Int. J. Curr. Res. Med. Sci. (2022). 8(2): 1-24

International Journal of Current Research in Medical Sciences

ISSN: 2454-5716

(A Peer Reviewed, Indexed and Open Access Journal)

www.ijcrims.com

Original Research Article

Volume 8, Issue 2 -2022

DOI: http://dx.doi.org/10.22192/ijcrms.2022.08.02.001

In docking Analysis of siddha formulation Kana Mantha Mathirai (KMM) inhibiting the Prostaglandin H synthases and M3 muscarinic acetylcholine receptors in gastroenteritis.

Gayathri V[1], Victoria S[2], Shanmuga Priya C[3], Manju Hemamalini N[4]

[1]Post Graduate, Department of Kuzhanthai Maruthuvam, Government Siddha Medical College

[2]Head of the Department, Department of Kuzhanthai Maruthuvam, Government Siddha Medical College.

[3]Lecturer -II, Department of Kuzhanthai Maruthuvam, Government Siddha Medical College

[4] Lecturer -II – Department of Kuzhanthai Maruthuvam, Government Siddha Medical College.

Abstract

Aim: To investigate the evaluation of antipyretic activity and anti diarrheal activity of kana mantha mathirai in docking method.

Study Design: Molecular study

Methodology: In molecular docking analysis was performed for phytocomponents present in kana mantha mathirai formulation for targets using Autodock tool.

Result: Among 8 active Phytocompounds present in the kana mantha mathirai.

Keywords: Siddha formulation, Kana mantha mathirai, Gastroenteritis, Molecular study.

Introduction

Gastroenteritis is a common childhood disease. It is defined as the inflammation of the mucus membrane of the gastrointestinal tract and is characterized by diarrhea or vomiting. In general developing countries have high rate of hospital admission as compared to developed countries. This may be due to the facts that children in developing countries have less nutritional status and primary care. Though there is a system, Siddha which providing solution to many pediatric health issues. Siddha system is guiding us to lead a perfect living in this world, starting from the first day of birth to the last day of death. Siddha system containing a large number of medicines which are different morphological categories, the method of preparation of each category is specific.

There are several medicines indicates in the treatment of Gastroenteritis. One of the medicine which is named as kana mantha mathirai. It is a polyherbalmedicine. Herbal medicine have a long history of use and are generally considered to be safer than synthetic drugs. Gastroenteritis is compared to kana mantham in siddha literature. And the kana mantha mathirai contains 6 ingredients which are Valmilagu (*Piper longum*), Vasambhu (*Acorus calamus*), lavangam

(*Syzygium aromaticum*), omam (*Trachyspermum ammi*), vellulli (*Allium sativum*), Senbagapoo (*Michelia champaca*). Bio active phytocomponents present in preparation of kana mantha mathirai medicine have the unique advantage of multiple mode of actions. All these used traditionally in the treatment of fever, inflammation, diarrhea respectively. This study intently describes the two important activities and binding capability to certain receptors of diarrhea and fever which are main symptoms of Gastroenteritis.

Methodology

Docking calculations were carried out using Auto Dock 4. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined.

Docking calculations were carried out for test drug Piperine, Zingiberene, Apigenin, Barlerin, Coumaric acid, Solasodine, Limonene and standard Salicylic acid 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*). Auto Dock 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.

List of Phytocomponents Selected for docking

Herbs	Scientific Name	Phyto components
Valmilaghu	*Piper cubeba*	α-copaene
Vellulli	*Allium sativum*	Alliin
Kirambhu	*Syzygium aromaticum*	Kaempferol
Omam	*Trachyspermum ammi*	Carvone
Vasambhu.	*Acorus calamus*	Magnolin
Shenbaga.	*Michelia champaca*	Gallic acid
Poduthalai juice	*Phyla nodiflora*	Nepetin

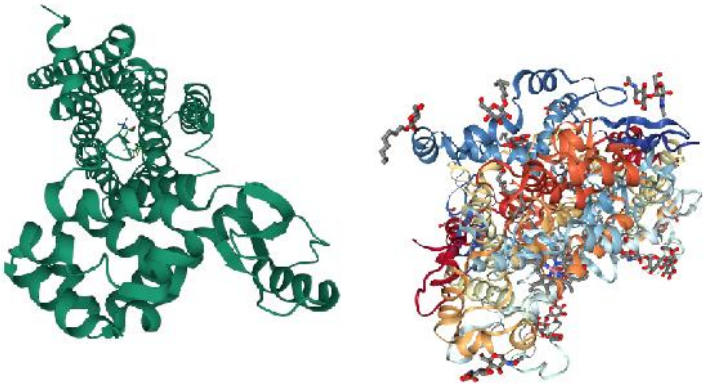
Standard Marketed Drug –Loperamide and salicylic acid.

Objective:

Binding of phytocomponents with the core amino acids of the targets by forming hydrogen bond will hinder the function of the target prostaglandin synthases and muscarinic receptor which is responsible for production of mediator senitize to fever and intestinal motility which mediates diarrhea. Thereby phytocomponents which inhibit this enzyme and muscarinic receptor through binding on amino acid present over the target may act as a potential therapeutic agent for management of fever and diarrhea symptoms.

PDB	Name of the Target
4U14	M3 muscarinic acetylcholine receptor
1I GX	Prostaglandin synthases

M3 muscarinic acetylcholine receptor -PDB- 4U14 and Prostaglandin H synthases

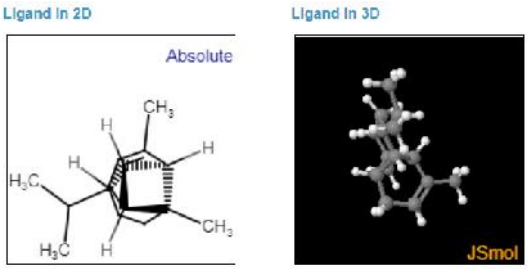


Receptor structure

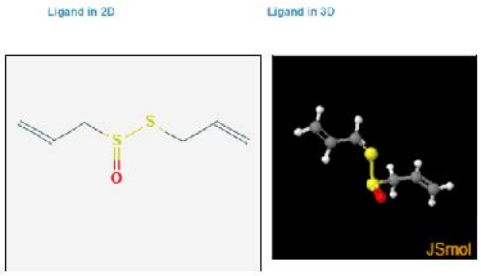
Crystalline structure of the target proteinM3 muscarinic acetylcholine receptor -PDB- 4U14 and Prostaglandin H synthases- 11GX was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atom were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis

