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CADD: An Emerging Approach in Plant Pathology Drug Discovery

Loitongbam Ashakiran Devi
Ph.D. Molecular Biology and Biotechnology, IARI, NIPB, New Delhi-110012, India

SUMMARY

According to the UN, the world population would hit 9 billion by 2050. Therefore, the main problem would be hunger. Many factors contribute to a decrease in yield. Amongst which the yield loses caused by disease alone is as high as 50%. Growers rely heavily on pesticides and other agrochemicals, even though breeders put greater efforts into the development and deployment of crop plants that are resistant to plant pathogen. To make agrochemicals more effective, molecular biologists are making efforts to find the target for the discovery of target-specific agrochemicals. Now, it is the time for agriculture to shift from traditional drug discovery method to burgeoning method such as computer-aided drug discovery/design (CADD) which are used exclusively in the pharmaceutical industry. With the available exhaustive information on genomics and three-dimensional structures of biological molecules along with advancement in computational and informational technologies, it opens up myriad possibilities for the application of CADD agrochemicals development.

INTRODUCTION

Millions of years ago, human existed on earth as foragers or hunter, gathering wild plants and hunting animals, for about 84000 generations. Later on, sapiens learn the art and science of agriculture. Thus, the end of nomadic life marks the beginning of the agricultural revolution (Bhargava, 2019). But one thing never changes that is human and agriculture share inseparable bonds. By 2050, the world population will hit as high as 9.7 billion (according to the UN) and the main problem will be limited land resources and increasing demand for food. Many factors contribute to the decrease in yield. Of which diseases are also one of the major contributing factors. The yield loses caused by disease alone is as high as 50%. Although efforts have been put into the development and deployment of crop plants that are resistant to plant pathogen, growers rely heavily on pesticides and other agrochemicals (Chandler et al., 2011). Therefore, one of the possible alternatives is to identify the target and discovering the agrochemicals for the targets to cut down the harmful effect caused by the chemicals. One such technology is CADD.

Computer Aided Drug Designing

ADD is defined as the design/discovery of molecules that have a strong binding affinity to biomolecular target in a computer-modelling dependent way. There are two major types of CADD: structure-based drug design (SBDD) and ligand-based drug design (LBDD). In SBDD, availability of 3D structure of the target sequence and its biological function(s) is important. Depending upon the structure of the target protein, SBDD allows design of candidate drugs that are predicted to bind to the target with high affinity and selectivity. (Fig 1).

Homology Modelling

If the 3D structure information of the target is unavailable, then the models are generated based on primary sequence of similar homologous proteins whose 3D structure is available.

Docking:

The stable adducts of the interacting molecules involved are identified based on the binding properties of target molecules and ligand or receptor protein. Based on scoring functions and total energy of the system, 3D conformation structure of complex is detected and are ranked (Dar & Mir., 2017). Models generated are visualized using visualization tools like PyMol.

High throughput screening (HTS):

Compounds exhibiting desirable characteristics are identified as hits and leads are generated.Structure base Virtual screening: Leads are selected by employing computational method that compares 3D structures of ligands with the putative active site of the target.

LBDD:

When 3D structure of target protein or its homolog is not available for SBDD approach, LBDD is generally used. Here, targets are identified or screened based on ligand or pharmacophore.

