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Role of Fatty Acids/Fat Soluble Component from Medicinal Plants Targeting BACE Modulation and Their Role in Onset of AD: An *in-silico* Approach

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Abstract
Fatty acids have been reported in several researches targeting cure and treatment of Alzheimer's disease (AD). Besides having so many contradictory reports about fatty acids related to the issues of human health, there are many evidences that point towards the beneficial effects of PUFAs and essential fatty acids on human health, even in AD. This study investigated the interaction of fatty acids and phyto-constituents for the inhibition of BACE enzyme (mainly responsible and prominent target for amyloid hypothesis) through *in-silico* approach. Phyto-compounds from *Picrorhiza kurroa*, *Cinnamomum tamala*, *Curcuma longa*, *Datura metel*, *Rheum emodi* and *Bacopa monnieri*, which are well known, were screened. For screening of drug molecules, Lipinski's rule is usually used. Because of this rule compounds like Bacoside A, Bacoside A3, Bacopaside II, Bacopasaponin C, Baimantuoluoline C, Daturameteline A, Cucurbitacin B, Cucurbitacin D, Cucurbitacin E, Cucurbitacin I, Cucurbitacin F, Cucurbitacin R, Picroside III, Kutkoside, Picroside II are usually excluded from docking/binding studies because of their higher molecular weight as they do now follow the Lipinski's rules. The same applies to fatty acids, like Linolinic acid. On the basis of *in-silico* experiments, our study suggests that certain polyunsaturated fatty acids (PUFA) and some saturated fatty acids of medicinal plants can have BACE inhibition activity and can possibly modulate Aβ formation. Our study also suggests that compounds that are excluded by Lipinski's rule/filter during bioinformatics based screening due to their molecular weight should also be tested in experiments as we hypothesize that Lipinski's rule is not absolute.

Keywords- Fatty Acids, PUFA, Alzheimer's disease, BACE, Amyloid beta, phyto constituents, Lipinski's rules.

1. Introduction

Fatty acids are building blocks of more complex lipids and are an important class of biochemical molecules. Fatty acids serve as both energy substrates in form of triglycerides and integral membrane components. Without having these fatty acids biomolecules, the biological entity cannot be imagined. Plasma membranes of all cells are made up of major fraction of lipids and different cells can have different amounts as well as different fatty acids in them. Neural plasma membranes are composed of glycerophospholipids, sphingolipids, cholesterol, and proteins. Glycerophospholipids and sphingolipids contain nonpolar fatty

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acyl, alkenyl, and alkyl chains. It is also important to note that fat is essentially the most abundant component in brain. The degree of unsaturation in polyunsaturated fatty acids (PUFA) determines many neural membrane properties including membrane order, packing pattern, and fluidity. Several of the lipids are also associated with signaling. Besides all this the roles and actions of fatty acids are always been under investigation for its good or bad impact on human health and several contradictory reports that are based on wither epidemiological studies or *in-vitro* / *in-vivo* models explore the role of fats on health.

Fatty acids are categorized in different forms, like saturated fats, unsaturated fats, polyunsaturated (PUFA) and monounsaturated fats (MUFA), essential fatty acids, trans fatty acids and so on. The role of fatty acids is important because it increased membrane fluidity by which it increase the number and affinity of receptors in the synapse and improve neurotransmission. Such fluidity is important in encouraging synaptic plasticity that is essential for learning, memory, and other complex cognitive processes. Moreover, several integral membrane proteins (especially APP) and the enzymes processing these proteins (like Secretase family of enzymes) are also functional within these lipid domains. Generally, PUFA have the role as secondary messenger after conversion to membrane phospholipid. It modulates oxidative stress, inflammation and neuronal health. PUFAs and MUFAs are considered as good fatty acids because they have been shown good effect on health like cardio vascular system, brain functioning, cognitive functions and neuronal health in late stage of life.

