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Molecular Docking Investigation on Anti-allergic potential of the Siddha formulation *Jathikaai Mathirai* against Histamine Receptor

K. Rajeswari[*1], V. Ramadass [2]

[1]Emergency Medical Officer, National Institute of Siddha, Tambaram sanatorium, Chennai 600047, Tamil Nadu, India.

[2]PG Scholar, Department of Pura Maruthuvam, Government Siddha Medical College, Chennai 600 106, Tamil Nadu, India

Corresponding Author: Dr. K.Rajeswari, Emergency medical officer, National Institute of Siddha, Tambaram sanatorium, Chennai 600047, Tamil Nadu, India

Abstract

The incidence and prevalence of allergic conditions has increased in recent years. Emerging air pollution and dietary habituation in turn severely impacts the health care security of the people from lower economic zone. Conventional anti-histamine agent's utilised for treating allergic disorders offers potential side effects. Therefore, research into naturally occurring anti-allergic therapeutics found in herbs is currently being conducted. Siddha system of medicine pioneers the art of traditional therapy, Since several centuries siddha therapy adequately compensate the health care need of the people. The main aim of the present investigation is to explore the anti-allergic potential of the herbal ingredients present in the siddha formulation *Jathikaai Mathirai* against the target histamine receptor by using AutoDock docking investigation tool. Results of the present investigation reveals that the compounds such as Elemicin, β-caryophyllene, Phellandrene, Linalool, Adamantane, Eudesmin, Ferulic acid and Palmitic acid reveals significant interaction with the core active amino acid residue present on the target histamine H1 receptor. It was concluded from the datas of the present study that the phytotherapeutics present in the siddha formulation *Jathikaai Mathirai* possess significant anti-allergic activity and may be recommended for the clinical management of the same in near future with prior clinical justification.

Keywords: Allergy, Siddha formulation, Phytocomponents, Docking, Auto-Dock, Anti-histamine activity.

1. Introduction

The common cold is widespread and can be incapacitating, despite the fact that it tends to resolve on its own. Because of this, people's abilities and output at work decrease [1] and it may even have an impact on other activities like driving [2]. It has far-reaching consequences for healthcare and society as a whole. Seven percent to seventeen percent of adults and 33 percent of children see a doctor when they have an upper respiratory tract illness [3]. Patient visits per month during cold and flu season are up by an estimated 12.5% due to upper respiratory tract diseases [4]. In 1997, it was estimated that the direct medical costs associated with the common

cold in the United States amounted to $17 billion annually (including costs for doctor visits, treatment for secondary illnesses, and medication). The annual indirect expenses of sick days and family caregiving were calculated at $25 billion [5].

Histamine plays a pivotal role in mediating the inflammatory response. The release of mast cell mediators like histamine is caused by degranulation of intestinal mast cells. As a result of binding to specific histamine receptors, histamine promotes epithelial ion transport in a variety of mammalian organs. This research set out to determine whether or not tissue mast cells and exogenous histamine play a part in controlling ion transport in avian mucosa [6].

The antihistamine class of drugs is chemically diverse and associated with a wide range of adverse effects. It is important to weigh the benefits of using antihistamines against the hazards involved [7]. The central nervous system depressive effects of antihistamines are well-known, while counterintuitive stimulating effects. Seizures, hallucinations, irritability, and sleeplessness are among these symptoms [8].

Anti-inflammatory, immunomodulatory, antihistaminic, smooth-muscle relaxing, and allergic action are all desirable qualities in a medicinal herbs [9]. Because they neutralise the effects of excess reactive oxygen species and reactive nitrogen species, antioxidant supplements are useful in lowering the severity of bronchoconstriction [10]. Patients seeking relief from allergy are turning to alternative treatments [11] since conventional anti-histamine medication has unfavourable side effects.

Jathikaai Mathirai is a poly herbal siddha formulation comprises of novel combination of herbs such as *Myristica fragrans, Syzygium aromaticum,Trachyspermum ammi, Nigella sativa, Zingiber officinale, Piper longum, Curcuma aromatic, Acorus calamus, Ferula asafoetida* and *Clitoria ternatea*. Screeing of herbs for its efficacy by availing docking simulation techniques gaining momentum in recent days.The main aim of the present investigation is to explore the anti-allergic potential of the herbal ingredients present in the siddha formulation *Jathikaai Mathirai* against the target histamine receptor by using AutoDock docking investigation tool.

