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IN-SILICO MOLECULAR DOCKING STUDIES OF SIDDHA HERBAL FORMULATION *MAHALAVANGATHI CHOORANAM FOR ITS* ANTI- INFLAMMATORY ACTIVITY

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ABSTRACT
The Indian system of medicine is of great antiquity. It is the culmination of Indian medical practice representing a healthy way of life cherished by a long and unique cultural history that also amalgamating the best of influences that have come into contact with other civilizations. Siddha medicine is one of the most ancient medical system of India. Psoriasis is one of the chronic inflammatory diseases that mentioned in siddha texts. Interleukin-6 which is an active cytokine in developing the psoriasis condition in an individual. Siddha medicine is known for its effectiveness in managing psoriasis. The aim of this article is to find out the intraction of siddha herbal drug *Mahalavangathi chooranam* (MC) with the Interleukin -6 with its Anti- Inflammatory action.

KEYWORDS: Psoriasis, Interleukin-6, Anti- inflammatory action.

1. INTRODUCTION

Psoriasis is a common chronic Inflammatory dermatosis. It affects the persons of all ages. Psoriasis sometimes associated with arthritis, myopathy, enteropathy, spondylitic joint disease or the acquired immune deficiency syndrome. Psoriasis most frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, inter gluteal cleft and glans penis. The typical lesion is a well-demarcated, pink to salmon coloured plaque covered by silver-white scales.

High level of Interleukin 6 (IL-6) is found in active psoriatic skin. Interleukin 6 (IL-6), a cytokine that is a major mediator of the host response to tissue injury and infection, is produced by both keratinocytes and leukocytes in culture. The histopathology is characterized by epidermal hyperplasia and inflammation. IL-6 is found in the papillary tip regions, superficial horizontal vascular plexus and dermal infiltrates of psoriatic skin. Thus, IL-6 could directly contribute to the epidermal hyperplasia seen in psoriatic epithelium as well as affect the function of dermal inflammatory cells.

In traditional siddha system of medicine, the clinical characteristics of psoriasis is widely correlated with the condition called "*Kaalaanjagam*". Lots of herbal and herbomineral medication given for the condition. *Mahalavangathi chooranam* (MC) is one of the herbal medicine which formulation is mentioned in the siddha classical text "*Anuboga vaithiya bramma ragasiyam - moondram gaandam". Cinnamomum verum, Mesua nagassarium, Elettaria cardamomum, Piper nigrum, Piper longum, Zingiber officinale, Withania somniferum, Saccharum officinarum* are the ingredients of this herbal formulation.

For a wider research perspective, the lead molecules of this formulation were interpreted on Interleukin 6 (IL-6) with its Anti-Inflammatory activity. This may help the adequecy of MC as an efficient Anti-Inflammatory herbal formulation.

2. In-Silico Anti-Inflammatory Activity
Name of the Formulation: Mahalavangathi Chooranam
List of Phytocomponents Selected for docking

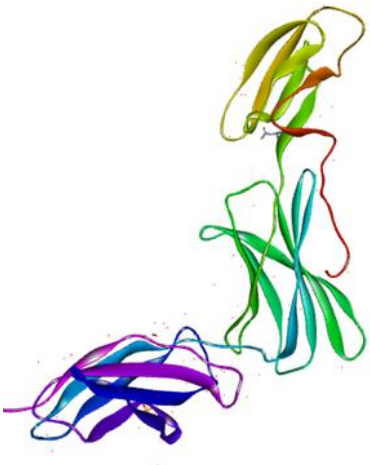
Herbs	**Phytochemicals**	**References**
Cinnamomum verum	Cinnamic acid	Singh N, Rao AS, Nandal A, Kumar S, Yadav SS, Ganaie SA, Narasimhan B. Phytochemical and pharmacological review of Cinnamomum verum J. Presl-a versatile spice used in food and nutrition. Food Chem. 2021 Feb 15;338:127773.
Mesua nagassarium	β-sitosterol	Hegde S, Saini A, Hegde HV, Kholkute SD, Roy S. Molecular identification of Saraca asoca from its substituents and adulterants. 3 Biotech. 2018 Mar;8(3):161.
Elettaria cardamomum	Nerolidol	Ashokkumar K, Murugan M, Dhanya MK, Raj S, Kamaraj D. Phytochemical variations among four distinct varieties of Indian cardamom Elettaria cardamomum (L.) Maton. Nat Prod Res. 2020 Jul;34(13):1919-1922. doi: 10.1080/14786419.2018.1561687
Piper nigrum	Piperic acid	Bahare Salehi. Piper Species: A Comprehensive Review on Their Phytochemistry, Biological Activities and Applications. Molecules. 2019 Apr; 24(7): 1364.
Piper longum	Piperine	Anshuly Tiwari. Piperine: A comprehensive review of methods of isolation, purification, and biological properties. Medicine in Drug Discovery .2020;7: 100027
Zingiber officinale	Gingerenone-A	Sahdeo Prasad. Ginger and Its Constituents: Role in Prevention and Treatment of Gastrointestinal Cancer. Gastroenterology Research and Practice. 2015:1-11
Withania somnifera	Withaferin A Chlorogenic acid	Saleem S, Muhammad G, Hussain MA, Altaf M, Bukhari SNA. Withania somnifera L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. Iran J Basic Med Sci. 2020;23(12):1501-1526.
Saccharum officinarum	Orientin Vitexin Swertisin	Singh, A., Lal, U. R., Mukhtar, H. M., Singh, P. S., Shah, G., & Dhawan, R. K. (2015). Phytochemical profile of sugarcane and its potential health aspects. Pharmacognosy reviews, 9(17), 45–54. https://doi.org/10.4103/0973-7847.15634

3. Objective

Binding of phytocomponents 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 phytocomponents 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 atom 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.

3.3 Ligand Preparation

Phytochemical 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).

