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ANTI-ULCER EFFECT OF SIDDHA POLYHERBAL FORMULATION *MAHALAVANGATHI CHOORNAM* BY USING IN-SILICO MODEL

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ABSTRACT

Background: The Siddha system of medicine, traditionally practiced in South India, particularly in Tamil Nadu, recognizes Gunmam (equivalent to Peptic Ulcer) as one of the 4448 documented diseases. This condition is described by Siddhar Yugi Muni in "Yugi Vaithiya Chinthamani". The present study focuses on Mahalavangathi choornam, a polyherbal formulation recommended for Gunmam treatment, as mentioned in *"Anuboga Vaidhya Brahma Ragasiyam Moondram Paagam"*. The primary objective of this research is to investigate the in-vitro anti-ulcer activity of Mahalavangathi choornam. **Aim:** This study aims to investigate the in-vitro anti-ulcer activity of Mahalavangathi choornam. **Methodology:** This study investigates the anti-ulcer potential of Mahalavangathi choornam by examining how its phyto components bind to specific amino acids (LYS-445, VAL-473, and TYR-475) on the H. pylori urease enzyme (PDB: 1E9Y), forming hydrogen bonds that disrupt enzyme activity. By inhibiting urease, which converts urea to ammonia and contributes to ulcer development, these phyto components may offer a therapeutic approach for managing H. pylori-associated ulcers. **Result:** Mahalavangathi choornam has significant Anti-ulcer activity.

KEYWORDS: *Gunmam, Peptic Ulcer, H pylori Urease, Siddha.*

INTRODUCTION

Peptic ulcers are characterized by a breach in the gastric or duodenal mucosa, extending through the muscularis mucosae. The primary causes of peptic ulcers are Helicobacter pylori (H. pylori) infection and nonsteroidal anti-inflammatory drugs (NSAIDs). Since its discovery in 1983, H. pylori has been implicated in gastritis and identified as a key factor in the pathogenesis of primary peptic ulcer disease, alongside acid and pepsin. This gram - negative bacteria thrives in the stomach's acidic environment due to its unique features, such as urease production, which enables it to alkalinize its surroundings and persist for years, leading to mucosal inflammation and exacerbating peptic ulcer disease in some individuals. Given H. pylori's role in inducing inflammation and worsening peptic ulcer disease, this study aims to investigate the anti-ulcer properties of Mahalavangathi choornam using in-vitro assay.

MATERIALS AND METHODS

DRUG SELECTION

The Siddha polyherbal formulation Mahalavangathi choornam is mentioned in Siddha literature *"Anuboga Vaidhya Brahma Ragasiyam"* Part-3.

INGREDIENTS OF MAHALAVANGATHI CHOORNAM

1. Lavangapattai *Cinnamomum verum)* - 1 Part
2. Naagakesaram (*Mesua nagassarium)* - 2 Parts
3. Yelakkaai (*Elettaria cardamomum)* - 4 Parts
4. Milagu (*Piper nigrum)* - 8 Parts
5. Thippili (*Piper longum)* - 16 Parts
6. Chukku (*Zingiber officinale)* - 32 Parts
7. Amukkara Kizhangu(*Withania somnifera)*-64 Parts
8. Sakkarai (*Saccharum officinarum)* - 127 Parts

ANTI-ULCER ACTIVITY EVALUATION OF MAHALAVANGATHI CHOORNAM

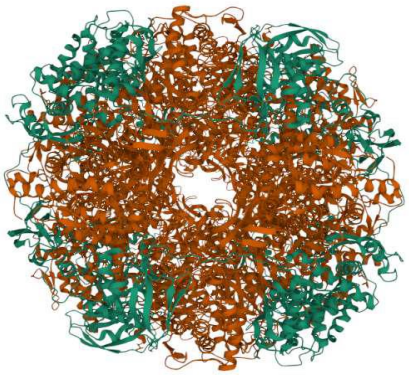
Docking calculations were carried out for retrieved phytocomponents against target enzyme H pylori urease. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity (grid) maps of ×× Å grid 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.

PDB	Name of the Target
1E9Y	H pylori Urease

Table 1: List of Phytocomponents Selected for docking.

