



# IN SILICO DOCKING STUDIES OF SOME FLAVONOIDS AGAINST MULTIPLE TARGETS OF ALZHEIMER'S DISEASE

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## Abstract

Alzheimer's disease (AD) is an eventually fatal deteriorating brain ailment that has an increasingly large burden on health and social care systems. The adverse effects, toxicity and limited targets in AD pathology limits use of current anti-AD agents. Therefore, it is vital to discover an effective compound to combat AD. Some flavonoids (such as kaempferol, myricetin, quercetin and syringetin) were reported to have beneficial effects in the treatment of AD. Based on this we had selected these flavonoids for molecular docking studies to investigate the binding interactions between these 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, butylcholine esterase and acetylcholine esterase). These compounds displayed appreciable docking interactions with the multiple targets involved in pathogenesis of AD. 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, Flavonoids, Multi-functional.

## Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative brain disorder characterized by mental symptoms including impaired cognitive and memory functions, communication, behaviour and personality depression, anxiety and dementia (Ballard *et al.*, 2011). 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). Thus, this disease will bring enormous financial and personal burdens to the current and future generations. In order to deal with this problem, effective therapeutic and preventive interventions should be developed immediately. The pathogenesis of AD remains unknown, although many hypotheses have been developed. Among them, brain cholinergic neuron damage, amyloid- $\beta$  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,

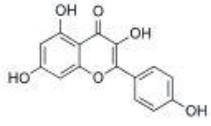
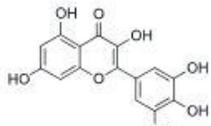
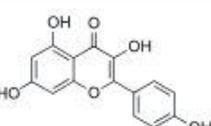
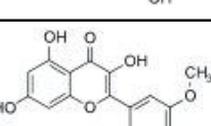
donepezil, galantamine, tacrine and memantine) that can temporarily attenuate the symptoms, or delay its progression (Russo *et al.*, 2013). Thus, the discovery of novel drugs for treating AD patients remains a challenge (da Rocha *et al.*, 2011; Chen *et al.*, 2018).

Nature has gifted us lots of natural remedies including fruits, leaves, bark, vegetables and nuts. Large range of bioactive nutrients present in these natural products play a vital role in prevention and cure of various neurodegenerative diseases (Russo *et al.*, 2013). Previous studies suggested that phytochemicals, such as flavonoids found in fruits, vegetables, herbs and nuts, may potentially hinder neurodegeneration and improve memory and cognitive functions (Kim *et al.*, 2017; Espargaró *et al.*, 2017). Some flavonoids including kaempferol, myricetin, quercetin and syringetin were reported to have beneficial effects for the treatment of AD (Beg *et al.*, 2018; Kouhestani *et al.*, 2018; Ramezani *et al.*, 2016; Zaplatić *et al.*, 2019; Caruana *et al.*, 2016).

Currently, medical research is focussed on multi-potent compounds against complex diseases owing to greater efficacy, improved safety profile and ease of administration. Molecular docking is one of the most

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**Table 1:** Chemical structures of the compounds selected for the *in-silico* docking studies.

Sr. No.	Name of compound	Structure
1	Kaempferol	
2	Myricetin	
3	Quercetin	
4	Syringetin	

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 (TNF $\alpha$ ), mono amine oxidase A (MAO-A), mono amine oxidase B (MAO-B), butylcholine esterase (BuChE) and acetylcholine esterase (AChE) (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 flavonoids (kaempferol, myricetin, quercetin and syringetin) (Table 1) in the binding site of multiple targets related to AD pathogenesis in order to explore the mechanism of anti-AD action and binding modes of these compounds.

