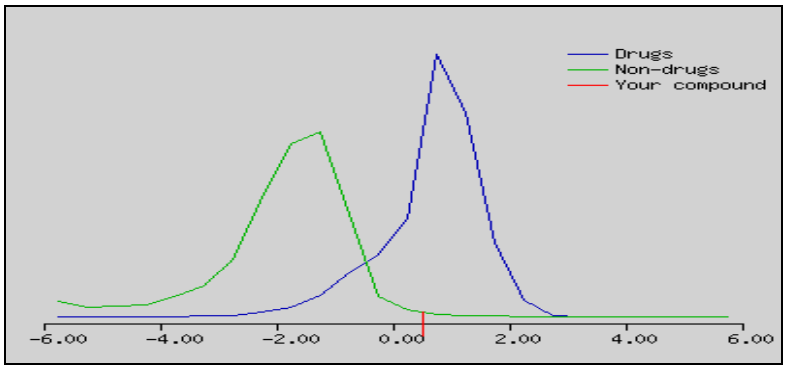

Figure 6. Curcumin: Druglikeness model score: 0.66

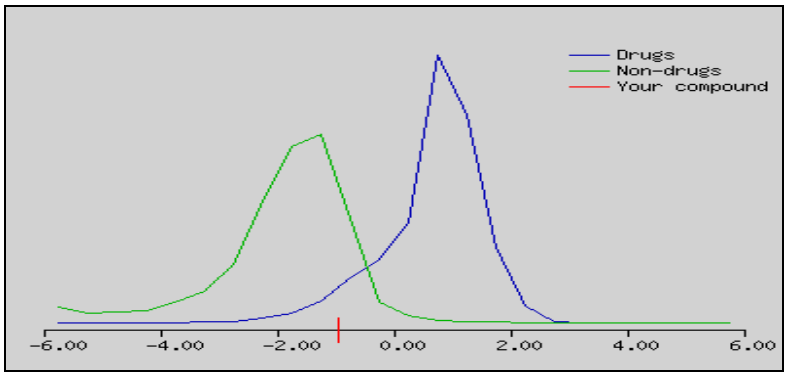

Figure 7. Histamine: Druglikeness model score: -0.95

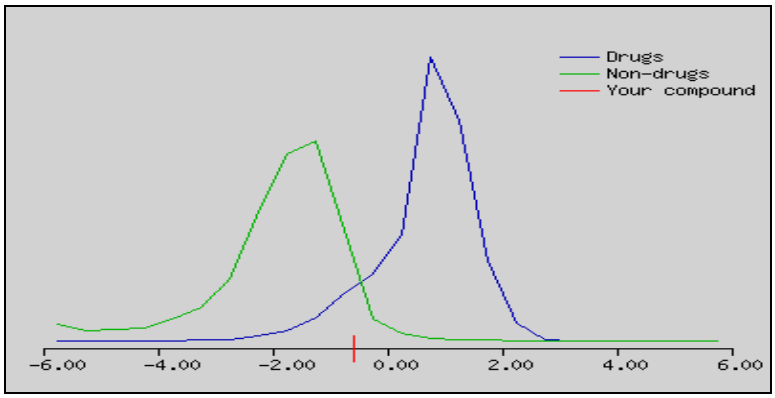

Figure 8. Formic acid: Druglikeness model score: -0.59

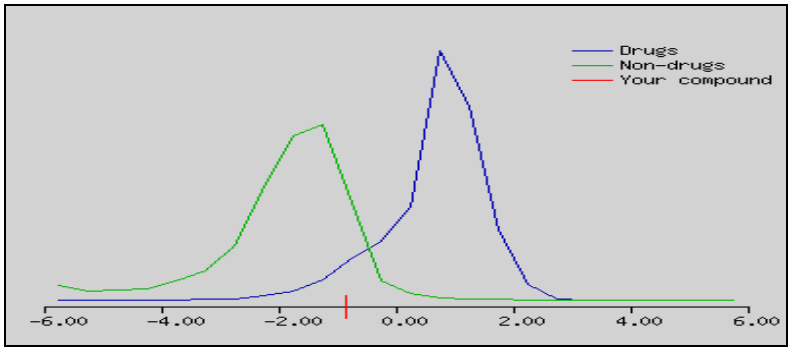

Figure 9.Huperzine: Druglikeness model score: -0.87

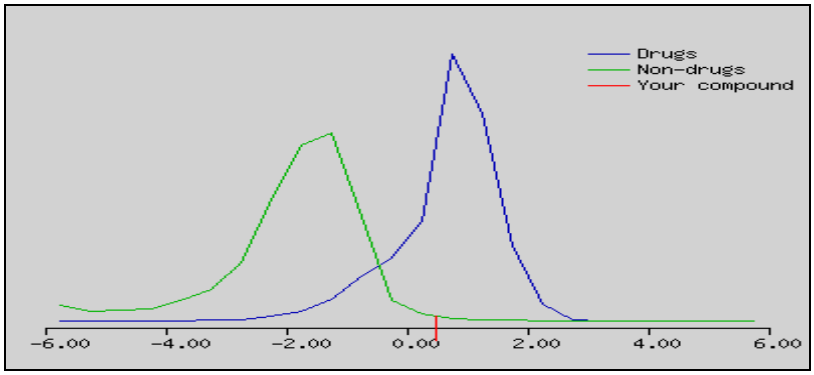

Figure 10.Ginsenoside: Druglikeness model score:0.49

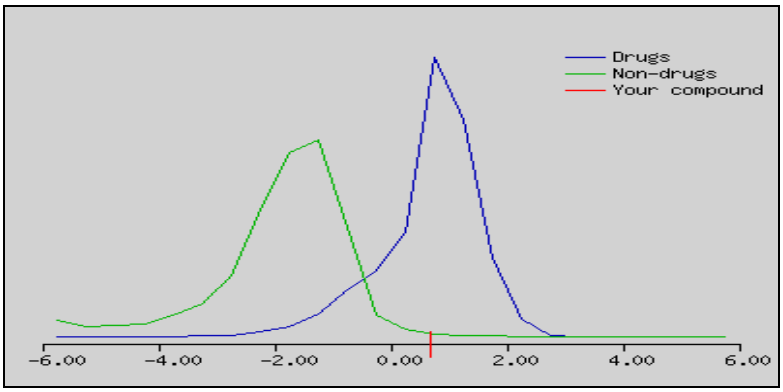

