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Comparative mode of action of some terpene compounds against octopamine receptor and acetyl cholinesterase of mosquito and human system by the help of homology modeling and Docking studies

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ABSTRACT

Mosquitoes are vectors of many diseases like malaria, encephalitis, dengue, filaria, yellow fever etc. and thus possess severe threat to public health. Essential oils of some aromatic plants and many pure terpene compounds have been reported effective against different strains of mosquitoes by many authors. In the present investigation, five reported terpene compounds namely eugenol, geraniol, coumarin, eucalyptol and carvacrol were allowed to dock against octopamine receptor and acetyl cholinesterase protein models of *Aedes aegypti* and *Homo sapiens* to evaluate their comparative efficacy in terms of docking performance. All the compounds were found to dock with both the protein models of the two animal systems while some of them were found to better perform against the protein models of *A.aegypti* than the protein models of *H.sapiens* which can further be explored in mosquito control programme as a comparatively safe compound(s). The results are discussed on the basis of energy value. 3D structures of proteins were modeled using Modeller9v8. The structures assessment were established using the Procheck, WhatCheck and WhatIF server of Swiss Model Workspace. Ligands were prepared using the Commercial Software Exome Horizon™.

INTRODUCTION

Mosquitoes are vectors of many diseases and mosquito borne diseases have been taking annually billions of life worldwide. *Aedes aegypti* is a primary carrier of viruses causing dengue fever, dengue haemorragic fever and yellow fever in tropical and subtropical region of the world (Kumar *et al*., 2011). 2-2.5 billion people are at risk globally for dengue (Prasittisuk, 2008). After realizing manifold ill effects of chemical pesticides, worldwide interest has been shifted once again on plant based control measures because of their environment friendly and selective mode of action. A large number of plants have been screened against different strains and stages of mosquitoes. A good number of essential oil(s) extracted from aromatic plants and their constituent terpene compounds were reported effective as repellent, larvicidal, pupicidal or adulticidal against different species of *Aedes*, *Anopheles*, *Culex* (Ezeonu *et al*.,2001; Tawatsin *et al*.,2001; Cavalcanti *et al*., 2004; Mansour *et al*.,2004; Mendonca *et al*., 2005; Ananth *et al*., 2009). The mode of action of these oil and oil compounds are mainly reported to be the nervous system. Octopamine receptor and acetyl cholinesterase enzyme are two of its target sites (Ryan and Byrne,1988; Coats *et al*., 1991; Kostyukovsky *et al*.,2002). In the present investigation, five terpene compounds (eugenol, geraniol, coumarin, eucalyptol, carvacrol) which have been already reported effective against mosquitoes and other dipteran flies (Samarasekera *et al*.,2006; Kelm,1999; Kang *et al*., 2009; Palacios *et al*., 2009;Kaufmann *et al*.,2010; Khanikor and Bora, 2011) were allowed to dock against octopamine receptor and acetyl cholinesterase protein models of *Aedes aegypti* and *Homo sapiens*. Octopamine and acetylcholine, the substrate of octopamine receptor and acetyl cholinesterase enzyme respectively were also allowed to dock to the protein models. Results are discussed on the basis of energy value.

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EXPERIMENTAL

Molecular Modeling and Drug Design (Docking)

Homology Modeling and Simulation techniques

The Modeller 9v8 was used to construct the octopamine B2 adrenergic coupled receptor and acetylcholine esterase protein of *Homo sapience* and octopamine receptor oamb and acetylcholine esterase of *Aedes aegypti*, It is a general program that is used for homology modeling. The sequences were downloaded from the NCBI site (http://www.ncbi.nlm.nih.gov) in fasta format.