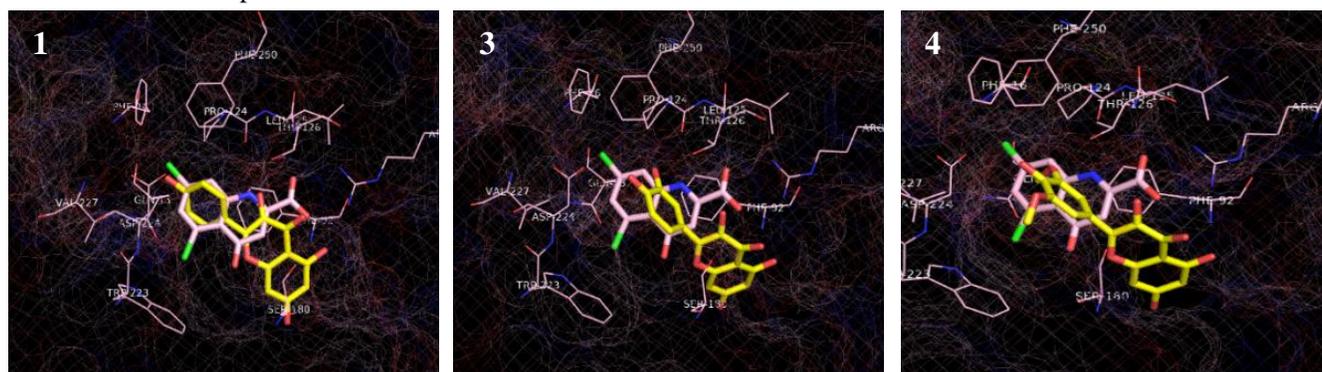
## Materials and Methods

### Prediction of pharmacokinetic parameters

Compounds selected for molecular docking studies were analyzed for the prediction of pharmacokinetic parameters related to absorption, distribution, metabolism and excretion (ADME) 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, 4B0P and 4EY5 for NMDA, NOS, BACE-1, TNF $\alpha$ , MAO-A, MAO-B, BuChE and AChE; respectively) using AutoDock Vina (Trott *et al.*, 2010) and AutoDock Tools (Morris *et al.*, 2009). The 2D chemical structures of all the ligands were prepared by MarvinSketch (ChemAxon) followed by conversion 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. 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. The binding free energy ( $\Delta G$ , kcal/mol) for each ligand was reported in log file and the binding



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

**Table 2:** Predicted ADME properties of the compounds selected for molecular docking studies.

Sr. No.	MW	log P	log D	log S <sub>w</sub>	tPSA	HBA	HBD	Solubility	NRB
1	286.24	1.90	1.35	-3.13	110.80	4	6	12543.7	1
2	318.24	1.18	0.63	-2.85	151.26	6	8	18421.9	1
3	302.24	1.54	1.01	-2.99	131.03	5	7	15228.1	1
4	346.49	1.84	0.99	-3.25	129.26	4	8	13403.2	3

**Table 3:** 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	AchE
1	-7.9	-9.2	-7.5	-7.4	-8.8	-7.6	-9.0	-7.3
2	-7.9	-7.5	-8.0	-6.7	-7.4	-9.0	-9.2	-7.9
3	-9.6	-9.3	-7.8	-6.4	-7.5	-9.2	-9.3	-7.6
4	-8.7	-8.9	-7.2	-7.2	-8.7	-8.7	-8.7	-8.0
Reference*	-8.8	-9.6	-8.1	-8.8	-9.6	-9.4	-9.5	-9.8

\*Co-crystallized ligand of the respective PDB ID.

interactions of the ligands in binding site of the target proteins were analysed using PyMOL (Charaya *et al.*, 2017).

## Results and Discussion

### Prediction of ADME parameters

ADME parameters including molecular weight (MW), partition coefficient (log P), distribution coefficient (log D), water solubility (log S<sub>w</sub>), topological polar surface area (tPSA), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), solubility (mg/L) and number of rotatable bonds (NRB) were predicted for all the compounds selected for molecular docking studies. Almost all of the compounds selected for *in silico* studies showed good pharmacokinetic parameters for oral bioavailability (Table 2) and drug-likeness as contrived by Lipinski's rule of five.

### In silico docking studies

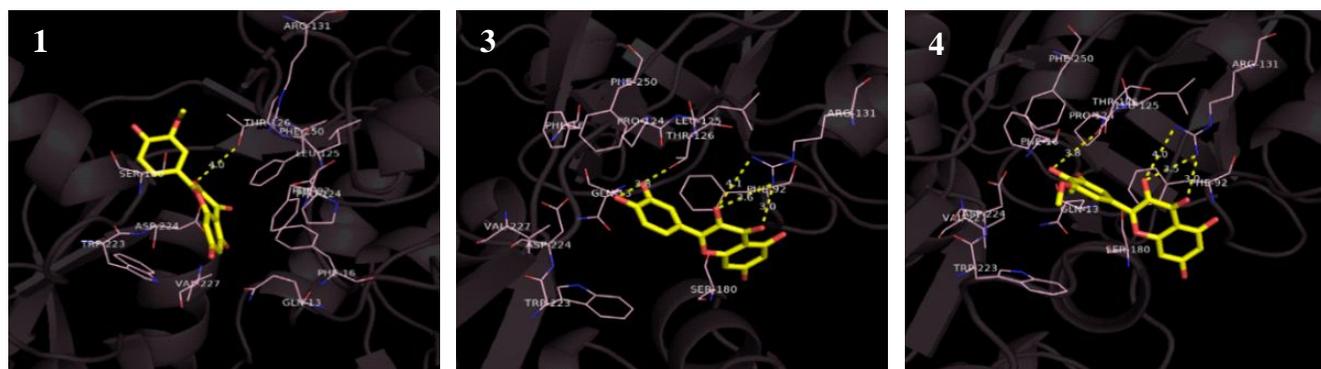
*In silico* molecular docking studies were performed to explore the affinity and binding interactions of the selected compounds in the binding site of the target

