Docking Studies on acetylcholinesterase with Methylparathion

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Abstract.

In the present study, the interaction between the amino acids of organophosphoruscompound (MethylParathion) and the principal neurotransmitter acetylcholinesterase (AChE) were assessed through docking studies (i.e.,) with the help of bioinformatics online toolswissdock.

Introduction.

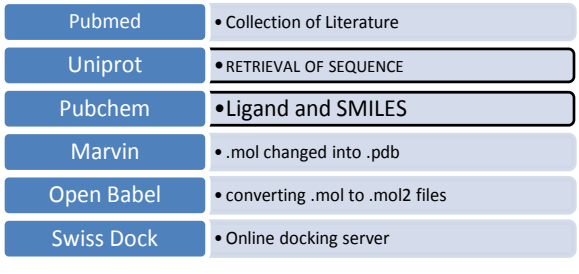
Methyl parathion ($C_8H_{10}NO_5PS$), (*O, O*-dimethyl *O*-4- nitrophenylphosphorothioate) is an OP insecticide with a broad range of activity which inhibits acetylcholinesterase activity (13, 9). Acetylcholine is a low molecular weight neurotransmitter presented in both the central and peripheral nervous system. It is responsible for signal transmission from nerves to terminal glands and muscles.AChE is an enzyme converting acetylcholine into choline and acetate. Neurotransmission is stopped by the AChE effect. AChE is a target for many drugs and toxins. Organophosphorus pesticides, carbamate pesticides and nerve agents are examples of toxic compounds inhibiting AChE.Organophosphorus (OP) compounds are a major component of many pesticides with widespread use in both agricultural and domestic situations (10.)Organophosphorus compounds are widely used in agriculture as insecticides and acaricides and also in medicine and industry. Residual amounts of organophosphate (OP) pesticides have been detected in the soil, water bodies, vegetables, grains and other foods products (7, 8, 11, and 9). Due to the wide availability of organophosphorus compounds, poisonings are common (3, 9). OP pesticides are known to cause inhibition of acetylcholinesterase and pseudocholinesterase activity in the target tissues (8). The primary mode of action for OP pesticides is initiated through inhibition of acetylcholinesterase, the enzyme responsible for degrading the neurotransmitter acetylcholine (12). Excessive acetylcholine accumulation due to enzyme inhibition results in over stimulation of cholinergic receptors and signs of cholinergic toxicity such as salivation, lacrimation, urination and defecation (SLUD) bradycardia, miosis, nausea and respiratory dysfunction (2)

Organophosphorus (OP) insecticides elicit toxicity through inhibition of acetylcholinesterase, leading to accumulation of acetylcholine in the nervous system and consequent signs of cholinergic toxicity (12).In addition to inhibiting acetylcholinesterase, a number of OP toxicants bind directly to muscarinic receptors, with relatively high potency towards the muscarinic m2 subtype.

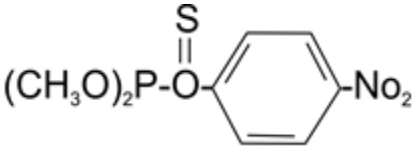
Materials and methods.

Retrieval of sequences:Acetylcholinesterase(AChE) sequence of albino rats *Rattus norvegicus* was obtained from Uniprot, a protein database (http://www.uniprot.org) (6). The accession id is 1q83A.The protein sequence was retrieved in the FASTA format.

Ligand: Methylparathion an organophosphate compound was used as a ligand. Methylparathion inhibits the activity of acetylcholinesterase which is the principal neurotransmitter. The ligand and the canonical SMILES was obtained from Pubchem database and using Marvin sketch software the .mol file is changed to .pdb format.



Structure of methyl parathion:



Swiss Dock: Interaction of acetylcholinesterase with methylparathion was done using Swissdock, aprotein small molecule docking web service based on EADock DSS (4). The Swiss dock website is available online at http:// www.swissdock.ch (5)

Results.

Swiss dock computed the lowest binding energy and the free binding energy of the docking.The binding energy of the ligand was in the range of -13.4291 to -11.7286kcal/mol. From the table it was found that the docking of the ligand methylparathion with the acetylcholinesterase has the minimum binding energy of -13.4291kcal/mol and the free binding energy of -7.481748kcal/mol with amino acid interactions of Asn-317, Asn-233(fig-1; Tab-1)

Discussion.

Methylparathion (0, 0-dimethyl0–4-nitrophenyl phosphorothioate)is a highly toxic organophosphorusinsecticide that is safelyused on agricultural crops, particularly cotton, because itdegrades and dissipates quickly in the environment (13).Methyl parathion poisoning caused the usual organophosphates cholinergic signs attributed to accumulations of acetylcholine at nerve endings. Methyl parathion becomes toxic when it is metabolized to methyl paraoxon. This conversion is rapid. Conversion of parathion-methyl to its toxic metabolite methyl paraoxon occurs within minutes of oral administration (14).

AChE inhibition results in the accumulation of acetylcholine (Ach), the neurotransmitter acting at the cholinergic synapses and neuroeffector junctions in the central and peripheral nervous system. The accumulation of Ach is responsible for an excessive cholinergic stimulation and results in acute toxicity both in mammals and in insects (1). With the help of docking studies we were able to predictthe binding sites of the ligand & protein molecule.Overall from the result it is understood that the effect of methylparathion has a significant binding activity on Ache of rat (*Rattus norvegicus*).

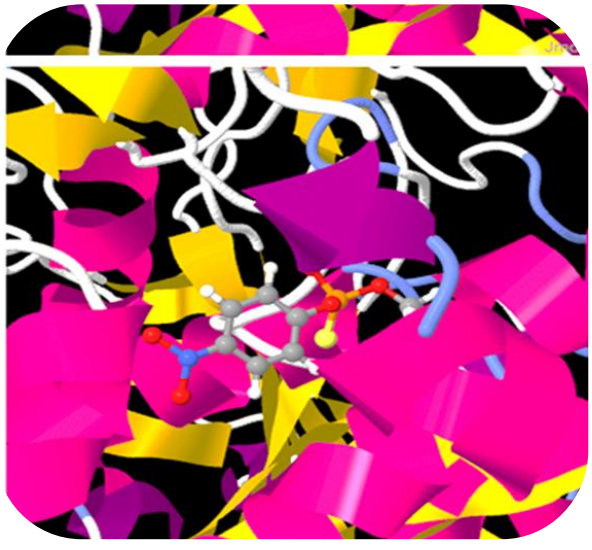
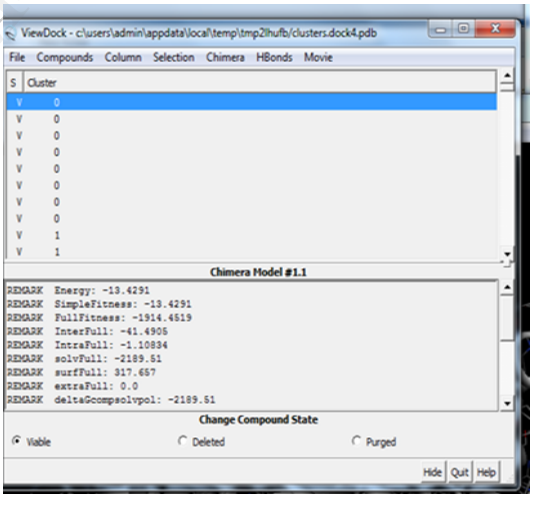


Fig-1 **Interaction of acetylcholinesterase with methylparathion**

Tab-1



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Acknowledgements.

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