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Identification of Natural Compound Inhibitors against Peptide Deformylase Using Virtual Screening and Molecular Docking Techniques

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ABSTRACT
Leptospirosis is widespread and globally concern disease, currently recognised as globally re-emerging disease, caused by spirochete pathogen Leptospira interrogans. For prevention and treatment of disease new drug need to be developed. In the development and design of new drug, drug targets play an important role. One such drug target present in Leptospira interrogans is Peptide deformylase, which plays a critical role in the survival of Leptospira interrogans. Peptide deformylase, a metalloproteinase responsible for removal of formyl group from the N-terminal methionine residue of ribosome-synthesized polypeptides, cause the maturation of proteins in Eubacteria. This process is essential for bacterial survival because mature proteins do not retain N-formyl-methionine, and formylated peptides cannot utilize by the N-terminal peptidases as substrate. Therefore to hinder the survival and growth of bacteria, inhibition of Peptide Deformylase is essential which causes the prevention of protein maturation process, provides a target for developing antileptospiral therapeutic treatment without interfering with the eukaryotic metabolism process. For this purpose, in the present study plant derived identified anti-bacterial and anti-viral phytochemical agents were used to interact against receptor protein PDF to identify the optimum molecular space in the cavity of receptor protein. Based on the molecular space, binding energy and pharmacological interactions optimum leads were identified and reported. In future a parallel wet lab and dry lab study will support to identify the more refined interactions among the same.
KEYWORDS: *Leptospirosis, Peptide Deformylase, Binding energy.*

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INTRODUCTION

Leptospirosis is one of the most infectious bacterial disease that caused by spirochete pathogen of the genus Leptospira. [1] The Leptospirosis was first observed in 1907 as the causative agent for Weil's disease, by Stimson. [2] This is transmitted through infected animals, indirect contact by exposure to water or soil, contaminated with urine of the infected animal and mother to her unborn child. Symptoms are High fever, Headache, Chills, Muscle aches, Vomiting, Jaundice (yellow skin and eyes), Red eyes, Abdominal Pain, Diarrhea and Rash. [1]

Doxycycline at a dose of 5 mg/kg for 14 days, this therapy clears bacteria both from blood stream and kidneys. [3] Although some other antibiotics such as penicillin's, tetracyclines, chloramphenicol, and erythromycin have antileptospiral activity in vitro and in animal models, it remains controversial whether antimicrobials produce a beneficial effect in mild human leptospirosis since the illness has a variable natural history. Antibiotic therapy is given when the illness is severe enough recognized through diagnosis. [4]

In order to get the prevention and treatment for leptospirosis, new or improved drugs need to be developed, and for this advanced methods of drug discovery process is used. Therefore the drug discovery and development process shifted to computational approaches such as comparative genomics for the identification of novel drug targets, molecular docking and virtual screening.

In the development and design of new drug, drug targets play an important role. One such drug target present in *Leptospira interrogans* is Peptide deformylase, which plays a critical role in the survival of *Leptospira interrogans*. [5]

It is an essential bacterial metalloproteinase which is responsible for removal of formal group from the N-terminal methionine residue of ribosome-synthesized polypeptides the maturation of proteins in Eubacteria. This process is essential for bacterial survival because mature proteins do not retain N-formyl-methionine, and formylated peptides cannot utilize by the N-terminal peptidases as substrate. Therefore to hinder the survival and growth of bacteria, inhibition of PDF is essential which causes the prevention of protein maturation process, provides a target for developing antileptospiral therapeutic treatment without interfering with the eukaryotic metabolism process. [6]

There are many antibiotics have been developed for its prevention and treatment. Doxycycline is a very efficient antibiotic used, but this also does not totally prevent an infection. Patients show mild sickness, and can be infectious to others through their urine. Antibiotics as drugs may produce some side effects and also bacteria can become resistance to antibiotics. Because of all these reasons, necessitates the development of the fast growing regime of support. In the present study we are using plant derived antibacterial and antiviral agents, to narrow down the problem associated with the antibiotic drug. Which is bind to specific site on the peptide deformylase using computational docking tool i.e. iGEMDOCK [7], and their interaction with the receptor protein is further analyzed by using another docking tool i.e. AutoDock Vina. [8]

MATERIALS AND METHODS

Receptor protein:

The protein, Peptide deformylase was selected as a target based on prior research publication (Novel Conformational States of Peptide Deformylase from Pathogenic Bacterium *Leptospira interrogans*). The Crystal Structure of PDF from *Leptospira interrogans* (LiPDF) at pH 7.5 was obtained from RCSB Protein Data Bank (1SZZ) known to be a stable dimmer. [6] The crystallographic structure of ISZZ shows a significant interaction with Actinotin with the following amino acid residues: VAL (A) 47, GLN (A) 53, GLY (A) 100, LEU (A) 102, ASP (A) 146, HIS (A) 147 and GLU (A) 144 at 3.30 resolutions (Figure 1). [6]

Active Site:

The active sites were mapped using CastP server with probe radius of 1.4 A [9] and further validation of active site is done by I-Gem dock [7], Auto dock 4.2 [10] and Discovery studio Visualizer 4.1 [11] packages.

Selection of ligands:

In the present study we have considered 452 ligands included 308 anti bacterial and 144 anti viral phytochemical from Dr. Duke's Phytochemical and Ethnobotanical Databases. [12]. The chemical structures were sketched and optimized using ACD/Chemsketch [13] (Supplementary data 1 (Table 1 and 2)).

Molecular Docking:

Molecular interactions play a key role in all biological reactions. Drugs are either mimicking or mitigating the effect of natural ligands binding to the receptor by exerting the pharmacological reactions. Computational methods are used to understand this mode of binding of ligands to their receptors which is called as Molecular Docking. It is an attempt to find out the “best” binding between different a set of molecules: a receptor and a ligand. We have used two different tools for docking i.e. iGEMDOCK [7] and AutoDock Vina. [8] For the screening purpose in iGEMDOCK the default binding site of Actinonin is considered with default parameters in iGEMDOCK. Where as in Auto dock the crystal structure of peptide deformylase from *Leptospira interrogans* complexes with inhibitor Actinonin (code ID: 1SZZ, resolution 3.30) was retrieved from PDB and cleaned by removing the co-crystallized ligand and water molecules from it and protein was converted to pdbqt file format using Autodock Tools. In AutoDock Vina [8] following parameters were set to determine the binding site with center-x = 19.85; center-y = -2.84; center-z = 25.23; size-x = 40; size-y = 40; size-z = 40 and exhaustiveness = 4. Finally, the conformation for the best free energy of binding was selected for analyzing the interactions between the macromolecule and selected inhibitors.

RESULTS AND DISCUSSION

The active site calculated with 530.6 A area and 978 A of volume and consisted of following amino acid residues.

ALA (A) 44, GLU (A) 45, GLY (A) 46, VAL (A) 47, GLY (A) 48, GLN (A) 53, ARG (A) 70, TYR (A) 71, THR (A) 74, PHE (A) 97, TRP (A) 98, GLU (A) 99, GLY (A) 100, CYS (A) 101, LEU (A) 102, VAL (A) 104, PRO (A) 105, GLY (A) 106, MET (A) 107, ARG (A) 107, TYR (A) 136, ILE (A) 139, VAL (A) 140, HIS (A) 143, GLU (A) 144, ASN (A) 166 (Figure 2).

Docking of small molecule compounds into the binding site of a receptor and estimating the binding affinity of the complex is an important part of the structure based drug design process.

Results from molecular docking:

The ligand molecules with high structure diversity were obtained from Dr Duke phytochemical database. Out of the 308 anti bacterial and 144 antiviral phytochemical 16 and 06 showed a good binding energy with appropriately placing the phytochemicals into the receptor cavity. These selected ligands were further subjected to molecular docking analysis using Auto dock vina and outcomes were compared (Table 3 and 4).

In anti-bacterial compounds Betulinic-Acid, Glycyrrhetinic-Acid, Oxyasiaticoside, Tomatine and Ursolic Acid has exhibited a better binding affinity where as from the pool of Anti-viral compounds Saikosaponin-A, Betulin and Bilobetin has exhibited the optimum.

Docking results shows that the selected phytochemicals (anti-bacterial and anti-viral properties) have successfully placed themselves in to active site / cavity region of the receptor protein. The hydrogen bonding between the selected phytochemicals and amino acid residue is very much similar to that of reference ligand Actinonin. The weak and strong bonding interactions from Vanderwaal, Covalent, Charge, Polar and Pi-interaction shows a cluster of interaction around these all selected ligands (Supplementary data 2 (Table 5 and 6).

