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Molecular docking studies of siddha medicine Perungaya leghiam on Cyclooxygenase -26 COX

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Abstract

Anti-inflammatory effects have been discovered in natural substances. By docking a study with the target protein, cyclooxygenase-2 (COX-2), the research sought to identify potential natural compounds that fall into the alkaloid, phenolic, flavonoid, and terpenoids categories. The RCSB Protein Data Bank was used to obtain the crystal structure of COX-2. Auto Dock Vina was used to facilitate the docking study. The natural chemicals demonstrated their anti-inflammatory capabilities by removing inflammation signs and symptoms. Selective COX-2, which is well-known for its anti-inflammatory characteristics, works by inhibiting COX-2 enzymes. Therefore, it is of interest to design and develop new yet effective compounds against COX-2 from medicinal plants such as the natural alkaloid compounds.

Keywords: Perungayaleghiam, COX-2, molecular docking

Introduction

The family of isozymes known as cyclooxygenase (COX) is in charge of catalyzing the reaction that uses arachidonic acid to create different prostaglandins and related substances." As of right now, the COX enzyme has been found in two primary isoforms: COX-1 and COX-2. Under normal physiological conditions, COX-1 demonstrates cytoprotective effect along with modulation of platelet activity, renal, and gastric functions. It provides a homeostatic function in most tissues where it is constitutively expressed. Cells that exhibit elevated prostaglandin levels during inflammatory reactions are typically home to COX-2. Unlike COX-1, which is constitutively present, COX-2 is triggered by inflammatory stimuli.

In addition to commercially available drugs, natural substances such as rutaecarpine, tryptanthrine, isolicoflavonol, lonchocarpol A, curcumin, resveratrol, and ursolic acid have also

been employed as selective COX-2 inhibitors to treat inflammation8–131. For these chemicals, no comparison research employing in silico techniques have been published as of yet. The ability to examine the interaction at the molecular level has been made possible by the application of in silico techniques. By docking the study against the target protein COX-2, the researchers hoped to investigate any potential anti-inflammatory properties of Perungayaleghiam.

Aim and objective:

Binding of phytocomponents with the core amino acids (His 90, Leu 352, Ser 353, Phe 381, Leu 384, Tyr 385, Trp 387, Phe 518, Gly 526, Ala 527, Ser 530) of the target by forming hydrogen bond will hinder the function of the enzyme Cyclooxygenase -2 with PDB – 6 COX. These amino acid residues are functionally responsible for binding of substrate and inhibitors. Thereby phytocomponents which inhibit the target Cyclooxygenase -2 may act as a potential therapeutic agent for management of inflammation and pain.

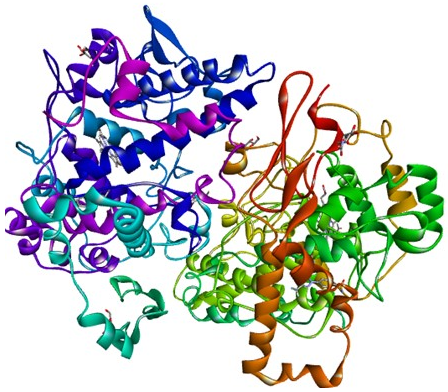
Methodology

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.

Table1: List of Phytocomponents Selected for docking

Herbs	Phytochemicals	PDB	Name of the target
Piper nigrum	Piperine Piperic acid	6 COX	Cyclooxygenase -2
Brassica nigra	Violaxanthin	6 COX	Cyclooxygenase -2
Ferula asafoetida	Ferulic acid	6 COX	Cyclooxygenase -2
Allium sativum	Ajoene	6 COX	Cyclooxygenase -2
Zingiber officinale	Gingerenone-A 6 Gingerol	6 COX	Cyclooxygenase -2
Saccharum officinarum Linn	Apigenin	6 COX	Cyclooxygenase -2
Cow ghee	Linoleic acid	6 COX	Cyclooxygenase -2

Cyclooxygenase – 2 (COX-II) – 6 COX



Receptor structure

Crystalline structure of the target protein Cyclooxygenase -2 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.

Protein preparation

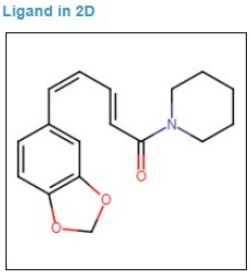
Three-dimensional protein structure of the target protein Cyclooxygenase -2 (PDB) 6 COX were retrieved from the online repository of Protein Data Bank and subjected to protein clean prior to docking simulation.

Ligand Preparation

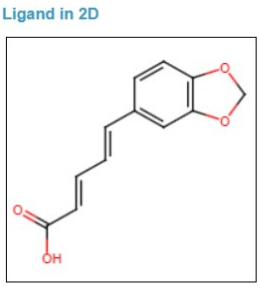
Phytochemical subjected to the investigation were retrieved from the herbs listed in the table based on the literature survey and 3D structure of the same were built using Chem Draw prof online tool version 12.0. Ligands prepared through geometry optimization method (MMFF94).