Figure 11.Glycryzzin: Druglikeness model score:0.68

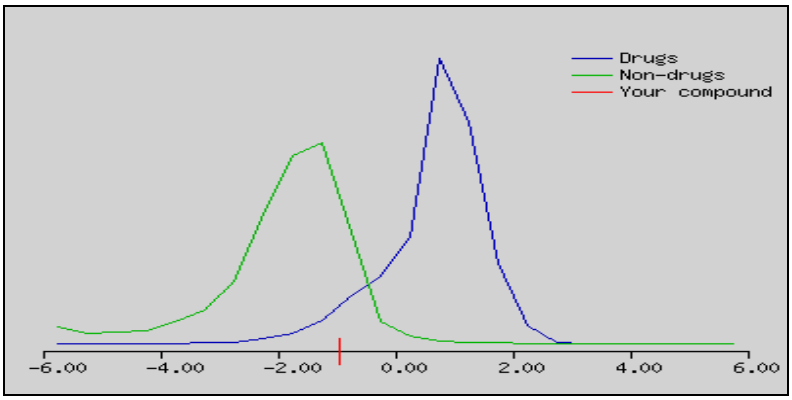

Figure 12.Resveratrol: Druglikeness model score: -0.94

FIGURES OF DOCKED COMPLEXES OF RECEPTOR AND LIGANDS

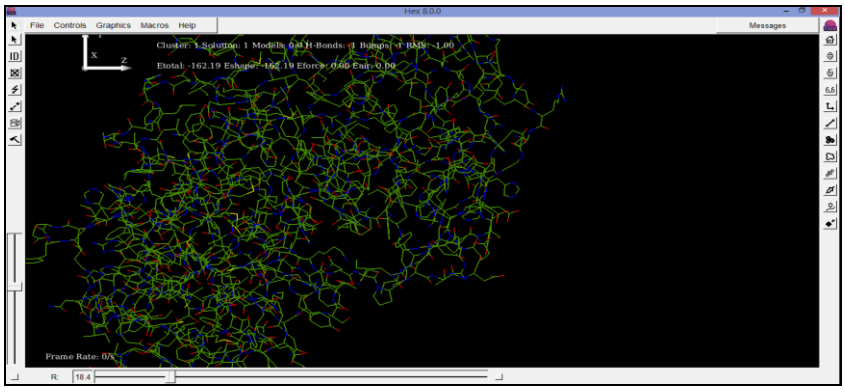

Fig 13: Docked complex of 4JPE and Caffeic acid

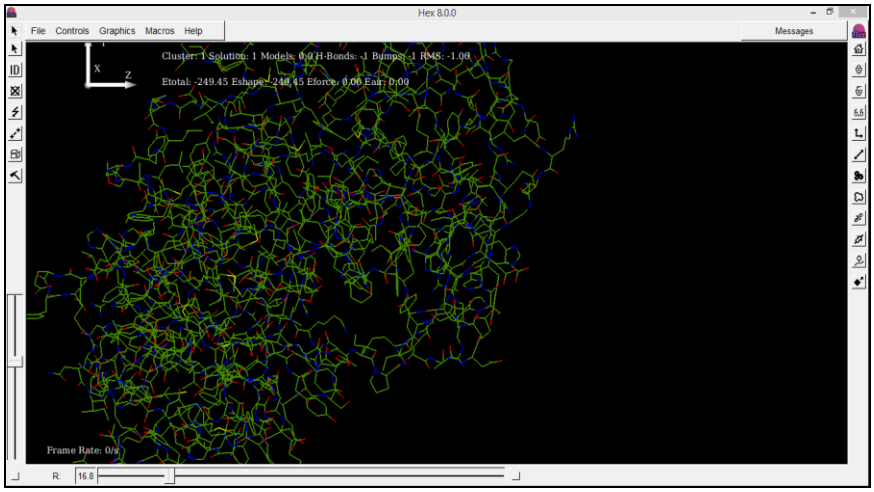

Fig 14: Docked complex of 4JPE and Curcumin

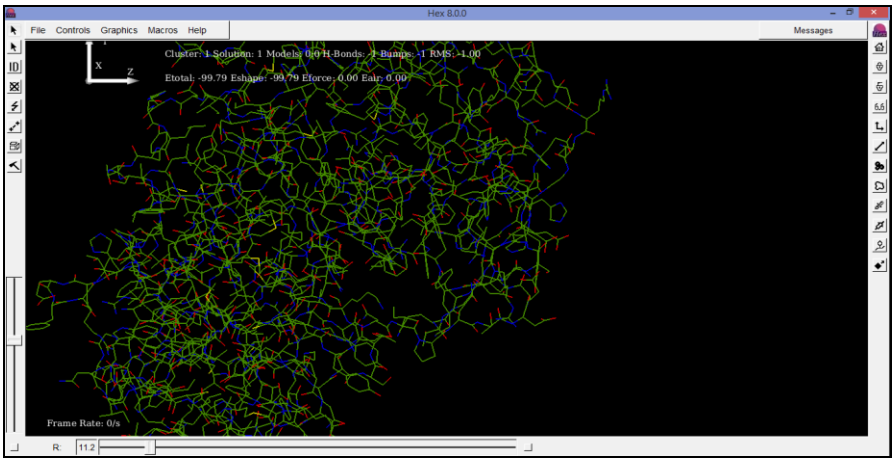

Fig 15: Docked complex of 4JPE and Formic acid

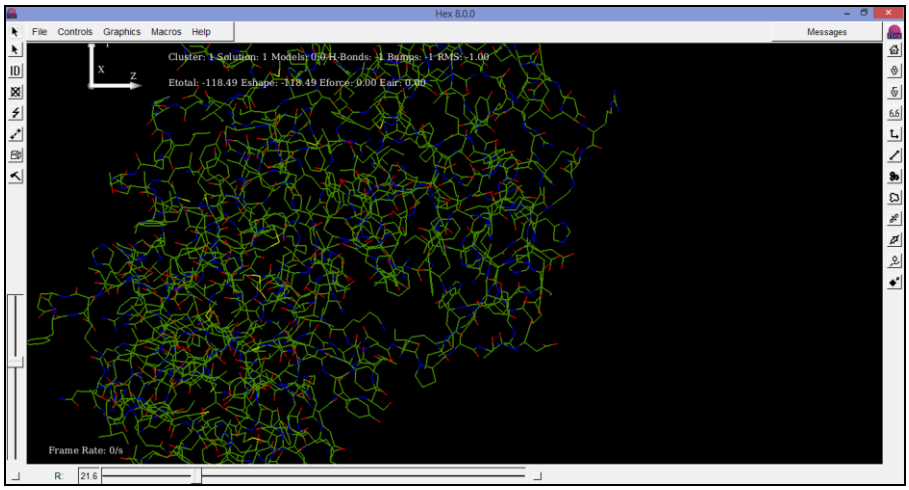

