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MOLECULAR DOCKING GUIDED SCREENING OF PHENOLIC COMPOUNDS FROM *GINKGO BILOBA* AS MULTI-POTENT ANTI-ALZHEIMER'S AGENTS

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Abstract

Alzheimer's disease (AD) is an ultimately fatal degenerative brain disorder that has an increasingly large burden on health and social care systems. There are only five drugs for AD on the market but their adverse effect, toxicity and limited targets in AD pathology limits their use. Therefore, it is crucial to find an effective compound to combat AD. Various medicinal plants have been used to treat diseases for thousands of years and screening herbal remedies is a way to develop new drugs. *Ginkgo biloba* was reported having potential in the treatment of AD and phenolic compounds were reported beneficial in treatment of AD. Based on this we had selected some phenolic compounds found in *G. biloba* for molecular docking studies to investigate the binding interactions between these phenolic compounds and eight anti-Alzheimer's drug targets (N-methyl-D-aspartate glutamate receptor, nitric oxide synthase, beta secretase 1, tumor necrosis factor alpha, mono amine oxidase A, mono amine oxidase B and butylcholine esterase). Amongst the compounds tested *in silico*, catechin and ginkgolic acid displayed appreciable docking interactions with five different targets of AD. Most of these compounds showed good pharmacokinetic properties that make them potentially promising drug candidates for the treatment of AD.

Key words: Alzheimer's disease, Anti-Alzheimer's, Docking, *Ginkgo biloba*, Multi-potent, Phenolic compounds.

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative brain disorder that is characterized by psychological symptoms including impaired cognitive and memory functions, communication, behaviour and personality depression, anxiety and dementia (Borisovskaya *et al*., 2014). According to one report, 36 million people in the world were living with dementia in 2010 and the number will double every 20 years, eventually leading to more than 115 million people with AD in 2050 (Khunnawutmanotham *et al*., 2016; Grewal *et al*., 2017). Thus, this disease will bring enormous financial and personal burdens to current and future generations. In order to deal with this problem, effective therapeutic and preventive interventions should be developed urgently. The pathogenesis of AD remains unknown, although many hypotheses have been developed. Among them, brain cholinergic neuron damage, amyloid-β cascade and oxidative stress hypotheses are widely recognized and are speculated to be the dominant causes of AD pathogenesis (Sadigh-Eteghad *et al*., 2015). There are no such drugs available that can cure or reverse AD completely. However, medications have been developed for AD (rivastigmine, donepezil, galantamine, tacrine and memantine) that can temporarily attenuate the symptoms, or delay it progression (Ji and Zhang, 2008; Russo *et al*., 2013). Thus, the discovery of new drugs for treating AD patients remains a challenge (da Rocha *et al*., 2011; Chen *et al*., 2018).

The various ranges of bioactive nutrients present in the natural products play a vital role in prevention and cure of various neurodegenerative diseases including AD, Parkinson's disease and other neuronal disorders (Russo *et al*., 2013). Previous studies suggested that phytochemicals, such as polyphenolic compounds found in fruits, vegetables, herbs and nuts, may potentially hinder

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Table 1: Predicted ADME properties of the compounds selected for the docking studies.

Sr. No.	MW	log P	log D	log S_w	tPSA	HBA	HBD	Solubility	NRB
1	552.48	5.36	3.28	-6.77	170.14	5	10	637.4	4
2	290.27	0.51	1.78	-2.15	110.38	5	6	33856.4	1
3	566.51	5.69	4.22	-6.98	159.47	4	10	528.6	5
4	346.50	8.55	4.85	-6.53	60.36	3	5	507.5	14
5	316.26	1.87	1.19	-3.19	120.03	4	7	13083.6	2

neurodegeneration and improve memory and cognitive functions (Kim *et al*., 2017). *Ginkgo biloba* (commonly known as ginkgo or gingko) is the best-known plant for AD and its associated symptoms. Extracts of *G. biloba* were widely used for various types of diseases, including cognitive dysfunctions, tinnitus, vertigo, inattention, mood disturbances and cardiovascular diseases. *G. biloba* contains terpenoids, polyphenolic compounds, ginkgolic acids, carbohydrates, fatty acids, inorganic salts and amino acids (Singh *et al*., 2008; Beek and Montoro, 2009).

Currently, medical research is focussed on multi-potent agents against complex diseases owing to greater efficacy, improved safety profile and ease of administration. Docking is one of the most widely used methods for the design of multi-target drugs (Scotti *et al*., 2017). Numerous types of proteins and enzymes are involved in the pathogenesis of AD including N-methyl-D-aspartate glutamate receptor (NMDA), nitric oxide synthase (NOS), beta secretase 1 (BACE-1), tumor necrosis factor alpha (TNFα), mono amine oxidase A (MAO-A), mono amine oxidase B (MAO-B) and butylcholine esterase (BuChE) (Grill *et al*., 2010; Cheng *et al*., 2015; Kumar *et al*., 2016; Chaudhary *et al*., 2018; Cummings *et al*., 2018). In the current investigation docking studies were performed for some phenolic compounds (bilobetin, catechin, ginkgetin, ginkgolic acid and isorhamnetin) found in various parts of *G. biloba* (Fig. 1) in the binding site of the multiple targets of AD in order to explore the mechanism of anti-AD action and binding modes of these compounds.

