INSILICO ANALYSIS OF ACETYLCHOLINESTERASE WITH MALATHION

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Abstract:

In the present study, the interaction between the amino acids of organophosphorus compound (Malathion) and the principal neurotransmitter acetylcholinesterase (AChE) were assessed through docking studies (i.e.,) with the help of bioinformatics online tool patchdock.

Keywords: Neurotransmitter, Acetylcholinesterase, organophosphate compound, Malathion, Interaction, amino acids, docking

Introduction.

Malathion is an organophosphate Para sympathomimetic which binds irreversibly to cholinesterase. Malathion is an insecticide of relatively low human toxicity (1). Malathion (O, O-dimethyl S-1, 2-ethoxycarbonyl) ethyl phosphorodithioate) is an organophosphate (OP) insecticide widely used in agriculture and residential settings as well as in public health programs for mosquito-borne disease control (18, 20). It is also used in some countries for the treatment of head lice (19). Like other OP insecticides, Malathion exerts its neurotoxic action in humans, as in insects, through cholinesterase (ChE) inhibition. This results in the accumulation of acetylcholine within synapses leading to over-stimulation of postsynaptic receptors (21). In acutely exposed individuals, clinical signs of OP intoxication usually appear at inhibition of 60–70% of acetylcholinesterase (AChE) activity in red blood cells (RBC). However, light clinical signs and symptoms were reported in subjects with 30–60% reduction in RBC–AChE activity (22). 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 (9) 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, and 11). Due to the wide availability of organophosphorus compounds, poisonings are common (4). 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 (11).

Organophosphorus (OP) insecticides elicit toxicity through inhibition of acetylcholinesterase, leading to accumulation of acetylcholine in the nervous system and consequent signs of cholinergic toxicity (11). 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 rat *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: Malathion, an organophosphate compound was used as a ligand. Malathion inhibits the activity of

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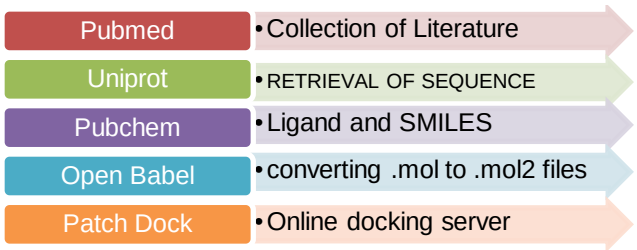
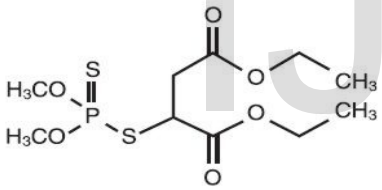
S.No	Score	Area	ACE	Transformation
1	4738	553.60	-111.38	-2.28 0.29 -0.18 20.49 27.24 22.49
2	4282	533.30	-108.44	-1.89 0.86 -1.38 18.15 27.85 23.07
3	4248	543.00	-146.84	0.52 1.08 -1.39 19.48 26.72 22.60
4	4216	569.00	-170.31	1.01 0.71 2.35 18.20 28.47 22.35

Tab.1

acetylcholinesterase which is the principal neurotransmitter. The ligand and the canonical SMILES was obtained from Pubchem database and using open babel .mol is converted to .mol 2



Structure of Malathion:



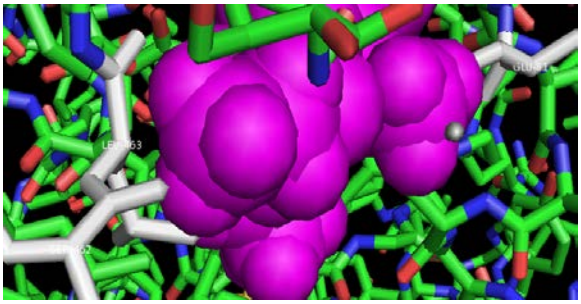
Formula: $C_{10}H_{19}O_6PS_2$

Patch Dock: Patch Dock is an algorithm for molecular docking. The input is two molecules of any type: proteins, DNA, peptides, drugs. The output is a list of potential complexes sorted by shape complementarity criteria (3, 12, 13 and 17). Interaction of acetylcholinesterase with malathion was done using patchdock, a Molecular Docking Algorithm Based on Shape Complementarity Principles. The patch dock website is available online at http://bioinfo3d.cs.tau.ac.il/PatchDock/(7)

Results

Patch dock computed the lowest score for the docking. From the table it was found that the docking of the ligand malathion with the acetylcholinesterase has the score of 4738,4282,4248,4216 with atomic contact energy of -111.38, -108.44, -146.84, -170.31 accordingly and the approximate interface area of the complex was 553.60,533.30, 543.00,569.00 respectively with amino acid interactions of Leu 463, Ser 462, Glu 81(fig-1; Tab-1)

Fig-1



Discussion

Malathion (O, O-dimethyl S-1, 2-di (ethoxycarbonyl) ethyl phosphorodithioate) is an organophosphate (OP) insecticide Widely used in agriculture and residential settings as well as in Public health programs for mosquito-borne disease control (23, 24, 25).Malathion poisoning caused the usual organophosphates cholinergic signs attributed to accumulations of acetylcholine at nerve endings. Malathion becomes toxic when it is metabolized to malaoxon. This conversion is rapid. Conversion of Malathion to its toxic metabolite malaoxon occurs within minutes of oral administration (14, 15, 16, and 17).

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 (2). With the help of docking studies we were able to predict the binding sites of the ligand & protein molecule. Overall from the result it is understood that the effect of malathion has a significant binding activity on Ache of rat (*Rattus norvegicus*).

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