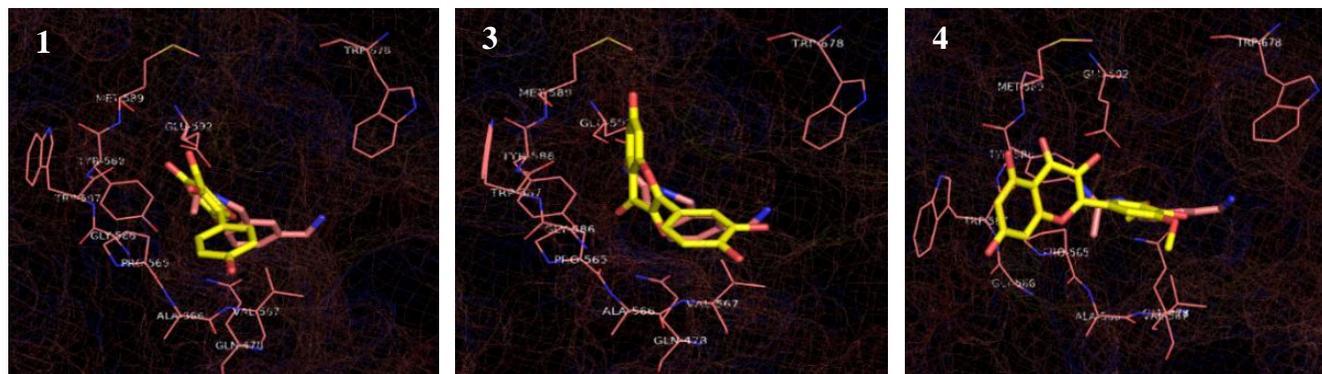
proteins. The docked reference ligands produced a similar binding pattern and superposition on the binding mode of co-crystallized ligands validating accuracy of the docking methodology. Docking score (binding free energy, ΔG) of the best docked poses of the selected compounds with the target proteins are presented in Table 3.

Compounds which showed good docking interactions with multiple targets involved in pathogenesis of AD and binding free energy were further analyzed in detail using PyMOL for exploring binding interactions of these selected molecules with binding site residues of the target proteins.

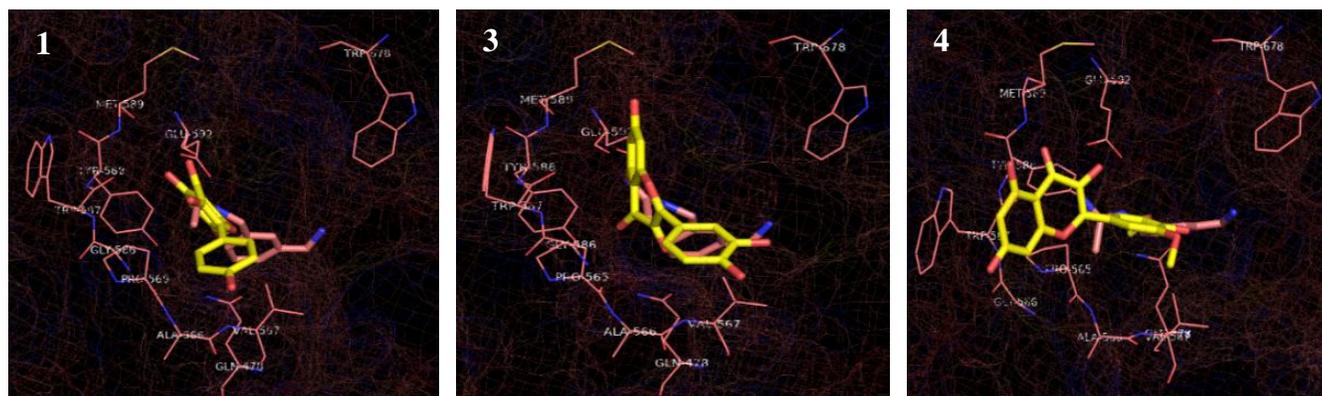
- **Docking with NMDA receptor:** Superimposes of the docked poses of compounds 1, 3 and 4 with that of PDB ligand 1PBQ (5, 7-dichloro-4-hydroxyquinoline-2-carboxylic acid) in the binding site of NMDA receptor showed that these compounds had the similar binding and orientation pattern in the binding site of protein as that of co-crystallized antagonist (Fig. 1). The docked poses of the compounds 1, 3 and 4 showed appreciable H-bond interactions with the binding site residues Thr126 (bond length in the range 3.1-3.3 Å) and Arg131 (bond length in the range 3.1-4.1 Å) of NMDA receptor. These compounds projected in the hydrophobic pocket showing interactions with Phe92, Pro124 and Asp224 residues in binding site of NMDA (Fig. 2).