One of the most important organs of humans, the Brain, has (is made of) 60% or more fat. There are several neurodegenerative disorders that occur due to one or the other problems in brain. One of the most common form of dementia i.e. Alzheimer's Disease (AD) is causing severe constraints on the health care systems as the number of patients is skyrocketing along with the cost of healthcare around the globe. Despite knowing all major pathways and having vast data sets, so far, efforts to find a cure for AD have met disappointment and the drugs currently available do not cure a patient. These drugs provide some relief in symptoms with limited effectiveness. Some side effects of current drugs have also been reported (Cummings et al., 2014). Till date, the U.S. Food and Drug Administration (FDA) approved only five drugs for AD. It is believed that therapeutic intervention that could delay the onset or progression of AD would dramatically reduce the number of cases in next 50 years.

Researches have shown the positive impact of fatty acids on (Docosahexaenoic Acid) DHA and omega 3 fatty acids on processing of amyloid precursor protein-β (APPβ) shifting it from the amyloidogenic to the non-amyloidogenic pathway by down-regulating β-secretase 1 (BACE1). In this paper, we investigated, *in silico*, the role of other fatty acids in modulation of BACE enzyme using bioinformatics tools. We show that BACE modulation activity is not limited only to DHA but other fatty acids and phyto-compounds from medicinal plants can also contribute to it. We also hypothesize that besides fatty acids, there is a possibility that a

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fat soluble component of medicinal plants, which is yet to be identified, might also modulate BACE family of enzymes.

2. Methodology

2.1 Preparation of Binding Site

The protein structure of the β-secretase required for docking analysis was retrieved from Protein Data Bank (PDB) (www.rcsb.org) as the only PDB format file can be used for simulations of the binding site in iGEMDOCK. The PDB ID's of β-secretase is "5ENM".

2.2 Ligand Preparation

The structures of the various plant active components in its mol2 formats were downloaded using the database ZINC AC (University of California Org, San Francisco) and PUBCHEM. These databases can be use to obtain the information about the chemicals. The mol2 files were converted into 3D structure by using open babel software (Babel, 2011). 3D structure of some chemicals was not available in both the databases. Hence their structures were downloaded through smile translators. (https://cactus.nci.nih.gov/ translate/) using Canonical SMILES. The ligand and analogues of fatty acids and plant active components listed in Table 3 are derived from PUBCHEM. PDB SUM is used for binding the active site, number of chains, the number of amino acids present in the each chain and motif details.

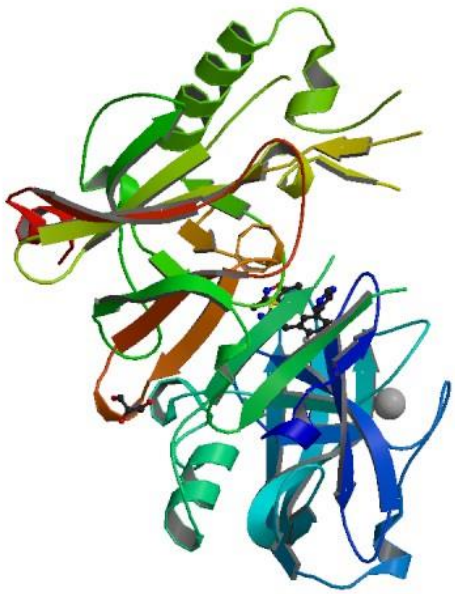

Figure 1. BACE protein file PDB file: 5ENM

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2.3 Shortlisting of Molecules as per Lipinski's Rule

The Lipinski's rule of five applied on the ligand compounds shows the results as per Table 1. Lipinski's rule of 5 helps in distinguishing between drug like and non-drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with two or more of the following rules:

(i) Molecular mass less than 500 Dalton
(ii) High lipophilicity (expressed as LogP less than 5)
(iii) Less than 5 hydrogen bond donors
(iv) Less than 10 hydrogen bond acceptors
(v) Molar refractivity should be between 40-130

During first phase of screening, all the probable candidates were subjected to Lipinski's test. For this we used online facility provided by IIT-Delhi as supercomputing facility for bioinformatics and computational biology of IIT-Delhi. By using it's website http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp. We also tried molecules especially fatty acids, which are usually excluded by Lipinski's rule.