Template Identification, Alignment of the Template Structure and Target Sequence

The templates were selected with the help of template identification tool of Swiss model server. i.e Crystal Structure Of The Human Beta2 adrenoceptor for Human octopamine B2 adrenergic coupled receptor, Recombinant Human Acetylcholinesterase for acetylcholine esterase protein of human and high resolution crystal structure of human b2-adrenergic G protein for octopamine receptor oamb of *Aedes aegypti*, Aged Form of Human Butyrylcholinesterase Inhibited By Tabun Analogue Ta5 for acetylcholine esterase protein of *Aedes aegypti*. The PDB ID for the selected templates were found to be 2RH1, 3LII, 2RH1 and 2WIL respectively. The protein structures were downloaded from the PDB site (http://www.rcsb.org). The folders were created with a specific name and the modeller files which were responsible for modeling of the 3D structure were copied to the specific folders i.e align2d.py and model-single.py. The target sequence and the template were also copied to this folder. Prior to modeling of 3D structure of the target sequence,alignment of the target sequence and the template was carried out with the help of the align2d.py command. The template sequences were converted into PIR format and provided the template name in the align2d.py file. The alignment between the target sequence and the template structure were made in Modeller command prompt with specific path of the desired folders**.**

The protein 3D structure modeling Model Validation and Protein Structure Analysis

The protein 3D structure models for Human octopamine B2 adrenergic coupled receptor and acetylcholine esterase protein, octopamine receptor oamb and acetylcholine esterase of *Aedes aegypti* were built after the alignment of the target sequence and the template structure with the help of mod9v8 command model-single.py. The desired models were generated and the structural assessment was carried out using ExomeTM Horizon 1.3 software. All the generated models were given in **Fig 1, 2, 3, 4.**

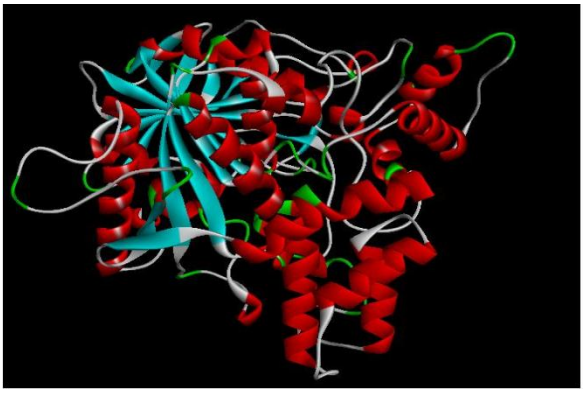


Fig. 1: Human octopamine B2 adrenergic coupled receptor model was generated by the Modeller9v8. The numbers of groups were 539, Numbers of atoms were 4180 and Numbers of bonds were 4309, data was obtained from Rasmol 2.6.

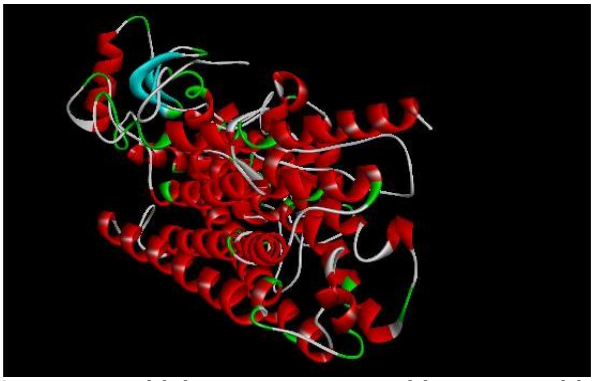


Fig. 2: Human acetylcholine esterase protein model was generated by the Modeller9v8. The numbers of groups were 539, Numbers of atoms were 4180 and Numbers of bonds were 4310, data was obtained from Rasmol 2.6.

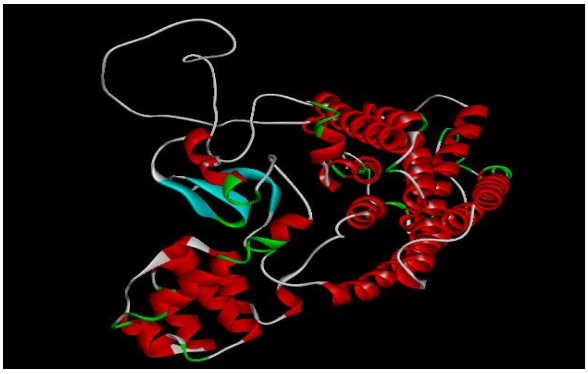


Fig. 3: Octopamine receptor oamb of *Aedes aegypti* model was generated by the Modeller9v8. The numbers of groups were 470, Numbers of atoms were 3789 and Numbers of bonds were 3899, data was obtained from Rasmol 2.6.