Materials and Methods

Prediction of pharmacokinetic parameters

All the compounds selected for molecular docking studies were analyzed for the prediction of pharmacokinetic parameters by employing FAF-Drugs4 server and accessed using Lipinski's rule of five (Lagorce *et al*., 2017).

Molecular docking studies

Molecular docking studies were carried out for the selected compounds in the binding site of the target proteins involved in pathogenesis of AD (PDB ID: 1PBQ, 1QWC, 1TQF, 2AZ5, 2Z5Y, 3PO7 and 4B0P for NMDA, NOS, BACE-1, TNFα, MAO-A, MAO-B and BuChE; respectively) using AutoDock Vina (Trott *et al*., 2010) and AutoDock Tools (Morris *et al*., 2009). The 2D structures of the ligands were sketched using MarvinSketch (ChemAxon) followed by conversion to to 3D by Frog2 server (Miteva *et al*., 2010). The ligands were converted to "pdbqt" files using AutoDock Tools. After assessing a number of co-crystallized structures for the target proteins available in the protein data bank; the best ligand bound complexes were selected based on higher resolution and key binding interactions between the ligands and proteins. The PDB files of the proteins were edited using PyMOL (Schrödinger, LLC.). The "pdbqt" files of target proteins were generated from the PDB files using AutoDock Tools (Rathee *et al*., 2019). The grid parameters were calculated using "Grid" tool of AutoDock Tools and all the data regarding target protein, ligand, grid size and geometry were saved in "txt" file. The reference ligands were docked in the binding site of the target proteins and compared with that of co-crystallized ligands for determining accuracy of docking protocol. The 3-D optimized ligands were docked in the binding site of the refined protein models and scored by scoring function and binding interactions of the ligands with the target proteins were analysed using PyMOL (Grewal *et al*., 2019).

Table 2: Binding free energy of selected compounds for docking with multiple targets of AD.

Ligand	ΔG (kcal/mol)						
	NMDA	NOS	BACE-1	TNFα	MAO-A	MAO-B	BuChE
1	-7.2	-9.7	-7.3	-8.9	-7.9	-7.4	-7.8
2	-8.5	-7.9	-7.8	-6.8	-9.7	-9.1	-8.9
3	-9.4	-7.5	-8.9	-6.8	-8.0	-7.8	-7.3
4	-8.5	-9.1	-6.4	-7.5	-7.7	-8.5	-8.8
5	-7.0	-8.3	-8.1	-6.5	-9.1	-8.8	-8.1
Reference*	-8.8	-9.6	-8.1	-8.8	-9.6	-9.4	-9.5

*Co-crystallized ligand of the respective PDB.

Results and Discussion

Prediction of pharmacokinetic parameters

Pharmacokinetic parameters including molecular weight (MW), partition coefficient (log P), distribution coefficient (log D), water solubility (log S_w), topological polar surface area (tPSA), hydrogen bond acceptors

Table 3: Binding interactions of compounds 2, 3 and 4 with NMDA receptor.

Ligand	H-bond interactions	Hydrophobic
	Residues and distance (Å)	interactions (residues)
2	Thr126 (3.1), Arg131 (2.9)	Phe92, Pro124, Asp224
3	Thr126 (3.5), Arg131 (2.7)	Phe92, Pro124, Asp224
4	Thr126 (2.7), Arg131 (4.9)	Phe92, Pro124, Asp224

Table 4: Binding interactions of compounds 1, 4 and 5 with NOS protein.

Ligand	H-bond interactions	Hydrophobic
	Residues and distance (Å)	interactions (residues)
1	Glu592 (2.7, 3.0)	Cys415, Val567
4	Trp587 (3.2, 3.9), Glu592 (3.3)	Cys415, Val567
5	Trp587 (3.4), Glu592 (3.8, 4.0)	Cys415, Val567

(HBA), hydrogen bond donors (HBD), solubility (mg/L) and number of rotatable bonds (NRB) were predicted for all the compounds selected for docking studies. All compounds showed good pharmacokinetic parameters for oral bioavailability (Table 1) and drug-likeness as contrived by Lipinski's rule of five.

In silico molecular docking studies were performed to explore the affinity and binding interactions of the selected compounds using AutoDock Vina in the binding site of the target proteins. The docked reference ligands produced a similar binding pattern and superposition on the binding mode of co-crystallized ligands validating accuracy of the docking methodology. Docking score (binding free energy, ΔG) of the best docked poses of the selected compounds with the target proteins are presented in table 2.

• *Docking with NMDA receptor:* Based on the binding free energy (ΔG) and docking interactions, compounds 2, 3 and 4 were further analyzed in details for exploring binding interactions of these selected molecules with binding site residues of NMDA (Table 3).

