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Research Article

An In Silico Study of Binding of Herbal Compounds to Cnidarian Phospholipase A2 Toxin in Alleviating TRPV1 Triggered Pain Sensation in Human

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ABSTRACT:

Cnidarian Condylactis gigantea releases Phospholipase A2 (PLA2) type toxin that hydrolyzes phospholipid releasing arachidonic acid. This arachidonic acid is modified into inflammatory mediators such as prostaglandin and bradykinin which activate TRPV1 channel of a human victim that trigger pain sensation. To alleviate such pain in full condition, this work aim towards in silico screening of drugs for effective binding to the catalytic site of PLA2 thus inhibiting it from generation of arachidonic acid. Consequently ten herbal compounds including aristolochic acid and Betulinic acid were selected. Molecular docking of these herbal compounds with PLA2 was carried out through Molecular Docking Server. It is observed that best binding occurred between PLA2 and Betulinic acid, whereas least binding is found in catechol-PLA2 as reflected through various scoring functions and binding parameters. Ligplot^{+} server revealed residue Histidine 46, Aspartic acid 47 and Tyrosine 67 present in catalytic site of PLA2 helped in binding of drug. Thus from the above result it is convincing to state that bioactive compounds bind with PLA2 and inhibit them competitively occupying the catalytic site of the PLA2 toxin. As a result PLA2 was not able to generate arachidonic acid through nucleophilic attack on sn-2 acyl bond of phospholipid. Hence absence of arachidonic acid, inflammatory mediators such as prostaglandin and bradykinin were not generated and thus there was no stimulation of TRPV1. Hence, there is no pain sensation due to sting from cnidarian Condylactis gigantea. As Betulinic acid get directly inserted into the active site and calcium binding site of PLA2 with lowest energy value, so it is proved that Betulinic acid is most potent inhibitor against PLA2 toxin.

Keywords: Cnidarian, Phospholipase A2 toxin, bioactive compounds, *in silico*, TRPV1 channel, betulinic acid,

[1] INTRODUCTION:

Codylactis gigantea belongs to Phylum Cnidaria. It releases phospholipase A2 (PLA2) type toxin which exerts a variety of relevant toxic action such as vascular inflammation correlating with coronary disease and coronary syndrome [1] and

possibly leading to acute respiratory distress syndrome and progression of tonsillitis [2].

PLA2 toxin catalyses the hydrolysis of glycerophospholipid through nucleophilic attack on sn-2 acyl bond of phospholipid and release fatty acid such arachidonic acid [3]. Upon downstream modification of cycloxygenase and lipoxygenase, arachidonic acid is modified into active compounds called Eicosanoids. Eicosanoids include prostaglandins and bradykinin which are inflammatory mediators and activate Human TRPV1 (Transient receptor potential Vanilloid) channel that trigger pain sensation [4].

Treatment of sea anemone bite is still carried out using traditional anti-venom therapy such as capsazepine which is used for relieving pain. Capsazepine blocks the painful sensation of heat caused by capsaicin (the active ingredient of chilli pepper) which activates the TRPV1 ion channel [5].

As capsazepine is a synthetic analogue of capsaicin [6], it may cause some side effects. Given the limitation of traditional therapy, research focusing on the interaction between PLA2 of *Codylactis gigantea* and some natural bioactive compounds (derived from plant extract) could allow the development of alternative treatments for the toxic and pharmacological effects of sea anemone bite. To develop alternative treatment against sea anemone bite, ten bioactive compounds were selected as drugs. These ten bioactive compounds were extracted from plants and had been used previously as drugs against PLA2 toxin of snake venom [7].

In this study, we have used Molecular docking server (*in silico* tool) to study the binding orientations and predict binding affinities of these phenolic compounds. Now a day *in silico* methods for drug designing have come into play, which helps in the identification of drug targets using various bioinformatics drug designing tools [8]. Such studies have been carried out to understand the interaction between phenolic compounds and active site of PLA2 receptor molecule. In our present study we have selected ten bioactive phenolic compounds which are distributed in the different plant extracts such as flavonoids, tritarpenoid and phenolic acids which can bind to the active site of PLA2 was studied by molecular docking.