2D and 3D Structure of Selected Ligands

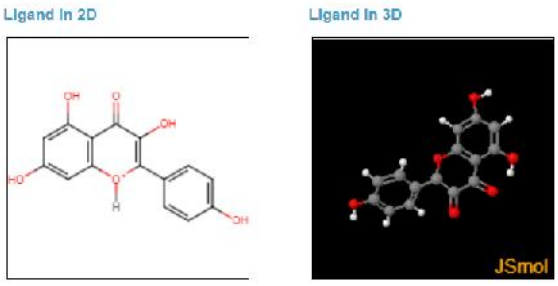
α-copaene



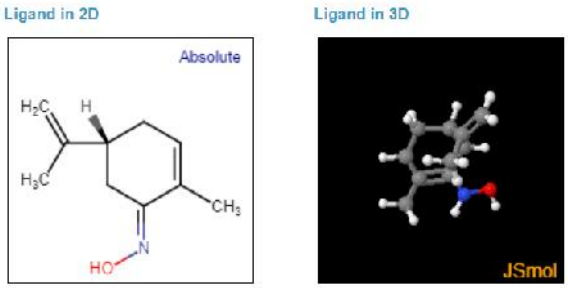
Allicin



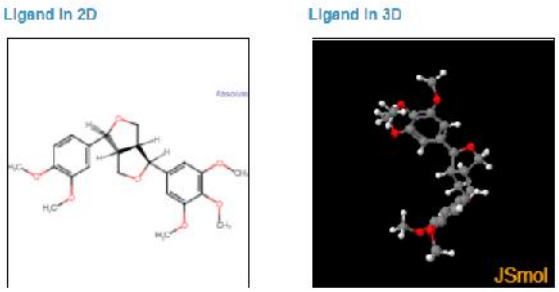
Kaempferol



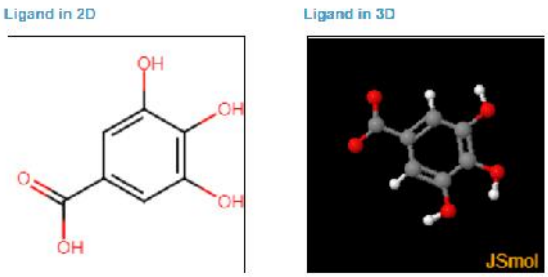
Carvone



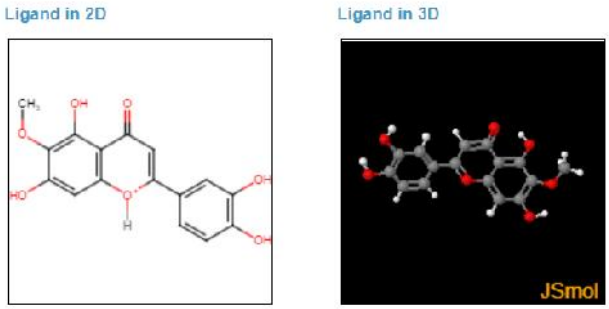
Magnolin



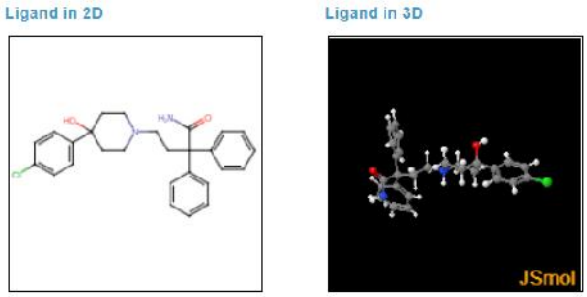
Gallic acid



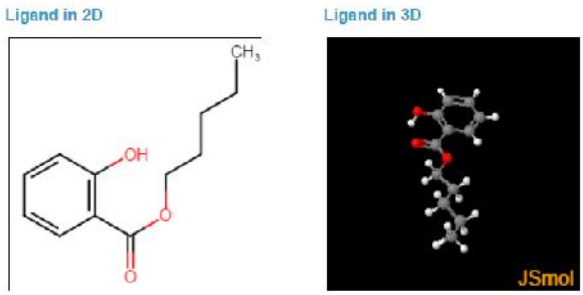
Nepetin



Loperamide



Salicylic acid



Ligand Properties of the Compounds selected for docking

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
α-copaene	204.35 g/mol	$C_{15}H_{24}$	0	0	1
Allicin	162.3 g/mol	$C_6H_{10}OS_2$	0	3	5
Kaempferol	286.239 g/mol	C15H10O6	4	6	1
Carvone	150.221 g/mol	C10H14O	0	1	1
Magnolin	416.5 g/mol	$C_{23}H_{28}O_7$	0	7	7
Gallic acid	170.12 g/mol	$C_7H_6O_5$	4	5	1
Nepetin	316.26 g/mol	$C_{16}H_{12}O_7$	4	7	2
Loperamide					
Salicylic acid	138.12g/mol	C7H6O3	2	3	1

Summary of the molecular docking studies of compounds against M3 muscarinic acetylcholine receptor -PDB- 4U14 and Prostaglandin H synthases-11GX

Compounds	Binding Free energy Kcal/mol	Inhibition constant Ki µM (*mM)(**nM)	Electrostatic energy Kcal/mol	Intermolecular energy Kcal/mol	Total Interaction Surface
α-copaene	-5.41	107.49	-1.53	-6.45	461.35
Allicin	-6.61	14.38	-1.23	-6.38	411.92
Kaempferol	-6.36	21.88	-0.05	-6.74	688.46
Carvone	-6.41	20.10	-1.57	-7.03	469.58
Magnolin	-6.30	24.08	-0.02	-5.61	783.69
Gallic acid	-5.02	209.74	-0.06	-4.57	402.16
Nepetin	-6.60	14.62	-0.02	-5.99	756.75
Loperamide	-7.97	1.43	-0.40	-8.27	590.84
Salicylic acid	-6.04	37.12	-0.09	-6.22	605.18

Amino acid Residue Interaction of Lead and Standard againstM3 muscarinic acetylcholine receptor - PDB- 4U14

Molecule	Interactions	Amino Acid Residue- Binding											
α-copaene	4	116 ILE	147 ASP	151 SER	503 TRP	506 TYR	507 ASN	529 TYR	532 CYS	533 TYR			
Allicin	4	116 ILE	147 ASP	148 TYR	151 SER	503 TRP	506 TYR	529 TYR	532 CYS	533 TYR			
Kaempferol	3	116 ILE	147 ASP	148 TYR	151 SER	225 LEU	231 THR	234 THR	506 TYR	529 TYR	533 TYR		
Carvone	4	116 ILE	147 ASP	148 TYR	151 SER	503 TRP	506 TYR	529 TYR	532 CYS	533 TYR			
Magnolin	3	148 TYR	151 SER	225 LEU	231 THR	234 THR	235 ALA	238 ALA	239 PHE	499 PHE	503 TRP	506 TYR	
Gallic acid	3	116 ILE	147 ASP	148 TYR	151 SER	506 TYR	529 TYR	532 CYS	533 TYR				
Nepetin	3	148 TYR	151 SER	225 LEU	231 THR	238 ALA	239 PHE	503 TRP	506 TYR	525 TRP			
Loperamide	4	151 SER	199 TRP	231 THR	234 THR	235 ALA	238 ALA	503 TRP	506 TYR	510 VAL	529 TYR	532 CYS	533 TYR

Amino acid Residue Interaction of Lead and Standard against Prostaglandin H synthases -1IGX

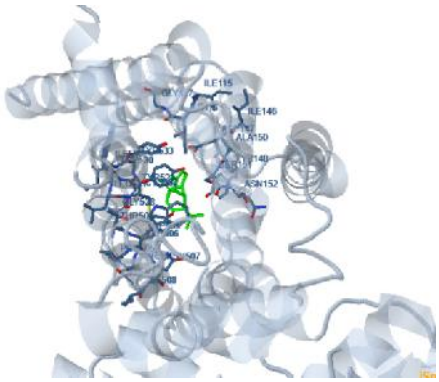
Molecule	Interactions	Amino Acid Residue- Binding						
α-copaene	4	33 VAL	35 PRO	38 TYR	40 PRO	55 TYR		
Allicin	2	38 TYR	39 TYR	40 PRO	42 GLN	68 ASN		
Kaempferol	1	38 TYR	39 TYR	165 THR	166 LYS	465 GLU	468 LYS	499 ASP
Carvone	2	38 TYR	39 TYR	40 PRO	42 GLN	68 ASN	468 LYS	
Magnolin	4	35 PRO	38 TYR	40 PRO	55 TYR			
Gallic acid	2	38 TYR	40 PRO	42 GLN	68 ASN	165 THR	166 LYS	468 LYS
Nepetin	4	35 PRO	38 TYR	40 PRO	55 TYR	68 ASN		
Salicylic acid	4	35 PRO	38 TYR	40 PRO	54 ARG	55 TYR	68 ASN	

