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ORGINAL RESERACH

An in-silico Approach for the Retrieval of Potential anti β- secretase Inhibitor abate Alzheimer's Disease

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Abstract: Alzheimer disease (AD) is a neurodegenerative disorder and still posing challenges to the scientific community for designing and developing a novel drug. The in-silico drug design approach dispenses tools for reducing time, cost, and energy associated with reducing the legends number for experimental and in-vivo assays. An extensive literature survey was performed for collection of bioactive phytochemicals. After that, a structure-based drug design approach was deployed to explore potential inhibitory phytochemicals against β- secretase for the treatment of AD. The molecular docking and pharmacokinetics analysis was performed. The present research, has led to the unraveling the poof potential of phytochemicals against β- secretase. The sanjoinenine, luteolin and vasicinone phytochemicals are identified as potential lead molecule for in-vivo studies.

Keywords: Neurodegenerative disorder; Phytochemicals; Computeraided drug design; β-secretase

1. Introduction

The rigorous search, validation and experimental evaluation of new potent molecules is now some days on the blooming stage. The joint effort of high-throughput screening (HTS) and combinatorial chemistry techniques are playing major roles in blooming in drug development. The computer-aided drug design (CADD) is a scientific discipline that allows the amalgamation of different chemical-molecular-quantum-mechanics-chemistry for discovering, designing and developing novel therapeutic targets. The CADD is multa idisciplinary approach aiming to improve bioactive molecules and exploring the biological interaction between two biomolecules at the molecular level. The CADD process passes three key stages, the discovery stage, the development phase and the registry phase(Ferreira et al., 2015)(Liu et al., 2021). With the new advancement in the artificial intelligence , it is possible to solve complex issues in the pharmaceutical field(Katiyar, 2022)(Srivastava et al., 2021).The CADD techniques allow the development of new therapeutic candidates against parasites that poses hurdles for in-vitro propagation and cultivation(Kalpna et al., 2018)(Katiyar et al., 2021)(Kalpana & Nath, 2020).The application of cheminformatics, big data ,deep learning, polypharmacology, target fishing, virtual screening, chemical space and structure multiple-activity relationship are also widening the role and prospects of the CADD (Kapetanovic, 2008)(Katiyar et al., 2022). Alzheimer disease (AD) is a notorious neurodegenerative dementia disorder resulting in neuropsychiatric, cognitive and behavioural disability. It is estimated that approximately 35 million people worldwide are suffering with AD(Kumar et al., 2017). About one in ten adults of age more than 65 years and 50 % of age more than 85 years develop AD symptoms. It is stipulated that reliable and versatile drug development for AD could save $1.2 trillion to $3.97 trillion fund by the year 2050(Barman & Prabhakar, 2014). Alzheimer's disease is classified as a composite brain dementia disorders that in in course of time crash down the thinking and memory skills. The patients suffering are faces challenges in performing simple cognitive functions. It has been documented that in 2022 more than 6 million Americans of age 65 year and more are pretentious with Alzheimer induced dementia. The mammalian

brain consist of millions of neurons specialized for message transmission among neurons, neurons to other body parts, muscles and organs. In Alzheimer disease, anomalous beta-amyloid protein forms clumps between neurons. In later stage, tau protein accumulated over clumps resulting in tangle formation in neurons. As diseases progresses, tau tangles and beta-amyloid plaques creates hindrance in neurons functioning and ultimately degeneration of neurons. AD and other neurodegenerative disease (amyotrophic lateral sclerosis, spinal cerebellar, bulbar muscular dystrophy and Parkinson's disease) are associated with 'protein -misfolding' and profound degeneration of neurons. In these pathologies, amyloid plaques (extracellular) and neurofibrillary tangles (intracellular) are considered main causative factors(Makhouri & Ghasemi, 2018). The amyloid beta (Aβ) peptides made up of 1-40/42 amino acid residues are begins to deposit and aggregation. Inside central nervous system, Aβ peptides are produced by sequential breakdown of plasma membrane associated amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase enzyme.

The beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) and BACE2 are plasma membrane associated secretase proteases of the pepsin family. The BACE1 and BACE2 show 59 % homology in primary structure. BACE1 is more abundant in nervous tissues whereas BACE2 is more abundant in pancreatic beta cells and melanocytes. β- Secretase (BACE 1) is an aspartyl protease type 1 transmembrane protein. The central nervous system cells specially neurons, astrocytes and oligodendrocytes constitutively express BACE1. The plasma membrane and endosomal compartments are intracellular sites of BACE1. The amyloid- β (A β) plaques and synaptic terminals are also laden with BACE1(Hampel et al., 2021). The literature documented two types of APP degradation pathway. The non-amyloidgenic pathway cleaves APP in absence of β- secretase enzyme. The amyloidgenic pathway cleaves APP in the presence of β- secretase. The amyloid precursor protein (APP) and β- secretase glycosylated in the endoplasmic reticulum before reaching the plasma membrane via Golgi body transportation machinery. The endosomal membrane system metabolizes more than 50 % of APP and the remaining amount is cleaved by α-secretase enzyme. During processing of APP, α-secretase and β-secretase competes in the trans-Golgi network (TGN) resulting in APP temporarily accumulation. The β-secretase induced cleavage of APP increases endosomal internalization. The γ-secretase present in ER, endosomes and ER clear off the APP cleaved part(Chen et al., 2017).

The acetylcholine enzyme (AChE) is another critical enzyme associated with neuronal signaling. The AD patients' neurons express higher level of AChE. The anti-acetylcholine drugs induce severe side effects. In search of alternative and safer drugs ,20 phytochemicals were identified and their anti-acetylcholine potential was evaluated in-silico mode. The procysnidin B2, hesperidin, glycyrrhizin ,narirutin and rutin emerges a promising bioactive phytochemicals possessing anti-AChE drug potential (Vijayakumar et al., 2018). The substrate β- secretase, a transmembrane protein whose active-site resides in the extracellular domain and made up of Asp228 and Asp32 aspartates residues. The R groups of both aspartates residues coordinated with a single water molecule. This coordination allows R groups f or nucleophilic attack on the carbonyl groups. A β hairpin loop termed as 'flap' lies over the active-site. When the protein in inactive form, the flap exist as open conformation. When the protein is active with substrate or inhibitor ligands, the flap stays in closed conformation. The flap conformation in different stages of β- secretase is a unique feature. Another important structural feature of β- secretase is the presence of 10s loop in the middle of S3 pockets of two β strands. The 10s loop consist of amino acid residues among which one residue is glycine. The open conformation of 10s loop allows higher binding affinity between substrate and S3 pockets. The hydrogen bond formation between glycine residue of 10s loop and substrate further enhances binding affinity and overall substrate and β- secretase interaction(Barman & Prabhakar, 2014)(Patel et al., 2004).

Greater binding between the substrate and the S3 pocket occurs when the 10s loop remains in open conformation. A glycine residue (Gly11) is also contained within which the substrate can form a hydrogen bond, allowing for further stabilization of the 10s loop, as well as the overall β-secretase-substrate interaction. The three parts come together to form a sort of binding pocket for β-secretase substrates or inhibitors. Binding to the active site activates the flap to close and initiates binding by the 10s loop, all to help stabilize the structure. The 2D structure of

β-secretase enzyme and mechanism are shown in Figure 1 and Figure 2, respectively.

