



**IN SILICO- MOLECULAR DOCKING STUDIES OF SIDDHA POLY HERBAL
FORMULATION FOR TREATMENT OF YONI SOOLAI (ENDOMETRIAL
INFLAMMATION) BY SUPPRESSION OF INTERLEUKIN-6 ACTIVITY**

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ABSTRACT

Background: Indian medicine is the most comprehensive and rich heritage of Traditional medicine in the world. Traditional medicine according to the definition of WHO is “The sum of Knowledge based on theories, beliefs and experiences skill, originating from different cultures”. WHO states that Endometriosis affects roughly 190 million of reproductive age women and girls globally. It is a chronic disease associated with severe, life impacting pain during menstruation, sexual intercourse, bowel movements and or urination, chronic pelvic pain, abdominal bloating, nausea, fatigue, and some times depression, anxiety and infertility. Access to early diagnosis and effective treatment of endometrial inflammation is important. Endometrial inflammation is one of the chronic inflammatory diseases that mentioned in siddha Literature. Inter leukin - 6 has extensive anti – inflammatory functions in its role as a to myokine. IL 6 was first myokine that was found to be secreted into the blood stream in response to muscle contractions.

KEYWORDS: Siddha formulation, Endometrial inflammation, Inter leukin-6, inflammatory action.

1. INTRODUCTION

Endometrial inflammation or endometritis is localized the to endometrium, the inner uterine lining, commonly due an infection etiology. Infection that extends to the fallopian tubes, ovaries, or pelvic peritoneum is termed pelvic inflammatory disease [PID]. Acute endometritis can happen after child birth or miscarriage, or after a surgical procedure involving your cervix or uterus. Chronic endometritis is more common after menopause due to common infection like Chlamydia or Gonorrhoea. Endometritis is caused by a bacterial infection in uterus. It can be due to sexually transmitted infection [STIs], Tuberculosis or from bacteria that occur naturally in vagina. A beneficial Bacterial flora is maintained in the Vagina in normal conditions, but in case of delivery or any invasive procedures involving Vagina causes “mixing” of bacteria which leads to infection and inflammation.

Interleukin 6 [IL – 6], promptly and transiently produced in response to infections and tissue injuries and immune reaction. Although its expression is strictly controlled by transcriptional and posttranscriptional mechanism, dysregulated continual

synthesis of interleukin 6 plays a pathological effect on chronic inflammation and autoimmunity.

In traditional siddha medicine the clinical picture of Endometrial inflammation is more or less correlated with the condition called *Yoni soolai*. Numerus herbal or herbomineral formulation are exclusively given for the condition. *KIYAZHAM CHOORANAM FOR YONI SOOLAI* is one among the herbal medicine used for Endometrial inflammation. The formulation is mentioned in the Tamil medical text *KANNUCHAMI PARAMPARAI VAITHTHIAYAM*.

IL-6 and endometriosis

IL-6 is elevated in the serum, endometriotic lesions, and peritoneal fluid of women with endometriosis. IL-6 can 1) Suppress NK cell activity: IL-6 can reduce the cytolytic activity of NK cells in the peritoneal fluid (PF) of endometriosis patients. This can be due to IL-6 down-regulating granzyme B and perforin. 2) Induce nerve fiber growth: IL-6 can cause nerve fiber growth in ectopic lesions, which can contribute to pain, a major symptom of endometriosis. 3) Transition acute inflammation to chronic inflammation: IL-6 can help

shift the inflammatory response from a neutrophilic leukocyte infiltrate to a monocyte/macrophage-dominated one.

IL-6 suppression

Some ways to suppress IL-6 include:

- 1) Anti-IL-6 antibodies: Adding anti-IL-6 to the PF of endometriosis patients can restore NK cell activity.

- 2) Soluble IL-6 receptor: Using a soluble IL-6 receptor could help rescue impaired NK cell activity in endometriosis patients.
- 3) Resveratrol: Resveratrol treatment can reduce IL-6 gene and protein expression.

IL-6 signaling pathways

Targeting specific IL-6 signaling pathways may help improve endometriosis management. This could lead to better outcomes, fewer side effects, and earlier detection of the disease.

2. In-Silico Anti-Inflammatory Activity

List of Phytochemicals Selected for docking

Herbs	Phytochemicals	References
Indigofera aspalathoides	Kaempferol	Authinarayanan Rajesh. Bioactivities of extracts and phytochemicals of Indigofera aspalathoides Vahl ex DC. <i>Thu Dau Mot University Journal of Science</i> , 2021; 3(1): 1-16.
Withania somnifera	Withaferin A Chlorogenic acid	Saleem S, Muhammad G, Hussain MA, Altaf M, Bukhari SNA. <i>Withania somnifera L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective</i> . <i>Iran J Basic Med Sci.</i> , 2020; 23(12): 1501-1526.
Clerodendron inerme	Betulinic acid Friedelin	Sabrin R.M. Ibrahim. Chemical constituents and biological investigations of the aerial parts of Egyptian Clerodendrum inerme. <i>Bulletin of Faculty of Pharmacy, Cairo University</i> , 2014; 52(2): 165-170. Ali Esmail Al-Snaf. <i>Chemical Constituents and Pharmacological Effects of Clerodendrum inerme- A Review</i> . <i>SMU medical Journal</i> , 2016; 3: 129-152.
Thespesia populnea	Gallic acid	Rangani J, Kumari A, Patel M, Brahmabhatt H, Parida AK. Phytochemical profiling, polyphenol composition, and antioxidant activity of the leaf extract from the medicinal halophyte Thespesia populnea reveal a potential source of bioactive compounds and nutraceuticals. <i>J Food Biochem</i> , 2019; 43(2): e12731. doi:10.1111/jfbc.12731
Emblia ribes	Embelin	Sreepriya, M., & Bali, G. (2005). "The role of embelin in experimental carcinogenesis and apoptosis: a review." <i>Phytotherapy Research</i> .
Azima Tetracantha	Azimine	Konda VR, Arunachalam R, Eerike M, Rao K R, Radhakrishnan AK, Raghuraman LP, Meti V, Devi S. Nephroprotective effect of ethanolic extract of Azima tetracantha root in glycerol induced acute renal failure in Wistar albino rats. <i>J Tradit Complement Med.</i> , Jun. 26, 2015; 6(4): 347-354.
Tephrosia purpurea	Tephrosin	Yadav, R. N., & Agarwala, M. (2011). "Phytochemical analysis of some medicinal plants." <i>Journal of Phytology</i> .
Plumbago zeylanica	Plumbagin	Zhang QR, Mei ZN, Yang GZ, Xiao YX. [Chemical constituents from aerial parts of Plumbago zeylanica Linn]. <i>Zhong Yao Cai.</i> , May 2007; 30(5): 558-60.
Encicostema littorale blume	Quercetin	Pandey, A., & Tripathi, S. (2014). "Flavonoids: A pharmacological and medicinal review." <i>International Journal of Pharmaceutical Sciences Review and Research</i> .
Daemonorops longipes	Dracorhodin	Wang, W., & Zhu, R. (2016). "Isolation and structure elucidation of dracorhodin from Dragon's Blood." <i>Journal of Natural Products</i> .
Zingiber officinale	Gingerenone-A	Sahdeo Prasad. <i>Ginger and Its Constituents: Role in Prevention and Treatment of Gastrointestinal Cancer</i> . <i>Gastroenterology Research and Practice</i> . 2015: 1-11
Vernonia Anthelmitica	Vernodalol	Prakash, O., & Jain, S. (2009). "Isolation and structural elucidation of sesquiterpene lactones from Vernonia species." <i>Journal of Ethnopharmacology</i> .

