



## Molecular Docking Studies of *Ginkgo biloba* against Acetylcholinesterase Enzyme

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### ABSTRACT

In this study we focus upon the extensive use of tool and graphical software for identification of binding energy of phytoconstituents from *Ginkgo biloba* to dock to acetylcholinesterase enzyme. The process involves the prediction of potential ligand in *ginkgo biloba* phytoconstituents for treatment of Alzheimer's disease. To be more practical & useful, this study will compare binding energy for cholinesterase enzyme with each of the following: Conventional acetylcholinesterase inhibitors (Denopozil, galantamine) and *Ginkgo biloba* phytoconstituents. We can conclude that the binding energy for the docked kaempferol and quercetin is almost the same as in Conventional acetylcholinesterase inhibitors. *Ginkgo biloba* extract contains extra constituents which contribute to extra side effects, so theoretically to get the best anti-Alzheimer action with the least side effects isolated kaempferol and quercetin could be used, we recommend more clinical trials to be conducted regarding the above mentioned idea to get the best to AD patients.

**Keywords:** kaempferol, Quercetin, Acetylcholinesterase, docking, molecular modeling, denopozil, galantamine.

### INTRODUCTION

Alzheimer disease (AD) is the most common form of the dementia which occurs among older people above the age of 60 years. The Alzheimer's disease was considered to be a rare disorder, and it is now seen as a major public health problem that is seriously affecting millions of older people and their families worldwide.<sup>1,2</sup> The incidence of AD ranges from 1 to 4 percent of the population per year rising from its lowest level at ages 65 to 70 years to rates that may approach 6 percent for those over the age of 85 years. Alzheimer's is characterized by massive loss of neurons and disrupted signaling between cells in the brain.<sup>3,14,15</sup>

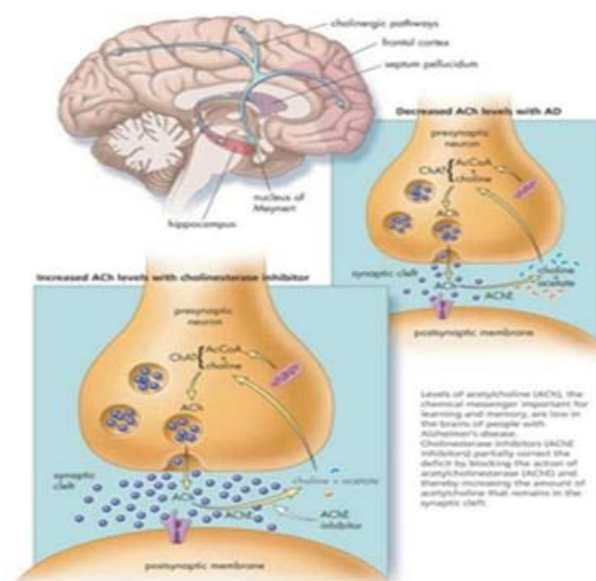
Since the introduction of the first cholinesterase inhibitor (ChEI) in 1997, most clinicians and probably most patients would consider the cholinergic drugs, donepezil, galantamine, tacrine and rivastigmine, to be the first line pharmacotherapy for mild to moderate Alzheimer's disease. The drugs have slightly different pharmacological properties, but they all work by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by blocking the enzyme acetylcholinesterase<sup>1</sup> (figure 1).

Side effects concomitant to the use of conventional cholinesterase inhibitors is the major reason pushing the patient to go towards natural substituent (in our case *Ginkgo biloba*).

Denopozil is known to cause (Nausea, vomiting, diarrhea, loss of appetite/weight loss, dizziness, drowsiness, weakness, trouble sleeping, shakiness (tremor), or muscle cramps).

Galantamine is known to cause (nausea, vomiting, diarrhea, and anorexia (weight loss), headache,

abdominal pain, fatigue, slow heart rate, depression, sleepiness and fainting).



**Figure 1:** mechanism of action of acetylcholinesterase inhibitors

While Tacrine today rarely prescribe because its serious side effects.<sup>5</sup>

*Ginkgo biloba*, frequently referred to as a "living fossil", is the oldest living tree species on earth and dates back more than 200 million years. The medicinal use of *Ginkgo* leaves dates back to 2 800 BC where it was documented in the first Chinese Materia Medica that brewed leaf extracts were effective for the treatment of cardiovascular and bronchial diseases, circulatory complications, swelling of extremities, as an anthelmintic. Nowadays *Ginkgo biloba* extract used for the treatment

of cerebral insufficiency, dementia, intermittent claudication.<sup>6-8</sup>

As with most herbal preparations, *Ginkgo biloba*'s pharmacological activity is attributed to the synergistic action of multiple chemical components. and it is generally accepted that both the flavonol glycosides and terpene trilactones are responsible for its beneficial effects.<sup>6</sup>