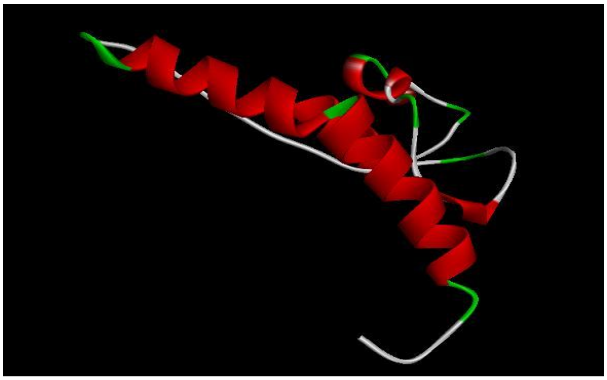
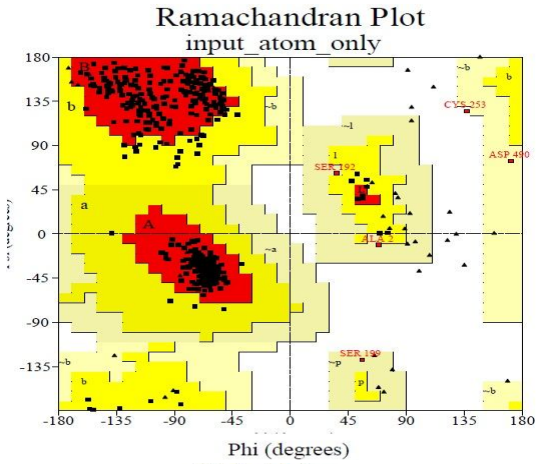


Fig. 4: Acetylcholine esterase of *Aedes aegypti* model was generated by the Modeller9v8. The numbers of groups were 91, Numbers of atoms were 755 and Numbers of bonds were 777, data was obtained from Rasmol 2.6.

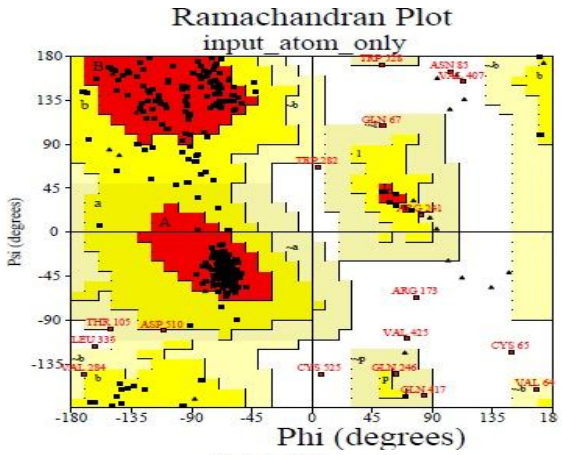


Plot statistics

Residues in most favoured regions [A,B,L]	401	91.8%
Residues in additional allowed regions [a,b,l,p]	31	7.1%
Residues in generously allowed regions [~a,~b,~l,~p]	4	0.9%
Residues in disallowed regions	1	0.2%
Number of non-glycine and non-proline residues	437	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	53	
Number of proline residues	47	
Total number of residues	539	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig. 5: Human ACHE Ramchandran plot analysis.

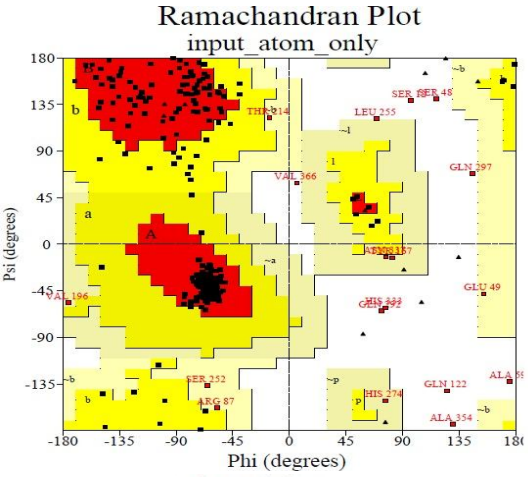


Plot statistics

Residues in most favoured regions [A,B,L]	374	85.6%
Residues in additional allowed regions [a,b,l,p]	46	10.5%
Residues in generously allowed regions [~a,~b,~l,~p]	9	2.1%
Residues in disallowed regions	8	1.8%
Number of non-glycine and non-proline residues	437	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	53	
Number of proline residues	47	
Total number of residues	539	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig. 6: human octopamine ramchandran plot analysis.