3. AIM AND OBJECTIVES

The main objective of the study is to carry out Molecular Docking studies of lead molecules from key ingredients of *KIYAZHAM CHOORANAM FOR YONI SOOLAI* to

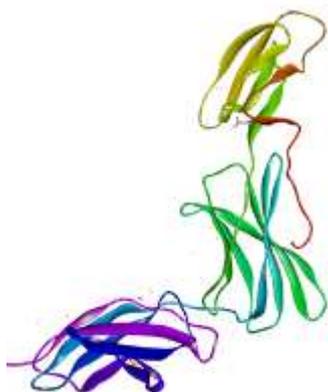
find out any interactions between interleukin 6 and the herbal ingredients.

Binding of phytochemicals with the core amino acids (His70, Asp71, Ser72, Val91, Pro117, Ser119, Thr120,

Pro121, Ser122, Thr124, Thr125) of the target by forming hydrogen bond will hinder the function of the inflammatory cytokine IL6 (Interleukin 6) with PDB – 1N26. These amino acid residues are functionally responsible for binding of substrate and inhibitors. Thereby phytochemicals which inhibit the target IL6 (Interleukin 6) may act as a potential therapeutic agent for management of inflammation.

PDB	Name of the Target
1N26	IL6 (Interleukin 6)

IL6 (Interleukin 6) (1N26)



3.1 RECEPTOR STRUCTURE

Crystalline structure of the target protein IL6 was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atoms were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis.

3.2 Protein preparation

Three-dimensional protein structure of the target protein IL6 (Interleukin 6) with PDB 1N26 were retrieved from the online repository of Protein Data Bank and subjected to protein clean prior to docking simulation.

3.4 Ligand Preparation

Phytochemicals subjected to the investigation were retrieved from the herbs listed in the table based on the literature survey and 3D structure of the same were built using Chem Draw prof online tool version 12.0. Ligands prepared through geometry optimization method (MMFF94).

4. METHODOLOGY

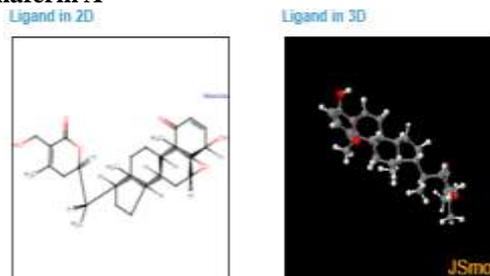
Docking calculations were carried out for retrieved phytochemicals against target protein. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell *et al.*, 1998). Affinity (grid) maps of $\times \times$ Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris, Goodsell *et al.*, 1998). AutoDock parameter set- and

distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

2D and 3D Structure of Phytochemicals Kaempferol



Withaferin A



Chlorogenic acid

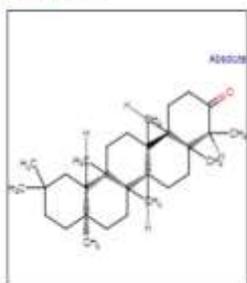


Betulinic acid



Friedelin

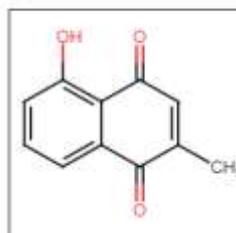
Ligand in 2D



Ligand in 3D

**Plumbagin**

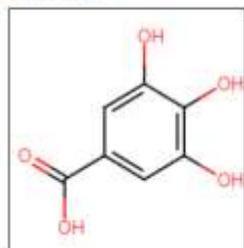
Ligand in 2D



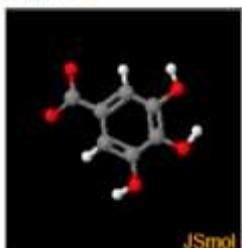
Ligand in 3D

**Gallic acid**

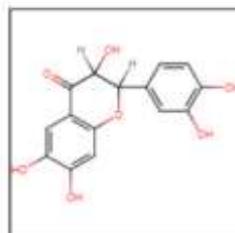
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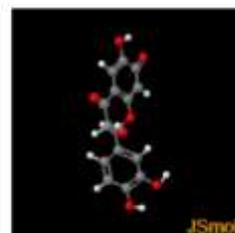
Ligand in 3D

**Quercetin**

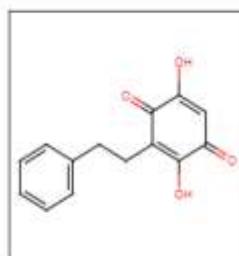
Ligand in 2D



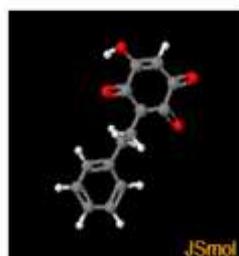
Ligand in 3D

**Embelin**

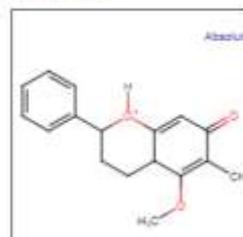
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Ligand in 3D

**Dracorhodin**

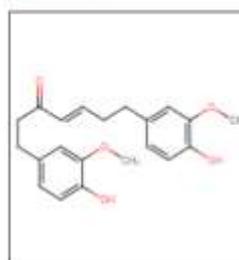
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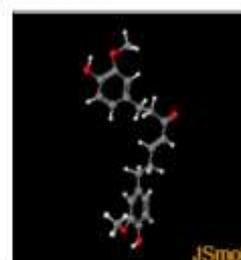
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**Gingerenone-A**

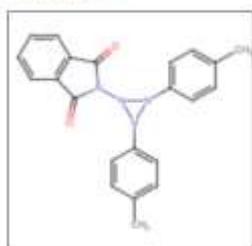
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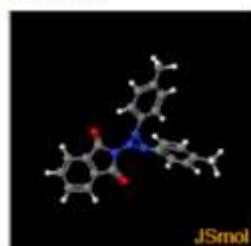
Ligand in 3D

**Azimine**

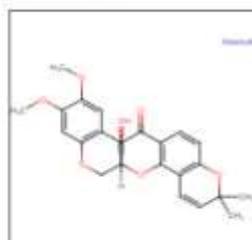
Ligand in 2D



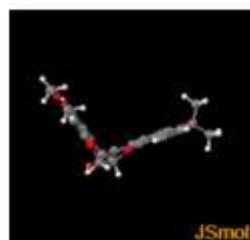
Ligand in 3D

**Tephrosin**

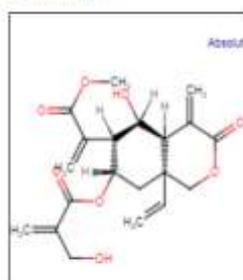
Ligand in 2D



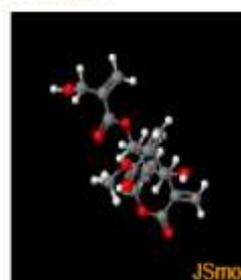
Ligand in 3D

**Vernodalol**

Ligand in 2D



Ligand in 3D



Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Kaempferol	286.24 g/mol	C ₁₅ H ₁₀ O ₆	4	6	1
Withaferin A	470.6 g/mol	C ₂₈ H ₃₈ O ₆	2	6	3
Chlorogenic acid	354.31 g/mol	C ₁₆ H ₁₈ O ₉	6	9	5
Betulinic acid	456.7 g/mol	C ₃₀ H ₄₈ O ₃	2	3	2
Friedelin	426.7 g/mol	C ₃₀ H ₅₀ O	0	1	0
Gallic acid	170.12 g/mol	C ₇ H ₆ O ₅	4	5	1
Embelin	294.4 g/mol	C ₁₇ H ₂₆ O ₄	2	4	10
Azimine	422.6 g/mol	C ₂₄ H ₄₂ N ₂ O ₄	2	6	0
Tephrosin	410.4 g/mol	C ₂₃ H ₂₂ O ₇	1	7	2
Plumbagin	188.182 g/mol	C ₁₁ H ₈ O ₃	1	3	0
Quercetin	302.23 g/mol	C ₁₅ H ₁₀ O ₇	5	7	1
Dracorhodin	266.29 g/mol	C ₁₇ H ₁₄ O ₃	0	3	2
Gingerenone-A	356.4 g/mol	C ₂₁ H ₂₄ O ₅	2	5	9
Vernodalol	392.4 g/mol	C ₂₀ H ₂₄ O ₈	2	8	8