Fig 16: Docked complex of 4JPE and Histamine

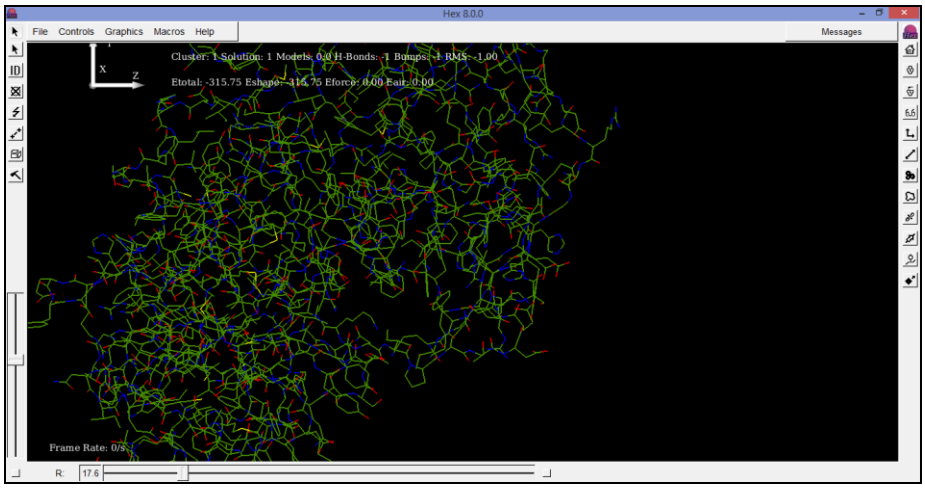

Fig 17: Docked complex of 4JPE and Proanthocyanidine

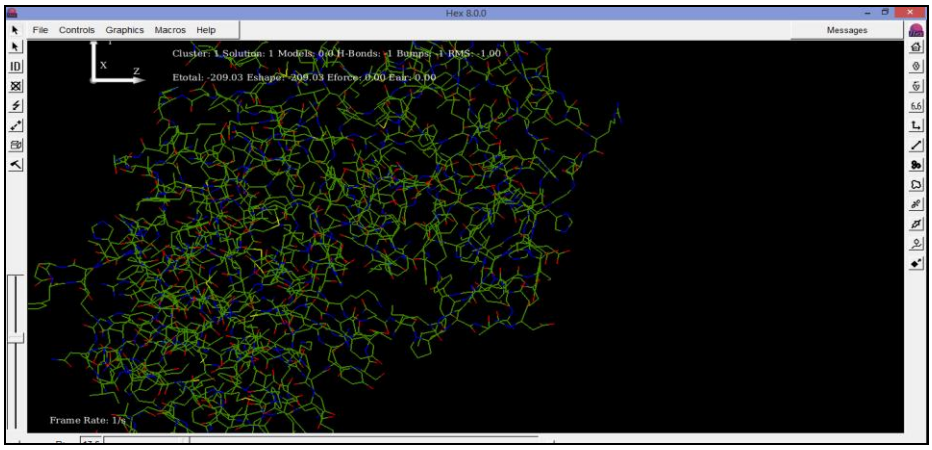

Fig 18: Docked complex of 4JPE and Huperzine

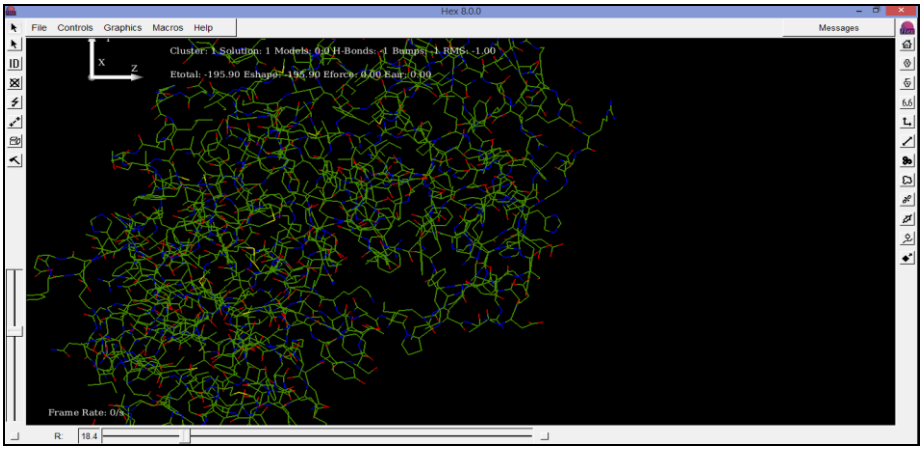

Fig 19: Docked complex of 4JPE and Resveratrol

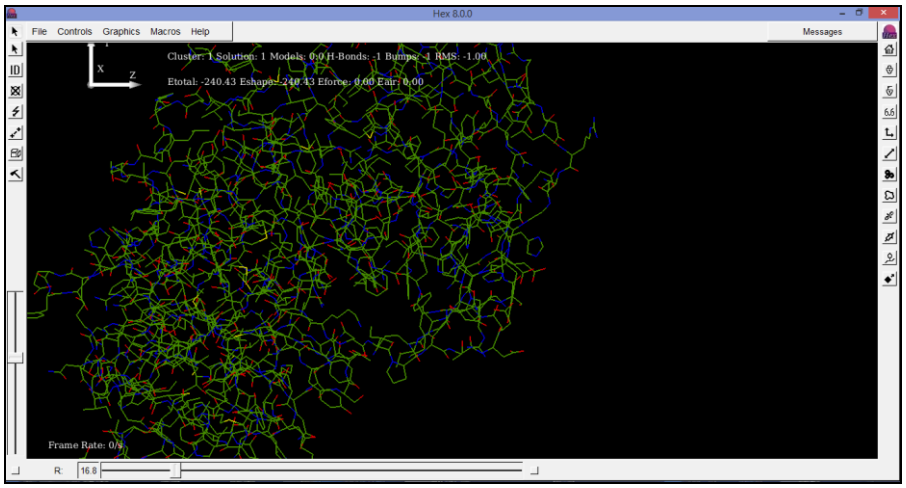

Fig 1.H: Docked complex of 4JPE and Rosemarinic acid

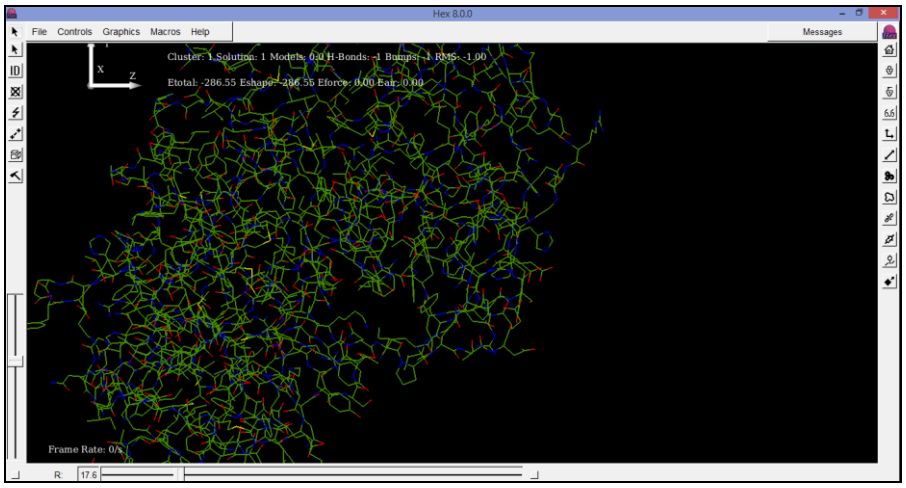

Fig 20: Docked complex of 4JPE and Withafern A

