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ANTIOXIDANT THERAPIES TO OXIDATIVE STRESS RELATED NEUROTROPHINS INVOLVED IN ALZHEIMER'S DISEASE

Amit Chaudhary, Rashmi Tripathi, Yashasvi Jain and Satyavani Guttula*

Department of Bioinformatics, Indian Institute of Information Technology, Allahabad-211012, India.

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***Correspondence for Author**

Satyavani Guttula

Department of Bioinformatics, Indian Institute of Information Technology, Allahabad-211012, India.

ABSTRACT

Alzheimer Disease (AD) is the most common form of dementia affecting aging population. The pathogenetic process and clinical manifestation of the dementing disorders includes pathophysiological hallmarks (a) extracellular β-amyloid protein's (Aβ) senile plaques deposition (b) intracellular deposition of the microtubule associated protein tau as neurofibrillary tangles (NFTs). Neurotrophins play a vital role in adult neuron survival, maintenance, regeneration besides being required for the correct development of the nervous system. Two neurotrophic factor candidates involved in the progression of AD are NGF and BDNF. Both are affected early in the disease and is initiates a cascade of events. Studies show that antioxidant therapies is a promising therapeutic strategy which show success in pre-clinical studies. Therefore, this paper mainly focuses on the recent developments of commonly used antioxidant therapies for AD and provides indications for future potential antioxidant therapeutic strategies for neurodegenerative diseases. Here, docking of some antioxidants with neurotrophins (like BDNF and NGF) is done using Glide 6.2v. The glide energy calculated can easily predict the rank poses of the different ligands and binding affinity of ten compounds. Theaflavin, Catechin, Luteolin, Kaemferol, Gallic acid, Myricetin, Eriodictyol, Uric acid, Ascorbic and Isorhamnetin acid are top ten highly ranked compounds that produced the best rank poses with three different proteins (1NT3, 1BND, 1B8M). The docking result reveals that these compounds can reduce the oxidative stress, play an important role in reducing the risk or postponing the clinical onset of progressive-dementia and further may enhance the efficacy of antioxidant based treatment strategy.

KEYWORDS: Alzheimer Disease, *β*-amyloid protein's, neurofibrillary tangles, Antioxidant, Neurotrophins BDNF, NGF, Oxidative stress

INTRODUCTION

Alzheimer's disease is one of the most common neurodegenerative disorder that frequently cause progressive dementia and affect the middle-aged to old-aged individuals targeting majority over the age of 80. The AD's patients show typical pathology involving marked atrophy of the brain, with thinning of the cerebral cortex's grey matter, extracellular amyloid plaques, contracted gyri, dilated ventricles indicating neuronal loss and atrophy of the amygdala and hippocampus. The neuropathological hallmarks of AD comprises of intracellular neurofibrillary tangles and cerebrovascular amyloid although these lesions are also found in normal individuals as well as other neurodegenerative patients. Classic neuritic plaques appear as a rounded structure bearing a central core of fibrous protein (amyloid) enclosed within a degenerating or dystrophic nerve endings (neurites).

Multiple etiological factors like chronic inflammatory reactions, genetics, oxidative and nitrosylative stresses, environmental factors and general lifestyle of a person (eg, high cholesterol levels, cigarette smoking, midlife high blood pressure, obesity, diabetes, and active social engagement) can also play an important role in initiating and promoting neurodegenerative changes in the person's brain other than an older age. Its pathophysiological hallmark includes extracellular *β*-amyloid protein (A*β*) deposition in the forms of senile plaques and intracellular deposition of the microtubule associated protein tau as neurofibrillary tangles (NFTs) in the AD brains. Subsequent clinical and neuropathological studies identified senile plaques and NFTs as the most common causes of the disease in the older individuals. A*β* is composed by sequential proteolytic processing of a larger A*β* protein precursor (APP) by *β*-secretase to generate a large secreted fragments A*β* and 99 amino acid cellular fragment CTF*β* that includes A*β*, the intracellular domain of APP and transmembrane domain.[7]

Approximately 5–10% of patients evolve an early age onset AD (before 65 years). The disease in up to 50% of such cases is elucidated by mutations in one of three genes: presenilin 1 (PS1), APP and presenilin 2 (PS2). Pathological mutations in these genes are liable for an autosomal dominant feature and cause A-beta accumulation in the brain.[1] The exact mechanism of AD is still not clear. The most common and peculiar indication lesions present within the AD brains are the *β*-amyloid (A*β*-) containing senile plaques and the NFTs

composed of hyperphosphorylated tau protein, which generate strong responses from the surrounding cellular environment and are responsible for much of the late-stage cognitive decline observed in AD patients. [2] Few researches show that the presence of NFT-containing neurons and mutation in the Aβ precursor protein (APP) protects against the neuronal damage since the declination in the steady-state production of Aβ reduces the level of oxidative stress which arises due to variance in radical production of reactive oxygen species (ROS). Antioxidative defense is also one of an important reason for oxidative stress. Oxidative stress may lead to neurodegeneration and cognitive decline. Al, Si, Pb, Hg, Zn, Cu, and Fe are some trace elements whose imbalance may lead to AD and significant homeostasis disruption in light increases the oxidative stress parameters.[2]

