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Computational Prediction of Binding of Methyl Carbamate, Sarin, Deltamethrin and Endosulfan Pesticides on Human Oxyhaemoglobin

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Abstract

Pesticides are used to control insects and pests. However, their use has become so frequent that they may create problems for non target animal species. Methyl carbamate, sarin, deltamethrin and endosulfan pesticides are used to control insects and pests. In the current study computational prediction of binding of these pesticides on human oxyhaemoglobin using Molegro Virtual Docker (MVD) and evaluating the comparative Mole Dock Score, Root-mean square deviation (RMSD), affinity, interacting residues of human oxyhaemoglobin, number of Hydrogen bond interaction, docking score, Protein steric interaction energy (Protein EvdW) and interacting interaction of residues. In the present study the energy bound conformation with lower value of selected ligands shows hydrogen bonding and electrostatic interactions. The binding affinity of selected pesticides is found to be in decreasing order i.e., sarin > methyl carbamate > deltamethrin > endosulfan. All the pesticides bind with the serine 133. Frequent alterations in the expression of serine (amino acid) due to pesticide interaction with oxyhemoglobin may lead to produce carcinogenic cells in human beings.

Key words: Pesticide, Human oxyhaemoglobin, MVD, RMSD, Protein steric interaction energy, Serine.

1. Introduction

Due to increase in population scarcity of food is likely to create immense pressure to full fill the demand of food production. Nearly 29% of food produced is destroyed by insects, pests, birds, rats, etc. With the increasing pressure for food production, there is a great increase in the use of insecticides and pesticides to reduce the loss due to insects and pests (Tomlin, 2006). Though their use reduces the loss from insects and pests, on the other hand, they have adverse effects on crops nutrient value and leads to hazardous results on non target animals as well as human beings (Dich *et al.*, 1997). Methyl carbamate, sarin, deltamethrin and endosulfan are widely used pesticides in homes, gardens and agriculture (Bradberry *et al.*, 2005, Ayaz *et al.*, 2013). They are used in commercial crops, recreational uses and control variety of pests and inhibit cholinesterase enzyme activity, thus they have similar symptomatology during exposure of acute and chronic toxicity (Lifshitz *et al.*, 1997, Burr & Ray, 2004). They can produce a variety of acute health problems and also carries several ecological risks (Lifshitz *et al.*, 1994, Goswamy *et al.*, 1994, Saxena and Saxena, 1997).Haemogrammic studies in albino rat after pesticide intoxication were revealed by Shakoori *et al.* (1992), Saxena and Tomer (2003), Shah *et al.* (2007) and Saxena and Saxena (2010). They reported that total erythrocyte count, hemoglobin concentration, packed cell volume, mean corpuscular volume were decreased after pesticide toxicity. It becomes necessary to carry out hematological examination to evaluate the normal and abnormal physiological states of the body. Our cells require regular supply of fuel and oxygen. Blood has capability to fulfill these requirements for proper functioning of cells resulting in maintaining good health. Low hemoglobin is the main cause of anemia. Further, low hemoglobin indicates lower levels of oxygen in the blood, which often causes shortness of breath (Shakoori *et al.*, 1988; Saxena *et al.*, 2009). Low hemoglobin level may also exasperate extant heart problems (Villarini *et al.*, 1998). In this work, we report computational prediction of binding of methyl carbamate, sarin, deltamethrin and endosulfan pesticides on human oxyhaemoglobin and evaluate the comparative Mole Dock Score, RMSD, binding affinity, interacting residues of receptor human oxyhaemoglobin, number of H-bond interaction, docking score, protein EvdW and interacting Interaction of residues using MVD.

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2. Materials and Methods

Three dimensional X ray crystallized structure of human oxyhaemoglobin (PDB: 1HHO, 2.1 Å resolution) was downloaded from the protein data bank (Shaanan, 1983). The downloaded protein have the two chain hemoglobin A (oxy) (alpha chain) with 141 residues and hemoglobin A(oxy) (beta chain) with 146 residues .The protein was taken as receptor protein and most suitable site was predicted by using q sitefinder ligand binding site prediction (http://www.modelling.leeds.ac.uk). Because of priority of site, oxyhaemoglobin has been selected for docking with ligand methyl carbamate (CID_11722), sarin (CID_7871), deltamethrin (CID_40585), and endosulfan (CID_6434141) pesticides, recently use for plant protection and control pests in homes & gardens. The selected ligands (pesticides) were downloaded from Pub Chem Compound (http://www.ncbi.nlm.nih.gov). Docking study was done with Molegro Virtual Docker (MVD). It is automated docking software with fast processing. The binding site cavity detection was performed by q site finder ligand binding site prediction tool (Figure 1). The docking simulation was performed by using docking software, namely MVD for the selected pesticides (ligands) and oxyhaemoglobin (protein).It shows mole dock score, RMSD, affinity (the estimated binding affinity in kj /mol), docking score, protein EvdW and interacting interaction (the interaction energy among the pose and the cofactor), number of H-bond and interaction between interacting residues of receptor human oxyhaemoglobin, which indicates towards the formation of stable complex among ligand and receptor molecule (Thomsen and Christensen, 2006). MVD visualizer is used for interaction site prediction.