2D and 3D Structure of Phytocomponents

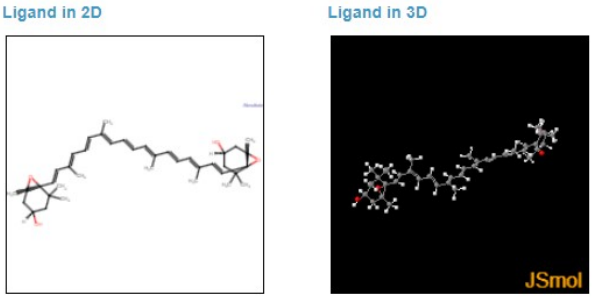
Piperine



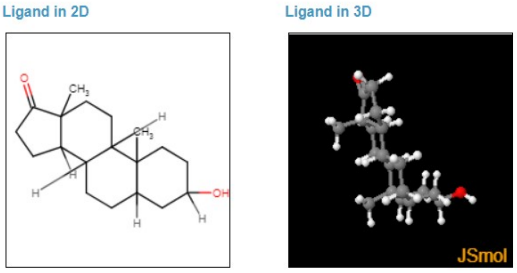
Piperic acid



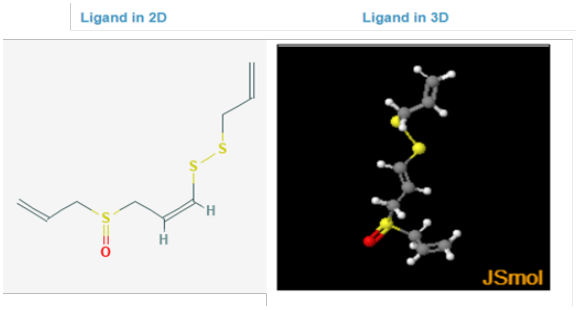
Violaxanthin



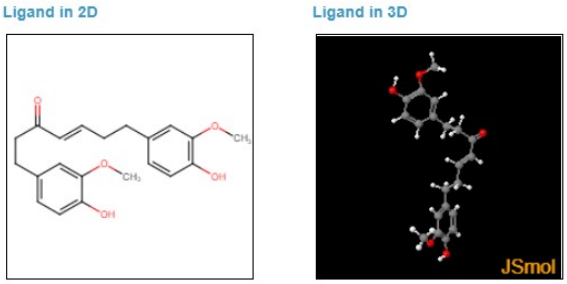
Ferulic acid



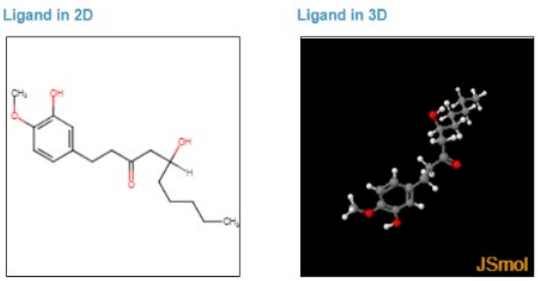
Ajoene



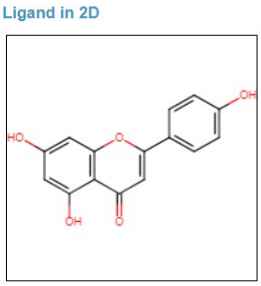
Gingerenone-A



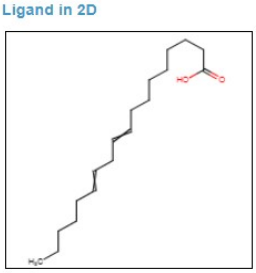
6 Gingerol



Apigenin



Linoleic acid



Celecoxib

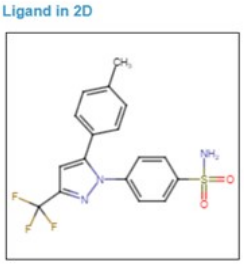


Table 2: Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Piperine	285.34 g/mol	$C_{17}H_{19}NO_3$	0	3	3
Piperic acid	218.2 g/mol	$C_{12}H_{10}O_4$	1	4	3
Violaxanthin	600.9 g/mol	$C_{40}H_{56}O_4$	2	4	10
Ferulic acid	194.18 g/mol	$C_{10}H_{10}O_4$	2	4	3
Ajoene	234.4 g/mol	$C_9H_{14}OS_3$	0	4	8
Gingerenone-A	356.4 g/mol	$C_{21}H_{24}O_5$	2	5	9
6 Gingerol	294.391g/mol	$C_{17}H_{26}O_4$	2	4	10
Apigenin	622.5 g/mol	$C_{27}H_{26}O_{17}$	9	17	7
Linoleic acid	280.452 g/mol	$C_{18}H_{32}O_2$	1	2	14
Celecoxib	381.4	$C_{17}H_{14}F_3N_3O_2S$	1	7	3

Table 3: Summary of the molecular docking studies of compounds againstCyclooxygenase -2 (PDB) – 6COX

Compounds	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Piperine	-9.00 kcal/mol	251.05 nM	-0.02 kcal/mol	-9.45 kcal/mol	524.247
Piperic acid	-6.75 kcal/mol	11.24 uM	-0.69 kcal/mol	-7.12 kcal/mol	428.409
Violaxanthin	-6.27 kcal/mol	25.46 uM	-0.15 kcal/mol	-6.62 kcal/mol	431.348
Ferulic acid	-5.77 kcal/mol	59.29 uM	-0.19 kcal/mol	-6.17 kcal/mol	406.816
Ajoene	-6.37 kcal/mol	21.41 uM	-0.04 kcal/mol	-8.45 kcal/mol	469.99
Gingerenone-A	-8.63 kcal/mol	473.75 nM	-0.12 kcal/mol	-8.32 kcal/mol	554.264
6 Gingerol	-7.67 kcal/mol	2.40 uM	-0.13 kcal/mol	-9.74 kcal/mol	526.931
Apigenin	-5.61 kcal/mol	76.95 uM	-0.13 kcal/mol	-7.13 kcal/mol	505.009
Linoleic acid	-8.02 kcal/mol	1.31 uM	-0.74 kcal/mol	-11.18 kcal/mol	565.281
Celecoxib	-11.62 kcal/mol	3.03 nM	-0.14 kcal/mol	-13.29 kcal/mol	582.065

Table 4: Amino acid Residue Interaction of Lead against Cyclooxygenase -2 (PDB) – 6COX

Compounds	Interactions																							
zPiperine	7	**90**	192	**353**	355	**384**	**385**	**387**	513	516	517	**518**	522	523	**527**									
		HIS	GLN	SER	TYR	LEU	TYR	TRP	ARG	ALA	ILE	PHE	MET	VAL	ALA									
Piperic acid	6	116	120	349	355	359	**384**	**385**	**387**	**518**	522	523	**527**	**530**	531									
		VAL	ARG	VAL	TYR	LEU	LEU	TYR	TRP	PHE	MET	VAL	ALA	SER	LEU									
Violaxanthin	4	113	117	345	349	359	**384**	**385**	463	466	475	481	501	503	506	507	510	521	522	525	**527**	**530**	531	534
		MET	LEU	ILE	VAL	LEU	LEU	TYR	LEU	TYR	TYR	LEU	MET	LEU	ALA	LEU	GLU	THR	MET	LEU	ALA	SER	LEU	LEU