Superimposes of the docked poses of compounds 2, 3 and 4 with the with that of PDB ligand 1PBQ (5,7-dichloro-4-hydroxyquinoline-2-carboxylic acid) in the binding site of NMDA receptor showed that these compounds had the similar binding and orientation pattern in the binding site of protein as that of co-crystallized antagonist (Fig. 2). The docked poses of compounds 2, 3 and 4 showed appreciable H-bond interactions with the binding site residues Thr126 and Arg131 of NMDA receptor. These compounds projected in the hydrophobic pocket showing interactions with Phe92, Pro124 and Asp224 residues in binding site of NMDA (Fig. 3).

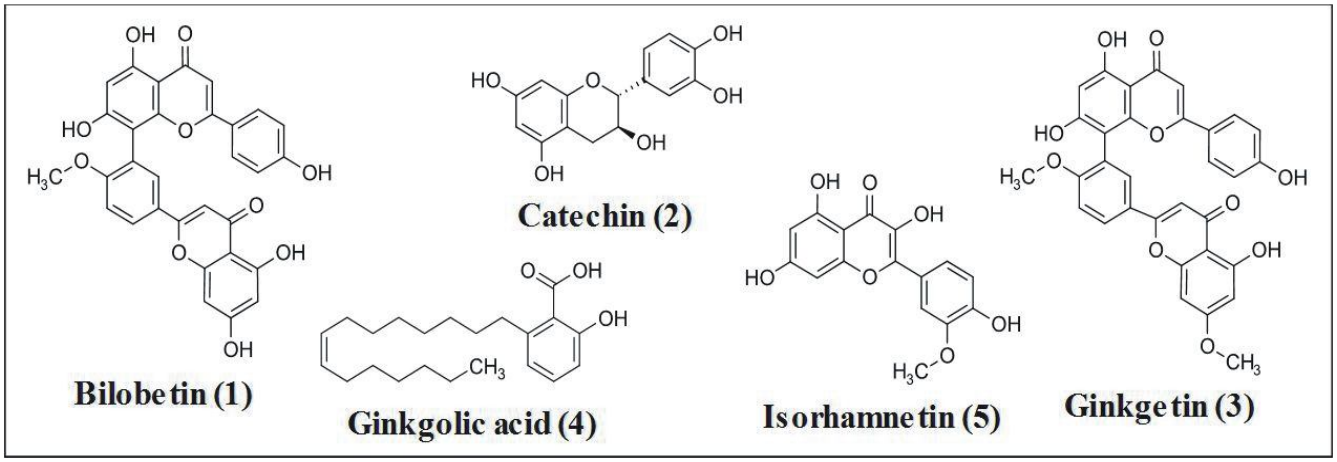

Fig. 1: Chemical structures of compounds selected for *in silico* molecular docking studies.

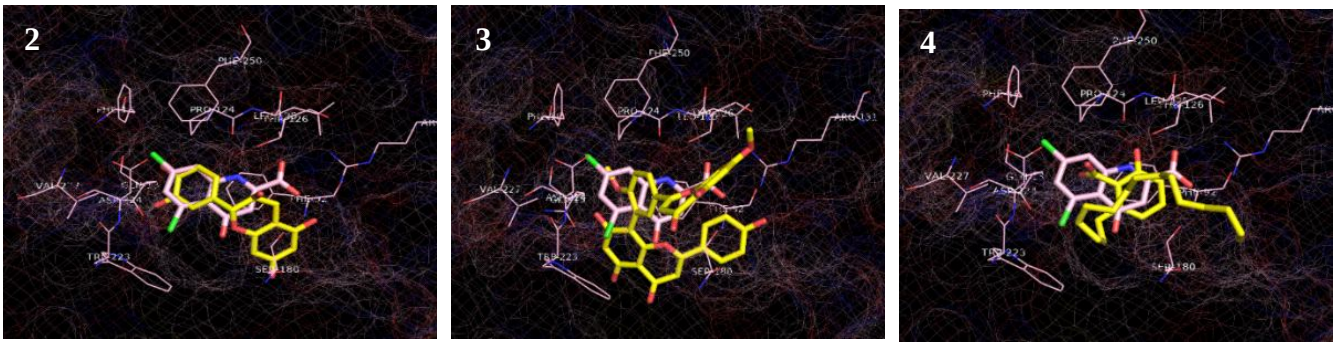

Fig. 2: Superposition of the docked poses of compounds 2, 3 and 4 (yellow stick) with that of 1PBQ ligand (pink stick) in the binding site of NMDA protein.

• *Docking with NOS:* Based on the binding free energy and docking interactions compounds 1, 4 and 5 were further analyzed in details for exploring binding interactions of these selected molecules with binding site residues of NOS protein (Table 4).

Superimposes of the docked poses of compounds 1, 4 and 5 with the with that of PDB ligand 1QWC (N-(3-(aminomethyl)benzyl)acetamidine) in binding site of NOS domain showed that these compounds had the similar orientation pattern in the binding site of NOS protein as that of co-crystallized inhibitor (Fig. 4).