The primary screening of structure based drug design may be helpful to develop an effective antioxidant based anti-inflammatory drugs.

[II] MATERIALS AND METHODS:

2.1. Protein sequence retrieval and 3D structure prediction

Protein sequence of PLA2 toxin was retrieved from uniprot [9] and homology modeling of PLA2 toxin was performed by swissmodel server [10] for 3D structure prediction.

2.2. Validation of 3D structure prediction

Validation of 3D structure of PLA2 toxin was performed by ANOLEA [11], PROSA-II [12] and Verify 3D [13] servers.

2.3. Active site prediction server

Active site of PLA2 toxin was predicted through Active site prediction server [14].

2.4. Ligand retrieval and ligand optimization server

Ten bioactive compounds were retrieved from Pubchem chemistry database [15] and Dundee PRODRG 2 server [16] was used for ligand optimization.

2.5. Prediction of physicochemical parameter of ligands

It was done by Molinspiration Chemiinformatics server [17].

2.6. Docking prediction server

Docking of bioactive compounds and PLA2 toxin was performed by Molecular docking server [18].

2.7. Amino acid interaction prediction server

Amino acid interaction of ten docked models between bioactive compounds and PLA2 toxin was known by Ligplot+ server [19].

[III] RESULTS:

PLA2 toxin of *Condylactis gigantea* causes pain and paralysis of human. PLA2 toxin of *Condylactis gigantea* is 119 amino acids long (Table 1). As no model of this toxin was found in the protein data bank, thus homology modeling was performed for this toxin to obtain its molecular model (Figure 1).

Name of toxin	Source	Length	Protein sequence
Phospholipase A2 toxin	*Condylactis gigantea*	119 aa	GVWQFAYMIAKYTGRNPLDYWGYGCWCGL GGKGNPVDAVDRCCYVHDVCYNSITQGPRP TCSRIAPYHKNYYFTGKKCSTGWLTSKCGRA ICACDIAAVKCFRRNHFNKKYRLYKKNIC

Table 1 depicts short description about Phospholipase A2 toxin of *Condylactis gigantea* such as source, length and protein sequence of this toxin.

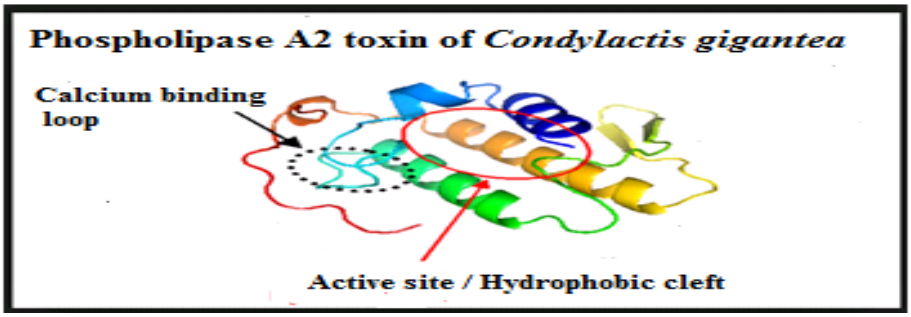

Figure 1 represents tertiary structure of Phospholipase A2 toxin of *Condylactis gigantea*. This structure shows calcium binding loop and active site of this toxin through which the corresponding receptor binds to it.

Name of Toxins	Sources	Validation of 3D structure		
		ANOLEA	PROSA II	VERIFY 3D
		Z-SCORE	Z-SCORE	Percentage of residues had an averaged 3D-1D>=0.2
Phospholipase A2	*Condylactis gigantea*	5.14	-3.95	76.27%

Table 2 represents validation report of 3D modeled structure of PLA2 toxin. Validations of 3D modeled structure of PLA2 toxin was done by three servers viz. ANOLEA, PROSA II and VERIFY 3D.

Amino acids that are present in the active site of PLA2 toxin and also participate in drug binding are depicted in Table 3.

