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Molecular docking and ADME/T analysis for identification of novel potential COX inhibitors of some isolated compounds from *Azadirachta indica* for Thrombolytic treatment

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Abstract
Developing a new agent in the thrombolytic field, plants are widely used for the management of myocardial infarction, thromboembolic strokes, deep vein thrombosis and pulmonary embolism. For this purpose we subjected the active compounds of to reveal its potentiality by molecular docking analysis to find out its potent compound against 1A5H which was done by Maestro v 10.1 (Schrodinger) docking analysis. Docking studies by Maestro v 10.1 (Schrodinger) showed that Gamma-Elemene of *Azadirachta indica* had the lowest docking score respectively against the 1A5H which are -3.001. Gamma-Elemene from *Azadirachta indica* detected with significant docking score which may be a potent thrombolytic compound because the less docking score, the compound will be more potent.

Keywords: *Azadirachta indica*, thrombolytic activity, molecular docking, ADME/T analysis

1. Introduction

Over the years plants and natural products were used by humankind as food and medicines to cure and prevent diseases. Nature always remains as a golden mark to exemplify the outstanding wonders of symbiosis. Natural products from plant, animal and minerals have been the basis of the treatment of human disease. About 500 plants with medicinal use are mentioned in ancient literature and around 800 plants have been used in indigenous systems of medicine (Verma and Singh, 2008) [20].

Thrombosis is that the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the cardiovascular system. Sometimes the blood coagulation arises from a complex interaction of varied mechanisms, including the activation of the clotting, fibrinolytic systems, disruption of the vascular endothelium, and the generalized activation of the cellular mechanisms leading to coagulation on the surface of monocytes and platelets in circulation (Rickles and Falanga, 2001) [18]. Platelets are essential in the maintenance of cardiovascular integrity and in the management of bleeding through forming blood clot. However, they are additionally involved in the pathological progression of atherosclerotic lesions and arterial vascular thrombosis (May, Seizer and Gawaz, 2008) [14]. Uncontrolled platelet aggregation is critical and may cause life threatening disorders (Davis, 1983; Davies and Thomas, 1985) [8, 7]. It can cause pulmonary emboli, deep vein thrombosis, strokes and heart attacks in developed countries (Dickneite *et al.*, 1995) [9]. Thrombolytics or fibrinolytics can remove established thrombi and emboli. The removing of the products of coagulation when they have served their functions of stopping a vascular leak is that the perform of the fibrinolytic system. This method depends on the formation of the fibrinolytic enzyme plasmin from its precursor protein called plasminogen in the blood. Plasminogen binds to specific sites on fibrin during the coagulation process. Simultaneously, the natural activators of plasminogen i.e. tissue plasminogen activator (tPA) and urokinase are released from endothelial and other tissue cells and act on plasminogen to form plasmin. Since fibrin is the framework of the thrombus its dissolution clears the clot away (Dar and Tabassum, 2012) [6]. Thrombolytic drugs rapidly lyse thrombi by catalyzing the formation of plasmin from plasminogen. These drugs create a generalized lytic state when administered intravenously. Thus, both protective hemostatic thrombi and target thromboemboli are broken down (Hambleton and O'Reilly, 2004; Zehnder, 2012) [13, 21].

In silico is an expression used to mean "performed on computer or via computer simulation". *In silico* methods can help in identifying drug targets via bioinformatics tools. They can also be used to analyze the target structures for potential binding/active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics. The utilization of computers and computational methods permeates all aspects of drug discovery nowadays and forms the core of structure-based drug design (Adams *et al.*, 1991; Banerjee, Chisti and Banerjee, 2004; Baruah *et al.*, 2006; Rao and Srinivas, 2011; Ramjan *et al.*, 2014) [1-3, 17, 16].

Azadirachta indica Linn is a tropical evergreen tree native to

India, Bangladesh and is also found in other southeast countries. It is a tree in the mahogany family Meliaceae. Azadirachta indica is locally known as Neem. It is a tree in the mahogany family of Meliaceae. It is one of two species in the genus of Azadirachta. It is native to India, Bangladesh, Thailand, Nepal and Pakistan. It grows well in tropical and sub-tropical regions. The tree has been used in Ayurvedic medicine due to its medicinal properties. Neem is also, called 'arista' in Sanskrit- a word that means 'perfect, complete and imperishable'. Fruit, seeds, oil, leaves, roots, bark and almost every part of the tree is bitter and contain compounds with proven antiviral, antiretroviral, antiinflammatory, anti-ulcer and antifungal, antibacterial, anti plasmodial, antiseptic, antipyretic and anti diabetic properties (Subapriya and Nagini, 2005; Pandey *et al.*, 2012; El-Hawary *et al.*, 2013) [19, 15, 10].

Neem is a fast-growing tree that can reach a height of 15–20 metres (49–66 ft), and rarely 35–40 metres (115–131 ft). It is evergreen, but in severe drought it may shed most of its leaves or nearly all leaves.

The chemical constituent of Butyl Palmitate, Gamma-Elemene, methyl isoheptadecanoate, Nonadecane and Octacosane.