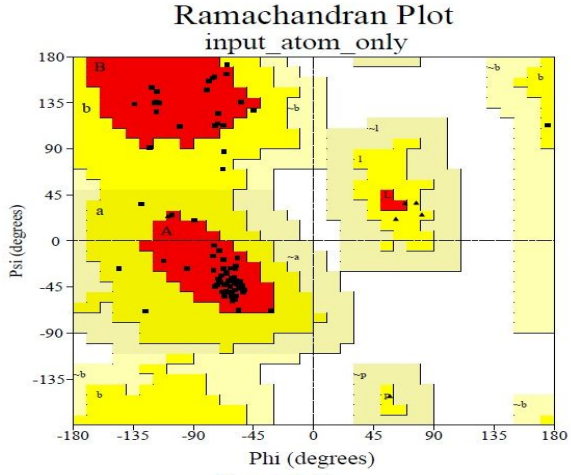


Plot statistics

Residues in most favoured regions [A,B,L]	372	87.1%
Residues in additional allowed regions [a,b,l,p]	37	8.7%
Residues in generously allowed regions [~a,~b,~l,~p]	8	1.9%
Residues in disallowed regions	10	2.3%
Number of non-glycine and non-proline residues	427	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	21	
Number of proline residues	20	
Total number of residues	470	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig. 7: *Aedes aegypti* octopamine Ramchandran plot analysis.



Plot statistics

Residues in most favoured regions [A,B,L]	68	88.3%
Residues in additional allowed regions [a,b,l,p]	9	11.7%
Residues in generously allowed regions [~a,~b,~l,~p]	0	0.0%
Residues in disallowed regions	0	0.0%
Number of non-glycine and non-proline residues	77	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	7	
Number of proline residues	5	
Total number of residues	91	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig. 8: *Aedes aegypti* ACHE ramchandran plot analysis.

Model validation in Swiss Model

The homology models of Human octopamine B2 adrenergic coupled receptor and acetylcholine esterase protein, octopamine receptor oamb and acetylcholine esterase of *Aedes aegypti* were sent to Exome Horizon for model validation and energy minimization. The Ramchandran Plot, Ramachandran plots for all residue types, Chi1-Chi2 plots, Main-chain parameters, Side-chain parameters, Residue properties, Main-chain bond length, Main-chain bond angles, RMS distances from planarity and distorted geometry were analyzed for input atoms only. The Ramchandran Plot for input atoms only of the developed models was provided in Fig 5, 6, 7, 8.

Energy Minimisation in Exome™ Horizon 1.3

The energy minimization of Human octopamine B2 adrenergic coupled receptor and acetylcholine esterase protein, octopamine receptor oamb and acetylcholine esterase of *Aedes aegypti* were observed with the help of Exome Horizon™1.3. The results were obtained as G-95 angle, Total energy, Temperature, Pressure, Mu-X, Mu-Y, Mu-Z, Proper-Dih, Improper-Dih, LJ-14, Coulomb-14, LJ-SR, Potential, Kinetic Energy, G-96 bond.

Ligand Preparation

The ligands were drawn using Moldraw tool of **Exome™ Horiz**on in 2D and were converted into 3D before submission of docking. The Molecular formulae and the IUPAC name of all the selected ligands were given in Table 1.