Neurotrophins are a family of proteins that belong to class of growth factors and secretory proteins. These neurotrophins induces the improvement, survival, differentiation and function of neurons by signaling particular cell. Commonly occurring structurally related four neurotrophins are: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). The neurotrophins bind with two classes of receptors: p75 and "Trk" family of Tyrosine kinase receptors. They all bind with nanomolar affinity to a pan-neurotrophin receptor p75NTR, and each bind individually along with picomolar affinity, to specific tyrosine kinase receptors (Trks): BDNF and NT-4 bind TrkB, NGF binds TrkA, and NT-3 binds TrkC.[3] NGF is secreted by a neuron's target cell and is critically required for the survival and maintenance of sympathetic and sensory neurons. BDNF has activity on certain neurons of the central nervous system and the peripheral nervous system; it helps to support the survival of actual neurons, and boost the growth and differentiation of new neurons and synapses through axonal and dendritic sprouting. BDNF is one of the most active substances to stimulate neurogenesis. NT-3 is a protein growth factor that has activity on certain neurons of the peripheral and central nervous system; it helps to support the survival and differentiation of actual neurons, and boost the growth and differentiation of new neurons and synapses. NT-3 is unique among the neurotrophins in the number of neurons it has potential to stimulate, given its capability to stimulate two of the receptor tyrosine kinase neurotrophin receptors (TrkC and TrkB). NT-4 is a neurotrophic factor that signals predominantly through the TrkB receptor tyrosine kinase. Thus interruption of expression of either BDNF or NGF, or a change in the levels of TrkB or TrkA receptors, may result in defective memory formation and neuronal degeneration. This hypothesized that each of these disorders was due to the lack of a specific neurotrophic

hormone. Two neurotrophic factor candidates for such a pivotal role in the progression of Alzheimer's disease are NGF and BDNF. [3]

NGF Receptors in Alzheimer's disease

The p75NTR receptor along with it co-receptors in presence of TrkA can interact and increase affinity of NGF for TrkA as well as can act in a ligand dependent or independent manner. P75NTR in combination with other receptors is likely to induce apoptosis.[4, 5]. In addition, using single cell expression profiling methods individual ChBF neurons showed down adjustment of TrkA, TrkB, and TrkC expression during the progression of Alzheimer's disease from MCI, whereas p75NTR mRNA levels remained balanced even in the end stage of the disease. This is in agreement with previous studies of basal forebrain membranes from Alzheimer's disease brain in which no difference from normal was seen in p75NTR mRNA levels or in NGF binding at p75NTR receptors.[6]

ProNGF and NGF interactions with receptors

ProNGF is processed to NGF extracellularly by plasmin, and intracellularly by furins, whereas the vice versa occurs in case of Alzheimer brain. Processed NGF acts on TrkA in presence of p75NTR and stimulates the release of ACh and enhances activation of M1 muscarinic receptors. M1 musacrinic receptors increase the alpha-secretase activity and further lead to the increase in AB production.[10] Due to an increase in MMP9 activity NGF is degraded more quickly due to which less Ach is produced, which leads to decrease communication among neurons and less activation of M1 receptors. These linked activities lead to increase in beta secretase activity followed by increased AB formation. Whereas in the diseased brain the increased level of proNGF will lead to increased binding at p75NTR and sortilin. The lethal combination of p75NTR and sortilin increases the chances of cell death.[8, 9]

BDNF and Synaptic Plasticity

BDNF and Long Term Potentiation

BDNF plays an important role in maintaining various neuronal groups and synaptic plasticity. BDNF is of profound importance to both early and late forms of Long Term Potentiation (LTP) which is an important component of synaptic plasticity increases synaptic strength by inducing high frequency stimulation. In the hippocampus and limbic structures, LTP contribute the cellular mechanism for memory acquisition and consolidation. BDNF assists induction of early-LTP by acting through TrkB to increase the synaptic response to weak

tetanus stimulation comparatively late-LTP is protein synthesis dependent and is associated with structural changes at synapses, produced with high frequency stimulation. After induction of L-LTP, Ca^{2+} influx occurs through NMDA (N-methyl-D-aspartate) receptors or voltage-gated Ca2+ channels leading to secretion of BDNF. BDNF then binds to TrkB localized at pre- or postsynaptic glutamatergic synapses; at postsynaptic sites, TrkB accomplice with NMDA receptors and PSD95.[3]

ProBDNF and BDNF interactions with receptors

ProBDNF is processed to BDNF extracellularly by plasmin and proconvertases or intracellularly by furins. BDNF acts at TrkB facilitating the production of LTP. The presence of LTP leads in synapse strengthening. In Alzheimer brain due to proBDNF not processed properly which leads to the decrease in the BDNF production and this generally takes place due to Aβ which ultimately leads to the reduction in LTP and weakened synapse formation.[3]