DISCUSSION

In this study plant derived antibacterial and antiviral agents are used to evaluate its inhibitory properties on the selected receptor protein Peptide deformylase, by observing its binding affinity energy and pharmacological interaction features with the receptor protein (1SZZ) for inhibiting the growth of pathogenic bacteria *Leptospira interrogans*.

Table:1 Phytochemical as antibacterial agent

S. no	Phytochemical as antibacterial agent	S. no	Phytochemical as antibacterial agent	S. no	Phytochemical as antibacterial agent
1	(+) Alpha-Pinene	36	Berberine	71	Colchicine
2	(+)-ß-Thujone	37	Beta TERPINEOL	72	Columbamine
3	(-) Alpha-Pinene	38	Beta-Ionone	73	Colupulone
4	(-)-A-Thujone	39	Beta-Sitosterol	74	Cosmosiin
5	1,8-Cineole	40	Betulinic-Acid	75	Costic-Acid
6	1-Methoxycanthin-6-One	41	Bilobalide	76	Cryptotanshinone
7	4- Terpineol	42	Borneol	77	Cuminaldehyde
8	Alpha-Bisabolol	43	Bromelain	78	Curcumin
9	Alpha-Citral	44	Caffeic-Acid	79	Cycloartenol
10	Alpha-Phellandrene	45	Canavanine	80	Cycloeucalenol
11	Alpha-Terpineol	46	Cannabidiol	81	Cynarin
12	Alpha-Thujone	47	Canthin-6-One	82	Daphnetin
13	Alstonine	48	Capillin	83	Dehydroabietane
14	Amphibine	49	Carpaine	84	Dehydrocostus-Lactone
15	Anacardic-Acid	50	Carvacrol	85	Dehydrofalcarindiol
16	Andrographolide	51	Caryophyllene	86	Dehydroisoeugenol
17	Anemonin	52	Catechin	87	Delta-3-Carene

18	Anethole	53	Chaulmoogric-Acid	88	Delta-Cadinene
19	Anisic-Acid	54	Chelerythrine	89	Diallyl-Disulfide
20	Anonaine	55	Chelidonine	90	Diallyl-Sulfide
21	Apigenin	56	Chelirubine	91	Diallyl-Tetrasulfide
22	Arbutin	57	Chimaphilin	92	Diallyl-Trisulfide
23	Aristolochic-Acid-I	58	Chlorogenic-Acid	93	Dictamnine
24	Artemisic-Acid	59	Chlorophyll	94	Dicumarol
25	Asarinin	60	Chrysin	95	Dihydrohelenalin
26	Ascorbic-Acid	61	Chrysophanol	96	Dihydropinosylvin
27	Atractylodin	62	Cinnamaldehyde	97	Dillapiol
28	Aucubin	63	Cinnamic-Acid	98	Diosphenol
29	Azulene	64	Cis-Ocimene	99	Dipentene
30	Bakuchiol	65	Citral	100	Dracorhodin
31	Barbaloin	66	Citric-Acid	101	Dracorubin
32	Benzaldehyde	67	Citronellal	102	Echinacoside
33	Benzoic-Acid	68	Citronellol	103	Ellagic-Acid
34	Berbamine	69	Cnicin	104	Embelin
35	Berberastine	70	Cocaine	105	Emodin
Sr no	Phytochemical as antibacterial agent	Sr no	Phytochemical as antibacterial agent	Sr no	Phytochemical as antibacterial agent
106	Enmein	141	Glycyrrhetinic-Acid	176	Lauric-Acid
107	Epicatechin	142	Glycyrrhizin	177	Lawsone
108	Epipolygodial	143	Gossypetin	178	Lignin
109	Eriodictyol	144	Gossypol	179	Limonene
110	Esculetin	145	Guaiacol	180	Linalool
111	Ethanol	146	Hardwickic-Acid	181	Liriodenine
112	Ethyl-Gallate	147	Harmaline	182	Lucidin
113	Eudesmin	148	Harmalol	183	Lupulone
114	Eugenol	149	Helenalin	184	Luteolin
115	Eupatorin	150	Helenin	185	Lycorine
116	Falcarindiol	151	Herniarin	186	Magnocurarine
117	Falcarinol	152	Hesperetin	187	Magnoflorine
118	Ferulic-Acid	153	Hexanal	188	Magnolol
119	Flavone	154	Hispaglabridin-A	189	Malabaricone-B
120	Fraxetin	155	Hispaglabridin-B	190	Malabaricone-C
121	Fulvoplumierin	156	Honokiol	191	Malic-Acid
122	Fumarine	157	Humulone	192	Mangostin
123	Furocoumarin	158	Hydnocarpic-Acid	193	Matrine
124	Fustin	159	Hydrastine	194	Medicarpin
125	Gallic-Acid	160	Hydroquinone	195	Menthol
126	Gamma Terpineol	161	Hyperforin	196	Menthone