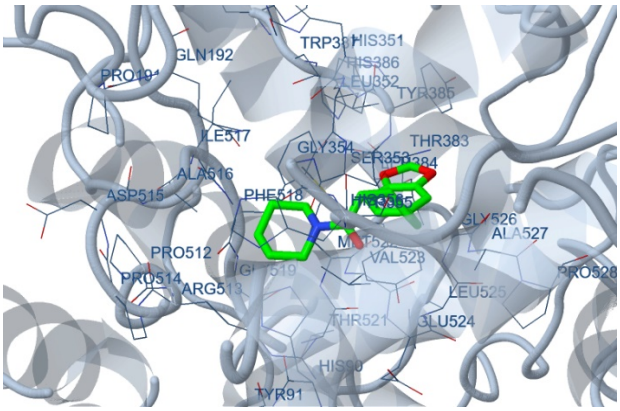
Ferulic acid	9	**90**	**352**	**353**	**381**	**384**	**385**	**387**	**518**	522	523	**530**												
		HIS	LEU	SER	PHE	LEU	TYR	TRP	PHE	MET	VAL	SER												
Ajoene	7	**352**	**353**	**384**	**385**	**387**	516	**518**	523	**530**														
		LEU	SER	LEU	TYR	TRP	ALA	PHE	VAL	SER														
Gingerenone-A	10	**90**	**120**	349	**352**	**353**	355	**384**	**385**	**387**	**518**	522	523	**527**	**530**	531								
		HIS	ARG	VAL	LEU	SER	TYR	LEU	TYR	TRP	PHE	MET	VAL	ALA	SER	LEU								
6 Gingerol	8	116	**120**	349	**352**	**353**	355	359	**384**	**385**	**387**	**518**	522	523	**530**	531								
		VAL	ARG	VAL	LEU	SER	TYR	LEU	LEU	TYR	TRP	PHE	MET	VAL	SER	LEU								
Apigenin	9	**90**	192	349	**352**	**353**	**384**	**385**	**387**	516	**518**	523	**527**	**530**										
		HIS	GLN	VAL	LEU	SER	LEU	TYR	TRP	ALA	PHE	VAL	ALA	SER										
Linoleic acid	7	120	192	349	**352**	**353**	355	**385**	**387**	513	516	**518**	523	**527**	**530**									
		ARG	GLN	VAL	LEU	SER	TYR	TYR	TRP	ARG	ALA	PHE	VAL	ALA	SER									
Celecoxib	5	**90**	120	192	349	**352**	**353**	355	359	516	517	**518**	523	**527**	531									
		HIS	ARG	GLN	VAL	LEU	SER	TYR	LEU	ALA	ILE	**PHE**	VAL	**ALA**	LEU									

Observation and inference

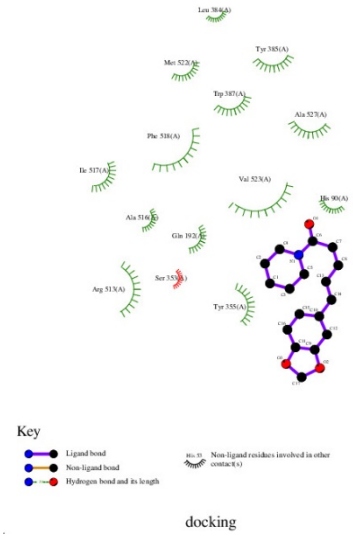
Total of 9 bioactive lead compounds were retrieved from the herbs present in the siddha formulation *Perungayaleghiam*, From reported data, the phytochemicals such as Piperine, Ferulic acid, Ajoene,Gingerenone-A, 6 Gingerol, Apigenin and Linoleic acid possess maximum of seven to ten interactions with the core active amino acid residues present on the target enzyme cyclooxygenase 2.

Docking Pose

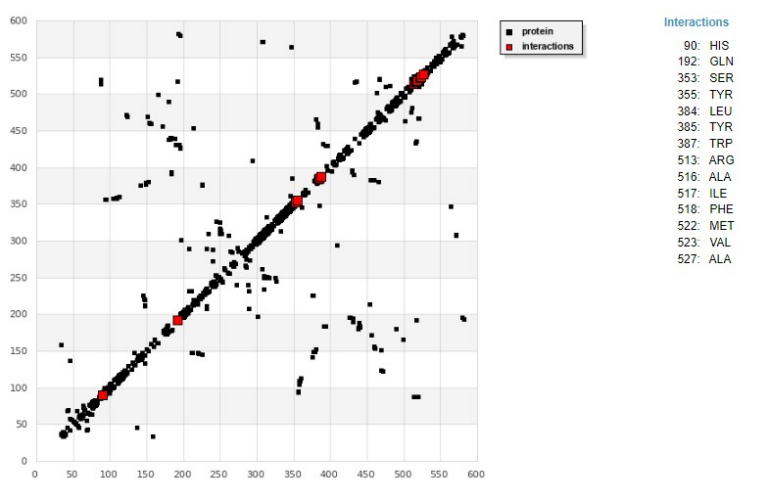
Piperine with Cyclooxygenase -2 (PDB) – 6COX



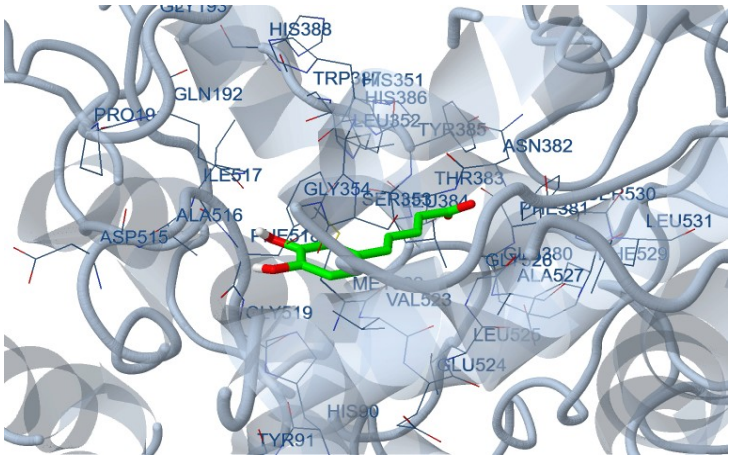
2D Interaction Plot Analysis



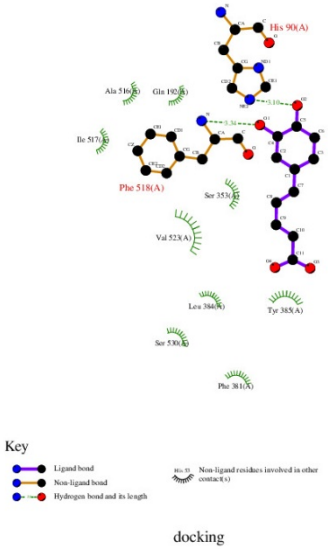
Hydrogen bond plotting with core amino acid Analysis