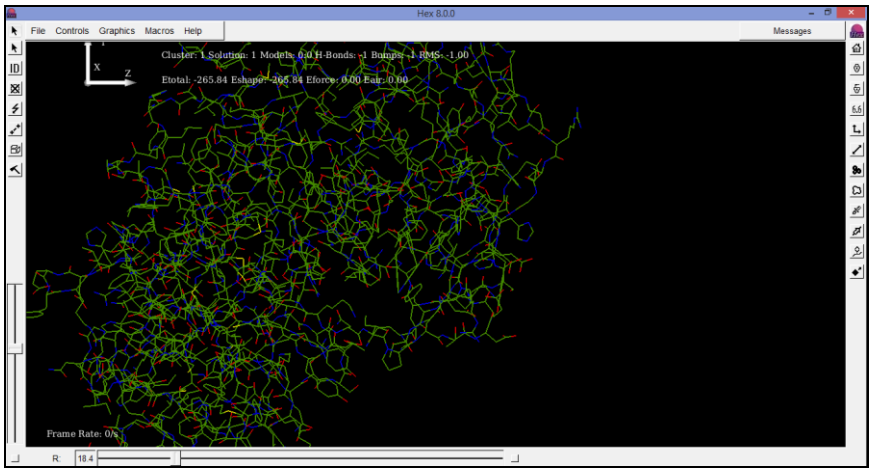

Fig 21: Docked complex of 4JPE and Diovan

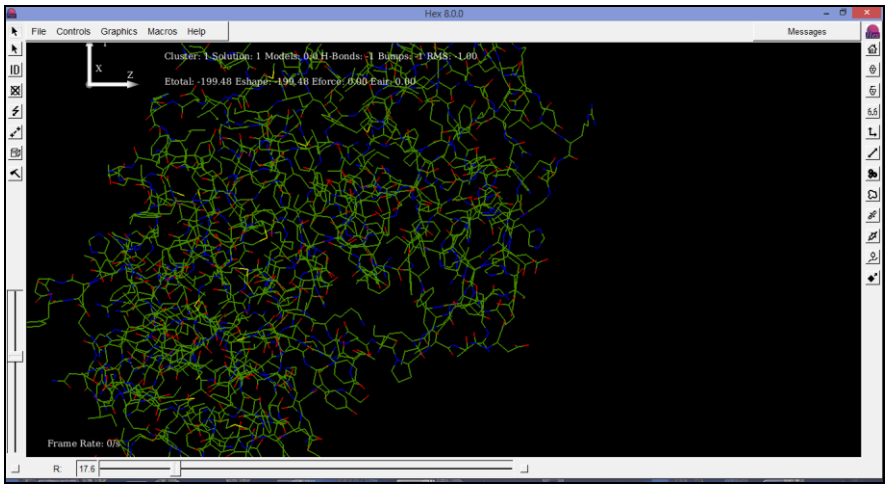

Fig 22: Docked complex of 4JPE and Galanthamine

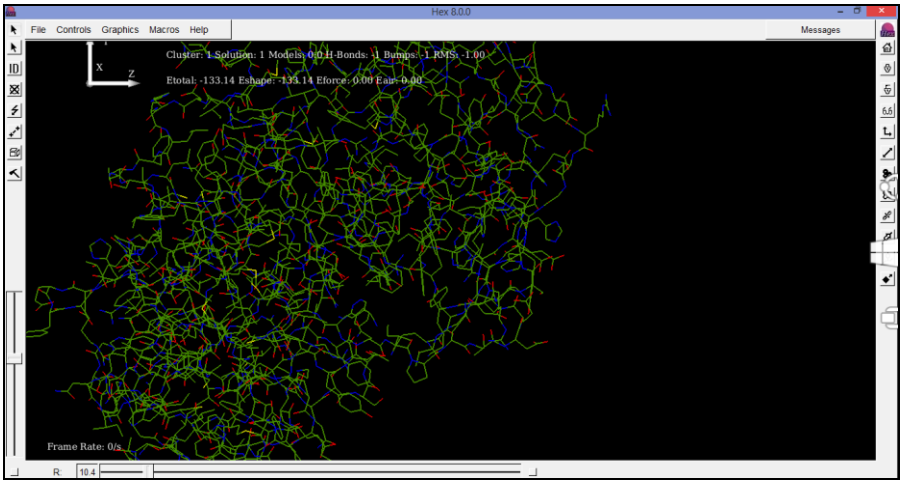

Fig 23: Docked complex of 4JPE and Hydralazine

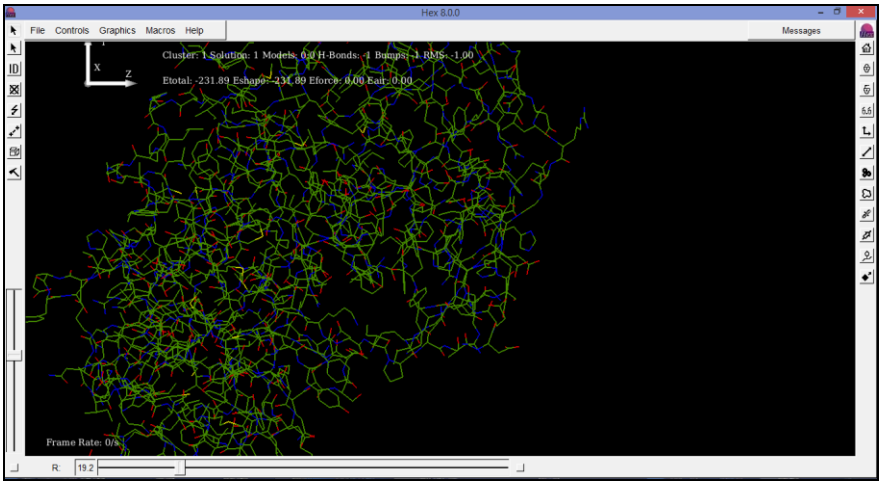

Fig 24: Docked complex of 4JPE and Propranolol

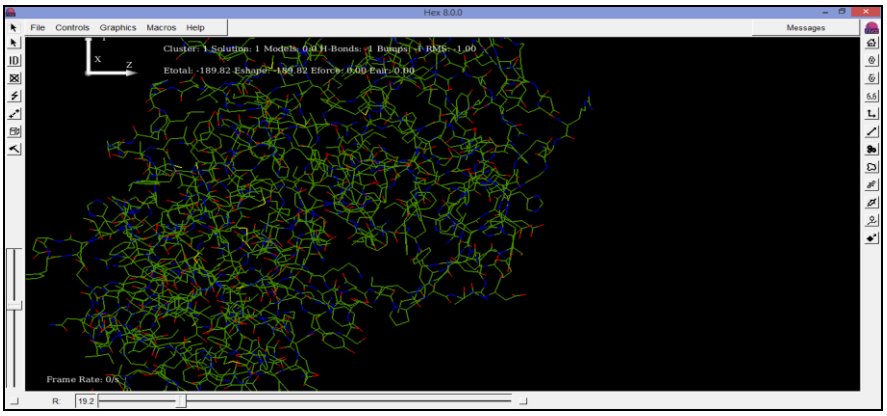

Fig 25: Docked complex of 4JPE and Rivastigmine

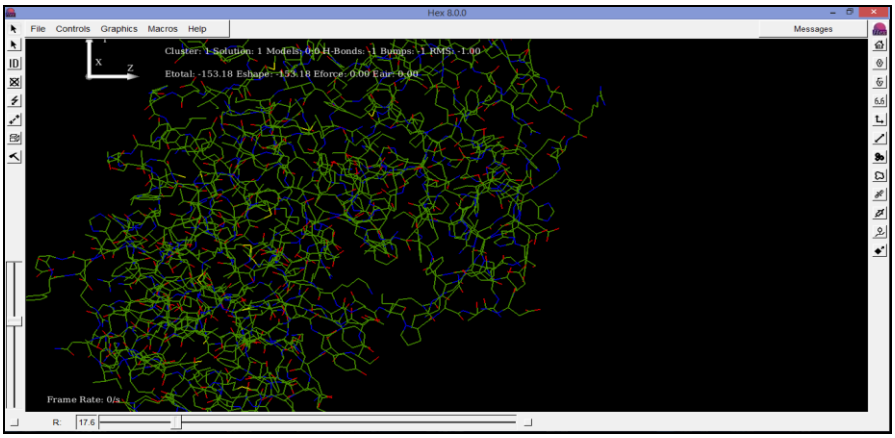

Fig 26: Docked complex of 4JPE and Tacrine