127	Geniposide	162	Hyperin	197	Methyl-Eugenol
128	Genkwanin	163	Hyperoside	198	Methyl-Gallate
129	Gentianine	164	Indole	199	Methyl-Isoeugenol
130	Gentisein	165	Isoalantolactone	200	Myrcene
131	Gentisic-Acid	166	Isohumulone	201	Myricetin-3-Rhamnoside
132	Geranial	167	Isoquercitrin	202	Myricetin
133	Geraniol	168	Isorhamnetin-3-Rutinoside	203	Myricitrin
134	Ginkgolic-Acid	169	Isorhamnetin	204	Naringenin
135	Ginkgolide-A	170	Jasmone	205	Neoandrographolide
136	Ginnol	171	Juglone	206	Neobavaisoflavone
137	Glabridin	172	Kaempferol	207	Neral
138	Glabrol	173	Kaurenic-Acid	208	Nerol
139	Glyceollin-I	174	Kievitone	209	Nerolidol
140	Glyceollin-Ii	175	Lapachol	210	Nimbidin

Sr no	Phytochemical as antibacterial agent	Sr no	Phytochemical as antibacterial agent	Sr no	Phytochemical as antibacterial agent
211	Nordentatin	246	Pterostilbene	281	Suspensaside
212	O-Coumaric-Acid	247	Pterygospermin	282	Sweroside
213	Odorinol	248	Pulegone	283	Tannin
214	Oleanolic-Acid	249	Pyrogallol	284	Terpinen-4-Ol
215	Oxyacanthine	250	Quercetagetin	285	Terpineol
216	Oxyasiaticoside	251	Quercetin-3'-Glucoside	286	Terpinyl-Acetate
217	P-Coumaric-Acid	252	Quercetin-7-O-Glucoside	287	Tetramethyl-Pyrazine
218	P-Cymene	253	Quercetin	288	Theaflavin
219	P-Hydroxy-Benzoic-Acid	254	Quercitrin	289	Thiocyanic Acid
220	Paba	255	Quinine	290	Thymohydroquinone
221	Paeonal	256	Raphanin	291	Thymol
222	Paeoniflorin	257	Resorcinol	292	Thymoquinone
223	Paeonol	258	Resveratrol	293	Tomatine
224	Palmatine	259	Reticuline	294	Trans-Isoasarone
225	Parthenolide	260	Rhamnetin	295	Tuberosin
226	Patchouli-Alcohol	261	Rhamnocitrin	296	Umbelliferone
227	Pectin	262	Rhein	297	Ursolic Acid
228	Perillaldehyde	263	Rishitin	298	Vanillic Acid
229	Perillyl-Alcohol	264	Robinin	299	Verbascoside
230	Phaseolin	265	Rosmarinic-Acid	300	Withaferin-A
231	Phenethyl-Alcohol	266	Rutin	301	Withaphysacarpin
232	Phenol	267	Sabinene	302	Wogonin
233	Phloretin	268	Safrole	303	Xanthotoxin
234	Piceid	269	Sakuranetin	304	Yangonin
235	Pimpinellin	270	Salicylic-Acid	305	(+)-ß-Thujone
236	Pinocembrin	271	Salvin	306	(-)-A-Thujone
237	Pinosylvin	272	Salviol	307	Hexanal

238	Piperine	273	Sanguinarine	308	Hexenal
239	Pisatin	274	Sclareol		
240	Plumbagin	275	Scopoletin		
241	Polydatin	276	Serpentine		
242	Proanthocyanidins	277	Sesamin		
243	Procyanidins	278	Sinapic-Acid		
244	Protoanemonin	279	Sorbic-Acid		
245	Protocatechuic-Acid	280	Squalene		

