Original Article

Efficacy of Flavonoids and Xanthonoids on Alzhiemer's Through Multiple Targeting as Evidenced by Cross Docking

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ABSTRACT

Aim: The present study aims for comparative molecular multiple docking to recognize the potential Anti-Alziehmers Drug among flavonoids and Xanthonoids.
Study design: The multiple docking approach was taken using Schrodinger to identify flavonoids and xanthonoids as potential drug leads for Alziehmer's.
Place and duration of study: The study was conducted at "Bioinformatics Infrastructure Facility", CAS in Crystallography and Biophysics, University of Madras, Chennai. The study began in August 2015 and got culminated in January 2016.
Result: Docking of flavonoids and Xanthonoids has been performed against different protein targets as well as with the final best target viz: CDK5/p25 using Induced fit docking module of Schrodinger 09 and rational binding mode has been discussed and determined . The results revealed the following: 1) several targets such as CDK5/p25, JNKs, Hfpps, HSP90 and Aminotransferases, identified in this study are proposed as best putative targets for flavones and flavonoids rather than Xanthonoids. Docking studies predicted the binding mode of flavonoid compounds were very well as compared to Xanthonoids.
Conclusion: This study opens the path for optimizing luteolin as potential Drug candidate for the treatment of AD.

Keywords: Flavnoids, Xanthonoids, Cyclin dependent Kinases, Multiple Docking, Alziehmer's Disease.

INTRODUCTION

Cyclin-dependent kinase 5 (CDK5) belongs to the family of proline-directed serine/threonine kinases[1-4]. Adult neurons get developed by the regulation of CDK5 which plays an important role in neuronal migration during the reinforcement of the central nervous system[5.6]. Uncontrolled upregulation of CDK5 by the shortened

activators paves the way for neurodegeneration by changing the phosphorylation state of cytoskeletal and cytosolic proteins. This increased CDK5 activity is implicated in Alzheimer's Disease[7,8,9]. In AD, senile plaques formed by aggregation of 40- to 42-amino acid (aa) long, 39 and 43-aa peptides have been described, amyloid-β (Aβ) peptide. Amyloid-β is formed by cleavage of Amyloid precursor protein (APP) B by β and γ-secretases. Cleavage of APP by γ-secretase produces a 42-aa Aβ-42 or a 40-aa Aβ-40 formation when it occurs in endoplasmic reticulum or trans-Golgi network respectively[10-12]. Gamma-secretase is a trans-membrane aspartyl protease comprising of four subunits, viz- Anterior Pharynx Defective Phenotype (APH-1), Presenilin (PSEN), Nicastrin (Nct), and (PEN2) i.e Presenilin 2 Enhancer. Presenilin is recognised as the catalytic nerve center of gamma-secretase bearing two aspartyl residues at the catalytic site[13,14]. The consequent step in the processing of Amyloid Precursor Protein (APP) to yield Amyloid Beta peptide (Aβ) is governed by Gamma-secretase[15]. Inhibition of processing of APP by gamma-secretase is a fortuitous arbitration strategy for AD therapeutics.

Previous structural studies have revealed the interactions between the inhibitors and the binding site, prioritize CDK5 for the (*R*)-roscovitine stereoisomer and comprise an arena for drug design of more efficacious and eclectic inhibitor as compared to aloisine-A and indirubin-3'-oxime inhibitor moieties. For this reason we docked the R-roscovitine – CDK5/p25 complex as a cocrystalised complex[15]. p35 or p39 act as the neuronal-specific activator which regulates CDK5 activation. CDK5 Deregulation in Alzheimer patients has been found due to p25 accumulation, a truncated fragment of p35[16-18]. Essence of CDK5 in neuronal activity modulation opens up the path for us to design inhibitors which might restrict the phosphorylation of tau and neurofibrillary pathology. Amyloid precursor protein (APP) proteolysis, involving the combined effort of β and γ-secretases leads to the production of Aβ peptides via the amyloidogenic pathway . Considerable synthesized compounds like R-roscovitine have been reported for inhibition of CDK5/p25 inhibitor[19] . There are only meager US Food and Drug Administration (FDA) proven drugs in the market for treating AD patients as of today such as tacrine, donepezil, rivastigmine. Even though, by administering these drugs, there has been an improvement in the cognitive function of AD patients yet disease progression remains standstill eventually. Furthermore, ample number of drugs with variety of targets and clusters of mechanisms being straightaway in various stages of clinical investigation, yet the therapeutic development for this disastrous disorder has been big hurdle for physicians, researchers, pharmaceutical industry, with many drugs showing potential at one stage of clinical research fizzle at the next barricade. The scantiness of currently available drugs and their limited targets in AD pathology with proved side effects implicates the dire need for the evolvement of new generation drugs.