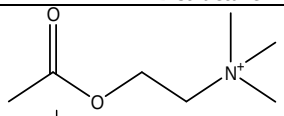
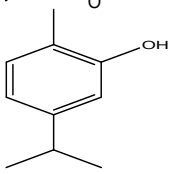
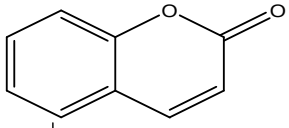
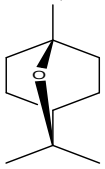
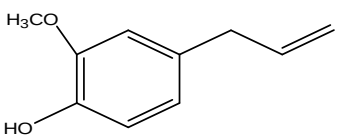
Protein-Ligand Docking Studies

Protein-ligand docking is used to check the structure, position and orientation of a protein when it interacts with small molecules like ligands. Protein-ligand docking aims to predict and rank the structures arising from the association between a given ligand and a target protein of known 3D structure. Protein-Ligand Docking module is further divided into different parts for user convenience like Receptor Preparation, Ligand Preparation, Binding Site Analysis, Dock and Analysis.

Binding Site Analysis

Binding Site analysis is a fast detection program for the identification and visualization of possible binding sites and the distribution of surrounding residues in the active sites. The centre of active site was chosen as grid map values for preparation of the grids. The spacing of grid was set to 1.00 ^{0}A and the no. of grid point were taken as 60 x 60 x 60 ^{0}A and protein-ligand docking was performed using Lamarckian genetic algorithm using default parameter (Morris *et al.,* 1998). The key result in a docking log file (DLG) are the docked structure or conformation found at the end of each run, the energies of these docked structures and their similarities to each other. The DLG file provides docked confirmations, orientations and the binding energies. The similarity of docked structures is measured by computing the root-mean-square deviation (RMSD) between the coordinates of selected molecular confirmation with the molecular confirmation having lowest interaction energy which is ranked on top. Clusters are created based on the comparison of conformations using RMSD values. The docking results consist of the PDBQT of the transformed 3D Cartesian coordinates of the ligand atoms as docked to the receptor molecule (Morris *et al, 1998*). The binding energy of the selected ligands was given (Table 2). All the docked complexes were given in figure 9, 10, 11, 12.

Table. 1: The selected ligands with its IUPAC name, Molecular formulae and the 2D structures.

Sl. No	Name of the Ligand	IUPAC Name	Molecular Formula	2D structure
1	Acetylcholine	(2-Acetoxy-ethyl)-trim ethyl ammonium	$C_7H_{16}NO_2$	
2	Carvacrol	5- Isopropyl-2-methyl- Phenol	$C_{10}H_{14}O$	
3	Coumarin	Chromen-2-One	$C_9H_6O_2$	
4	Eucalyptol	1,3,3-Trimethyl-2-oxa-bicyclo[2.2.2]octane	$C_{10}H_{18}O$	
5	Euganol	4-Allyl-2-methoxy-Phenol	$C_{10}H_{12}O_2$	

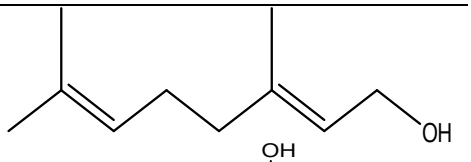
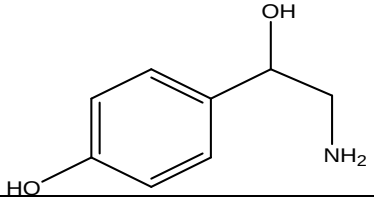
6	Geraniol	3,7-Dimethyl-octa-2,6-dien-o1	$C_{10}H_{18}O$	
7	Octopamine	4-(2-amino-1-hydroxy-ethyl)-phenol	$C_8H_{11}NO2$	

Table. 2: The active sites and Centre of active sites of the modeled proteins with different protein code.