Oxidative Stress and Alzheimer's disease

Oxidative stress (such as protein oxidation, lipid oxidation, DNA oxidation, glycoxidation) is majorly responsible for the development of age-related neurodegeneration and cognitive declination leading to Alzheimer's disease. Researches propose that diseased brain tissues are exposed to oxidative stress during the progression of the disease. Oxidative stress may occur due to (a) an imbalance production of Reactive Oxygen Species (ROS), or (b) an improper functioning of antioxidative defense system which removes ROS. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), superoxide anion radical (O_2 •−), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), singlet oxygen ($^1O_2$), alkoxyl radicals (RO•), peroxyl radicals (ROO·), and peroxynitrites (ONOO−) are responsible cause of numerous human degenerative diseases. Certain antioxidants like glutathione, *α*-tocopherol (vitamin E), carotenoids, ascorbic acid, antioxidant enzymes (such as catalase and glutathione peroxidases) have potential to detoxify H_2O_2 by converting it to O_2 and H_2O under certain physiological conditions [2]. However, these antioxidants fail to work when the ROS level is highly exceeded, this biological dysfunctioning may occur due to aging factor or oxidative stress. Factors generally responsible for the oxidative stress or damage noticed in AD's brain are (a) oxidation of lipid, protein, DNA, glycoxidation end products, (b) formation of toxic substances such as alcohols, peroxides, aldehydes, ketones, free carbonyls, cholestenone, and (c) oxidative modifications in nuclear and mitochondrial DNA.

Therapeutic Strategies for Alzheimer's disease

Therapeutic agents such as cholinesterase/acetylcholinesterase inhibitors are the major treatments available nowadays for Alzheimer's disease. These agents mainly targets specific symptoms of AD whereas other therapeutic agents and strategies including anti-inflammatory drugs (NSAIDs), neurotrophins, antioxidants, statins, nonsteroidal hormone replacement therapy, the immunotherapy, blocking of excitotoxicity, secretase effectors and Aβ vaccine trials, have also been studied. Preventive and disease-modifying treatment strategies still has more scope in eradicating the disease by including these newly studied agents whose use is still controversial.

Antioxidant therapy, as one of the promising therapeutic approaches for AD, has been studied for years. It has been reported that antioxidants such as lipoic acid, vitamin E, vitamin C and β-carotene may help in breaking down intracellular and extracellular superoxide radicals and H_2O_2-cell-damaging compounds that are byproducts of normally functioning cells before these radicals' damage cells or activate microglia through their action as intracellular second messengers. [2].

The docking studies were done on Neurotrophins BDNF and NGF PDB ID: 1BND 1NT3 and 1B8M with an antioxidants. The protein was taken from the Protein Data Bank (www.rcsb.org). Few of the best-fit ligands were studied for their ADME properties. To the perfect of our knowledge, it is the first study to examine the binding interaction of the Antioxidant ligands with Neurotrophins.

MATERIALS AND METHODOLOGY

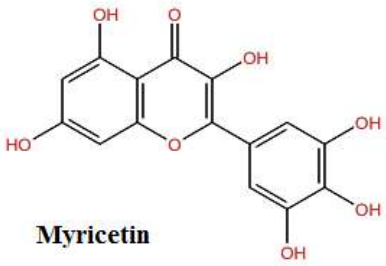
All computational analysis was carried out using Schrodinger Maestro version 9.7 build panel. Ligands were prepared using LigPrep application and optimized by means of the OPLS 2005 (Optimized Potentials for Liquid Simulations) force field. The protein was prepared by deleting a chain of the dimer before docking the ligands into the active site of the protein. Further the crystallographically observed water molecules and the active site of the protein was defined for generation of grid. The energy minimized ligands were docked into the prepared grid using Glide (Glide, version 6.2, Schrödinger, Inc.) on a Linux based (CentOS release 6.5 Linux- 86x -64 platform in Lenovo Intel(R) core(TM) i3-3220 CPU @ 3.30GHz processor 6 GB RAM workstation. The QikProp program (QikProp, v3.9, Schrödinger) was used to obtain the ADME properties of the antioxidants. The best-fit ligands were neutralized before being used by QikProp. The neutralizing step is incapable, as

QikProp is unable to neutralize a structure and no properties will be generated in the normal mode.

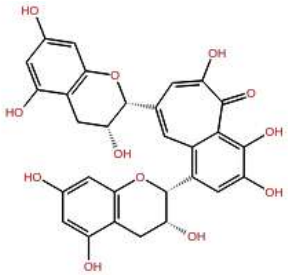
Preparation of Antioxidants (Ligands)

The Ligands (antioxidants) were obtained from the Ligand Expo, ZINC database (zinc.docking.org/) and PDBchem (www.ebi.ac.uk/pdbe-srv/pdbechem/). LigPrep tool was used to prepare high quality, 3D structures for large number of drug-like molecules, starting with low-energy, 2D to 3D conversion, structure with correct chiralities, addition of hydrogen, realistic bond lengths and bond angles, ionization and tautomeric states with Epik, stereo-chemistries and ring conformation whereas unwanted molecules such as water, small ions were removed and optimized by means of the OPLS- 2005 force field using default settings. [11]