As per the complexity of AD pathogenesis is concerned, Classic "Each target, One molecule" key may not be adequate enough. Recent research has revealed that multi target direct strategy has received keen attention of researchers for multi targeted drugs having curative potential.[20] Anti Alzhiemer Potential of Flavonoids has been disclosed more precisely as it was reported that they drastically reduce the β-amyloid production. Statistical studies have observed different pattern of Grey Matter (GM) volume reductions may help us in understanding

different behaviours in people with AD.[21] Certain Methanolic Extracts have been shown to have Neuropharmacological Activity using mice model.[22] Various Findings have emphasized the importance of dietary flavonoids in AD therapy.[23-25] For now multiple targeted drugs would have a recuperative window than those hitting a single target and thus paving the way for safer drugs. Therefore, the current study explores molecular docking studies to probe the binding interaction between flavonoids and different anti-Alzheimer drug targets. To identify the lead compounds, Natural Products are the rich sources. The biggest treasure for Modern Medicine are either obtained from the natural sources or obtained from the lead compound which might have been originally obtained from the natural source. (Natural products are rich sources of lead compounds from which many modern medicines have evolved). The level of activity associated with the lead compound may not be gigantic and there may be inexpedient side effects. But the lead compounds do have pharmacotherapeutic capability in context of the drug design and development process.

Molecular docking Procedures

The aim of molecular docking is to adumbrate the binding modes of protein-ligand complex and thus, define the orientation of molecule with respect to the other. In this method, according to the affinity score in terms of (kcal/mol),for ranking all the binding poses of the molecule inside the catalytic site of an enzyme the Schrodinger software has been used .We performed the Docking studies of various Xanthonoids and flavonoids with different protein targets as shown in table 1.

Herbal Ligands Screening

Herbal leads were identified from ethnobotanical literature and their 3D structures were generated by their SMILES notations obtained from Pubchem, using ONLINE SMILES TRANSLATOR. Compounds (1a-9i) like Luteolin (1a) , Bacoside (2b) ,Kaempferol (3c) ,α Mangostin (4d), β Mangostin (5e), γ Mangostin (6f), Genistein (7g), Acridone (8h) and Asiaticoside (9i) shown in Fig 1, were taken for Docking procedure. (Luteolin (1a), Bacoside (2b), Kaempferol(3c), α-Mangostin(4d), β-Mangostin (5e), γ-Mangostin(6f), Genistein (7g), Acridone (8h), Asiaticoside(9i) flavonoids and xanthonoids from plant sources were taken as ligands for molecular docking. The targets CDK5/p25 were used for the docking analysis. This study is strongly focused on targets, ligands, used to search out the best inhibitors for AD therapy.

MATERIAL AND METHODS

Preparation of the Ligands and Protein

The reported phyto compounds (flavonoids cum xanthonoids) were taken for minimization using Ligprep module of Schrodinger 09,[26,27] where (with) probable tautomeric and ionization states at pH = 7 ± 1 followed by minimization with OPLS 2005 force field. The protein preparation of different targets with PDB ID's : CDK 5(PDB ID:1UNG), 3OX1, 4LPG , 4LPH, 4NH9 and 2ABJ was executed applying Protein preparation wizard of Schrodinger 09 where missing hydrogen bond order were assigned followed by energy minimization.