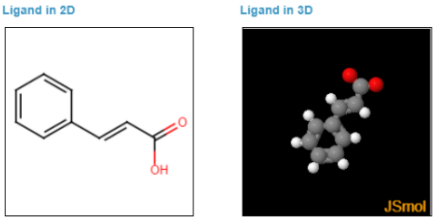
4. METHODOLOGY

Docking calculations were carried out for retrieved phytocomponents 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 ×× 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

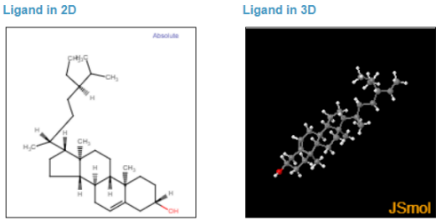
terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. 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 Phytocomponents

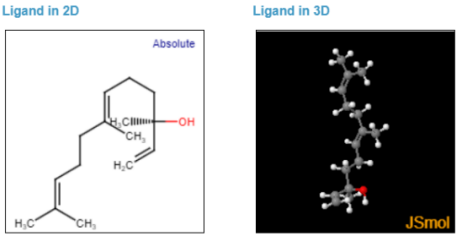
Cinnamic acid



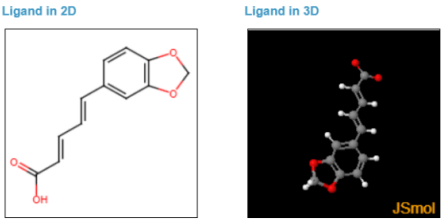
β-sitosterol



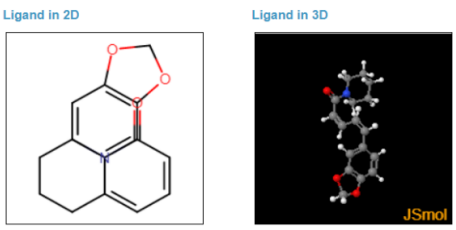
Nerolidol



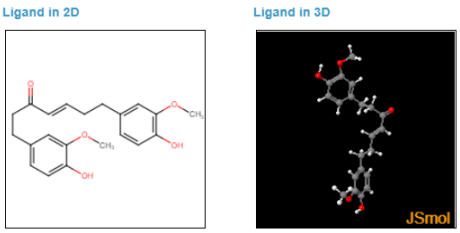
Piperic acid



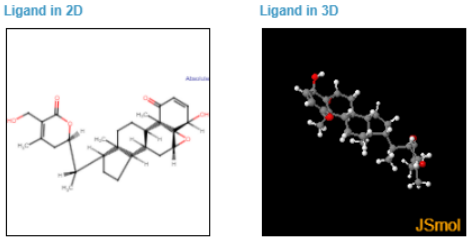
Piperine



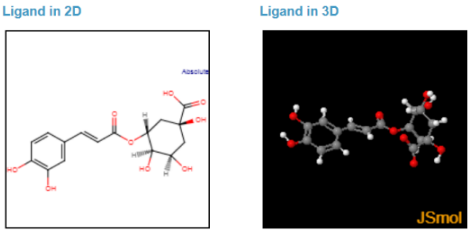
Gingerenone-A



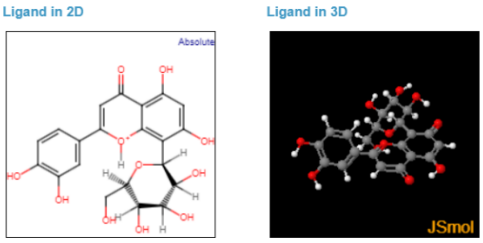
Withaferin A



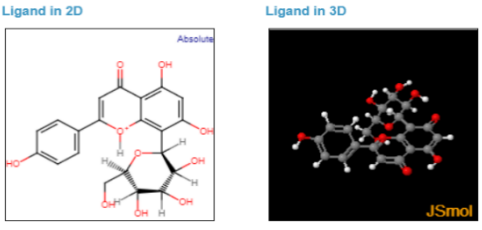
Chlorogenic acid



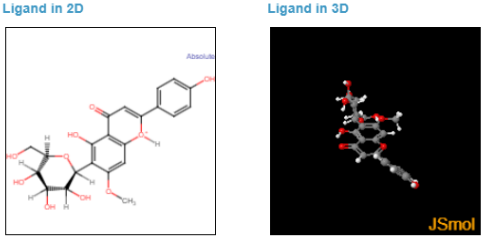
Orientin



Vitexin



Swertisin



Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Cinnamic acid	148.16 g/mol	$C_9H_8O_2$	1	2	2
β-sitosterol	414.7g/mol	$C_{29}H_{50}O$	1	1	6
Nerolidol	222.37 g/mol	$C_{15}H_{26}O$	1	1	7
Piperic acid	218.2 g/mol	$C_{12}H_{10}O_4$	1	4	3
Piperine	285.34 g/mol	$C_{17}H_{19}NO_3$	0	3	3
Gingerenone-A	356.4 g/mol	$C_{21}H_{24}O_5$	2	5	9
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
Orientin	448.4 g/mol	$C_{21}H_{20}O_{11}$	8	11	3
Vitexin	432.4 g/mol	$C_{21}H_{20}O_{10}$	7	10	3
Swertisin	446.4 g/mol	$C_{22}H_{22}O_{10}$	6	10	4

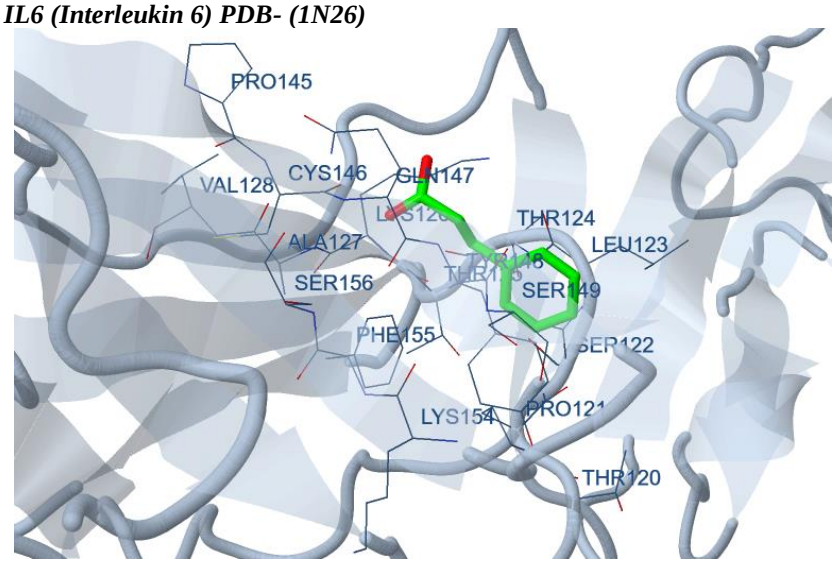
5.1 Results of the molecular docking studies of compounds against IL6 (Interleukin 6) (1N26)