2D Diagrams of docked complexes in Discovery Studio 3.5 Visualizer

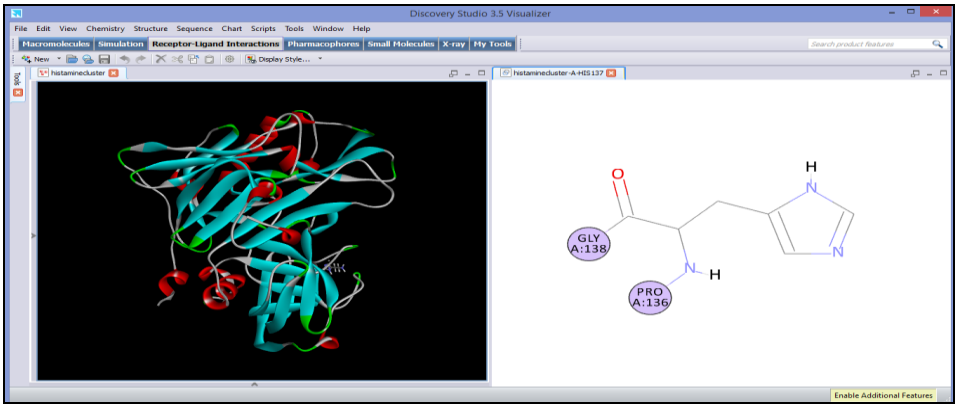

Figure No.28: Histamine docked with BACE1 shown in 2d and 3 D using DS visualize

Figure No. 1.2 : Curcumin docked with BACE1 shown in 2d and 3 D using DS visualize

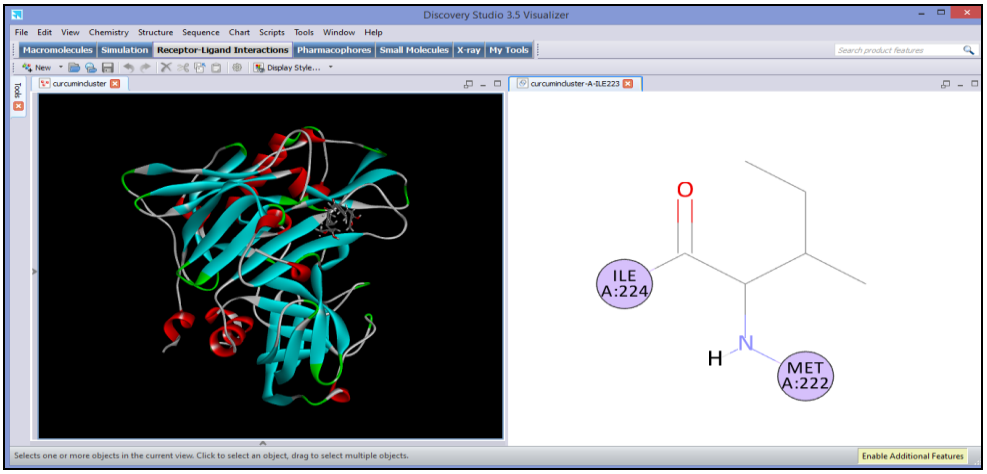

Figure No. 29: Caffeicacid docked with BACE1 shown in 2d and 3 D using DS visualize

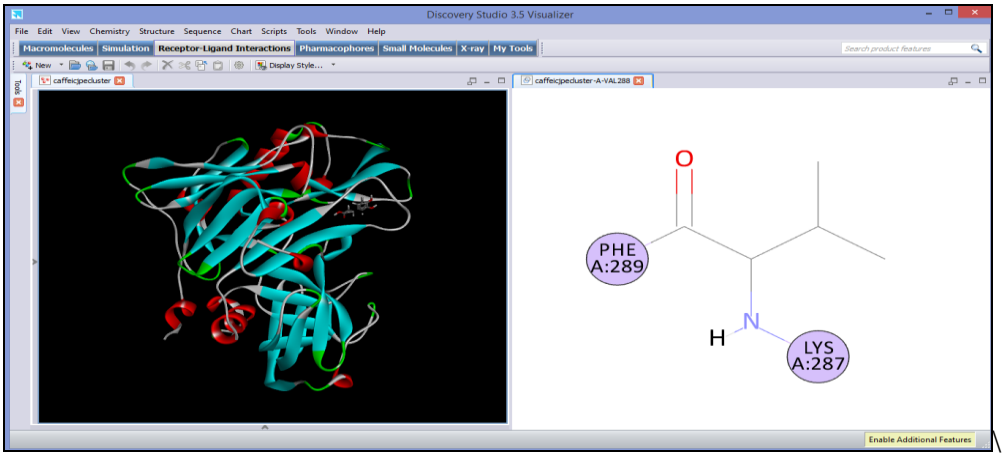

Figure No.30: Formicacid docked with BACE1 shown in 2d and 3 D using DS visualize