The *Ginkgo biloba* extract seems to produce neuroprotective effects in neurodegenerative diseases of multifactorial origin. The main effects of *Ginkgo biloba* extract in the central nervous system seem to be related to its antioxidant properties and free radical scavenging which have been considered the mediators of the excessive lipid peroxidation and cell damage observed in Alzheimer's disease.<sup>9</sup>

In brief, several mechanisms of action have been described to explain the nootropic properties of *Ginkgo biloba*: increased tolerance to hypoxia; improvement of blood rheology and vasoregulating capacity, resulting in increased blood flow; prevention of post-traumatic or toxin-induced brain edema; platelet activating factor inhibition; neuroprotective action by direct or by indirect influences on the nervous system.<sup>10-13</sup>

This study will compare binding energy for cholinesterase enzyme with each of the following: Conventional acetylcholinesterase inhibitors (Denopezil, galantamine) and *Ginkgo biloba* phytoconstituents, and try to discover the actual phytoconstituent responsible for the anti Alzheimer action to end up with a drug which offers the best action with minimum side effects.

## MATERIALS AND METHODS

Various tools and softwares were used to analyse this protein sequence and assign its structure, and to study its docking properties. Receptor sequence (pdb ID 1ACJ) was obtained from protein data bank (WWW.Pdb.org/pdb) figure (2) shows 3D of 1ACJ. molecular properties and drug likeness for Ginkgolide A, Ginkgolide B, Ginkgolide C, Bilobalide, Kaempferol, Quercetin, Isorhamnetin was taken from (<http://pubchem.ncbi.nlm.nih.gov>) &

(<http://cssp.chemspider.com/>), the prediction ADME is done by using (<http://preadmet.bmdrc.org/>) online. leadIT2 software was used for docking purpose and visualizing molecular structure docking.

## RESULTS AND DISCUSSION

Drug likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties are mainly hydrophobicity, electronic distribution, Hydrogen bonding characteristics, molecule size and flexibility. This was given from pubchem and chemspider.

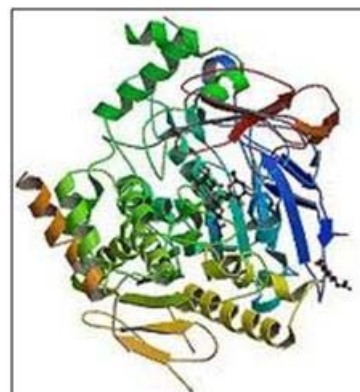


Figure 2: 3D structure of 1ACJ

Quercetin, Kaempferol, isorhamnetin, Ginkgolide A, Ginkgolide B, Ginkgolide C, Bilobalide have the Hydrogen bonding acceptor values :7,6,7,9,10,11,8 respectively.

Because Ginkgolide C has Hydrogen bonding acceptor value =11 then it is not recommended to be given orally with reference to lipinski rule (rule of 5).

Quercetin, Kaempferol, Isorhamnetin, Ginkgolide A, Ginkgolide B, Ginkgolide C Bilobalide have Hydrogen bonding donor values : 5,4,4,2,3,4,2, respectively.

For oral drugs for AD, it is important to know whether they can be absorbed by the human intestine.

The PreADME software used for predicting the human intestinal absorption (HIA). The value of HIA varies between 36% to 81%.

HIA values = 60.16%, 77.8%,

87.19%, 61%, 36.6%, 54% for Quercetin, Kaempferol, Isorhamnetin, Ginkgolide A, Ginkgolide B, Bilobalide, respectively. So all of the above mentioned constituents are absorbed and could contribute to anti Alzheimer action, docking can clearly decide which of the intestinally absorbed constituents actually contribute to anti-Alzheimer disease.