2. Materials and Methods

2.1. Protein-ligand docking

Computational molecular investigation was performed using Auto Dock version 4 which predicts interaction binding affinity between selected therapeutic lead with that of the protein target histamine H1 receptor-PDB- 3RZE.

2.2. Protein preparation

Three dimensional (3D) structure of histamine H1 receptorwith protein data bank (PDB) - 3RZE (Figure 1) retrieved from Research Collaboratory for Structural Bioinformatics (RCSB) [12].

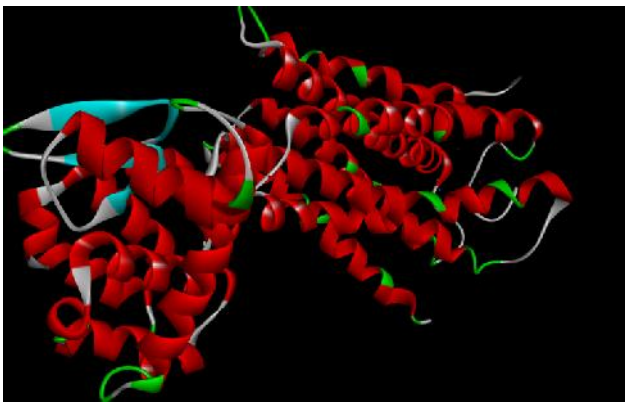

Figure 1: 3D crystalline structure of the target protein against histamine H1 receptor (PDB) - 3RZE

Table 1: Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Elemicin	208.25 g/mol	$C_{12}H_{16}O_3$	0	3	5
β-caryophyllene	204.35 g/mol	$C_{15}H_{24}$	0	0	0
β-pinene	136.23 g/mol	$C_{10}H_{16}$	0	0	0
Phellandrene	136.23 g/mol	$C_{10}H_{16}$	0	0	1
Linalool	154.25 g/mol	$C_{10}H_{18}O$	1	1	4
Adamantane	136.23 g/mol	$C_{10}H_{16}$	0	0	0
ß-elemene	204.35 g/mol	$C_{15}H_{24}$	0	0	3
Eudesmin	386.4 g/mol	$C_{22}H_{26}O_6$	0	6	6
Ferulic acid	194.186 g/mol	$C_{10}H_{10}O_4$	2	4	3
Palmitic acid	256.42 g/mol	$C_{16}H_{32}O_2$	1	2	14

2.3. Ligand model preparation

Structures of the phytocomponents such as Elemicin, β-caryophyllene, β-pinene, Phellandrene, Linalool, Adamantane, β-elemene, Eudesmin, Ferulic acid and Palmitic acid subjected to docking investigation were outlined using ChemDraw sketch software and converted from two dimension (2D) to3D structures. Figure 2 summarizing 2D and 3D structure of approved ligand subjected to molecular docking Investigation against histamine H1 receptorwith protein data bank (PDB) - 3RZE.