Observation and Inference

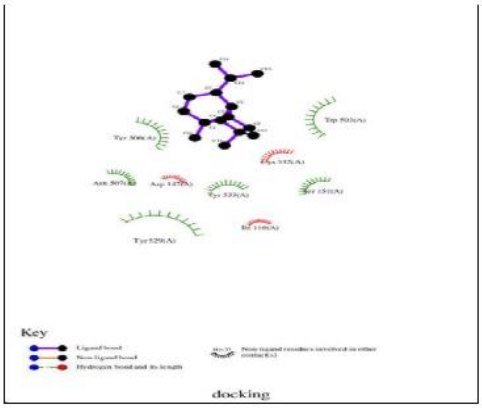
Total of 8 bioactive lead compounds were retrieved from the herbs present in the formulations Kana Mantha Mathirai. From reported data of the herb, the leads such as α-copaene, Allicin and Carvone,Magnolin and leptin possess80% binding efficacy by interacting with both the core target amino acids (Ser151 , Tyr529, Tyr506, and Trp503,35PRO, 38 TYR, 40 PRO, 54 ARG, and 55 TYR) present on the target, followed by which the compounds like Kaempferol ,Magnolin, Gallic acid and Nepetin,Qllicin, Carvone, Gallic acid reveals 90% binding efficacy with target amino acid when compared with the standard Loperamide and Salicylic acid with 90% binding efficacy present on the target receptor M3 muscarinic acetylcholine receptor -PDB- 4U14 and Prostaglandin H synthases.

Docking Pose

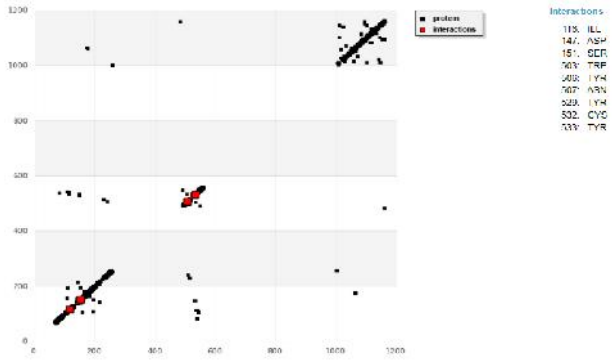
α-copaene with M3 muscarinic acetylcholine receptor -PDB- 4U14



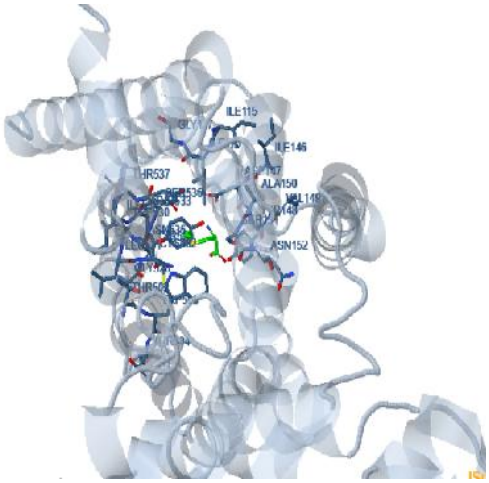
2D Interaction Plot



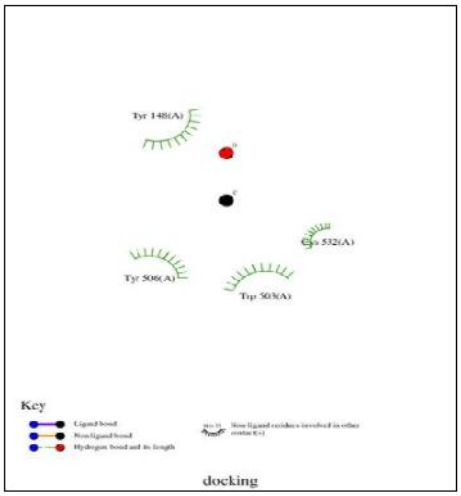
Hydrogen bond plotting Analysis with core amino acid



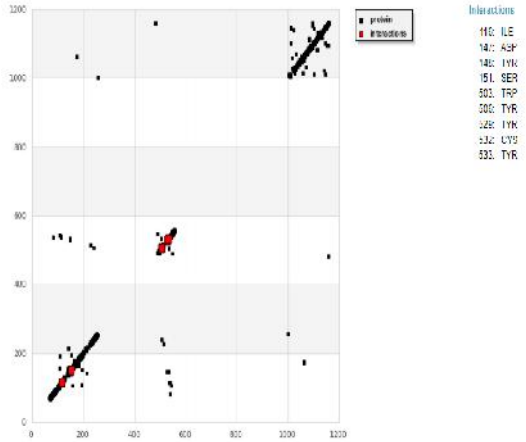
AllicinwithM3 muscarinic acetylcholine receptor -PDB- 4U14



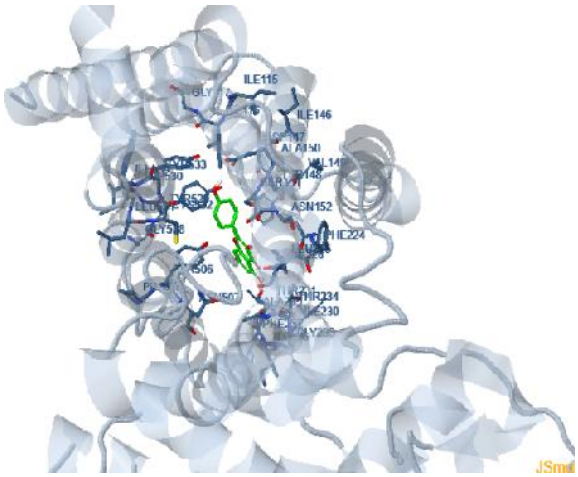
2D Interaction Plot



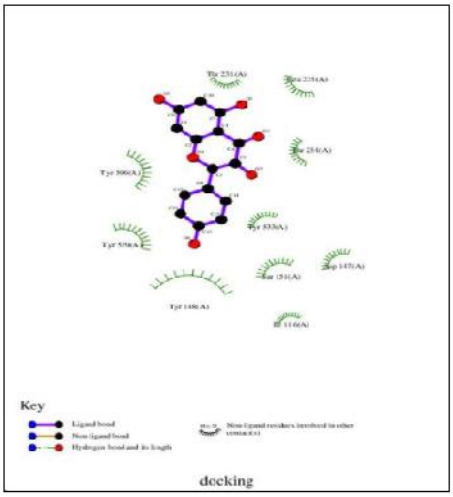
Hydrogen bond plotting Analysis with core amino acid



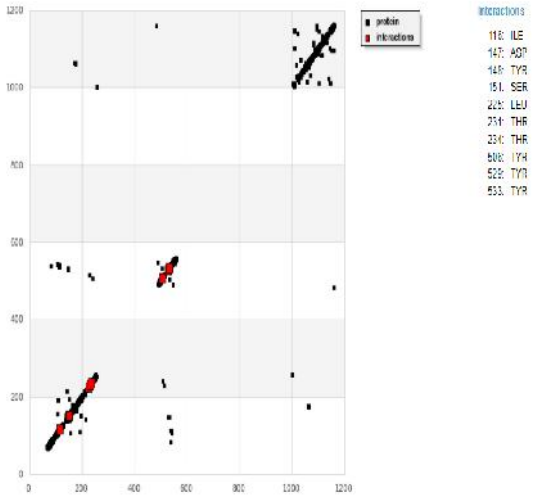
Kaempferol withM3 muscarinic acetylcholine receptor -PDB- 4U14