Compounds	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Cinnamic acid	-5.48 kcal/mol	95.80 uM	-0.82 kcal/mol	-6.08 kcal/mol	447.748
β-sitosterol	-7.91 kcal/mol	1.59 uM	-0.05 kcal/mol	-9.29 kcal/mol	824.906
Nerolidol	-5.54 kcal/mol	86.44 uM	-0.06 kcal/mol	-7.50 kcal/mol	595.46
Piperic acid	-5.39 kcal/mol	112.77 uM	-0.42 kcal/mol	-6.24 kcal/mol	549.698
Piperine	-7.28 kcal/mol	4.64 uM	-0.01 kcal/mol	-8.09 kcal/mol	649.9
Gingerenone-A	-7.19 kcal/mol	5.39 uM	-0.06 kcal/mol	-5.77 kcal/mol	659.92
Withaferin A	-8.34 kcal/mol	773.98 nM	-0.06 kcal/mol	-8.77 kcal/mol	888.84
Chlorogenic acid	-6.87 kcal/mol	9.28 uM	-0.26 kcal/mol	-6.43 kcal/mol	682.904
Orientin	-8.08 kcal/mol	1.19 uM	-0.09 kcal/mol	-5.78 kcal/mol	639.786
Vitexin	-7.43 kcal/mol	3.57 uM	-0.24 kcal/mol	-6.99 kcal/mol	636.133
Swertisin	-7.92 kcal/mol	1.57 uM	-0.17 kcal/mol	-7.10 kcal/mol	881.372

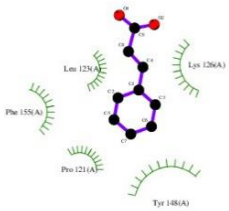
5.2 Amino acid Residue Interaction of Lead against IL6 (Interleukin 6) PDB- (1N26)

Compounds	Interactions	Amino acid Residues											
Cinnamic acid	1	121	123	126	148	155							
		PRO	LEU	LYS	TYR	PHE							
β-sitosterol	4	46	69	72	90	93	119	122	123	124			
		PRO	LEU	SER	LEU	VAL	SER	SER	LEU	THR			
Nerolidol	4	69	93	95	96	115	119	121	122	125			
		LEU	VAL	PRO	GLU	TRP	SER	PRO	SER	THR			
Piperic acid	2	120	121	123	126	148	150	155					
		THR	PRO	LEU	LYS	TYR	GLN	PHE					
Piperine	6	69	93	95	96	115	117	119	120	121	122	123	125
		LEU	VAL	PRO	GLU	TRP	PRO	SER	THR	PRO	SER	LEU	THR
Gingerenone-A	3	46	69	72	90	122	123	124					
		PRO	LEU	SER	LEU	SER	LEU	THR					
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	2	46	69	72	90	93	122	123					
		PRO	LEU	SER	LEU	VAL	SER	LEU					
Orientin	2	20	69	93	95	96	119	121	125				
		PRO	LEU	VAL	PRO	GLU	SER	PRO	THR				
Vitexin	2	93	94	95	96	115	119	121	125				
		VAL	PRO	PRO	GLU	TRP	SER	PRO	THR				
Swertisin	4	46	47	69	70	72	90	92	93	96	119	122	123
		PRO	ALA	LEU	HIS	SER	LEU	ASP	VAL	GLU	SER	SER	LEU

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

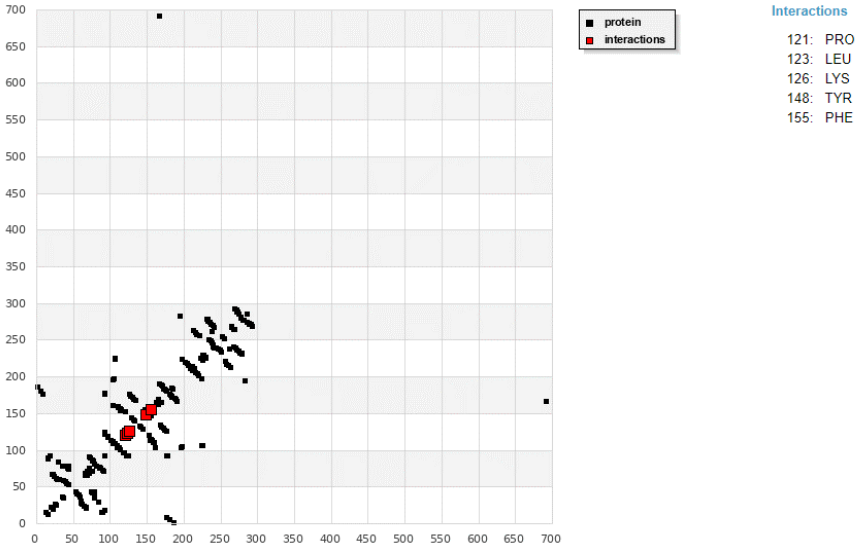


2D Interaction Plot Analysis

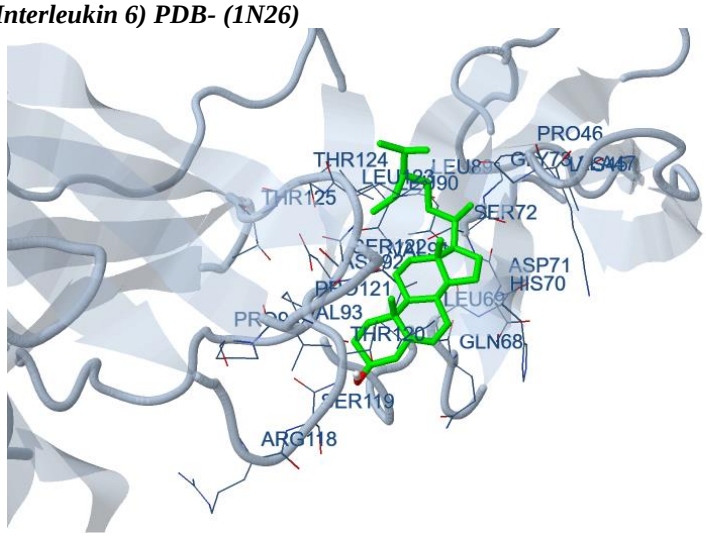


docking

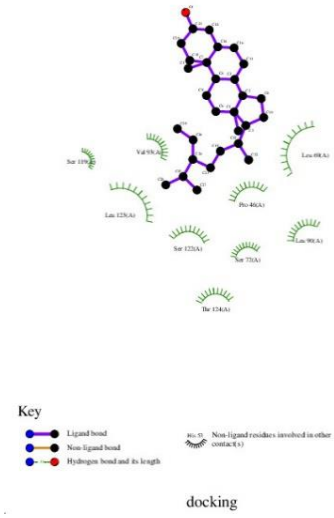
Hydrogen bond plotting with core amino acid Analysis



β-sitosterol with IL6 (Interleukin 6) PDB- (1N26)