Herbs	*Compound*
Cinnamomum verum	Cinnamic acid
Mesua nagassarium	β-sitosterol
Elettaria cardamomum	Nerolidol
Piper nigrum	Piperic acid
Piper longum	Piperine
Zingiber officinale	Gingerenone-A
Withania somnifera	Withaferin A, Chlorogenic acid
Saccharum officinarum	Orientin, Vitexin, Swertisin

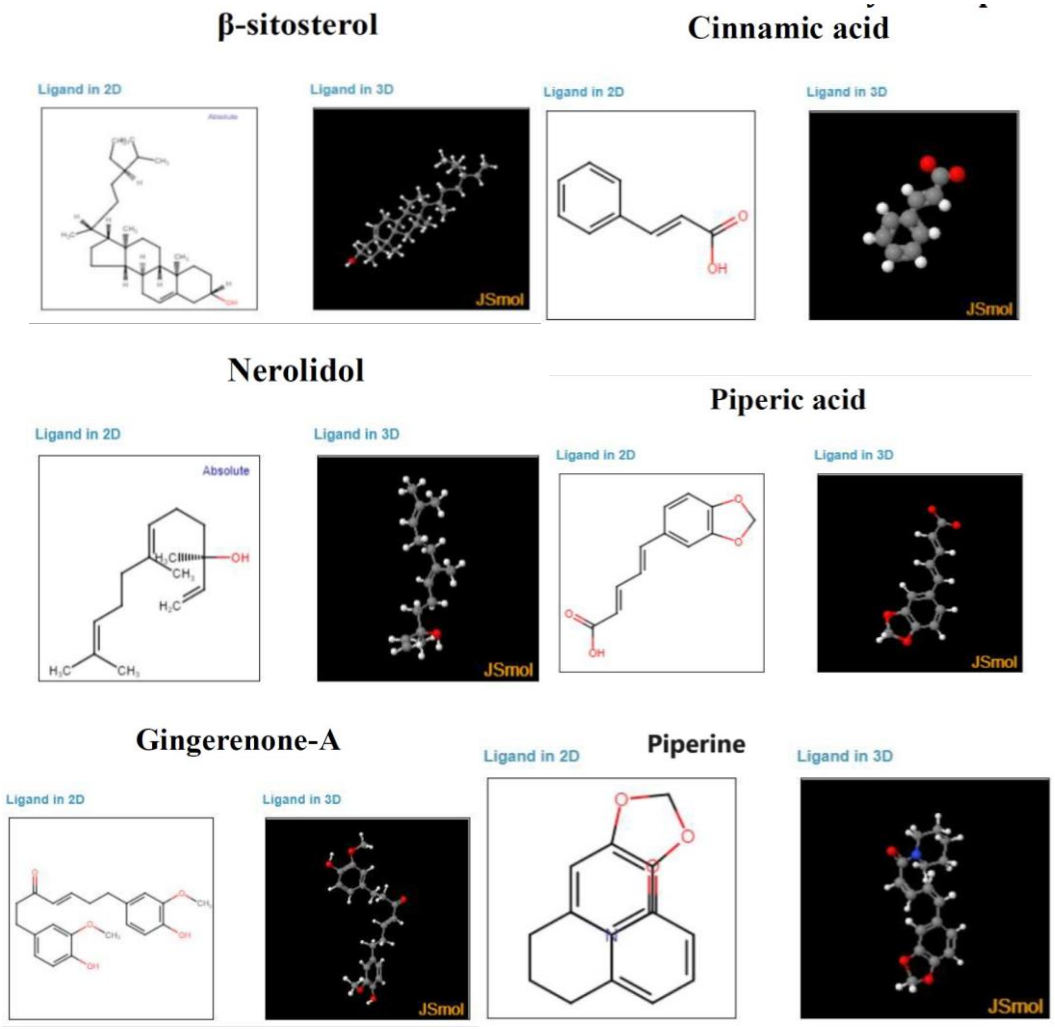


3D- Structure of H pylori Urease (PDB) - 1E9Y

RECEPTOR STRUCTURE

Crystalline structure of the target enzyme H pylori Urease (PDB) - 1E9Y was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atoms were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by the Autodock program and the best dock pose was selected based on the interaction study analysis.