Piperic acid with Cyclooxygenase -2 (PDB) – 6COX

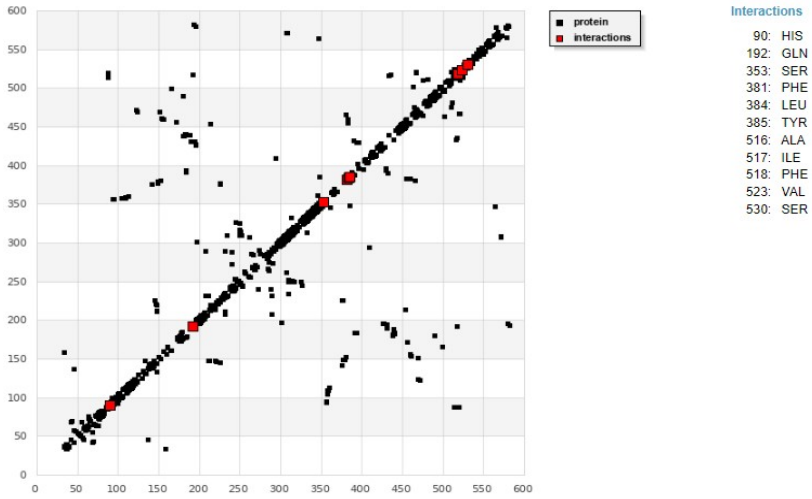


2D Interaction Plot Analysis

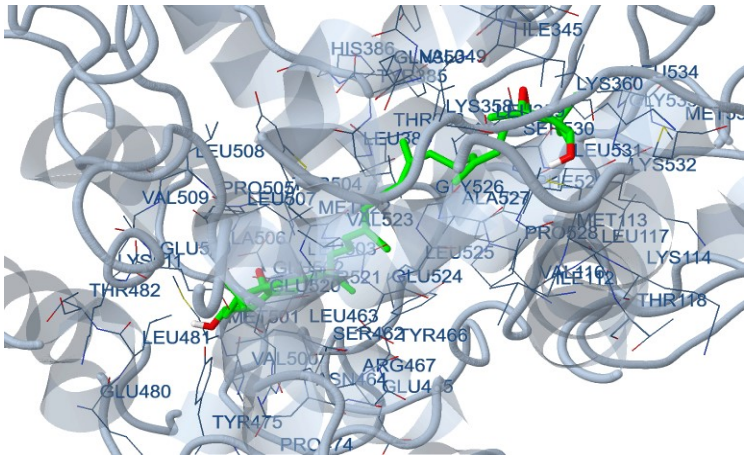


docking

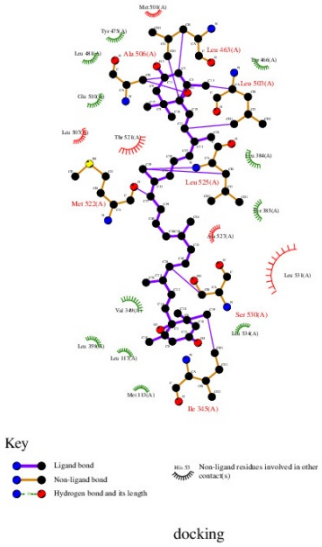
Hydrogen bond plotting with core amino acid Analysis



Violaxanthin with Cyclooxygenase -2 (PDB) – 6COX

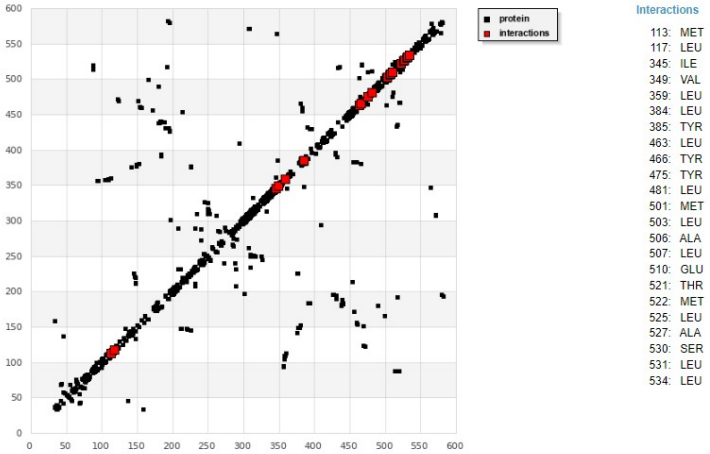


2D Interaction Plot Analysis



docking

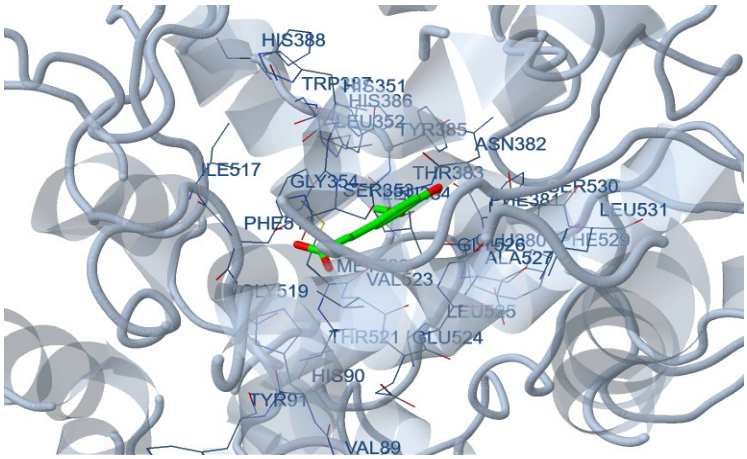
Hydrogen bond plotting with core amino acid Analysis