Table 2: Phytochemical as antiviral agent

Sr no	Phytochemical as antiviral agent	Sr no	Phytochemical as antiviral agent	Sr no	Phytochemical as antiviral agent
1	(+) Alpha-Pinene	36	Chebulagic-Acid	71	Galloyl-Geraniin
2	(-) Alpha-Pinene	37	Chelerythrine	72	Gambiriin-A1
3	8-Methoxy-Psoralen	38	Chelidonium Majus	73	Gambiriin-B3
4	Adenine	39	Chrysin	74	Genistein
5	Ajoene	40	Chrysoeriol	75	Gentisic-Acid
6	Alginic Acid	41	Cichoric-Acid	76	Geranial
7	Aloe-Emodin	42	Cinchonain	77	Geraniin
8	Aloin	43	Cinchonidine	78	Ginkgetin
9	Alpha-Peltatin	44	Cinnamaldehyde	79	Gitoxin
10	Amentoflavone	45	Citrusinine	80	Glabranin
11	Angelicin	46	Codeine	81	Glaucarubolone
12	Anthocyanine	47	Colchamine	82	Glaucarubolone
13	Ar-Curcumene-1	48	Cyanin	83	Glycyrrhizic-Acid
14	Ar-Curcumene-2	49	D-Glucosamine	84	Glycyrrhizin
15	Arctigenin	50	Daidzein	85	Homatropine
16	Aristolochic Acid	51	Dammaradienol	86	Hydroxyhopanone
17	Artemisinin	52	Dammarenolic-Acid	87	Hyoscyamine
18	Ascorbic Acid	53	Deoxyartemisinin	88	Hyperin
19	Atropine	54	Deoxypodophyllotoxin	89	Hyperoside
20	Axillarin	55	Diallyl-Disulfide	90	Isoborneol
21	Baicalein	56	Diallyl-Trisulfide	91	Isoliquiritigenin
22	Bakuchiol	57	Diosmetin	92	Isoquercetin
23	Benzyl-Isothiocyanate	58	Dipentene	93	Isoscutellarein
24	Berbamine	59	Echinacoside	94	Juglone
25	Beta Sitosterol	60	Emetine	95	Kaempferol-3-O-Glucoside
26	Beta-Bisabolene Ic50	61	Emodine	96	Kaempferol
27	Betulin	62	Ephedrine	97	Lanatoside-A
28	Bilobetin	63	Epilupeol	98	Lapachol
29	Bornyl-Acetate	64	Ergosterol Peroxide	99	Lauric-Acid
30	Camptothecin	65	Ergosterol	100	Licochalcone-A
31	Canavanine	66	Escin	101	Lignans
32	Castanospermine	67	Eugenol	102	Linalool
33	Catechin	68	Fisetin	103	Lupeol
34	Catechol	69	Fustin	104	Luteolin-7-Glucoside
35	Chaparrinone	70	Galangin	105	Luteolin

S no	Phytochemical as antiviral agent	S no	Phytochemical as antiviral agent
106	Lycorine	126	Phenol
107	Mangiferin	127	Podophyllotoxin
108	Maslinic Acid	128	Polydatin
109	Methyl-Gallate	129	Pretazettine
110	Morin	130	Procyanidin
111	Narcotine	131	Proscillaridin-A
112	Naringenin	132	Protoanemonin

113	Naringin	133	Pseudohypericin
114	Neryl-Acetate	134	Psoralen
115	Nonacosane	135	Quercetagitrin
116	Octacosanol	136	Quercetin-3,3'-Dimethylether
117	Oleanolic-Acid	137	Quercetin
118	Ouabain	138	Quercimeritrin
119	P-Cymene	139	Quercitrin
120	Pachypodol	140	Rhein
121	Papaverine	141	Saikosaponin-A
122	Pelargonidin	142	Sanguinarine
123	Penduletin	143	Scillarenin
124	Pentagalloyl-Glucose	144	Scopolamine
125	Perivine		

Table. 3.The best anti bacterial ligand selected from the iGEMDOCK based on their energy.

Sr. No.	**Name of compounds (Antibacterial)**	**i-Gem Dock**	**Auto dock vina**	**Sr no**	**Name of compounds (Antibacterial)**	**i-Gem Dock**	**Auto dock vina**
1	Betulinic-Acid	-125.605	-11.0	9	Oleanolic-Acid	-124.484	-9.7
2	Carpaine	-118.303	-9.9	10	Oxyasiaticoside	-153.813	-10.0
3	Cycloartenol	-116.125	-9.9	11	Procyanidins	-121.241	-9.3
4	Echinacoside	-117.024	-9.2	12	Quercetin-1	-117.511	-7.9
5	Ginkgolide-A	-119.797	-9.5	13	Quercitrin-1	-117.536	-8.7
6	Glycyrrhetinic-Acid	-125.881	-10.6	14	Tomatine	-129.949	-10.3
7	Gossypol-0	-121.818	-8.1	15	Ursolic Acid	-116.818	-10.8
8	Nimbidin	-119.657	-9.3	16	Verbascoside	-117.852	-8.9

Table 4. The best anti viral ligand selected from the iGEMDOCK based on their energy.