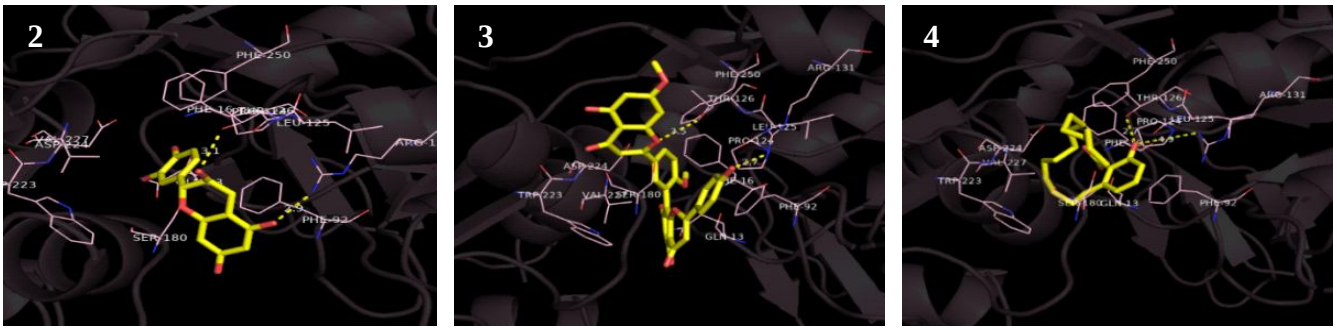

Fig. 3: Docked poses showing H-bond interactions of the compounds 2, 3 and 4 with the binding site residues of NMDA protein.

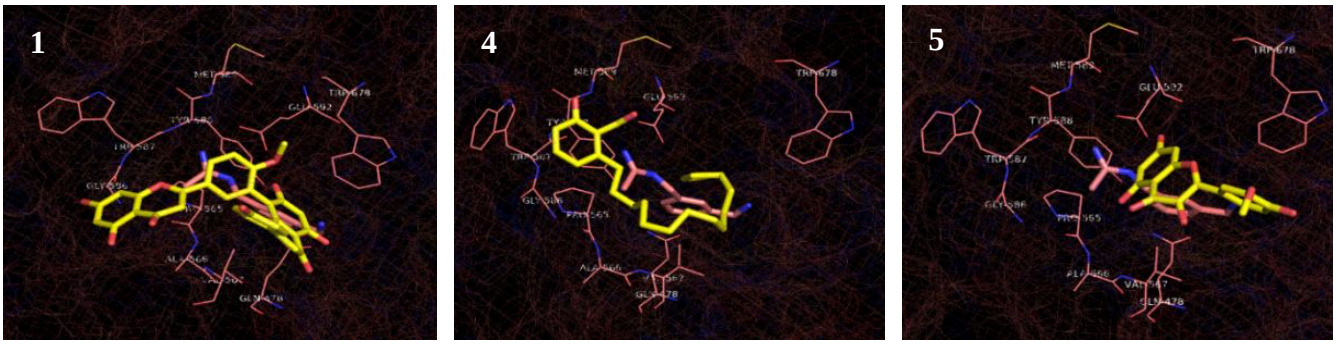

Fig. 4: Superposition of the docked poses of compounds 1, 4 and 5 (yellow stick) with that of 1QWC ligand (pink stick) in the binding site of NOS.

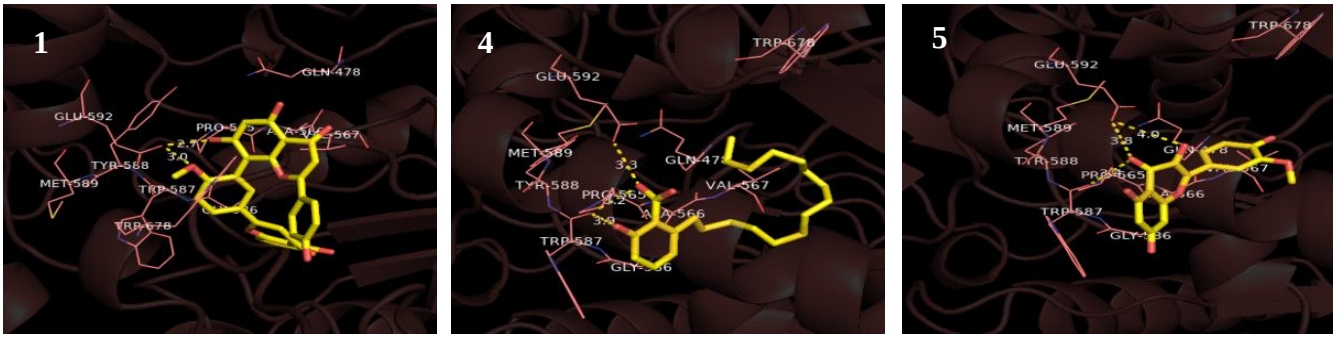

Fig. 5: Docked poses showing H-bond interactions of the compounds 1, 4 and 5 with the binding site residues of NOS.