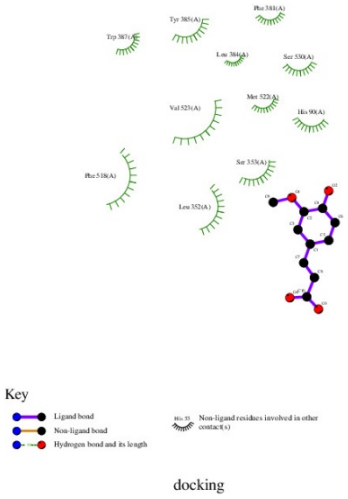
Interactions

113: MET
117: LEU
345: ILE
349: VAL
359: LEU
384: LEU
385: TYR
463: LEU
466: TYR
475: TYR
481: LEU
501: MET
503: LEU
506: ALA
507: LEU
510: GLU
521: THR
522: MET
525: LEU
527: ALA
530: SER
531: LEU
534: LEU

Ferulic acid with Cyclooxygenase -2 (PDB) – 6COX

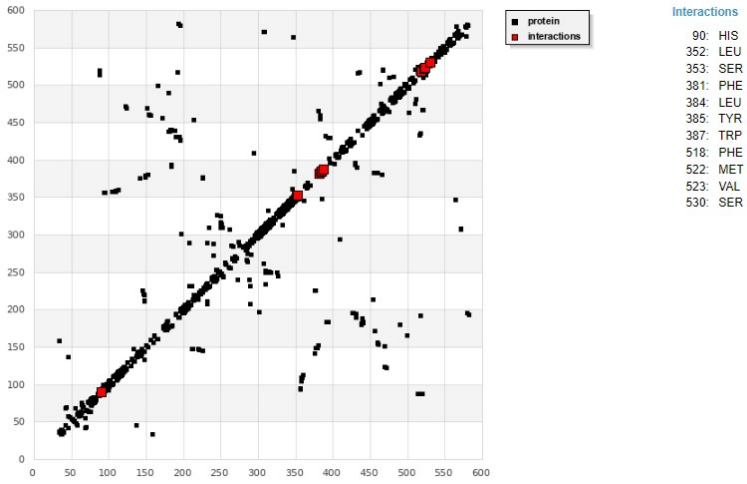


2D Interaction Plot Analysis

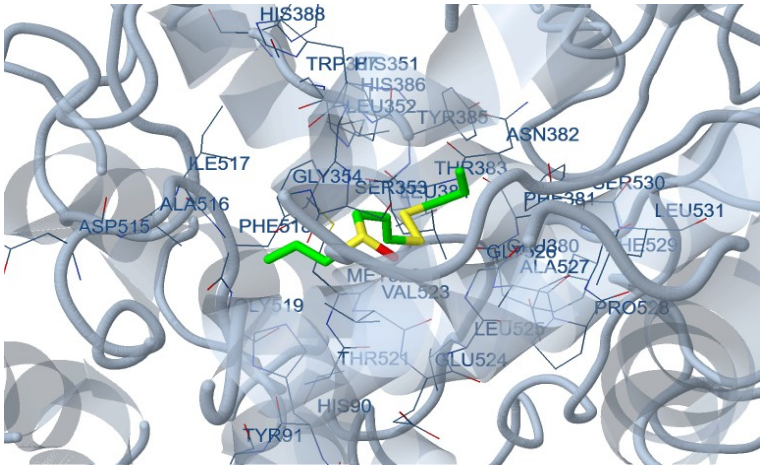


docking

Hydrogen bond plotting with core amino acid Analysis



Ajoene with Cyclooxygenase -2 (PDB) – 6COX



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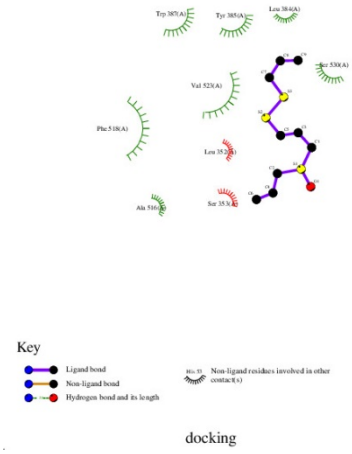
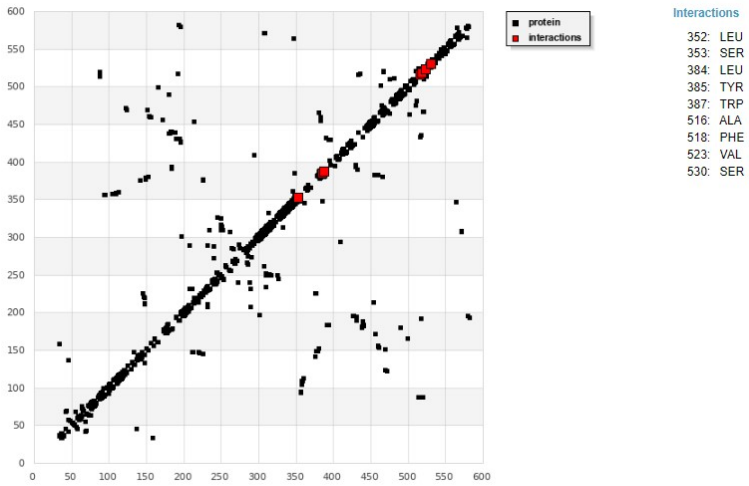
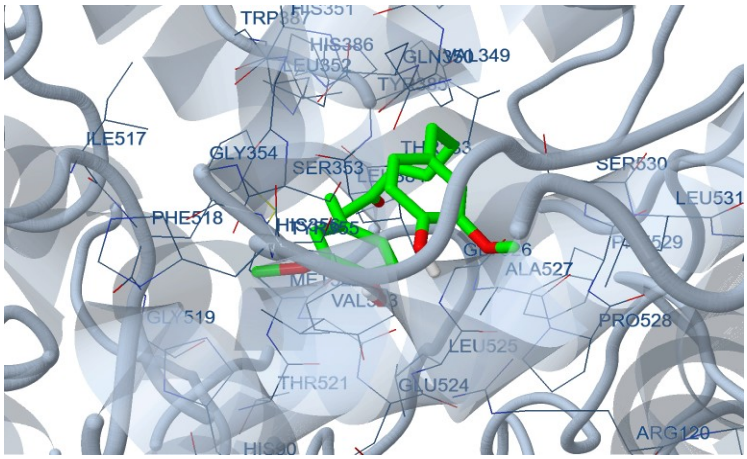