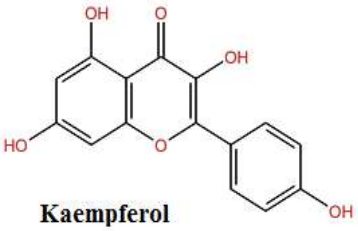
Isorhamnetin



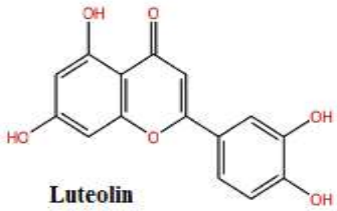
Myricetin



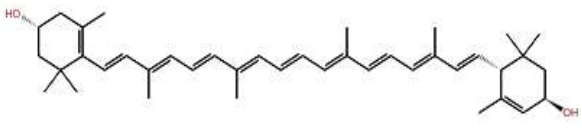
Theaflavin



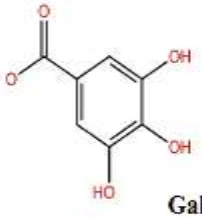
Kaempferol



Luteolin



Lutein



Gallic acid

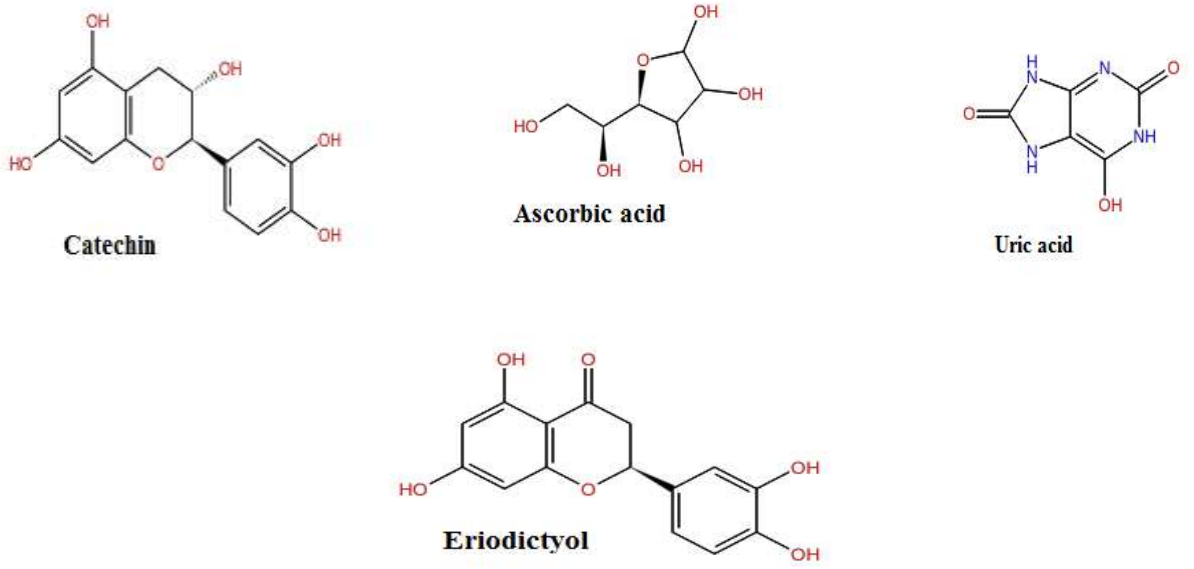


Fig. 1: Two dimensional structures of top ten selected molecules (Antioxidants).

Preparation of Protein Target Structure

The starting coordinates of the proteins (PDB ID: 1B8M, 1BND, 1NT3) were taken from the Protein Data Bank (www.rcsb.org) and were further modified for Glide docking calculations. For Glide calculations, proteins were imported to Maestro, the co-crystallized ligand were identified and removed from the structures. Protein were further minimized using the Protein Preparation Wizard by applying an OPLS-2005 force field. Increasingly, weaker restraints were applied to non-hydrogen atoms only.[11] This refinement process was done based on the recommendations by Schrodinger software, because Glide usage the full OPLS-2005 force field at an intermediate docking stage and is claimed to be more sensitive to geometrical details than other docking tools. [11, 12] Water molecules which are 5 A° away from the active site were removed and H atoms were added to the structure. The most acceptable positions of hydroxyl and thiol hydrogen atoms, tautomers of His residues, and protonation states and Chi 'flip' assignments for Gln, Asn and His residues were selected. Minimizations were performed before the average root mean square deviation of the non-hydrogen atoms arrived 0.3A°. [11]

RESULTS AND DISCUSSION

Glide Docking and Scoring Function

a) Receptor Grid Generation- The receptor grid is the three dimensional boundary for the binding of ligands. The receptor grid was produced using Receptor Grid Generation in the

Glide application of Maestro build. The receptor grid for the proteins in this study was generated by specifying the binding (active) site residues, SiteMap was used for 1BND, 1NT3 and 1B8M to obtain additional information on their binding site residues. Glide calculations were carried out with Impact version v6.2. It performs grid-based ligand docking with energetics and searches for favorable interactions between one or more typically small ligand molecules and commonly larger receptor molecule, ordinarily a protein. A more negative the glide score indicates better fitting to the receptor active sites. The glide score of ligands were obtained after performing the ligand docking on a Linux. Hydrophobic interaction as depicted by the hydrophobic enclosure reward that indicates the surrounding of the ligand lipophilic atoms or group by the lipophilic protein atoms.

b) Glide docking- Once the receptor grid is produced, the ligands are docked to the receptor using Glide version 6.2 (Grid based Ligand Docking with Energetics) docking protocol. The ligands were docked using ‘‘xtra precision mode’’ (XP). During docking, the protein was rigid although the ligands were flexible. Glide generates various conformations internally and these are passed through a set of filters namely euler angles, grid based force field assessment and refinement and Monte Carlo energy minimization.[11] Finally, the docked conformers are calculated using Glide (G) Score and a single best pose per ligand is generated as output. The GScore is calculated by this formula:

GScore = a*vdW+b* Coul + Lipo + Hbond + Metal + BuryP + RotB + Site

Where in vdW denotes van der Waals energy, Lipo denotes lipophilic contact, Coul denotes Coulomb energy, Metal indicates metal-binding RotB indicates penalty for freezing rotatable bonds, BuryP indicates penalty for buried polar groups, HBond indicates hydrogen-bonding Site denotes polar interactions in the active site and the a = 0.065 and b = 0.130 are coefficients of vdW and Coul.

