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NOVEL LIGAND –BASED DOCKING STUDIES OF GINGER TO ANALYZING POTENTIAL ACHE INHIBITORS FOR ALZHEIMER'S DISEASE

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ABSTRACT

Ginger (*Zingiber officinale*), despite being a regular dietary Nutritional supplement adding to the taste and aroma of foods, contains several potentially bioactive photochemical having valuable medicinal properties. Even if modern studies have emphasized their benefits in Alzheimer's disease. Hence the current research work seeks to utilize molecular docking studies for investigation of binding interactions between active ginger components i.e. Gingerol, Shagoal and Ginerol for various anti-Alzheimer drug targets. All the bioactive photochemical that show predicted activity and follows rules were docked into the receptor of 1QWC, 4ey5 downloaded form (WWW.RCSB.COM). The structures were drawn using Vlife2D Draw software based on the 1QWC, 4ey5E receptor by altering the ligands. After that, they were converted to 3D structures using the same Vlife 3D Modules software by which they were subjected to energy minimization using the Compute menu and then saved as Mol extension files which can be accessed using the docking interface. Vlife MDS 4.6.1 software version was used for molecular docking study. The docking results evaluated on basis hydrogen bonds (H-bond) and Vander Waals (VDW) Interaction and Hydrophobic bond, Aromatic Ligand's relationship with the receptor. The study result that Gingerol showed the maximum activity against the 1QWC (acetylcholine esterase) with the binding affinities of -49.72 and for 4ey5 protein, it predicts -49.44 respectively. This helps in identifying the best possible molecular target for AD.

Keywords*:* - *In-silico* Molecular Docking, *Zingiber officinale*, Alzheimer's disease

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition of the central nervous system that accounts for 60%-70% of cases of dementia among people having age 65 worldwide[1]. Also, Alzheimer's disease is one of the best common forms of neurodegenerative disease in which the extracellular accumulation of fibrils and tangles of amorphous amyloid β- peptide aggregation is located in some part of the brain, mainly in the region responsible for thinking, memory and emotional behavior. Neurofibrillary tangles are an intracellular fibrillary aggregation of the microtubules associated with tau proteins required for the growth and maintenance of neurons[2]. The real cause of this disease is not so far known but it has been seen that in some parts of the brain, one of the main causes of this disease is the accumulation of amyloid β-peptide protein. Amyloid β-peptide aggregate fragments resulting in fibril-like structure have an irreversible cross-β structure Amyloid β-peptides are formed from the breakdown of APP (amyloid precursor protective). The amyloid hypothesis was based on the observation that amyloid-beta (Aβ), a 39–43 amino acid peptide forming fibrillar, β-sheet rich structures, is the key constituent of protein deposits found in Alzheimer's patients ' brains. Evidence involving Aβ in Alzheimer's disease pathogenesis involves the presence of Alzheimer's symptoms in animal models demonstrating Alzheimer's disease pathogenesis[3]. AD has been reported to be a multi-factorial disease, and several macromolecules have been found to involve in the progression of the disease. Inhibitions of any of these macromolecules are therefore known to be an important means of controlling AD. Cholinesterase enzymes such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), amyloid precursor protein (APP), secretase enzymes such as α, β, and ÿ, N[4].

Zingiber officinale also known as ginger is commonly used as a food or beverage portion. Gingerol and shogaol have been discovered as active ginger compounds that are responsible for their pharmacological action Gingerol and shogaol have a similar capsaicin structure and have been classified as 1QWC and 4ey5E agonists. Gingerol and shogaol are known as 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerol, 4-shogao l, 6-shogaol, 8-shogaol, 10-shogaol, and 12-shogaol. Substances with strong antioxidant activity may have other beneficial activities, according to previous reports, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol; 8-shogaol and 10-shogaol have outstanding antioxidant activities. Those 3 active ginger compounds will be tested in this analysis for their predictive binding energy for 1QWC and 4ey5E respectively[5]. Computer-assisted drug design or computational drug discovery was

one of the main methods used in drug discovery programs to reduce the cost and time of the project. The main parts of computer-aided drug design are structure-based drug design, ligand-based drug design, and sequence-based approaches. Docking is a statistical method that predicts the one-meter binding preferred orientation[6].