- **Docking with NOS:** Based on the binding free energy and docking interactions; compounds 6, 8 and 9 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, 3 and 4 with the with that of PDB ligand 1QWC (N-(3-(aminomethyl)benzyl)

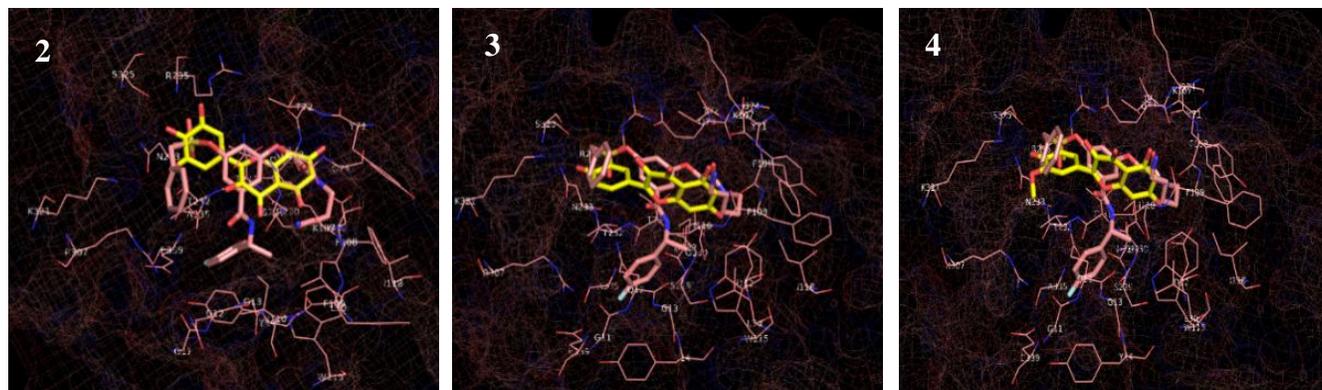
**Fig. 2:** Docked poses showing H-bond interactions of compounds 1, 3 and 4 with the binding site residues of NMDA protein.



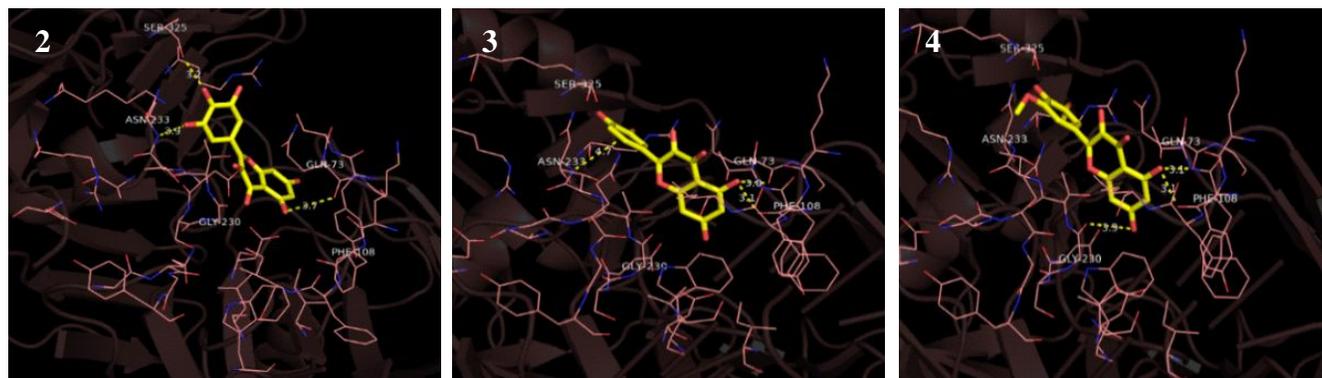
**Fig. 3:** Superposition of the docked poses of compounds 1, 3 and 4 (yellow stick) with that of 1QWC ligand (pink stick) in the binding site of NOS.



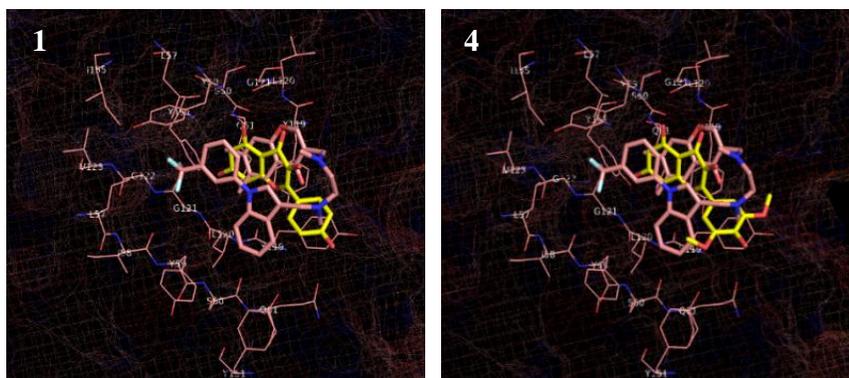
**Fig. 4:** Docked poses showing H-bond interactions of compounds 1, 3 and 4 with the binding site residues of NOS.



