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CAPSAICIN ($C_{18}H_{27}NO_3$) AND PHYTOL ($C_{20}H_{40}O$) FROM *CAPSICUM ANNUM* L. LEAF DOCKED AGAINST SALIVARY GLAND PROTEIN OF *CULEX QUINQUEFASCIATUS*

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Keywords:

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ABSTRACT: Overpopulation leads to rapid urbanization, and industrialization has directed an unplanned town expansion with no sanitary facilities and proper wastewater disposal arrangements drains in the pond. Mosquitoes create a significant public health problem in India and serve as vectors for transmitting various diseases like malaria, filariasis, dengue, chikungunya, *etc*., to humans. This results in the creation of water bodies which are highly conducive for the breeding of mosquitoes. The study revealed the biological activity of the compounds Capsaicin ($C_{18}H_{27}NO_3$), and Phytol ($C_{20}H_{40}O$) from *Capsicum annum* L. docked against salivary gland protein (PMDBID PM 0079099). The Pharmacophore model development and 3D QSAR analysis of the selected compounds were carried out using the Pharmacophore alignment scoring engine (PHASE) module of Schrodinger. The 3D structures of proteins are of vital importance in providing insights into their molecular functions. The glide score of the compound Capsaicin was -2.63 and 2 two number of H-bond interactions with the distance of 2.298 and 1.485 and Phytol was -1.46 and one number of H-bond with a distance of 1.900. Docking results showed that compounds, Capsaicin, and Phytol actively on the target protein, and it can be used as a candidate in vector control. Hence, the present study on vector control has explored by *in-silco* molecular docking study between compounds of Capsaicin and Phytol with salivary gland protein of *Culex quinquefasciatus*.

INTRODUCTION: Plants have been known to relieve various diseases in traditional medicine and Ayurveda. Secondary metabolites are responsible for the therapeutic activity of plants bioactivity, phytoremediation, and toxicity effect on the pests [5]. Isolation of individual phytochemical constituents and subjecting it to drug designing will give fruitful results in phytopharmaceuticals [1]. Biologically active plants show great promise for their potential efficiency as larvicides.

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Mosquitoes are causative agents for many diseases and affect millions of people worldwide. They produce humming in shadows near our ears are irritating, and after that, they bite like pricking with a needle causes swelling and itching [2]. Vector-borne diseases (VBDs) are illnesses caused by pathogens and parasites in human populations.

These vector-borne diseases are malaria, dengue, schistosomiasis, African human trypanosomiasis, Leishmaniasis, Chagas disease, yellow fever, Japanese encephalitis (JE), *etc*. Emerging and resurging vector-borne diseases cause significant morbidity and mortality, especially in the developing world [8, 17]. An obvious method for the control of contact between vector and human beings is the use of repellents and many synthetic agents that have developed and employed

successively. But the growing toxicity problem, together with the incidence of insect resistance, has called attention for the search of insecticides [4].

Molecular docking approaches are generally used in the modern drug design process to understand the protein-ligand interactions. The three-dimensional structure of the protein-ligand composite could be work as a considerable source of understanding the way proteins interact with one another and perform biological functions [3]. Homology modeling mainly adopted for the prediction of protein structure, and it constructs an atomic-resolution model of a protein from the amino acid of the query sequence. The quality of the homology model is dependent on the quality of the sequence alignment and template structure [9].

MATERIALS AND METHODS:

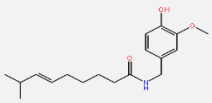
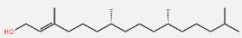
Preparation of Extracts: Fresh leaves of *Capsicum annum* L. was collected washed in water and air-dried under shade. Dried leaves are powered using electric pulverizer. These powders subjected to extraction with 500 ml of the solvent for 8 h using a Soxhlet apparatus [7, 15]. Petroleum ether (60-80 ºC) extraction was followed by chloroform extraction and ethanol extraction so that the powders subjected to extraction with solvents of increasing polarity. The extracts thus obtained were concentrated by distillation and dried by evaporation in a water bath at 40 ºC. The residue thus obtained was stored in tightly closed glass vials in the refrigerator for further use.