Name and position of amino acids in the active sites of PLA2 toxin
Val2,Phe5, Ala6, Ile9, Asn16, Tyr20, Trp21, Cys27, His46, Asp47, Tyr50, Tyr67

Table 3 depicts amino acids that are present in active sites of PLA2 toxin through which corresponding receptor binds to it.

Serial no.	Name of Bioactive compounds	Chemical nature	Origin
1	Aristolochic acid	Alkaloid	*Aristolochia sp*
2	Betulinic acid	Tritarpenoid	*Betula alba*
3	Caffeic acid	Phenolic compound	*Eucalyptus globulus*
4	Catechol	Phenolic compound	*Acacia catechu*
5	Rosmarinic acid	Hydroxylated Phenolic compound	*Cordia verbenacea*
6	Primetin	Flavonoid	*Primula sp*
7	Naringenin	Flavonoid	Grapes, citrus fruit
8	Quercetin	Flavonoid	Fruit, vegetables, leaves, grain
9	Kaempferol	Flavonoid	*Aloe vera, Coccinia grandis, Cuscuta chinensis, Euphorbiapekinensis sp*
10	Galangin	Flavonoid	*Alpinia officinarum, Helichrysum aureonitens*

Table 4 exhibits description of bioactive compounds with inhibitory potential against PLA2 toxin. This table shows name of bioactive compounds, their chemical natures and origin.

Name of Bioactive compound	Hydrogen Acceptor	Hydrogen Donor	Log of partition coefficient (LogP)	Typological polar surface area (TPSA)	Molecular Weight (MW) (g/mol)	Rotable bonds (rb)	Volume	Inhibition capability
Aristolochic acid	8	1	3.67	110.83	341.27	3	271.84	0.10
Betulinic acid	3	2	7.04	57.53	456.71	2	472.04	0.55
Caffeic acid	4	3	0.94	77.75	180.16	2	154.50	-0.09
Rosmarinic acid	8	5	1.63	144.52	360.32	7	303.54	0.24
Catechol	2	2	0.99	40.46	110.11	0	100.08	-2.67
Primetin	2	0	2.97	70.67	254.24	1	216.03	0.22
Naringenin	3	0	2.12	86.99	272.26	1	230.26	0.21
Quercetin	7	5	1.68	131.35	302.24	1	240.08	0.28
Kaempferol	6	4	2.17	11.12	286.24	1	232.07	0.26
Galangin	3	0	2.65	90.89	270.24	1	224.05	0.28

Table 5 represents physicochemical properties of ten bioactive compounds. Physicochemical properties include no. of hydrogen acceptor, typological molar surface, molecular weight, volume, rotable capacity and inhibition capacity.