Figure 1



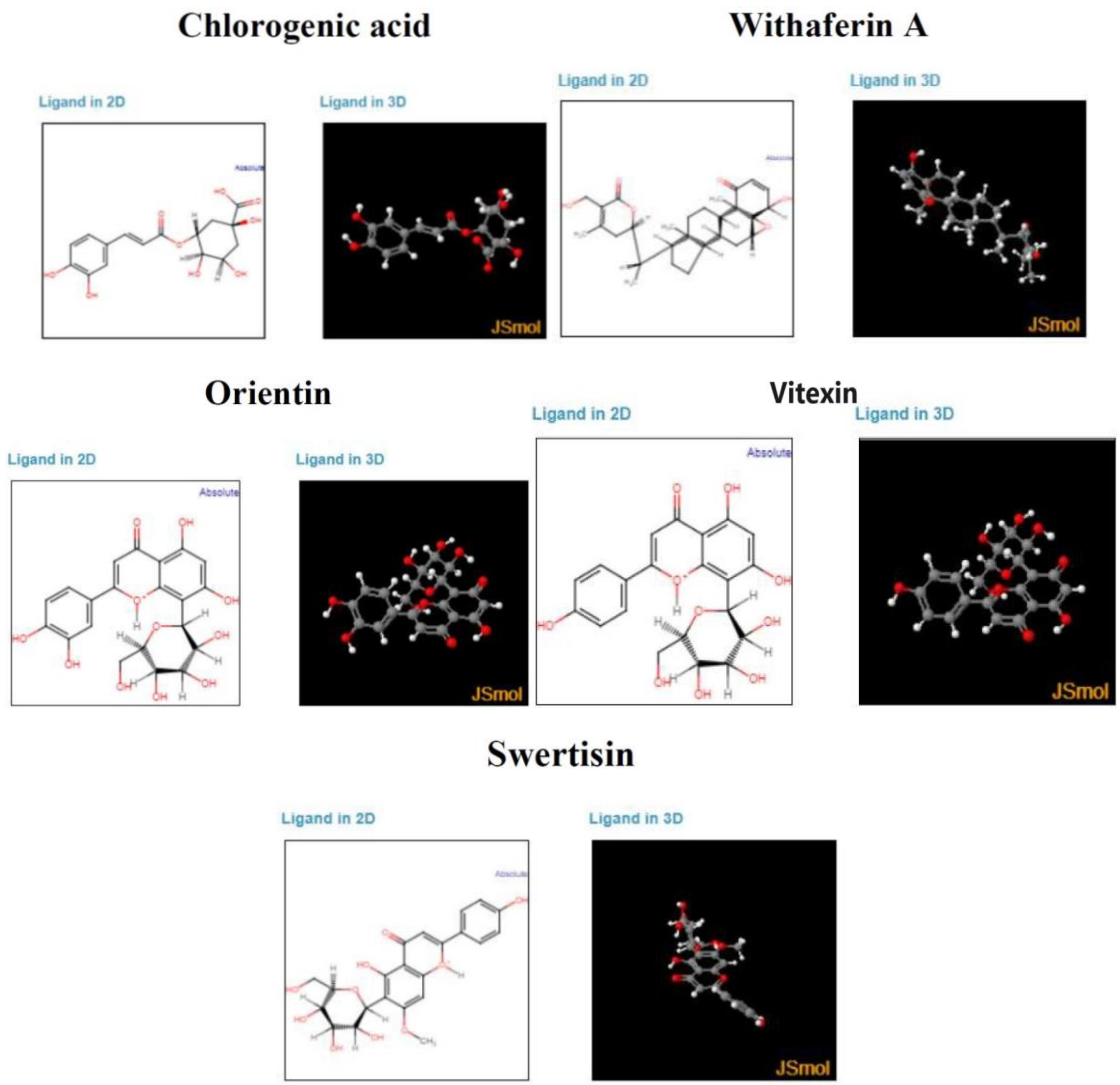


Figure 2: 2D and 3D Structure of Selected Ligands.

Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Cinnamic acid	148.16 g/mol	$C_9H_8O_2$	1	2	2
β-sitosterol	414.7g/mol	$C_{29}H_{50}O$	1	1	6
Nerolidol	222.37 g/mol	$C_{15}H_{26}O$	1	1	7
Piperic acid	218.2 g/mol	$C_{12}H_{10}O_4$	1	4	3
Piperine	285.34 g/mol	$C_{17}H_{19}NO_3$	0	3	3
Gingerenone-A	356.4 g/mol	$C_{21}H_{24}O_5$	2	5	9
Withaferin A	470.6 g/mol	$C_{28}H_{38}O_6$	2	6	3
Chlorogenic acid	354.31 g/mol	$C_{16}H_{18}O_9$	6	9	5
Orientin	448.4 g/mol	$C_{21}H_{20}O_{11}$	8	11	3
Vitexin	432.4 g/mol	$C_{21}H_{20}O_{10}$	7	10	3
Swertisin	446.4 g/mol	$C_{22}H_{22}O_{10}$	6	10	4

RESULTS

Table 2: Summary of the molecular docking studies of compounds against H pylori Urease (PDB) - 1E9Y.