5. Summary of the molecular docking studies of compounds against IL6 (Interleukin 6) (1N26)

Compounds	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Kaempferol	-6.36 kcal/mol	21.75 uM	-0.49 kcal/mol	-6.73 kcal/mol	593.579
Withaferin A	-8.49 kcal/mol	596.90 nM	-0.14 kcal/mol	-9.56 kcal/mol	894.783
Chlorogenic acid	-7.29 kcal/mol	4.55 uM	-0.28 kcal/mol	-7.13 kcal/mol	697.161
Betulinic acid	-9.40 kcal/mol	129.24 nM	-0.10 kcal/mol	-11.85 kcal/mol	1066.766
Friedelin	-8.23 kcal/mol	926.69 nM	-0.01 kcal/mol	-8.23 kcal/mol	748.807
Gallic acid	-5.88 kcal/mol	48.90 uM	-0.40 kcal/mol	-5.41 kcal/mol	394.443
Embelin	-6.77 kcal/mol	10.85 uM	-0.11 kcal/mol	-7.07 kcal/mol	504.088
Azimine	-8.23 kcal/mol	928.79 nM	-0.12 kcal/mol	-9.47 kcal/mol	706.126
Tephrosin	-6.79 kcal/mol	10.47 uM	-0.06 kcal/mol	-7.05 kcal/mol	713.908
Plumbagin	-5.26 kcal/mol	139.40 uM	-0.03 kcal/mol	-5.56 kcal/mol	449.073
Quercetin	-7.37 kcal/mol	3.93 uM	-0.35 kcal/mol	-6.88 kcal/mol	572.463
Dracorhodin	-6.45 kcal/mol	18.60 uM	-0.02 kcal/mol	-6.78 kcal/mol	566.139
Gingerenone-A	-7.32 kcal/mol	4.29 uM	-0.01 kcal/mol	-6.33 kcal/mol	691.311
Vernodalol	-6.22 kcal/mol	27.70 uM	-0.03 kcal/mol	-6.53 kcal/mol	687.587

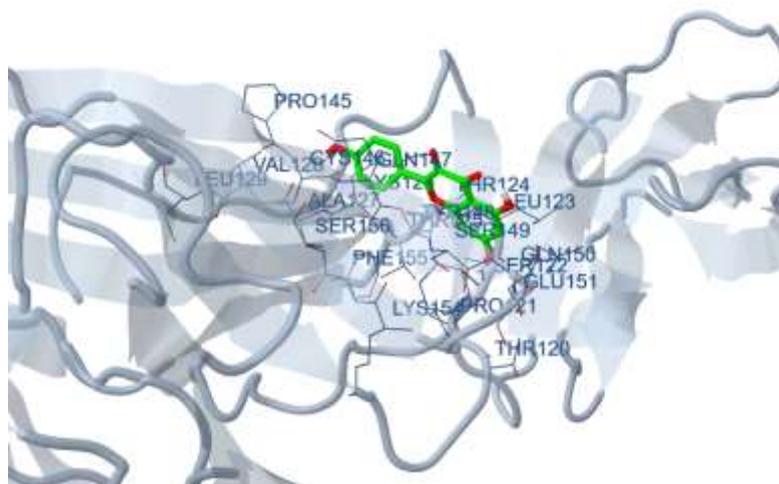
5.2 Amino acid Residue Interaction of Lead against IL6 (Interleukin 6) PDB- (1N26)

Compounds	Interactions	Amino acid Residues											
		121	123	126	128	148	150	155					
Kaempferol	1	PRO	LEU	LYS	VAL	TYR	GLN	PHE					
Withaferin A	4	46	69	72	90	93	96	119	120	122	123		
		PRO	LEU	SER	LEU	VAL	GLU	SER	THR	SER	LEU		
Chlorogenic acid	3	46	69	70	72	90	120	122					
		PRO	LEU	HIS	SER	LEU	THR	SER					
Betulinic acid	4	46	69	72	90	93	96	119	121	122	123	125	
		PRO	LEU	SER	LEU	VAL	GLU	SER	PRO	SER	LEU	THR	
Friedelin	4	46	69	72	90	120	122	123	124				
		PRO	LEU	SER	LEU	THR	SER	LEU	THR				
Gallic acid	1	121	126	147	148	155							
		PRO	LYS	GLN	TYR	PHE							
Embelin	4	93	95	96	115	117	119	121	125	175			
		VAL	PRO	GLU	TRP	PRO	SER	PRO	THR	VAL			
Azimine	6	69	93	95	96	115	117	119	120	121	122	125	175
		LEU	VAL	PRO	GLU	TRP	PRO	SER	THR	PRO	SER	THR	VAL
Tephrosin	4	20	68	69	93	95	96	119	121	122	125	177	
		PRO	GLN	LEU	VAL	PRO	GLU	SER	PRO	SER	THR	SER	
Plumbagin	4	93	95	96	115	117	119	121	125				

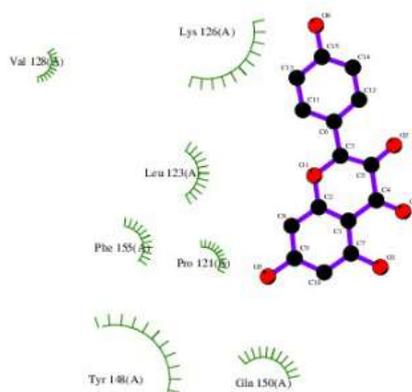
		VAL	PRO	GLU	TRP	PRO	SER	PRO	THR				
Quercetin	0	123	126	148	150	155							
		LEU	LYS	TYR	GLN	PHE							
Dracorhodin	3	69	93	95	96	115	117	121	125	155	175		
		LEU	VAL	PRO	GLU	TRP	PRO	PRO	THR	PHE	VAL		
Gingerenone-A	3	46	69	72	90	92	122	123	124				
		PRO	LEU	SER	LEU	ASP	SER	LEU	THR				
Vernodalol	4	46	47	69	70	72	90	122	123	124			
		PRO	ALA	LEU	HIS	SER	LEU	SER	LEU	THR			

Docking Pose

Kaempferol with IL6 (Interleukin 6) PDB- (1N26)