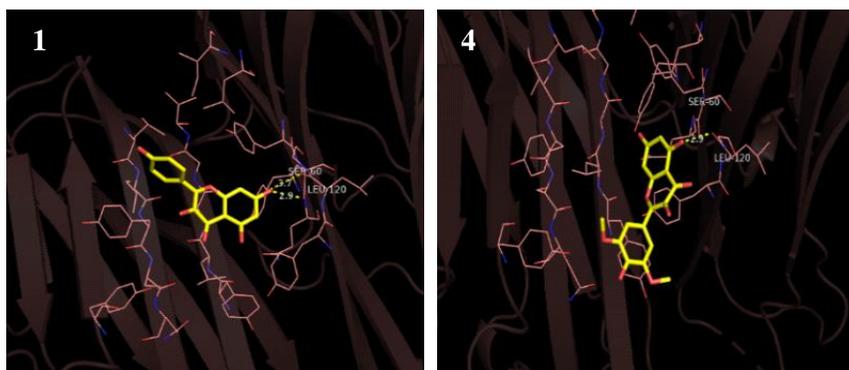
**Fig. 5:** Superposition of the docked poses of compounds 2, 3 and 4 (yellow stick) with that of 1TQF ligand (pink stick) in the binding site of BACE-1.



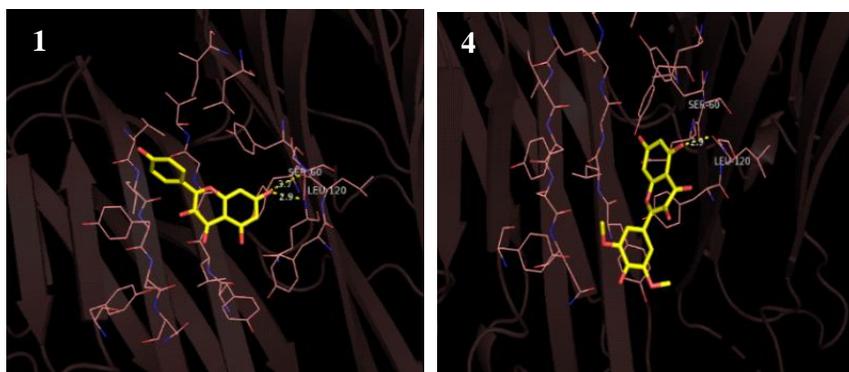
**Fig. 6:** Docked poses showing H-bond interactions of the compounds 2, 3 and 4 with the binding site residues of BACE-1.



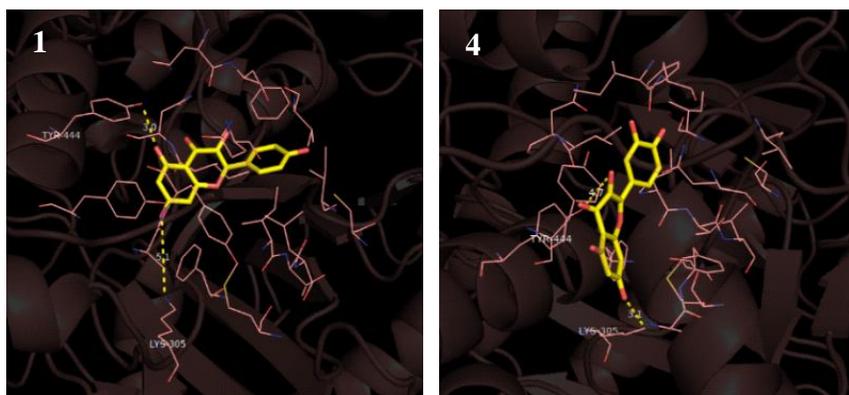
**Fig. 7:** Superposition of the docked poses of compounds 1 and 4 (yellow stick) with that of 2AZ5 ligand (pink stick) in the binding site of TNF $\alpha$ .



**Fig. 8:** Docked poses showing H-bond interactions of the compounds 1 and 4 with the binding site residues of TNF $\alpha$ .



**Fig. 9:** Superposition of the docked poses of compounds 1 and 4 (yellow stick) with that of 2Z5Y ligand (pink stick) in the binding site of MAO-A.