The Glide score is an empirical scoring function that is an approximation of the ligand binding free energy and incorporates many parameters such as force fields and penalties for interactions that influence ligand binding as stated by Schrodinger knowledge base (http://www.schrodinger.com/kb/1027).

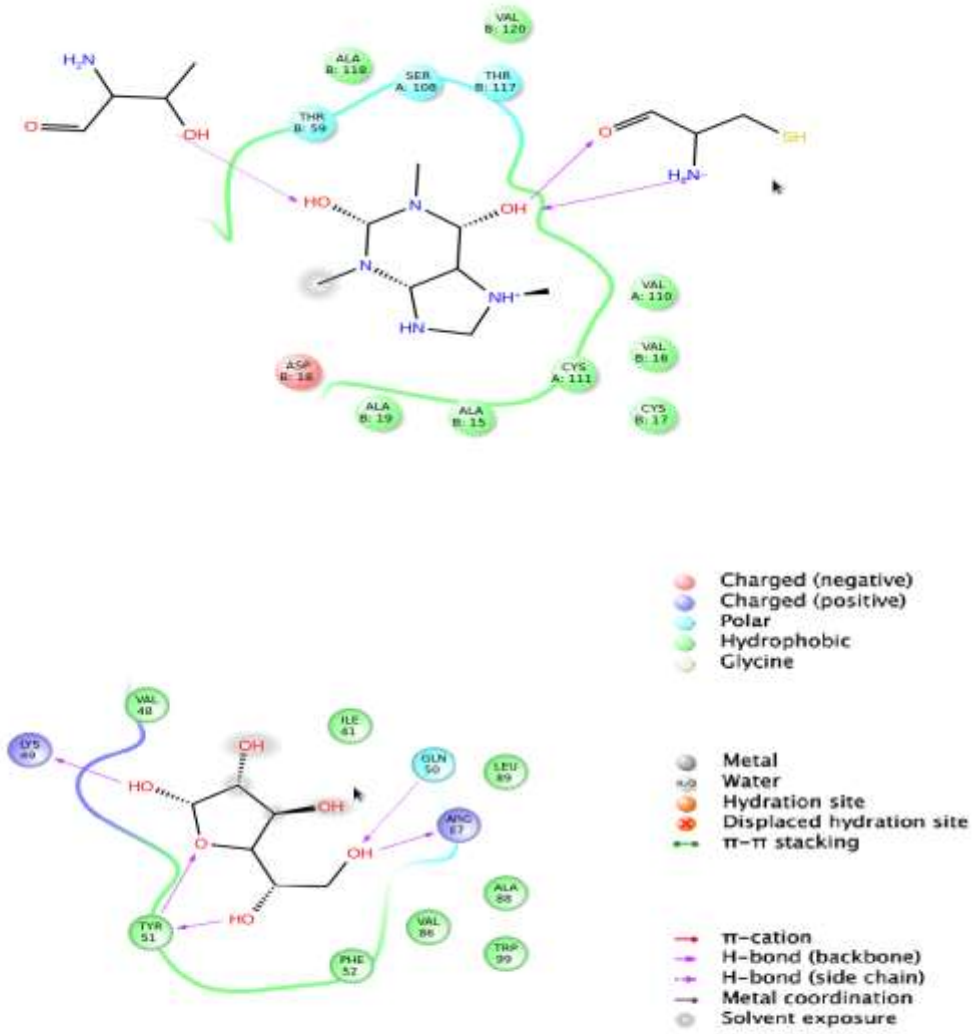


Fig. 2 Graphical system for automatically generating multiple 2D diagrams of ligand–protein interactions from 3D coordinates. The diagrams portray the hydrogen-bond interaction patterns and hydrophobic contacts between the ligand(s) and the main-chain or side-chain elements of the protein. The system is able to plot, in the same orientation, related sets of ligand–protein interactions. This facilitates popular research tasks, such as analysing a series of small molecules binding to the same protein target, a single ligand binding to homologous proteins, or the completely general case where both protein and ligand change.

