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RESEARCH ARTICLE

In silico Molecular Docking Studies on Phytocompounds from the Plant *Tagetes erecta* targeting the Odorant Binding Protein of *Culex quinquefasciatus*

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ABSTRACT

Mosquito are a serious threat to public health through which several dangerous diseases are transmitted in both animals and human beings. The residual spraying of insecticides is the most common method of vector control, but usefulness of insecticides in the control of vector-borne diseases is limited. Majority of the chemical pesticides are harmful to man and animals, some of which are not easily degradable and spreading toxic effects. In recent years interest in plant based products has been revived because of the development of resistance, cross-resistance and possible toxicity hazards associated with synthetic insecticides and the rise of their cost. In the present study molecular docking studies were performed using the secondary metabolites selected from the plant *Tagetes erecta* against the odorant binding protein of the *Culex quinquefasciatus* mosquito. Results suggested that among the two bioactive compounds, viz., linalool and zeaxanthin, linalool bonded with the odorant binding protein 2L2C producing a good glide score. Whereas, zeaxanthin bonded with the odorant binding protein, but didn't produced any hydrogen bond. Therefore, since the compound linalool is natural in origin, it may be used in the formulations of mosquito control agents to produce safe and easily biodegradable chemicals.

KEYWORDS

Tagetes erecta, *Culex quinquefasciatus*, Molecular docking

INTRODUCTION

Mosquito spread various vector-borne diseases such as malaria, Japanese encephalitis, filariasis and dengue fever, transmitted by the four genera of mosquitoes namely *Anopheles*, *Culex*, *Aedes* and *Monsonoids*. Approximately 40 million people in India suffer from mosquito borne diseases annually. There are more than 3000 mosquito species belonging to 34 genera in the world, among them, only about 300 transmit human and animal diseases. These diseases devastate Indian economy every year[1].

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Filariasis, a disease affecting the arms, legs and genitals, is much prevalent in India. Filariasis caused by *Wuchereria bancrofti* is transmitted by *C. quinquefasciatus* mosquitoes, which are widespread in the country now and lymphatic filariasis infect 80 million people annually of which 30 million cases exist in chronic infection. There are 45 million cases of lymphatic filariasis in India alone[2].

The vast number of mosquitoes present naturally tempts the civilians to use mosquito coils and liquidators, which release chlorofluro carbon in a considerable amount that depletes the ozone, which is very harmful for the earth and human's future. These mosquitoes are

vastly present in the developing countries, where not much importance is given to the sanitation. Rain water and sewage can easily get stagnant in the roads and in the open spaces. These water stagnant and open sewage passages acts as a very good habitat for the mosquitoes to breed, which seriously concerns the civilian's day to day life[3].

For all blood feeding insects, olfaction is the principal sensory modality which helps in host recognition. This feature is especially true for disease vector mosquitoes, among them many species of which locate the vertebrate hosts during scotophase[4]. Tropical regions of the world are particularly affected, mostly due to the economic and logistical problems associated with conventional control methods, such as insecticides sprays. Although early efforts to control vectors with insecticides were largely effective, their reliance on spraying of these insecticides inside houses to kill resting female has raised environmental and public health concerns[5].

Research on the potential of natural plants to protect against mosquitoes and other insect pests are being carried out historically. But the interest in herbal based products was subsequently reduced due to the advent of synthetic chemicals. However, the interest in anti-mosquito products derived from natural origin is being revived because the continued applications of synthetic compounds have some drawbacks, including the widespread development of insecticide resistance[6]. In this context, the present investigation has been based on the platform to understand the interaction mechanism of the odorant binding protein of *Culex quinquefasciatus* mosquito with the selected important ligands of the plant *Tagetes erecta*.

