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Molecular Docking Analysis of Siddha Medicine Pain Balm with Human Prostaglandin H Synthases

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Abstract: Molecular docking has become an important constituent of the drug detection process. Since first being developed in the 1980s, advancements in the power of computer hardware and the increasing number and ease of access to small molecule and protein structures have contributed to the development of improved methods, making docking more popular in both industrial and academic settings. In Siddha medicine, herbal formulations were the interactions of the lead molecules of the formulation with that of receptors which can be elucidated at the molecular level. Pain Balm is Traditional Siddha formulation used in external medicine for Arthritis. Molecular docking studies of Siddha Traditional formulation PB and to screen the lead component interaction on the Prostaglandin H synthases. Docking calculations were carried out using Auto Dock. The compounds present in PB like Quercetin, Kaempferol, Eugenol, Thymol, Linoleic acid and cineole showed maximum interactions with Prostaglandin H synthases. Hence , these compounds of PB possess promising Prostaglandin H synthases inhibition activity.

Keywords: Siddha medicine, Molecular Docking, Pain Balm, Prostaglandin H synthases

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Introduction

Arthritis is a type of musculoskeletal disease (MSD) prevalent in many parts of the world. The highest incidence of arthritis is found in India followed by America. In India, arthritis affects 13–15 % of the population of which 80 % of patients are women. Such disorders make it hard for patients to carry out daily activities (Batiha *et al.*, 2020). Osteoarthritis (OA) is the most common

Table 1: List of Phytocomponents Selected for docking studies

S. No.	Name of the Herb	Phytocomponents
1.	*Syzygium aromaticum*	Quercetin, Kaempferol, Eugenol,Thymol
2.	*Cocos nucifera*	Linoleic acid
3.	*Cinnamomum camphora*	1,8-cineole