GC-MS Analysis: Mass experiments performed on GC (T8000 Top CE) combined with Mass Spectrometer (M d 800 FIS ONS). The sample was dissolved in methanol and introduced into the column TR-5-MS capillary standard non-polar by the splitless injection system.

Ultra high purity helium introduced as the buffered collision gas with a flow rate of 1.0 ml/min. The source temperature for ionization set at 250 °C. All the experiments performed on the positive ion mode.

Pharmacophore and 3D QSAR Model Development: The pharmacophore model development and 3D QSAR analysis of the selected compounds were carried out using the Pharmacophore Alignment and Scoring Engine (PHASE) module of Schrodinger showed in **Table 1**.

TABLE 1: STRUCTURE AND PROPERTIES OF CAPSAICIN AND PHYTOL

S. no.	Plant Source	Compound Structure	Compound Name	Molecular Formula	Molecular Weight [g/mol]
1	*Capsicum annum* L.		Capsaicin	$C_{18}H_{27}NO_3$	305.41188
2	*Capsicum annum* L.		Phytol	$C_{20}H_{40}O$	296.531

Molecular Docking: The receptor grids and the basic glide settings for the ligand docking were specified. A set of inhibitory molecules docked according to the output options. The options in the remaining three tabs, core, constraints, and similarity leave at their defaults for the exercise. Appropriated inhibitory molecules were selected from workspace for docking with target proteins. There are several methods for specifying the ligand structure to be docked with receptor grids. The docked complex was examined with an emphasis on visual rather than numerical appraisal, and the docked complex were visualized using XP Visualizer is showed in **Fig. 1.**

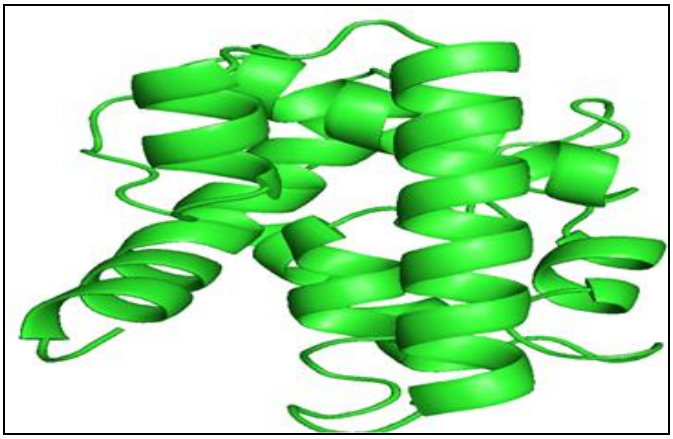
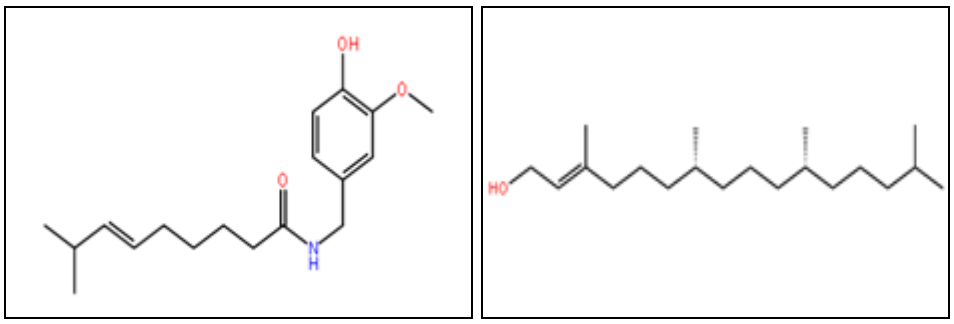


FIG. 1: DOCKED COMPLEX WERE VISUALIZED USING XP VISUALIZER

Retrieval and Homology Modelling of Protein: The putative salivary gland protein sequence retrieved from the NCBI database. It has no X-ray 3D structure, and hence homology modeling techniques were adopted for predicting structure.