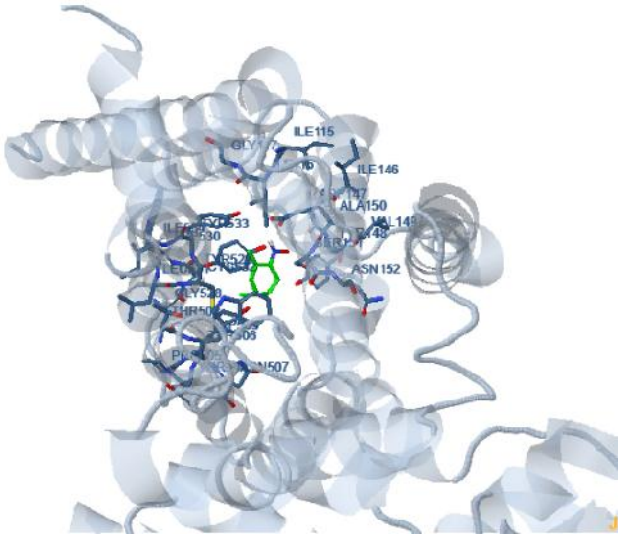
2D Interaction Plot



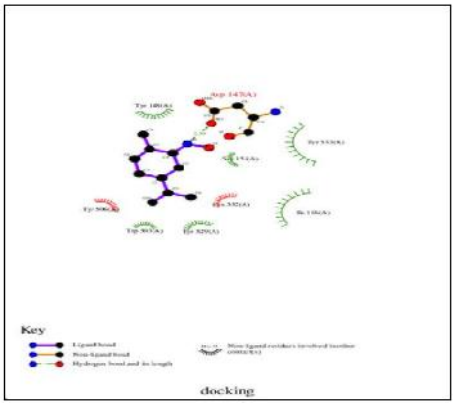
Hydrogen bond plotting Analysis with core amino acid



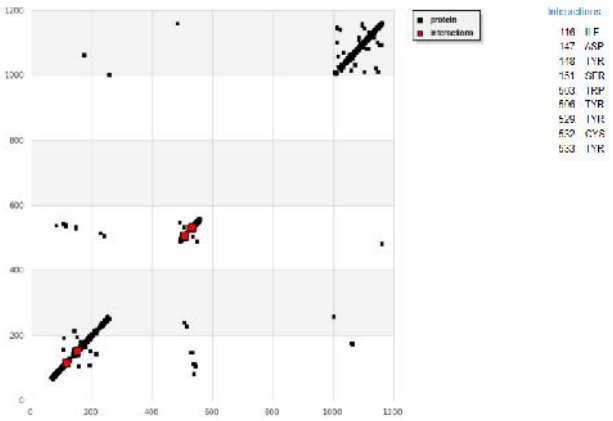
Carvone with M3 muscarinic acetylcholine receptor -PDB- 4U14



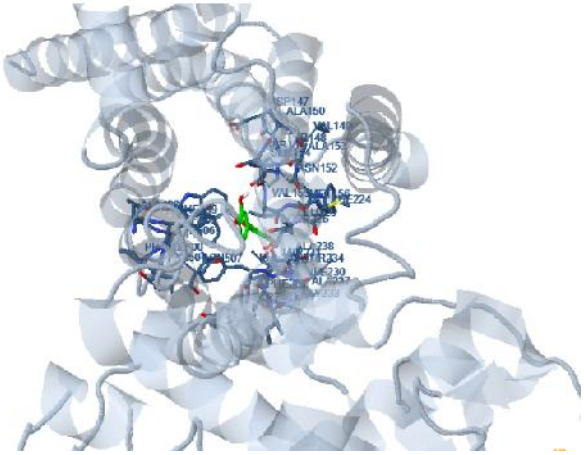
2D Interaction Plot



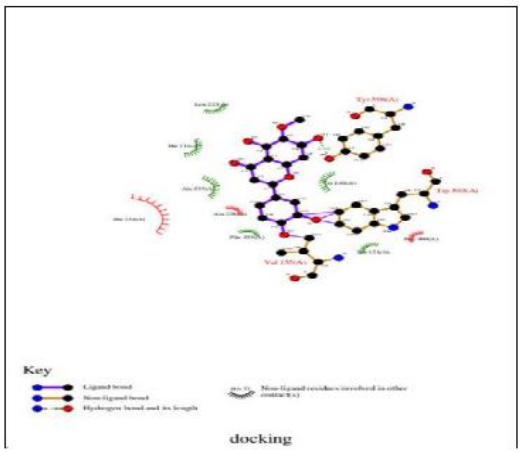
Hydrogen bond plotting Analysis with core amino acid



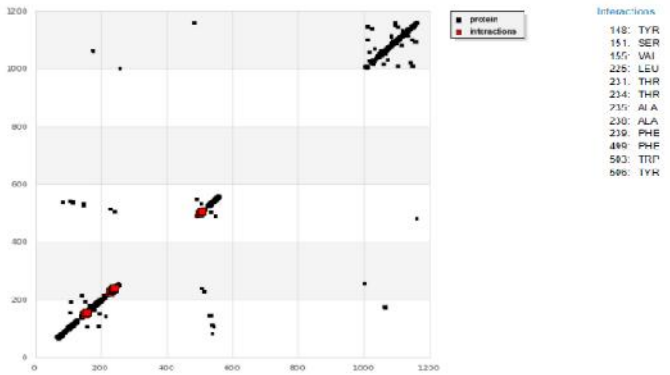
MagnolinwithM3 muscarinic acetylcholine receptor -PDB- 4U14



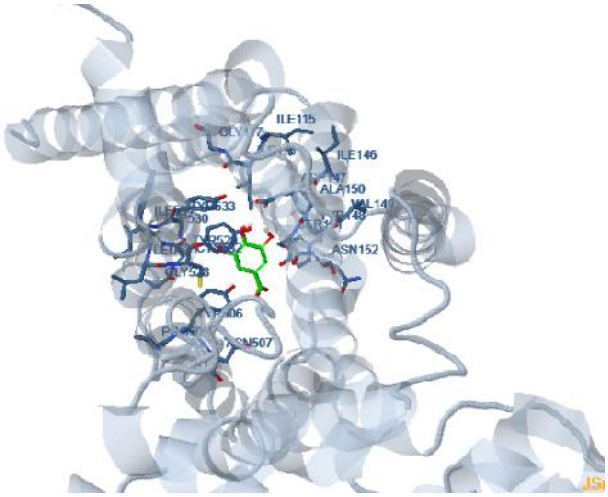
2D Interaction Plot



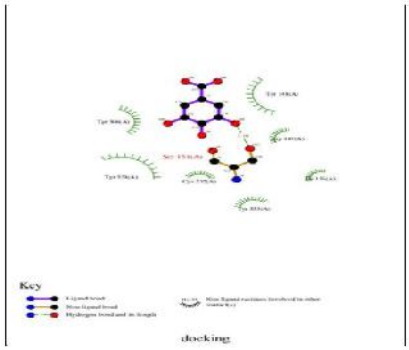
Hydrogen bond plotting Analysis with core amino acid



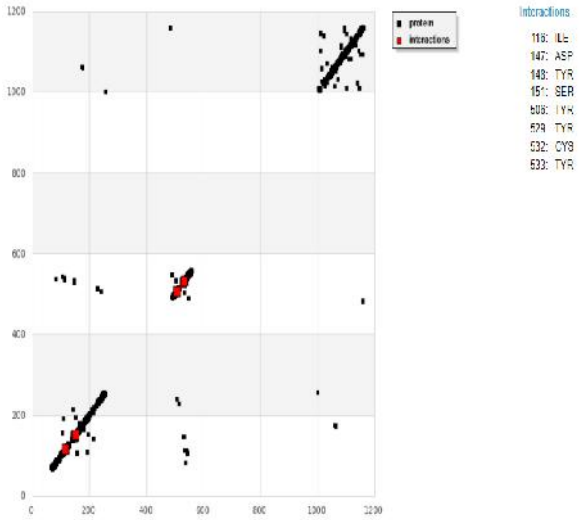
Gallic acidwithM3 muscarinic acetylcholine receptor -PDB- 4U14