Molecular Docking

The receptor grid was prepared keeping cocrystal (R-roscovitine) ligand on CDK 5 (PDB ID:1UNG) at the centre of grid with 20Å edges bearing catalytic site. Similar procedure of receptor grid preparation was followed for the rest of the Protein targets- PDB ID's as mentioned above. Initially docking study of the cocrystal was performed on prepared

receptor grid for cross-validating the binding mode with respect to X-ray crystal structure binding mode. Further, molecular docking was performed for both flavonoids and xanthonoids as ligands against CDK and different protein targets using Glide XP 5.8 Program.[27] The top poses of flavonoids cum Xanthonoids were parameterized based on docking score as well as (and) binding interaction with catalytic residues were allowed for induced fit docking.[28] The results were compared with the cocrystal after Glide XP. Corresponding to the lowest free energy (or highest score) provided by Glide program the docked conformation was selected as the most probable binding pose of top compounds.

RESULTS

Docking studies of Flavonoids and Xanthonoids with Different targets as well as CDK5/p25

In this study, docking of flavonoids and Xanthonoids has been performed against different protein targets as well as with the final best target viz: CDK5/p25 using Induced fit docking module of Schrodinger 09 and rational binding mode have been discussed and determined the binding free energies in terms of docking score. Docking studies predicted the binding mode of flavonoid compounds were very well, binding orientation was compared with R-roscovitine.

DISCUSSION

Visualisation of Docking Results

Once docking was performed, best poses for hydrogen bonding, Hydrophobic and π interactions were analysed using Chimera Visualisation tool.[29] , PyMol version 1.3 (The PyMOL Molecular Graphics System;) and Glide (Schrödinger, LLC, New York, NY, USA) programs.

Interaction of flavonoids and Xanthonoids with potential targets

Six potential protein receptors with anti-alzheimers effect were selected for docking. Based on the interaction of protein receptors with different Compounds, docking score and Glide energy of the best docked ligand-receptor complex poses are cited in table 1. For every target protein a total of 8 poses, in some cases 10 poses , for each of the flavonoid and xanthonoid (Compound 1a-9i) so as to identify the model with best minimum binding energy cum ligand-receptor interaction. To further scrutinize the ligand-receptor interaction in terms of Hydrogen bonding interaction, best three ligand-receptor interaction were taken into consideration to predict the best binding mode with best receptor for being effective Drug candidate. Comparison of best docking predicted activities of compounds viz: Luteolin (1a), Bacoside (2b) and Asiaticoside (9i), against targets viz: PDB ID's:1UNG, 4LPG & 4LPH respectively are shown in Table 2, and signified that all the docked compounds bound very well with preferably binding orientation and conformation. The hydrogen bond interactions of the selected best compounds at the active site of the target protein is shown in Figures 2,3 and 4. Fig 2 (a &b) represent the binding of CDK5/p25 with compound (2b), while as the Fig 3 (c&d) show the binding mode of compound (1a) with Hfpps at its active site, and Fig 4 (e&f) represent binding mode of CDK5/p25 with best lead (1a). Among the all ligand-receptor complexes, compound (1a) - CDK5/p25 docked complex came to be more effective in terms of binding, hydrogen bonding and Hydrophobic interactions. Compared to Xanthonoids like Mangostins , Flavonoid compounds, as discussed above, particularly Luteolin, were more competent, interacting with all docked targets showing variable affinities, thus indicating that these

ligands possess comprehensive structural features that qualify them proficient for recognizing numerous significant target proteins and thereby, having a therapeutic potential to curb Alzheimers disorder.

Inter molecular interaction of luteolin with CDK5/p25

Hydrogen bond interaction between CDK5/p25 and best docked compound viz: luteolin- compound (1a) showed similar hydrogen bonding interaction patterns with residues like Cys 83, Asp 86 and Lys 89 compared to co-crystallized R-roscovitine. Compound (Luteolin) (1a) also contributed to more hydrophobic interactions with Ile10, Leu133, Ala143, Phe145, Val18, Ala 31, Phe 32, Leu 55, Val64, Glu81, Phe82, Asp 84, Gln 85, compared to R- roscovitine, compound 2b and 3c. Among the given set of flavonoids, compound (Luteolin) 1a has more hydrophobic interactions compared to R-roscovitine. Although all flavones and flavonoid derivatives mostly interact with hydrogen bonding and Hydrophobic interaction, yet interaction was more prominent in Compound 1a compared to compound 2b and 3c. Although all flavonoids and xanthonoids interact with hydrogen bonding and exhibit hydophobic interaction, luteolin (1a) interaction was more prominent when compared to bacoside (2b) and kaempferol (3c).