Inhibitory Molecules Retrieval and Preparation: Inhibitory molecules retrieved from PubChem database. These compounds retrieved in 3D SDF format showed in **Fig. 2** (PubChem id: 1548943 and 5280435), and the retrieved molecules were docked using LigPrep module from Schrodinger suit. This process consists of a series of steps that perform conversions, apply corrections to the structures that generate variations on the structures that eliminate unwanted structures, and optimize the structures.



Capsaicin (1548943) **Phytol (5280435)**

FIG. 2: COMPOUND RETRIEVED FROM PUBCHEM DATABASE

Visualization of Docked Complex: The docked complex was examined with an emphasis on visual rather than a numerical appraisal.

RESULTS AND DISCUSSION:

GC MS Analysis: The results of GC MS analysis led to the identification of some compounds from the GC fractions of the *C. annum* L. leaf chloroform extracts.

The gas chromatogram shows the relative concentrations of various compounds getting eluted as a function of retention time. The heights of the peak indicate the relative concentrations of the components present in the plant. The mass spectrometer analyses of the compounds eluted at different times to identify the nature and structure of the compounds [16, 12, 10].

Leaf extract of *C. annum* L.: Chloroform extract confirmed the presence of 11 significant peaks shown in **Fig. 3**. The retention time 5.94, 10.31, 14.73, 17.26, 18.77, 22.89, 23.23, 27.33, 31.34, 35.53, and 37.41 exhibited its respected base peaks, and the other characteristic peaks were displayed in **Fig. 4 a-j**. The fragmentation pattern showed (M-14) (M-15)(M-18) (M-27) (M-28 & M-29) and (M-44) indicated the presence of hydrocarbon fragments, a methyl group, OH group, nitrogen, carbonyl containing compounds and the carboxyl group.

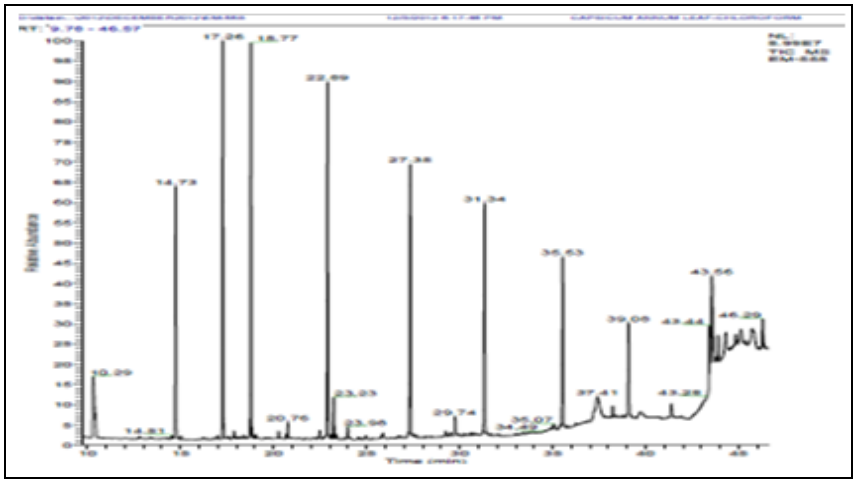


FIG. 3: GAS CHROMATOGRAM OF CHLOROFORM LEAF EXTRACT OF *C. ANNUM* L.