Compound	Est. Free Energy of Binding	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy
Cinnamic acid	-4.86 kcal/mol	275.05 uM	-0.54 kcal/mol	-5.45 kcal/mol	430.016
β-sitosterol	-8.24 kcal/mol	907.65 uM	-0.04 kcal/mol	-9.69 kcal/mol	810.29
Nerolidol	-4.83 kcal/mol	286.90 uM	-0.02 kcal/mol	-6.97 kcal/mol	654.055
Piperic acid	-5.58 kcal/mol	81.58 uM	-0.54 kcal/mol	-6.44 kcal/mol	532.595

Piperine	-6.60 kcal/mol	14.51 uM	-0.12 kcal/mol	-7.39 kcal/mol	626.305
Gingerenone A	-7.03 kcal/mol	7.05 uM	-0.24 kcal/mol	-5.84 kcal/mol	697.611
Withaferin A	-8.07 kcal/mol	1.22 uM	-0.07 kcal/mol	-8.59 kcal/mol	843.947
Chlorogenic acid	-6.77 kcal/mol	10.96 uM	-0.32 kcal/mol	-6.45 kcal/mol	598.026
Orientin	-8.08 kcal/mol	1.20 uM	-0.83 kcal/mol	-6.51 kcal/mol	685.845
Vitexin	-7.58 kcal/mol	2.80 uM	-0.08 kcal/mol	-6.23 kcal/mol	678.299
Swertisin	-7.41 kcal/mol	3.67 uM	-0.46 kcal/mol	-6.83 kcal/mol	818.368

Table 3: Amino acid Residue Interaction of Lead against H pylori Urease (PDB) - 1E9Y.

Compounds	**Interactions**	**Amino acid Residues**									
Cinnamic acid	2	441	445	447	459	474	475				
		PHE	LYS	ASN	GLN	TYR	TYR				
β-sitosterol	2	146	147	150	151	374	444	445	457	475	477
		PRO	THR	ALA	SER	THR	VAL	LYS	LEU	TYR	GLU
Nerolidol	2	150	151	374	444	445	446	475	563	567	569
		ALA	SER	THR	VAL	LYS	PRO	TYR	ALA	SER	PHE
Piperic acid	2	438	441	445	447	459	474	475			
		SER	PHE	LYS	ASN	GLN	TYR	TYR			
Piperine	2	150	441	445	447	459	474	475			
		ALA	PHE	LYS	ASN	GLN	TYR	TYR			
Gingerenone-A	2	150	151	371	374	445	475	567	568		
		ALA	SER	GLU	THR	LYS	TYR	SER	ILE		
Withaferin A	2	147	150	151	371	374	445	475	567	569	
		THR	ALA	SER	GLU	THR	LYS	TYR	SER	PHE	
Chlorogenic acid	2	146	147	150	151	445	446	457	474	475	
		PRO	THR	ALA	SER	LYS	PRO	LEU	TYR	TYR	
Orientin	2	151	368	371	374	445	446	475	567	568	569
		SER	ARG	GLU	THR	LYS	PRO	TYR	SER	ILE	PHE
Vitexin	2	146	147	149	150	151	445	457	474	475	
		PRO	THR	PHE	ALA	SER	LYS	LEU	TYR	TYR	
Swertisin	1	150	151	371	374	444	445	474	567	569	
		ALA	SER	GLU	THR	VAL	LYS	TYR	SER	PHE	

DISCUSSION

Total of 11 bioactive lead compounds were retrieved from the herbal ingredients, From the reported data of the herb, the phytochemical Cinnamic acid, β-sitosterol, Nerolidol, Piperic acid, Piperine, Gingerenone-A, Withaferin A, Chlorogenic acid, Orientin, Vitexin and Swertisin present in the siddha formulation Mahalavangathi Chooranam reveals maximum of 2 interactions with the core active amino acid residues present on the target protein enzyme H pylori urease.

CONCLUSION

Based on the results of the computational analysis it was concluded that the bioactive compounds like Cinnamic acid, β-sitosterol, Nerolidol, Piperic acid, Piperine, Gingerenone-A, Withaferin A, Chlorogenic acid, Orientin, Vitexin and Swertisin reveals present in the Mahalavangathi Chooranam possess significant binding against the target H pylori urease by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts promising anti-ulcer activity by inhibiting the enzyme H pylori urease that catalyzes the hydrolysis of urea to ammonia. Urease has been reported to be a prominent virulence determinant of H pylori in the pathogenesis of ulcer. Thereby phyto components which inhibit the target H pylori urease may act as a potential therapeutic agent for management of ulcer. It was concluded that the phytochemicals present in the herb reveal significant anti-ulcer activity.

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