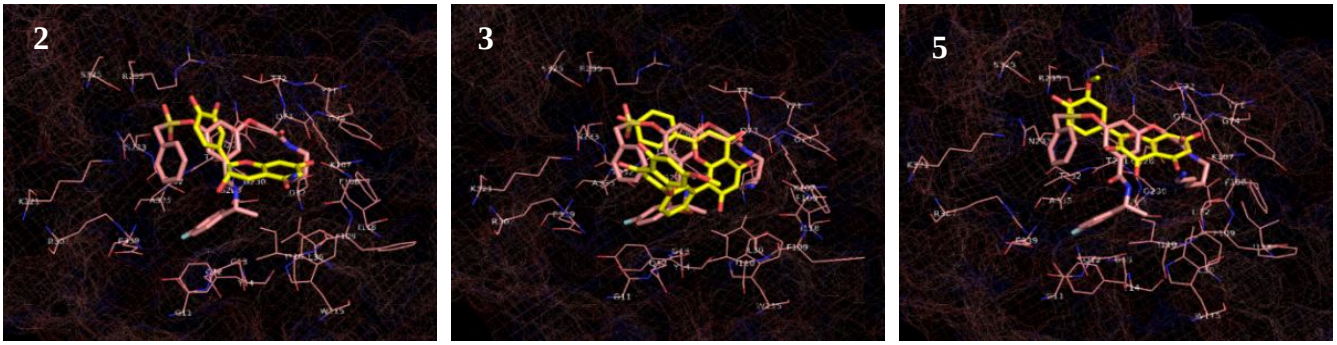

Fig. 6: Superposition of the docked poses of compounds 2, 3 and 5 (yellow stick) with that of 1TQF ligand (pink stick) in the binding site of BACE-1.

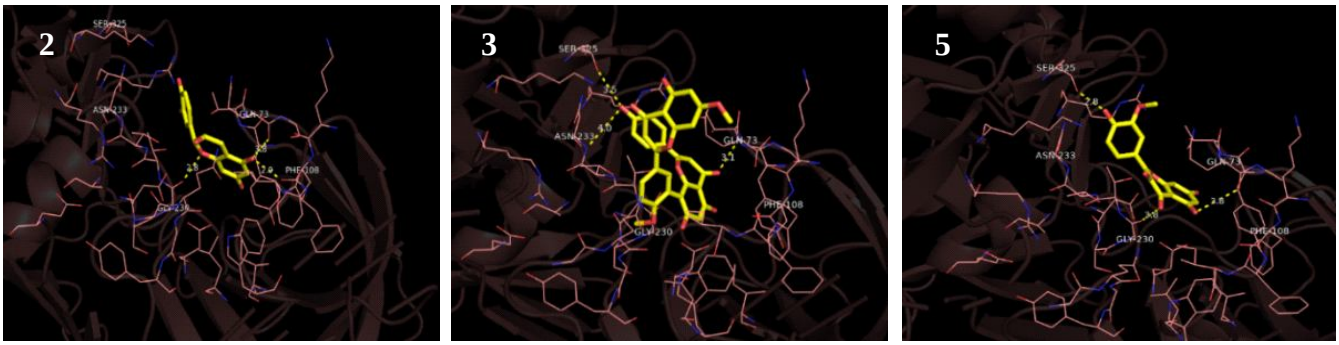

Fig. 7: Docked poses showing H-bond interactions of the compounds 2, 3 and 5 with the binding site residues of BACE-1.

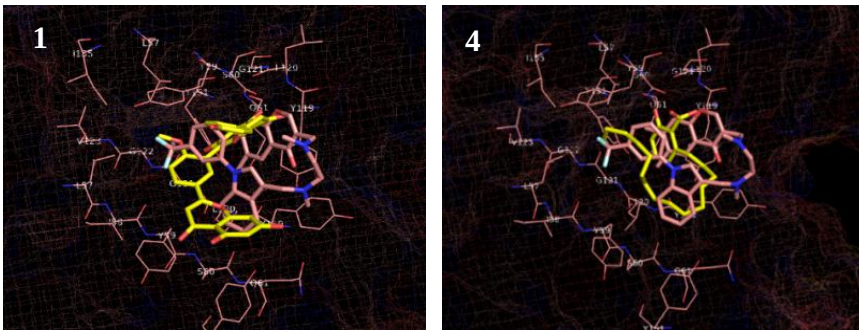

Fig. 8: Superposition of the docked poses of compounds 1 and 4 (yellow stick) with that of 2AZ5 ligand (pink stick) in the binding site of TNFα.