2.4 Molecular Docking of BACE Enzymes and Plant Active Compounds using iGEMDOCK

To study the interactions between the protein and ligands, PDB format were used as input file in the iGEMDOCK software. iGEMDOCK (a docking software developed by Jinn-Moon Yang, a professor of the Institute of Bioinformatics, National Chiao Tung University) generates protein-compound interaction profiles of electrostatic (E), hydrogen bonding (H), and Van der Waal's (V) interactions. It is a Generic Evolutionary Method for molecular docking. iGEMDOCK is a program for computing a ligand conformation and orientation relative to the active site of target protein. Based on these profiles and compound structures, iGEMDOCK infers the pharmacological interactions and clusters the screening compounds for the post-screening analysis. It is a graphical-automatic drug discovery system used for integrating docking, screening, post- analysis, and visualization of various ligands. The main features of iGemdock are scoring function and evolutionary algorithm. In scoring function, the complicated AMBER-based energy function is replaced by local minima. Finally, iGEMDOCK as described by (Hsu et al., 2011; Kapoor et al., 2013; and Semwal et al., 2015) was used to rank or visualize the ligand target docking and energy-based scoring was tabulated for each potential active components form medicinal plants. Ranks or visualizes the screening compounds by combining the pharmacological interactions and energy-based scoring function of iGEMDOCK.

Using the PDB format of the BACE and the mol2 format of the phyto-components, we checked their mutual interactions with the help of molecular docking software (iGEMDOCK). PDB and mol2 structural format were uploaded onto iGEMDOCK (components named mentioned in Table 2 and docking was simulated with β-secretase

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(BACE) enzyme. After the docking between the protein and ligands was complete, the results were obtained as output (Figure 2 and 3). All the plant active components also showed a binding energy (Hydrogen bond, Van Der Waal's force of attraction, and electrostatic force). Binding energies of the protein - ligand interactions are important to describe how well/fit the ligand binds to its target macromolecule. The result for each binding simulation was tabulated an analyzed.

3. Results

The drug-likeness is necessary to be evaluated at the primary stage as this reduces the chances of selecting the false positive result and for this Lipinski's rule is usually followed. Various basic physicochemical properties as specified by this rule like log P, H-bond acceptors; H-bond donor, molecular weight and molar refractivity were calculated to evaluate a molecule to act as drug. The value of log P should be ≤ 5 and this value specifies the distribution coefficient important for binding the solubility of the drug that is lipophilicity.

The results of Lipinski's filter shows that out of all 55 molecules, only 40 compounds passed the criteria Table 3. 15 phytochemical compounds i.e. Bacoside A, Bacoside A3, Bacopaside II, Bacopasaponin C, Baimantuoluoline C, Daturameteline A, Cucurbitacin B, Cucurbitacin D, Cucurbitacin E, Cucurbitacin I, Cucurbitacin F, Cucurbitacin R, Picroside III, Kutkoside, Picroside II were considered as non-drug molecules for BACE modulation because these active compounds do not follow the Lipinski's rule of 5. Remaining molecules followed Lipinski's rule and were further subjected to docking simulations. However, we also tried other molecules that were excluded by Lipinski's rule.

de-novo drug designing has become an essential process now a days and molecular docking is widely used in screening of candidate molecular for drug development. (Jorgensen, 2004). Our docking simulations show that among various fatty acids: palmitic acid and stearic acid, showed the best docking energy with BACE enzyme, and their binding energies were -98.9952 and -98.4931 respectively. Along with them, curcumin and baimantuoluoline B also showed good binding energy pattern of -93.9818 and -92.325. Other phyto-constituents like anthraquinone, aucubin, apocynin, baimantuoluoline A emodin etc. and fatty acids like linoleic acid, lauric acid, tetradecanoic acid also have shown negative binding energy. This suggests that these phytochemicals and fatty acids have immense potential to modulate BACE. BACE is the potential target for the treatment of AD.

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Table 1. Values for different ligands after applying Lipinski's filter on plant active-compounds and fatty acids tested. Molecules in Bold letters do not follow Lipinski's rule.