3. Results and Discussion

The comparative results obtained (using MVD) from docking simulation are given inTable-1. The interaction analysis for binding of human oxyhaemoglobin with methyl carbamate, sarin, deltamethrin and endosulfan have been done to find out the residues that are involved in binding site residues and number of hydrogen bonds are involved in interaction among selected pesticides, Table - 2.The energy bound conformation with lower value of selected ligands shows hydrogen bonding and electrostatic interactions are given in Figures 2a, b, 3a, b, 4a, b and 5a, b, for methyl carbamate, sarin, deltamethrin and endosulfan respectively.

Docking energy for most of pesticides were found favorable for hemoglobin A (oxy) (alpha chain) rather than hemoglobin A (oxy) (beta chain) which shows that these compounds can get stuck into hemoglobin A (oxy) (alpha chain) due to positive interaction (Singh, 2012). The methyl carbamate shows very high affinity to bind with human oxyhaemoglobin and it interacts with Phe 98, Ser133, Val132, Ser102, Leu 120 residues of human oxyhaemoglobin. All these residues involved in binding belong to the cavity-1. The methyl carbamate forms 5 hydrogen bonds with Phe 98, Ser133, Val132, Ser102,Leu 120 (Table 2 and Figure 2 (a, b)). The hydogen bonding is very significant for interaction of biomolecules. Sarin forms low binding energy complex as compare to methyl carbamate which shows binding affinity with Ser 133, Thr 134, Phe 98, Lys 99, Ala 130, Thr137and forms three hydrogen bond with Ser 133, Thr 134 (Table 2 and Figure 3 (a,b)). The deltamethrin forms low binding energy complex as compare to sarin, it shows binding affinity with Ser133, Ser102, Tyr 35, Ala 130, Asp 126, Phe 98, Lys 99, Leu 105 residues of human oxyhaemoglobin. Whereas, deltamethrin formed three hydrogen bond with Ser133, Ser102, Tyr 35 residues (Table 2 and Figure 4 (a,b)).The Endosulfan forms low binding energy complex as compare to methyl carbamate shows binding affinity with Ser133, Asp 126, Leu 129, Ser102, Phe 98, Lys 99, Ala 130, Tyr35 and forms one hydrogen bond with Ser133 residue of human oxyhaemoglobin [Table 2 and Figure 5 (a, b)). The binding affinity of selected pesticides methyl carbamate, sarin, deltamethrin and endosulfan at the active site of human oxyhaemoglobin using MVD is in decreasing order i.e. sarin > methyl carbamate > deltamethrin > endosulfan. The binding of pesticide with oxyhaemoglobin also supported by *in vitro* studies. Mourad, 2005 reported a fall in hemoglobin contents after insecticide intoxication in farm workers. Further, Shakoori *et al.* (1992), Khan and Ali (1993), Saxena *et al.* (2009), and Saxena and Saxena (2010) also observed a significant reduction in heamoglobin concentration after pesticide toxicity.

Even today our understanding of the relationship between pesticides and human health is limited due to numerous methodological problems faced in laboratory studies. Computational methods can turn out very useful for comparing vitro results for new hypotheses. Docking study shows that amino acid residue i.e., Ser133 is common in binding for all the pesticides. Serine is a polar amino acid and important for catalytic function of many enzymes (Serine, 2013).Further, the OH group of serine phosphorylates and form kinase enzyme. Serine kinases also play an important role in cellular homeostasis due to phosphorylate transcription factors, regulate cell cycle, and arrange properly cytoplasmic and nuclear effectors (Blume-Jensen and Hunter, 2001; Weichenthal *et al.*, 2012). Capra *et al.* (2006) revealed that some serine kinase might play a tumor suppressor role and have a causal role in certain malignancies. The misregulation of kinases enzyme stimulate tumor growth, metastasis and poor clinical outcome (Warner *et al.,* 2003; Freeman and Whartenby, 2004; Eckerdt *et al.,* 2005). It has been also reported that frequent alterations in the expression of serine kinases causes cancer in human being (Edelman *et al*., 1987).

Table 1. Comparative Docking Simulation Result of Selected Pesticides Methyl Carbamate, Sarin, Deltamethrin and Endosulfan with Human Oxyhaemoglobin Protein from X-ray Crystallized Data of Protein Data Bank (PDB:1HHO) using MVD.