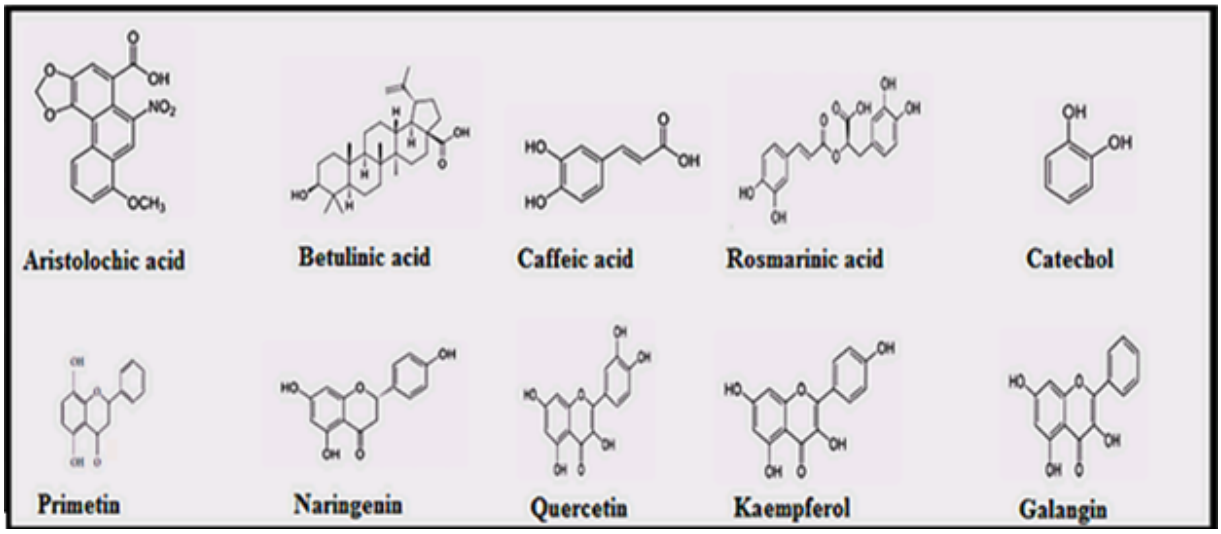

Figure 2 depicts chemical structure of ten bioactive compounds which inhibit potential lethality of PLA2 toxin.

Sl no.	Name of docked models	Estimated free energy of binding (Kcal/mol)	Vander Waals+H-bond+desolv-ation energy (Kcal/mol)	Electrostatic energy (Kcal/mol)	Total intermolecular energy (Kcal/mol)	Interacting surface
1	Aristolochic acid-PLA2	-7.48	-8.80	-0.02	-8.83	712.95
2	Betulinic acid-PLA2	-9.11	-10.49	-0.08	-10.56	969.985
3	Caffeic acid-PLA2	-5.09	-5.63	-0.04	-5.60	485.279
4	Rosmarinic acid-PLA2	-6.37	-8.45	-0.32	-8.76	832.756
5	Catechol-PLA2	-4.41	-4.50	-0.01	-4.55	297.906
6	Primetin-PLA2	-6.99	-6.86	-0.11	-6.75	648.571

7	Naringenin-PLA2	-6.12	-6.61	-0.04	-6.65	678.031
8	Quercetin-PLA2	-5.19	-6.88	-0.13	-7.02	683.425
9	Kaempferol-PLA2	-6.07	-6.63	-0.02	-6.62	693.512
10	Galangin-PLA2	-6.89	-7.24	-0.13	-7.11	666.474

Table 6 represents estimated predicted values of ten docked models between PLA2 toxin and ten bioactive compounds.