MATERIALS AND METHOD

Selection of ligands from *Tagetes erecta*

For the computational prediction of potential drugs by the process of molecular docking, the important phytochemicals of the plant *Tagetes erecta* such as linalool[7] and zeaxanthin[8] were selected with the help of the previously published literatures and were used in the present investigation

Molecular Docking Studies

Target Protein Retrieval and Preparation

Three dimensional NMR structure of mosquito odorant binding protein (PDB id: 2L2C) was obtained from PDB databank (Fig. 1). The preparation of a protein involves importing of the mosquito odorant binding protein structure. The water molecules have been deleted but water that bridge between the ligand and the protein were retained, charges were stabilized, missing residues were filled in and side chains were generated according to the parameters available.

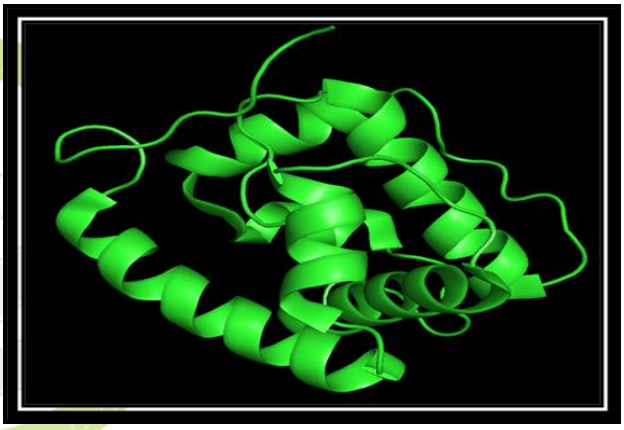

Figure 1: Three dimensional structure of mosquito Odorant Binding Protein (PDB id 2L2C)

Grid Generation

Glide was used for receptor grid generation. The prepared mosquito odorant binding protein was displayed in the Workspace. The volume of grid was calculated. The entire complex was shown with several types of markers. The enclosing box was made small so that it will be consistent with the shape and character of the protein's active site and with the ligands that were expected to be docked.

Ligands Retrieval and Preparation

Ligand molecules were retrieved from PubChem database. The following compounds were retrieved in 3D SDF format (PubChem id:

CID_6549 and CID_5280899. The two compounds were processed, unwanted structures were eliminated and optimized using LigPrep module from Schrodinger.

The generation of ionization states and tautomers can be carried out with tools that are part of LigPrep. A separate product, Epik was used to perform the structural adjustments during a LigPrep run. Epik more rigorously adjusts the tautomerization and ionization states than separate ionizer and tautomerized treatments. Finally Hydrogen atoms were added and charged groups were neutrilized for all compounds.

Molecular Docking of Target Protein with Ligands

In order to explore the binding mechanism of phytochemicals with the target proteins, molecular docking studies have been performed. All the three ligands were docked against mosquito odorant binding protein (2L2C). The entire docked complex was visualized by using XP visualizer. The hydrogen bonding interaction between the receptor and the ligands were also visualized.

RESULTS AND DISCUSSION

***In silico* Molecular Docking**

The 3D SDF structures of the processed two secondary metabolites of the plant *Tagetes erecta* were retrieved from PubChem database and were prepared to dock with the mosquito odorant binding protein 2L2C (Fig. 1). The chemical structures of the two ligands were shown in Fig. 2.

Glide ligand docking jobs require a set of previously calculated receptor grids and one or more ligand structures. Preparation of the ligands before docking is strongly recommended. If a correct Lewis structure cannot be generated for a ligand, it will be skipped by the docking job. Glide also automatically skips ligands containing unparametrized elements, such as arsenic or atom types, not supported by the OPLS force fields, such as explicit lone pair "atoms."

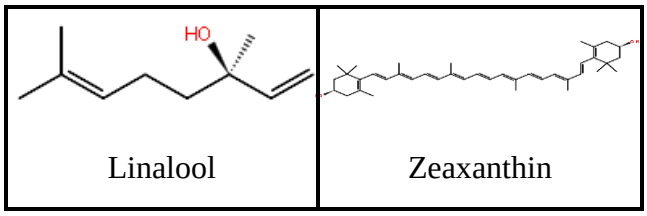

Figure 2: 2D structure of ligand compounds retrieved from PubChem database

Perfectly prepared ligands were docked against the target odorant binding protein. The results of the docking study showed that the two compounds were highly binding with the target protein (PDB id 2L2C). The glide score, number of H-bonds, distance of H-bonds, interacted residues and ligand atom of docked compounds were showed in table 1. The entire docked complex was visualized by using XP visualizer.