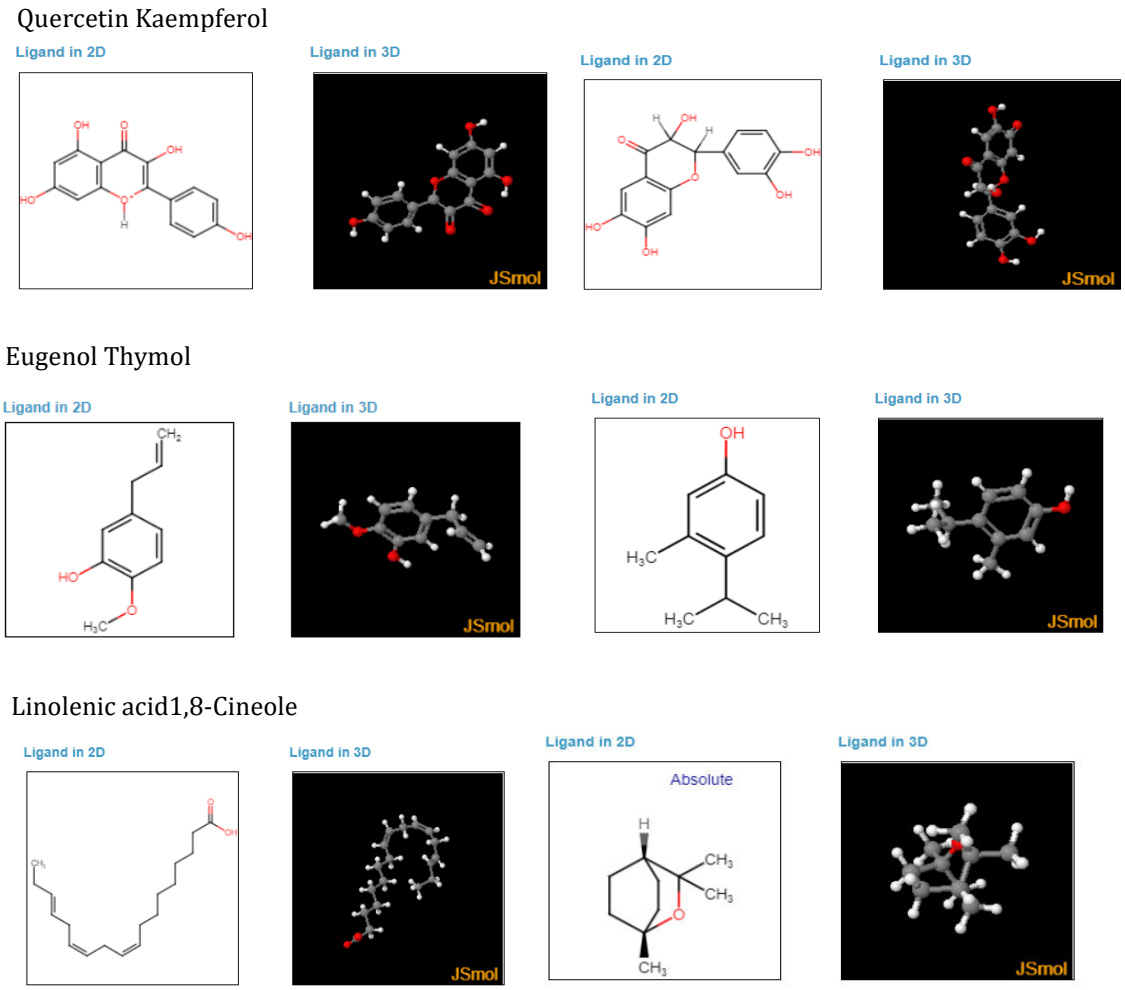


Fig. 1: 2D and 3D Structure of Phytocomponents.

type of Arthritis and is no longer viewed as a simple degenerative process due to ageing. For instance, hip OA is less common and knee OA more common in Asians than in Europeans. Beyond 55 years of age, women are affected more commonly than men, with a familial pattern of inheritance in nodal and primary generalized forms of OA (Bikadi and Hazai, 2009).

The main symptoms of Arthritis are pain and inflammation. These symptoms are mostly mediated through Prostaglandin H synthases and therefore in a modern approach, drugs of Analgesic and Anti inflammatory category is effectively used for Arthritis management. There are numerous amino acids responsible for mediating the Prostaglandin H synthases. The drugs or biomolecules that effectively targets the core residues block the receptor activity

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
Linolenic acid	278.4 g/mol	$C_{18}H_{30}O_2$	1	2	13
1,8-Cineole	157.27 g/mol	$C_{10}H_{18}O$	0	1	0
Kaempferol	286.239 g/mol	$C_{15}H_{10}O_6$	4	6	1
Eugenol	164.2 g/mol	$C_{10}H_{12}O_2$	1	2	3
Thymol	150.221 g/mol	$C_{10}H_{14}O$	1	1	1
Quercetin	302.238 g/mol	$C_{15}H_{10}O_7$	5	7	1

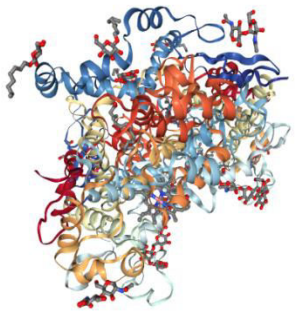


Fig. 2: Receptor structure of Prostaglandin H Synthase.

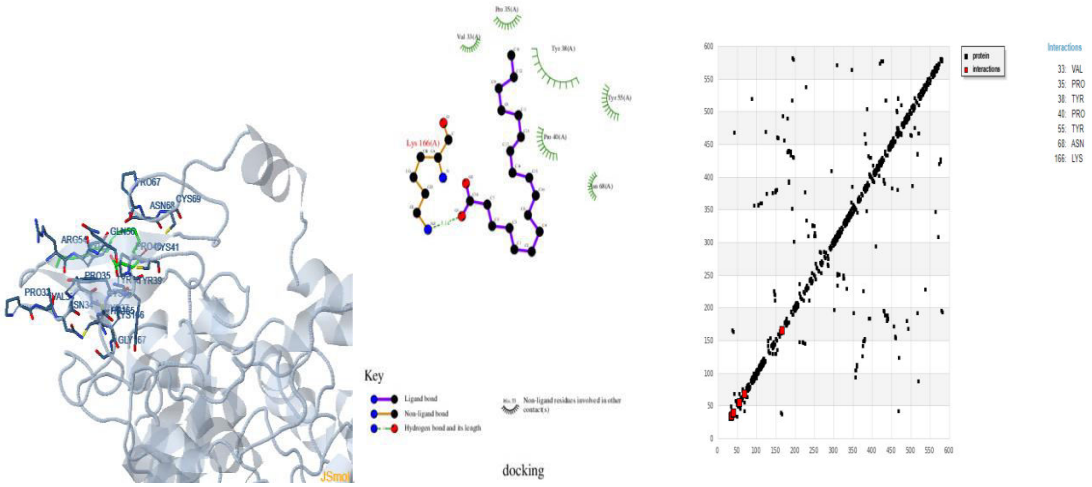
Table 3: Summary of the molecular docking studies of compounds against Prostaglandin H synthases

Compounds	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Linolenic acid	-3.86 kcal/mol	1.48 mM	-0.78 kcal/mol	-7.24 kcal/mol	617.192
1,8-Cineole	-3.88 kcal/mol	1.43 mM	-0.02 kcal/mol	-3.88 kcal/mol	356.428
Kaempferol	-5.49 kcal/mol	93.92 uM	-0.16 kcal/mol	-5.89 kcal/mol	462.137
Eugenol	-3.63 kcal/mol	2.20 mM	-0.00 kcal/mol	-4.10 kcal/mol	372.833
Thymol	-4.73 kcal/mol	342.40 uM	-0.07 kcal/mol	-5.47 kcal/mol	487.353
Quercetin	-6.25 kcal/mol	26.20 uM	-0.27 kcal/mol	-5.42 kcal/mol	447.126