Sl. no.	Name of bioactive compounds	H-bonded contacts	Polar contacts	Hydrophobic contacts	Cation-pi contacts	Other contacts
1	Aristolochic acid-PLA2	----------	**$O1^{L}$-$His46^{R}$** $O6^{L}$-$Asn16^{R}$ $C13^{L}$-$Cys43^{R}$	----------	----------	$N1^{L}$-$Phe5^{R}$ **$O1^{L}$-$His46^{R}$** $O2^{L}$-$Cys27^{R}$ $O3^{L}$-$Val2^{R}$ $O4^{L}$-$Trp21^{R}$ $O5^{L}$-$Tyr20^{R}$ $O6^{L}$-$Ala6^{R}$ $O7^{L}$-$Ile9^{R}$ $C15^{L}$-$Tyr50^{R}$
2	Betulinic acid-PLA2	----------	**$O4^{L}$-$Asp47^{R}$** **$C24^{L}$-$Asp47^{R}$**	$C10^{L}$-$Tyr50^{R}$ $C14^{L}$-$Trp21^{R}$ **$C24^{L}$-$Tyr67^{R}$** $C28^{L}$-$Val2^{R}$ $C29^{L}$-$Phe5^{R}$	----------	$O3^{L}$-$Trp21^{R}$ **$C18^{L}$-$His46^{R}$** **$C27^{L}$-$Tyr67^{R}$** $C29^{L}$-$Tyr50^{R}$
3	Caffeic acid-PLA2	**$O1^{L}$-$Tyr67^{R}$** **$H1^{L}$-$Tyr67^{R}$**	**$O2^{L}$-$Tyr67^{R}$** **$O3^{L}$-$His46^{R}$** **$O4^{L}$-$Asp47^{R}$**	**$C7^{L}$-$His46^{R}$** **$C8^{L}$-$His46^{R}$**	----------	$O3^{L}$-$Cys43^{R}$ **$C1^{L}$-$His46^{R}$** **$C2^{L}$-$Asp47^{R}$** **$C3^{L}$-$Asp47^{R}$** **$C4^{L}$-$Tyr67^{R}$**
4	Rosmarinic acid-PLA2	----------	**$O2^{L}$-$His46^{R}$** $O4^{L}$-$Asn16^{R}$ **$O7^{L}$-$Asp47^{R}$** **$O8l^{L}$-$Tyr67^{R}$**	$C10^{L}$-$Phe5^{R}$ **$C12^{L}$-$His46^{R}$**	----------	$O1^{L}$-$Phe5^{R}$ $O2^{L}$-$Phe102^{R}$ $O3^{L}$-$Val2^{R}$ **$O8^{L}$-$Asp47^{R}$** **$C12^{L}$-$His46^{R}$**
5	Catechol-PLA2	----------	----------	C^{L}-$Met8^{R}$ C^{L}-$Ile96^{R}$ C^{L}-$Val99^{R}$	H^{L}-$Phe73^{R}$	H^{L}-$Lys11^{R}$ C^{L}-$Lys100^{R}$
6	Primetin-PLA2	----------	**$O4^{L}$-$Asp47^{R}$**	$C13^{L}$-$Ile9^{R}$	$H2^{L}$-$Trp21^{R}$	$O1^{L}$-$Trp21^{R}$ **$H1^{L}$-$Asp47^{R}$** **$C9^{L}$-$Tyr67^{R}$**
7	Naringenin-PLA2	**$O5^{L}$-$Tyr67^{R}$**	$O4^{L}$-$Asn16^{R}$ $H2^{L}$-$Asn16^{R}$ **$H3^{L}$-$Tyr67^{R}$**	$C7^{L}$-$Ile9^{R}$	$H1^{L}$-$Tyr20^{R}$ $H1^{L}$-$Phe102^{R}$	$O4^{L}$-$Val2^{R}$ $O4^{L}$-$Ala6^{R}$ **$C9^{L}$-$Asp47^{R}$**
8	Quercetin-PLA2	**$O4^{L}$-$His46^{R}$**	**$H2^{L}$-$His46^{R}$** **$O3^{L}$-$Asp47^{R}$** **$O2^{L}$-$Tyr67^{R}$**	$C11^{L}$-$Cys43^{R}$	**$H4^{L}$-$Tyr67^{R}$**	$O1^{L}$-$Trp21^{R}$ $O7^{L}$-$Tyr50^{R}$
9	Kaempferol-PLA2	**$O6^{L}$-$Tyr67^{R}$**	**$O6^{L}$-$Asp47^{R}$** **$H3^{L}$-$Tyr67^{R}$**	----------	$H1^{L}$-$Tyr20^{R}$ **$H3^{L}$-$Tyr67^{R}$**	$O2^{L}$-$Cys43^{R}$ $O3^{L}$-$Ile9^{R}$ $O4^{L}$-$Tyr20^{R}$ $O5^{L}$-$Pro17^{R}$ $C10^{L}$-$Asn16^{R}$ **$C11^{L}$-$Asp47^{R}$**
10	Galangin-PLA2	----------	**$O4^{L}$-$Asp47^{R}$** **$H2^{L}$-$Tyr67^{R}$**	$C14^{L}$-$Ile9^{R}$	**$H2^{L}$-$Tyr67^{R}$**	$C15^{L}$-$Asn16^{R}$ $O1^{L}$-$Trp21^{R}$ $O2^{L}$-$Cys43^{R}$ **$O3^{L}$-$Asp47^{R}$** **$O5^{L}$-$Tyr67^{R}$** $H2^{L}$-$Leu29^{R}$

Table 7 depicts amino acid interaction between PLA2 and bioactive compounds in docked molecules.

