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IN SILICO ANALYSIS FOR COMPETENT BIOINSECTICIDES

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ABSTRACT: From several years entomological and plant pest interactions research is focusing on protease inhibitors (PIs) based strategies for controlling insect pests. Present review signifies the importance of in silico analysis of interactions between insect gut proteases with PIs and provides the information of tools and techniques such as molecular docking and molecular dynamics required for analysis. In silico prediction of insect gut protease and PIs interactions could provide significant information for identification and development of novel promising PI candidate for the transgenic approach. This will also minimize the cost and period of in vitro screening of PIs.

KEYWORDS: Molecular docking, Molecular dynamics, Plant Protease Inhibitor

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1. INTRODUCTION

The adaptability of insect pest to prolong chemical insecticides is a gradually increasing problem facing worldwide [1]. Additionally health and environmental issues have arisen due to the use of these insecticides [2-4]. As efforts of the scientific community in last two decades; genetically modified insect resistance crops (e.g. BT crops), a useful era of insect pest control is worthwhile up-to-date [5-7]. These crops are considered to be having less threat to the environment and to human health with effective control of insect pests [8-12]. Insect pests are found to be successful in adapting to these toxins and proteins and corroborating pitfall in this promising technology [13]. Since last few years, entomological research has been focused on targeting digestive enzymes of insect pests and PIs based strategy established effectively [14-18]. Serine proteases are found dominant in insect's gut and having an important role in the digestion of proteinaceous diet [19]. It's been reported in some studies that during the evolution plants have developed their own strategies in

order to survive by secreting peptides or other phenolic compounds to defend against the insects by inhibiting insect proteases. PIs comprise one of the most abundant classes of proteins in plants. Most storage organs such as seeds and tubers contain 1 to 10% of their total proteins as PIs [20]. To shield the inhibitory action of insect proteases molecules insects secretes insensitive proteases in their gut. The degradation of PIs by the action of insect gut serine proteases generates small molecular weight peptides. Some inhibitors are adapted and develop resistance to this action and survive. The impending action of these peptides certainly not known and the digging into interactions between these two molecules i.e. insect gut protease and PI small peptides of host plants is necessary. From this observation, several queries are raised in our mind based on the interactions of insect gut protease and PIs which are well depicted in Figure 1. And are as follows: a) Whole inhibitor inhibits the proteases or having some active domains which are responsible for the inhibition phenomenon? b) During insect feeding on a proteinaceous diet (e.g. seed) why feeding interrupt? c) Is there any small degraded peptide act as digestive enzyme blocker? d) The small molecular weight site-specific slice peptide can act as potential inhibitor? e) Many studies report protein toxins as inhibitors of insect proteases, adapted inhibitors which are resistant to protease activity are acting as toxins to digestive proteases? The full phenomenon of gut protease and PIs interactions need to be explored to design future strategies to manage insect pests in agricultural crops. The current review focuses on PIs based strategies for insect pest management and explores the various computational approaches which could be utilized to study the interactions of insect gut proteases with PIs. The preliminary utilization of these bioinformatics approaches will provide a firm platform to design competent strategies against insect pests.

2. PLANT PIs: A DEFENSE MECHANISM OF PLANT

Proteases help to digest protein diet in the insect's gut by hydrolyzing the peptide bonds [19]. Functional group present in the active site of protease leads to be categorized into four classes of protease i.e. serine protease, aspartic protease, cysteine protease, and metalloprotease [21]. Inhibition of insect gut protease and protect other defense proteins from proteolytic degradation, with this dual benefit PIs is a key element to develop insect resistance transgenic verities. Therefore, intensive research is going on to isolate and characterize these proteins and their genes and to produce a transgenic crop [14-18]. In recent years, research communities trying to focus on PIs that affect the growth and development of plant pests [22-24]. Inhibitors of insect alpha-amylase, protease and other plant proteins have already been investigated to be a significant biological system in the management of insect pests [25,26].

