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Molecular docking studies of siddha medical plant Seendhil (*Tinospora cordifolia)* on human histamine h1 receptor (3RZE)

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Abstract

In Siddha medicine, molecular docking is very useful for herbal formulations because it can clarify the molecular interactions between the formulation's lead molecules and receptors and provide insight into the basic biochemical processes that the formulation is intended to address. The siddha drug *Tinospora cordifolia*(seendhil) is used for treating many diseases including allergic reactions. When it comes to allergies, the primary core residues involved in mediating the human histamine receptor (3RZE) are amino acids such asparagine (ASN), tryptophan (Trp), aspartate (Asp), tyrosine (Tyr), serine (Ser), isoleucine (Ile), lysine (Lys), threonine (Thr), and phenylalanine (Phe). When lead compounds bind to this core residue, the activity of the enzyme may be inhibited. Research on the Siddha herbal drug seendhil's molecular docking and screening of the lead component interaction on the human histamine receptor (3RZE). Auto Dock 4 was utilized to do docking computations. The ligand atoms received the addition of Gasteiger partial charges. Using the Solis & Wets local search technique and the Lamarckian genetic algorithm (LGA), docking simulations were carried out. The ligand molecules were first positioned, oriented, and torsored randomly. During docking, every rotatable torsion was freed. Finding of this docking is that comparing 3RZE's interactions with *Tinospora cordifolia* (Seendhil) constituents, such as Tinosporide, Tembetarine and Berberine revealed the highest levels. Therefore, the test drug's molecules have encouraging human histamine 1 receptor (3RZE) inhibitory action. The docking studies were an essential step in the scientific justification of *Tinospora cordifolia* (Seendhil) for its potential pharmacological validation.

Keywords: Seendhil, Anti allergic, anti-inflammatory, molecular docking, siddha herbal plant,*Tinospora cordifolia*

Introduction

Allergies arise when your immune system perceives certain chemicals (such as pet dander, pollen, or particular foods) as harmful intruders. IgE antibodies are produced by the immune system to combat these allergens. IgE antibodies cause an allergic reaction by releasing histamine when you come into contact with the same allergen again, which results in symptoms. Pollen, mold, dust mites, cat fur, and cockroaches are examples of environmental allergies. Foods such as peanuts and shellfish, latex, insect venom, and prescription drugs are the examples of the allergies that could be fatal. Symptoms are runny nose, sneezing, red eyes, and itching are signs of seasonal or environmental allergies. Anaphylaxis may result from severe symptoms, such as swelling and breathing difficulties. In India, the incidence of allergic rhinitis varies between 20% and 30%. Pregnant women, older adults, teenagers, and children are vulnerable groups. India is experiencing a rise in allergies due to a number of factors, including genetic predispositions, dietary habits, and air pollution. Since the majority of allergy symptoms are mediated by H1 receptors (Human Histamine Receptor-3RZE), non-sedating antihistamine medications are an effective treatment option in the modern era. Numerous amino acids play a role in mediating the 3RZE. The medications or biomolecules that efficiently target the core residues block the receptor activity, which in turn regulates the hypersensitivity symptoms.

The clinical manifestation of hypersensitivity is roughly associated with the illness known as "Silvidam" in traditional Siddha medicine. The ailment is treated exclusively using a variety of herbal or herbomineral compositions. One herbal remedy used to treat traditional allergic problems is called . The Gunapadam Moologai textbook makes reference to the plant drug Seendhil. In order to examine the formulation from a broader scientific standpoint, the lead compounds were analyzed for their ability to block the human histamine receptor (3RZE). This could facilitate the greater acceptance of seendhil as a potent herbal remedy for allergies.

Aim and objective:

Binding of phytocomponents with the core amino acid (428 TRP) of the target by forming hydrogen bond will hinder the function of the histamine H1 receptor with PDB –3RZE. These amino acid residues are functionally responsible for binding of substrate and inhibitors. Thereby phytocomponents which inhibit the target H1 receptor may act as a potential therapeutic agent for management of allergic conditions.