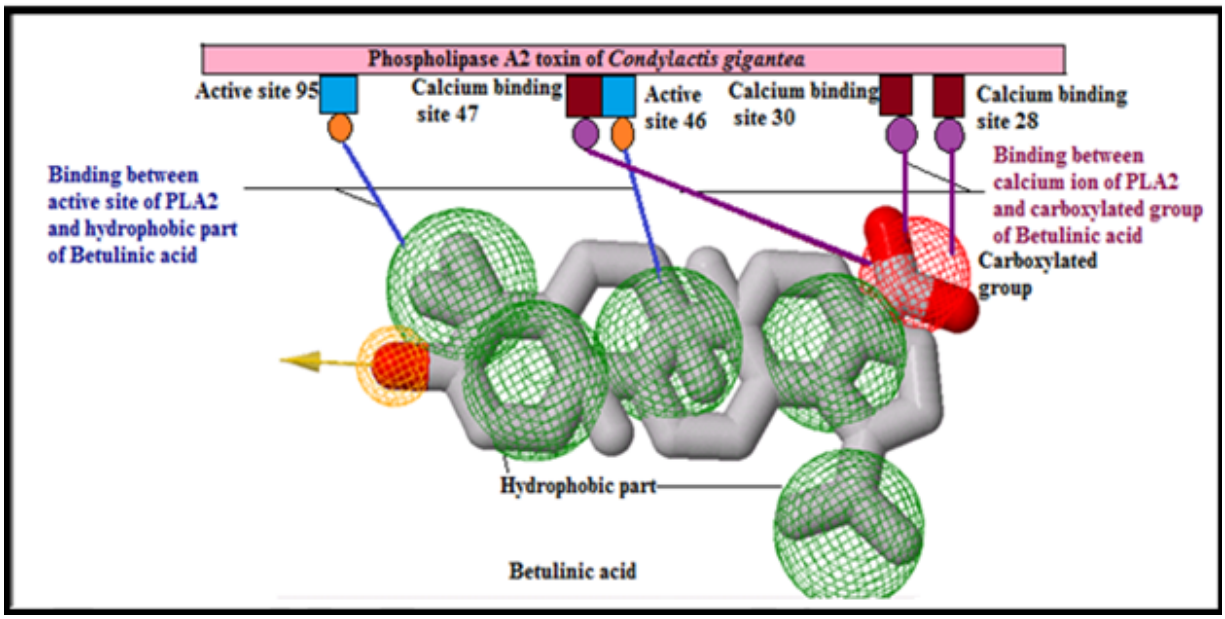

Figure 3 represents interacting model of Betulinic acid and PLA2 toxin showing main binding residues.

[IV] DISCUSSION:

Validation of 3D structure of PLA2 toxin was performed through Verify 3D, ANOLEA and PROSA II. Table 2, shows the Z-scores of these three servers. Z-score indicates overall model quality. PROSA II gave Z-score of -3.95 for PLA2 toxin which suggest its acceptable structure. Similarly using ANOLEA and Verify 3D of the structure of PLA2 toxin, was found to be confined within the acceptable range of energy calculation and atom packing. Thus, in the present study, results obtained with these tools confirmed the good quality of our modeled structure.

Ten bioactive compounds were selected for docking with PLA2 toxin due to their inhibition capability against snake PLA2 venom [7]. Bioactive compounds were retrieved from Pubchem chemistry database. The small molecule topology generator Dundee PRODRG 2 server was used for ligand optimization and generated molecular topologies. Table, and Figure 2, depicted ten molecular topologies of ten bioactive compounds. Aristolochic acid is alkaloid in nature whereas Betulinic acid is tritarpenoid. Phenolic bioactive compounds are Caffeic acid, Rosmarinic acid and Catechol. Flavonoids are Primetin, Naringenin, Quercetin, Kaempferol and Galangin.