Sl No.	Protein Code	Protein Name	H1 residues in Active site	Centre of active site
1	M1	Human octopamine B2 adrenergic coupled receptor model	YLQQWEAQRLM	-40.649, 5.564, 13.351
2	M2	Human acetylcholine esterase protein model	CAQLGRYAQLRACALR	68.368, 93.263, 6.502
3	M3	octopamine receptor oamb of *Aedes aegypti* model	TKVSGELTRIHRGG	-34.949, 61.947, 18.068
4	M4	acetylcholine esterase of *Aedes aegypti* model	FTYLYTVMHGE	-40.687,-16.143, 18.058

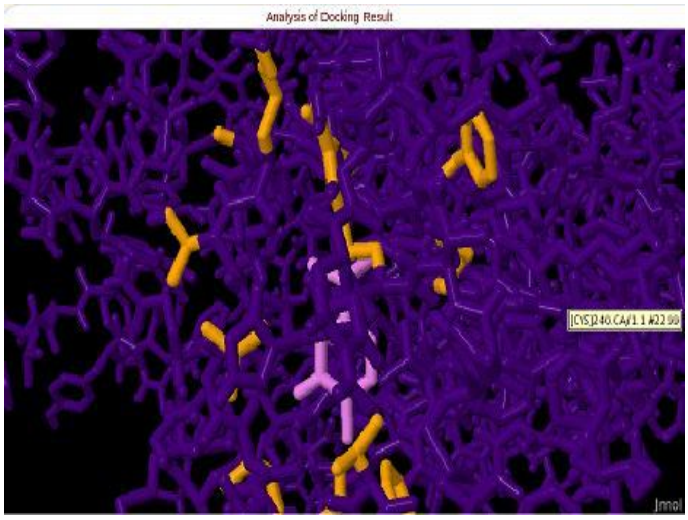


Fig. 9: Docking of human ACHE with ligands.

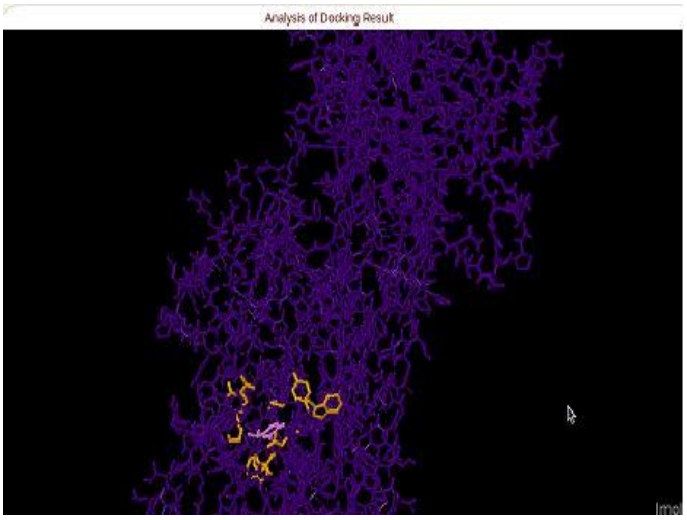


Fig. 10: Docking of human octopamine receptor with ligands.

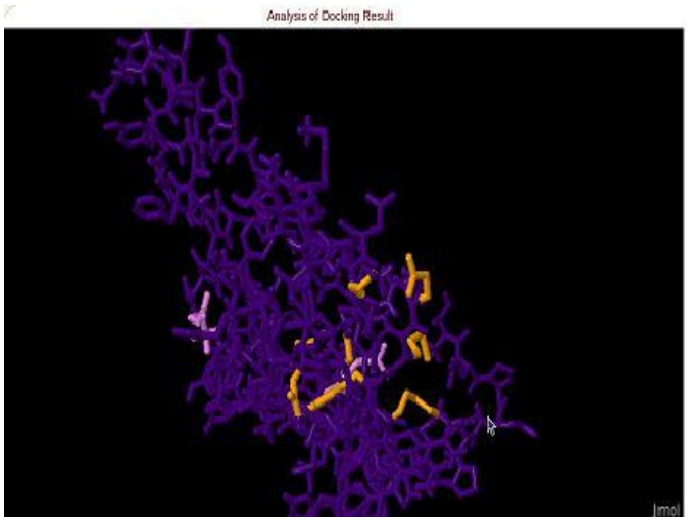


Fig. 11: Docking of A. aegypti octopamine receptor with ligands.