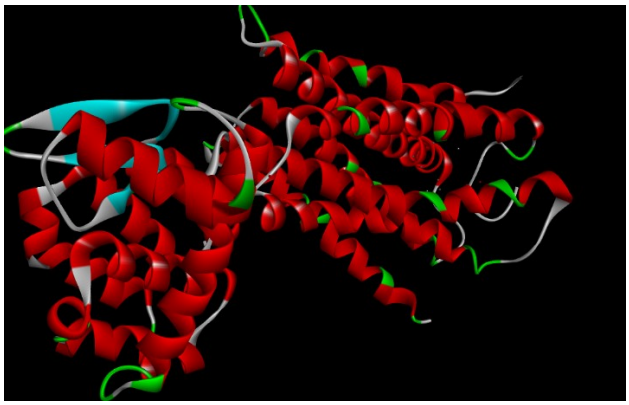
Methodology

Docking calculations were carried out for retrieved phytocomponents against target enzyme H1 receptor. 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
Tinospora cordifolia	Tinosporide Tembetarine Berberine	3RZE	Histamine H1 receptor

3D- Structure of the histamine H1 receptor (PDB) - 3RZE

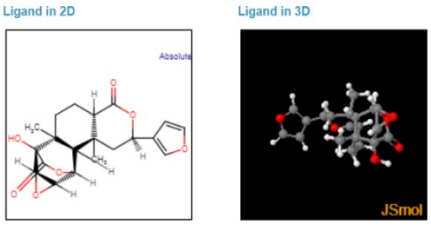


RECEPTOR STRUCTURE

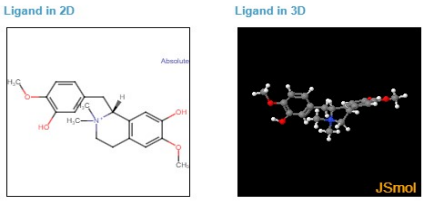
Crystalline structure of the target H1 receptor with PDB – 3RZE was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atom were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis.

2D and 3D Structure of Phytocomponents

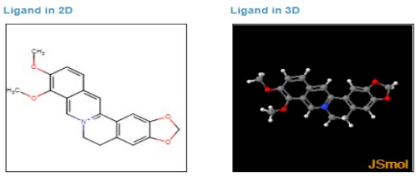
Tinosporide



Tembetarine



Berberine



Cetirizine

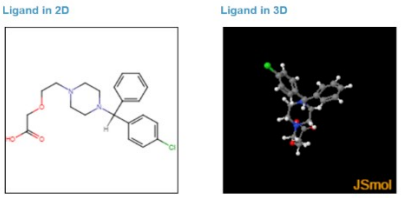


Table 2: Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Tinosporide	374.4 g/mol	$C_{20}H_{22}O_7$	1	7	1
Tembetarine	344.4 g/mol	$C_{20}H_{26}NO_{4+}$	2	4	4
Berberine	336.4 g/mol	$C_{20}H_{18}NO_4$	3	0	4
Cetirizine	461.808 g/mol	$C_{21}H_{27}Cl_3N_2O_3$	3	5	8

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

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Tinosporide	-6.65 kcal/mol	13.33 uM	-0.45 kcal/mol	-7.14 kcal/mol	849.587
Tembetarine	-7.01 kcal/mol	7.25 uM	-0.01 kcal/mol	-7.50 kcal/mol	812.53
Berberine	-5.00 kcal/mol	215.51 uM	-0.60 kcal/mol	-6.27 kcal/mol	824.773
Cetirizine	-11.38 kcal/mol	4.52 nM	-0.83 kcal/mol	-13.28 kcal/mol	895.24