In this present study to understand the formation of hydrogen bonded contacts and non bonded contacts between bioactive compounds and active site of PLA2 toxin, Molecular docking server was used. Table 6, represents estimated energy values of ten docked model. Ten docked models show negative values in all forces (Electrostatic force, Vander Waals force and solvent intermolecular force) that mediate docking. Negative values indicate a related binding between ligand and protein. Betulinic acid-PLA2 model has the lowest binding energy (-9.11Kcal/mol) than all other docked models. This docked model also shows lowest value in electrostatic energy (-0.08kcal/mol), VdW+H-bond+desolV energy (-10.49 Kcal/mol) and total inter molecular energy (-10.56 Kcal/mol) than other docked models. Interacting surface of this docked model is highest (969.985) among other. As interacting surface area increases binding capability also increases. This result proved that Betulinic acid has highest binding affinity with PLA2 toxin and is a potent inhibitor of PLA2 toxin secreted by *Condylactis*

gigantea (Figure 3).Similar type of work had been done in 2005 against snake PLA2 toxin. AM Soares *et. al.* performed *in silico* docking which indicated Betulinic acid as the best PLA2 inhibitor with a very low energy value [20]. Only Catechol-PLA2 docked model has highest binding energy (-4.41 Kcal/mol) than others. Interacting surface of this docked model is lowest (297.906). Electrostatic energy (-0.01 Kcalmol), VdW+H-bond+desolV energy (-4.50 Kcal/mol) and total inter molecular energy (-4.55 Kcal/mol) are also highest in case of Catechol-PLA2 docked model. This result proves that Catechol has lower binding affinity with PLA2 toxin. The other drugs such as Aristolochic acid, Galangin, Naringenin, Rosmarinic acid, Kaempferol and Primetin all show intermediate negative energy values thus reflecting good binding affinity with PLA2. The rest two drugs Quercetin and Caffeic acid show moderate binding capability with PLA2 toxin as evident from its negative energy values.

Table 5 represents physicochemical properties of ten bioactive compounds. Number of acceptor atoms for H-bonds is a measure of hydrogen bonding ability of a molecule expressed in terms of number of possible H-bond acceptors. Aristolochic acid and Rosmarinic acid have maximum number of Hydrogen acceptor i.e. 08. Catechol and Primetin have lowest number of Hydrogen acceptor (2). Number of donor atoms for H-bonds is a measure of hydrogen bonding ability of a molecule expressed in terms of number possible H-bond donors. Rosmarinic acid and Quercetin have maximum numbers i.e. 05 Hydrogen donors. Aristolochic acid has lowest number i.e. 01 Hydrogen donors. Galangin, Primetin and Naringenin have no ability to donate Hydrogen. Log of partition coefficient (LogP) is the logarithm of the ratio of concentrations of un-ionized compound between two solutions (Octanol and water). LogP is used in QSAR studies and rational drug design as a measure of molecular hydrophobicity [21]. Betulinic acid shows highest (7.04) molecular hydrophobicity among other ten bioactive compounds. Catechol (0.99) and Caffeic acid (0.94) show lowest molecular hydrophobicity. Typological polar surface area is defined as the surface sum over all polar atoms (usually oxygen and nitrogen), including also attached hydrogen. It is useful parameter for cell permeability [22]. Rosmarinic acid highest (144.52) TPSA and Catechol has lowest (40.46) TPSA among ten bioactive compounds. Drug compounds of molecular weight more than 100, which are primarily transported across the bio-membrane by passive diffusion. Here all ten bioactive compounds are good transporter. Number of rotable bonds is the number of bonds which allow free rotation around themselves. These are defined as any single bond, not a ring, bound to a non-terminal heavy atom (except C-N bond). This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [23]. Rosmarinic acid has highest number i.e. 07 rotable bonds and Quercetin, Kaempferol, Galangin, Naringenin and Primetin have lowest number i.e. 01 rotable bonds among ten bioactive compounds. Catechol has no rotable bonds. Betulinic acid has highest volume (472.04gm/mol) and Catechol has lowest volume (100.08 gm/mol) among ten bioactive compounds. Betulinic acid has maximum (0.55) inhibition capability and Catechol has minimum (-2.67) inhibition capability among ten bioactive compounds. Thus Betulinic acid is potentially best inhibitor amongst ten bioactive compounds.