S. No	Molecule	Molecular Mass	Lipophilicity (Log P)	Hydrogen bond donors	Hydrogen bond acceptor	Molar refractivity
1.	**Bacoside A**	**826.000000**	**0**	**7**	**13**	**0**
2.	**Bacoside A3**	**1000.000000**	**0**	**0**	**0**	**0**
3.	**Bacopaside II**	**1016.000000**	**0**	**0**	**0**	**0**
4.	**Bacopasaponin C,**	**978.000000**	**0**	**0**	**0**	**0**
5.	**Baimantuoluoline C**	**518.000000**	**1.933800**	**4**	**8**	**134.018188**
6.	**Daturameteline A**	**600.000000**	**2.995099**	**4**	**9**	**156.186356**
7.	**Cucurbitacin B**	**558.000000**	**3.499300**	**3**	**8**	**147.766479**
8.	**Cucurbitacin D**	**516.000000**	**2.928500**	**4**	**7**	**138.219208**
9.	**Cucurbitacin E**	**556.000000**	**4.190199**	**3**	**8**	**147.854492**
10.	**Cucurbitacin I**	**514.000000**	**3.619399**	**4**	**7**	**138.307220**
11.	**Cucurbitacin F**	**518.000000**	**2.720300**	**5**	**7**	**139.219009**
12.	**Cucurbitacin R**	**518.000000**	**3.152500**	**4**	**7**	**138.313202**
13.	**Picroside III**	**538.000000**	**-1.611801**	**6**	**13**	**124.107735**
14.	**Kutkoside**	**528.000000**	**5.230770**	**1**	**13**	**131.918793**
15.	**Picroside II**	**541.000000**	**6.126582**	**3**	**13**	**145.818436**
16.	Anthraquinone	208.000000	2.462000	0	2	59.748989
17.	Chrysophanein.	254.000000	2.181620	2	4	67.815590
18.	Anthraquinones	208.000000	2.462000	0	2	59.748989
19.	Rhein	283.000000	0.236700	2	6	67.409096
20.	Aloe-emodin	270.000000	1.365500	3	5	69.001389
21.	Chrysophanol,	254.000000	2.181620	2	4	67.815590
22.	Emodin,	270.000000	1.887221	3	5	69.480392
23.	Trans-Stilbene	180.000000	3.856999	0	0	61.811985
24.	Resveratrol	228.000000	2.973799	3	3	66.806389
25.	Curcumin	368.000000	3.369899	2	6	102.016571
26.	Withametelin C	474.000000	3.560499	3	6	126.520340
27.	Withametelin D	472.000000	3.336499	3	6	126.426346
28.	Withametelin E	486.000000	2.323700	3	7	125.853348
29.	Baimantuoluoline A	470.000000	3.351300	2	6	124.441551
30.	Baimantuoluoline B	490.000000	2.531300	4	7	127.910141
31.	Daturameteline D	468.000000	4.893700	0	5	127.815956
32.	Withameteline E	486.000000	2.323700	3	7	125.853348
33.	Withameteline D	472.000000	3.336499	3	6	126.426346
34.	Withameteline C	474.000000	3.560499	3	6	126.520340
35.	Apocynin	166.000000	1.603400	1	3	44.663296
36.	Aucubin	346.000000	-2.801500	6	9	77.020782
37.	Tetradecanoic acid	227.000000	3.437399	0	2	66.084984
38.	Stearic acid	267.000000	3.789889	0	2	68.513985
39.	Palmitoleic acid	253.000000	3.993598	0	2	75.224976
40.	Palmatic acid	452.000000	7.450963	0	2	124.230965
41.	Oleic acid	281.000000	4.773799	0	2	84.458977
42.	MK-8931	338.000000	2.573500	2	5	96.463387
43.	Margaric acid	269.000000	4.607699	0	2	79.935974
44.	LY2886721	390.000000	2.515300	3	6	98.615585
45.	Linoleic acid	279.000000	4.549799	0	2	84.364975
46.	Lauric acid	199.000000	2.657199	0	2	56.850983
47.	Arachidinoic acid	303.000000	4.882000	0	2	93.410980
48.	Asiatic acid	487.000000	3.697998	3	5	132.784363
49.	Berberine	337.000000	2.958499	0	5	90.765968
50.	Hypericin	504.000000	4.741202	6	8	132.700806
51.	Taraxerol	535.000000	8.428803	0	4	160.954681
52.	Sinapic acid	223.000000	0.172500	1	5	55.251793
53.	Taraxerol	426.000000	8.168903	1	1	130.719757
54.	Kutkin	395.000000	2.509150	1	2	114.816673
55.	Triethyl-2-phosphonobutyrate	385.000000	2.976000	2	8	106.318390

