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Original Article

HOMOLOGY MODELLING AND MOLECULAR DOCKING STUDY OF ORGANOPHOSPHATES AND PYRETHROIDS IN TERMS OF POTENTIAL TOXICITY

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ABSTRACT

Objective: Though the adverse effects of pesticides used in agriculture may not immediately be visible in the human population however its long term exposure may cause detrimental effects by biomagnifications and bioaccumulation. Nowadays bioinformatics serves as an *in silico* tool not only for homology alignment but also for prediction of quaternary structures of biochemicals. The present study was aimed to compare the potential toxicities of triazophos and chlorpyrifos (organophosphates; OPs) and cypermethrin and deltamethrin (pyrethroids) and their interactions with cytochrome P_{450} functioning.

Methods: The authors performed the BLAST for homology alignment for cytochrome P_{450} of human and Zebra fish and further proceeded for docking analysis of all the pesticides with cytochrome P_{450}.

Results: It was noted that 99% of query cover with 32% of homology in the sequences of cytochrome P_{450} between human and Zebra fish. Upon docking, the pesticide deltamethrin showed the highest interaction with cytochrome P_{450} with highest binding energy and least dissociation constant for Deltamethrin which was found to be 8.233 [kcal/mol] and 922849.687 [pM].

Conclusion: Our preliminary results thus encompass/indicate that the deltamethrin is not only having detrimental effect on enzyme kinetics in general but also such similar effects be apprehended for human also.

Keywords: Cytochrome P_{450}, Homology modelling, Molecular docking, Organophosphate, Pyrethroids

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INTRODUCTION

Synthetic pesticides of any origin can exert varied effects on different target as well as non-target organisms which further may also affect humans by biomagnification [1]. The organophosphate group of pesticides (like triazophos and chlorpyrifos) can directly affect the synapses present between neuronal and neuro-motor junctions by affecting acetylcholinesterase (AChE) activity [2]. The pyrethroids (like deltamethrin and cypermethrin) can also exert a similar effect by altering the voltage gated Na^+ion channels present on neurolemma [3]. Thus, under both acute and chronic exposures, these pesticides are harmful and toxic to the aquatic biota particularly fishes [4] and further the human population as well due to the inability of detoxification of these pesticides [1].

The main detoxifying enzyme which is present in almost all cells ubiquitously as well as evolutionarily conserved one is cytochrome P_{450} (CYP) family proteins which use Haem as a cofactor for their functions [5]. Among a number of cytochrome P_{450} proteins, the mitochondrial cytochrome P_{450} is of the highest importance as it is primarily responsible for detoxifying drugs, drug metabolites, alcohol and others [6]. In human, there are about 57 genes reported for coding cytochrome P_{450} [7]. There are few reports, delineating the interactions of chlorpyrifos with cytochrome P_{450} in human, rat and mouse [8] but, till date reports are lacking in the field of homology alignment of cytochrome P_{450} in human and fishes and further the comparative interactions of cytochrome P_{450} with different pesticides.

The previous studies lacked the information on the structural homology of cytochrome P_{450} in human and a key representative of fish (Zebra fish; *Danio rerio*), therefore the present study was undertaken to note their similarities in functional activities. Further, the study was elaborated to note the interactions of pesticides (organophosphates and pyrethroids) with cytochrome P_{450} to get a speculative analogy of effects as exerted by these pesticides in fish are similar in human or not.

MATERIALS AND METHODS

Homology alignment of cytochrome P_{450} between human and zebra fish

We compared the sequence of cytochrome P_{450} of Zebra fish and *Homo sapiens* using Basic Local Alignment Search Tool (BLAST).

Molecular docking

For *in silico* study, the protein structure of Cytochrome P_{450} with PDB ID: 4R21 were retrieved from RCSB protein databank [9]. Further, the geometry optimisation and active site prediction of this compound were done by using Discovery studio 3.0 [10]. The 2D structure of selected pesticides namely triazophos, deltamethrin, chlorpyrifos and cypermethrin were retrieved from Pubchem compound database [11] and converted into 3D format using Discovery studio 3.0. Then the best-docked compound was taken for interactive 2D-3D visualization using Discovery studio 3.0. Further molecular docking calculation was done by using YASARA software [12]. Using YASARA, receptors and ligands files were set and macro was run. The result log files were prepared for all the ligands. Binding energy and dissociation constant were used for sorting the docking result. The compound with more positive binding energy shows more interaction with the receptor.

RESULTS

Homology alignment of cytochrome P_{450} between human and zebra fish

We found 99% query cover with 32% identity showing homology between human and zebra fish upon BLAST (fig. 1).

