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Virtual Screening of Phytocompounds from Andrographis Paniculata as Antivenom for Bungarus caeruleus

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Abstract:

Every year innumerable mortalities were reported in India due to snake bites. Traditional medicinal plants from local region of India were applied as an antidote for snake bites by tribes. Medicinal plants can be used as alternative treatment for antiserum therapy. Venoms constitute a rich source of phospholipase A2 (1DPY) enzymes, which show remarkable diversity in their structure and function. The antivenom activity of *Andrographis paniculata* which were computationally evaluated against PLA2 of *Bungarus caeruleus* (common krait). In this investigation, an In-silico drug designing studies for antivenom potentials against PLA2 was carried out by computational screening of *Andrographis paniculata* compounds with PLA2 molecule using Autodock 4.0 program.

Keywords **— Antivenom, Phospholipase A2, Andrographis paniculata, Bungarus caeruleus, Computational Screening, Autodock 4.0**

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I. INTRODUCTION

In India, on an average of 2,50,000 envenomation cases are recorded every year. India is richest source for existence of venomous species of frogs, insects and snakes. Among these majority of the bites and mortality are attributed to snake species like *Ophiophagus hannah* (King cobra), *Naja naja* (Spectacled cobra), *Daboia russelli*(viper), *Bungarus caeruleus* (Common krait), *Echis carinatus* (Saw scaled viper) etc [1]. Among them most reports are on haemolytic venomous snakes. These snake haemolytic venoms comprise of PLA2 enzymes. Snake venom phospholipase A2 (svPLA2) can cause numerous physiological effects such as cardiotoxicity, platelet aggregation inhibition, edema, hemolysis, myotoxicity, pre or postsynaptic neurotoxicity, hypotension, convulsion, and anticoagulation [2-6].

Antiserum, the only remedy for envenomation, may be associated with various reactions such as early anaphylactoid reaction, pyrogenic and late serum sickness, and several other manifestations [7]. In several cases death of victim occur due to wrong choice of antiserum because of misidentified snake species by physicians which results in severe life-threatening envenoming to casualty [8]. Antiserum development in animal is time consuming, expensive, It is associated with various side effects like pyrogen reactions [9].

An alternative treatment that involves application of different venom inhibitor, synthetic or natural agents. The neutralizing activity of plant extracts against snake venom has long been acknowledged, but scientist paid attention to these medicinal plants only past 20 years [10]. Many Indian medicinal plants have been recommended by the traditional physicians for the treatment of snakebite [11]. Several plants are scientifically studied for snake

bites; *Andrographis paniculata* leaf extracts inhibit snake venom and could be used for curative purposes for snake bite envenomations [12]. Computational screening of antivenom compounds was carried out by docking in elucidated active pocket by molecular docking approach to shortlist potent compounds that can act as an effective inhibitor against PLA2 enzyme.

II. MATERIALS AND METHODS

A. Collection of PLA2 Crystal Structures

The crystal structure determination of a basic PLA2 from common krait (*Bungarus caeruleus*) (PDB: 1DPY) obtained from the RCSB Protein Data Bank (PDB) was used in computational study.

B. Collection of phytocompounds

3D coordinate's file of phytocompounds of *Andrographis paniculata* was retrieved from NCBI database. The 3D coordinate file compatible for Autodock 4.0 was generated. The 3D coordinate files of compounds were used for computational screening.

C. Docking program

Auto Dock calculations were performed in several steps: 1) preparation of coordinate files using Auto Dock Tools, 2) precalculation of atomic affinities using Auto Grid, 3) docking of ligands using Auto Dock and 4) analysis of results using Auto Dock Tools. The primary method for conformations searching is a Lamarckian Genetic Algorithm [13] and Auto Dock is shown to be an effective tool capable of quickly and accurately predicting binding conformations and binding energies of ligands with macromolecular targets [14, 15]. Docking is performed for protein and ligand molecules using one of several search methods. The most efficient method is Lamarckian genetic algorithm (LGA), but traditional genetic algorithms and simulated annealing are also available. For various systems, AutoDock is repeated several times to produce various docked conformations and analysis of binding energy and consistency of results are combined to recognize best solution.