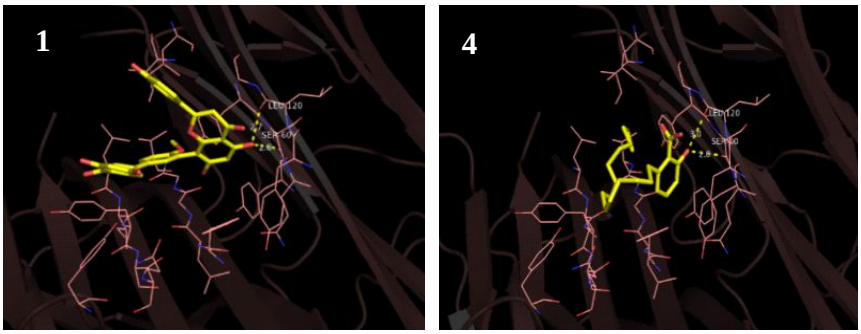

Fig. 9: Docked poses showing H-bond interactions of the compounds 1 and 4 with the binding site residues of TNFα.

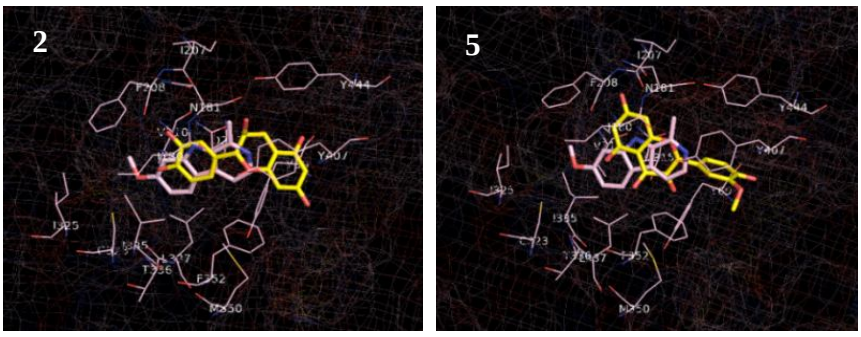

Fig. 10: Superposition of the docked poses of compounds 2 and 5 (yellow stick) with that of 2Z5Y ligand (pink stick) in the binding site of MAO-A.

Table 5: Binding interactions of compounds 2, 3 and 5 with BACE-1.

Ligand	H-bond interactions Residues and distance (Å)	Hydrophobic interactions (residues)
2	Gln73 (3.8), Phe108 (2.9), Gly230 (2.8)	Ile110, Trp115, Thr231, Thr232
3	Gln73 (3.1), Asn233 (4.0), Ser325 (3.5)	Ile110, Trp115, Thr231, Thr232
5	Gln73 (3.8), Gly230 (3.8), Ser325 (2.8)	Ile110, Trp115, Thr231, Thr232

The docked poses of compounds 1, 4 and 5 showed appreciable H-bond interactions with the binding site residues Trp587 and Glu592 of the NOS protein. These compounds projected in the hydrophobic pocket showing interactions with Cys415 and Val567 residues in binding site of NOS (Fig. 5).

• *Docking with BACE-1:* Based on the binding free energy (ΔG) and docking interactions; compounds 2, 3 and 5 were further analyzed in details for exploring binding interactions of these selected molecules with binding site residues of BACE-1 (Table 5).

• *Docking with TNFα:* Based on the binding free energy (ΔG) and docking interactions; compounds 1 and 4 were further analyzed in details for exploring binding interactions of these selected molecules with binding site residues of TNFα (Table 6).

Superimposes of the docked poses of compounds 1 and 4 with the with that of PDB ligand 2AZ5 in the binding site of TNFα showed that these compounds had the similar binding and orientation pattern in the binding site of TNFα as that of co-crystallized small molecule inhibitor (Fig. 8). The docked poses of compounds 1 and 4 showed significant H-bond interactions with Ser60 and Leu120 residues in binding site of TNFα (Fig. 9).

• *Docking with MAO-A:* Based on the binding free energy (ΔG) and docking interactions; compounds 2 and 5 were further analyzed in details using PyMOL for exploring binding interactions of these selected molecules with binding site

Table 6: Binding interactions of compounds 1 and 4 with TNFα.

Ligand	H-bond interactions Residues and distance (Å)	Hydrophobic interactions (residues)
1	Ser60 (2.8), Leu120 (2.7)	Leu57, Tyr59, Tyr119
4	Ser60 (2.8), Leu120 (3.0)	Leu57, Tyr59, Tyr119

Table 7: Binding interactions of compounds 2 and 5 with MAO-A.

Ligand	H-bond interactions Residues and distance (Å)	Hydrophobic interactions (residues)
2	Lys305 (3.1), Tyr444 (3.0)	Ile180, Ile335
5	Lys305 (3.9), Tyr444 (3.0)	Ile180, Ile335

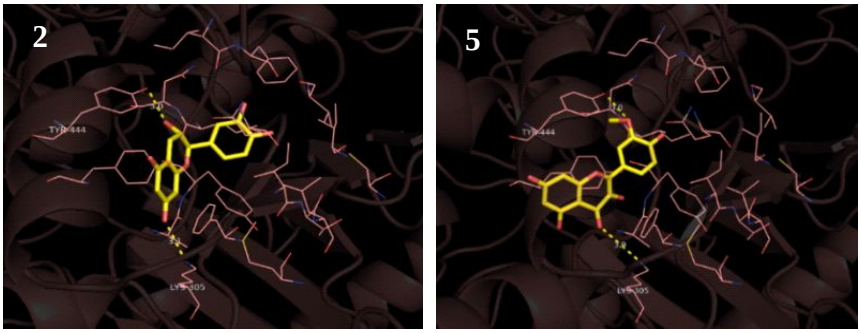

Fig. 11: Docked poses showing H-bond interactions of the compounds 2 and 5 with the binding site residues of MAO-A.