2D Interaction Plot Analysis



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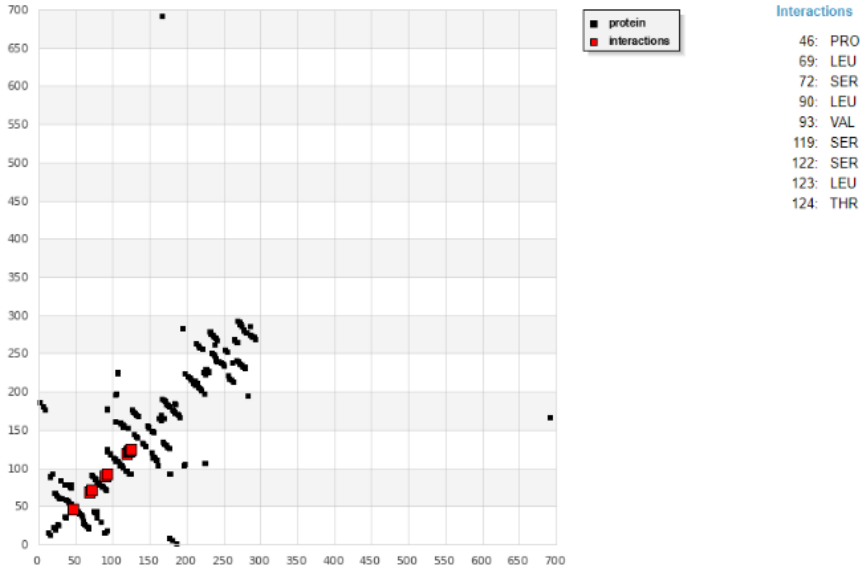
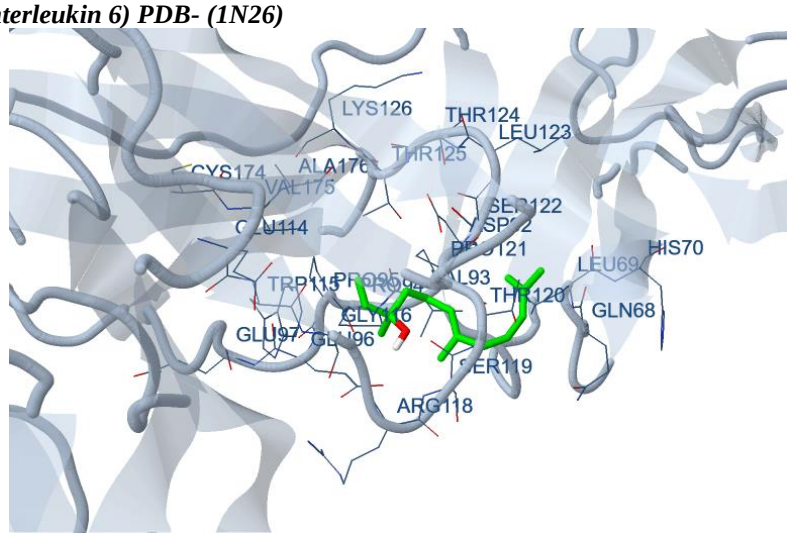
Hydrogen bond plotting with core amino acid Analysis



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



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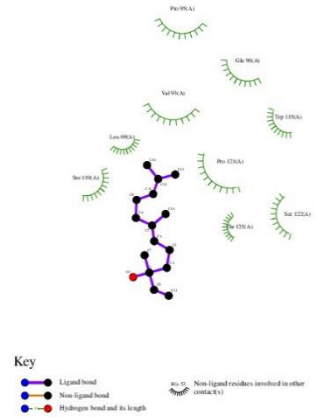

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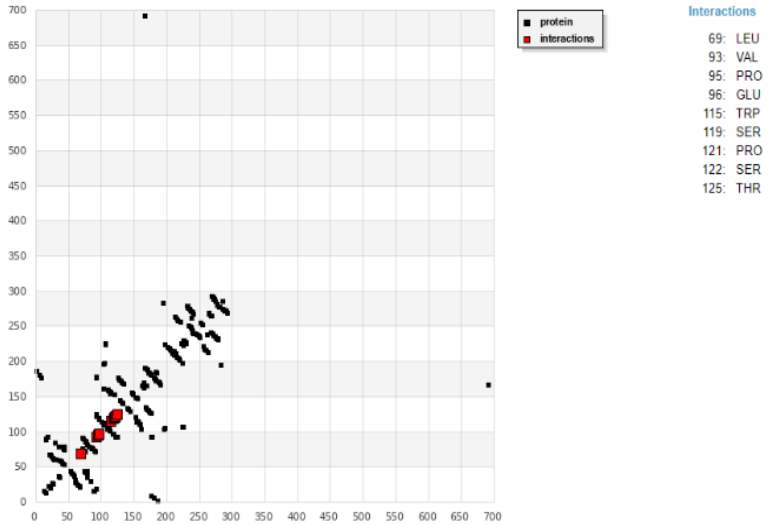
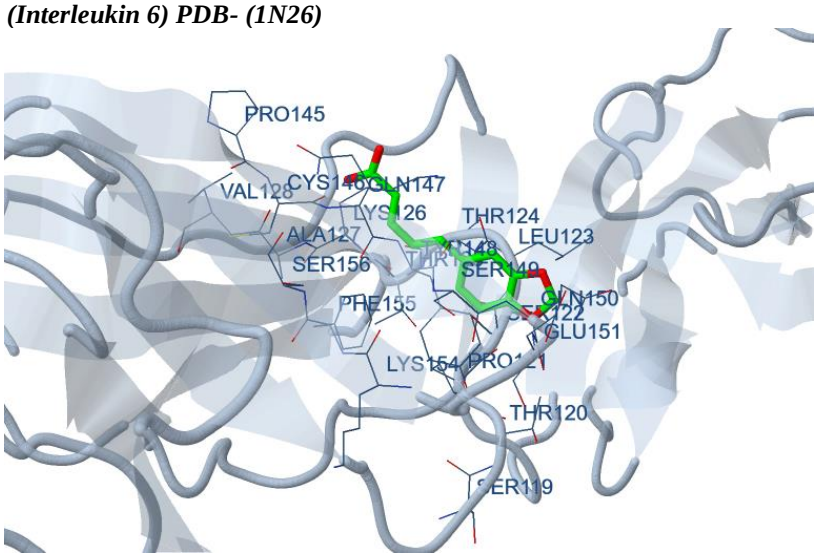
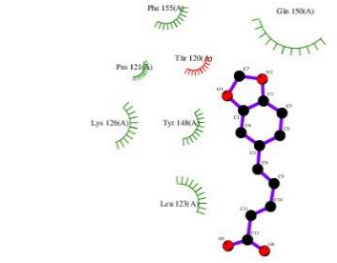
Hydrogen bond plotting with core amino acid Analysis