FURTHER STUDIES

Studies are under process to investigate the effect of Flavonoid and Xanthonoid Derivatives in Induced models of Alzheimer's Disease.

CONCLUSION

As all the compounds were from natural source bound very well, In current Study a comparative molecular multiple docking approach was taken using Schrodinger to identify the potential Anti-Alziehmers Drug for flavonoids cum Xanthonoids. The results revealed the following: 1) several targets such as CDK5/p25, JNKs, Hfpps, HSP90 and Aminotransferases, identified in this study are proposed as best putative targets for flavones and flavonoids rather than Xanthonoids; 2) a number of targets identified by docking, such as CDK5/p25, JNKs and HSP90 have already been verified by experiments for their inhibition by flavones; 3) it is proposed here that the compound Luteolin 1a binds to the CDK5/p25 active site with preferable orientation and conformation so that it may act as an inhibitor of that enzyme. Structure analysis shows that binding free energy, electrostatic interaction and hydrogen bonding play a pivotal role in their binding process and seems to be better as compared to R-roscovitine. This study opens the path for optimizing Luteolin as a potential drug candidate for the treatment of AD.

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CONFLICT OF INTEREST

The author(s) confirm that this article has no conflict of interest.

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Table 1: Results obtained after docking of Flavoniod compounds (1–9) with various protein targets

COMPOUNDS	Luteolin (1a)		Bacoside (2b)		Kaempferol(3c)		α-Mangostin (4d)		β-Mangostin (5e)		γ-Mangostin (6f)		Genistein (7g)		Acridone (8h)	Asiaticoside (9i)		
Targets	GS	GE	GS	GE	GS	GE	GS	GE	GS	GE	GS	GE	GS	GE	GS	GE	GS	GE
1UNG (CYCLIN DEPENDENT KINASE 5 (CDK 5))	-12.69	-51.74	-7.97	-63.07	-9.23	-43.82	-6.39	-43.17	-4.93	-32.15	-9.5	-53.06	-7.66	-47.60	-8.47	-33.24	-12.98	-81.25
3OXI (c-Jun N-TERMINAL KINASES (JNKs))	-12.76	-50.54	-10.13	-44.53	-9.70	-45.10	-9.26	-43.88	-6.67	-36.56	-10.65	-51.36	-8.81	-41.50	-7.23	-34.72	-7.86	-53.28
4LPG (FARNESYL PYROPHOSPHATE SYNTHASE (hFPPS))	-8.25	-46.57	-8.90	-68.09	-8.25	-47.68	-8.74	-51.29	-6.18	-41.29	-6.15	-43.78	-7.22	-43.25	-5.68	-33.24	-9.47	-71.61
4LPH (FARNESYLPYROPHOSPHATE SYNTHASE (hFPPS))	-7.90	-48.93	-9.23	-71.51	-7.88	-43.79	-6.39	-43.17	-8.73	-49.11	-8.73	-49.10	-7.35	-43.58	-6.41	-32.39	-11.48	-72.10
4NH9(HEAT SHOCK PROTEIN(HSP90))	-7.97	-49.77	-13.73	-64.20	-7.66	-45.52	-6.72	-50.14	-6.55	-41.34	-6.73	-47.51	-7.50	-48.01	-6.13	-32.35	-11.69	-59.69
2ABJ(AMINOTRANSFERASE)	-7.94	-49.72	-10.04	-75.19	-6.64	-42.39	-6.72	-50.14	-6.31	-43.64	-7.59	-41.79	-7.50	-48.01	-6.08	-40.14	-13.51	-77.26

Where GS Represents Glide Energy, DS represents Docking Score , H-BOND represents Hydrogen Bond

Table 2: Induced Fit Docking (IFD) results of the best two ligand-receptor and their Hydrogen bonding interactions