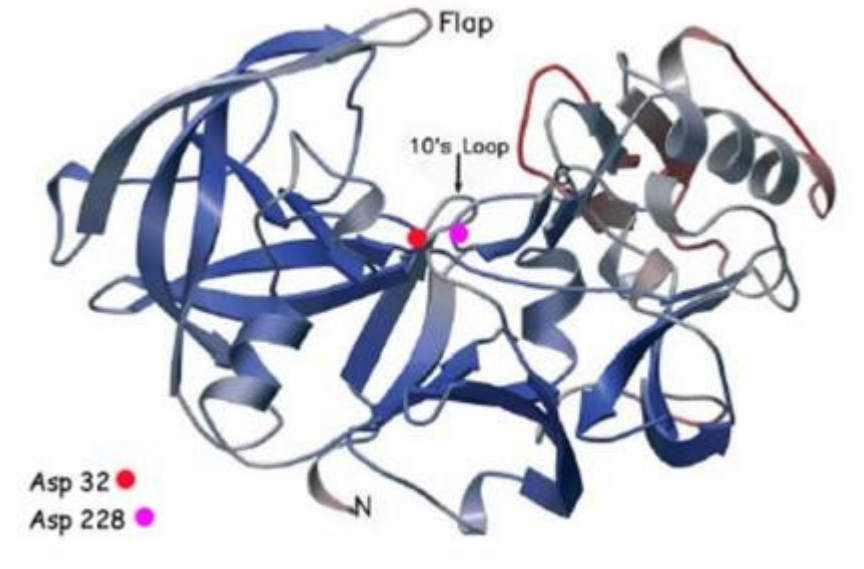

Figure 1. The 2D structure of β-secretase enzyme showing 'flap' and '10s'loop (Chen et al., 2017).

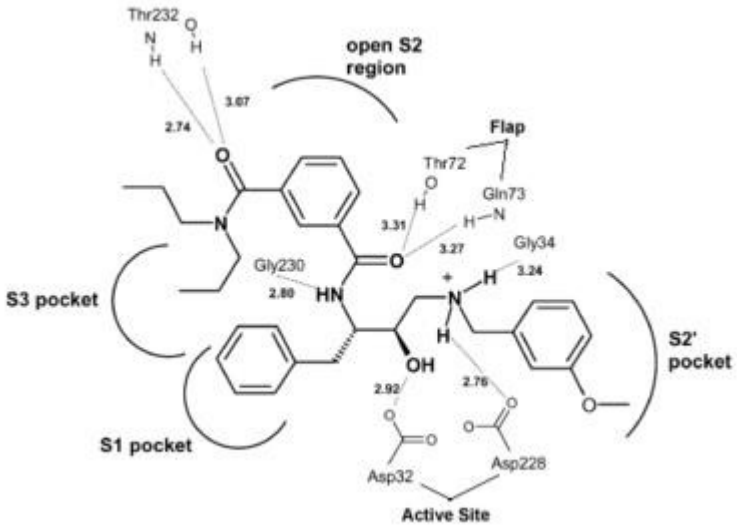

Figure 2. Inhibition mechanism of β-secretase enzyme

Once the inhibitor moves into place, its positively charged amine group and its hydroxyl group start to interact with β-secretase's active site. The nucleophilic attack on the aspartates carbonyls binds selected ligand to β-secretase. As ligand becomes situated within β-secretase's binding pocket, the flap closes upon ligand. The flap's residues are binds to inhibitors

groups Inhibitors should remain stabilized in the pocket by binding to the other pockets of β-secretase(Chen et al., 2017). The inhibitor works well when it is stabilized within β-secretase, the fact that it does not always stabilize keeps the inhibitor from being consumed by human, and for these various other tools are used to minimize drug toxicity . Due to β-secretase function in the production of Aβ, it has become a very popular target for therapeutic drug.

2. Materials and Methods

2.1. Ligand Data Set

In this study, 40 bioactive phytochemicals library were created from the extensive literature survey. These phytochemicals possess anti tuberculosis, anti cancerous, antimicrobial, anti fungal, antioxidant antibacterial and antiviral properties. The structured data format (SDF) coordinates of selected phytochemicals were retrieved from PubChem database (Kim et al., 2019) and converted to Protein Data Bank (PDB) format by Pymol tool.β-secretase (PDB ID :1W51)enzyme 3D coordinates was retrieved from Protein Data Bank (PDB)(Patel et al., 2004).The selected phytochemicals used for this study are shown in Table1.