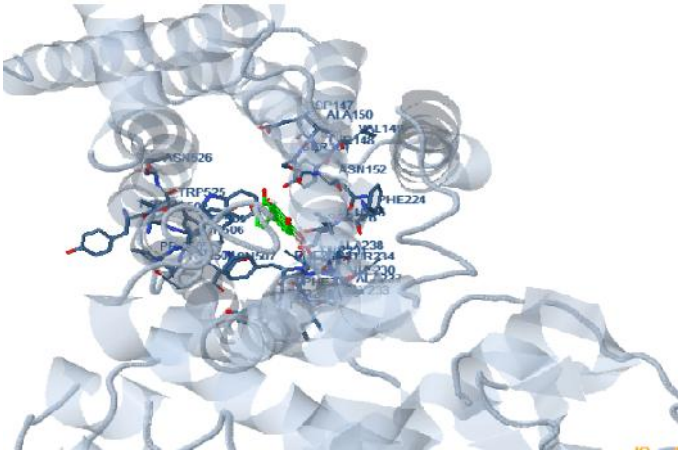
2D Interaction Plot



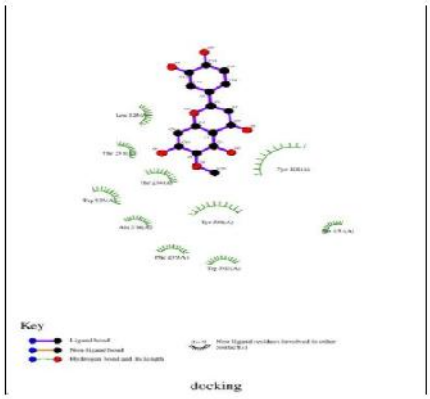
Hydrogen bond plotting Analysis with core amino acid



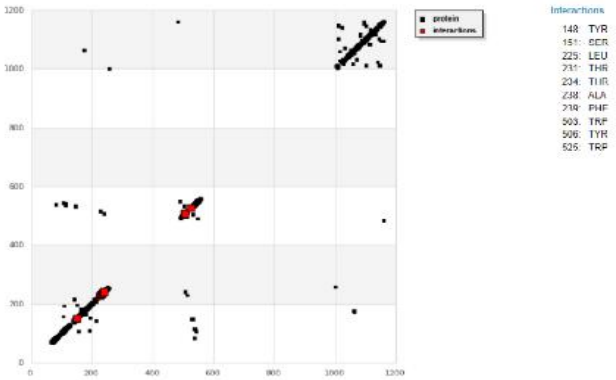
NepetinwithM3 muscarinic acetylcholine receptor -PDB- 4U14



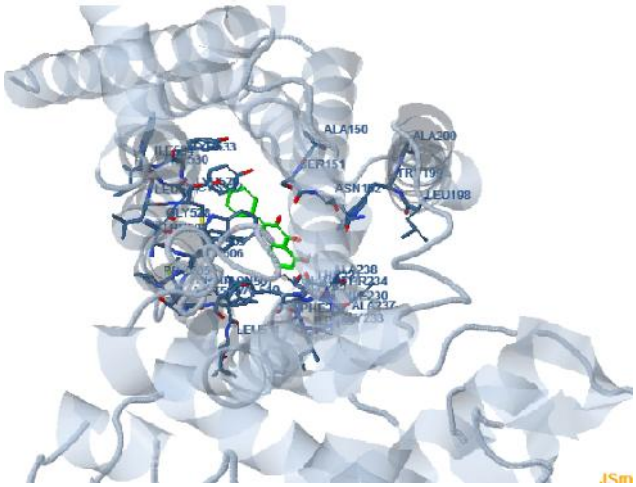
2D Interaction Plot



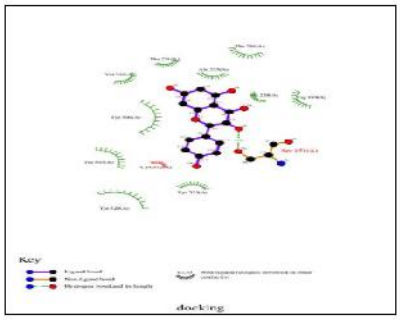
Hydrogen bond plotting Analysis with core amino acid



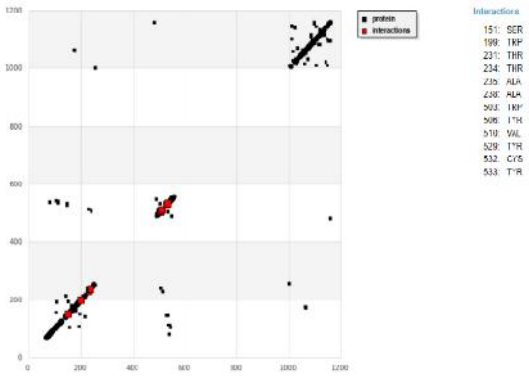
LoperamidewithM3 muscarinic acetylcholine receptor -PDB- 4U14



2D Interaction Plot

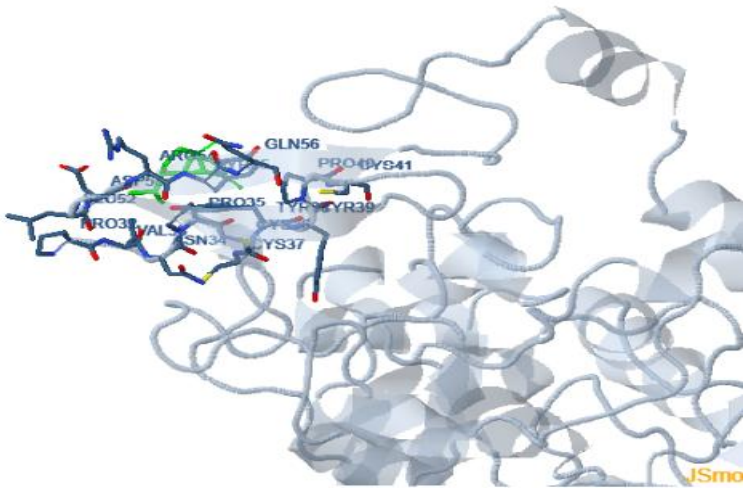


Hydrogen bond plotting Analysis with core amino acid

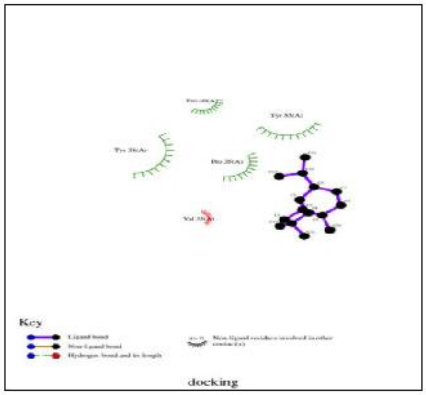


Docking Pose

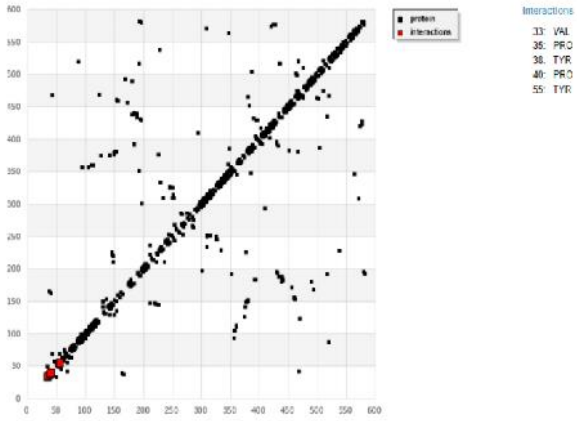
α-copaene with Prostaglandin synthases -PDB- 1IGX