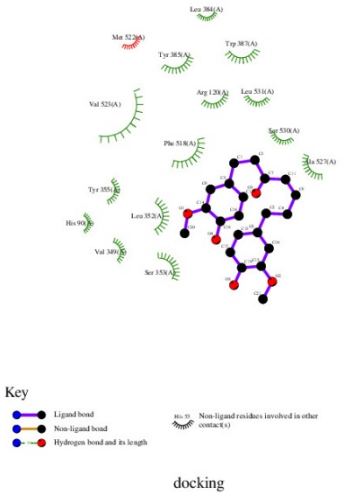
Hydrogen bond plotting with core amino acid Analysis



Gingerenone-A with Cyclooxygenase -2 (PDB) – 6COX

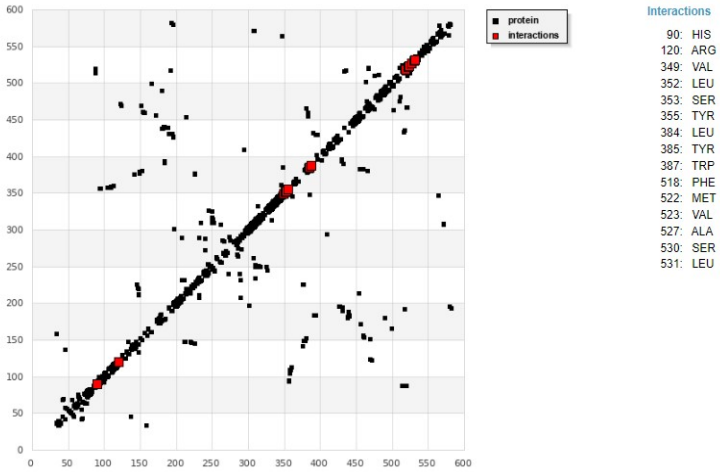


2D Interaction Plot Analysis

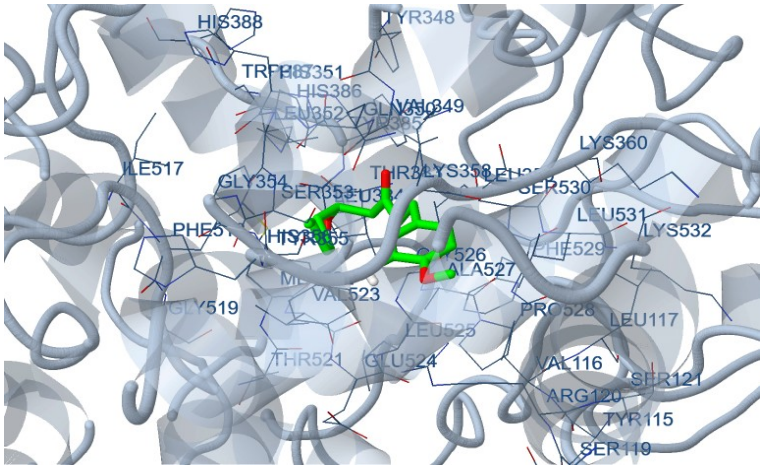


docking

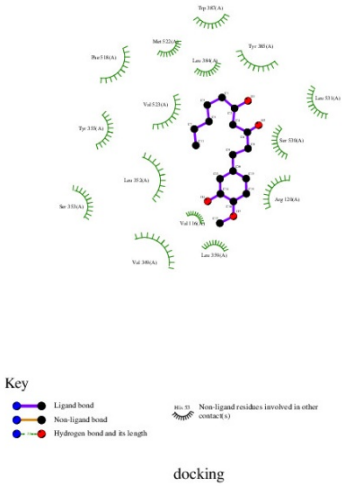
Hydrogen bond plotting with core amino acid Analysis



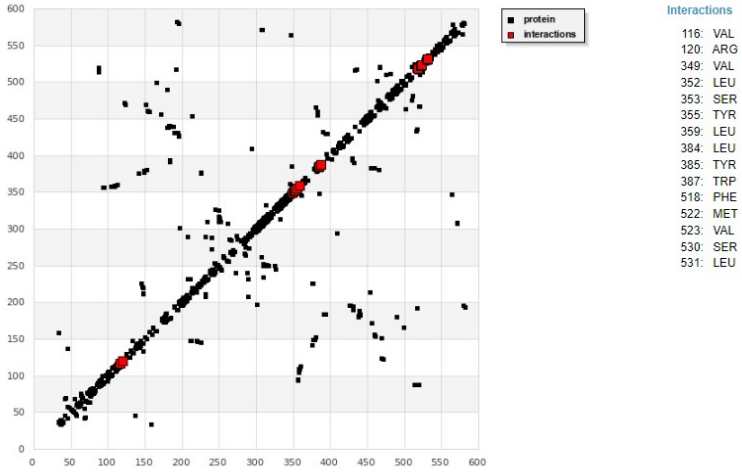
6 Gingerol with Cyclooxygenase -2 (PDB) – 6COX