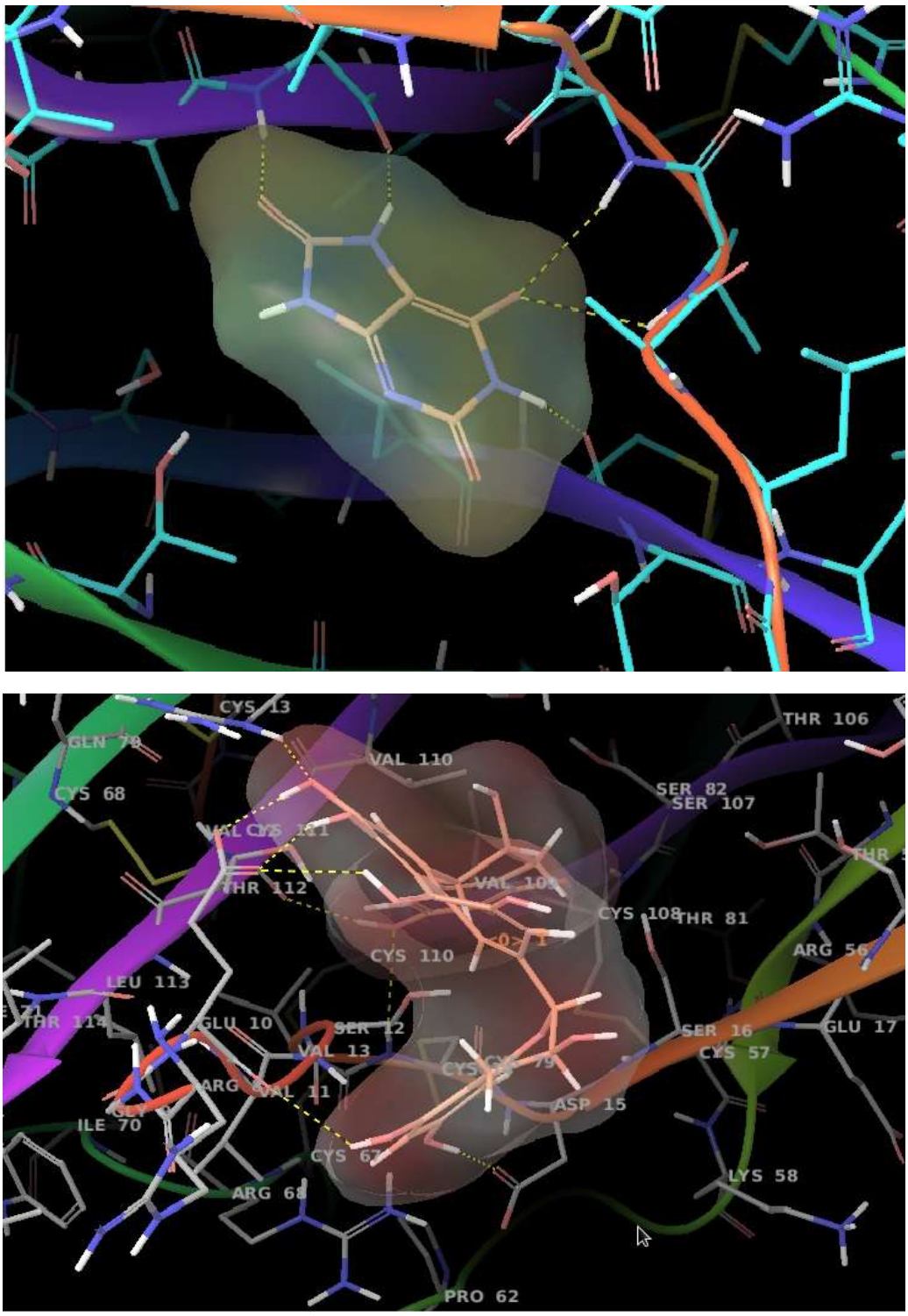


Fig. 3 Co-crystallization studies show antioxidant to be bound at the protein active site. The protein active site of this co-crystal was in its fully liganded conformation bound. Hydrogen bonds between the inhibitor and the enzyme active site are shown with yellow dashed lines.

Table 1: Docking score of antioxidants with 1NT3.

Title	Potential Energy-OPLS-2005	RMS Derivative-OPLS-2005	Docking Score	Glide Score	Glide emodel
ASC	168.180618	0.001848	-6.663904	-6.663904	-34.95391
ZINC00119983	71.297874	0.02212	-6.463412	-6.465212	-44.753715
ZINC02041003	151.764908	0.000049	-6.20753	-6.30073	-35.715859
CFF	136.957886	0.038653	-6.131746	-6.131746	-31.313111
ZINC18185774	55.937813	0.000719	-6.006218	-6.018918	-43.159925
ZINC00001504	20.513794	0.026465	-5.740332	-5.740332	-34.69382
SAL	44.094624	0.001055	-5.669096	-5.669096	-31.000883
ZINC00058117	83.041855	0.04763	-5.631468	-5.631468	-43.868422
J3Z	274.03186	0.001113	-5.630539	-5.630539	-30.812567
EOL	55.497231	0.015615	-5.560236	-5.560236	-23.402427
ZINC03869768	68.676888	0.02373	-5.333572	-5.338872	-42.159241
ESL	244.504395	0.008565	-5.237132	-5.237132	-35.340787
ZINC00517261	87.281097	0.012912	-5.190925	-5.196225	-42.574996
ZINC03830891	-48.660332	0.034062	-5.15156	-5.15156	-48.510094
ZINC13514011	123.048843	0.029005	-4.057835	-4.057835	-34.511344
ZINC03830891	-57.882217	0.029544	-3.970512	-3.970512	-40.599309
BER	294.228302	0.01873	-2.652459	-2.652459	-19.455785

Table 2: Docking score of antioxidants with 1BND.