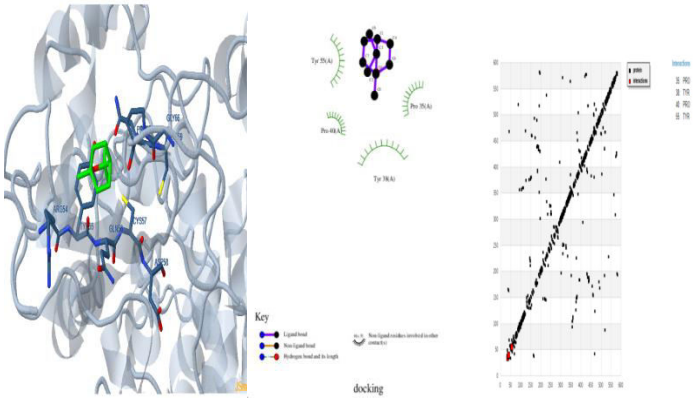
Table 4: Amino acid Residue Interaction of Lead against Prostaglandin H synthases

Compounds	Interactions	Amino acid Residue Interaction							
Linolenic acid	4	33 VAL	35 PRO	38 TYR	40 PRO	55 TYR	68 ASN	166 LYS	
1,8-Cineole	3	35 PRO	38 TYR	40 PRO					
Kaempferol	2	35 PRO	54 ARG	55 TYR	56 GLN	57 CYS	67 PRO		
Eugenol	4	33 VAL	35 PRO	38 TYR	40 PRO	55 TYR			
Thymol	3	33 VAL	35 PRO	38 TYR	53 ASP	55 TYR			
Quercetin	4	35 PRO	38 TYR	40 PRO	55 TYR	68 ASN			

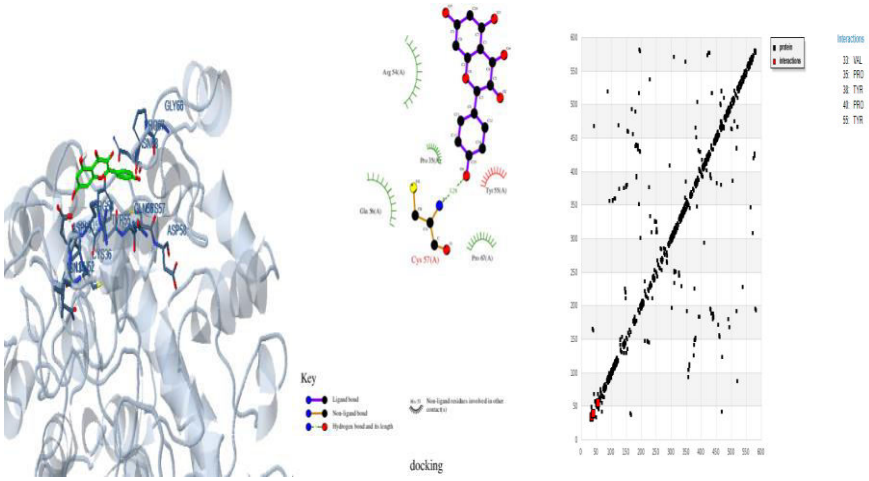
Linolenic acid with Prostaglandin H synthases



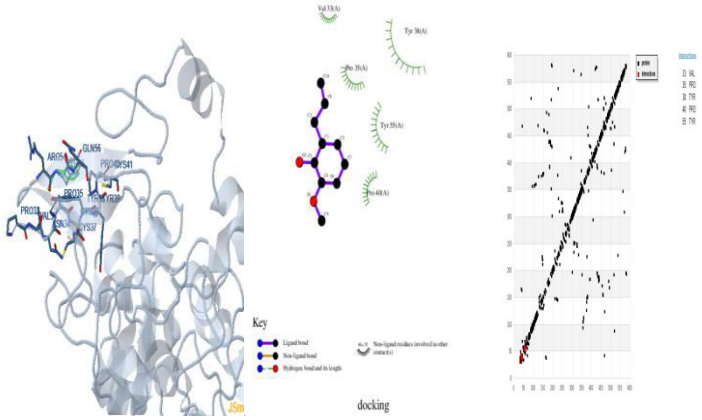
1,8-Cineole with Prostaglandin H synthases –PDB-1IGX