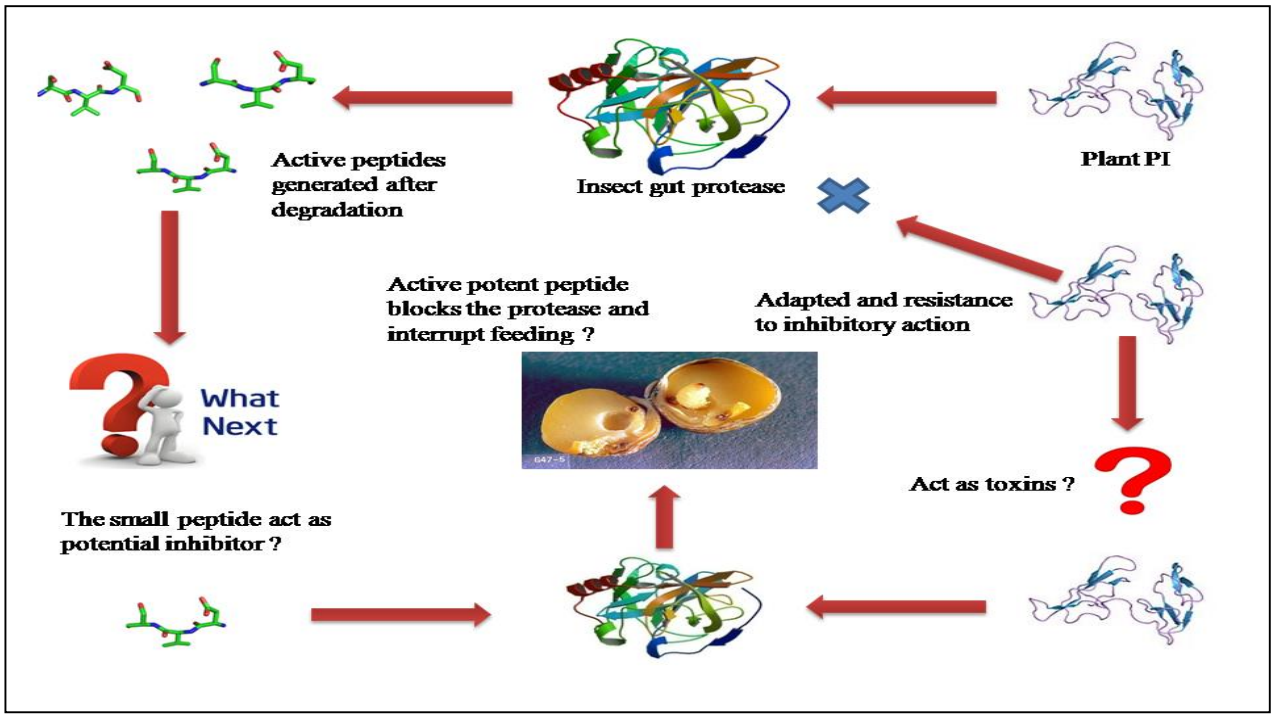

Figure 1: The adaptive/proteolytic action of insect gut proteases on the plant PIs?

3. COMPUTATIONAL APPROACH HELP TO INVESTIGATES THIS STUDY

Protein-protein interactions are involved in most biological processes and are important targets for drug design. Over the past decade, there has been increased interest in the design of small molecules that mimic functional epitopes of protein inhibitors. The amalgamation of computational and experimental approach has been of great value in the identification and development of novel promising results. In silico prediction of functional regions on protein surfaces, i.e. sites of interaction with DNA, ligands, substrates and other proteins, is of utmost importance in various applications in the emerging fields of proteomics and structural genomics [27]. Detection of the amino acid positions that are essential for activities, such as catalysis, protein-protein interactions or protein–ligands interactions, is a critical step in the study of the biological function of proteins [28]. Determination of protein structure by the experimental method has often limitations. For that need, computational approach such as molecular docking plays a vital role [29]. Protein-protein interaction has considerable attention in drug discovery [30-32]. In silico prediction of insect gut protease and PIs interactions could provide significant information for identification and development of novel promising PI candidate for the transgenic approach. This will also minimize the cost and period of in vitro screening of PIs. Table 1 represents some useful databases which utilized for protein-protein interaction studies.

Table 1: Protein-Protein interaction database

Sr No	Name	Link	Reference
1	BIND	http://www.bindingdb.org/bind/index.jsp	[33]
2	MINT	http://mint.bio.uniroma2.it/mint/Welcome.do	[34]
3	Prolinks	http://prl.mbi.ucla.edu/prlbeta/	[35]
4	InterDom	http://interdom.i2r.a-star.edu.sg/	[36]
5	iPfam	http://www.ipfam.org/	[37]
6	ProtCom	http://www.ces.clemson.edu/compbio/protcom	[38]
7	STRING	http://string-db.org/	[39]
8	HPRD	http://www.hprd.org/	[40]
9	BioGRID	http://thebiogrid.org/	[41]
10	SCOPPI	http://scoppi.biotec.tu-dresden.de/scoppi/	[42]