2D Interaction Plot Analysis

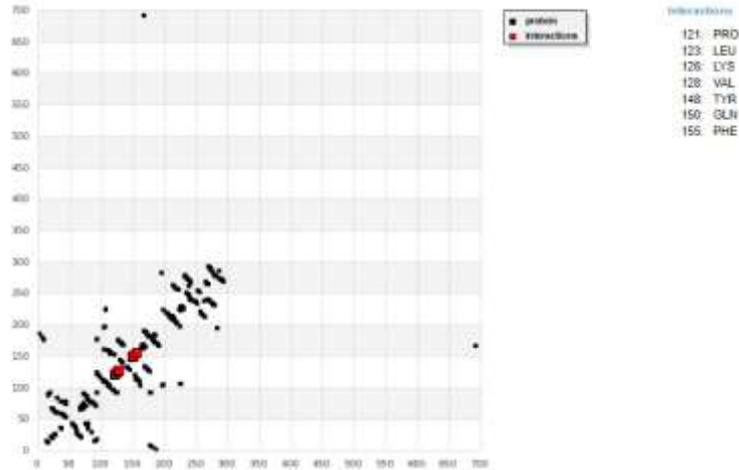


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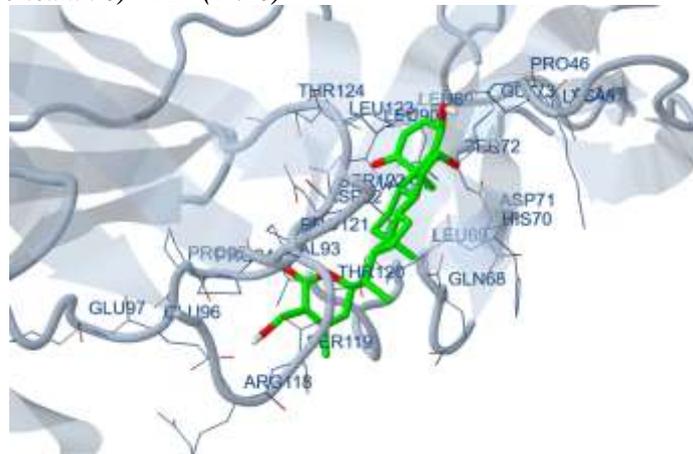
- Ligand bond
- Non-ligand bond
- Hydrogen bond and its length
- Non-ligand residues involved in other contacts

docking

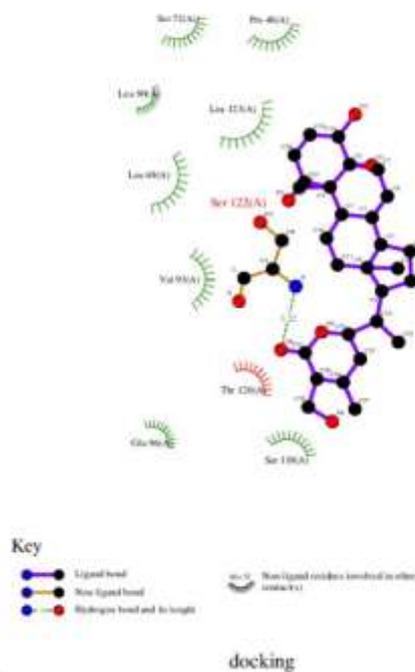
Hydrogen bond plotting with core amino acid Analysis



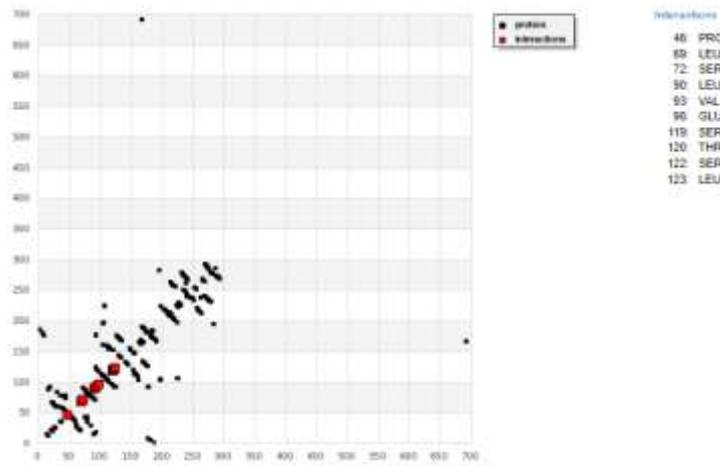
Withaferin A with IL6 (Interleukin 6) PDB- (1N26)



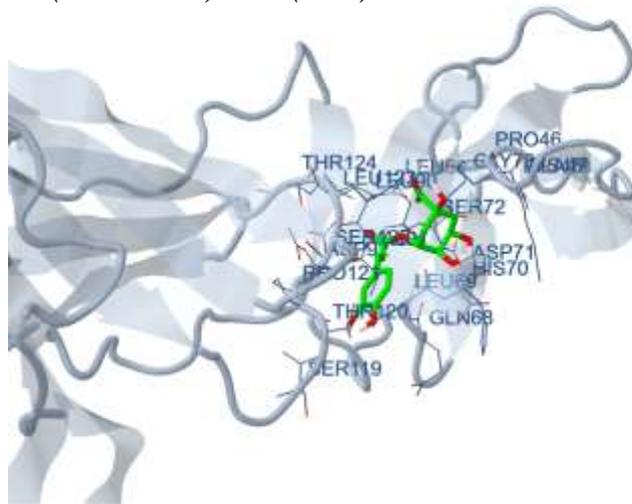
2D Interaction Plot Analysis



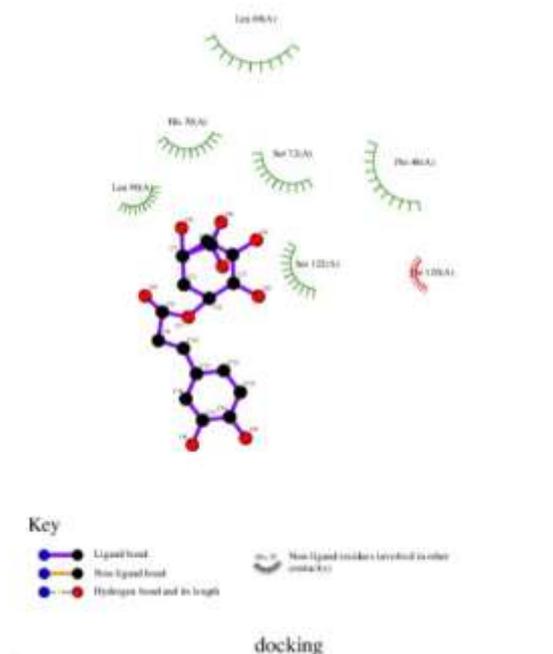
Hydrogen bond plotting with core amino acid Analysis



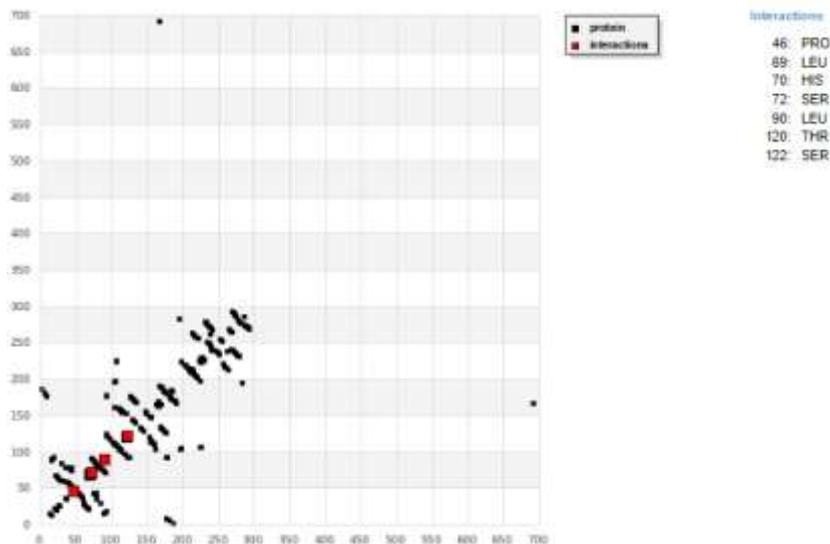
Chlorogenic acid with IL6 (Interleukin 6) PDB- (1N26)