Molecular docking experiments are used to evaluate the interaction at the atomic level between a ligand/drug and a protein that helps us to describe the actions of our compounds in target binding sites as well as clarify fundamental biochemical processes. Each of the natural compounds was individually docked with 2 AD proteins to determine the best binding affinity against Alzheimer's disease[7].

In the current study, the subtractive genomics method was applied to identify the specific potential drug targets in cholinesterase enzymes. Application of the in-silico subtractive genomics method nullifies the host toxicity typical in traditional drug development strategies toward Alzheimer's diseases[8].

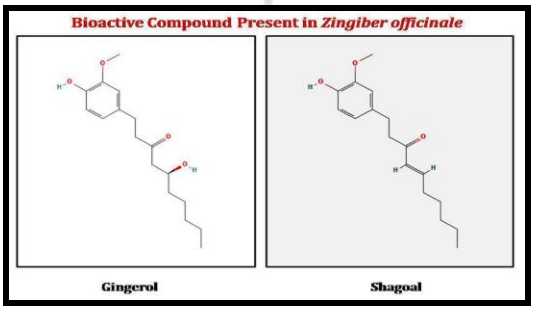

Figure No. 1: Active bioactive compounds present in the *Zingiber officinale*

MATERIAL AND METHODS:

Spectrometric techniques verified the structure of Gingerol and Shagoal. (Sanghai et al 2014) Shown and by further evaluation of the Alzheimer's disease ability of silico molecular docking[9].

a. In silico molecular docking of *Zingiber officinale* constituent against W1400 inhibitor and Acetylcholinesterase in Complex Proteins files selection and generation:

Here we present high-resolution human AChE crystal structures, alone and in drug ligand complexes; Donepezil, an Alzheimer's disease drug, binds to human AChE differently than it does to human AChE than it does to Torpedo AChE. These human AChE crystals provide a

more precise drug development framework than previously available. Molecular docking The studies were conducted using Vlife MDS 4.6.1 version. Where the protein is used for this study are of two different by which are responsible to wound healing and the receptors searched such as the structural basis of the Rat neuronal nitric oxide synthase oxygenase domain in complex with W1400 inhibitor. PDB ID: 1QWC second is Crystal Structure of Recombinant Human Acetylcholinesterase in Complex with (-)-huperzine A PDB ID: 4EY5 were obtained from the Protein Data Bank (www.rcsb.com). The receptor extracted by the X-ray diffraction method with having a resolution of less than **2.**5A°. These structures contain four complexes that were determined with the molecular replacement method using AMoRe. The search functions for rotation and translation were computed with data between the resolution ranges between 12.0–4.0 A°[10].

b. Ligand Preparation

Gingerol ligand and Shagoal isolated from the constituents of Zingiber's officinal farm were drawn on Chemdraw Ultra 8.0 program has prepared and converted 2D Ligand Structure to 3D. Then further these 3D structures were built using batch optimization for a collection of molecules for the energy minimization process. MMFF is applied to molecular mechanics. For this, the parameter is set as Select MMFF from the drop-down list in Force Field. The MMFF Atomic charges are automatically elected for MMFF Force Field. Set the electrostatic and vdW interaction values 20 and 10 respectively[11]. The systematic search method produced by compound conformers. The docking results were classified according to the diminishing energies of the various possible conformers for each of the ligands. The drawn 3D structure represents as follows.