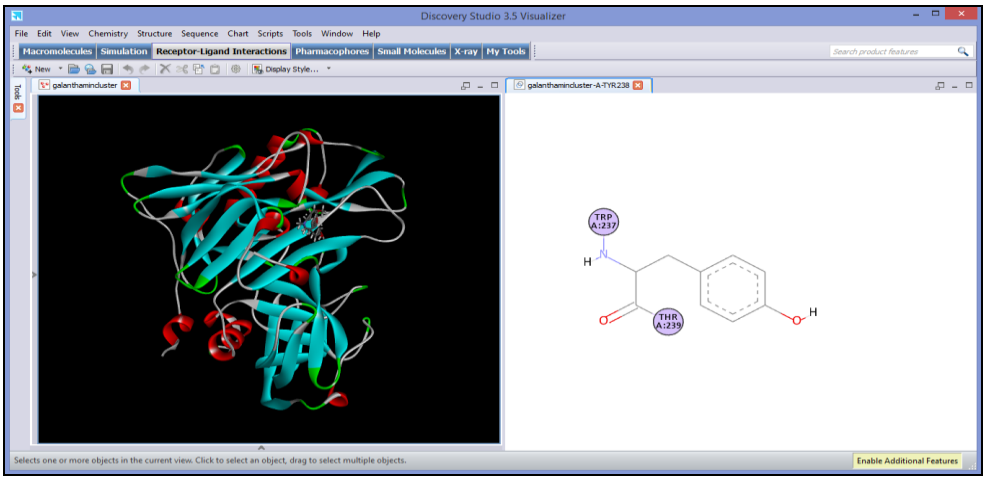

Figure No.31: Galanthamine docked with BACE1 shown in 2d and 3 D using DS visualize

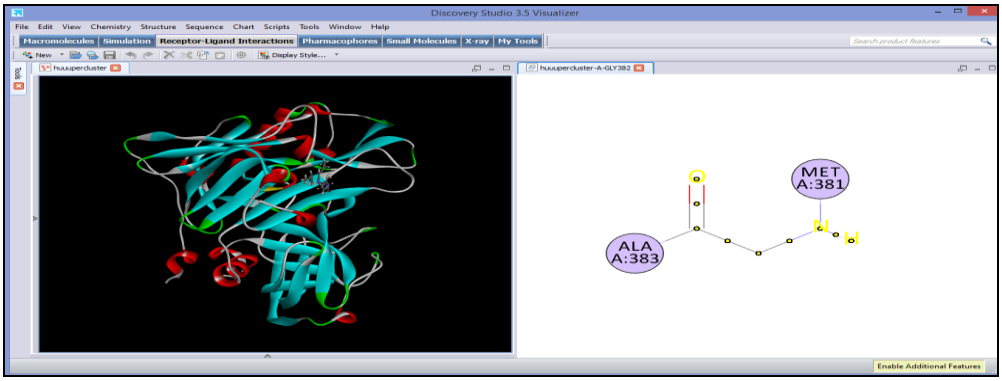

Figure No.32: Huperzine docked with BACE1 shown in 2d and 3 D using DS visualize

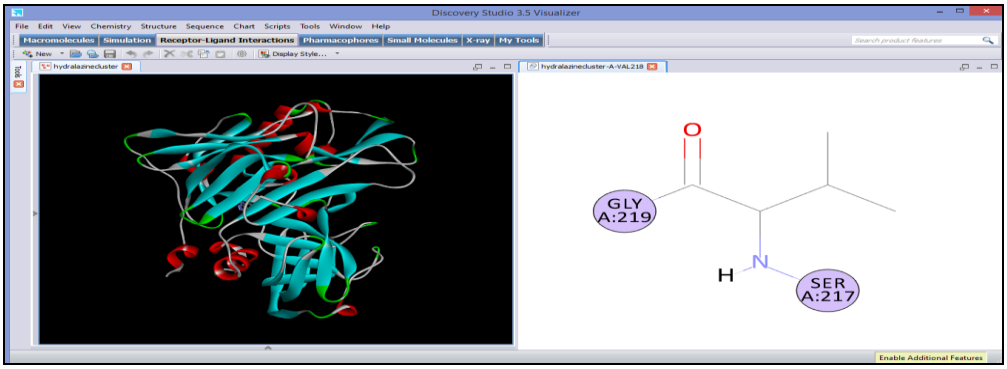

Figure No.33 Hydralazine docked with BACE1 shown in 2d and 3 D using DS visualize

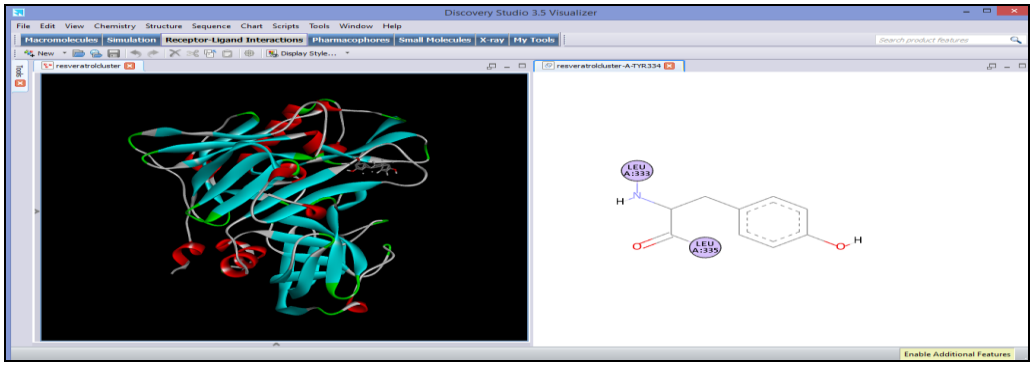

Figure No.34: Resveratrol docked with BACE1 shown in 2d and 3 D using DS visualize 4

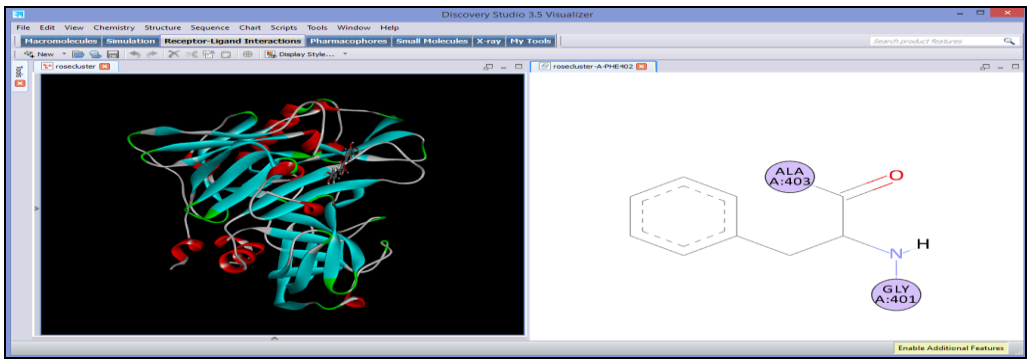

Figure No. 35: Rosemarinicacid docked with BACE1 shown in 2d and 3 D using DS visualize 4