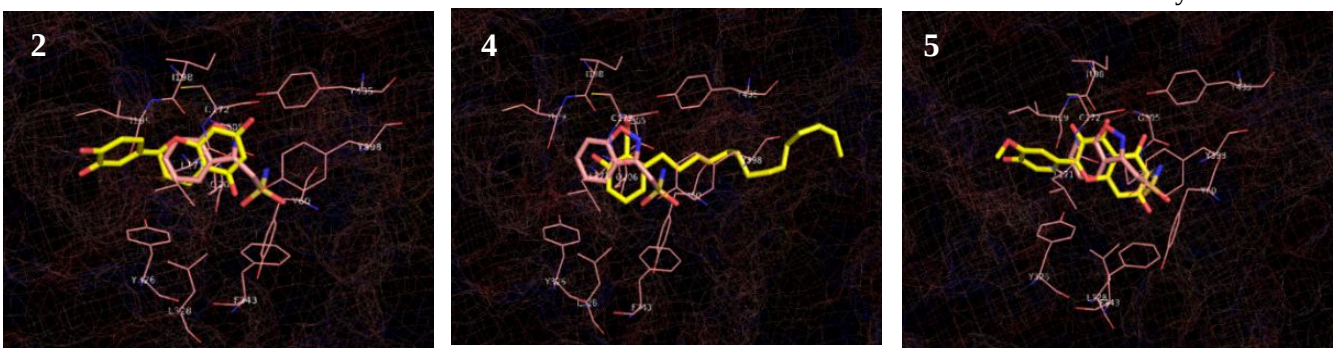

Fig. 12: Superposition of the docked poses of compounds 2, 4 and 5 (yellow stick) with that of 3PO7 ligand (pink stick) in the binding site of MAO-B.

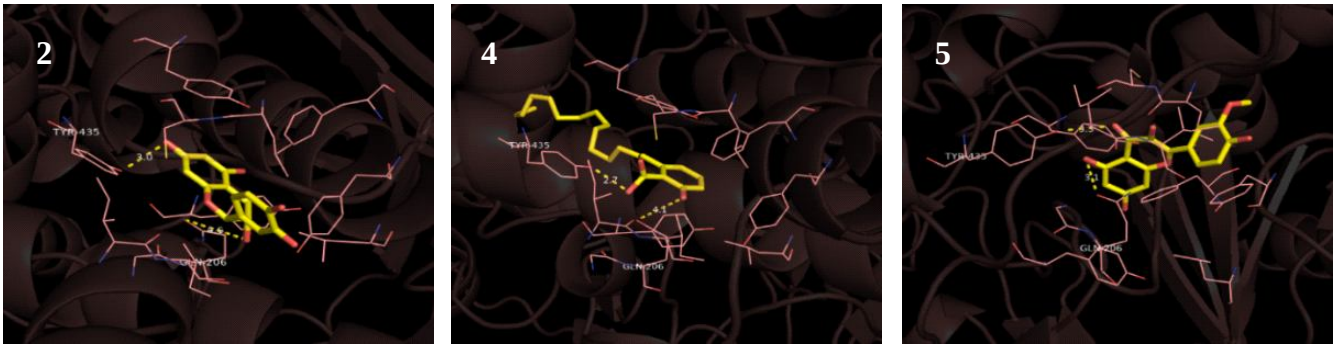

Fig. 13: Docked poses showing H-bond interactions of the compounds 2, 4 and 5 with the binding site residues of MAO-B.

residues of MAO-A (Table 7). Superimposes of the docked poses of compounds 2 and 5 with the with that of PDB ligand 2Z5Y in the binding site of MAO-A protein showed that these compounds had the similar binding and orientation pattern in the binding site of MAO-A as that of co-crystallized inhibitor (Fig. 10). The docked poses of compounds 2 and 5 showed significant H-bond interactions with the binding site residues Lys305 and Tyr444 of MAO-A enzyme. These compounds projected in the hydrophobic pocket showing interactions with Ile180 and Ile335 residues in binding site of MAO-A (Fig. 11).

• *Docking with MAO-B:* Based on the binding free energy (ΔG) and docking interactions; compounds 2, 4 and 5 were further analyzed in details using PyMOL for exploring binding interactions of these selected molecules with binding site residues of MAO-B (Table 8). Superimposes of the docked poses of compounds 2, 4 and 5 with the with that of PDB ligand 3PO7 in the binding site of MAO-B protein showed that these compounds had the similar binding and orientation pattern in the binding site of protein as that of co-crystallized MAO-B inhibitor (Fig. 12).