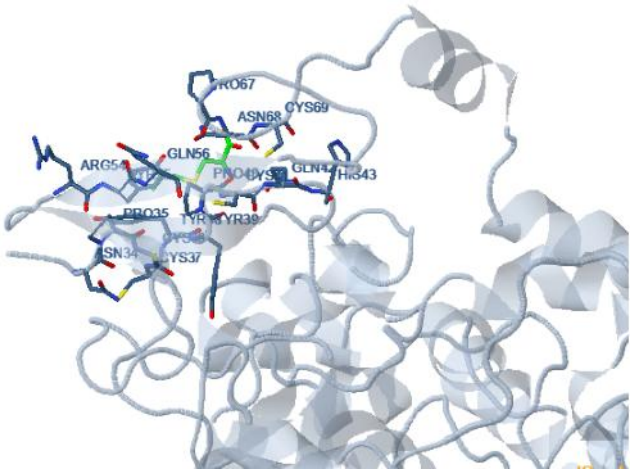
2D Interaction Plot



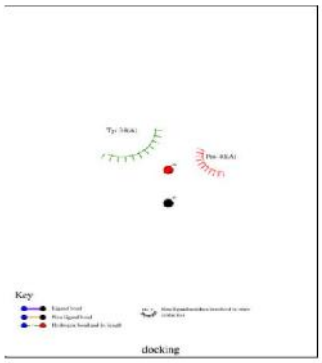
Hydrogen bond plotting Analysis with core amino acid



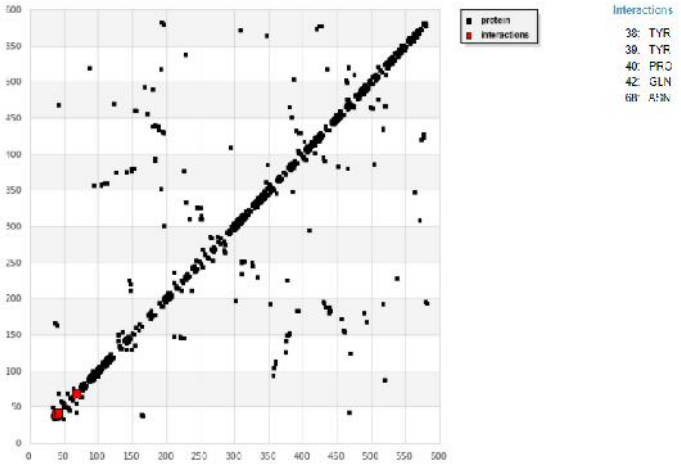
Allicin with Prostaglandin synthases -PDB- 1IGX



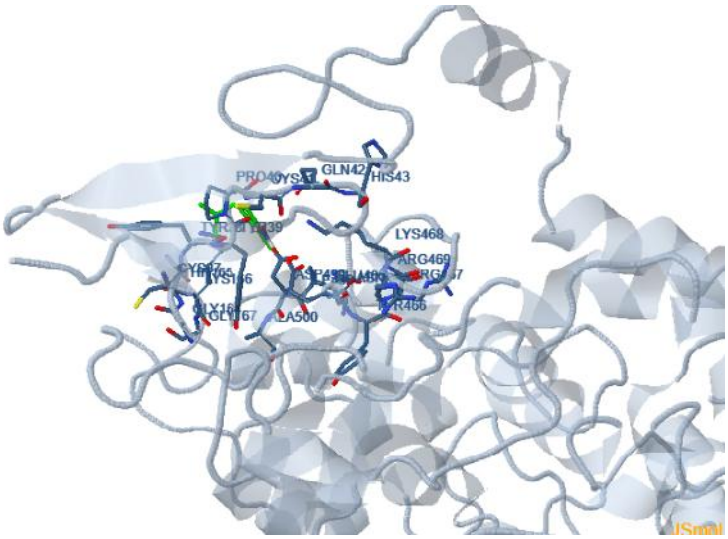
2D Interaction Plot



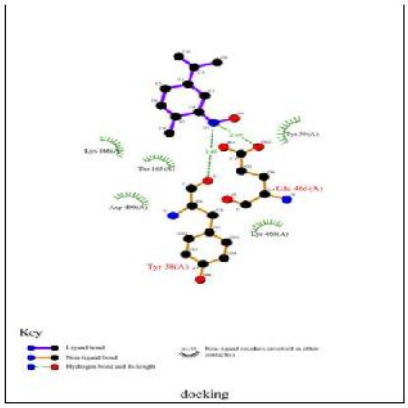
Hydrogen bond plotting Analysis with core amino acid



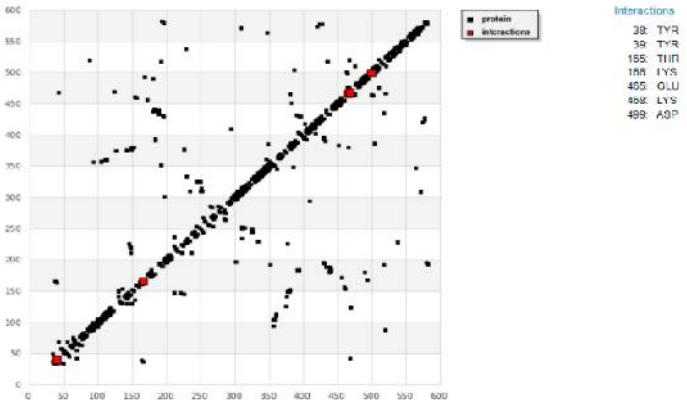
Kaempferol with Prostaglandin synthases -PDB- 1IGX



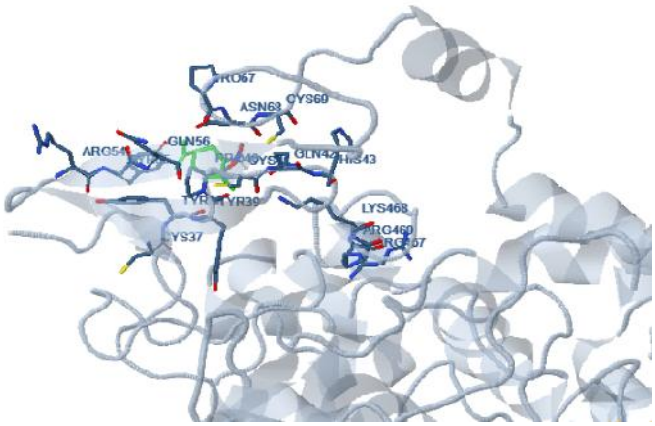
2D Interaction Plot



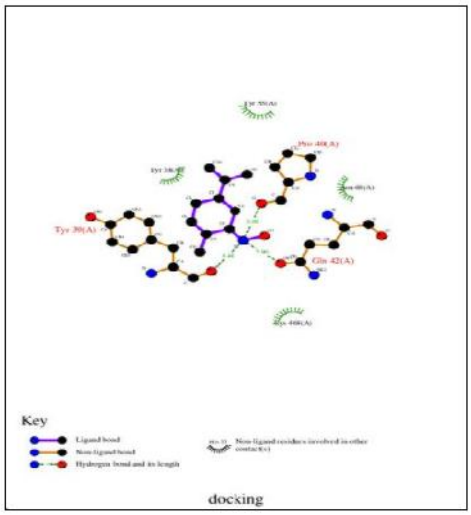
Hydrogen bond plotting Analysis with core amino acid