**Fig. 10:** Docked poses showing H-bond interactions of compounds 1 and 4 with the binding site residues of MAO-A.

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. 3). The docked poses of compounds 1, 3 and 4 showed appreciable H-bond interactions with the binding site residues Trp587 (bond length in the range 2.7-3.5 Å) and Glu592 (bond length in the range 2.8-3.5 Å) of the NOS protein. These compounds projected in the hydrophobic pocket showing interactions with Cys415 and Val567 residues in binding site of NOS (Fig. 4).

• *Docking with BACE-1:*

Superimposes of the docked poses of compounds 2, 3 and 4 with that of PDB ligand 1TQF in the binding site of BACE-1 showed that these compounds had the similar binding and orientation pattern in the binding site of BACE-1 protein as that of co-crystallized inhibitor (Fig. 5).

The docked poses of compounds 2, 3 and 4 showed appreciable H-bond interactions with the binding site residues Gln73 (3.7 Å), Asn233 (3.9 Å) and Ser325 (3.2 Å); Gln73 (3.0 Å), Phe108 (3.1 Å) and Asn233 (4.7 Å); and Gln73 (3.1 Å), Phe108 (3.1 Å) and Gly230 (3.9 Å) respectively of the BACE-1 protein. Compounds 2, 3 and 4 projected in the hydrophobic pocket showing interactions with Ile110, Trp115, Thr231 and Thr232 residues in binding site of BACE-1 protein (Fig. 6).

• *Docking with TNF $\alpha$ :*

Superimposes of the docked poses of compounds 1 and 4 with that of PDB ligand 2AZ5 (6,7-dimethyl-3-[(methyl{2-[methyl({1-[3-(trifluoromethyl)phenyl]-1H-indol-3-yl)methyl}amino)ethyl}amino)methyl]-4H-chromen-4-one) in the binding site of TNF $\alpha$  showed that these compounds had the similar binding and orientation pattern in the binding site of TNF $\alpha$  as that of the co-crystallized small molecule inhibitor of TNF $\alpha$  protein (Fig. 7).

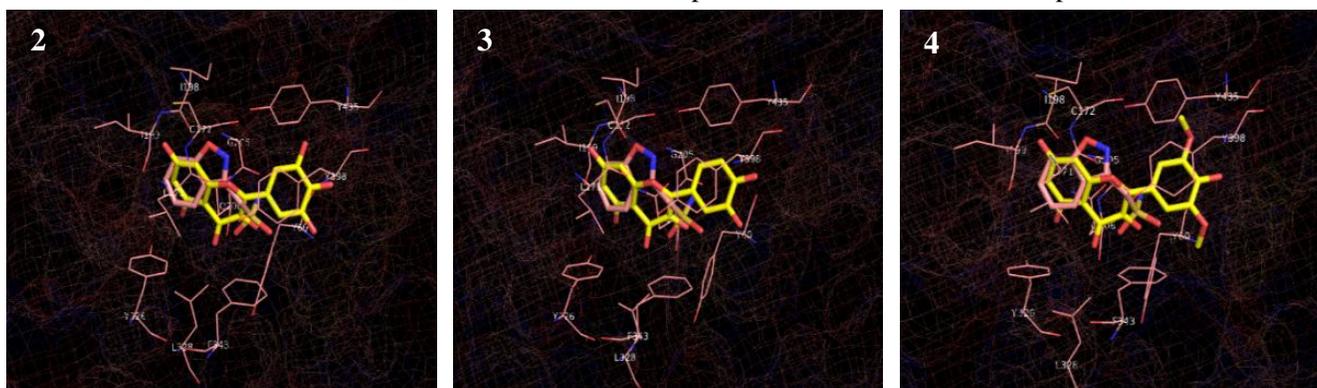
The docked poses of the compounds

1 and 4 showed significant H-bond interactions with residues Ser60 (bond length in the range 2.8-2.9 Å) and Leu120 (bond length in the range 2.9-3.7 Å) in the binding site of TNF $\alpha$ . These compounds displayed hydrophobic interactions with Leu57, Tyr59 and Tyr119 residues of TNF $\alpha$  protein (Fig. 8).