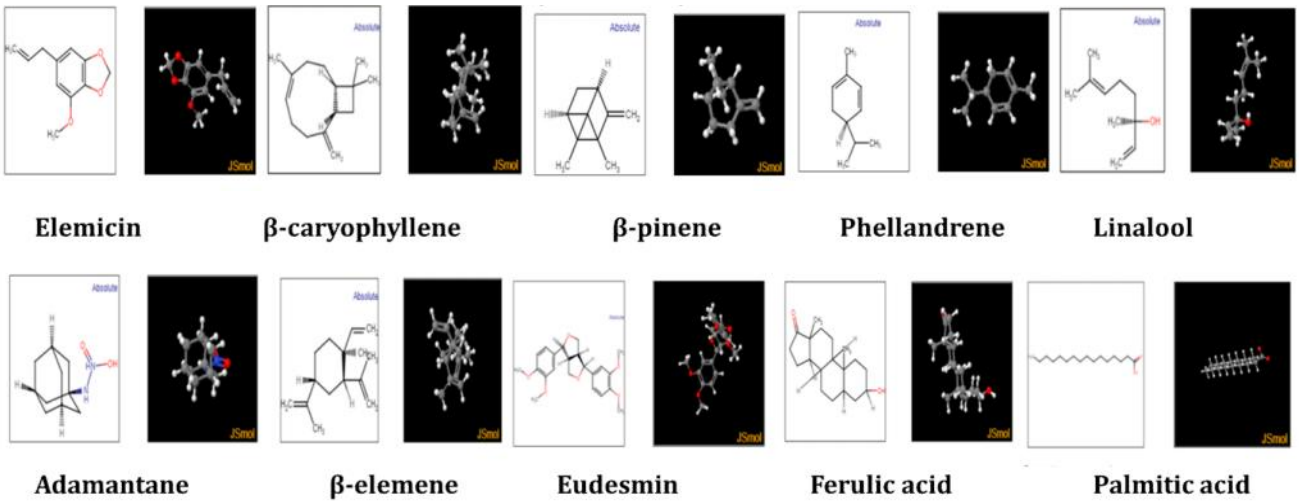

Figure 2: 2D and 3D Structure of Selected ligands of herbal origin

2.4. Docking simulations

Molecular docking analysis were performed using licensed version of Auto Dock 4, which predicts interactions between phytocomponents with that of the selected protein target (H1 receptor) with protein data bank (PDB)- 3RZE retrieved from Research Collaboratory for Structural Bioinformatics (RCSB). 3D componential structure of lead molecules and protein were docked using AutoDock analytical tool version 4. Docking simulations were performed using

the programmed algorithm inbuilt with pre automation in the software. 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 [13,14].

3. Results

Docking score implicates the binding affinity between the lead and target higher the negativity in the value that showcase the level of potency of the drug. Development and advancement in the field of computational analysis increased the precision level in identifying the potential drug molecule and deriving its mechanism of action at target site. Selective alterations in the functional groups greatly minimize the non-specific binding and impedes the adverse event at clinical level. Total of 10 bioactive lead compounds were subjected to the docking screening. Out of ten compounds' the lead molecules such as Elemicin, β-caryophyllene, Phellandrene, Linalool, Adamantane, Eudesmin, Ferulic acid and Palmitic acid reveals significant interaction with the core active amino acid residues present on the target histamine H1 receptor. As shown in Table 2 and 3.

Table 2: Summary of the molecular docking studies of compounds against histamine H1 receptor (PDB) - 3RZE

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Elemicin	-5.80 kcal/mol	56.35 uM	-0.06 kcal/mol	-6.64 kcal/mol	562.146
β-caryophyllene	-8.48 kcal/mol	603.99 nM	-0.00 kcal/mol	-8.48 kcal/mol	573.006
β-pinene	-6.26 kcal/mol	25.67 uM	-0.01 kcal/mol	-6.26 kcal/mol	429.795
Phellandrene	-6.56 kcal/mol	15.54 uM	-0.06 kcal/mol	-6.86 kcal/mol	449.968
Linalool	-6.04 kcal/mol	37.68 uM	-0.01 kcal/mol	-7.40 kcal/mol	515.34
Adamantane	7.97 kcal/mol	1.45 uM	-0.01 kcal/mol	-8.24 kcal/mol	496.937
ß-elemene	-7.44 kcal/mol	3.50 uM	-0.04 kcal/mol	-8.52 kcal/mol	598.718
Eudesmin	-6.17 kcal/mol	29.96 uM	-0.50 kcal/mol	-7.95 kcal/mol	953.724
Ferulic acid	-6.39 kcal/mol	20.72 uM	-1.44 kcal/mol	-6.79 kcal/mol	546.064
Palmitic acid	-7.81 kcal/mol	1.89 uM	-0.27 kcal/mol	-11.20 kcal/mol	666.754