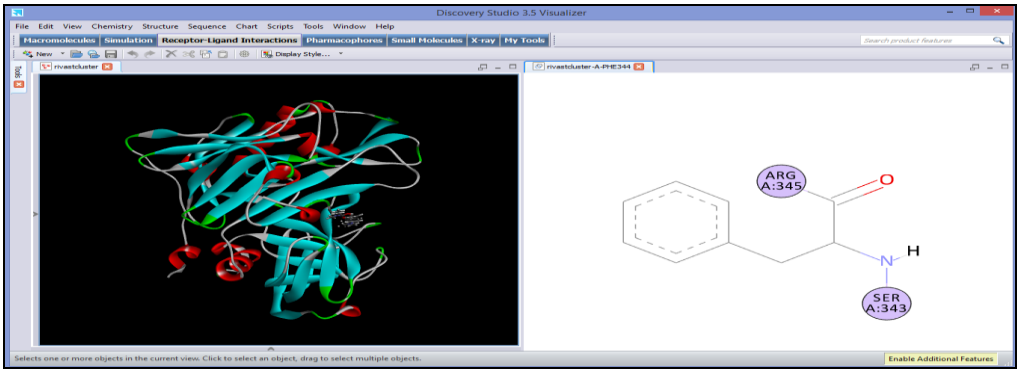

Figure No. 36: Rivastigmine docked with BACE1 shown in 2d and 3 D using DS visualize 4

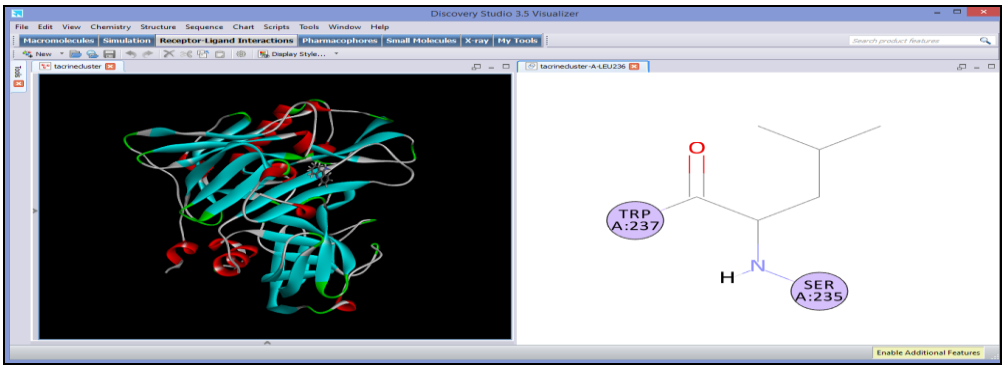

Figure NO. 37: Tacrine docked with BACE1 shown in 2d and 3 D using DS visualize

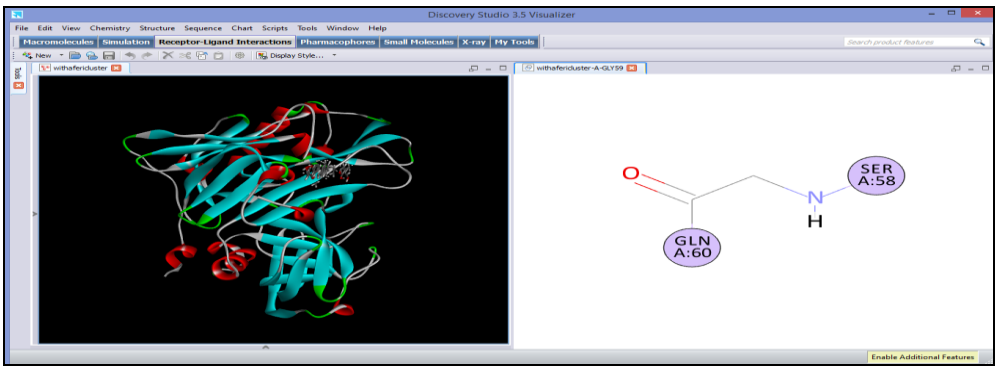

Figure NO. 38: Withaferin A docked with BACE1 shown in 2d and 3 D using DS visualize

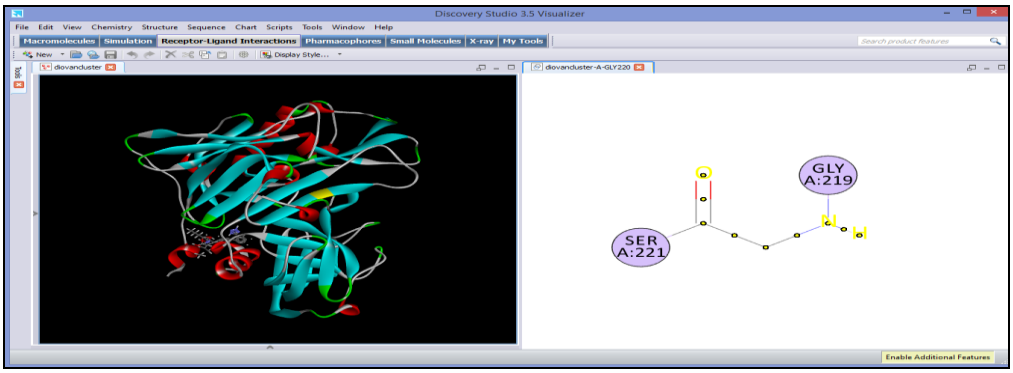

Figure No.39. 11: Diovan docked with BACE1 shown in 2d and 3 D using DS visualize

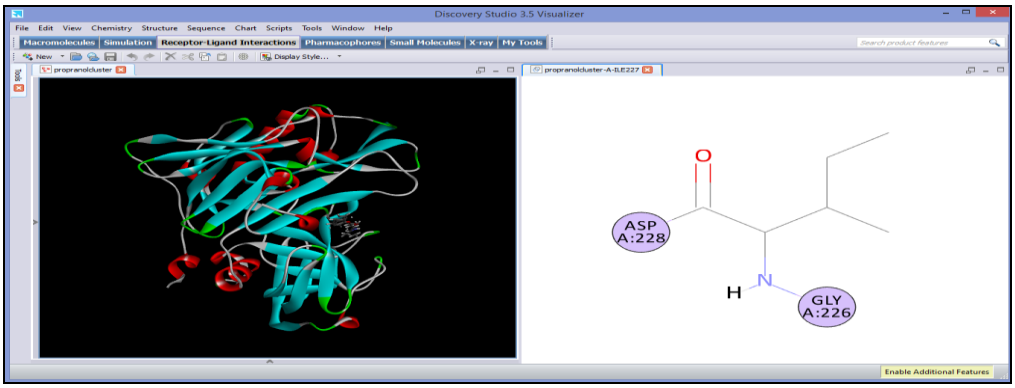

Figure No. 40: Propranolol docked with BACE1 shown in 2d and 3 D using DS visualize