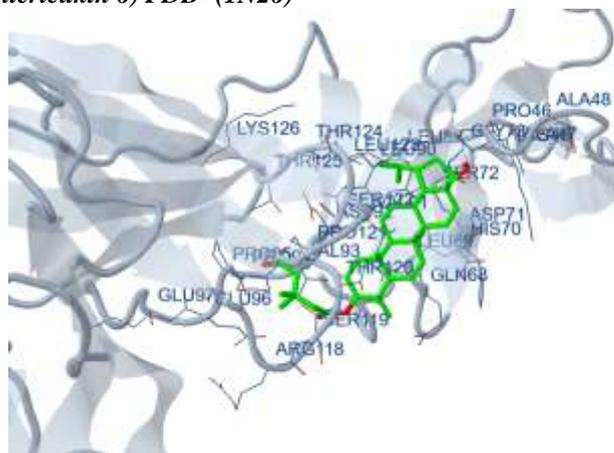
2D Interaction Plot Analysis



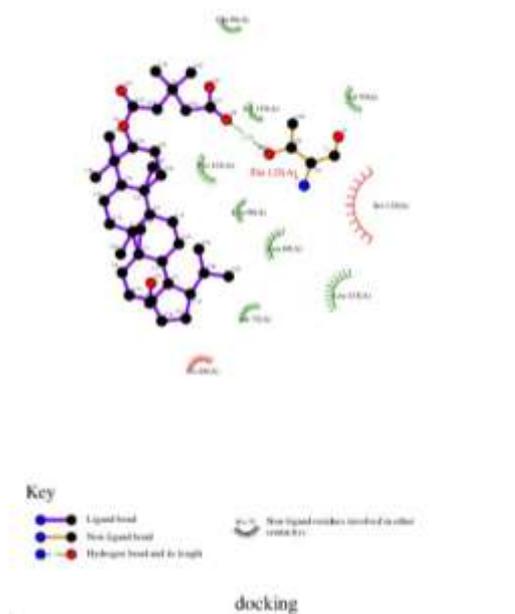
Hydrogen bond plotting with core amino acid Analysis



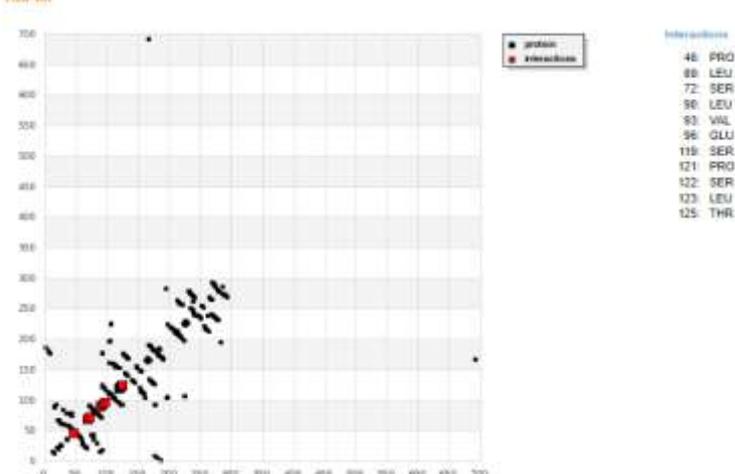
Betulinic acid with IL6 (Interleukin 6) PDB- (1N26)



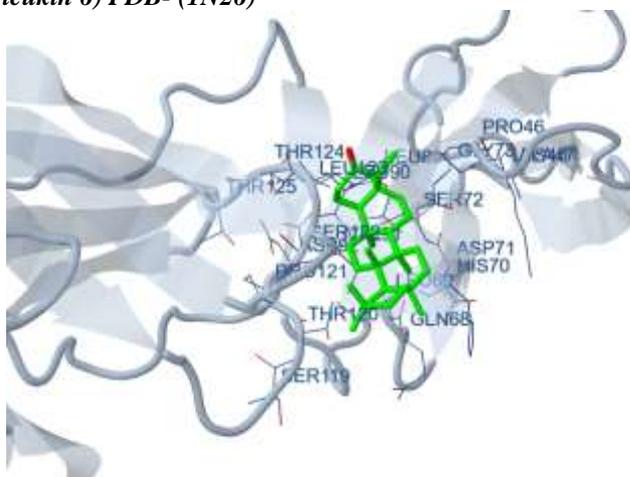
2D Interaction Plot Analysis



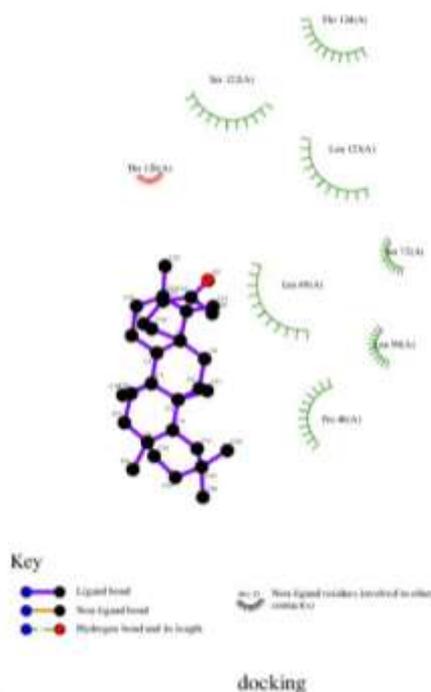
Hydrogen bond plotting with core amino acid Analysis



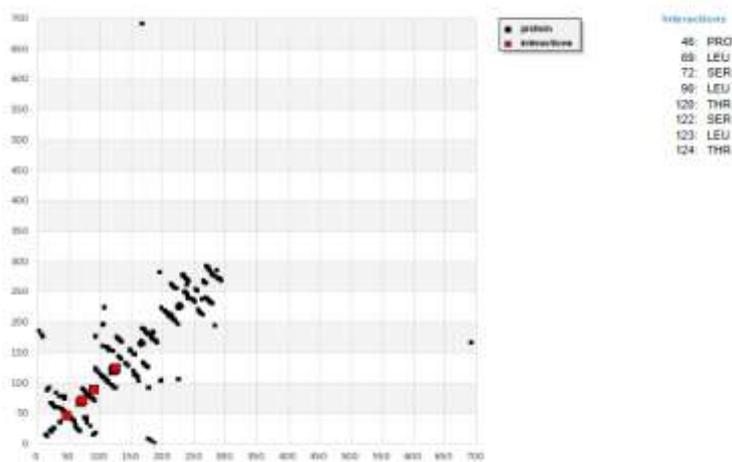
Friedelin with IL6 (Interleukin 6) PDB- (1N26)