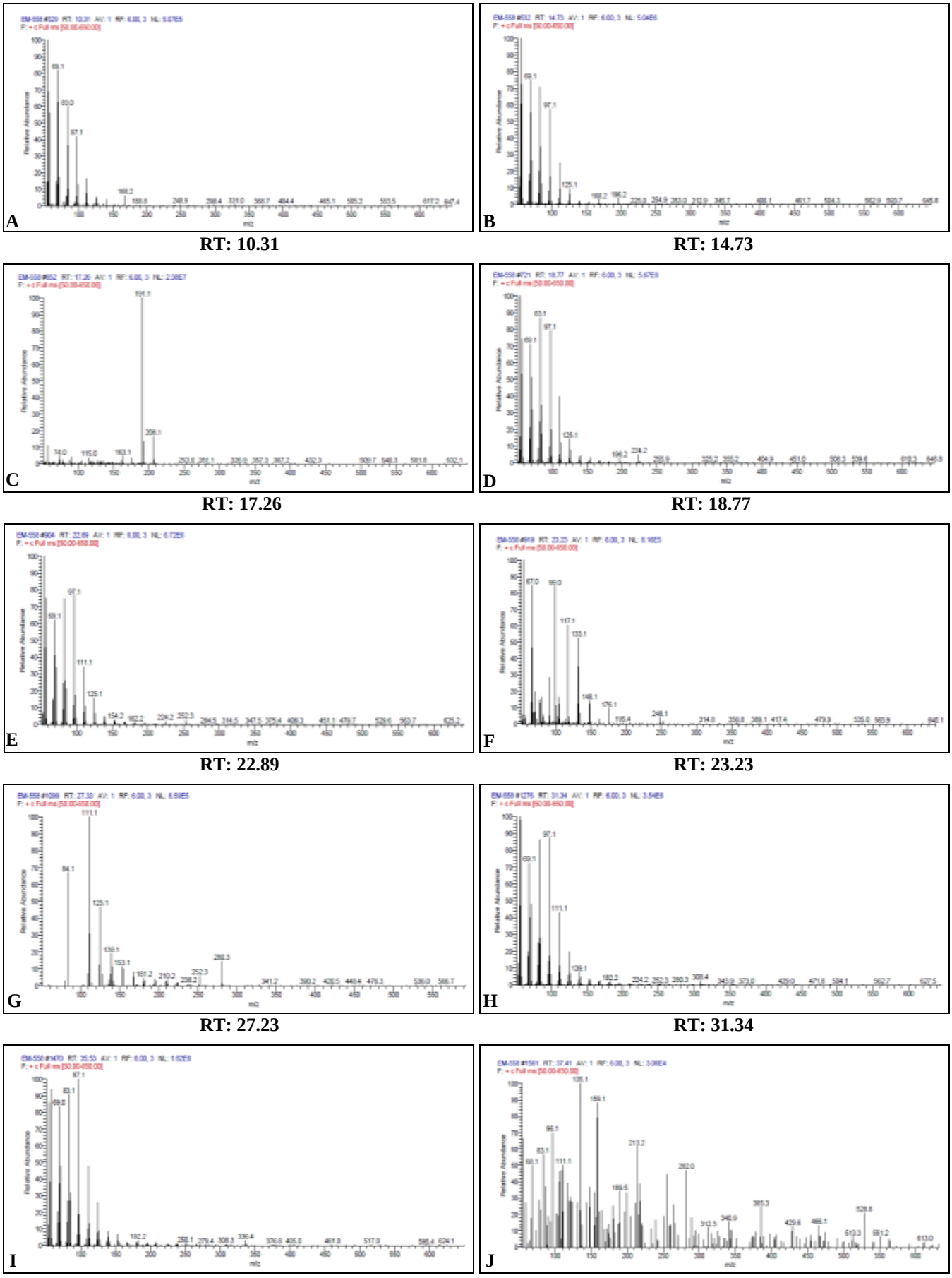


FIG. 4: MASS SPECTRA OF CHLOROFORM LEAF EXTRACT OF *C. ANNUM* L.

The hexane extract of leaves of *Ehretia laevis* using GC MS, and eleven compounds identified by the similarity index of NIST and WILEY libraries. *E. laevis* is a medicinally important plant belonging to family Boraginaceae analyzed [14]. All parts of the plant have medicinal properties [10] and determined the chemical profile of *A. paniculata* leaf chloroform extracts using GC MS analysis and observed the presence of phenols, aromatic carboxylic acids, and esters. Other metabolites like fatty acids and corresponding esters, hydrocarbons, aldehydes, alcohols, and terpenoids randomly distributed in all the genotypes of *C. chinense, C. frutescens* and *C. annum* analyzed using GC-MS. These sixty-one different metabolites identified after acetonitrile extraction of dried capsicum fruit.