The docked poses of compounds 2, 4 and 5 showed appreciable H-bond interactions with the binding site residues Gln206 and Tyr435 of the MAO-B enzyme. These compounds protruded in the hydrophobic pocket showing interactions with Phe168, Leu171, Cys172 and Ile199 residues in binding site of MAO-B (Fig. 13).

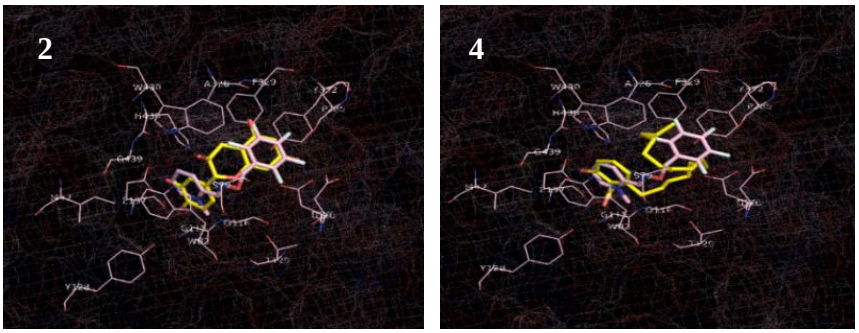

Fig. 14: Superposition of the docked poses of compounds **2** and **4** (yellow stick) with that of 4B0P ligand (purple stick) in the binding site of BuChE.

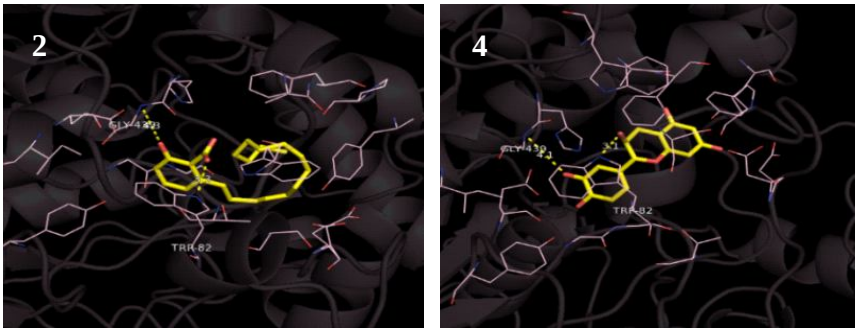

Fig. 15: Docked poses showing H-bond interactions of the compounds 2 and 4 with the binding site residues of BuChE.

Table 8: Binding interactions of compounds 2, 4 and 5 with MAO-B protein.

Ligand	H-bond interactions Residues and distance (Å)	Hydrophobic interactions (residues)
2	Gln206 (4.6), Tyr435 (3.0)	Phe168, Leu171, Cys172, Ile199
4	Gln206 (4.1), Tyr435 (2.7)	Phe168, Leu171, Cys172, Ile199
5	Gln206 (3.1), Tyr435 (3.3)	Phe168, Leu171, Cys172, Ile199

Table 9: Binding interactions of compounds 2 and 4 with BuChE.

Ligand	H-bond interactions Residues and distance (Å)	Hydrophobic interactions (residues)
2	Trp82 (3.1), Gly439 (4.1)	Trp82
4	Trp82 (3.3), Gly439 (4.3)	Trp82

• *Docking with BuChE:* Based on the binding free energy (ΔG) and docking interactions; compounds 2 and 4 were further analyzed in details using PyMOL for exploring binding interactions of these selected molecules with binding site residues of BuChE (Table 9).

Superimposes of the docked poses of compounds 2 and 4 with the with that of PDB ligand 4B0P (methyl-2-(pentafluorobenzyloxyimino)pyridinium) in the binding site of BuChE protein showed that these compounds had the similar binding and orientation pattern in the binding site of BuChE as that of co-crystallized inhibitor (Fig. 14).

The docked poses of compounds 2 and 4 showed appreciable H-bond interactions with the binding site residues Trp82 and Gly435 residues. These compounds projected in the hydrophobic pocket showing interaction with Trp82 residue in binding site of BuChE protein (Fig. 15).

Conclusions

Ginkgo biloba was reported having potential in the treatment of AD and phenolic compounds such as flavonoids were reported beneficial in treatment of AD. Based on this, we had selected some phenolic compounds found in *Ginkgo biloba* for molecular docking studies to investigate the binding interactions between these phenolic compounds and eight anti-AD drug targets. The drug-ability and potential toxicity of the selected compounds were also studied using online computer tools. Amongst the compounds tested *in silico*, catechin and ginkgolic acid showed strong binding interactions and complementary orientation pattern in the binding site of five different targets of AD. All of these compounds showed good pharmacokinetics properties that make them potentially promising drug candidates for the treatment of AD.

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Conflict of Interest

The authors declare no conflict of interest.

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