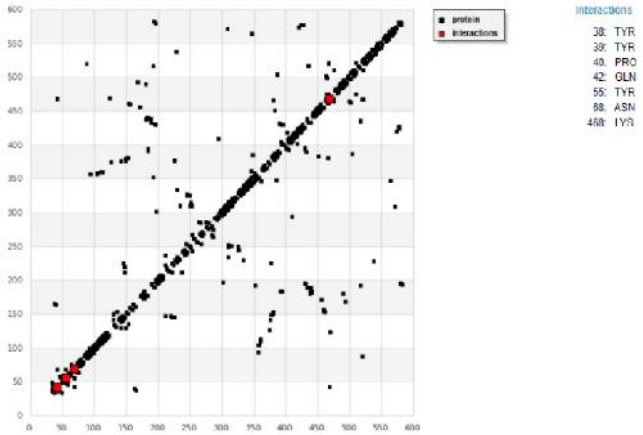
Carvone with Prostaglandin synthases -PDB- 1IGX



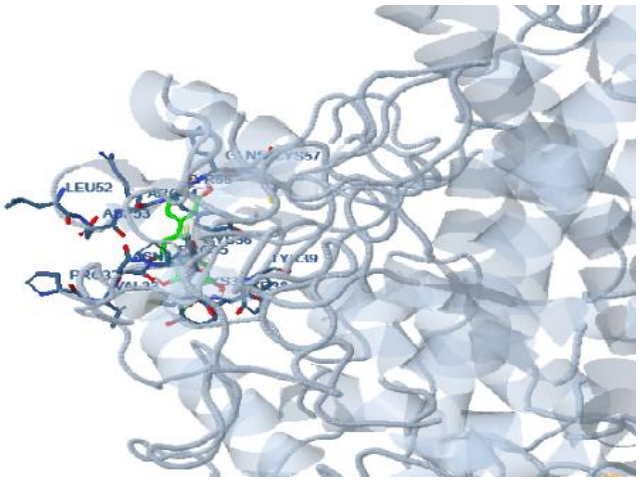
2D Interaction Plot



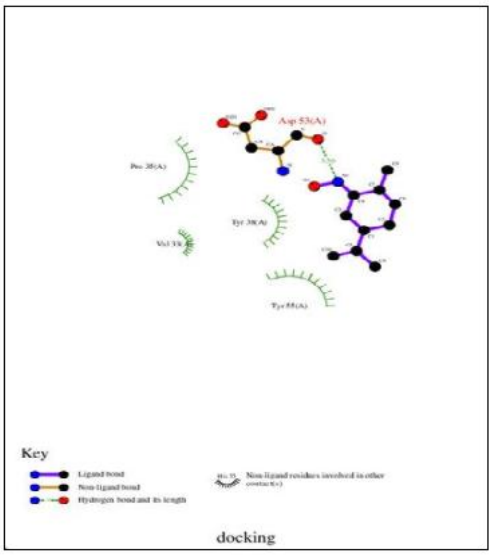
Hydrogen bond plotting Analysis with core amino acid



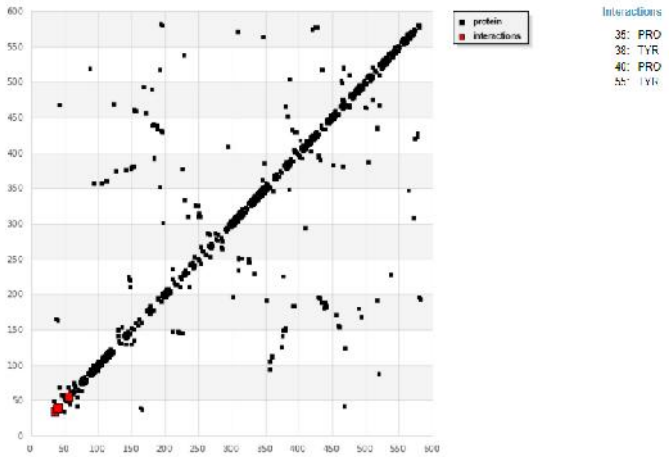
Magnolin with Prostaglandin synthases -PDB- 1IGX



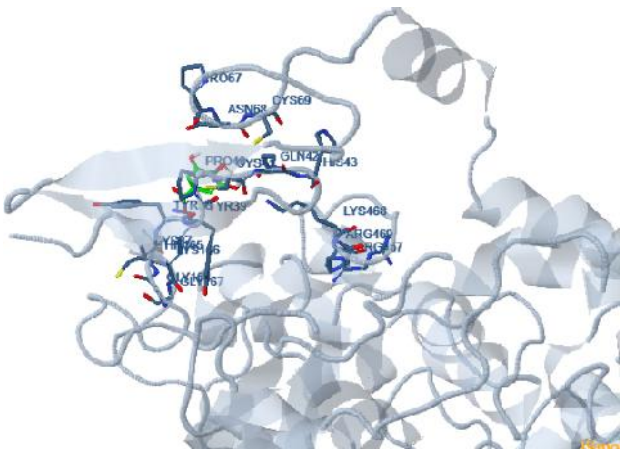
2D Interaction Plot



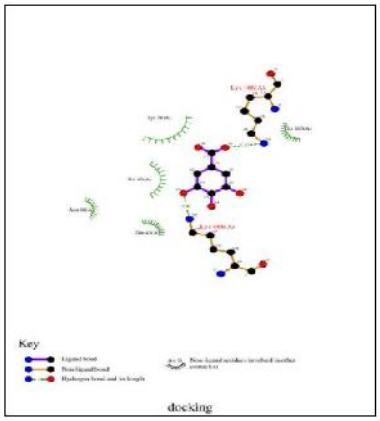
Hydrogen bond plotting Analysis with core amino acid



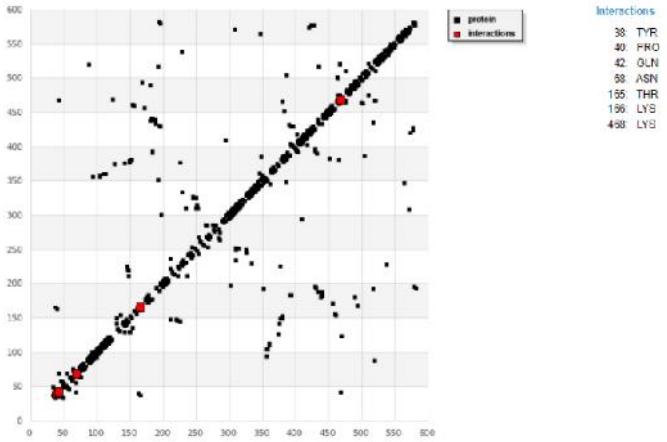
Gallic acid with Prostaglandin synthases -PDB- 1IGX



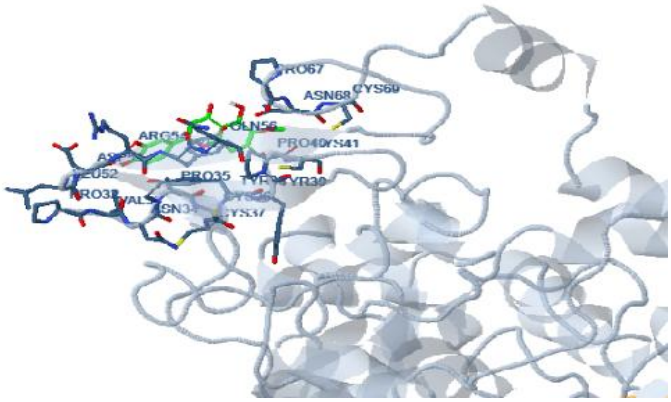
2D Interaction Plot



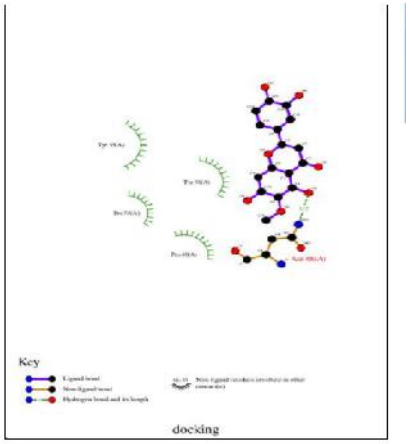
Hydrogen bond plotting Analysis with core amino acid