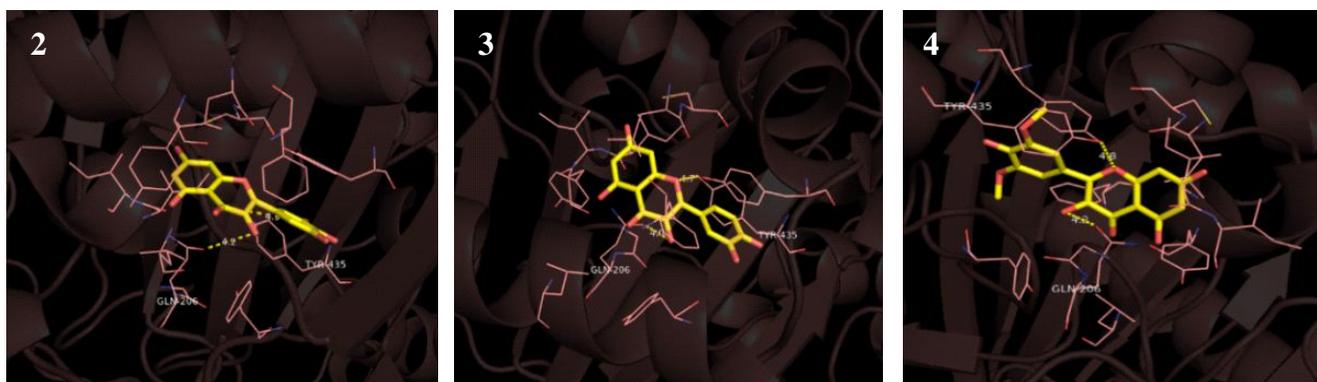
- *Docking with MAO-A*: Superimposes of the docked poses of compounds 1 and 4 with the with that of PDB ligand 2Z5Y in the binding site of MAO-A protein showed that these compounds had the similar binding and orientation pattern in the binding site of MAO-A as that of co-crystallized inhibitor (Fig. 9).

The docked poses of compounds 1 and 4 showed significant H-bond interactions with the binding site residues Lys305 (bond length in the range 4.1-5.1 Å) and Tyr444 (bond length in the range 3.0-3.7 Å) of MAO-A enzyme. Compounds 1 and 4 projected in the hydrophobic pocket showing interactions with Ile180 and Ile335 residues in binding site of MAO-A (Fig. 10).

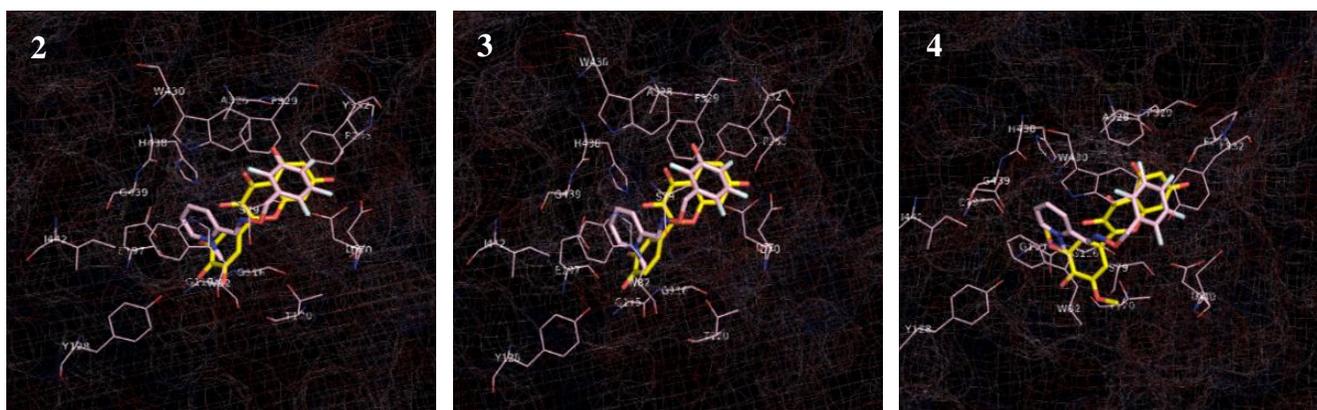
- *Docking with MAO-B*: Superimposes of the docked poses of compounds 2, 3 and 4 with the with that of PDB ligand 3PO7 (1-(1,2-benzoxazol-3-yl) methanesulphonamide) in the binding site of the MAO-B protein showed that these compounds had the similar