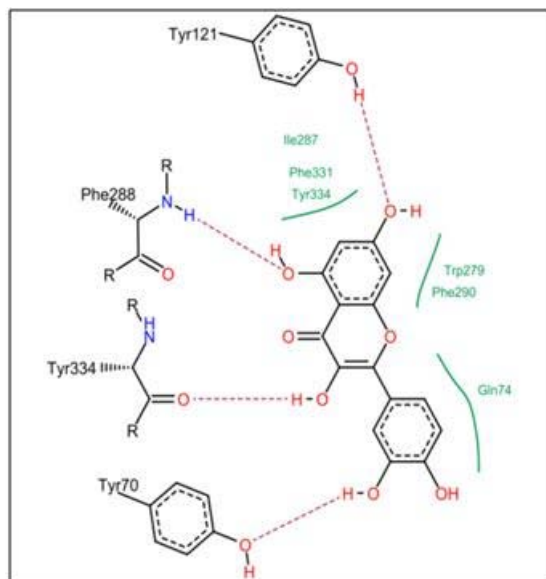
Docking was done to identify the binding energy interaction of Quercetin, Kaempferol, isorhamnetin, Ginkgolide A, Ginkgolide B, Bilobalide against acetylcholinesterase enzyme and compare the binding energy with the Galantamine and Denopezil. The protein was uploaded as protein.pdb and the ligands were uploaded as ligand.sdf. docking energy values for Quercetin, Kaempferol, Isorhamnetin were -16, -18, -5 KJ/mol respectively and the ligand efficiency were 0.18, 0.20, 0.05 Kcal/mol per heavy atom respectively.

While the Ginkgolide A, Ginkgolide B and Bilobalide were not docked.

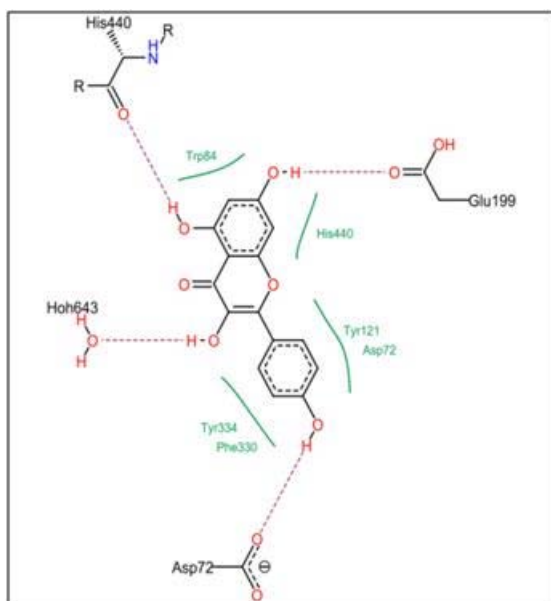
Whereas the binding energy values for Galantamine and Denopezil were -29, -16 kJ/mol respectively and ligand efficiency values were 0.25, 0.18 Kcal/mol per heavy atom respectively.

The docking energy value between the active site and the phytoconstituents under investigation was taken into

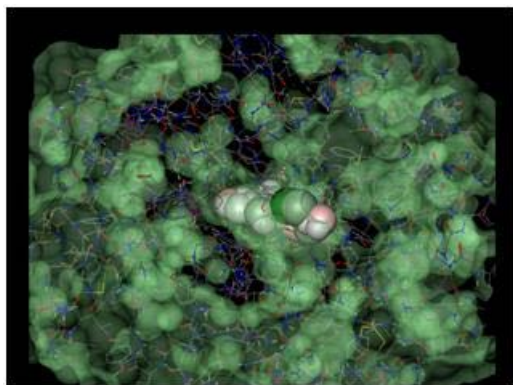
consideration for coming into the best pose and binding ability. (Figure 3,4,5,6)



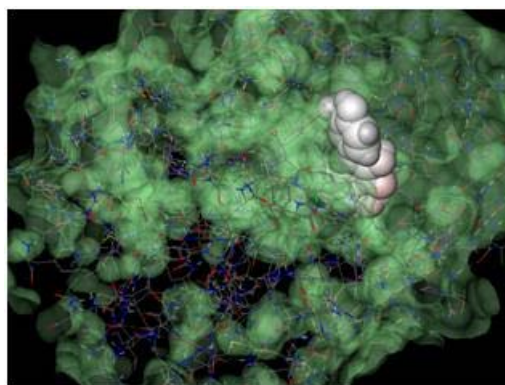
**Figure 3:** Pose view of quercetin with active site of acetylcholine esterase.



**Figure 4:** Pose view of kaempferol with active site of acetylcholine esterase.



**Figure 5:** 3D of docked kaempferol with acetylcholine esterase.



**Figure 6:** 3D of docked quercetin with acetylcholine esterase.

## CONCLUSION

This study concludes that the binding energy for the docked kaempferol and Quercetin is almost the same as in Conventional acetylcholinesterase inhibitors. *Ginkgo biloba* extract contains extra constituents which contribute to extra side effects, so theoretically to get the best anti-alzheimer action with the least side effects, isolated Kaempferol and Quercetin could be used, we recommend more clinical trials to be conducted regarding the above mentioned idea to get the best to AD patients.

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