A. Docking Methodology:

i. Parameters for scoring functions:

The parameters set as the mode of the docking method running are exhaustive for the molecular docking analysis and the input Rotation Angle phase size of 30o will rotate the ligand for different poses. Input Number of Placements as 30 and Ligand wise Results as 5 to get 5 top poses for each ligand The docking scoring feature, Escore, is distinct by the energy terms below: Escore = E inter + E intra Where E inter is the ligand-protein interaction energy, E intra is the internal power of the ligand[12].

ii. The function of the re-ranking score:

The re-ranking score used was computationally more costly than the scoring system used during the docking simulation, but it is generally better than the docking score function to determine the best pose among several poses from the same line. While in Vlife the re-rank score provides an estimation of the interaction power, it is not calibrated in chemical units and it does not take complex contributions (such as entropy) into account. Free binding energy (FEB) has been described as the sum of final intermolecular energy (Van Der Waals + Hydrogen bond + Desolvation energy), total internal energy, torsional free energy, and unbound energy of the system.

Interpretation of results:

In this method, we compare the bond interaction present on atoms and receptors mainly with four forms of interaction such as Van Dar Waals interaction, charged interaction, pi-stacking interaction and hydrogen bonding (as the maximum number of hydrogen bonding observed in the sample was considered to be greater as the ligand and protein interaction) so this binding score and interaction can be observed. Successfully predict the antiasthmatic activity of respective plants[13].

RESULTS AND DISCUSSION

The 2 identified bioactive constituents have been testing their ability to assemble their capacity against Alzheimer's diseases by evaluating their binding interactions with two different types of proteins that play specific roles in the various stages of the human body's disease procedure. When compared to the docked ligand, the compounds were docked to each of the different proteins and their binding interactions were evaluated. In the course of Alzheimer's disease, all the molecules from the current study were docked to each protein concerned. The molecules show major interactions with the respective proteins relative to the native ligand interactions, have been shown in the following figures, For this reason, the 3 bioactive constituents identified in the *Zingiber officinale* plant have been compared with those of the native ligand for the purpose behind validation and interactions. The behaviors of the molecules under study were predicted based on their ability to dock into the receptor's active site. The molecular activity values based on the predictive ability of the molecules

Tables no.1 display different receptors by Alzheimer's disease as determined based on the docking tests.

Table No. 1: Molecular docking results of bioactive constituents present in *Zingiber officinale* with cholinesterase receptors

Sr. No.	Molecule	Final energy	Final GRMS value	Dock Score	
				1QWC	4EY5
1.	Gingerol	-37.9008	**0.5747**	**-49.72**	**-49.44**
2.	Shagoal	-29.410	0.5223	-48.79	-47.65

GRMS*: conjugate gradient optimization until a root mean squared deviation of the gradient (GRMS) of 0.01 kcal · mol−1·Å

Gingerol shows receptor results 1QWC shown in table and receptor 1QWC dock score -49.72 showed minimum dock score than other bioactive compounds. As we compared the result of receptors to the literature this docking score indicated that designed compounds have a good binding affinity for binding to Zingiber officinale. The best pose obtained by docking results is reported (fig no.1.) where the main interaction between receptor and ligand can be observed. All designed compound adopts a very similar conformation at receptor binding for Zingiber officinale. Complex binding pocket shows Vander Waals interaction, hydrogen bonding, hydrophobic bonding, and aromatic interaction. Which shown by the 2D representation diagram (fig no.3.).

Table No. 2: Data for the interaction of Receptor 1QWC with Amino Acid

Amino acid	Atom of Ligand	Type of Interaction
ARG343A	17O	VDW_INTERACTION
ARG343A	16C	HYDROPHOBIC_INTERACTION
LYS344A	15C	HYDROPHOBIC_INTERACTION
LYS344A	14C	VDW_INTERACTION
ARG343A	16C	VDW_INTERACTION

Gingerol shows 4EY5 receptor results shown in the table. No. 3 and 4EY5 dock score receptor -49.44 showed a second minimum dock score than the anther receptor. This docking score suggested that developed compounds have a strong binding affinity for binding to Zingiber officinale as we compared the findings of receptors to the literature. The best pose obtained by docking results is stated (fig. no.4.) where it is possible to observe the key interaction between receptor and ligand. All compounds built to follow a very similar conformation at the Zingiber officinale receptor binding. Also stronger binding pocket experiences by the interaction with Vander Waals and hydrophobic binding. That is shown in the 2D diagram (fig no.5.).