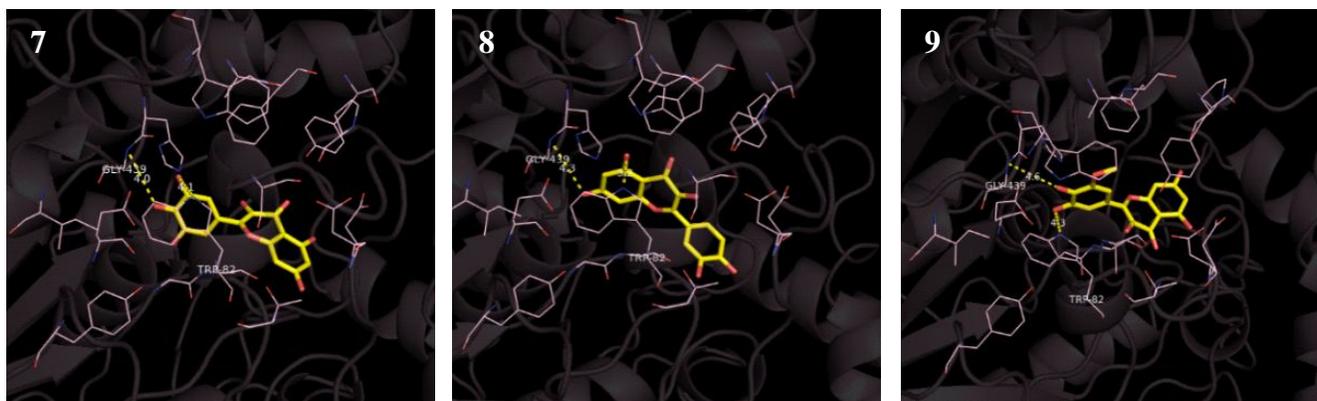
**Fig. 11:** Superposition of the docked poses of compounds 2, 3 and 4 (yellow stick) with that of 3PO7 ligand (pink stick) in the binding site of MAO-B.



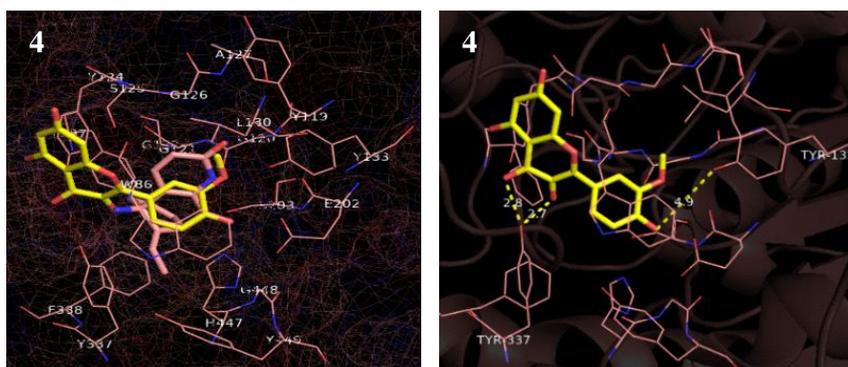
**Fig. 12:** Docked poses showing H-bond interactions of compounds 2, 3 and 4 with the binding site residues of MAO-B.



**Fig. 13:** Superposition of the docked poses of compounds 2, 3 and 4 (yellow stick) with that of 4B0P ligand (purple stick) in the binding site of BuChE.



**Fig. 14:** Docked poses showing H-bond interactions of compounds 2, 3 and 4 with the binding site residues of BuChE.



**Fig. 15:** Left: Superposition of the docked pose of compound 4 (yellow stick) with that of 4EY5 ligand (pink stick); Right: Docked poses showing H-bond interactions of compound 4 with the binding site residues of AchE.

binding and orientation pattern in the binding site of protein as that of the co-crystallized MAO-B inhibitor (Fig. 11).

The docked poses of compounds 2, 3 and 4 showed appreciable H-bond interactions with the binding site residues Gln206 (bond length in the range 4.0-4.2 Å) and Tyr435 (bond length in the range 4.3-4.8 Å) of the MAO-B enzyme. These compounds protruded in the hydrophobic pocket showing interactions with Phe168, Leu171, Cys172 and Ile199 residues in the binding site of MAO-B (Fig. 12).

• **Docking with BuChE:** Superimposes of the docked poses of compounds 2, 3 and 4 with that of the 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 the co-crystallized inhibitor of BuChE enzyme (Fig. 13).

The docked poses of the compounds 2, 3 and 4 showed appreciable H-bond interactions with the binding site residues Trp82 (bond length in the range 3.2-4.1 Å) and Gly435 (bond length in the range 4.0-4.3 Å) of BuChE protein. These compounds projected in the hydrophobic pocket showing interaction with Trp82 residue in the binding site of the BuChE protein (Fig. 14).

• **Docking with AchE:** Compound 8 displayed H-bond interactions with the residues Tyr133 (4.9 Å) and Tyr337 (2.8 Å and 2.7 Å) of AchE; and hydrophobic interactions with Trp86, Gly121 and Tyr337 residues in the binding site of AchE enzyme (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

flavonoids for molecular docking studies to investigate the binding interactions between these phenolic compounds and eight anti-Alzheimer 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*, syringetin showed strong binding interactions and complementary orientation pattern in the binding site of all the targets involved in pathogenesis of AD. Quercetin showed good binding interactions with 5 targets of AD. These compounds showed good pharmacokinetics properties that make them potentially promising drug candidates.

## Acknowledgement

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## Conflict of Interest

The authors declare no conflict of interest.

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