4. MOLECULAR DOCKING

Molecular docking is a significant technique in structural biology and computer-aided drug discovery (CADD). It attempts to find the best matching between the two molecules. The main docking aspect is to predict primary binding fashion of ligand with the known functional cavity of the receptor molecule. Prediction of the binding conformation of ligands to the suitable target binding site makes docking often use method [43]. The identification of potential compounds which interacting with wide drug targets is helpful in the treatment of abnormalities. An inhibitor molecule is one which can bind to the catalytic site of the enzyme. The inhibitor may be developed as libraries (collection) of many potential molecules (short fragments) or individual ligands. Natural compound libraries are most widely used for screening with target catalytic site. Virtual screening is a docking approach used to computationally screen large libraries of chemical compounds/inhibitors of enzymes [44-46]. Various small polypeptides (fragment released by proteolytic digestion of parent proteins) facilitate the development of drugs by inhibiting certain enzymes expressed in diseased condition and preliminary virtual screen by docking approaches. Protein fragmentation and domain swapping are valuable methods for the study of inter and intradomain and subdomain interactions in proteins. Individual protein domain also may have evolved in the same manner, by assembly and exchange of small gene segments [47]. The potent lead/inhibitor compound with high molecular weight results in reducing stability [48]. To come upon this problem, the fragment-based approach was proposed [49-52]. The fragmentation of lead/inhibitor compound into small pieces has been used to simplify the computational analysis of ligand high-affinity binding [53,54]. Proper optimization of every unique interaction in the catalytic site should produce a compound with sum

of the individual interaction [55]. Several peptides from proteins and PIs are released in the insect gut while feeding. The libraries of these peptides can be generated in vitro and could be a screen for healthy inhibitory interactions with insect gut proteases. Table 2 provides Tools and software for docking and interaction study.

Table 2: Tools and software for docking and interaction study

Sr. No	Docking Program	Website	Type
1	Autodock	http://autodock.scripps.edu/	Software
2	Autodock Vina	http://vina.scripps.edu/	Software
3	DOCK	http://dock.compbio.ucsf.edu/	Software
4	GOLD	https://www.ccdc.cam.ac.uk/solutions/csd-discovery/components/gold/	Software
5	GLIDE	https://www.schrodinger.com/glide	Software
6	FRED	https://www.eyesopen.com/oedocking	Software
7	FlexiDock	http://www.tripos.com/software/fdock.html	Software
8	ICM	http://www.molsoft.com/docking.html	Software
9	HomDock	http://www.chil2.de/HomDock.html	Software
10	SCIGRESS	http://www.fqs.pl/chemistry_materials_life_science/products/scigress	Software
11	MOE	https://www.chemcomp.com/MOE-Molecular_Operating_Environment.htm	Software
12	MS-Dock	https://www.microsoft.com/surface/en-in/support/hardware-and-drivers/docking-station-surface-dock	Software
13	ADAM	http://www.immd.co.jp/en/product_2.html	Software
14	GEMDOCK	http://gemdock.life.nctu.edu.tw/dock/igemdock.php	Software
15	Fleksy	http://www.cmbi.ru.nl/software/fleksy/index.spy?site=fleksy&action=Quick%20Start%20Guide	Software
16	ParaDockS	https://github.com/cbaldauf/paradocks	Software
17	Molegro Virtual Docker	http://molegro-virtual-docker.software.informer.com/5.5/	Software
18	HYBRID	https://docs.eyesopen.com/oedocking/hybrid.html	Software
19	POSIT	https://www.eyesopen.com/oedocking	Software
20	Rosetta Ligand	https://www.rosettacommons.org/manuals/rosetta3_user_guide/app_ligand_docking.html	Software

21	Surflex-Dock	http://www.jainlab.org/downloads.html	Software
22	Lead Finder	http://www.biomoltech.com/	Software
23	GriDock	http://nova.disfarm.unimi.it/manual/pages/tu_gridock.htm	Software
24	PLANTS	http://www.uni-tuebingen.de/fakultaeten/mathematisch-naturwissenschaftliche-fakultaet/fachbereiche/pharmazie-und-biochemie/pharmazie/pharmazeutische-chemie/pd-dr-t-exner/research/plants.html	Software
25	HADDOCK	http://www.nmr.chem.uu.nl/haddock/	Software
26	SwissDock	http://www.swissdock.ch/	Web-based
27	Blaster	http://blaster.docking.org/	Web-based
28	Pardock	http://www.scfbio-iitd.res.in/dock/pardock.jsp	Web-based
29	PatchDock	https://bioinfo3d.cs.tau.ac.il/PatchDock/	Web-based
30	iScreen	http://iscreen.cmu.edu.tw/	Web-based
31	Score	http://www.vls3d.com/links/bioinformatics/protein-protein-interaction/protein-protein-docking	Web-based
32	kinDOCK	http://abcis.cbs.cnrs.fr/kindock/	Web-based
33	BioDrugScreen	http://www.biodrugscreen.org/	Web-based