2.2. Molecular Docking Platform

The AutoDock Vina 4.2 tool was used for docking analysis. The docking analysis is used to predict the bound conformations and binding free energies when ligands bound to complementary binding sites on the target receptor macromolecule. Docking is the most widely used preliminary tools for prioritizing tens of thousands of ligands molecule in structure-based drug design approaches.

AutoDock is the most versatile free source modeling tool for the virtual screening and docking of ligands against a target macromolecule. The AutoDock follows rapid gradient-optimization conformational search approach and empirical free energy force field algorithm for binding energy of phytochemicals with receptor macromolecule was calculated. The three-dimensional coordinates of β-secretase (PDB ID 1W51) bounded with inhibitor was retrieved from PDB. The receptor protein was prepared by removing inhibitor molecule, water and hetro atom removal. The receptor and ligands pdbqt files preparation and grid box generation was done using GUI program of AutoDock Tools. In the protein molecule preparation, polar hydrogen were added, Kollman charges assigned, solvation parameters fixed and the output file is saved in pdbqt format. A grid box was used for grid map preparation with help of AutoGrid tool.

The grid size was fixed at 80x 80x80 xyz points and was generated at the catalytic site of β-secretase (PDB ID 1W51). The catalytic residues of protein receptor macromolecule was accommodated inside grid box. The grid box spacing was set at 1 Å and exhaustiveness was set at 100.The ligands and receptors were treated as rigid during docking. The output less than 0.8 Å in positional RMSD (root mean square deviation) was clustered and saved in the form of most favorable free energy of binding. The Lamarckian genetic algorithm and empirical-free energy was deployed for binding free energy calculations.The docking pose having lowest binding affinity was saved and used for further analysis. The Pymol tool was used for docking result analysis and visualization. The lig Plot+ tool was used for intermolecular interactions analysis.

2.3. Pharmacokinetics Analysis

The success story of any leads after virtual screening determined by the pharmacokinetics analysis. The SwissADME tool was deployed for pharmacokinetics and ADMET analysis of the phytochemiclas. The SwissADME is a free tool for the computational analysis of the ADME parameters, medicinal chemistry stability, pharmacokinetics properties and drug likeness nature prediction. The SMILES notations of the phytochemicals were submitted to SwissADME web server and output were analyzed (Daina et al., 2017).The SwissADME evaluates ligands based on various parameters. The critical parameters are Lipinski Rule of 5, molecular weight (120-800 Da), GI absorbtion, hydrogen bond donor (0-6),hydrogen bond acceptor (2-20) log P (>5) and number