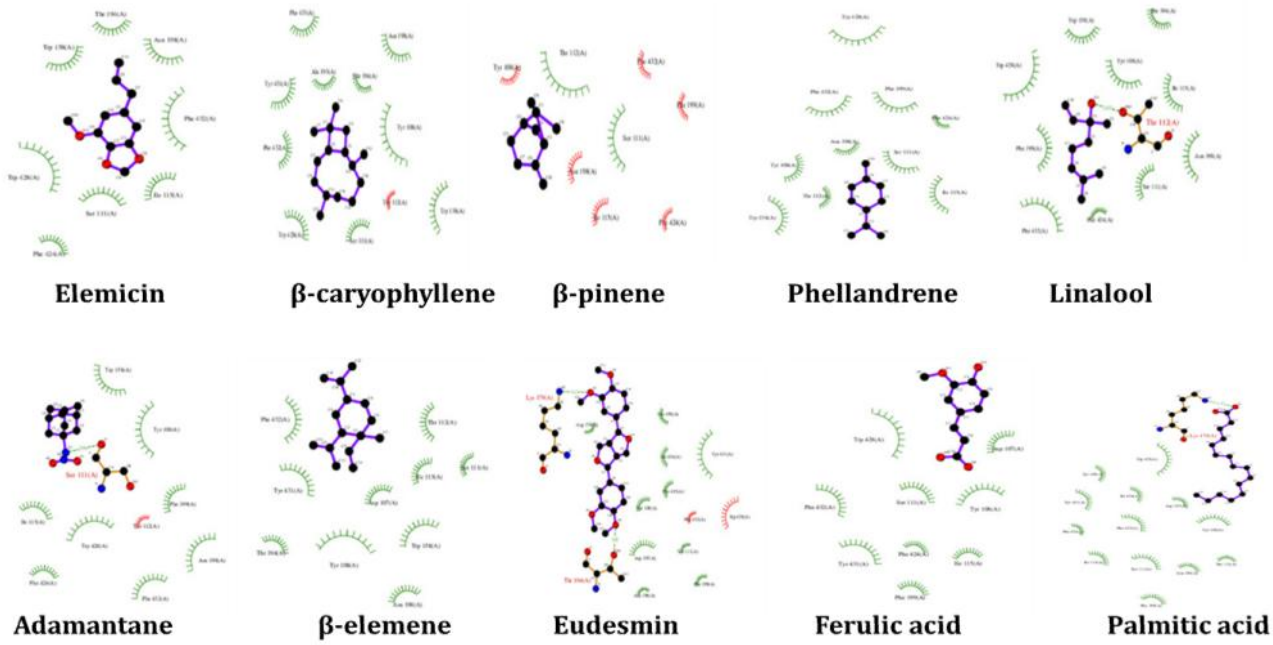

Figure 3: 2D Interaction plot of selected ligands with protein against histamine H1 receptor (PDB) - 3RZE

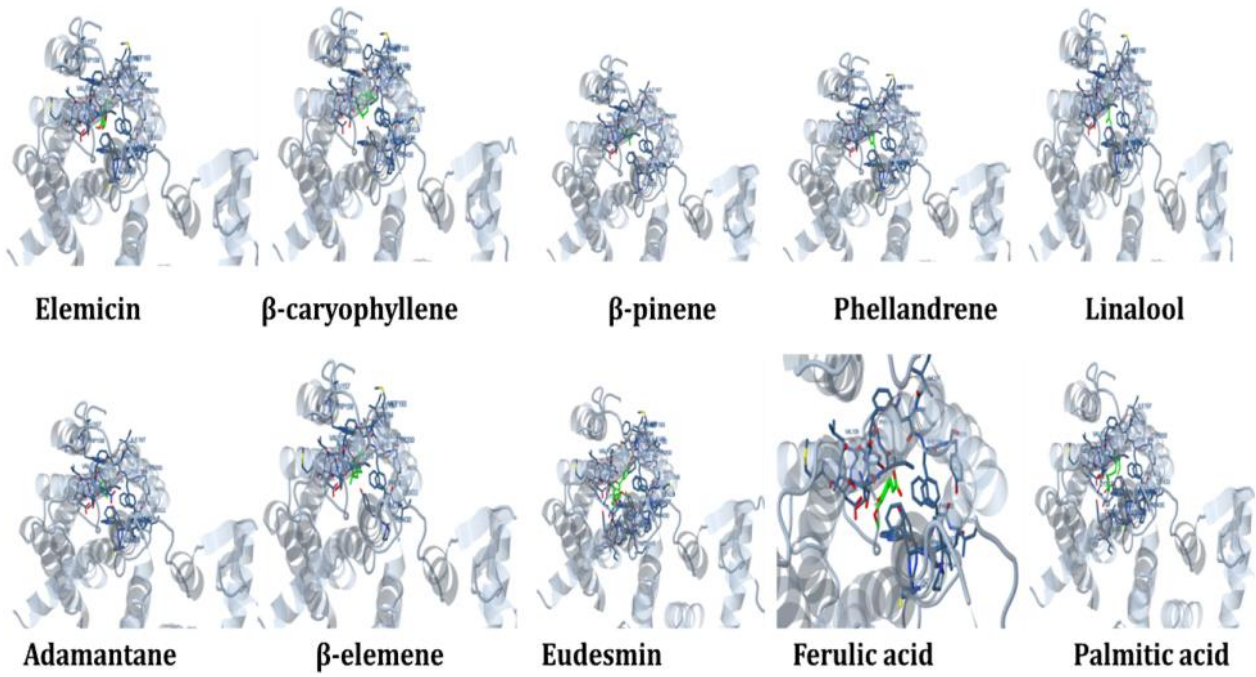

Figure 4: Docking pose of selected ligands with protein against histamine H1 receptor (PDB) - 3RZE