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

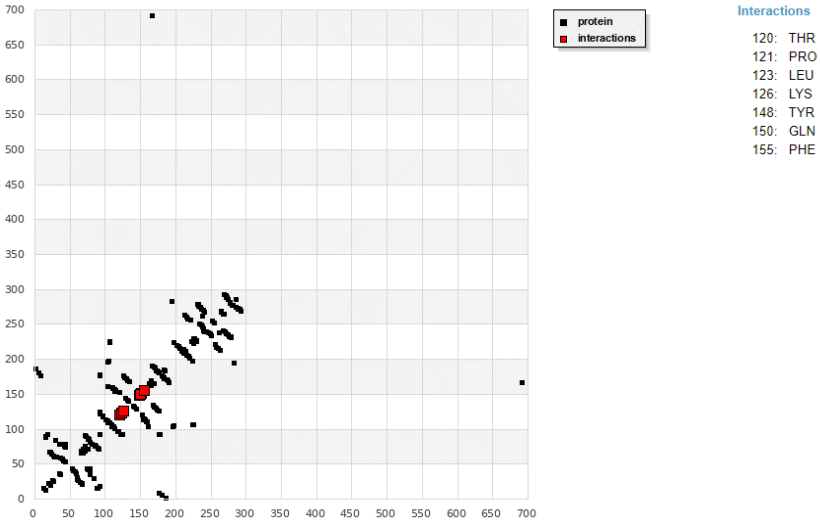


2D Interaction Plot Analysis

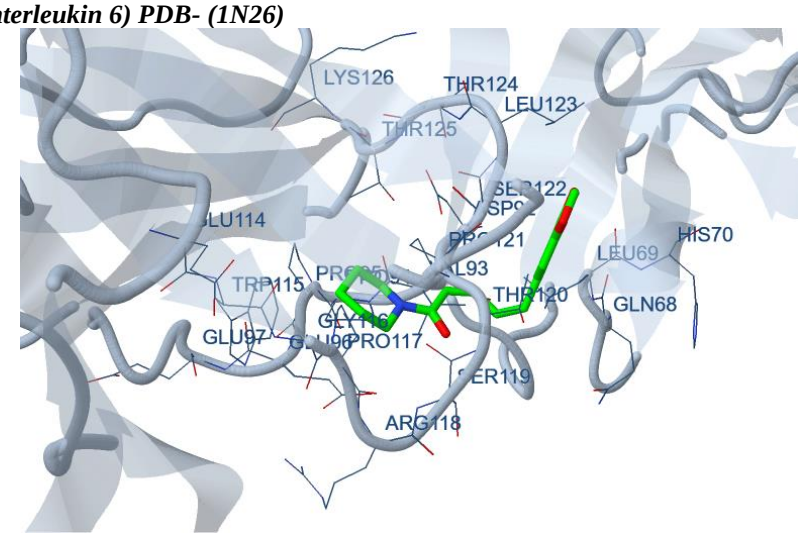


docking

Hydrogen bond plotting with core amino acid Analysis



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



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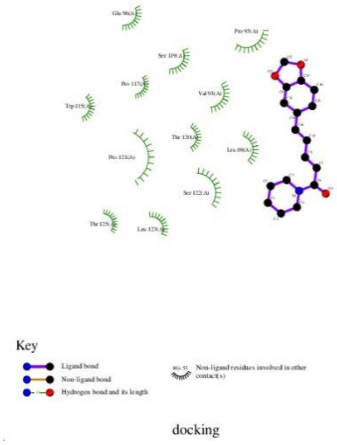
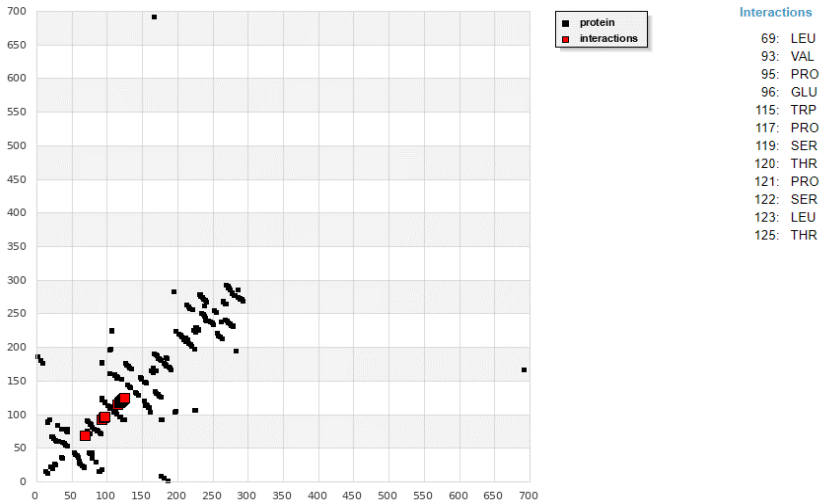
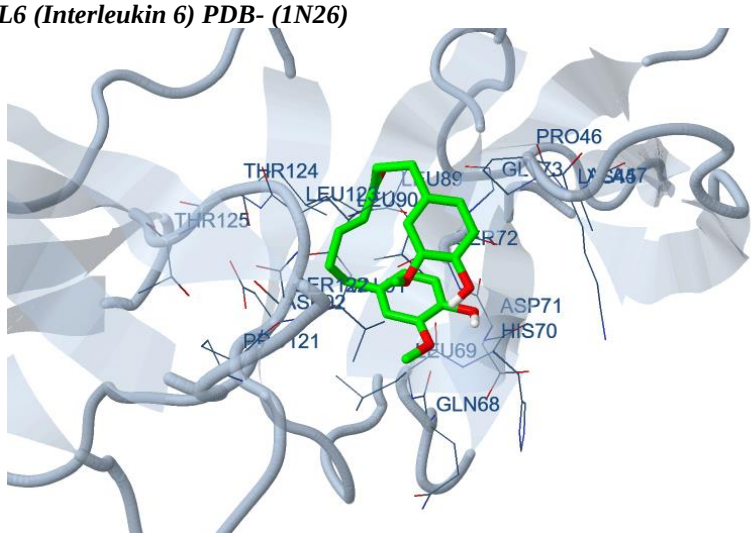