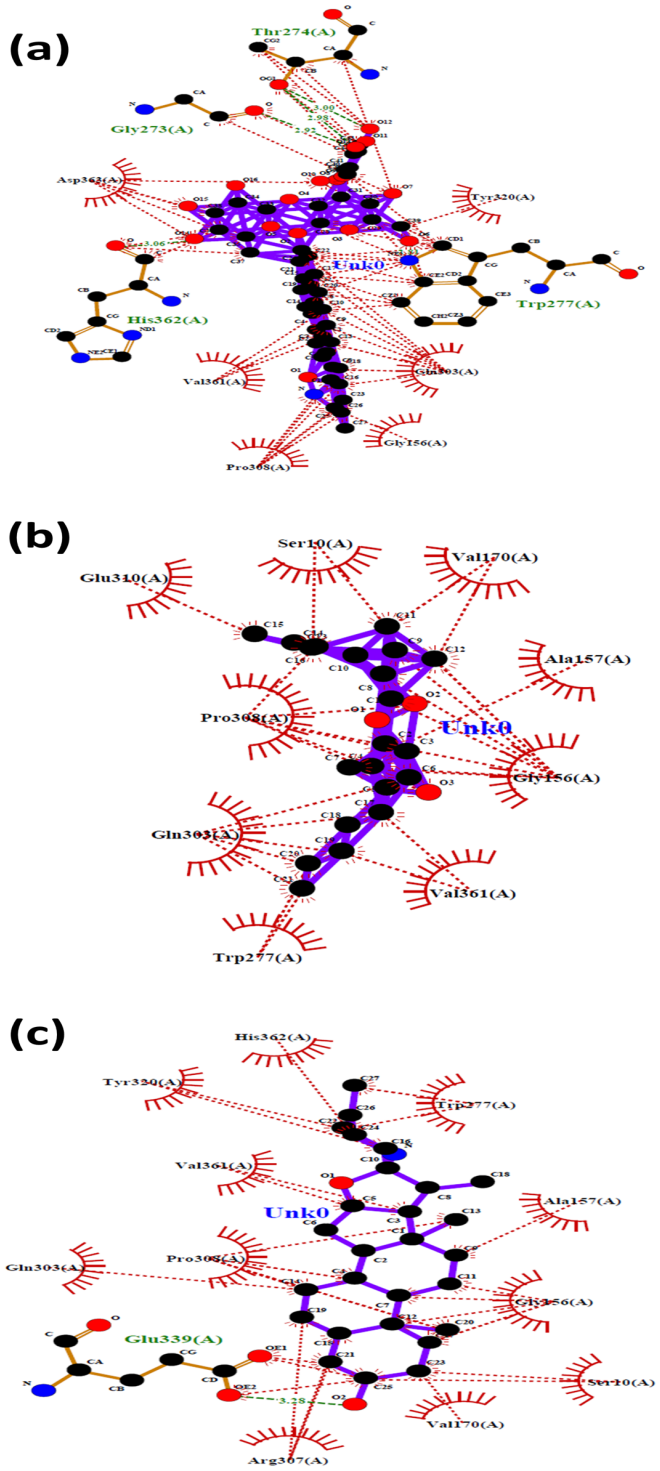

Figure 3. The ligplot interaction diagram of sanjoinenine with β-secretase (a), luteolin with β-secretase (b) and vasicinone with β-secretase (c).

Table 1. List of Phytochemicals

S.No.	Pub-Chem ID	Phytochemical Name	Molecular Weight	Chemical Formula
1	115067	Gastrodin	286.28	C13H18O7
2	44154	Resveratrol	228.24	C14H12O3
3	9793905	S-allyl-L-cysteine	161.22	C6H11NO2S
4	2353	Berberine	336.4	C20H18NO4+
5	965116	N-(imidazo[1,2-a]pyridin-2-ylmethyl)-3-nitroaniline	268.27	C14H12N4O2
6	9651	Galanthamine	287.35	C17H21NO3
7	11702557	Galanthamine hydrochloride	323.8	C17H22ClNO3
8	5288394	Galanthamine Derivative	529.6	C32H37N2O5+
9	89594	Nicotine	162.23	C10H14N2
10	23915	Schisandrin	432.5	C24H32O7
11	72616	Cryptopine	369.4	C21H23NO5
12	119247	Solasonine	884.1	C45H73NO16
13	13250	Ethyl Gallate	198.17	C9H10O5
14	14729078	Sanjoinenine	489.6	C29H35N3O4
15	5280445	Luteolin	286.24	C15H10O6
16	119247	Solasonine	884.1	C45H73NO16
17	702	Ethanol	46.07	C2H6O
18	442935	Vasicinone	202.21	C11H10N2O2
19	5281555	Pyrethrin II	372.5	C22H28O5
20	370	Gallic acid	170.12	C7H6O5
21	5280343	Quercetin	302.23	C15H10O7
22	5321	Toralactone	272.25	C15H12O5
23	6443098	Pyrethrin I and II mixture	700.9	C43H56O8
24	5471349	Bergamottin	338.4	C21H22O4
25	6549	Linalool	154.25	C10H18O
26	1549026	Geranyl Acetate	196.29	C12H20O2
27	99856	Cyperene	204.35	C15H24
28	10955174	Patchouli alcohol	222.37	C15H26O
29	3000322	Scopolamine	303.35	C17H21NO4
30	154417	Hyoscyamine	289.4	C17H23NO3
31	996	Phenol	94.11	C6H6O
32	124052	Glabridin	324.4	C20H20O4
33	128861	Cyanidin	287.24	C15H11O6+
34	7504	Benzylamine	107.15	C7H9N
35	6047	Levodopa	197.19	C9H11NO4
36	5288826	Morphine	285.34	C17H19NO3
37	637858	Piperlongumine	317.34	C17H19NO5
38	638024	Piperine	285.34	C17H19NO3
39	442985	Purapuridine	413.6	C27H43NO2
40	2355	Bergapten	216.19	C12H8O4