2. Materials and Methods

In silico analysis

Molecular docking analysis of isolated compounds

Protein Preparation

Three dimensional crystal structure of (PDB id: 1A5H) was downloaded in pdb format from the protein data bank(Berman *et al.*, 2000a, 2000b). After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. Butyl Palmitate, Gamma-Elemene, methyl isoheptadecanoate, Nonadecane and Octacosane.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v10.1 (Friesner *et al.*, 2004; Halgren *et al.*, 2004) [11-12] within which penalties were applied to non-cis/trans amidebonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

3. Results

In silico analysis

Molecular docking analysis

In this study, the binding mode of α-amylase enzyme was investigated by doing computational analysis, glide docking. Both glide standard (SP) and extra precision (XP) mode had been introduced, where extra precision mode used for cross validation purpose. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1. Among all the compounds, Gamma-Elemene showed well docking score againt TISSUE PLASMINOGEN ACTIVATOR.

Table 1: Docking score of different compounds with the receptors.

Compound Name	Compound ID	Docking Score	Glide energy
BUTYL PALMITATE	8090	-1.755	-22.338
Gamma-Elemene	6432312	-3.001	-19.58
methyl isoheptadecanoate	522345	2.165	-4.042
NONADECANE	12401	1.697	-12.038
OCTACOSANE	12408	0.103	-16.336

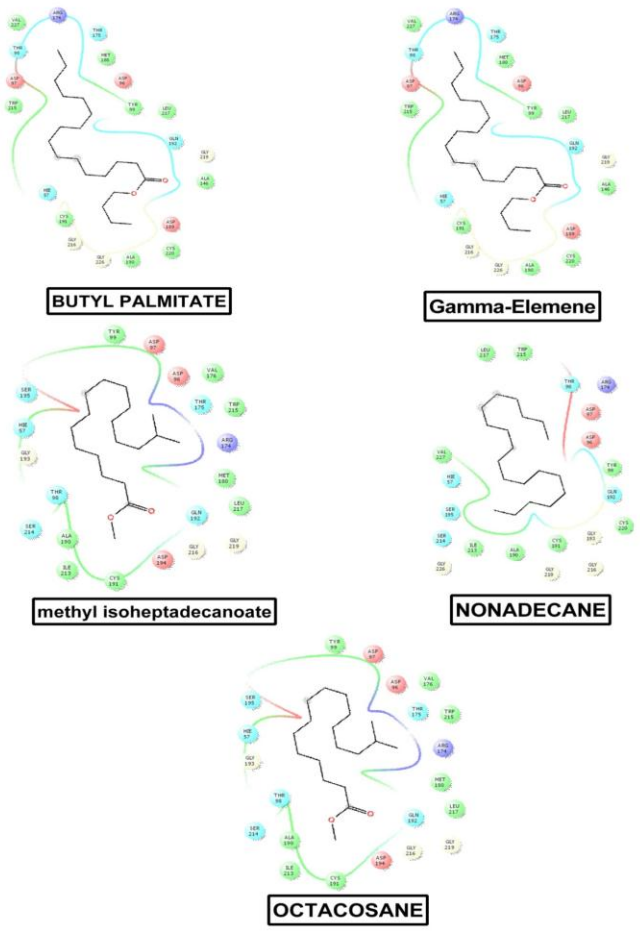

Fig 1: Docking figure of compounds with the receptors.

4. Discussions

From the earliest starting point of progress, human are tried and true on plants for the treatment of numerous diseases. Nowadays psychopharmacological examination has made another field to revelation plant subsidiary medications, which are viable in therapeutic of specific infections, and reestablished the consideration in natural prescriptions. It is evaluated that 30% of the pharmaceuticals are set up from plants subordinates. Bangladesh is an extraordinary asset with a bunch of restorative plants that are yet to be completely investigated. Since various research works have been directed

to find the plants and common nourishment sources and their supplements having antithrombotic (anticoagulant and antiplatelet) impact and there is sign that expending such sustenance prompts counteractive action of coronary occasions and stroke (Adams *et al.*, 1991; Banerjee, Chisti and Banerjee, 2004; Baruah *et al.*, 2006; Ramjan *et al.*, 2014) [1-3, 16]. The objective of molecular docking is the precise expectation of the structure of a ligand inside the requirements of a receptor restricting site and to accurately assess the quality of official. The coupling method of tissue plasminogen activator was examined by doing computational examinationglide docking both glide standard (SP) had been introduced. The aftereffects of docking investigation were portrayed in Table 1 and the docking figure appeared in Figure 1. Among every one of the mixes, Gamma-Elemene demonstrated the well docking score, glide emodel and glide energy. Since the negative and low estimation of glide energy of strongly favorable bond is preferable for best docking study. And unequivocally positive bond is ideal for best docking examination. So the docking score in the vicinity of 1A5H and in Gamma-Elemene is most great compliances.

5. Conclusion

From the above study we can say that the compound Gamma-Elemene could be an incredible medication for the thrombolytic treatment. Since it also can be found from medicinal plant we can expect less side effects. In this way, we can do further in vivo examination need to distinguish the thrombolytic movement.

Competing Interests

The authors declare that they have no competing interests.

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