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4. Discussion

There are currently no cures for AD and there are multiple drugs that have been proven to slow disease progression and treat symptoms. In this scenario, several groups are screening plant-derived compounds with multiple target mechanisms for drug development and discovery. Docosahexaenoic acid (DHA) and arachidonic acid (ARA) promotes translocation and subsequent activation of AKT and RAF1, which have a role in neurogenesis. In neurons, DHA and/or its mediator neuroprotectin D1 (NPD1) shift the processing of amyloid precursor protein-β (APPβ) from the amyloidogenic to the non-amyloidogenic pathway by down-regulating β-secretase (BACE) enzyme. Several groups of researchers are investigating role of polyunsaturated fatty acids (PUFAs) in Alzheimer's disease (Tan, 2012; Bazinet and Layé, 2014; Torres, 2014). These groups have suggested two key roles for fatty acids; firstly - neurotransmission and prostaglandin formation (Haag, 2003) and secondly - improvement of membrane fluidity (Yang et al., 2014). Several other studies and their collective evidence suggest that PUFA modulate many neural membrane properties and functions (Yehuda *et al.*, 2002; Farooqui and Horrocks, 2007; Farooqui, 2009). (Jicha and Markesbery ,2010) reviewed the potential role of omega 3 fatty acid in management of early AD conditions. (Bazinet and Layé 2014) have reported the inhibition of BACE enzyme for non-amyloidogenic pathway along with several other modifications by PUFAs like DHA etc., which ultimately prevents AD and other cognitive dysfunctions. Our data also suggest that fatty acids from medicinal plants can also modulate BACE activity. These all evidences suggest a potential role of fatty acids from medicinal plants in delaying onset of AD. (Cunnane et. al., 2012) had demonstrated that in patients of AD, level of esterified DHA is reduced in both plasma and brain tissue samples. (Nasaruddin et al., 2016) reported that levels of 20 fatty acids increased in brain of AD patient's in Brodmann' 7 region. It was also reported (Snowden et al., 2017), that unsaturated fatty acids have a strong relationship with both severity of AD pathology and the expression of AD symptoms. He reported similar findings in same region of brain but saw that only fatty acids like oleic, linoleic, linolenic, and arachidonic acid level decreased in brain while DHA levels remained unchanged.

Amen et. al. (2017), followed 166 participants and reported that higher level of omega-3, EPA and DHA are directly correlated to higher blood flow in the brain, which can improve the neuropsychological functions of the subjects and is also helpful in learning, memory, depression and dementia. Our results also focus on the beneficial roles of fatty acids and fat-soluble compounds for management of AD/dementia. However, the new dimension and unique feature of our study is that it specifies the target of these fatty acids, i.e. beta secretase enzyme. No other study except (Bazinet and Layé, 2014) specify the target of fatty acids. We have also gone a step further in our studies and actually shown in laboratory experiments (not published yet) that other fatty acids besides DHA can modulate BACE enzyme. This lab data supports our simulation experiments. We also hypothesize that there might also be another possibility. In brain, because of over 60% fat content, various enzymes systems must be working under an environment that is predominantly fatty in nature. Hence, under test

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conditions also, if we provide predominantly fatty environment, it would be more ideal situation. As the fatty fraction of medicinal plants is used, a simulated situation which is more similar to condition in brain develops for the enzyme system under test. It is possible that a component of medicinal plants, that has probably not yet been identified, and is soluble in fat, might also be involved in modulation of beta secretase enzyme. Further experimentation is ongoing for generating lab data for this hypothesis.

Table 2. Interaction of BACE with different plant ligands and fatty acids showing its binding energy, van der Wall's forces, hydrogen bond and its electrostatic force.