of rotatable bonds(>5).

3. Result and Discussion

In this study, computational studies were performed for the identification of most favourable and stable interactions between selected phytochemicals and β-secretase active sites. The results were analyzed and evaluated in relation to the free binding energy value and the phytochemicals possessing lowest binding energy in compare to reference inhibitor were considered as the best lead one that interacts with β-secretase.

Initially the docking calculations were preformed between β-secretase (PDB ID 1W51) and native inhibitor ligand to validate docking protocol. The 3-[({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino)(hydroxy)methyl]-N,N-dipropylbenzamide was used as reference inhibitor for docking protocol validation. The molecular docking was performed to identify the accurate binding site and the potent phytochemicals against β-secretase protein. After the docking, the best-bonded phytochemicals were retrieved. The estimated binding energies of the phytochemicals were summarized in Table 1.By nature, phytochemicals possess more than one medicinal properties. In this work, the binding-free energy of selected 40 phytochemicals were analyzed . The sanjoinenine (PubChem ID 14729078) shows the highest binding affinity of -12.4 Kcal/mol. The solasonine (PubChem ID 5280445) and vasicinone (PubChem ID 442935) shows -10.8 Kcal/mol and -8.5 Kcal/mol binding affinity respectively. These three phytochemicals also shows interactions with key residues of the β-secretase protein as shown in Table 4. The binding affinity of sanjoinenine, solasonine and vasicinone phytochemicals were higher than reference inhibitor ligand. The pharmacokinetics parameters of these three phytochemicals were found in acceptable range.

Table 2. Molecular docking analysis of studied phytochemicals against β-secretase (PDB ID: 1W51)

S.N.	Ligands ID	Free Energy of Binding (Kcal/mol)	S.N.	Ligands ID	Free Energy of Binding (Kcal/mol)
1	14729078	-12.4	**21**	638024	-5.7
2	5280445	-10.8	**22**	115067	-5.6
3	442935	-8.5	**23**	7504	-5.6
4	5281555	-8.1	**24**	3000322	-5.5
5	5288826	-8	**25**	637858	-5.4
6	119247	-7.6	**26**	5280343	-5.4
7	99856	-7.6	**27**	124052	-5.4
8	2353	-7.2	**28**	89594	-5.4
9	1549026	-6.9	**29**	6443098	-5.3
10	154417	-6.8	**30**	442985	-5.3
11	72616	-6.6	**31**	13250	-5.2
12	6047	-6.6	**32**	965116	-5.1
13	10955174	-6.5	**33**	6549	-5
14	2355	-6.5	**34**	9793905	-4.2
15	996	-6.4	**35**	11702557	-4.1
16	5288395	-6.2	**36**	5471349	-4.0
17	5321980	-6.0	**37**	9651	-4.0
18	370	-5.9	**38**	5471349	-4.0
19	702	-5.7	**39**	128861	-3.5
20	23915	-5.7	**40**	445154	-2.7