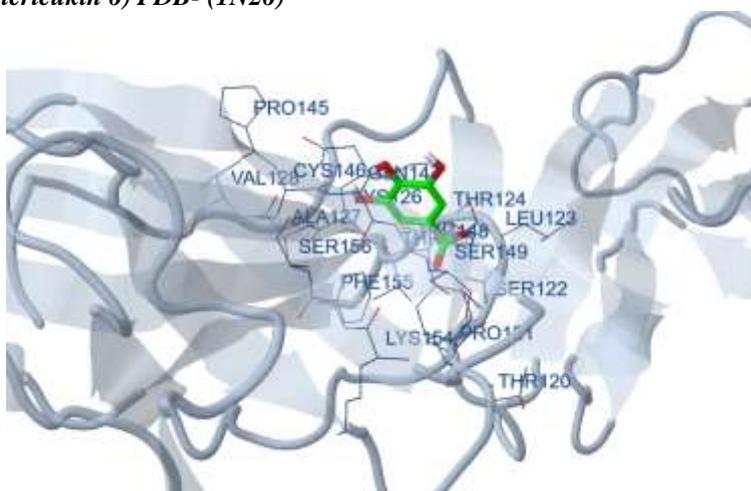
2D Interaction Plot Analysis



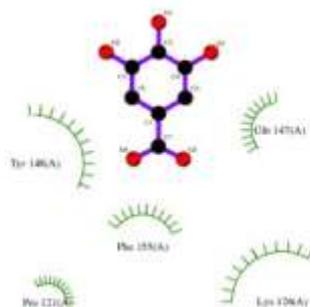
Hydrogen bond plotting with core amino acid Analysis



Gallic acid with IL6 (Interleukin 6) PDB- (1N26)

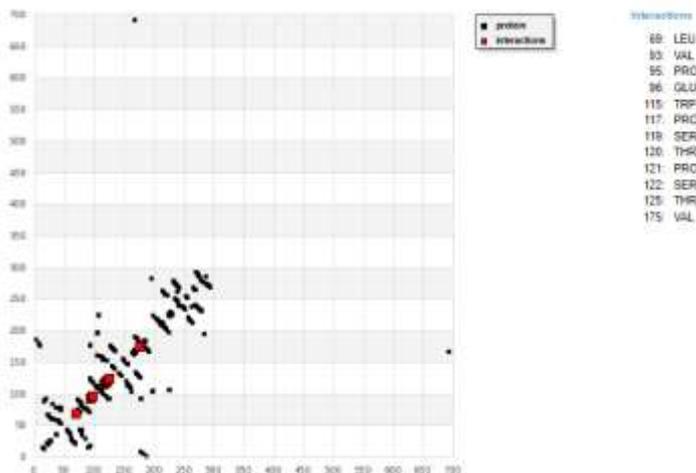


2D Interaction Plot Analysis

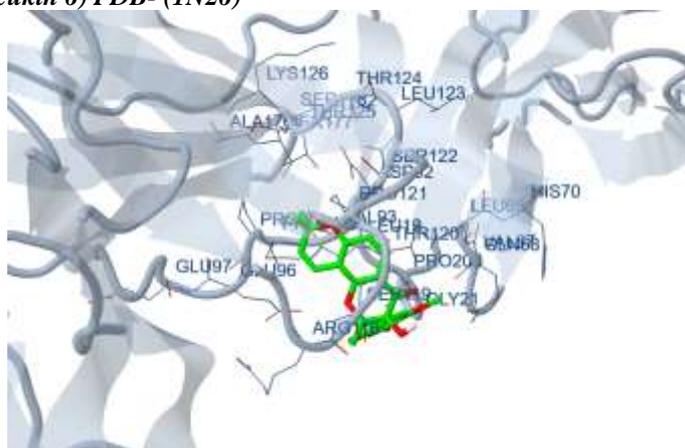


docking

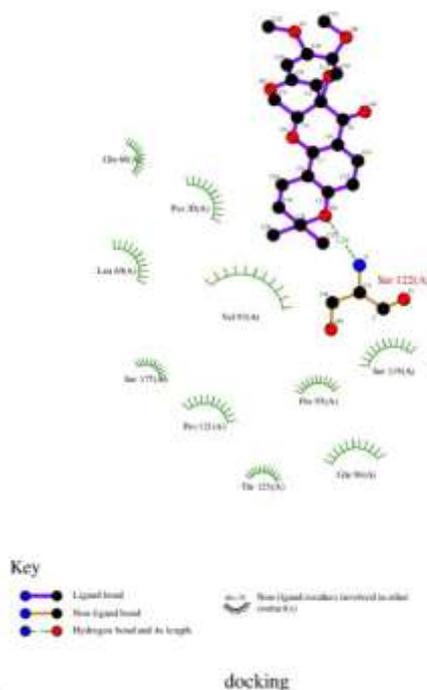
Hydrogen bond plotting with core amino acid Analysis



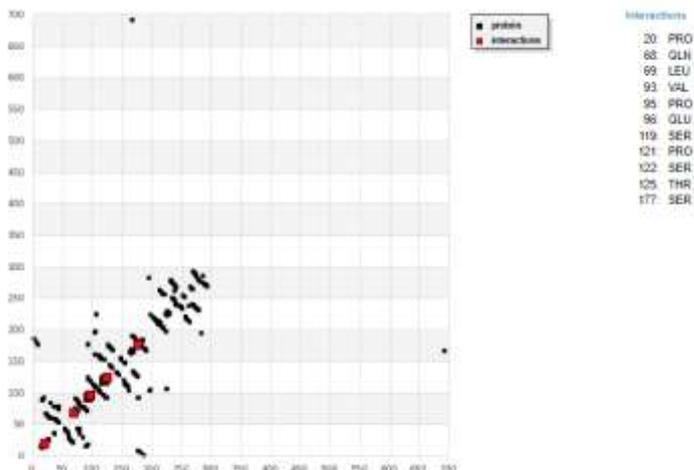
Tephrosin with IL6 (Interleukin 6) PDB- (1N26)



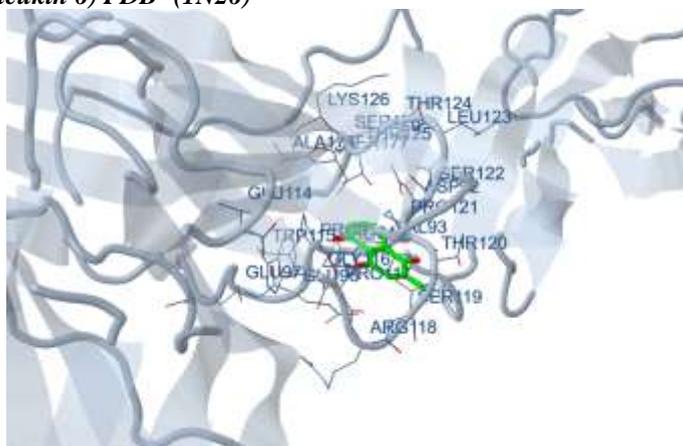
2D Interaction Plot Analysis



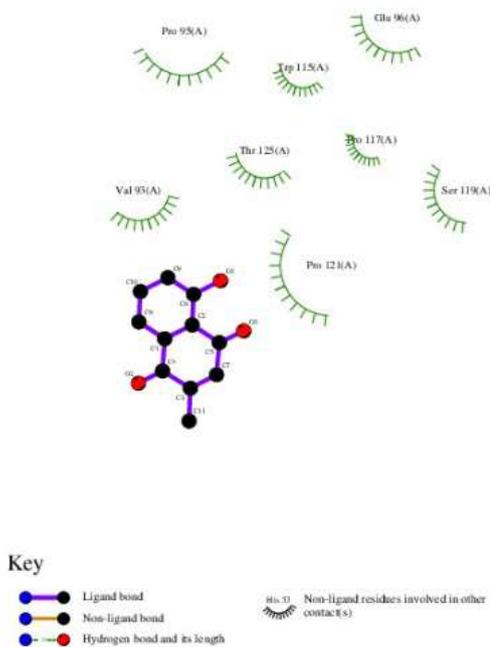
Hydrogen bond plotting with core amino acid Analysis



Plumbagin with IL6 (Interleukin 6) PDB- (1N26)