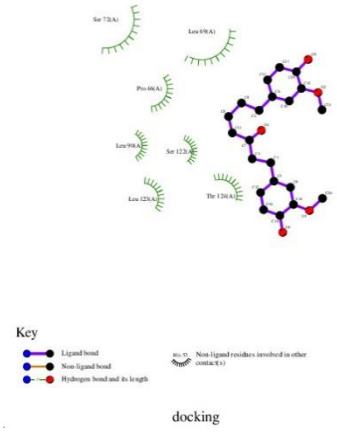
Hydrogen bond plotting with core amino acid Analysis



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

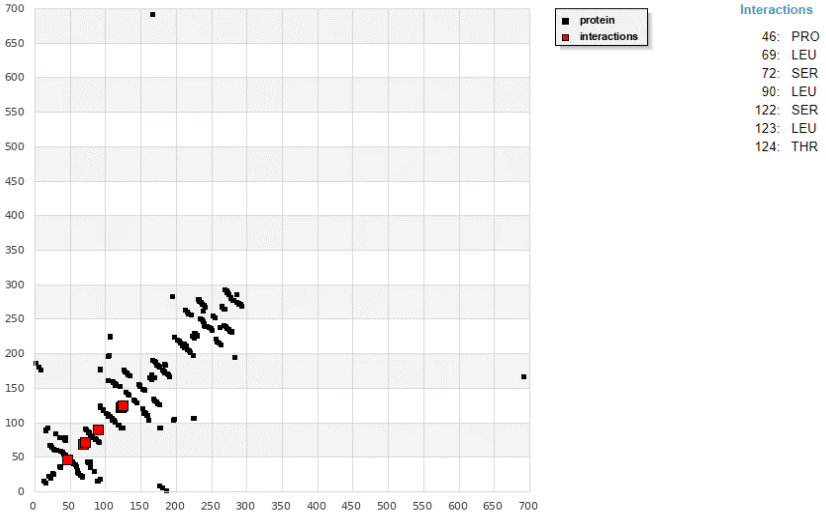


2D Interaction Plot Analysis

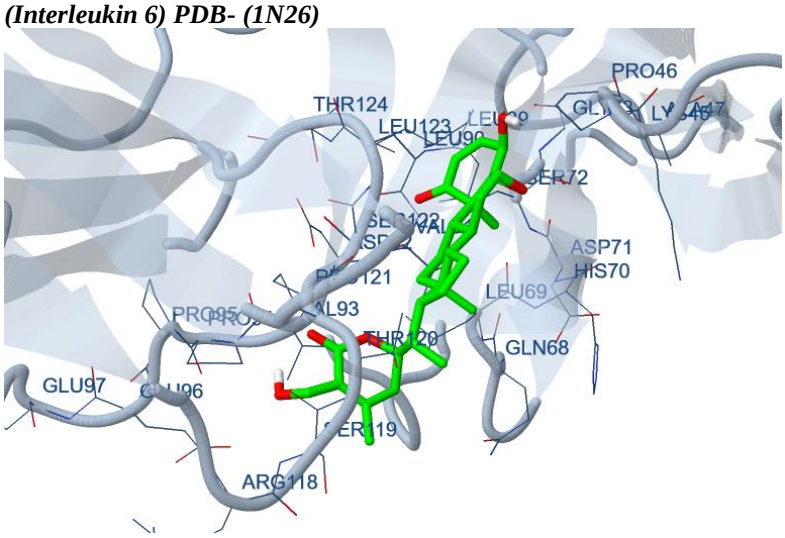


docking

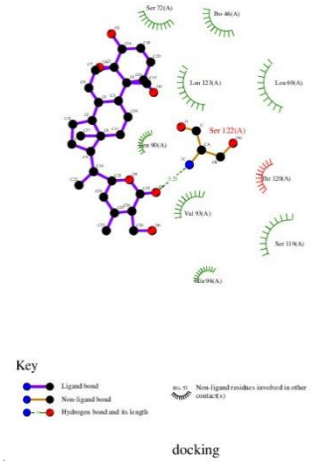
Hydrogen bond plotting with core amino acid Analysis



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

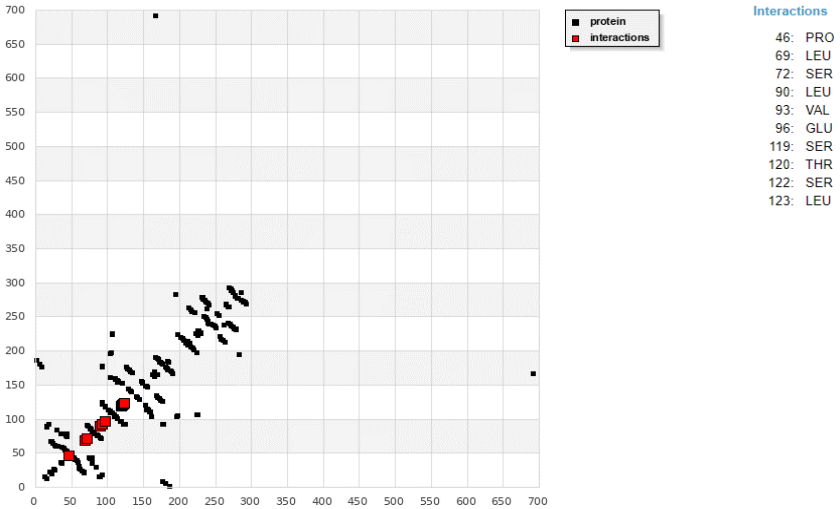


2D Interaction Plot Analysis

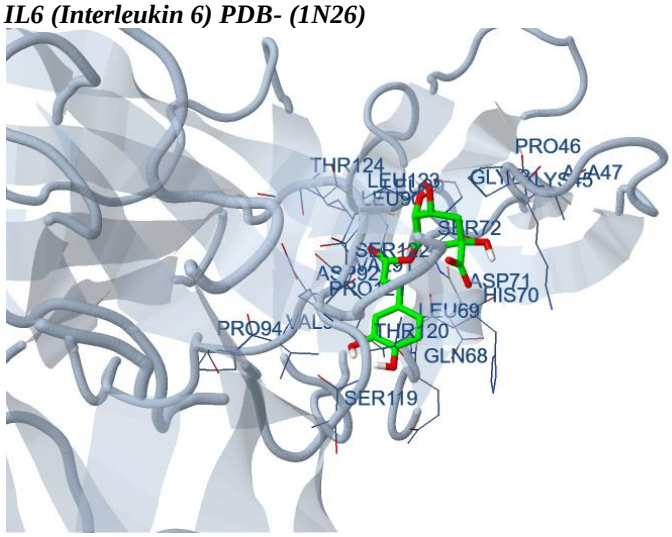


docking

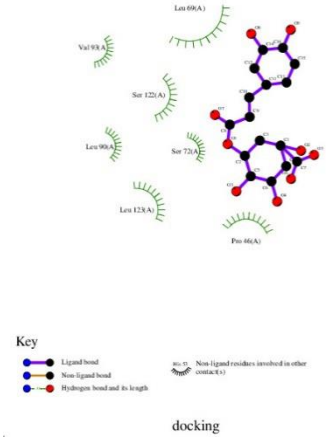
Hydrogen bond plotting with core amino acid Analysis