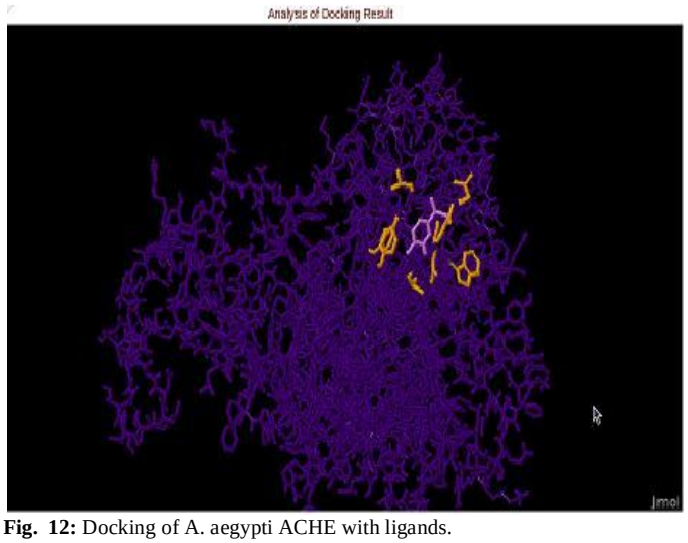


Fig. 12: Docking of A. aegypti ACHE with ligands.

RESULTS AND DISCUSSION

All the terpene compounds were found to perform docking with the protein models (Fig. 9,10,11,12). Total energy values of eugenol, eucalyptol, coumarin and carvacrol against octopamie receptor and acetyl cholinesterase protein model of *Homo sapiens* were found lower than octopamine (-22.27) and acetylcholine (-18.90). However, total energy value of geraniol against these protein models were found higher than octopamine and acetylcholine (Fig. 13). On the basis of the total energy value, the order of binding efficiency of the ligands to octopamine receptor model of *Homo sapiens* can be presented as Geraniol (-19.91) < Octopamine (-22.27) < Eugenol (-24.53) < Eucalyptol (-26.18) < Carvacrol (-28.93) < Coumarin (-30.87). Similarly, the order of binding efficiency of the ligands to acetyl cholinesterase model of *Homo sapiens* can be presented as Geraniol (-17.78) < Acetylcholine (-18.90) < Eugenol (-23.56) < Coumarin (-27.12) < Carvacrol (-29.50) < Eucalyptol (-31.11). Total energy value of eucalyptol, coumarin and carvacrol against octopamie receptor model of *A.aegypti* were found lower than octopamine (-25.54) and the order of binding efficiency of the ligands to octopamie receptor model of the fly can be presented as Geraniol (-22.28) < Eugenol (-23.49) < Octopamine (-25.54) < Eucalyptol (-25.90)< Carvacrol (-30.56) < Coumarin (-31.77). Thus the total energy value of Geraniol and Eugenol were recorded higher than the substrate octopamine. In case of docking with acetylcholinesterage protein model of *A.aegypti*, total energy value of all the selected terpene compounds were found lower than the substrate acetylcholine and the order of binding efficiencies in terms of total energy can be presented as Acetylcholine (-15.30) < Geraniol (-16.85) < Eugenol (-17.78) < Coumarin (-21.17) < Carvacrol (-21.69) < Eucalyptol (-22.58) (Fig. 13).

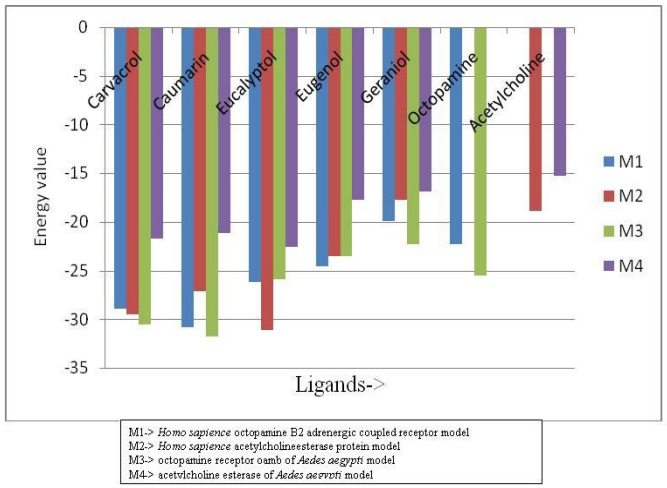


Fig. 13: Energy value of different ligands after docking with protein models of A. aegypti and H.sapience.