Table 3: Amino acid Residue Interaction of Lead against histamine H1 receptor (PDB) - 3RZE

Compounds	Interactions	Amino acid residue interactions									
Berberine	2	151 SER	371 GLU	374 THR	378 GLN	445 LYS	475 TYR	563 ALA	567 SER	569 PHE	
Ellagic acid	2	151 SER	371 GLU	374 THR	445 LYS	446 PRO	475 TYR	567 SER	568 ILE	569 PHE	
Gallic acid	2	438 SER	441 PHE	445 LYS	447 ASN	459 GLN	475 TYR				
Huperzine A	2	151 SER	370 GLY	371 GLU	374 THR	444 VAL	445 LYS	446 PRO	475 TYR	567 SER	
Nicotinic acid	2	441 PHE	445 LYS	447 ASN	459 GLN	475 TYR					
Palmatine	2	147 THR	150 ALA	151 SER	374 THR	445 LYS	474 TYR	475 TYR			
Pyridoxine	3	441 PHE	445 LYS	447 ASN	459 GLN	473 VAL	475 TYR				
Rivastigmine	2	150 ALA	151 SER	371 GLU	444 VAL	445 LYS	446 PRO	475 TYR	567 SER	569 PHE	
Spathulenol	2	147 THR	150 ALA	151 SER	371 GLU	374 THR	444 VAL	445 LYS	446 PRO	475 TYR	567 SER

4. Discussion

The common cold is a temporary, viral infection affecting the nasal cavity, sinuses, throat, and voice box. Transmission of the virus occurs through direct or indirect hand-to-hand contact with secretions from an infected individual, or through inhalation of an aerosol containing the secretions and virus [15].Even though the incubation period for rhinoviruses can be as short as two days, it is often closer to three days. Symptoms, which are frequently related to the infected mucosa, peak between the first and third days and linger between the seventh and thirtieth days [16]. A sore throat, runny nose, stuffy nose, cough, and general malaise are all symptoms [17].

Inflammation has been recognised as a key pathophysiological feature of allergies for the past two decades. Activation of mast cells, a key player in allergic reactions, may be all that's required for rapid development of microvascular leakage and tissue edoema in sensitised subjects exposed to allergen. Histamine, neutral proteinases, proteoglycans, prostaglandin D2, leukotriene C4, and some cytokines are all produced by mast cells, making them an important source of potent mediators of allergic inflammation [18].

Histamine plays a pivotal role as a mediator with a wide range of actions that are mediated by receptors on the cell surfaces of target cells. The first three of the four types of histamine receptors known pharmacologically are found in the digestive tract. Histamine receptor antagonists have been shown to reduce mast cell degranulation, suggesting that they could be further investigated as a class of mast cell stabilisers [19].

Virtual screening is currently the preferred method for screening a library of phytotherapeutic compounds and refining the best candidates of biological interest [20]. In order to define the behaviour of small molecules in the binding site of target proteins and to elucidate essential biochemical processes, the molecular docking technique can be used to model the interaction between a small molecule and a protein at the atomic level [21,22]. In several areas of molecular modelling, molecular dynamics (MD) [23] is employed as a sophisticated simulation tool. MD simulation more accurately portrays the adaptability of the ligand and the protein during

docking because it allows each atom to move independently in the field of the remainder atoms [24]. However, MD simulations can have problems with proper sampling since they move in such small increments and have trouble jumping over high energy conformational barriers. In the present investigation total of 10 bioactive lead compounds were subjected to the docking screening. Out of ten compounds' the lead molecules such as Elemicin, β-caryophyllene, Phellandrene, Linalool, Adamantane, Eudesmin, Ferulic acid and Palmitic acid reveals significant interaction with the core active amino acid residues present on the target histamine H1 receptor.

5. Conclusion

Histamine is a chemical that causes an allergic reaction, and antihistamines work by blocking the action of histamine at the cell surface. Conventional antihistamine provokes undesirable side effects which in turn widen the scope of alterative therapeutics from herbal origin.Based on the results of the computational analysis it was concluded that the bio-active compound's like Elemicin, β-caryophyllene, Phellandrene, Linalool, Adamantane, Eudesmin, Ferulic acid and Palmitic acid present in the herbal ingredients of the formulation *JathikaaiMathirai* possess significant binding affinity against the target histamine H1 receptor by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts promising anti-allergic and anti-inflammatory activity.

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