Sr. No.	**Name of compounds (antiviral)**	**i-Gem Dock**	**Auto dock vina**
1	Betulin	-125.432	-10.6
2	Bilobetin	-126.888	-10.9
3	Epilupeol	-125.147	-9.9
4	Escin	-134.119	-8.3
5	Glaucarubolone	-141.343	-9.2
6	Saikosaponin-A	-131.786	-12.7

Table 5: Molecular interactions of Antibacterial agents

Sr no	LIGAND	van der Waals interactions	Covalently bonded residues	Hydrogen-bond interactions with amino acid main chains	Hydrogen-bond interactions with amino acid side-chains	Pi interact-tions	solvent accessible surface
1	Betulinic acid	ALA 44, GLU 45, GLY 46, VAL 47, GLY 48, TYR 71, PHE 97, TRP 98, GLU 99, GLY 100, ARG 108, VAL 140, HIS 143, GLU 144, ASN 166.	TYR 136	---	TYR 136	---	TYR 71, GLY 100, ARG 108,
2	Carpaine	GLY 46, ARG 70, TYR 71, PRO 72, THR 74, PHE 97, GLU 99, GLY 100, LEU 102, VAL 140.	VAL 47, ARG 108, TYR 136, ASN 166	---	TYR 136	---	VAL 47, ARG 70, GLY 100, ARG 108, ASN 166
3	Cycloartenol	GLY 46, VAL 47, TYR 71, THR 74, PHE 97, TRP 98,	GLY 48, HIS 143, GLU 144.	---	GLU 144	TYR 71	TYR 71, PHE 97, TRP 98, ARG 108

		GLY 100, LEU 102, ARG 108, TYR 136,					
4	Echinacoside	ALA 44, GLY 46, THR 74, PHE 97, GLU 99, PRO 105, VAL 140.	GLU 45, VAL 47, GLY 48, ARG 70, TYR 71, PRO 72, GLY 72, TRP 98, GLY 100, CYS 101, VAL 104, MET 107, ARG 108, GLY 106, LEU 102, HIS 143, GLU 144, ASN 166.	GLY 48, GLY 106, MET 107.	GLU 45, ARG 70, ARG 108, HIS 143.	ARG 108.	TYR 71, THR 74, PHE 97, GLY 100, LEU 102 ARG 108, HIS 143.
5	Ginkgolide-A	VAL 47, TYR 71, THR 74, PHE 97, GLU 99, VAL 140, HIS 143	TRP 98, GLY 100, ARG 108, TYR 136	GLY 100	ARG 108, TYR 136	---	VAL 47, TYR 71, THR 74, PHE 97, TRP 98, GLY 100, ARG 108
6	Glycyrrhetinic-Acid	GLY 46, THR 74, PHE 97, TRP 98, GLY 100, LEU 102, TYR 136, HIS 143	VAL 47, GLY 48, TYR 71, ARG 108, GLU 144.	---	TYR 71, ARG 108	---	TYR 71, THR 74, GLY 100, ARG 108,
7	Gossypol-0	GLY 46, VAL 47, TYR 71, THR 74, PHE 97, GLU 99, CYC 101, LEU 102, ILE 139.	TRP 98, GLY 100, ARG 108, TYR 136, VAL 140, HIS 143, GLU 144.	---	ARG 108	ARG 108	TYR 71, GLY 100, ARG 108, HIS 143.
8	Nimbidin	GLU 45, VAL 47, TYR 71, PRO 105, TYR 136, ILE 139, ASN 166.	TRP 98, GLU 99, GLY 100, CYS 101, LEU 102, GLY 106, ARG 108, HIS 143	GLY 100, GLY 106.	HIS 143		VAL 47, TYR 71,TRP 98, GLU 99, GLY 100, CYS 101, LEU 102, PRO 105, GLY 106, ARG 108, TYR 1386, HIS 143
9	Oleanolic-Acid	ALA 44, GLU 45, GLY 46, VAL 47, ARG 70, TYR 71, GLU 99, ARG 108, VAL 140, ASN 166.	GLY 48, GLN 53, GLY 100, CYS 101, LEU 102, HIS 143, GLU 144.	GLY 100	GLU 144	HIS 143	Ala 44, VAL 47, ARG 70, TYR 71, GLU 99, LEU 102, ARG 108, VAL 140, HIS 143, ASN 166
10	Oxyasiaticoside	GLY 46, VAL 47, THR 74, PHE 97, TRP 98, PRO 105, HIS 143, GLU 144	ARG 70, TYR 71, PRO 72, GLY 100, CYC 101, VAL 104, GLY 106, MET 107, ARG 108, ASN 166, GLU 167, ASP 170.	---	ASN 166, ASP 170.	TYR 71.	VAL 47, ARG 70, TYR 71, THR 74, PHE 97, TRP 98, GLY 100, ARG 108, ASN 166.
11	Procyanidins	VAL 47, THR 74, PHE 97, LEU 102, VAL 140, HIS 143	ALA 44, GLU 45, GLY 46, GLY 48, TYR 71, GLY 100, CYS 101, VAL 104, PRO 105, GLY 106, MET 107, ARG 108, TYR 136, GLU 144, ASN 166	GLY 48, MET 107.	TYR 71, TYR 136	ARG 108	VAL 47, TYR 71, GLY 100, LEU 102, ARG 108, ASN 166.
12	Quercetin-1	---	GLU 45, GLY 46, VAL 47, GLY 48, GLU 99, GLY 100, ARG 108,	GLY 48	GLU 144, ARG 108.	---	VAL 47, GLY 100, ARG 108, HIS 143, VAL 140