Title	Potential Energy-OPLS-2005	RMS Derivative-OPLS-2005	Docking Score	Glide gscore	Glide emodel
ZINC03978446	148.754211	0.004447	-7.866317	-7.866317	-76.710372
ZINC02041003	151.764908	0.000049	-6.823889	-6.917089	-48.493248
ZINC18185774	55.937813	0.000719	-6.646332	-6.659032	-51.439039
ZINC00058117	83.041855	0.04763	-6.581555	-6.581555	-52.360434
ZINC00119983	64.385544	0.007384	-6.405837	-6.407637	-54.183538
ASC	148.061081	0.009453	-6.060514	-6.060514	-35.327971
ZINC03869768	68.676888	0.02373	-6.047743	-6.053043	-48.36309
ZINC00001504	20.513794	0.026465	-6.014212	-6.014212	-41.010368
ZINC03874317	67.478371	0.000132	-5.97223	-5.97753	-55.13495
ZINC00517261	87.281097	0.012912	-5.730719	-5.736019	-50.996766
J3Z	233.100967	0.005037	-5.614331	-5.614331	-36.768347
ASC	183.147629	0.001895	-5.507243	-5.507243	-31.508077
J3Z	242.076248	0.006432	-5.445824	-5.445824	-39.305998
EOL	55.497231	0.001154	-5.423384	-5.423384	-28.057839
ZINC03830891	-57.882217	0.029544	-5.421939	-5.421939	-50.671077
J3Z	274.03186	0.001113	-5.343561	-5.343561	-34.176415
ASC	112.808815	0.005614	-5.325101	-5.325101	-35.398586
ZINC03830891	-48.660332	0.034062	-5.309707	-5.309707	-51.676664
ZINC00057060	26.27084	0.008374	-4.867008	-4.867008	-37.034325

Table 3: Docking score of antioxidants with 1B8M.

Title	Potential Energy-OPLS-2005	RMS Derivative-OPLS-2005	Docking Score	Glide gscore	Glide emodel
ZINC02041003	151.764908	0.000049	-8.174437	-8.267637	-46.589144
ZINC03978446	167.929733	0.004933	-7.653452	-7.653452	-65.078047
ZINC00119983	71.297874	0.014735	-7.649406	-7.651206	-48.418034
ZINC00058117	83.041855	0.04763	-6.915786	-6.915786	-50.31095
ZINC03869768	68.676888	0.02373	-6.649981	-6.655281	-45.961778
ZINC18185774	55.937813	0.000719	-6.162924	-6.175624	-48.859997
CFF	115.321281	0.01268	-6.117634	-6.117634	-28.94646
ZINC00001504	20.513794	0.026465	-6.042195	-6.042195	-39.794452
ZINC00517261	87.281097	0.012912	-6.031086	-6.036386	-50.68759
ASC	168.180618	0.005328	-5.753149	-5.753149	-29.700766
ZINC00057060	26.27084	0.008374	-5.571018	-5.571018	-37.62378
ZINC03830891	-58.086182	0.03778	-5.53738	-5.53738	-49.943665
EOL	55.497231	0.001154	-5.171842	-5.171842	-23.089562
SAL	59.22591	0.000142	-5.108967	-5.108967	-28.473235

ADME Screening

One of the main goals in drug discovery is the identification of innovative small molecular scaffolds exhibiting high binding affinity and selectivity for the target together with a reasonable absorption, distribution, metabolism and excretion (ADME) profile, lead and/or drug likeness. Alike chemical entities are likely to be able to enter higher phases of the drug development process. This has produced in a paradigm shift in identifying the drug likeness properties of lead molecules early in the drug discovery process.

The QikProp program was used to obtain the ADME properties of the analogues. It concludes both physically significant descriptors and pharmaceutically significant properties. All the analogues were neutralized before being used by QikProp. The neutralizing step is necessary, as QikProp is unable to neutralize a structure and no properties will be generated in the normal mode.[13]

Thus, *in vitro* approaches are mostly used to examine the ADME properties of new chemical entities and, more recently, computational (*in silico*) modeling has been investigated as a tool to optimize selection of the most suitable candidates for drug development. The program was run in normal mode, and anticipated the properties for the best-fit molecules, consisting of principal descriptors and physiochemical properties with analysis of the log P (Octanol/Water), % human oral absorption, Lipinski's rule of five violation, CNS activity

(Tables 4 and 5). It also evaluates the acceptability of the analogues based on Lipinski's rule of 5 that are essential for rational drug design.[14]

Table 4: Physiochemical descriptors calculated for antioxidants by Qikprop simulation.

Molecule	MW	QP logP o/w	QPlog HERG	QPP Caco	QPP MDCK	Rule of Five	Percent Human Oral Absorption
ASC	180.157	-2.267	-2.151	59.006	-	0	45.369
AXT	623.054	7.174	-4.939	279.119	124.542	2	86.811
BER	351.485	0.513	-2.187	2470.581	1454.786	0	90.674
CFF	202.256	-2.66	-5.143	30.582		0	37.958
EOL	172.267	1.378	-1.388	3349.898	1827.456	0	100
ESL	294.433	1.521	-2.157	506.714	237.265	0	84.263
J3Z	278.434	2.358	-1.836	1217.684	612.072	0	95.98
SAL	146.186	-0.533	0.513	669.16	320.456	0	74.398
ZINC00001504	170.121	-0.582	-1.391	-	-	0	41.903
ZINC00057060	232.282	1.803	-3.405	706.56	661.739	0	88.495
ZINC00058117	288.256	0.93	-4.866	52.143	20.314	0	63.126
ZINC00119983	290.272	0.408	-4.788	56.234		0	60.657
ZINC00517261	316.267	1.115	-5.011	63.949	25.328	0	65.796
ZINC02041003	168.112	-1.466	-3.067	-	-	0	38.768
ZINC03830891	307.321	-3.234	1.155	-	-	1	-
ZINC03831417	286.456	5.148	-4.695	2788.924	1499.044	1	100
ZINC03869768	286.24	1.017	-5.024	65.158	25.846	0	65.365
ZINC03874317	318.239	-0.318	-4.832	-	-	1	28.855
ZINC03978446	564.501	0.08	-6.247	-	-	3	-
ZINC08143568	610.568	-1.421	-5.701	-	-	3	-
ZINC08214943	536.882	18.081	-7.966	9906.038	5899.293	2	100
ZINC08221225	568.881	10.107	-7.017	1143.791	572.026	2	100
ZINC13514011	388.546	6.135	-5.194	2250.065	1188.587	1	100
ZINC17653971	564.85	10.062	-6.923	1410.798	717.635	2	100
ZINC18185774	286.24	0.897	-4.967	46.604	-	0	62.059
ZINC27646615	372.374	3.4	-4.8	4395.124	2450.901	0	100