	1UNG			4LPG			4LPH		
Compound	**GS**	**GE (Kcal/mol)**	**H-Bond**	**GS**	**GE (Kcal/mol)**	**H-Bond**	**GS**	**GE (Kcal/mol)**	**H-Bond**
Luteolin (1a)	-12.69	-71.74	(Cys83) N-H---O O-H---O(Cys83) (Lys 33) N-H---O O-H--O(Asn144) (Cys83) N-H---O O-H---O (Cys83) O-H---O (Asp86) (Lys 89) N-H---O O-H---O (Glu 51)	-12.76	-50.54	O-H---O (Ser205) O-H---O (Ser205) O-H---O(Asp 243) (Arg 60) N-H---O	-7.97	-52.57	O-H---O (Ser205) O-H---O (Ser205) (Ser205) O-H---O (Lys 57)O-H---O
Bacoside(2b)	-10.97	-63.07	(Asn144)O-H---O (Tyr15)N-H...O (Lys 128) N-H---O (Lys 89) N-H---O	-10.13	-44.53	O-H---O (Tyr 349) O-H---O (Tyr 349) (Arg 60) N-H---O (Arg 60) N-H---O (Arg 113) N-H---O O-H---O (Tyr 349) O-H---O (Tyr 349) O-H---O (Asp8)	-10.04	-75.19	O-H---O (Gln 241) (Tyr 191) O-H---O O-H---O (Phe 47 (Arg161) N-H---O (Tyr 159) O-H---O
Asiaticoside (9i)	-12.98	-81.25	(Lys33)N-H...O O-H---O(Asn114) (Tyr15)N-H...O O-H---O(Asn131) O-H---O(Cys83) (Asn144)N-H---O	-9.47	-71.61	(Asn243)O-H...O O-H---O(Lys347) O-H---O(Gly55) O-H--O(Arg113)	-13.51	-77.26	(Arg161)N-H---O O-H---O(Gln242) (Lys220)N-H...O O-H---O(Gly248) (Gln242)N-H---O (Cys333)N-H---O