			ILE 139, VAL 140, HIS 143M ASN 166.				
13	Quercitrin-1	TYR 71, PHE 97, GLU 99, CYS 101, LEU 102, ARG 108, VAL 140.	ALA 44, VAL 47, GLY 48, THR 74, GLY 100, TYR 136, HIS 143, GLU 144, ASN 166	GLY 48, GLY 100	GLU 144	TYR 71, ARG 108	VAL 47, TYR 71, GLY 100, LEU 102, ARG 108, ASN 166.
14	Tomatine	VAL 47, GLY 48, ARG 70, TYR 71, PHE 97, GLU 144, ASP 170	GLN 53, TRP 92, GLU 99, GLY 100, CYS 101, LEU 102, VAL 104, GLY 106, MET 107, ARG 108, TYR 136, ILE 139, VAL 140, HIS 143, ASN 166.	TRP 92, GLY 100, LEU 102, ILE 139.	ARG 108, TYR 136, ASN 166.	HIS 143	VAL 47, ARG 70, TYR 71, PHE 97, GLU 99, GLY 100, LEU 102, ARG 108, TYR 136, ASN 166, ASP 170
15	Ursolic Acid	ALA 44, VAL 47, TYR 71, PHE 97, TRP 98, GL;U 99, LEU 102, ARG 108, ILE 139, ASN 166.	GLU 45, ARG 70, GLY 100, HIS 143.	---	---	---	VAL 47, ARG 70, TYR 71, GLY 100, ARG 108.
16	Verbascoside	GLY 46, GLY 48, ARG 70, THR 74, PHE 97, LEU 102, GLU 144	VAL 47, TYR 71, TRP 98, GLU 99, GLY 100, CYS 101, ARG 108, ILE 139, VAL 140, HIS 143.	VAL 47, GLY 100.	TYR 71, ARG 108.	HIS 143	ARG 70, TYR 71, GLY 100, ARG 108