Amino acid Residue Interaction of Lead againsthistamine H1 receptor (PDB) - 3RZE

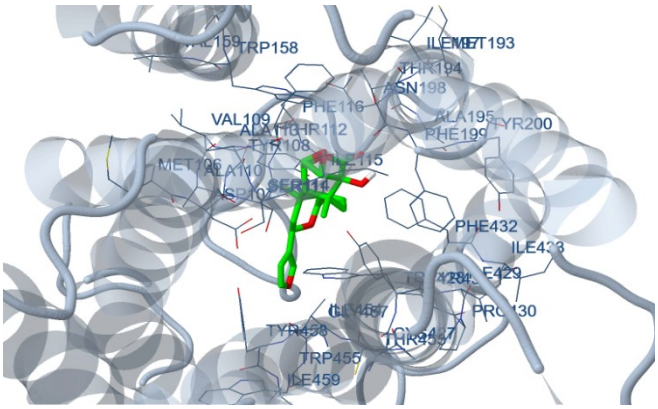
Compounds	Interactions	Amino acid Interaction														
Tinosporide	1	107 ASP	108 TYR	111 SER	112 THR	115 ILE	198 ASN	199 PHE	428 TRP	431 TYR	432 PHE	454 ILE	458 TYR			
Tembetarine	1	107 ASP	108 TYR	111 SER	112 THR	158 TRP	179 LYS	194 THR	195 ALA	198 ASN	428 TRP	431 TYR	432 PHE	435 PHE	454 ILE	458 TYR
Berberine	1	84 ASN	103 TRP	107 ASP	108 TYR	111 SER	112 THR	179 LYS	198 ASN	428 TRP	431 TYR	432 PHE	450 HIS	454 ILE	458 TYR	
Cetirizine	1	84 ASN	107 ASP	108 TYR	111 SER	112 THR	178 ASP	179 LYS	191 LYS	428 PHE	431 TYR	432 PHE	435PHE	450 HIS	454 ILE	458 TYR

Observation and Inference

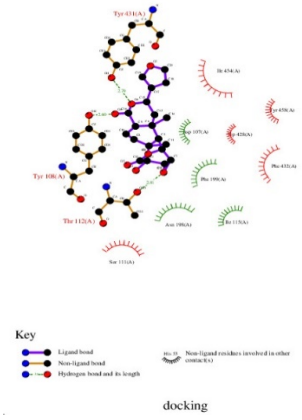
Total of three bioactive lead compounds were retrieved from the herb *Tinosporacordifolia*. From the reported data of the literature, it was observed from the outcome of the present investigation that three phytochemicals such as Tinosporide, Tembetarine and Berberine reveals significant interaction with the core active amino acid residues present on the target histamine H1 receptor.

Docking Pose

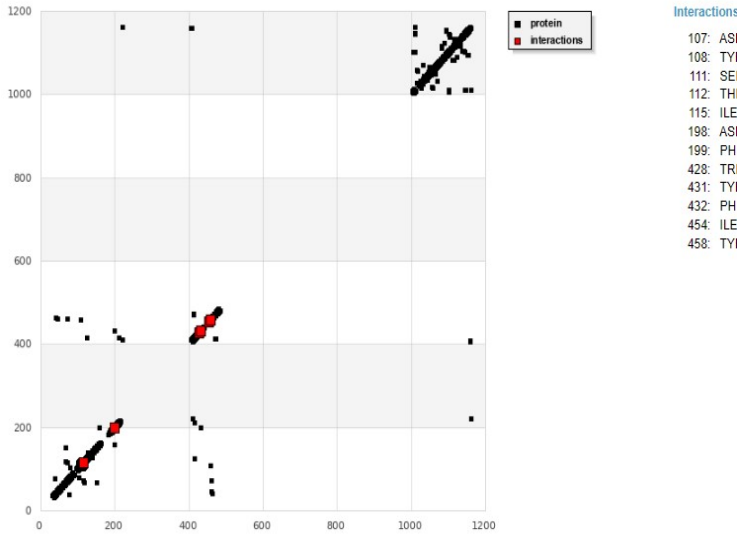
Tinosporide with Histamine H1 receptor (PDB) - 3RZE



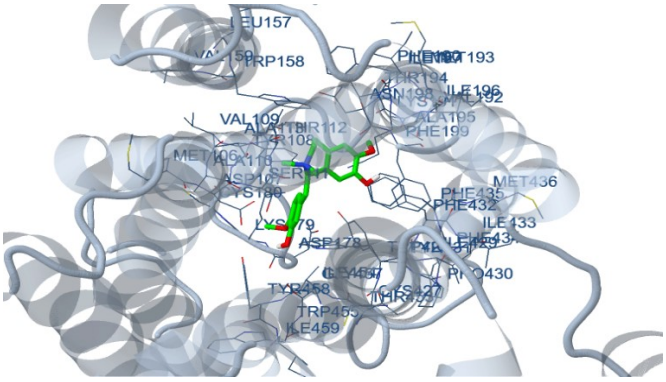
2D Interaction Plot Analysis



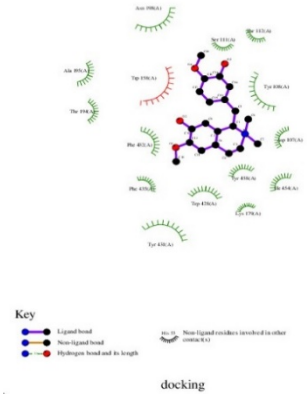
Hydrogen bond plotting with core amino acid Analysis