4.2 DISCUSSION

From the data (Table 1), it was observed that among the 12 phytoconstituents selected, Ashwagandhanolide, has high molecular weight (974.52) followed by Glycyrrhizin (822.40), Ginsenoside (784.50) and Proanthocyanidine (592.16), and rest of the phytoconstituents are having molecular weight less than 500D which indicates that these phytoconstituents follows one of the Lipinky's rule for oral bioavalibility. Molecular weight is also a significant parameter for determining the toxicity and absorption of the selected ligand, there is a limit of 500D for molecules to be selected as a drug candidate as more is the molecular weight more is the risk of side effects and toxicity. Ashwagandhanolide has high milog P value (5.23) followed by Resveratrol (3.65), Proanthocyanidine (3.63) , Curcumin (3.41) , Withaferin A(3.21), Ginsenoside(2.94), Huperzine(2.71), Rosemarinicacid(2.44), Glycyrrhizin(2.06), Caffeic acid(1.69), Formic acid(-0.34) etc. and least was for Histamine (-1.01). An orally active anti-Alzheimer's phytoconstituents needs not only sufficient metabolic stability to maintain integrity in the intestine and liver but also should cross the Blood-Brain Barrier (BBB). At the molecular level, the BBB is not homogenous but consists of a number of partially overlapping zones contained in a highly anisotropic lipid layer.[5] The conformational mobility of the lipid chains is relatively low at or near the water (blood)/ lipid interface and interface at the center of the bilayer. In addition, the hydrophilic/lipophilic interface at the blood/membrane boundary consists of perturbed and bound water, charged polar lipid head moieties connected to long lipid chains. As a result, a phytoconstituents approaching the BBB is confronted with a thick layer that is capable of non-covalent interactions with the phytoconstituents, similarly to that of receptor but with much looser steric requirements. High lipophilicity frequently leads to compounds with high rapid metabolic turnover[6] and low solubility and poor absorption. As lipophilicity (LogP) increases, there is an increased probability of binding to hydrophobic protein targets other

than the desired one, and therefore, there is more potential for toxicity. The biological activity of a phytoconstituents was almost entirely due to their Log P and their rate of metabolism was linearly related to LogP. Furthermore, optimal activity is observed at LogP = 2.[7] The phytoconstituents used to treat neurological disorders have LogP value mostly between 2 to 4.Subsequently, indicated that LogP is predominantly a measure of phytoconstituents volume or surface area, plus hydrogen bond acceptor potential. Thus, both hydrogen bonding potential and phytoconstituents volume contribute to permeability. Lipophilicity was the first of the descriptors to be identified as important for CNS penetration,[8] reasoned that highly lipophilic molecules will be partitioned into the lipid interior of membranes and will be retained there. The Polar Surface Area (PSA) and the molecular volume components were the most important descriptors, with PSA strongly predominating.[9] Histamine (43.19 $A^{2)}$, Huperzine (45.34 A^2), Formicacid (29.25 A^2), and Resveratrol (52.82 A^2) were showing respective PSA values[10] developed a dynamic PSA approach whereby the set of available conformations were used and the contribution of each to the overall PSA was calculated using a Boltzman distribution thereby taking into account conformational flexibility.[11] found that the phytoconstituents can be targeted to the CNS with a PSA less than 60–70 Å2. Similar conclusions were made by van de Waterbeemed based on a study of marketed CNS and non-CNS phytoconstituents.[12] Their cutoff for PSA cutoff for CNS penetration is 90 Å2 or below and a molecular weight cutoff of 500. The PSA was in range for all the phytoconstituents. HBA and HBD of the corresponding molecules that are Ginsenoside, Glycyrrhizin, Ashwagandhanolide and Proanthocyanidine were found to be higher than the maximum level ie; HBA more than 10 and HBD more than 5, with rest of them showing vales within the range . All the QSAR equations emphasize the importance of hydrogen bonding whether through polarity, PSA, hydrogen bond donor and acceptor counts, or simply counting heteroatoms capable of hydrogen bonding. All of these measurements are correlated, for instance, (O + N) atom count is highly correlated with PSA but measures hydrogen bond acceptors. CNS penetration requires a sum of these Compounds with high hydrogen bond forming potential, such as peptides with their amide groups, peptides even as small as di- or tripeptides, have minimal distribution through the BBB. Increasing hydrogen bonding decreases BBB penetration. It should be pointed out that there are other heteroatoms in phytoconstituents that can function as hydrogen bond acceptors (HBA) and total HBA, including (N + O) would probably give a better measure.

From Table 2, the rotatable bonds were present in Caffeic acid, Histamine and Resveratrol[2], Withaferin,[3] Proanthocyanidine[4], Glycyrrhizin and Rosemarinicacid,[7]and Ashwagandhanolide[8] Huperzine and Formicacid does not have any nrotb. Rotatable bond count is now a widely used filter following the finding that greater than ten rotatable bonds correlates with decreased rat oral bioavailability[13] CNS phytoconstituents have significantly fewer rotatable bonds than other phytoconstituents. Most centrally acting compounds have rotatable bond count of five or less. Apart from these, it was also observed that Ashwagandhanolide has high volume (1130.51 A^3), followed by Glycyrrhizin (862.79 A^3) rest as per mentioned in table 2 and Formicacid has least (36.86 A^3). Figures 1, 2, 3, 4, 5, 6 7, 8, 9,10, 11, 12 showing drug likeness model score based on molsoft software prediction. Drug likeness score was highest for Proanthocyanidine and lowest for Caffeicacid. The subtle modification in Glycyrrhizin, Ginsenoside, Proanthocyanidine and Ashwagandhanolide which violates Lipinski's rule of 5 can make it good oral drug candidate.

These property was selectively applied to chosen phytoconstituents which were not violating rule of Lipinsky. Withaferin was showing significant value for enzyme inhibitor(0.94) and nuclear receptor ligand(0.76), Rosemarinicacid was showing significant value for nuclear receptor ligand(0.57) and Huperzine has significant value as enzyme inhibitor(1.13) . As per the data presented in the Table 3, it was evident that three phytoconstituents were having property to be druglike and could be targeted against nuclear receptor and may act as enzyme inhibitor also, further computational and statistical studies to support the current findings.

Docking

Docking is done by Hex 8.0.0 for BACE1 receptor against six drugs- diovan, galanthamine, tacrine, hydralazine, propranol, rivastigmine and eight phytoconstituents- caffeic acid, curcumin, formic acid, histamine, huperzine, resveratrol, rosemarinic acid, withaferin A. The selection of target protein was done from the literature. The selected protein was docked and the free energy of binding were obtained. The docking study showed that phytoconstituents Curcumin, Huperzine, and Rosemarinicacid were showing better energy score compared to Galanthamine whereas Withaferin A, has better energy score comparing to Diovan . The non-covalent interactions of each drug molecule with active site amino acid resides were shown in Figure No (28-40), the common amino acids which shows interaction with most of the selected phytoconstituents and drugs were serine, glycin tryptophan and asparagine, Most of the interactions were contributed by hydrophobic, ionic and hydrogen

bonds. Though drugs and phytoconstituents interact with BACE1 receptor; it is required to understand the mechanism and binding energy and non-covalent interactions, this shall be considered as base work for further *In vivo* study.

CONCLUSION

The phytoconstituents which were selected for study out of which Withfarin A and Rosamarinic acid had shown better results in terms of ADME properties as well as druglikness model score and bioactivity , docking energy of Withafarin A and rosamarinic acid was better than standard drug galanthamine on the basis of these results it can be predicted that Withfarin A and Rosamarinic may act as better leads and can be considered as novel effective treatment against AD alongwith standard drugs.

Conflict of Interest: None Declared

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