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

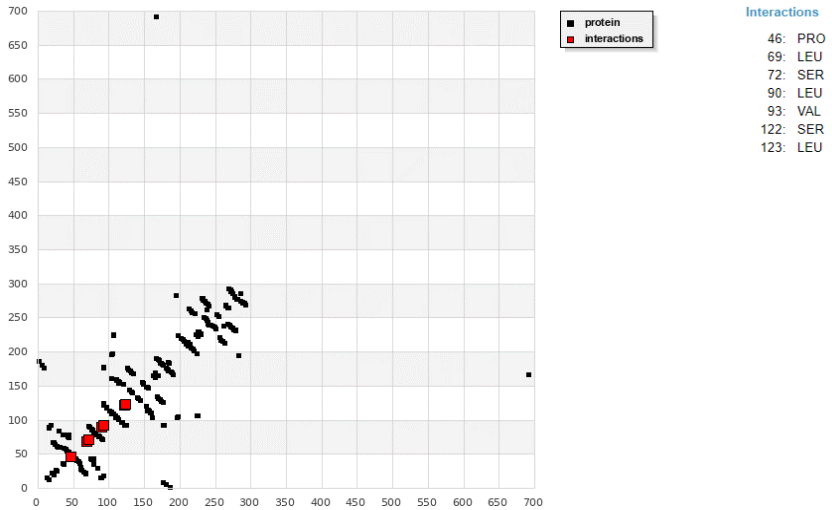


2D Interaction Plot Analysis

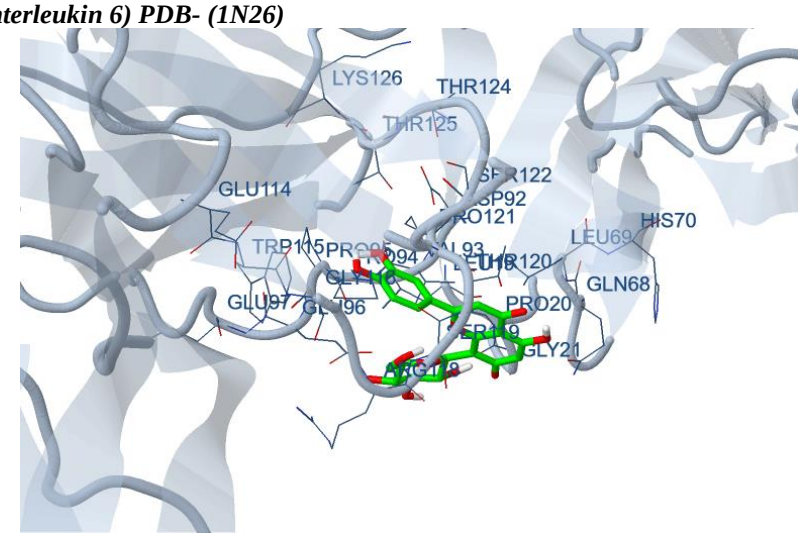


docking

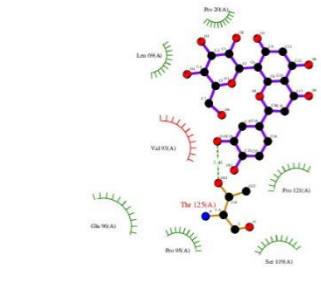
Hydrogen bond plotting with core amino acid Analysis



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

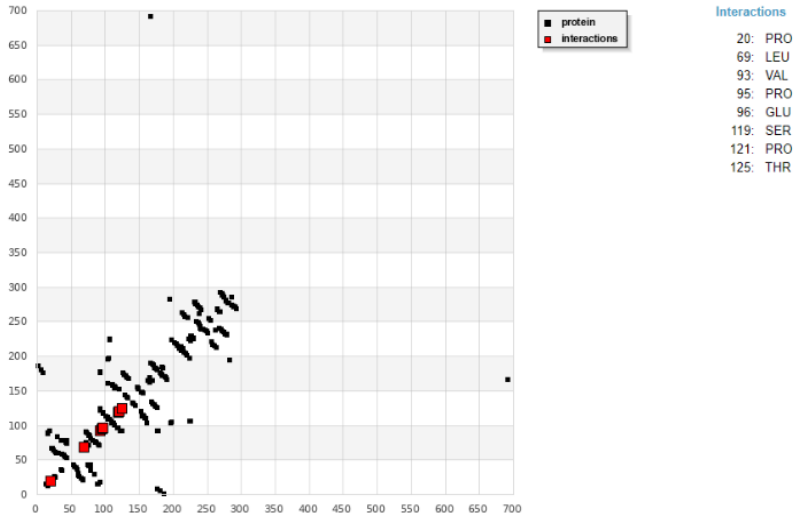


2D Interaction Plot Analysis

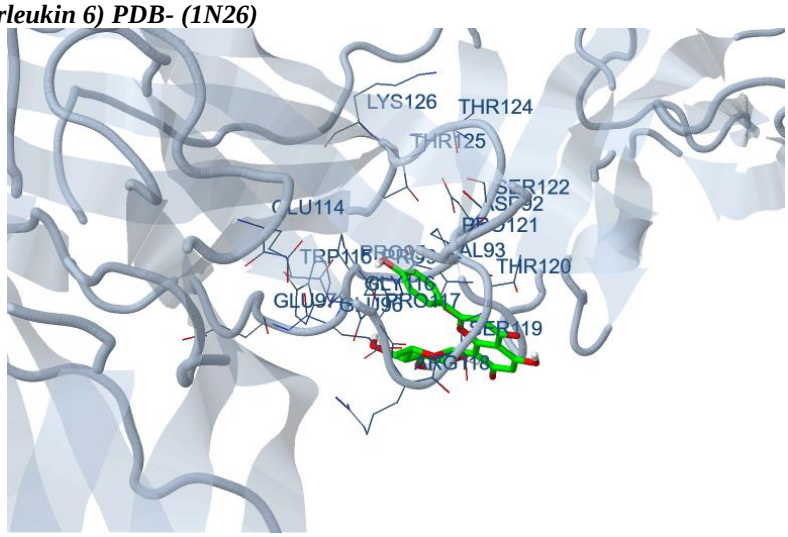


docking

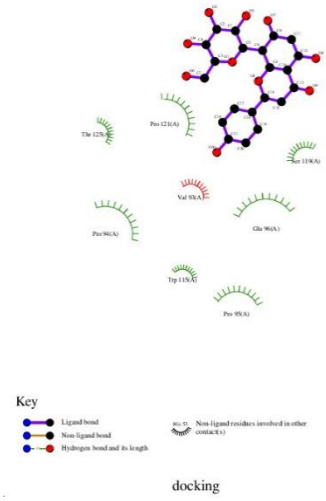
Hydrogen bond plotting with core amino acid Analysis