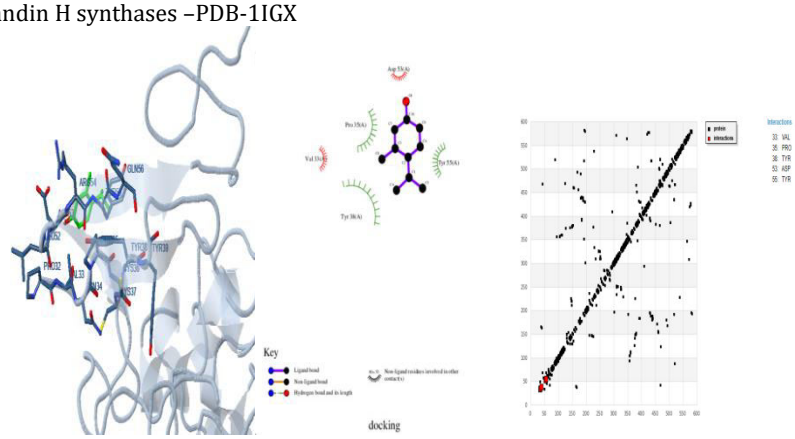
Kaempferol with Prostaglandin H synthases –PDB-1IGX



Eugenol with Prostaglandin H synthases –PDB-1IGX



Thymol with Prostaglandin H synthases –PDB-1IGX



Quercetin with Prostaglandin H synthases –PDB-1IGX

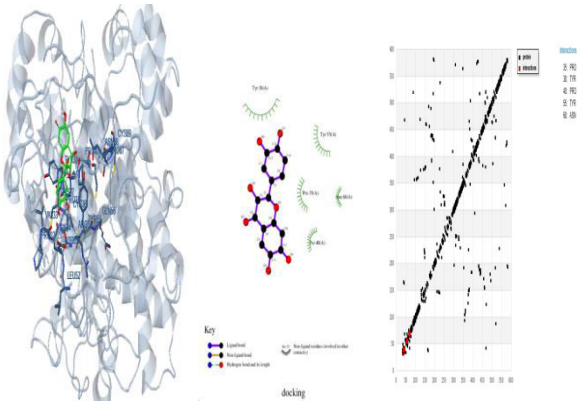


Fig. 3: Amino acid Interactions of Lead molecules of PB.

ultimately controlsthe symptoms of Arthritis (Boateng *et al*., 2016).

Pain Balm (PB) is one among the traditional external medicine used for Arthritis. *Syzygium aromaticum*, *Cinnamomum camphora*, and Coconut Oil are the main ingredients of this formulation (Elakkiya *et al*., 2020). For research perspective the lead molecules of this formulation were interpreted for its Prostaglandin H Synthase inhibitor activity. This may help in wider acceptability of PB as efficient Analgesic and Anti-inflammatory.

The main objective of the study was to carry out Molecular Docking (MD) studies of molecules

from key ingredients of PB to find its interaction on Prostaglandin H synthases.

Materials and Methods

Molecules from PB:

Docking calculations were carried out for the compounds retrieved from the herbal sources such as Quercetin, Kaempferol ,Eugenol, Thymol, Linoleic acid and cineole against target protein model (Table 1, Fig. 1) (Halgren, 1998; Lee *et al*., 2020). The ligand molecular properties are illustrated in Table 2.

Target details and Receptor Structure:

Crystalline structure of the target protein Prostaglandin H synthases (Fig. 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 Auto-dock program and the best dock pose was selected based on the interaction study analysis.

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 Auto-Dock tools (Morris *et al*., 1998). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris *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 and 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 (Morris *et al.*, 1998; Ricciotti and FitzGerald, 2011; Solis and Wets, 1981).

Results and Discussion

Binding of phytocomponents with the core amino acids (35 PRO, 38 TYR, 40 PRO, 54 ARG, 55 TYR) of the target by forming hydrogen bond will hinder the function of the enzyme Prostaglandin H synthases with PDB – 1IGX. These amino acid residues are functionally responsible for binding of substrate and inhibitors. Thereby phytocomponents which inhibit the target Prostaglandin H synthases may act as a potential therapeutic agent for management of pain and inflammation. Total of 6 bioactive lead compounds were retrieved from the herbs. From reported data of the herb, the phytochemicals such as Linolenic acid, Kaempferol, Eugenol, Thymol and Quercetin possess maximum of three to four interactions with the core active amino acid residues present on the target enzyme Prostaglandin H synthases. Summary of the molecular docking studies of PB lead compounds against Prostaglandin H synthases –PDB 11GX and its amino acid binding interactions are shown in Table 3, 4 and Figure 3.

Conclusion

Based on the results of the computational analysis it was concluded that all the bio-active compound's like Linolenic acid, Kaempferol, Eugenol, Thymol and Quercetin reveals significant binding affinity against the target enzyme Prostaglandin H synthases 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 activity of the enzyme Prostaglandin H synthases. It was concluded that the phytocomponents may act as a potential therapeutic agent for management of pain and inflammation.

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