S. No.	Compound PDB ID	Energy	VDW	H Bond	Electrostatic
1.	5enm-Arachidonic acid-1.pdb	-59.5176	-52.769	-6.74858	0
2.	5enm-Lauric acid-1.pdb	-66.8396	-45.9785	-19.4163	-1.44478
3.	5enm-Linoleic acid-0.pdb	-78.9022	-66.3823	-10.1861	-2.33376
4.	5enm-Linolenic acid-0.pdb	0	0	0	0
5.	5enm-LY2886721-1.pdb	-77.5328	-66.9448	-10.588	0
6.	5enm-Margaric acid-1.pdb	-65.546	-63.0394	-2.28237	-0.224269
7.	5enm-MK-8931-0.pdb	-85.3636	-71.9903	-13.3733	0
8.	5enm-Oleic acid-0.pdb	-73.8717	-68.4519	-5.21395	-0.205821
9.	5enm-Palmatic acid-1.pdb	-98.9952	-95.4952	-3.5	0
10.	5enm-Palmitoleic acid-0.pdb	-73.9182	-68.0759	-5.82168	-0.0205701
11.	5enm-Stearic acid-0.pdb	-98.4931	-85.1763	-14	0.683163
12.	5enm-Tetradecanoic acid-1.pdb	-68.3117	-55.3641	-13.9253	0.977668
13.	5enm-aloe-emodin-1.pdb	-86.4976	-60.8909	-25.6067	0
14.	5enm-anthraquinone-0.pdb	-69.6501	-59.3608	-10.2893	0
15.	5enm-Anthraquinones-0.pdb	-69.68	-59.8757	-9.80431	0
16.	5enm-Apocynin-1.pdb	-71.1731	-57.0395	-14.1336	0
17.	5enm-Aucubin-1.pdb	-87.5421	-62.7052	-24.8369	0
18.	5enm-Baimantuoluoline A-0.pdb	-86.5234	-69.9458	-16.5776	0
19.	5enm-Baimantuoluoline B-1.pdb	-92.325	-68.5325	-23.7925	0
20.	5enm-chrysophanol-0.pdb	-82.1927	-62.7649	-19.4278	0
21.	5enm-Curcumin-0.pdb	-93.9818	-62.4128	-31.569	0
22.	5enm-Daturametelin D-1.pdb	-83.6774	-72.8165	-10.8609	0
23.	5enm-D-Glucose-0.pdb	-78.9912	-48.4607	-30.5305	0
24.	5enm Acid-1.pdb	-44.839	-41.339	-3.5	0
25.	5enm-Behenic acid-1.pdb	-40.9458	-37.4458	-3.5	0
26.	5enm-Butyric Acid-1.pdb	-32.5325	-14.5087	-17.7958	-0.228025
27.	5enm-Cerotic acid-1.pdb	26.4159	26.4159	0	0
28.	5enm-Enanthic acid-1.pdb	-41.3705	-31.6626	-7	-2.70787
29.	5enm-Geddic acid-0.pdb	284.315	284.315	0	0
30.	5enm-Lauric Acid-1.pdb	-44.8118	-36.0349	-7	-1.77687
31.	5enm-Melissic acid-0.pdb	-13.134	-13.134	0	0
32.	5enm-Montanic acid-0.pdb	47.0624	47.0624	0	0
33.	5enm-Myristic acid-0.pdb	-41.9319	-35.3005	-6.89255	0.261123
34.	5enm-Octatriacontanoic acid-0.pdb	79.0911	79.0911	0	0
35.	5enm-Pelargonic acid-0.pdb	-44.4335	-29.8004	-14.3828	-0.250267
36.	5enm-PENTACOSANOIC ACID-0.pdb	10.6102	10.6102	0	0
37.	5enm-Pentadecylic acid-0.pdb	-40.6602	-34.6472	-5.37229	-0.64068
38.	5enm-Propionic Acid-1.pdb	-30.4137	-12.3158	-17.9903	-0.107556