Table 6: Molecular interaction of Antiviral agent

Sr no	LIGAND	van der Waals interactions	Covalently bonded residues	Hydrogen-bond interactions with amino acid main chains	Hydrogen-bond interactions with amino acid side-chains	Pi interact-tions	solvent accessible surface
1	BETULIN	ALA 44, GLU 45, VAL 47, GLY 48, TYR 71, PHE 97, TRP 98, GLU 99, GKY 100, ARG 108, HIS 143, VAL 140, GLU 144, ASN 166.	TYR 136	----	---	---	VAL 47, TYR 71, GLY 100, ARG 108
2	Bilobetin	ARG 07, ALA 44, GLY 46, CYS 101, PRO 105, ASN 166.	ILE 05, GLU 45, VAL 47, GLY 48, ARG 70, TYR 71, GLY 100, LEU 102, GLY 106, TYR 136, GLU 144	GLY 48.	GLU 45, ARG 70, TYR 136.	---	ILE 05, VAL 47, ARG 70, TYR 71, GLY 100, LEU 102, PRO 105.
3	Epilupeol	GLY 46, VAL 47, GLY 48, TYR 71, THR 74, PHE 97, GLY 100, LEU 102, ARG 108, TYR 136, VAL 140, HIS 143, GLU 144.	---	---	---	---	TYR 71, GLY 100, ARG 108.
4	Escin	VAL 47, TYR	GLY 48, GLN	GLY 48, LEU	ARG 108,	---	VAL 47, TYR

		71, GLY 73, THR 74, PHE 97, GLU 99, VAL 140.	53, TRP 98, GLY 100, CYS 101, LEU 102, GLY 106, ARG 108, TYR 136, HIS 143, GLU 144, ASN 166.	102, GLY 106.	TYR 136, GLU 144.		71, GLY 73, THR 74, PHE 97, TRP 98, GLY 100, ARG 108
5	Glaucarubolone	GLY 46, VAL 140, ASN 166.	GLU 45, VAL 47, GLY 48, TRP 98, GLY 100, CYS 101, LEU 102, ARG 108, GLU 144.	GLY 100	TYR 71, ARG 108	--	VAL 47, TYR 71, GLY 100, LEU 102, ARG 108.
6	Saikosaponin-A	VAL 02, LYS 04, ARG 07, VAL 47, TYR 71, PHE 97, GLY 100, CYS 101, PRO 105, GLY 106, ARG 108, TYR 136, VAL 140, HIS 143, ASN 166	ARG 03, ILE 05, THR 40, HIS 43, ALA 44, TRP 98, LEU 102.	ILE 05	HIS 43	---	ILE 05, HIS 43, ALA 44, VAL 47, TYR 71, GLY 100, LEU 102, PRO 105, ARG 108,

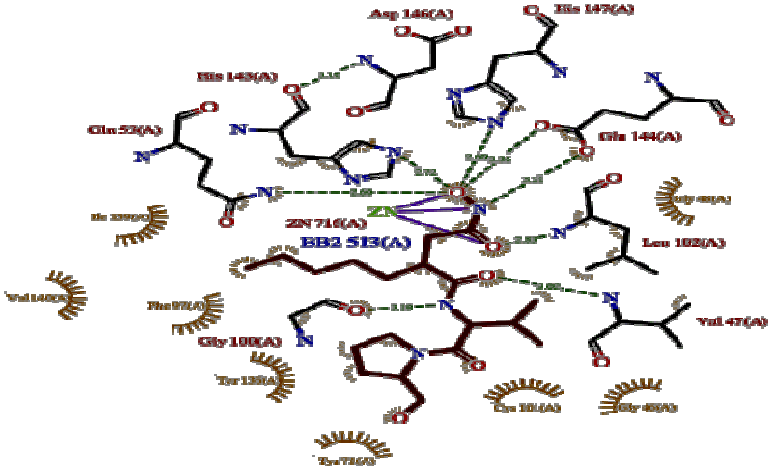

Figure1: Molecular interaction of Actinoin with Peptide deformylase crystallized structure

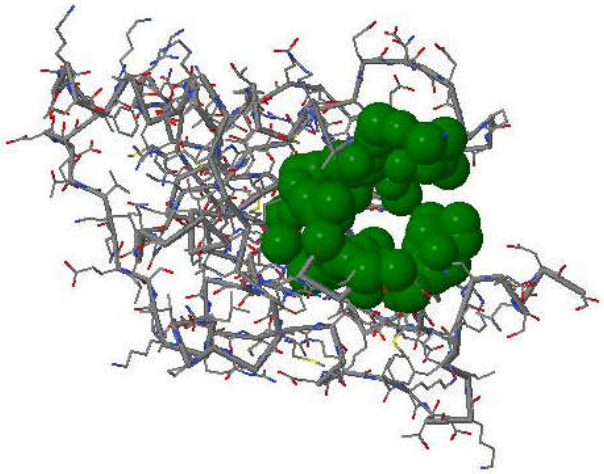

Figure 2: Active site at Chain A PDB-id: 1SZZ.

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