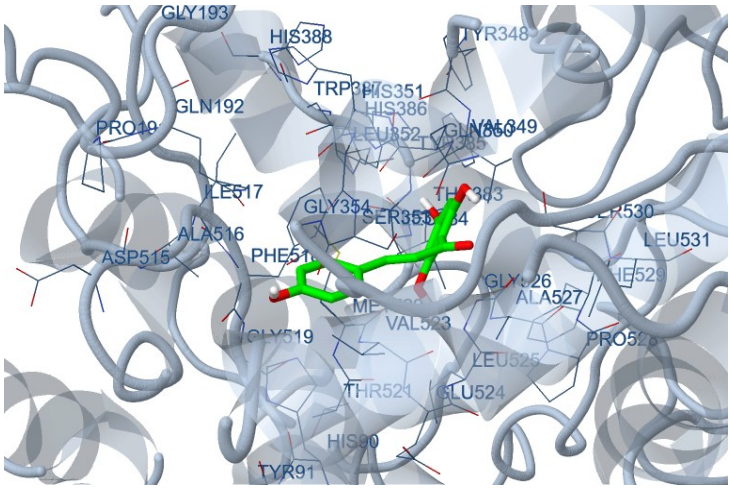
2D Interaction Plot Analysis



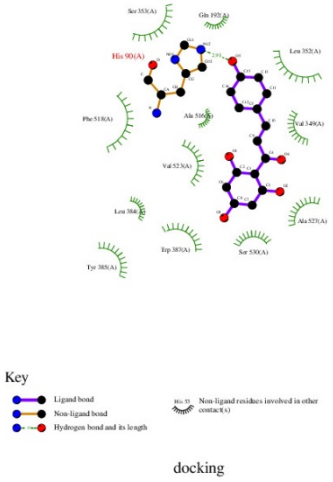
Hydrogen bond plotting with core amino acid Analysis



Apigenin with Cyclooxygenase -2 (PDB) – 6COX

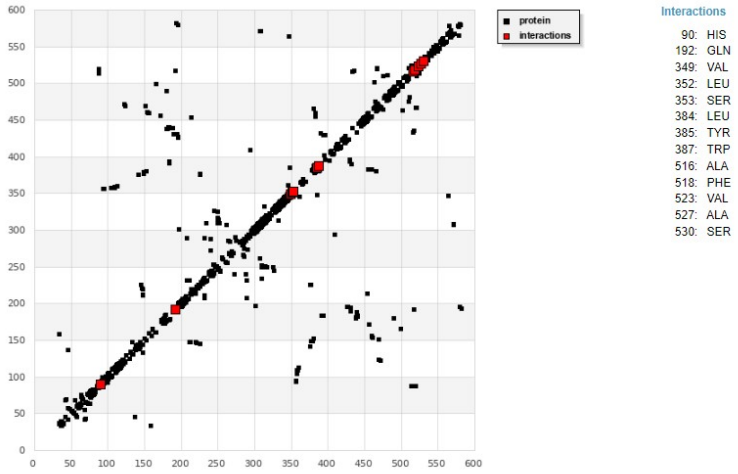


2D Interaction Plot Analysis

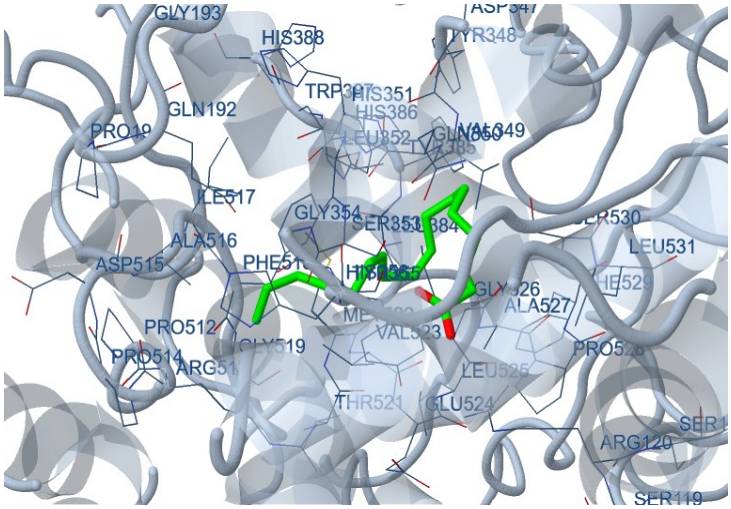


docking

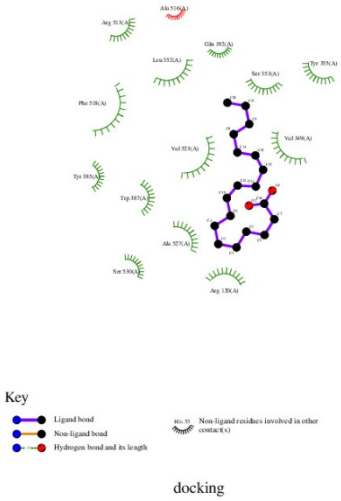
Hydrogen bond plotting with core amino acid Analysis