5. A POSSIBLE MECHANISM OF VIRTUAL SCREENING OF FRAGMENT LIBRARY

Figure 2 depicts a possible mechanism of virtual screening of fragment library. An inhibitor molecule is one which has the ability to bind to the catalytic site of the enzyme. The inhibitor may be developed as libraries (collection) of many potential molecules (short fragments) or individual ligands. Natural compound libraries are most widely used for screening with target catalytic site. Virtual screening is a docking approach used to computationally screen large libraries of chemical compounds (inhibitors). The expensive high-performance computation platforms have changed the way to performing virtual screening which gives detailed and relevant biological data.

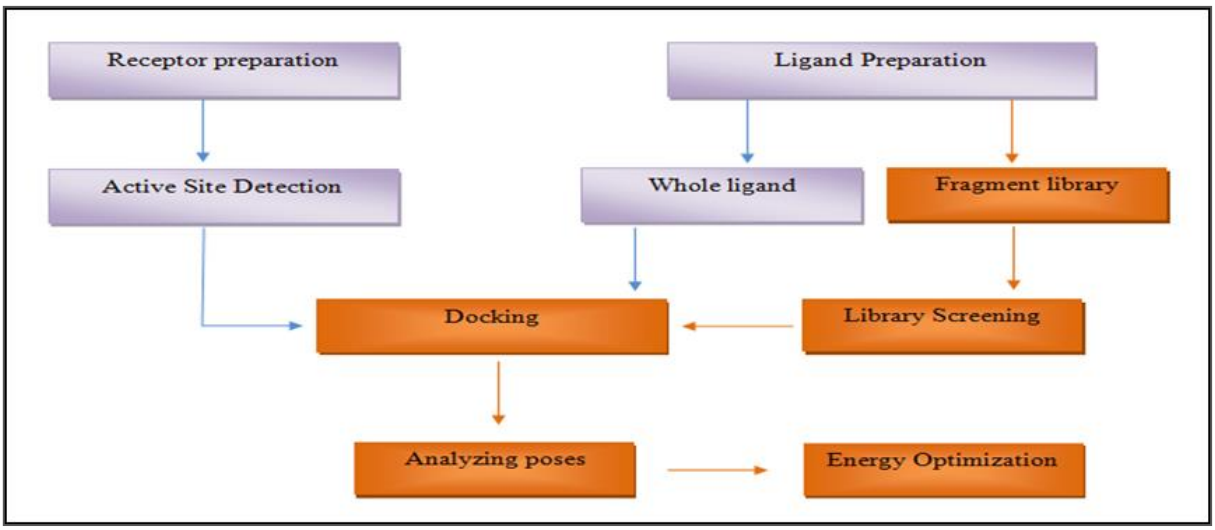

Figure 2: Possible mechanism of virtual screening of fragment library

6. MOLECULAR DYNAMICS

The molecular mechanics or molecular dynamics allow prediction of equilibrium geometries and energies between different molecules. Molecular mechanics results in the geometry of the motionless molecule. Dynamics studies often important to understand the protein folding and unfolding [56]. Misfolding will lead to malfunctioning such as causing disease, interruptions in signal transduction and genetically changes in evolution time [57-60]. Its more often need to study how the movements affect the function of the protein and how their dynamics are related to the 3D folding. Molecular dynamics gives details change in individual particle motion respect with time [61]. Computational evolution provides significant developments in molecular dynamics studies. Protein-protein interaction refers to a physical binding between two or more proteins. Such a physical interaction can be categorized based on the composition of the complex, the function of the complex versus that of a monomer, the binding affinity of subunits in the complex, the duration of the complex formation, or interactions between specific functional groups. Protein-protein interactions in plant-arthropod interactions can be studied by above mentioned computational approaches to design competent strategies against insect pests.

7. CONCLUSION

Advances in computational biology tools led to the foundation to in silico study of protein-protein interactions prior to in vitro screening of target molecules. These approaches could be implemented to design lead/inhibitor molecule against digestive proteases of insect pests to design capable strategies against insect pests.

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CONFLICT OF INTEREST

All authors declare that there is no conflict interest.

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