Acetylcholine and Octopamine are substrates of acetylcholinesterase and octopamine receptor respectively. Octopamine is an analogue of vertebrate hormone noradrenaline. This biogenic amines present in high concentrations in various insect tissues and have been established to possess multifunctional properties like a neurotransmitter by controlling the firefly light organ and endocrine gland activity in other insects; a neurohormone by inducing mobilization of lipids and carbohydrates; a neuromodulator by acting peripherally on muscles, fat body, corpora cardiaca and the corpora allata, and a centrally acting neuromodulator by influencing motor patterns, habituation and even memory in various invertebrate species including insects (Evans, 1993; Hirashima *et al*., 2003). The action of octopamine is mediated through various receptor classes which is called octopamine receptors in general and are widely distributed in the insect nervous system. These receptors carry out a range of functions equivalent to the adrenergic receptors of the vertebrate sympathetic nervous system (Evan, 1993). Therefore on the basis of their similarities in structure and in signaling properties with vertebrate adrenergic receptors, insect octopamine receptors can be classified into "alphaadrenergic- like octopamine receptors (OctalphaRs)", "beta-adrenergic-like octopamine receptors (OctbetaRs)" and "octopamine/tyramine (or tyraminergic) receptors (Evans and Maqueira, 2005). These are G-protein coupled receptors (Verlinden *et al*., 2010) and the substrate octopamine mediates its effect either by increasing or decreasing in intracellular cyclic AMP levels or by the generation of intracellular calcium signals. AChE is a key enzyme involved in the termination of nervous signals through the hydrolysis of acetylcholine (Barnard, 1974). Thus acetylcholine is the substrate of acetylcholinesterase enzyme. Acetylcholinesterase inhibitors have been tried for the treatment of myasthenia gravis, glaucoma, Alzheimer's disease in human (Leonetti *et al*., 2004). A large series of coumarin derivatives were reported as acetylcholinesterase (AChE) and butyrylcholin esterase (BChE) inhibitors (Pisani *et al*., 2010). A good number of essential oils and its constituents have been found effective to control flies and most of them have been reported to target on octopamine receptor and acetylcholinestearse enzyme (Ryan and Byrne,1988; Coats *et al*.,1991; Kostyukovsky *et al*.,2002). Essential oil components like cuminaldehyde, limonene, α-pinene and α-phellandrene of *Cuminum cyminum* and *Piper nigrum* might be responsible for AChE inhibitory activities of rice weevil *Sitophilus oryzae* (Chaubey, 2011). Monoterpenoids like fenchone, γ-terpinene, geraniol, linalool, S-carvone, camphor were reported to inhibit the enzyme acetylcholinesterase in different stored grain pests (Lopez and Pascual-Villalobos, 2010). Enan (2005) proposed that octopamine receptor mediates the toxicity of cinnamic alcohol, eugenol, trans-antehole, and 2-phenethyl propionate against fruit flies. In the present study, Carvacrol, Caumarin, Euvalyptol, Eugenol and Geraniol were found to perform docking with octopamine receptor and acetylcholinesterase protein models and these may be the probable target site of these terpene compounds. Total energy of some terpene compounds viz. caumarin, carvacrol, eucalyptol and eugenol were found lower than the substrate acetylcholine and octopamine. Comparing the binding efficiencies of these terpene compounds in *H.sapiens* and *A.aegypti* protein models, some of the compounds can further be explored for successful management of *A.aegypti* fly.

CONCLUSION

The tested terpene compounds are neurotoxic and mediate their toxic action via acting on acetylcholinesterase and octopaminergic system. Docking performance of the compounds are variable against *H.sapiens* and *A.aegypti* protein models. Total energy of some terpene compounds viz. caumarin, carvacrol, eucalyptol and eugenol were found lower than the substrate acetylcholine and octopamine. Therefore these compounds may act as acetylcholinesterase inhibitor and can block the octopamine receptor pathway. Some of the compounds can further be explored for successful management of *A.aegypti* fly.

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