Table 3. Drug likeness properties of studied phytochemicals

S.N.	Ligands ID	Bioavailability score	HBA	HBD	Log Po/w (iLOGP)	GI absorption
1	115067	0.55	7	5	1.27	Low
2	445154	0.55	3	3	1.71	High
3	9793905	0.55	3	2	1.22	High
4	2353	0.55	4	0	0	High
5	965116	0.55	3	1	2.37	High
6	9651	0.55	4	1	2.66	High
7	11702557	0.55	4	1	0	High
8	5288394	0.55	5	1	1	High
9	89594	0.55	2	1	2.04	High
10	23915	0.55	7	1	3.91	High
11	72616	0.55	6	0	3.36	High
12	119247	0.17	17	10	1.91	Low
13	13250	0.55	5	3	1.21	High
14	14729078	0.55	4	3	3.3	High
15	5280445	0.55	6	4	1.86	High
16	702	0.55	1	1	1.1	Low
17	442935	0.55	3	1	1.67	High
18	5281555	-	5	0	-	-
19	370	0.55	5	4	0.21	High
20	5280343	0.55	7	5	1.63	High
21	5321980	0.55	5	2	2.79	High
22	6443098	0.17	8	0	8.34	Low
23	5471349	0.55	4	0	4.02	High
24	6549	0.55	1	1	2.7	High
25	1549026	0.55	2	0	3.27	High
26	99856	0.55	0	0	3.17	Low
27	10955174	0.55	1	1	2.91	High
28	3000322	0.55	5	1	2.61	High
29	154417	0.55	4	1	2.99	High
30	996	0.55	1	1	1.24	High
31	124052	0.55	4	2	2.97	High
32	128861	0.55	6	5	-2.62	High
33	7504	0.55	1	1	1.43	High
34	6047	0.55	5	4	0.72	High
35	5288826	0.55	4	2	2.55	High
36	637858	0.55	5	0	2.46	High
37	638024	0.55	3	0	3.38	High
38	442985	0.55	3	2	4.26	High
39	2355	0.55	4	0	2.29	High

Table 4. List of interacting amino acids of β-secretase with sanjoinenine, luteolin and vasicinone phytochemicals.

S.N.	Phytochemical name	Interacting amino acid residues
1	Sanjoinenine	His362A,Pro308,Gly156,Val361, Trp277,Gly273,Thr274,Tyr320, Trp277,Val361,Glu303
2	Luteolin	Ser10,Val170,Ala157,Pro308, Gly156,Gln303,Val361,Trp277, Glu310
3	Vasicinone	Glu339,Val170,Ser10,Gly156, His362,Tyr330,Trp277,Pro308, Ala157,Arg307,Val361

4. Conclusion

The β-secretase protein is known to play important roles in the pathology of Alzheimer disease so β-secretase is a promising and likely target to nullify dementia. The three phytochemicals (sanjoinenine, solasonine and vasicinone) were found to be effective inhibitor against β-secretase in computational study. The sanjoinenine (2E)-N-[(10E)-3-isopropyl-7-(2-methylpropyl)-5,8-dioxo-2-oxa-6,9-diazabicyclo [10.2.2] hexadeca-1(14),10,12,15-tetraen-4-yl]-3-phenylprop-2-enamide) phytochemical is obtained from Ziziphus jujuba and Ziziphus lotus. It is alkaloid in nature. The molecular docking studies shows that ligands form desirable bonding with requisites active-site residues of β-secretase as shown in Figure 3((a)-(c)).

The luteolin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one), is a flavonoid present in Verbascum lychnitis . It is very potent anti-oxidant along with chemopreventive, anti-inflammatory and free-radical scavengers properties. The ligplot interaction diagram of luteolin with β-secretase is shown in Figure 3 (b).

The vasicinone ((3S)-3-hydroxy-2,3-dihydro-1H-pyrrolo[2,1-b] quinazolin-9-one) is present in Anisotes trisulcus and Justicia adhatoda and other species. The vasicinone belongs to the quinazolines family. The vasicinone possess anti-mycobacterial, butyrylcholinesterase and acetylcholinesterase activity and results are well documented in literature. The interaction diagram of vasicinone with β-secretase is shown in Figure 3 (c). The in-silico studies shows that sanjoinenine, luteolin and vasicinone are potent lead molecules for in-vivo studies.

Conflict of Interest

The authors declare no conflict of interest.

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