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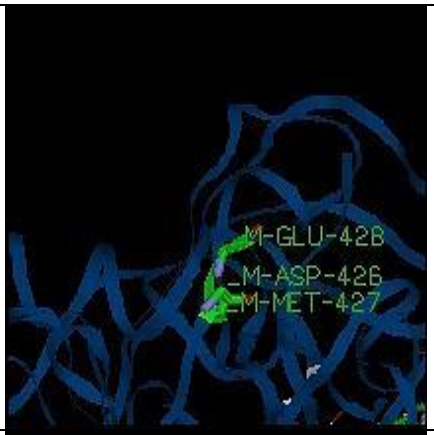
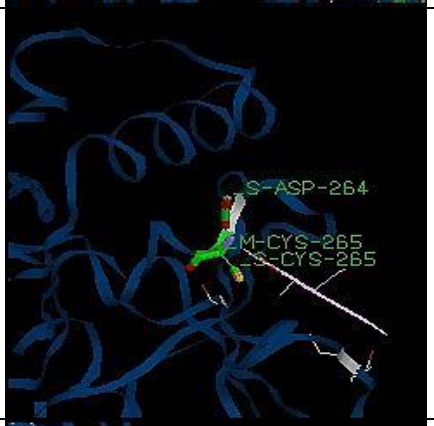
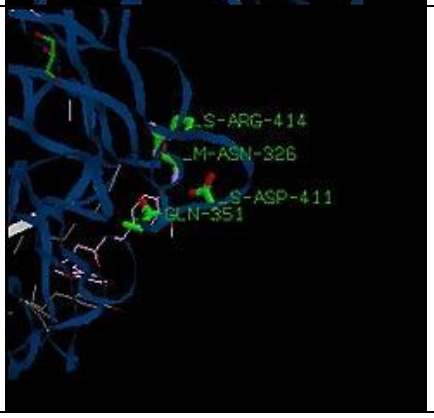
Table 3. Interaction analysis of amino acids with BACE with selected phytochemicals and fatty acids. H-S signifies hydrogen bond with side chain; H-M signifies hydrogen bond with the main chain

Compound	Interaction with BACE1	Interactions
Stearic acid	H-M ASP 426 -3.5 H-M MET 427 -7 H-M GLU 428 -3.5	
Palmatic Acid	H-S ASP 264 -2.6 H-M CYS 265 -2.5 H-S CYS 265 -5	
Curcumin	H-M ASN 326 -3.5 H-S GLN 351 -3.5 H-S ASP 411 -3.5 H-S ARG 414 -3.5	

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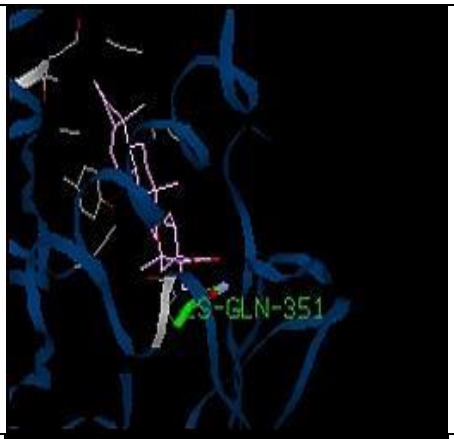
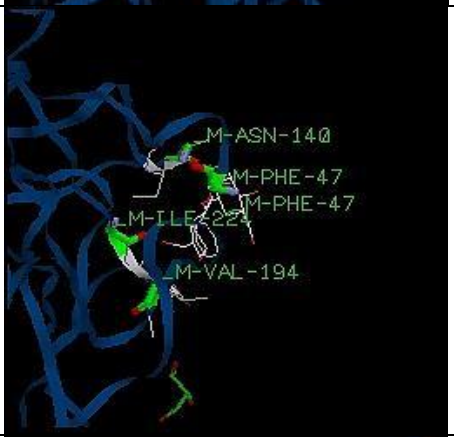
Daturametelin	H-S GLN 351 -3.5	
Apocynin	H-M SER 84 -3.5 H-M ILE 174 -2.5 H-S TYR 246 -2.5	
Aucubin	H-M PHE 47 -7 H-M ASN 140 -3.5 H-M VAL 194 -3.5 H-M ILE 224 -2.5	
Baimantuoluoline	H-S TYR 119 -2.5 H-S TYR 246 -4 H-S LYS 272 -3.5	

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5. Conclusion

Through our *in-silico* study using iGEMDOCK, we found that fatty acids have the potential to modulate BACE enzyme. Our simulation data is backed up by the laboratory data (not yet published). Ultimately we suggest that either fatty acids or a component from medicinal plants which is soluble in fats has the potential to inhibit BACE enzyme. Our findings have applications in developing new and novel process, predominantly targeting fatty acids components, for the treatment and cure of AD. Our study also suggests that fatty acids/phospholipids component in plasma membrane have prominent role in onset of AD

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References

Amen, D. G., Harris, W. S., Kidd, P. M., Meysami, S., & Raji, C. A. (2017). Quantitative erythrocyte omega-3 EPA plus DHA levels are related to higher regional cerebral blood flow on brain SPECT. Journal of Alzheimer's Disease, 58(4), 1189-1199.