Range: Solute Molecular Weight **(130.0 / 725.0)**, Solute Molecular Volume (A^3) **(500.0 /2000.**0), Solute vdW Polar SA (PSA) **(7.0 / 200.0)**, Solute No. of Rotatable Bonds **(0.0 / 15.0)**, Solute as Donor - Hydrogen Bonds **(0.0 / 6.0)**, Solute as Acceptor - Hydrogen Bonds **(2.0 / 20.0).**

Table 5: Principle Descriptors calculated for antioxidants by Qikprop simulation.

Molecule	CNS	MW	Volume	Donor HB	Accept HB	Percent Human Oral	PSA	Rule of Five
ASC	-2	180.157	529.69	5	10.2	45.369	116.506	0
AXT	-2	623.054	1976.779	4	6.8	86.811	79.978	2
BER	2	351.485	924.346	0	8.8	90.674	38.262	0
CFF	2	202.256	637.202	3	9.2	37.958	52.812	0
EOL	0	172.267	602.541	1	3.4	100	30.192	0
ESL	-1	294.433	873.633	3	5.1	84.263	64.012	0
J3Z	0	278.434	842.78	2	3.4	95.98	43.592	0
SAL	-1	146.186	432.333	3	5.1	74.398	58.47	0
ZINC00001504	-2	170.121	519.984	4	4.25	41.903	113.386	0
ZINC00057060	0	232.282	823.234	2	3.25	88.495	62.861	0
ZINC00058117	-2	288.256	848.826	3	4.75	63.126	118.757	0
ZINC00119983	-2	290.272	858.076	5	5.45	60.657	113.646	0
ZINC00517261	-2	316.267	899.967	3	5.25	65.796	123.917	0
ZINC02041003	-2	168.112	488.559	4	5.5	38.768	137.458	0
ZINC03830891	-2	307.321	933.447	4.5	8	0	187.549	1
ZINC03831417	0	286.456	1103.519	1	1.7	100	23.135	1
ZINC03869768	-2	286.24	827.172	3	4.5	65.365	116.181	0
ZINC03874317	-2	318.239	868.006	5	6	28.855	158.693	1
ZINC03978446	-2	564.501	1465.316	8	11.15	0	219.9	3
ZINC08143568	-2	610.568	1631.384	7	20.05	0	237.606	3
ZINC08214943	2	536.882		0	0	100	0	2
ZINC08221225	-2	568.881	2049.971	2	3.4	100	44.598	2
ZINC13514011	-1	388.546	1389.604	2	3	100	54.331	1
ZINC17653971	-2	564.85		0	4	100	52.915	2
ZINC18185774	-2	286.24	827.881	3	4.5	62.059	118.798	0
ZINC27646615	0	372.374	1103.335	0	6.25	100	67.803	0

Range: QP log P for octanol/water **(-2.0 / 6.5)**, Lipinski Rule of 5 Violations = **(maximum is 4),** % Human Oral Absorption in GI (+-20%) **(<25% is poor)** Predicted CNS Activity (-- to ++) = --, Apparent Caco-2 Permeability (nm/sec) **(<25 poor, >500 great)**, Apparent MDCK Permeability (nm/sec) **(<25 poor, >500 great).**

CONCLUSION

The availability of NMR and X-ray crystallographic structures of neurotrophins represents an enormous advantage in the fields of structural biology and medicinal chemistry. Nowadays, new computational tools are being employed successfully for the verification of the interactions emerging from crystal structures, because they associate conformational search procedures with scoring function. In this paper, comparative docking study was carried out with the selected antioxidants. Based on the docking score, glide energy and number of

hydrogen bonding it was found that antioxidants gives good scoring function. From the result it is concluded that these antioxidants can act as potential drug against neurotrophins. This study facilitates initiation of the drug discovery process for the oxidative stress involved in AD with better inhibitors, a potential effective drug. The antioxidants compounds shows favorable results in physiochemical properties of partition coefficient of QplogPw, QPlogPoct, QplogHERG, QplogCaco and surface area calculations of SASA, and PSA. According to molecular weight calculation and the human oral absorption properties, some of the compounds are under 500 Dalton with high oral absorption value. These compounds gratify all the *in silico* parameters like docking score, glide emodel, glide energy, binding free energy, non-bonded interactions and ADME/Tox.

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