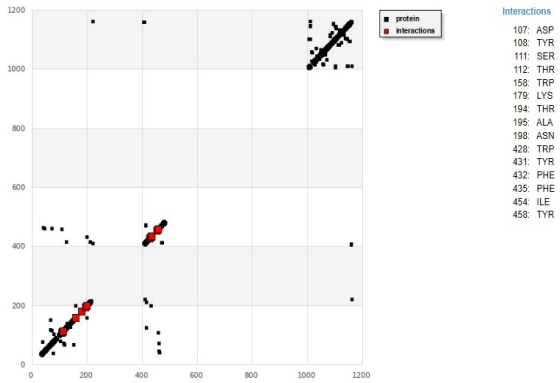
Tembetarine with Histamine H1 receptor (PDB) - 3RZE



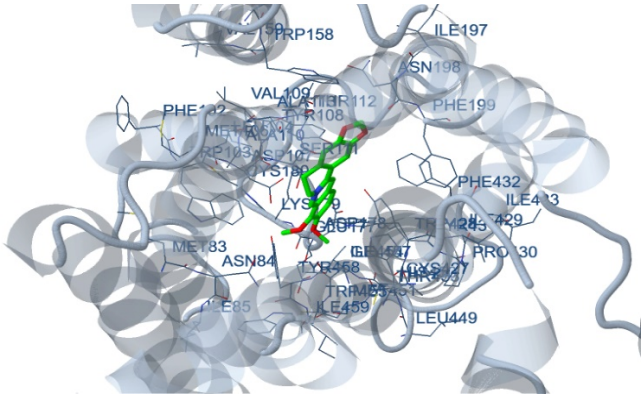
2D Interaction Plot Analysis



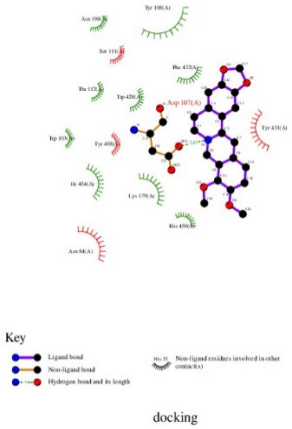
Hydrogen bond ploting with core amino acid Analysis