The results of *in silico* docking tabulated in table 1 showed that the compound linalool and zeaxanthin bound with the mosquito OBP 2L2C. Compound id 6549 (Linalool) exhibited good glide score (-3.0 A^0**)** and formed 1 H-bond with target OBP. The protein residue was observed to be VAL 125: (O) OXT. The distance was recorded to be as 2.256. The other compound id 5280899 (Zeaxanthin) were highly binding with the mosquito OBP, but didn't produce any hydrogen bond. The compound zeaxanthin, when docked with the mosquito odorant binding protein (PDB id 2L2C) recorded a glide score of (-5.42 A^0). The diagrammatic representation of the ligand linalool docked against mosquito odorant binding protein (PDB id 2L2C) is depicted in Fig. 3.

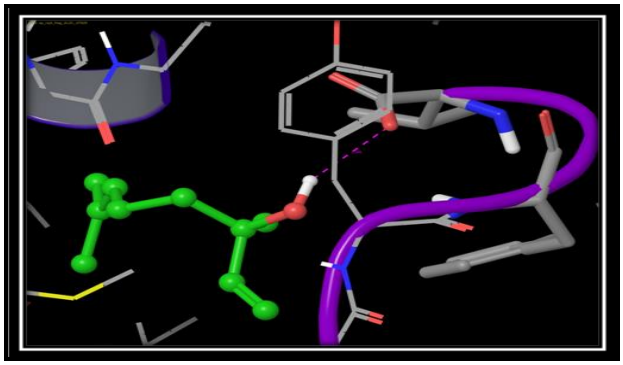

Figure 3: Compound 6549 (Linalool) docked against mosquito odorant binding protein (PDB id 2L2C)

Table 1: Docking Score and H-bond interaction of ligands against mosquito Odorant Binding Protein (PDB id 2L2C)

Sl. No	Name of compound	Compound id	G score	No. of H bonds	Distance	Protein residues	Ligand atom
1	Linalool	6549	-3.0	1	2.256	VAL 125: (O)OXT	H
2	Zeaxanthin	5280899	-5.42	-	-	-	-

The results of the present study were in concordance with the early reports of many researchers. Kee *et al*[9] carried out a protein-ligand binding interaction study by performing docking of the ligands that were found to be competitively inhibiting the activities of the DEN2 NS2B/NS3 serine protease onto the catalytic triad of a model of DEN2 NS2B/NS3 protease. Shekinah and Rajadurai[10] made an attempt to identify the potential drug and to inhibit as well as to modify their side chain to impure the binding efficiency of the enzyme that catalyses the isomerization of D-Glyceraldehyde 3 phosphate to dihydroxy acetone phosphate in the glycolysis of the protozoan *Plasmodium falciparum* which helps in its energy supply.

The docking results confirmed that the compound linalool, ie., compound id 6549 was best among the two compounds, as it exhibited a good glide score and also recorded the formation of one hydrogen bond. When the ligand binds with protein, the conformation of the protein structure will change so the function of the protein will alter automatically. Therefore, the compound may have an ability to inhibit the contact between human and vector.

CONCLUSION

In the present work, the compounds linalool and zeaxanthin were docked with the odorant binding protein of *C. quinquefasciatus* (PDB id 2L2C0. From the results, it can be concluded that linalool could be a potential inhibitor as it possessed the entire theoretical drug like properties. However, additional *in vitro* studies would help in characterizing the compounds in order to confirm the conclusions. This study also insists the importance of novel molecules showing selective interaction towards the odorant binding protein of *C. quinquefasciatus* which will be a useful strategy in controlling the mosquito borne diseases. As the compound linalool in the present investigation is a natural compound of plant origin, it may play a crucial role in being designed as an effective mosquito repellent, that could make mosquito borne diseases the next modern medical and public health success story.

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