Linoleic acid with Cyclooxygenase -2 (PDB) – 6COX

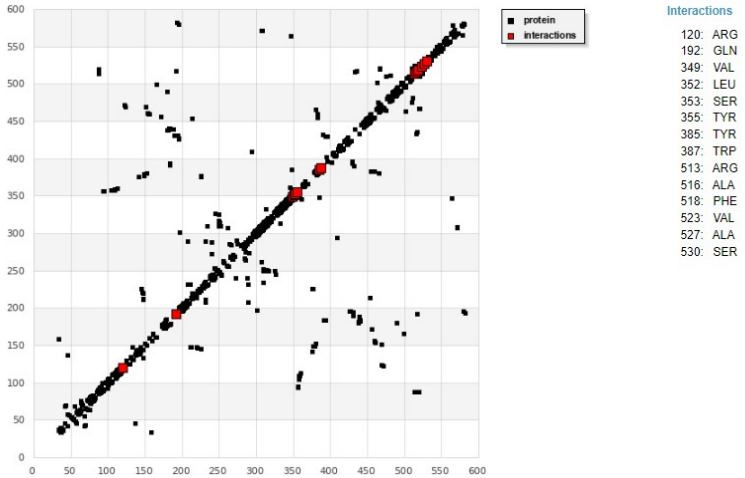


2D Interaction Plot Analysis

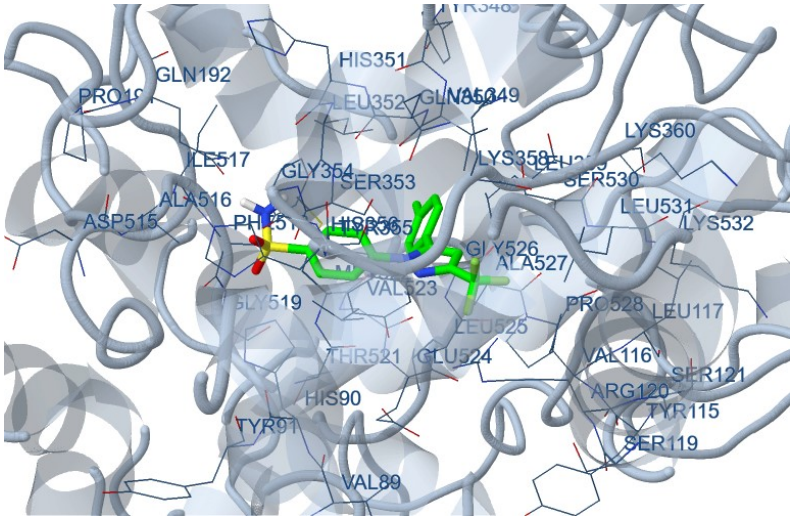


docking

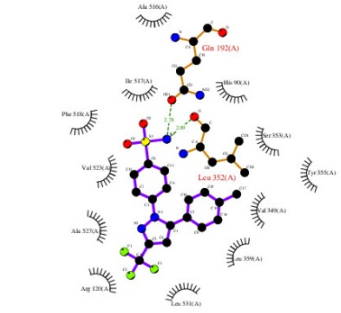
Hydrogen bond plotting with core amino acid Analysis



Celecoxibwith Cyclooxygenase -2 (PDB) – 6COX

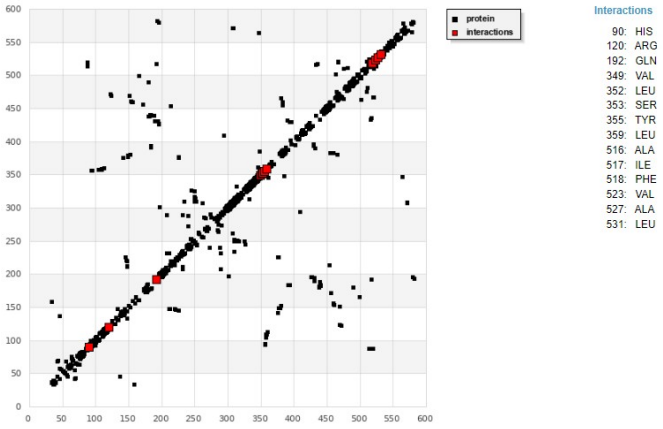


2D Interaction Plot Analysis



docking

Hydrogen bond plotting with core amino acid Analysis



Conclusion

Based on the results of the computational analysis it was concluded that all the bio-active compound's like Piperine, Ferulic acid, Ajoene ,Gingerenone-A, 6 Gingerol, Apigenin and Linoleic acid revels significant binding affinity against the target enzyme cyclooxygenase 2 by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts promising analgesic activity by inhibiting the action of the enzyme cyclooxygenase. It was concluded that the phytocomponents may act as a potential therapeutic agent for management of pain and inflammation.

References

1. Bahare Salehi. Piper Species: A Comprehensive Review on Their Phytochemistry, BiologicalActivities and Applications. Molecules. 2019 Apr; 24(7): 1364.
2. Frazie MD, Kim MJ, Ku KM. Health-Promoting Phytochemicals from 11 Mustard Cultivars at Baby Leaf and Mature Stages. Molecules. 2017;22(10):1749.
3. Poonam Mahendra, Shradha Bisht. Ferula asafoetida: Traditional uses and pharmacological activity. Pharmacognosy Reviews.2012;6(12):141-146
4. Leyla Bayan. Garlic: a review of potential therapeutic effects. Avicenna J Phytomed. 2014 Jan-Feb; 4(1): 1–14.El-Saber Batiha G, Magdy Beshbishy A, G Wasef L, Elewa YHA, A Al-Sagan A, Abd El-Hack ME, Taha AE, M Abd-Elhakim Y, Prasad Devkota H. Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): A Review. Nutrients. 2020 Mar 24;12(3):872
5. Sahdeo Prasad. Ginger and Its Constituents: Role in Prevention and Treatment of Gastrointestinal Cancer. Gastroenterology Research and Practice. 2015:1-11Rampogu S, Baek A, Gajula RG, et al. Ginger (Zingiber officinale) phytochemicals-gingerenone-A and shogaol inhibit SaHPPK: molecular docking, molecular dynamics simulations and in vitro approaches. Ann Clin MicrobiolAntimicrob. 2018;17(1):16.
6. 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
7. Carolina pena-serna. Chemical, physicochemical, microbiological and sensory characterization of cow and buffalo ghee. Food Sci. Technol, Campinas, 40(2): 444-450.2020
8. Bikadi, Z., Hazai, E.*Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock*. J. Cheminf. 1, 15 (2009)
9. T. A. Halgren. *Merck molecular force field. I. Basis, form, scope, parametrization, and performance of MMFF94*. Journal of Computational Chemistry 17 (5-6), 490-519 (1998)
10. 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 19 (14), 1639-1662(1998)
11. Solis, F.J. and Wets, R.J.B. (1981) Minimization by Random Search Techniques. Mathematics of Operations Research, 6, 19-30.
12. Panchamita Basumatary, Manas Das, Pranjan Barman and Manisha Choudhury,. Molecular Docking Study of 2, 3-Dimethylmaleic Anhydride (3, 4-Dimethyl-2, 5-Furandione) as Anti-inflammatory Agent. Trends in Bioinformatics, 2018; 11: 56-63.
13. Huang, S.Y Zou, Advances and challenges in protein-ligand docking, Int. J. Mol. Sci, 11, pp.3016-3034, 2010.
14. Ramalho TR de 0, Oliveira MTP de, Lima AL de A, Bezerra-Santos CR, Piuvezam MR. Gamma-Terpinene Modulates Acute Inflammatory Response in Mice. Planta Med. 2015 Sep;81(14):1248-54.
15. 1bada ME. Cuminaldehyde: A Potential Drug Candidate. Journal of pharmacology & clinical research. 2017 Mar 8 [cited 2019 May 24];2(2).

16. Duke, J., 2016. Dr. Duke's Phytochemical and Ethnobotanical Databases. U.S.Department of Agriculture, Agricultural Research Service.
17. kanthasamymuthaliaraathmarakchamirthamen numvaithyasaarasangiragam , page num : 497

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