Berberine with Histamine H1 receptor (PDB) - 3RZE

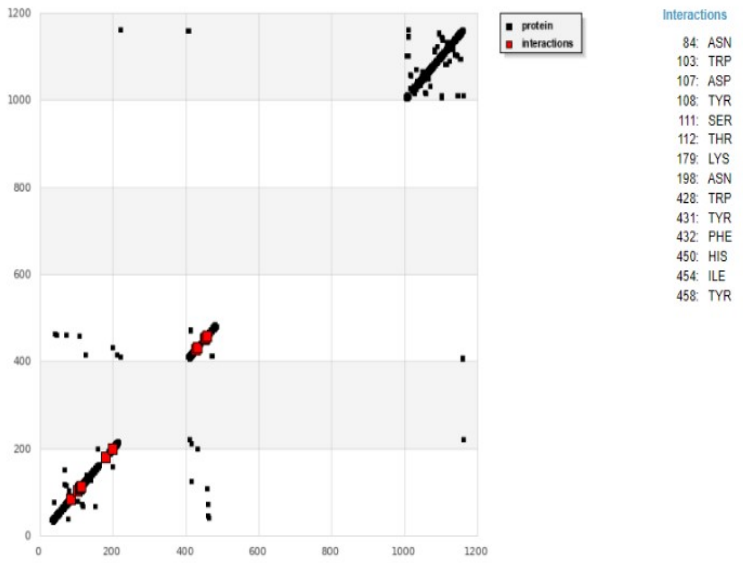


2D Interaction Plot Analysis

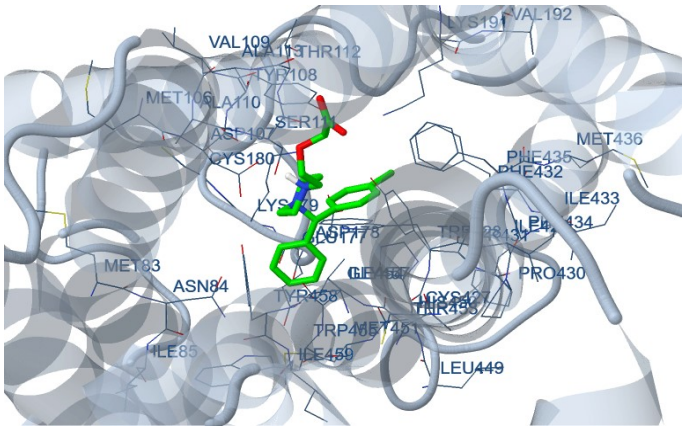


docking

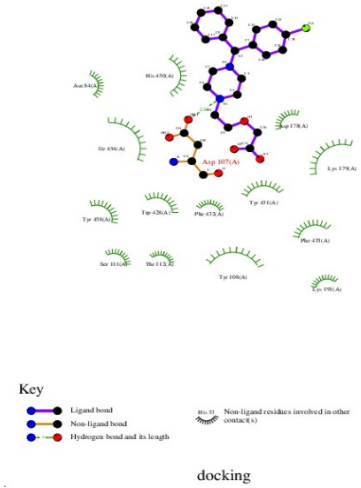
Hydrogen bond plotting with core amino acid Analysis



Cetirizine with Histamine H1 receptor (PDB) - 3RZE

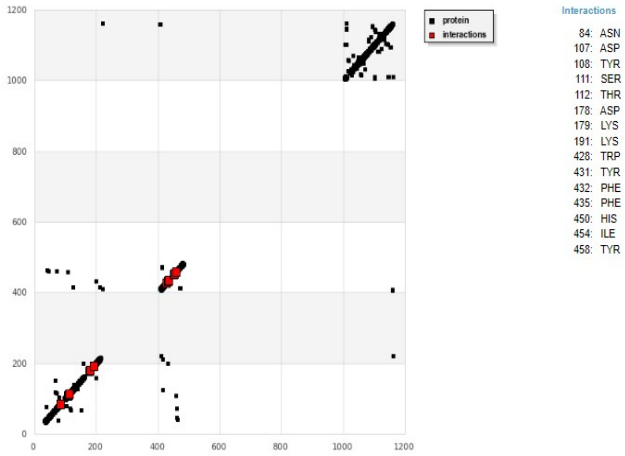


2D Interaction Plot Analysis



docking

Hydrogen bond plotting with core amino acid Analysis



Discussion

Molecular docking is a widely accepted tool, which allows the researcher to predict the pharmacological efficiency of a drug or formulations. This approach has tremendous applications in the field of Siddha medicine especially herbal formulations were the interactions of the lead molecules of the formulation with that of receptors can be elucidated at the atomic level and furthermore to reach an assumption of its fundamental biochemical processes to which the formulation is targeting. As far as allergy is concerned amino acids such as asparagine (Asn), tryptophan (Trp), aspartate (Asp), tyrosine (Tyr), serine (Ser), isoleucine (Ile), lysine (Lys), threonine (Thr), phenylalanine (Phe) are the main core residues involved in mediating Human histamine receptor (3RZE). When lead compounds bind to this core residue, the activity of the enzyme may be inhibited. Using comparison standard cetirizine, the lead molecule from both components was chosen for the docking investigations. Nearly all of the lead compounds exhibited the highest level of interaction with H1R.

Table 4: Pharmacological significance of lead molecules from Seendhil:

S.NO	Name of the compound	Pharmacological significance
1.	Tinosporide	Anti-allergic, Anti inflammatory
2.	Tembetarine	Anti-allergic, Anti inflammatory
3.	Berberine	Anti-allergic, Anti inflammatory

Conclusion

Based on the results of the computational analysis it was concluded that all three bio-active compounds' including Tinosporide, Tembetarine and Berberinepresent in herb *Tinospora cordifolia* possess significant binding 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-inflammatoryactivity.

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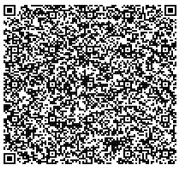	Website: www.ijcrims.com
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