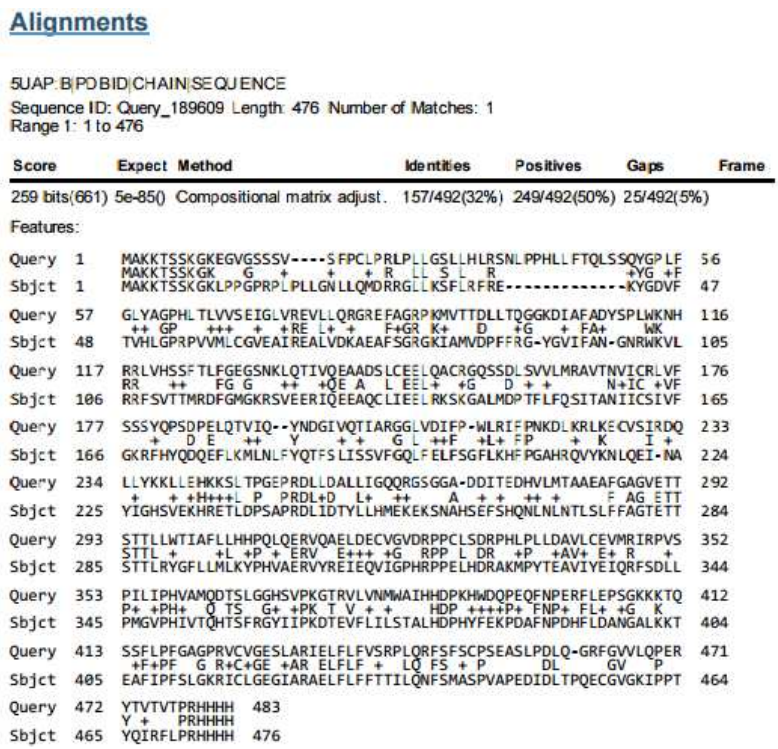

Fig. 1: Showing sequence homology alignment between human and zebra fish

Molecular docking

Molecular docking result showed that pesticide, deltamethrin exerted the best interaction with cytochrome P_{450}. All other pesticides namely triazophos, chlorpyrifos and cypermethrin also shows interaction but lesser than deltamethrin (table 1). The binding energy and dissociation constant for deltamethrin were found to be 8.233 [kcal/mol] and 922849.687 [pM] respectively. Further, the best-docked compound deltamethrin was taken for interactive 2D-3D visualization using Discovery studio 3.0. The active site amino acid residues, $ArgA^{103}$ $IleA^{119}$ $AlaA^{120}$ $TrpA^{128}$ $ArgA^{132}$ $AlaA^{302}$ $ThrA^{306}$ $ThrA^{310}$ $MetA^{361}$ $ValA^{366}$ $SerA^{367}$ $LeuA^{370}$ $IleA^{371}$ $HisA^{373}$ $ProA^{432}$ $PheA^{433}$ $GlyA^{434}$ $ArgA^{438}$ $ValA^{439}$ $CysA^{440}$ $ValA^{441}$ $GlyA^{442}$ and $AlaA^{446}$ of cytochrome P_{450} were involved in interaction with deltamethrin.

The pink colour residues show electrostatic interaction while green colour residues show Vander Waals interactions. The residue $ArgA^{103}$ shows direct interaction as well as Pi-Pi interaction with deltamethrin which shows its inhibition activity (fig. 2A and fig. 2B).

Table 1: Binding energy and dissociation constant for all selected pesticides with cytochrome P_{450}

Pesticides	Cytochrome P_{450}	
	Binding energy [kcal/mol]	Dissociation constant [pM]
Deltamethrin	8.233	922849.687
Cypermethrin	7.533	3007722.75
Triazophos	6.497	17283666
Chlorpyrifos	5.433	104125760