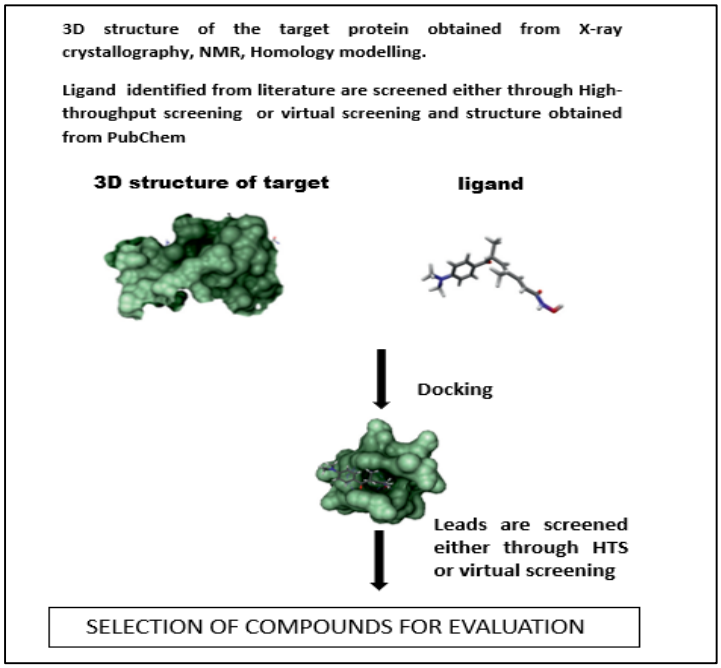

Fig 1: SBDD workflow

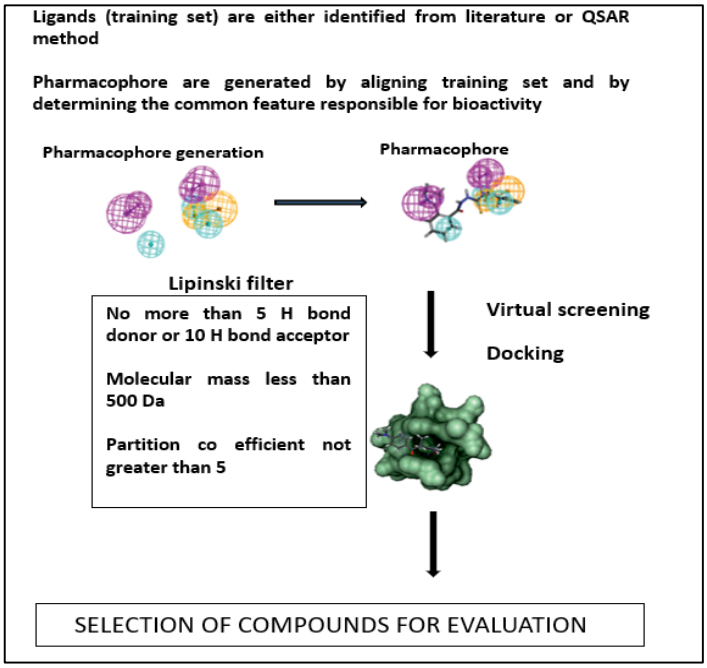

Fig 2: LBDD work flow

Pharmacophore Modelling:

Pharmacophore is an abstract representation of set of ligands (training set) by identifying common feature responsible for binding to target receptor and hence biological activity (Shanmugam & Jeon.,2017, Geppert et al., 2010). It can also be generated by QSAR (Quantitative structure-activity relationship) method, which gives information about relationship between chemical structure and biological activity based on mathematical relationship (Abdulfatai *et al*., 2017).

Ligand base virtual screening:

Candidate ligands are selected depending on the likeliness to bind to target by comparing to pharmacophore model. This process is later followed by docking.

* Fig 1 and 2, table 1 adopted from Shanmugam & Jeon., 2017)

Few examples of drug identified by CADD.

Drug target	Target pathogen	Function	Reference
Type III secretion system	Pathogenicity	*P. syr, R. sol, X. axo*	Mansfield *et al*., 2012 Jovanovic *et al*., 2011 Boucher *et al*., 1985
Mur Enzymes	Peptidoglycan synthesis	Bacterial pathogens	El Zoeiby *et al*., 2003
Ergosterol biosynthesis pathway	Generation of a major constituent of the plasma membrane	Fungal pathogens	Siegel, 1981
Dihydrofolate reductase	Nucleotide precursor biosynthesis	*P.* spp., *U*, spp., *P.* spp.	Jain *et al*., 2017

Threonyl-tRNA synthetases	Protein translation and cell viability	*P. sojae*	Gao *et al*., 2012
Lanosterol 14α-demethylase	Steroid biosynthesis	Fungal pathogens	Sagatova *et al*., 2015
Rpf gene products	Regulate pathogenicity factors	*X. o, X. camp, X. axo*	Mole *et al.*, 2007 Boch and Bonas, 2010 Mansfield *et al*., 2012
MAPK signalling and calcium signalling pathways	Invasive hyphal growth, Morpho-genesis, Biogenesis of the cell wall, Dimorphism, and the stress response	*M. gri, B. cin, F. o, B. gra. C.* spp., *U. may, M. lini*	Dean *et al*., 2012 Takano *et al*., 2000
Pectate lyase	Cell wall degrading enzymes	Bacterial and fungal pathogens	Herron *et al*., 2000
Asparagine synthase (Asn1p)	Pathogenecity	*M. gri. B. cin, F. gram, C.* spp., *U. may*	Ramakrishnan *et al*., 2016 Dunn *et al*., 2009

Xanthomonas axonopodis = X. axo, Ralstonia solanacearum= R. sol, Pseudomonas syringae = P. syr, Leptosphaeria maculans = L. ma, Magnaporthe grisea= M. gri, Stagonospora nodorum = S. nod, Colletotrichum lagenarium= C. lag, Rhodococcus fascians = R. fas, P. spp= Phytophthora spp., Ustilago spp= U. spp., Puccinia spp. = P. spp. Xanthomonas campestris= X. camp, Phytophthora sojae= P. sojae, Xanthomonas oyzae = X. o, Magnaporthe grisea =M. gre, Botrytis cinerea = B. cin, Fusarium oxysporum = F. o, Blumeria graminis = B. gra, Colletotrichum spp.= C. spp., Ustilago maydis= U. may, Melampsora lini= M. lini, Fusarium graminearum= F. gram

Conclusions:

In this narrative article, I have mentioned the concepts of CADD, listed out the process to identify the possible target proteins based on pharmacophore and lead based on target molecules information for developing agrochemicals. Assuming the pace, at which the pathogenicity factor is being identified, it is better to harness the possibilities that CADD could do to develop more target specific agrochemicals in management of disease. From these perspectives, I strongly urge researchers to adopt these robust technologies to combat important crop diseases.

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