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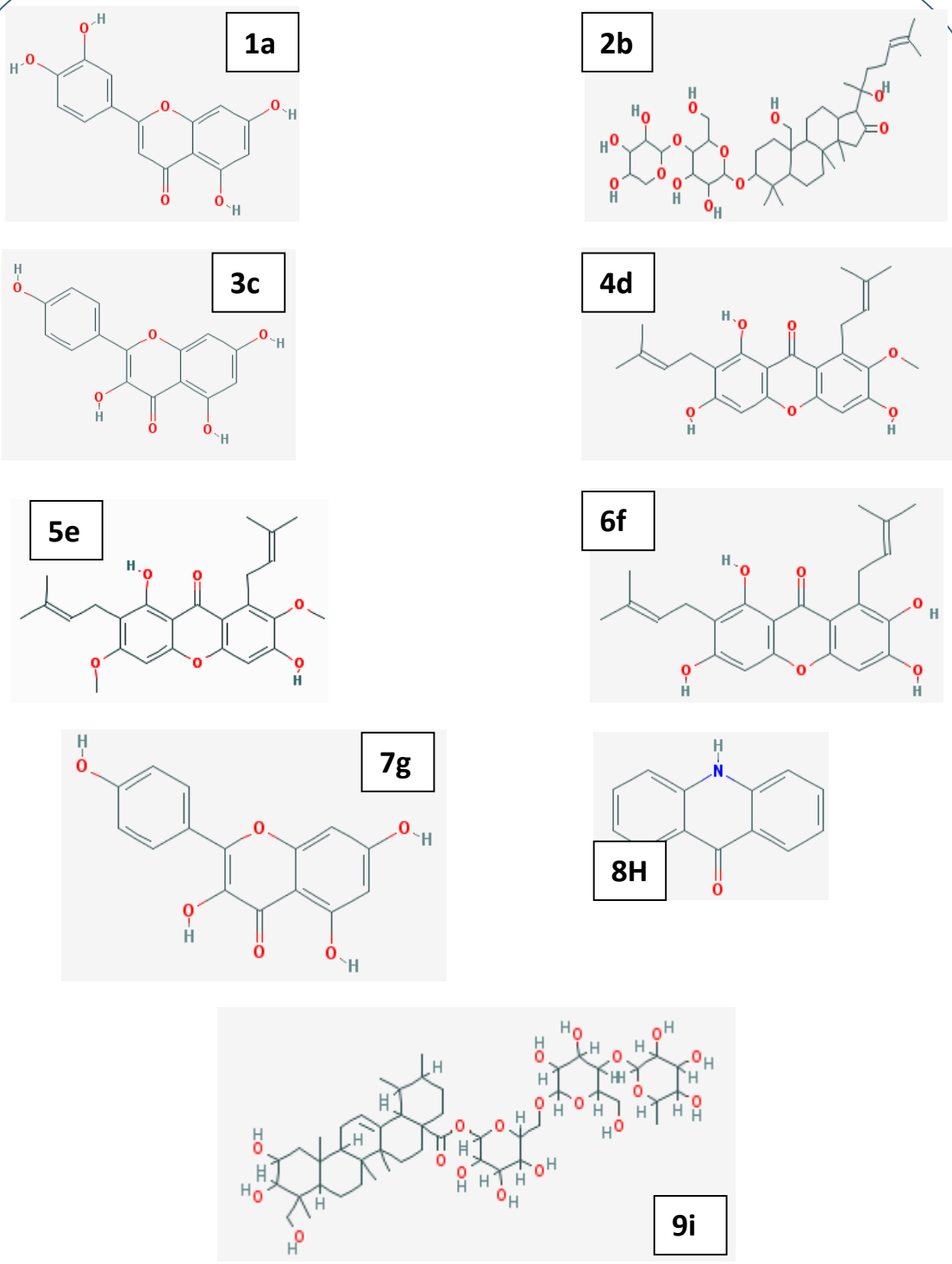
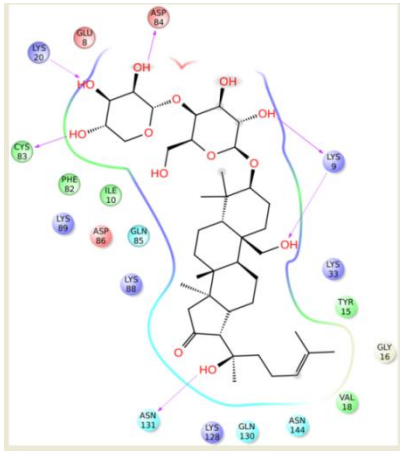
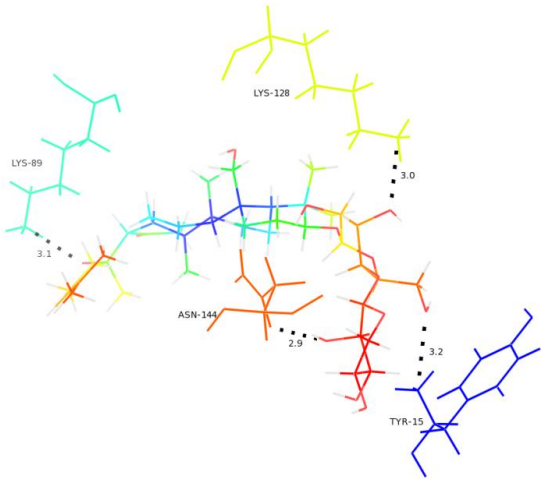