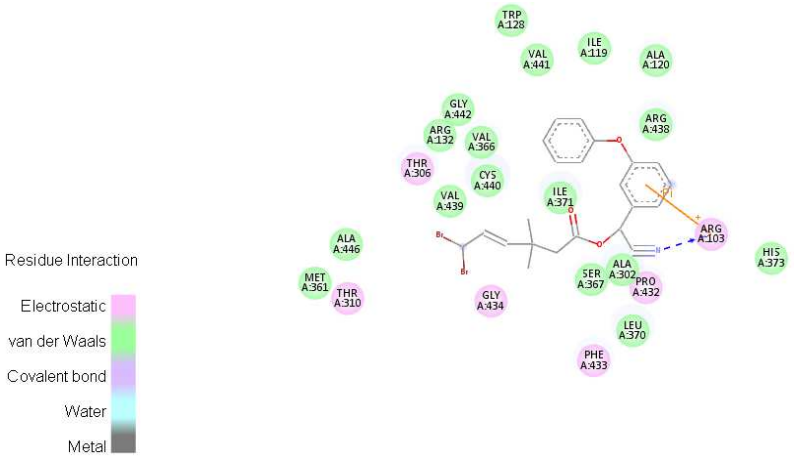

Fig. 2A: 2D interaction of deltamethrin with cytochrome P_{450}. The pink colour residues show electrostatic interaction while green colour residues show Vander Waals interactions. The residues $ArgA^{103}$ shows direct interaction with deltamethrin

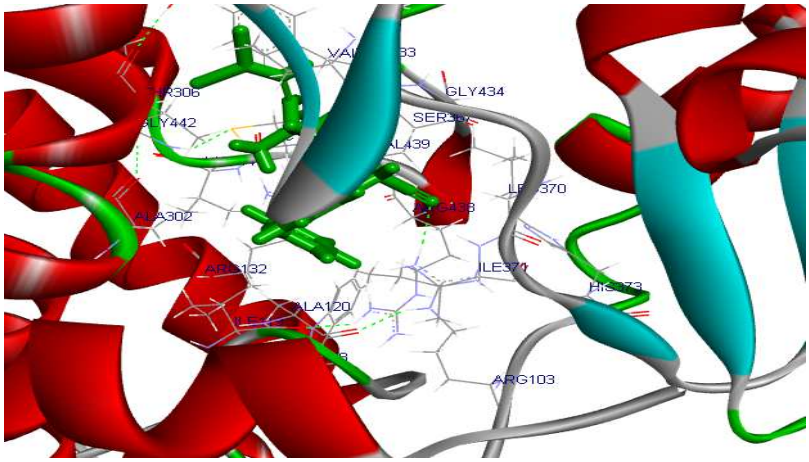

Fig. 2B: 3D interaction of deltamethrin with cytochrome P_{450}

DISCUSSION

Fishes are the most economically important aquatic animals which are affected highly by pesticide contamination though being non-target organisms [4]. The detrimental effect of pesticides can be ameliorated/detoxified by a key enzyme cytochrome P_{450}. The interactions of cytochrome P_{450} with the pesticides like chlorpyrifos, triazophos, cypermethrin and deltamethrin individually and in combination has been analysed. It was noted that among four pesticides, the deltamethrin presented the highest binding with cytochrome P_{450} with highest binding energy and least dissociation constant. Thus, it may be speculated that, upon pesticide intoxication, deltamethrin can show the highest level of toxicity as it can directly bind with the active site of the enzyme with amino acid residues particularly with ArgA[10][3] by direct as well as Pi-Pi interactions. Further, the toxicity effects would be more detrimental as these pesticides can also degenerate the basic histo-architecture of a number of tissues like gills, kidney and liver. The degeneration of these tissues in fishes can, in turn, affect severely other haematological and cell mediated immune parameters in fishes [13].

In the next step of the present study, the structural homology of cytochrome P_{450} of fishes with have been human was executed. For this, the known sequences of cytochrome P_{450} of fish (Zebra fish) and human from literature data base [14] was retrieved on 15. 05.2017 and the BLAST tool was run. Out of 99% of sequences, 32% of sequence homology between human and zebra fish was found. However similar studies of molecular docking of antidiabetic activity of cinnamon compounds have been reported earlier [15] but probably, these results for the first time have suggested that the structural homology of cytochrome P_{450} of human and zebra fish might have the same structure at the amino acid level and based on this structural homology it may be speculated that this enzyme might be performing the same function both in fishes and human.

CONCLUSION

From the present *in silico* study, it may be concluded that the potential toxicity in the terms of reaction kinetics and binding efficiency of two groups of pesticides namely organophosphates and pyrethroids are variable being higher in deltamethrin followed by cypermethrin, triazophos and chlorpyrifos respectively. Further, we can also speculate that the mode of action of these pesticides are almost similar even in human and fishes due to the structural homology of cytochrome P_{450} in both of the organisms.

AUTHORS CONTRIBUTION

Conceptualization of the study was suggested by RSP. The relevant literature survey and structural analysis of pesticides were done by RKT and SS (contributed equally). The analysis of results, writing of paper was done by SG. The docking analysis was done by SKR and PS.

CONFLICT OF INTERESTS

All the authors declare that they do not have any conflict of interest.

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