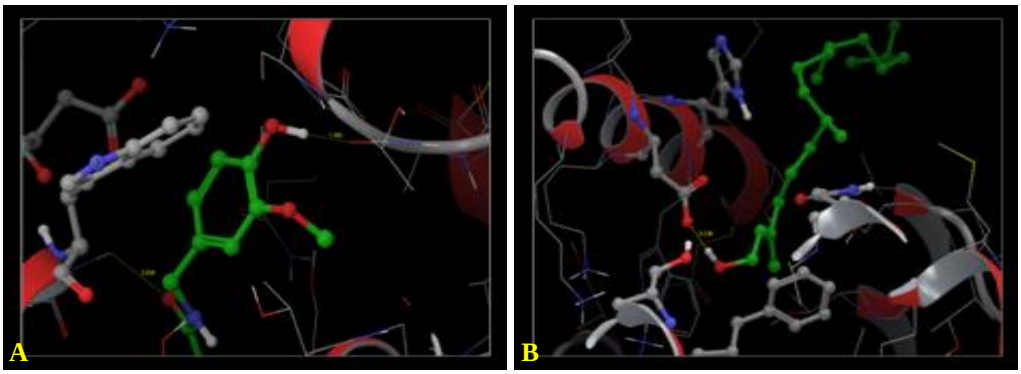
The fragmentation pattern (M-14) (M-15) (M-18) (M-27) (M-28 & M-29) and (M-44) indicated the presence of hydrocarbon fragments, a methyl group, OH group, nitrogen, carbonyl containing compounds and a carboxyl group. Similar observations were made in the present study also. These findings helped in the selection of compounds from PubChem database for molecular studies.

Molecular Docking against Salivary Gland Protein: Molecular docking results based on the glide score, number of H-bond, residue interaction shows the binding affinity of the ligand towards salivary gland protein depicted in **Table 2**.

TABLE 2: DOCKING SCORE OF INHIBITORY MOLECULES AGAINST SALIVARY GLAND PROTEIN OF *C. QUINQUEFACIATUS*

S. no.	Compound	Glide score	No. of H bonds	Distance	Protein residues	Ligand atom
1	1548943	-2.63	2	2.298	‘HID32:(H) HDI	(O)
	(Capsaicin)			1.485	ALA 6:(O) O	(H)
2	5280435 (Phytol)	-1.46	1	1.900	ASP 29: (O) OD2	(H)

The compounds (1548943) capsaicin and (5280435) Phytol was binding with *C. quinquefasciatus* salivary gland protein. Compound capsaicin with 2 hydrogen bonds and -2.63 glide score followed by Phytol with one hydrogen bond and -1.46 glide score against salivary gland protein, Capsaicin interacted more than Phytol showed in **Fig. 5**. Compound id 5281243 (Lutein) was also binding with OBP but didn’t produce any hydrogen bond. However, the compound Lutein, when docked with the Odorant Binding Protein, provided an excellent glide score of -6.12 13. The compound id 5281515 (Beta caryophyllene) and the compound id 6987 (Piperitone) were also highly binding with the mosquito OBP 2L2C but didn’t produce any hydrogen bonding with the protein [5]. In the present study, the capsaicin highly binding with the salivary gland protein of *C. quinquefasciatus*.



Capsaicin (1548943) **Phytol (5280435)**

FIG. 5: COMPOUNDS DOCKED AGAINST SALIVARY GLAND PROTEIN (PMDB ID PM0079099) OF *C. QUINQUEFASCIATUS*

Docking studies of four hydrogen bonds formed between 2-nitro-5-sulfosulfanyl-benzoic acid into PDI [11]. Besides hydrogen bonding, van der Waals interaction was also taking part in the stabilization of inhibitors binding with a high frequency of residues such as Ala34, Trp36, His39, Thr68 and Phe80 in PDI. The redox inhibitory model of all six inhibitors with PDI was consistent with the experimental laboratory results.

CONCLUSION: Chemical-based interventions for mosquito control and repeated use of insecticides leads to resistance among vectors. Hence, its control has been explored by *in-silico* molecular docking study of the compound, *C. annum* L. and salivary gland protein of *C. quinquefasciatus.* Docking results showed that these two compounds were acting on the target protein. Hence, Capsaicin and Phytol compounds used as a candidate in vector control.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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