Fig 1. Chemical structure of compounds 1a-9i used for Docking



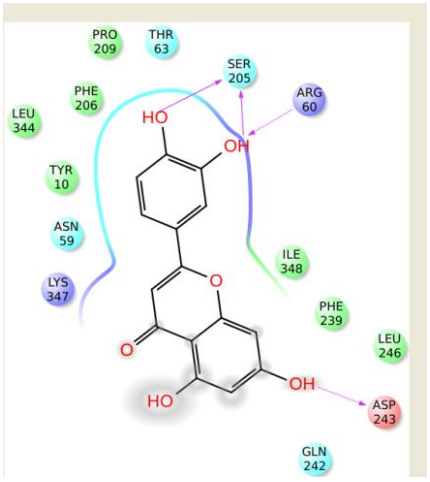


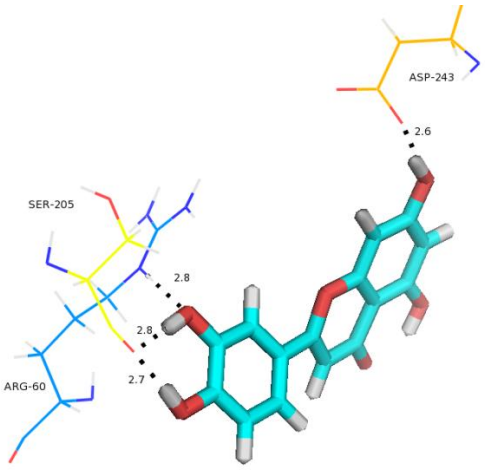
(a) **(b)**

Interaction Diagram showing interaction of Bacoside with Cdk5/p25

Diagram showing interaction of Bacoside with Cdk5/p25 using Pymol Software

Fig 2. Induced fit docking results of the Cdk5/p25 with the lead 2b



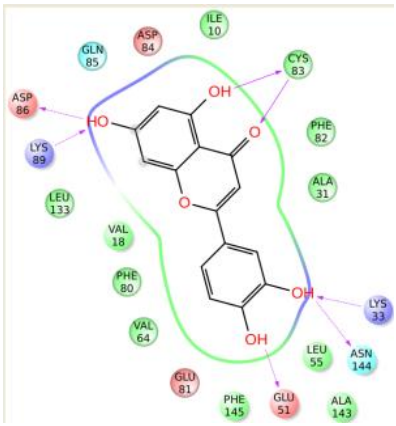


(a) **(b)**

Interaction Diagram showing interaction of Luteolin with hFPPS.

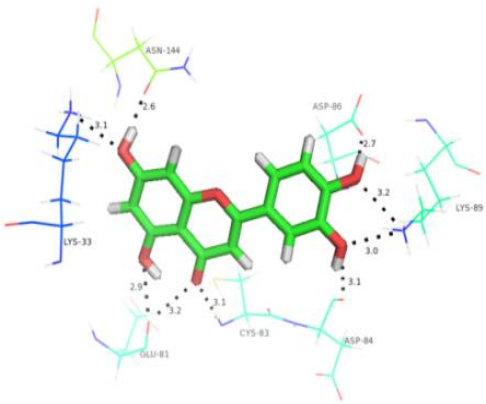
Diagram showing interaction of Luteolin with hFPPS using Pymol Software tool.

Fig 3. Induced fit docking results of the hFPPS with the best lead 1a



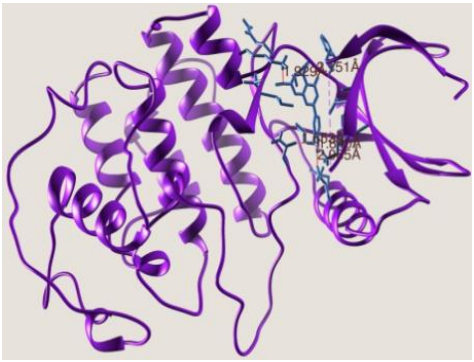
(a)

Interaction Diagram showing interaction of Luteolin with Cdk5/p25.



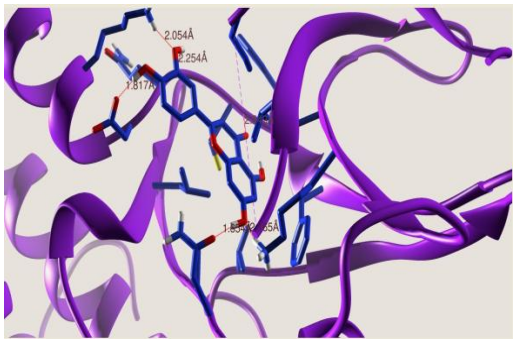
(b)

Diagram showing interaction of Luteolin with Cdk5/p25 as viewed in Pymol.



(c)

Diagram of Best pose showing interaction of Luteolin in ribbon model with Cdk5/p25 using Chimera Visualiser.



(d)

Diagram showing hydrogen bonding interaction of Luteolin with Cdk5/p25 using Chimera Visualiser.

Fig 4. Induced fit docking results of the Cdk5/p25 with the best lead.