The detection of active site of PLA2 toxin is often the starting point for protein function identification and drug discovery. The active site of PLA2 comprises of amino acid residues such as Val 2, Phe 5, Ala 6, Ile 9, Asn 16, Tyr 20, Trp 21, Cys 43, His 46, Asp 47, Tyr 50, Asn 51, Tyr 67, and Phe 102. The amino acid predicted through active site prediction server corroborates with the same amino acid residues in the PLA2 toxin that is found to be bind with different bioactive compounds as predicted through Ligplot^{+} server seen molecular docking server. The result of Ligplot^{+} contacts of PLA2 with different bioactive

compounds are exhibited in Table 7. As most of the amino acid residues in the active site are hydrophobic, so they are main contributors to the drug-protein binding interaction. The molecular docking studies of ten bioactive compounds into cnidarian PLA2 toxin revealed very clear preference for His 46, Asp 47 and Tyr 67 due to their maximum continuation in ten docked model. Beside this His 46, Asp 47 and Tyr 67 have lowest decomposed interacting energy i.e -2.159 Kcal/mol, -2.218 Kcal/mol and-2.084 Kcal/mol respectively. Any ligand which can bind to His 46, Asp 47 and Tyr 67 and prevent substrate from binding to active site can behave as an inhibitor of PLA2.These three key residues are positioned at the active site. Usually binding of substrate to PLA2 occurs through a well formed hydrophobic channel [24].

So blocking the hydrophobic channel is an effective way to inhibit PLA2 toxin. Bioactive compounds except Catechol in general bind with PLA2 toxin through His 46, Asp 47 and Tyr 67. This result reveals that bioactive compounds bind with PLA2 toxin competitively occupy the active site of PLA2 toxin. Aristolochic acid, Rosmarinic acid, Primetin and Galangin exert their inhibitory effect through hydrophobic interaction with PLA2 toxin. Caffeic acid can interact with PLA2 toxin via hydrophobic interaction and two hydrogen bonds. Naringenin, Quercetion and Kamepferol interact with PLA2 toxin through hydrophobic interaction and one hydrogen bond. Pharmacophore model of ten bioactive compounds was generated though Zinc Pharmer [25] that revealed Betulinic acid has carboxylate group that is important for inhibition of PLA2 toxin [7].

In silico study predicts that Betulinic acid is directly inserted into the active site and calcium binding site of PLA2 with lowest energy value [26, 27]. Figure 3, depicts interacting structure of Betulinic acid and PLA2 toxin. Here PLA2 toxin structure was drawn through modification of linear structure of PLA2 toxin retrieved from Protein data bank. Calcium binding sites (28, 20, 47 amino acids) of PLA2 toxin binds carboxylated group of Betulinic acid. Further, 46 and 95 amino acids in active site of PLA2 toxin interact with hydrophobic part of Betulinic acid. This type of work had been done by Muhammad *et al*. in 2014 for designing potential inhibitor of schizencephaly. They retrieved some inhibitors from Pubchem and showed maximum binding affinity with particular protein kinase inhibitor. They actually performed comparative docking study with docking energies and drug likeliness rules which illustrated that selected inhibitor protein kinases are potential inhibitor [28, 29].

[V] CONCLUSION:

Analysis of ligand-binding interaction with PLA2 receptor can be useful for identification of new preventive and therapeutic drug against PLA2 toxin of *Condylactis gigantea*. The result obtained from this study would be helpful in understanding the inhibitory mode of bioactive compounds and perfectly predicting their inhibition against PLA2 toxin on the basis of docking scores. These models also provide some favorable clues in designing of natural inhibitors for the treatment of inflammation due to PLA2 toxicity. Thus Betulinic acid is most potent inhibitor against PLA2 toxin and has good therapeutic value to treat PLA2 toxicity.

The plant derived bioactive compound such as Betulinic acid, binds with PLA2 toxin through active site residues such as His 46, Asp 47 and Tyr 67 and reveals that Betulinic acid is a potent inhibitor of cnidarian PLA2 toxin.

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