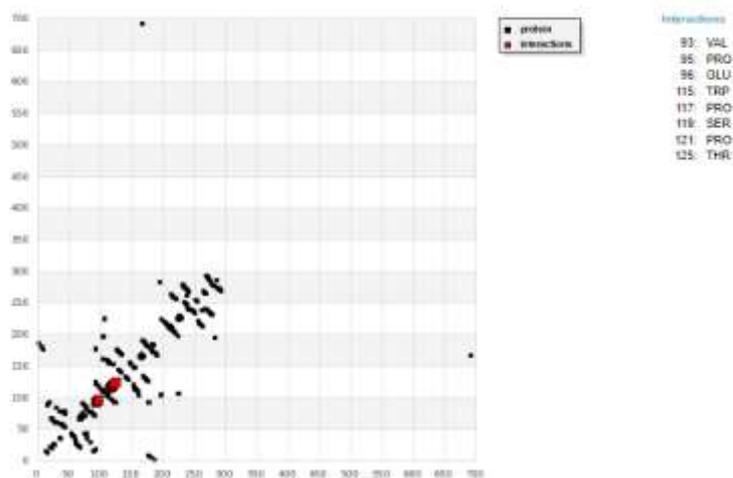


2D Interaction Plot Analysis

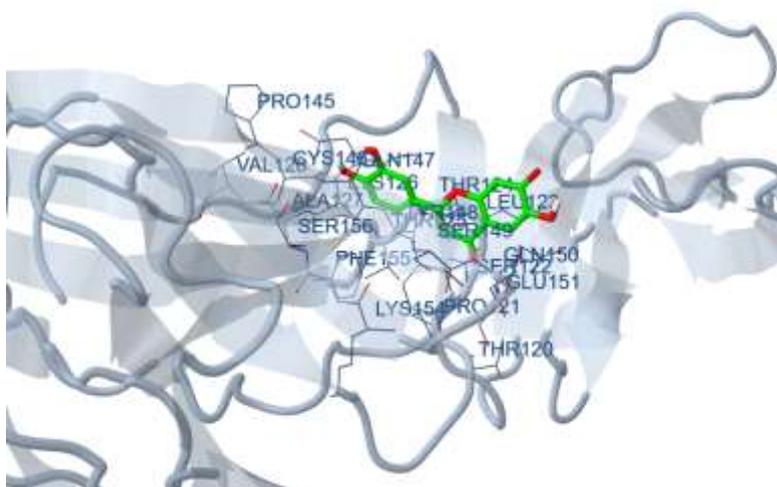


docking

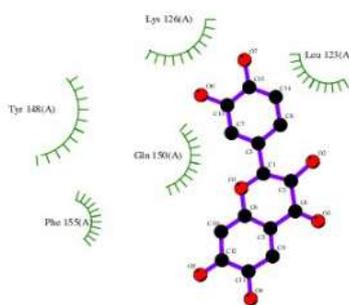
Hydrogen bond plotting with core amino acid Analysis



Quercetin with IL6 (Interleukin 6) PDB- (1N26)



2D Interaction Plot Analysis

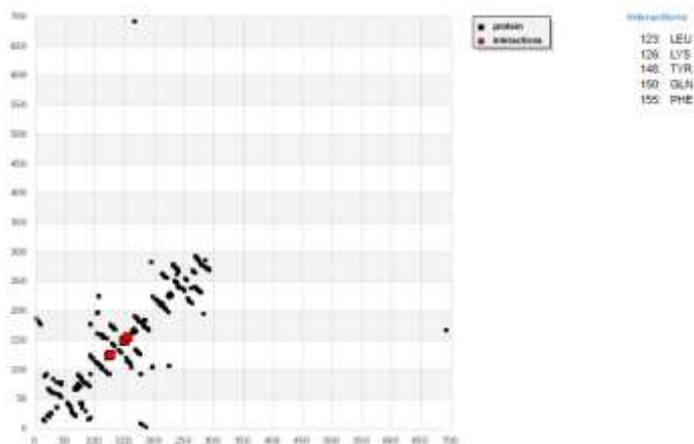


Key

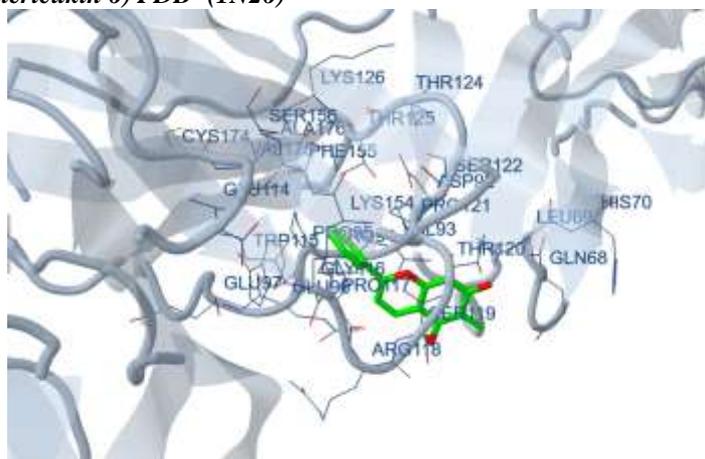
- ● Ligand bond
- ● Non-ligand bond
- ● Hydrogen bond and its length
- Non-ligand residues involved in other contacts

docking

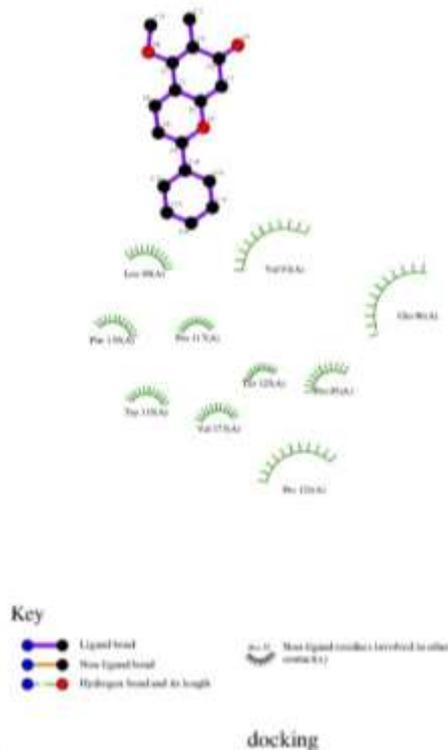
Hydrogen bond plotting with core amino acid Analysis



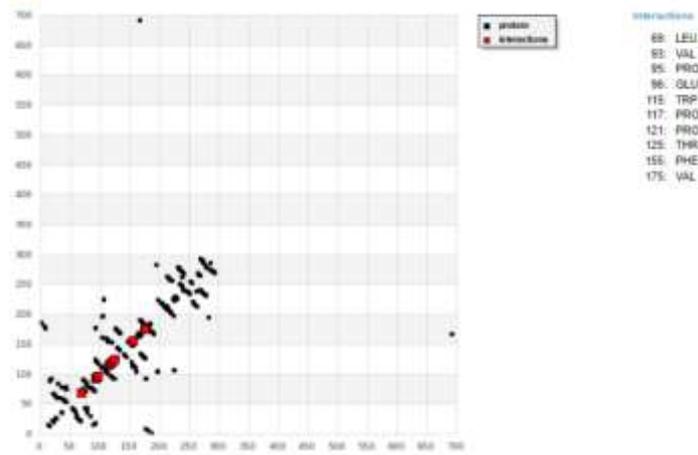
Dracorhodin with IL6 (Interleukin 6) PDB- (1N26)