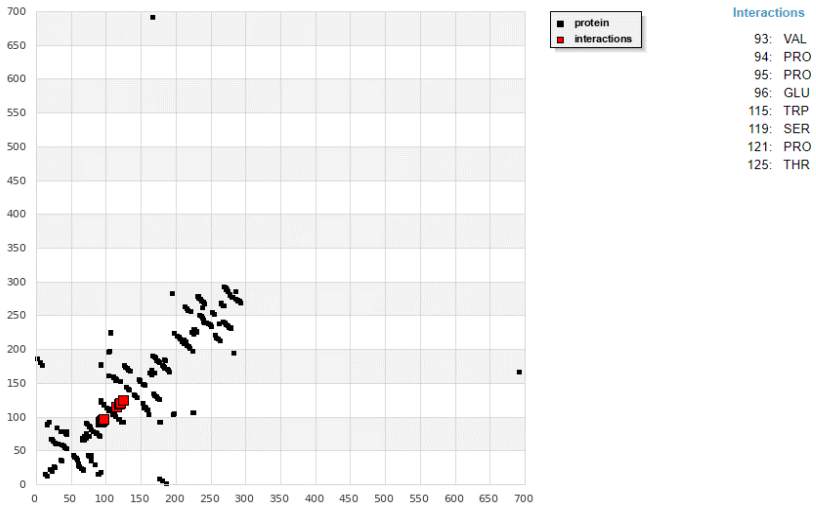
Vitexin with IL6 (Interleukin 6) PDB- (1N26)



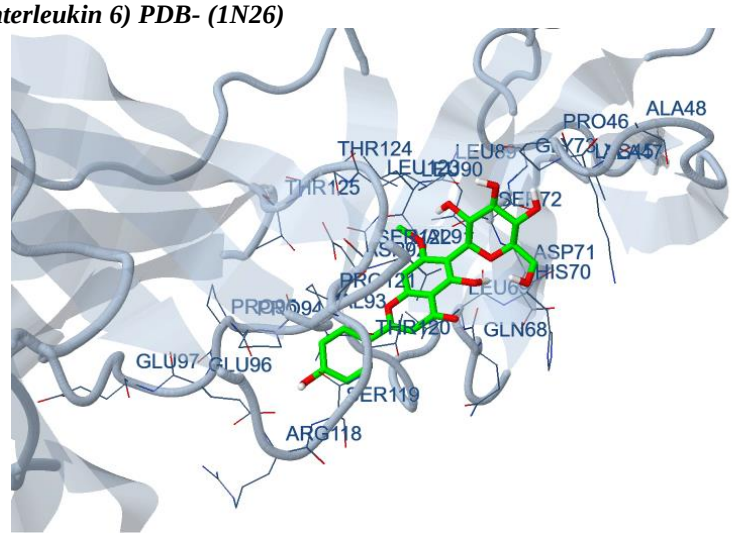
2D Interaction Plot Analysis



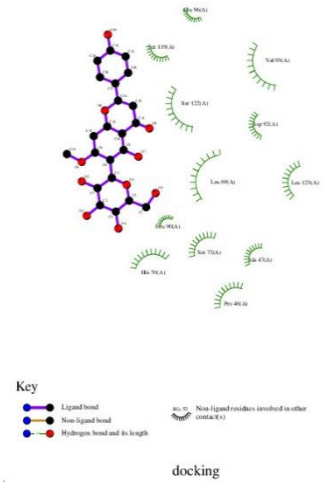
Hydrogen bond plotting with core amino acid Analysis



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



2D Interaction Plot Analysis



Hydrogen bond plotting with core amino acid Analysis

6. RESULT AND DISCUSSION

Total of 11 bioactive lead compounds were retrieved from the herbs present in the siddha formulation ***Mahalavangathi Chooranam***. From reported data of the herb, the phytochemicals such as β-sitosterol , Nerolidol, Piperine, Gingerenone-A, Withaferin A and Swertisin 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 β-sitosterol, Nerolidol, Piperine, Gingerenone-A, Withaferin A and Swertisin of the siddha formulation ***Mahalavangathi Chooranam*** revels 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.

8. REFERENCES

1. Bikadi, Z., Hazai, E.Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock. J. Cheminf., 2009; 1: 15.
2. T. A. Halgren. Merck molecular force field. I. Basis, form, scope, parametrization, and performance of MMFF94. Journal of Computational Chemistry, 1998; 17(5-6): 490-519.
3. G. M. Morris, D. S. Goodsell, et al. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of Computational Chemistry, 1998; 19(14): 1639-1662.
4. Solis, F.J. and Wets, R.J.B. Minimization by Random Search Techniques. Mathematics of Operations Research, 1981; 6: 19-30.
5. Shukla, P., Khandelwal, R., Sharma, D., Dhar, A., Nayarisseri, A., & Singh, S. K. Virtual Screening of IL-6 Inhibitors for Idiopathic Arthritis. Bioinformation, 2019; 15(2): 121–130.

6. Sivaraman Dhanasekaran, Pradeep Pushparaj Selvadoss, Solomon Sundar Manoharan. Anti-Fungal Potential of Structurally Diverse FDA-Approved Therapeutics Targeting Secreted Aspartyl Proteinase (SAP) of Candida albicans: an In Silico Drug Repurposing Approach. Applied Biochemistry and Biotechnology, 195(3): 1983-1998. doi: 10.1007/s12010-022-04207-w
7. Sivaraman Dhanasekaran, Pradeep Pushparaj Selvadoss, Solomon Sundar Manoharan, Srikanth Jeyabalan, Devi Rajeswari Vijayarangan. Revealing Anti-Fungal Potential of Plant-Derived Bioactive Therapeutics in Targeting Secreted Aspartyl Proteinase (SAP) of Candida albicans: A Molecular Dynamics Approach. Journal of Biomolecular Structure and Dynamics, 2023; 6: 1-15. https://doi.org/10.1080/07391102.2023.2196703
8. Anuboga vaithiya bramma ragasiyam - moondram gaandam.