Babel, O. (2011). An open chemical toolbox O'Boyle Noel M; Banck Michael; James Craig A; Morley Chris; Vandermeersch Tim; Hutchison Geoffrey R. Journal of Cheminformatics, 3, 33.

Bazinet, R. P., & Layé, S. (2014). Polyunsaturated fatty acids and their metabolites in brain function and disease. Nature Reviews Neuroscience, 15(12), 771-785.

Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: few candidates, freqHsu et al., 2011uent failures. Alzheimer's Research & Therapy, 6(4), 37.

Cunnane, S. C., Schneider, J. A., Tangney, C., Tremblay-Mercier, J., Fortier, M., Bennett, D. A., & Morris, M. C. (2012). Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. Journal of Alzheimer's Disease, 29(3), 691-697.

Farooqui, A. A. (2009). Lipid mediators in the neural cell nucleus: their metabolism, signaling, and association with neurological disorders. The Neuroscientist, 15(4), 392-407.

Farooqui, A. A., Horrocks, L. A., & Farooqui, T. (2007). Modulation of inflammation in brain: a matter of fat. Journal of Neurochemistry, 101(3), 577-599.

Haag, M. (2003). Essential fatty acids and the brain. The Canadian Journal of Psychiatry, 48(3), 195-203.

Hsu, K. C., Chen, Y. F., Lin, S. R., & Yang, J. M. (2011). iGEMDOCK: a graphical environment of enhancing GEMDOCK using pharmacological interactions and post-screening analysis. BMC Bioinformatics, 12(1), S33.

Jicha, G. A., & Markesbery, W. R. (2010). Omega-3 fatty acids: potential role in the management of early Alzheimer's disease. Clinical Investigations in Aging. 5, 45-61.

Jorgensen, W. L. (2004). The many roles of computation in drug discovery. Science, 303(5665), 1813-1818.

Kapoor, T., Semwal, P., Anthwal, P., Thapliyal, M., & Thapliyal, A. (2013). Quercetin, bergapten and barberineb as analogues of rifampicin and isoniazid screened in silico from herbal plants of Uttarakhand for the treatment of tuberculosis (TB). Biotech International, 6(4), 48-57.

Nasaruddin, M. L., Hölscher, C., Kehoe, P., Graham, S. F., & Green, B. D. (2016). Wide-ranging alterations in the brain fatty acid complement of subjects with late Alzheimer's disease as detected by GC-MS. American Journal of Translational Research, 8(1), 154.

Semwal, P., Tripathi, R., & Thapliyal, A. (2015). Herbal active components act as inhibitor against HCV NS3/4A protease by using bioinformatics approach. Drug Discovery, 10(23), 15-21.

Snowden, S. G., Ebshiana, A. A., Hye, A., An, Y., Pletnikova, O., O'Brien, R., & Thambisetty, M. (2017). Association between fatty acid metabolism in the brain and Alzheimer disease neuropathology and cognitive performance: A nontargeted metabolomic study. PLoS medicine, 14(3), e1002266.

Tan, Z. S., Harris, W. S., Beiser, A. S., Au, R., Himali, J. J., Debette, S., & Robins, S. J. (2012). Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. Neurology, 78(9), 658-664.

Torres, M., Price, S. L., Fiol-deRoque, M. A., Marcilla-Etxenike, A., Ahyayauch, H., Barceló-Coblijn, G., . & Ibarguren, M. (2014). Membrane lipid modifications and therapeutic effects mediated by hydroxydocosahexaenoic acid on Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Biomembranes, 1838(6), 1680-1692.

Yang, X., Sun, G. Y., Eckert, G. P., & Lee, J. C. (2014). Cellular membrane fluidity in amyloid precursor protein processing. Molecular Neurobiology, 50(1), 119-129.

Yehuda, S., Rabinovitz, S., Carasso, R. L., & Mostofsky, D. I. (2002). The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. Neurobiology of Aging, 23(5), 843-853.