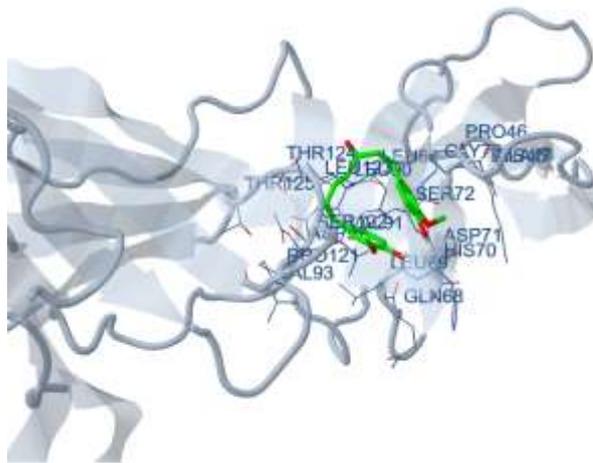
2D Interaction Plot Analysis



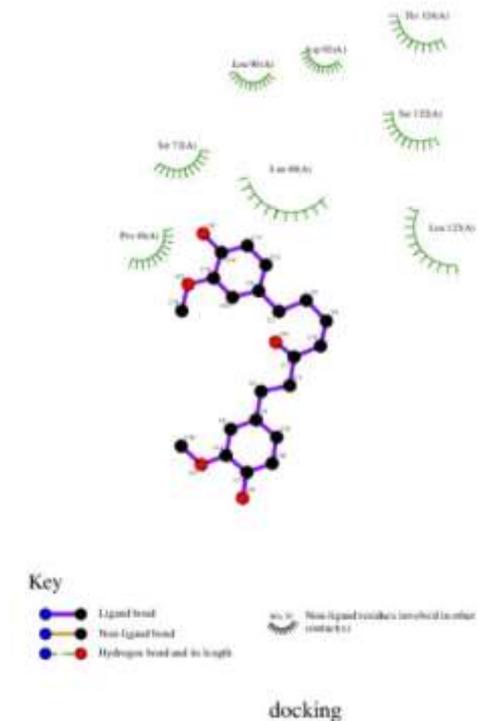
Hydrogen bond plotting with core amino acid Analysis



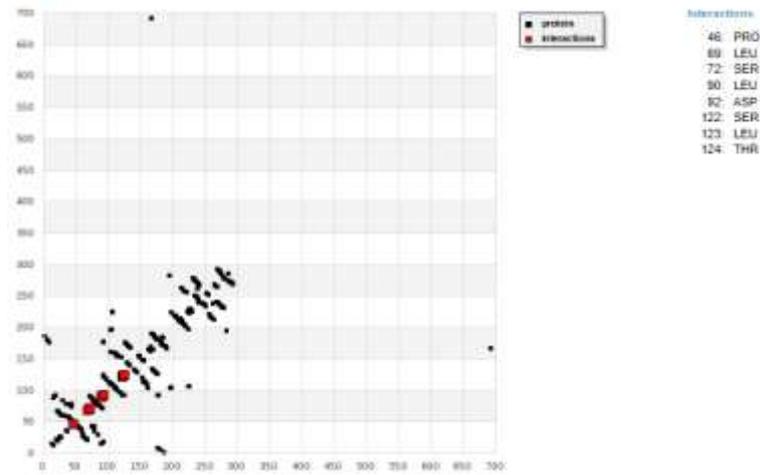
Gingerenone-A with IL6 (Interleukin 6) PDB- (1N26)



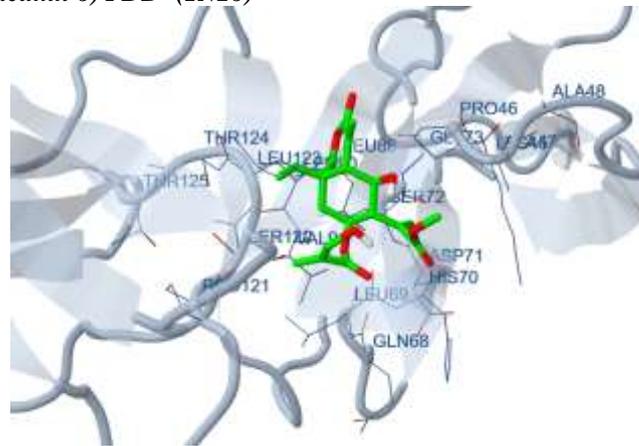
2D Interaction Plot Analysis



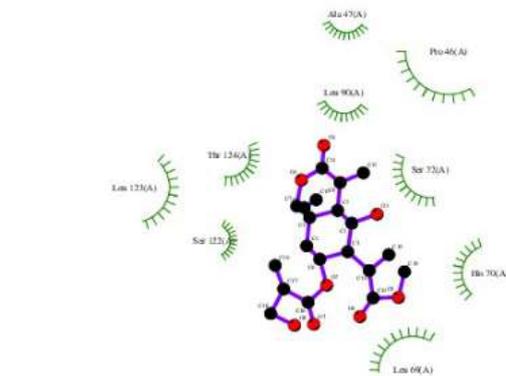
Hydrogen bond plotting with core amino acid Analysis



Vernodalol with IL6 (Interleukin 6) PDB- (1N26)



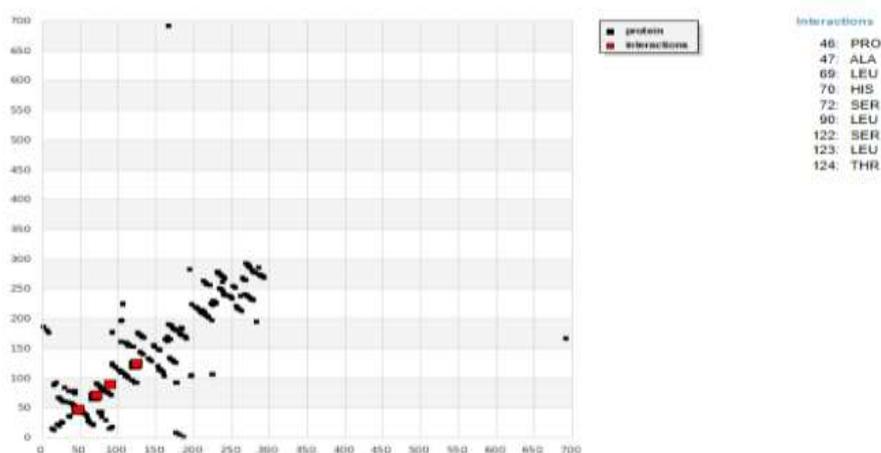
2D Interaction Plot Analysis



Key

- Ligand bond
- Non-ligand bond
- Hydrogen bond and its length
- Res 33 Non-ligand residues involved in other contacts

docking

Hydrogen bond plotting with core amino acid Analysis**6. INTERPRETATION**

Total of 14 bioactive lead compounds were retrieved from the herbs present in the siddha formulation. From reported data of the herb, the phytochemicals such as Withaferin A, Chlorogenic acid, Betulinic acid, Friedelin, Embelin, Azimine, Tephrosin, Dracorhodin, Gingerenone-A, Vernodalol and Plumbagin possess maximum of three to six interactions with the core active amino acid residues present on the target IL6 (Interleukin 6).

7. CONCLUSION

Based on the results of the computational analysis it was concluded that all the bio-active compound's like Withaferin A, Chlorogenic acid, Betulinic acid, Friedelin, Embelin, Azimine, Tephrosin, Dracorhodin, Gingerenone-A, Vernodalol and Plumbagin reveals significant binding affinity against the target cytokine IL6 by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts promising anti-inflammatory activity. Hence, we conclude that the Siddha medicine.

8. REFERENCES

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