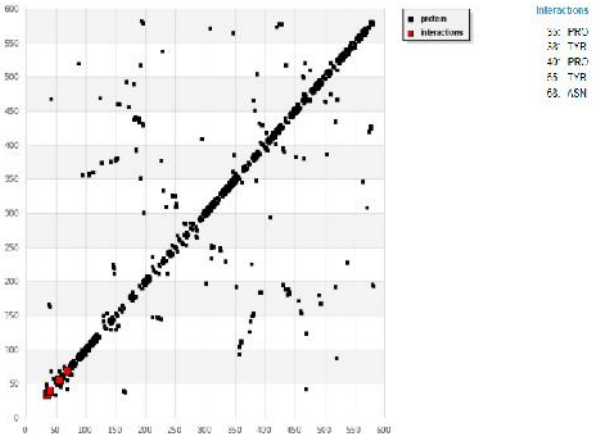
Nepetin with Prostaglandin synthases -PDB- 1IGX



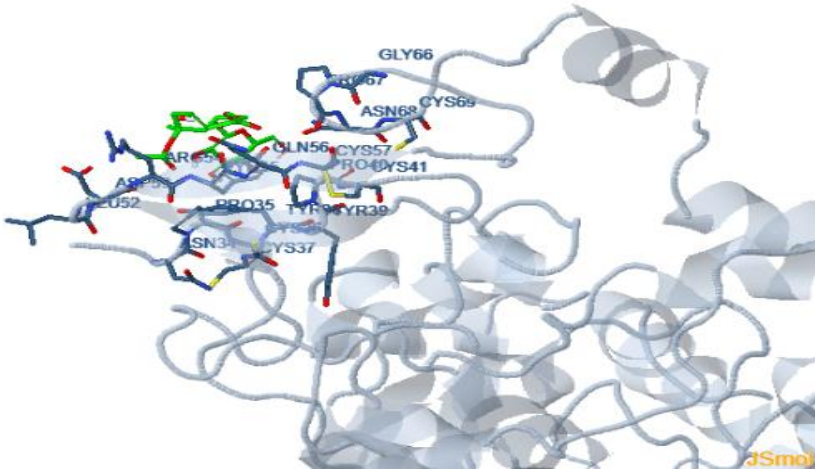
2D Interaction Plot



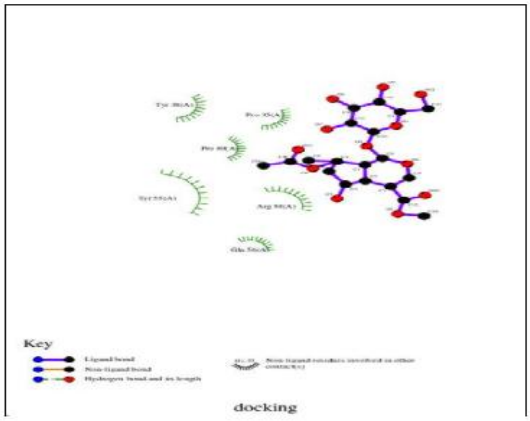
Hydrogen bond plotting Analysis with core amino acid



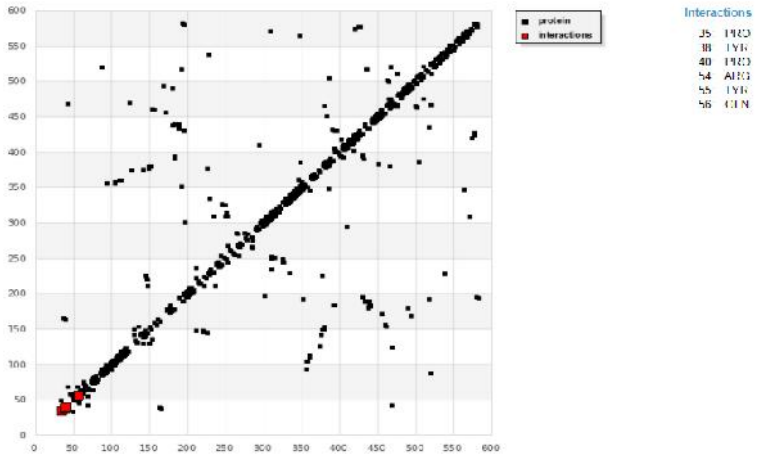
Salicylic acid with Prostaglandin synthases -PDB- 1IGX



2D Interaction Plot



Hydrogen bond plotting with core amino acid Analysis



Conclusion

Based on the results of the computational analysis it was concluded that the bio-active compound's like α-copaene, Magnolin, Nepetin, Allicin, Carvone and Gallic acidpresent in the formulation revels significant binding against the target protein thereby it was concluded that these compounds may exerts promising anti-pyretic and anti diarrheal property by hindering the synthesis of prostaglandin and M3 muscarinic acetylcholine receptor -PDB- 4U14that mediates the fever and diarrhea.

References

1. Bikadi, Z., Hazai, E.*Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of Auto Dock*. J. Cheminf. 1, 15 (2009)
2. 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)
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 19 (14), 1639-1662(1998)
4. F. J. Solis and R. J. B. Wets. *Minimization by Random Search Techniques.*
5. Andriana Y, xuan T.D, Quy TN, Tran HD, Le QT. Biological Activities and Chemical Constituents of essential oils from *Piper cubeba bojer* and *Piper nigrum* L. molecules. 2019 may 15; 24(10):1876.

6. Ameh. G.I. Phytochemical screening and Antimicrobial studies on the methanolic bulb extract of *Allium sativum* L. African Journal of Biotechnology Vol.12 (14), pp 1665-1668, 3 April, 2013.
7. Batiha G.E. Alkazmi L.M. Was ef LG, Beshbishy AM, Nadwa EH, Rashwan EK. *Syzygium aromaticum* L. (Myrtaceae). Traditional uses, Bioactive chemical Constituents, pharmacological and toxicological Activities, Biomolecules, 2020, 10(2):202.
8. Bairwa R. Sodha RS, Rajawat B.S. *Trachyspermum ammi*, Pharmacogn. Rev 2012; 6(11):56-60.doi.10.4130/0973-7847. 95871.
9. Oiao D, Gan LS,Mo JX, Zhou CX (chemical Constituents of *Acorus calamus*) Zhongguo zhong Yaoza zhi 2012 Nov; 37(22): 3430- 3.
10. S.Taprial.A review on phytochemical and pharmacological properties of *Michelia champaca* linn. Family: magnoliaceae International Journal of Pharmacology. 2015: 430-436.
11. R.A. Sharma ,Renu Singh. A Review on Phyla *Nodi flora* Linn.A wild wetland Medicinal Herb. Int. J. Pharm.Sci. Rev.Res, 20(1), 2013; 11, 57-63.

Access this Article in Online	
Quick Response Code	Website: www.ijcrims.com
	Subject: Siddha Medicine

How to cite this article:
Gayathri V, Victoria S, Shanmuga Priya C, Manju Hemamalini N. (2022). In docking Analysis of siddha formulation Kana Mantha Mathirai (KMM) inhibiting the Prostaglandin H synthases and M3 muscarinic acetylcholine receptors in gastroenteritis. Int. J. Curr. Res. Med. Sci. 8(2): 1-24.
DOI: http://dx.doi.org/10.22192/ijcrms.2022.08.02.001