III. RESULTS AND DISCUSSIONS

Several phytochemicals of Andrographis paniculata was selected.
(14–Deoxy–11–dehydroandrographolide, 14-Deoxy-11-oxoandrographolide, Andrographolide, Neoandrographolide, Paniculide-A, Paniculide-B, and Paniculide-C) were analysed for inhibition activity against PLA2 of Bungarus caeruleus. Molecular docking studies of PLA2 with selected compounds were performed by AutoDock4.2. In the docking studies, if a compound shows lesser binding energy, it proves that the compound has higher activity. The interaction of compounds with the amino acid residues of PLA2 was observed (table-1 & figure-1).

The results revealed that Neoandrographolide exhibited a lowest binding energy value of -9.37 kcal/mol. All other compounds showed binding energy values ranging between -7.56 to -8.89 kcal/mol.

TABLE I
TABLE-1. AMINO ACIDS RESIDUES INVOLVED IN HYDROGEN BOND INTERACTION WITH PHYTOCOMPOUNDS OF *ANDROGRAPHIS PANICULATA*

Compounds	Amino acids interactions	H-bonds	Binding energy
14–Deoxy–11–dehydroandrographolide	GLY32, GLY30, VAL23, HIS48, TRP19	5	-8.89
14-Deoxy-11-oxoandrographolide	ASP49	2	-8.53
Andrographolide	GLY32, GLY30	2	-8.89
Neoandrographolide	ASP49	2	-9.37
Paniculide-A	TRP19, VAL23	2	-7.35
Paniculide-B	ASP49	1	-7.19
Paniculide-C	ASP49	1	-7.56

14–Deoxy–11–dehydroandrographolide with binding score of -8.89 revealed five hydrogen bond interaction with amino acid residues of PLA2 protein.

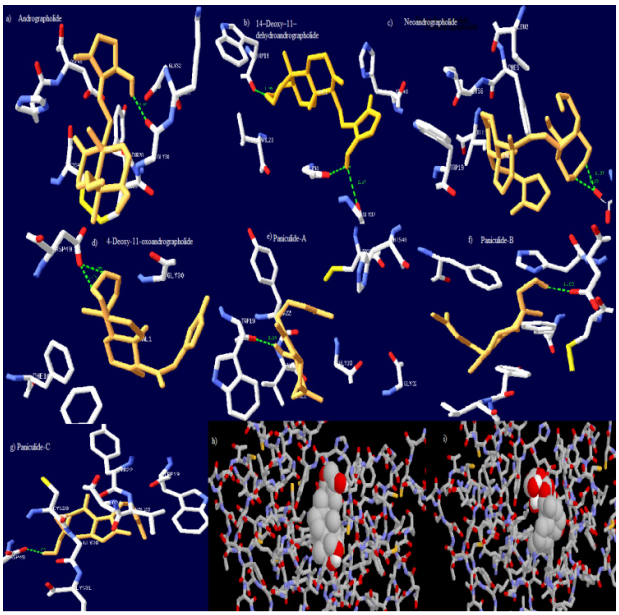

Figure-1: Summary of Docked Pose of the Compounds identified from Andrographis paniculata .

IV. CONCLUSIONS

The present work was an attempt to computationally identify compounds which can bind to the crucial sites of PLA2 protein. The docking scores and analysis of the interactions of the compounds suggest that Neoandrographolide and 14–Deoxy–11–dehydroandrographolide have the ability to bind to active site that involved in inhibition of PLA2 of Bungarus caeruleus. Insilico analysis has advantage over the Clinical trials, which take short time to reveal their efficacy as a drug. The selected phytoconstituents of Andrographis paniculata revealed good enzyme inhibition activities against PLA2 protein. This could be further studied for its anti-venom potential by pharmacological and in vivo studies.

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