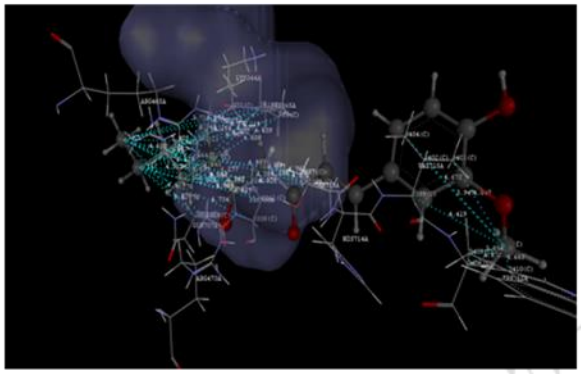

Fig. no.2. 3D Dock poses of Gingerol against 1QWC receptor

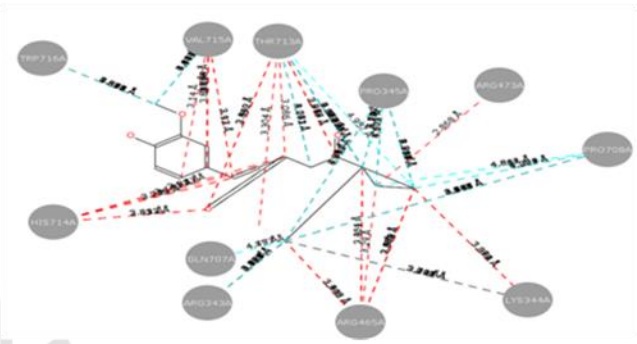

Fig. no.3. 2D representation of Gingerol against 1QWC receptor

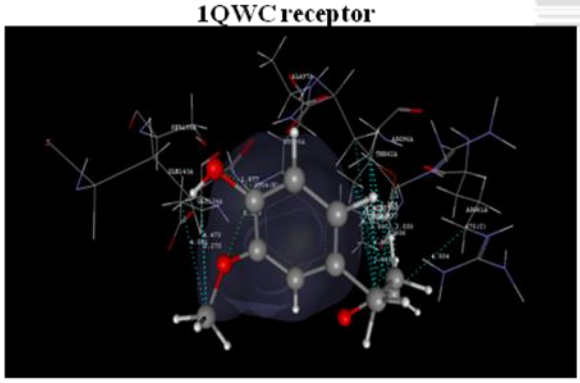

Fig. no.4. 3D Dock poses of Gingerol against 4EY5 receptor

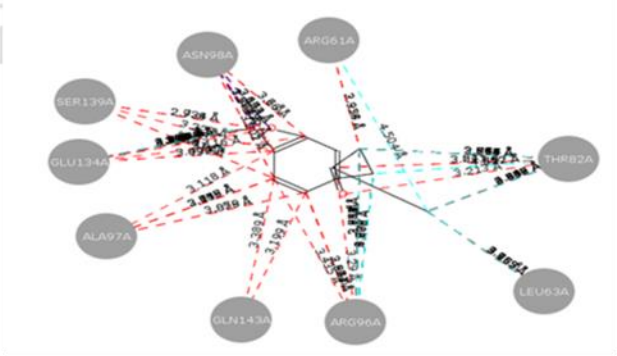

Fig. no. 5. 2D representation of Gingerol against 4EY5 receptor

Table No. 3: Data for the interaction of Receptor 1QWC with Amino Acid

Amino acid	Atom of Ligand	Type of Interaction
ALA505A	12C	HYDROPHOBIC_INTERACTION
ALA505A	13C	HYDROPHOBIC_INTERACTION
GLY506A	13C	HYDROPHOBIC_INTERACTION
ARG417A	4C	VDW_INTERACTION
ARG417A	3C	VDW_INTERACTION

CONCLUSION

From this analysis, it is concluded that the Gingerol isolated from *Zingiber officinale* with the best dock score for receptor 1QWC and 4ey5E thus predicts that plant bioactive components show prominent activity against Alzheimer which finally confirms that they have strong binding capability against 1QWC dock score of -49.72 and -49.44 respectively. It also observes that the bond between an amino acid and functional element has good binding ability and interaction is the interaction of VDw and the interaction of hydrophobic bonds etc. From this, we inferred that zingiber officinale with a phytoconstituent called Gingerol and Shagoal which has prominent anti-Alzheimer. Its activity will be used as an anti-Alzheimer agent.