S. No.	Ligands	MoleDock Score	RMSD	Affinity	Protein EvdW	Intracting	Docking Score
1.	Methyl Carbamate	-45.0674	0.118821	-26.473	-34.8891	-47.1982	-48.0108
2.	Sarin	-51.4733	1.51773	-24.1619	-49.6729	-53.5958	-52.1534
3.	Deltamethrin	-124.791	1.76639	-36.9168	-129.268	-134.458	-123.268
4.	Endosulfan	-80.0703	3.52641	-42.6401	-75.845	-76.882	-80.3116

Table 2. Human Oxyhaemoglobin from X-ray Crystallized data of Protein Data Bank (PDB: 1HHO), protein residues interact with selected pesticides Methyl Carbamate, Sarin, Deltamethrin and Endosulfan using MVD (highlighted residues are involved in H-bonding interaction with ligands).

S. No.	ligands	Interacting residues of receptor Human oxyhaemoglobin	No. of H-bond interaction
1.	Methyl Carbamate	Ser133, Ser102,Leu 120 Phe 98, Val132	05
2.	Sarin	Ser 133, Thr 134, Phe 98, Lys 99, Ala 130, Thr137,	02
3.	Deltamethrin	Ser133, Ser102, Tyr 35, Ala 130, Asp 126, Phe 98, Lys 99, Leu 105,	03
4.	Endosulfan	Ser133, Asp 126, Leu 129, Ser102, Phe 98, Lys 99, Ala 130, Tyr35,	01

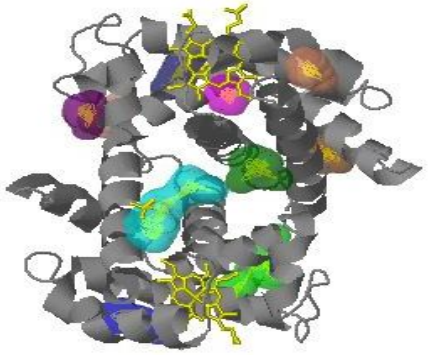

Figure1. Binding site for oxyhaemoglobin.

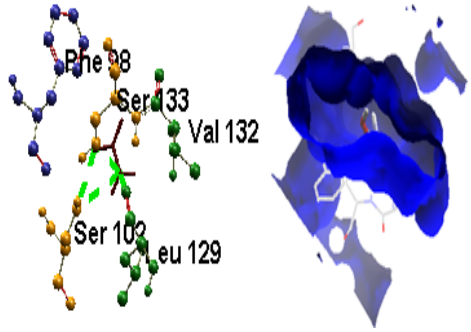

Figure2. (a) Docked conformation of hydrogen bonding view and (b) with Electrostatic interaction of Methyl Carbamate with interacting Human Oxyhaemoglobin protein at the active site cavity.

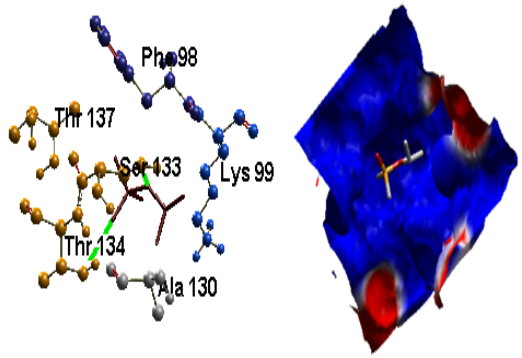

Figure3. (a) Docked conformation of hydrogen bonding view and (b) with Electrostatic interaction of Sarin with interacting Human Oxyhaemoglobin protein at the active site cavity.

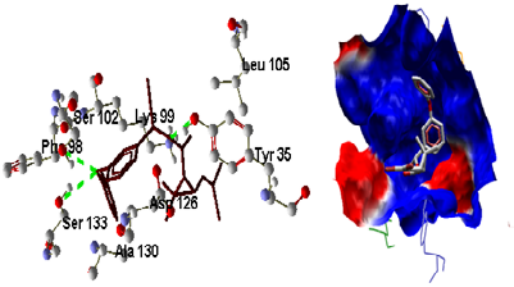

Figure4. (a) Docked conformation of hydrogen bonding view and (b) with Electrostatic interaction of Deltamethrin with interacting Human Oxyhaemoglobin protein at the active site cavity.

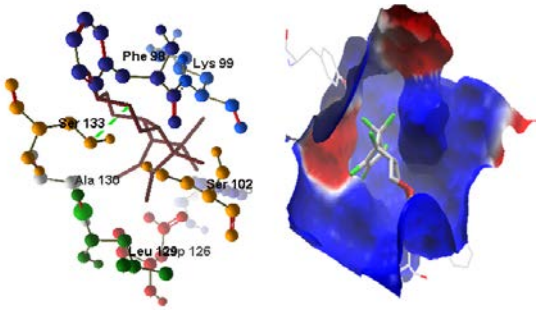

Figure5. (a) Docked conformation of hydrogen bonding view and (b) with Electrostatic interaction of Endosulfan with interacting Human Oxyhaemoglobin protein at the active site cavity.

4. Conclusions

We predict that pesticides bind human oxyhaemoglobin with varying affinities, and all tested pesticides bind to serine 133 which might lead to cancer. Thus, pesticides have both short term and long term

hazardous effects and, therefore, their use on crops & plants should be limited to a certain extent.

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