REFERENCES

1. Faizul, A., Abdualrahman, M A., Bdullah, R A., Mustafa, M E., 2014. Ginger components as new leads for the design and development of novel multi-targeted anti-Alzheimer's drugs: a computational investigation. Drug. Desi. Devel. Therapy. 8, 2045–2059.
2. Brahma, R., 2013. In silico protein structure prediction of the γ-secretase: a key enzyme to Alzheimer's disease. Department of Biotechnology and Medical Engineering, National Institute of Technology, Rourkela, Odisha-769008.
3. Jacques, PC., Arthur, L., Meytal, L., Minglei, Z., Angela, BS.,1, Lukasz, G., David, F., Duilio, C., Michael, RS., David, E., 2011. Molecular basis for amyloid-β polymorphism. Pro. Nation. Acad. Sci. Unit. Stat. America. 108(41), 16938–16943.
4. Fifteen, AF., Agung, EN., Arief N., Rina S., 2018. Molecular Docking Analysis of Ginger Active Compound on Transient Receptor Potential Cation Channel Subfamily V Member 1 (TRPV1). Indones. J. Chem., 18 (1), 179 – 185.
5. Alzheimer's disease, Neuroinflammation, Current drug targets, and Molecular docking: A General Introduction
6. Ashwini, K., Chaluveelaveedu, M., Nisha a., Chitrangda a., Sharma I., Kanukanti A., Gupta N., Nair P., Tripathi T., Kumar A., 2016. Current and novel therapeutic molecules and targets in Alzheimer's disease. J. Formosan Med.Asso.115, 3-10.

7. Aftab A., Naaila T., Nikhat I., Anam F., Mohd M., Shahnawaz A., Zubbair M., Romana I., 2018.Pharmacokinetics and Molecular Docking studies of Plant-Derived Natural Compounds to Exploring Potential Anti-Alzheimer Activity.
8. Zaveri K., Chaitanya A., Reddy I., 2015. Virtual screening and docking studies of identified potential drug target: Polysaccharide deacetylase in Bacillus anthracis. Inter. Lett. Nat. Sci., 34, 70-77, doi:10.18052.
9. Horn, J., Xi, Z., Riina, R., Peirson, J., Yang, Y., Dorsey, B., Berry, P., Davis, C., Wurdack K.,2014. Evolutionary bursts in Euphorbia (Euphorbiaceae) are linked with photosynthetic pathway. Evolution. 68-12, 3485–3504.
10. Sundaravadivelan, C., Padmanabhan, M., Sivaprasath, P., Kishmu, L., 2012. Biosynthesized silver nanoparticles from Pedilanthus tithymaloides leaf extract with anti-developmental activity against larval instars of Aedes aegypti L. (Diptera; Culicidae). Vol.2, DOI 10.1007/s00436-012-3138-9.
11. Blanco, T., Galetto, L., Machado, I., 2012. Nectar regulation in *Euphorbia tithymaloides L*., a hummingbird-pollinated Euphorbiaceae. Plant.Bio. 15, 910–918.
12. Jawade, A., Pingle, S., Tumane, R., Sharma, A., Ramteke, A., Jain, R.,2016. Isolation and characterization of lectin from the leaves of Euphorbia tithymaloides (L.). Trop. Plant Res.3(3): 634–641.
13. Jennings, E., Esposito, D., Rittinger, K., Thurston, T.,2018. Structure-function analyses of the bacterial zinc metalloprotease effector protein GtgA uncover key residues required for deactivating NF-κB. J. Biol. Chem. 293(39), 15316–15329.