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Molecular Screening of Aconitum Heterophyllum Identifies Potential Inhibitors of Typhoid Fever – Target Typhoid – 1,3- Dehydroquinate Dehydratase

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ABSTRACT

Background: Typhoid fever is a gram- negative bacterial infection caused by the bacterium called Salmonella typhi, a rod-like shaped pathogen. Salmonella typhi is both food-born and water-born pathogen. Developing nations exhibit a higher incidence of typhoid fever as a result of inadequate sanitation practices and incorrect use of antibiotics, hence fostering the emergence of drug resistance in the microorganisms known as bacteria *Salmonella typhi*. The enzyme "Typhoid-1, 3-dehydroquinate dehydratase" plays a crucial role in the biosynthesis of aromatic amino acids, particularly in the shikimate pathway. The shikimate pathway is accountable for the biosynthesis of aromatic amino acids, namely tyrosine, phenylalanine, and tryptophan.
Aim & Objective: The present study, we retrieved 3 bioactive Compounds such as Aconitine, Anthorine, Hypaconitine which inhibit the target enzyme Typhoid- 1,3- dehydroquinate dehydratase may act as a potential therapeutic agent for management of typhoid fever.
Materials and methods: Docking simulations were performed by using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly.
Results: Binding of phytocomponents with the core amino acids (His 143 and Lys-170) of the target Typhoid- 1, 3- dehydroquinate dehydratase by forming hydrogen bond will hinder the function of the enzyme and thereby inhibits biosynthesis of aromatic amino acids essential for the survival of the pathogen *S. Typhi*.
Conclusion: This characteristic renders the pathway a selective target for antibacterial drugs. Thereby phytocomponents which inhibit the target Typhoid-1,3-dehydroquinate dehydratase may act as a potential therapeutic agent for management of typhoid fever.

BACKGROUND

Developing nations exhibit a higher incidence of typhoid fever as a result of insufficient sanitation practices and improper usage of antibiotics, hence fostering the emergence of drug resistance in the microorganisms known as bacteria *Salmonella typhi*. *Salmonella typhi* is a Gram-negative, facultative anaerobe belonging to the family *Enterobacteriaceae*. It causes typhoid fever or enteric fever. Typhoid fever is one of the major public health problems in worldwide. It is also one of a notifiable disease in India. India records around 63,45,776 cases every year [1].

Enteric fever is endemic in all regions of India, making it a huge burden on both government and private healthcare centres [2] .The common mode of transmission is through the faeco-oral route via water and food contaminated with human faeces.

The clinical manifestations of typhoid fever start after an incubation period of 8-14 days [3]. Acute typhoid fever is characterized by prolonged step-ladder pattern of fever, bowel disturbances, malaise, headache and anorexia [5]. A fraction of the patients also exhibits "rose spots" (exanthems) on the abdomen, chest and back. Complications of the disease may manifest as occult blood in stools, intestinal perforation and peritonitis followed by hypotension, bradycardia, abdominal tenderness and abdominal rigidity. This is associated with high mortality [3].

In a study conducted by WHO in 5 Asian countries, it was found that India had 493.35 cases of typhoid per 1,00,000 population per year in all age groups [5] . Due to the widespread drug resistance used in the treatment of typhoid fever, it has become necessary to develop newer drugs for the treatment of typhoid fever.

S. Typhi has Typhoid 1, 3 dehydroquinate dehydratase, an enzyme involved in the Shikimate pathway, which converts 3-dehydroquinate to 3- dehydroshikimate [6]. The shikimate pathway is involved in the synthesis of chorismate, which is the precursor for the synthesis of p-hydroxy benzoate, p-amino benzoate and aromatic amino acids like phenylalanine, tyrosine and tryptophan [7]. These compounds are essential for survival of the bacteria Salmonella typhi. This characteristic renders the pathway a selective target for antibacterial drugs.

Aconitum heterophyllum, commonly called as Indian Atees, is a plant belonging to the family *Ranunculaceae* with medicinal properties which include antibacterial, antiviral, antimalarial and antifungal properties [8]. The fact that the shikimate pathway is absent in humans can be exploited in the development of antimicrobial drugs targeting this pathway, as these drugs will not interfere with normal human metabolism [9, 10].

List of Phytocomponents Selected for docking [11]

Herb	Phytochemicals
Aconitum heterophyllum	❖ Aconitine ❖ Anthorine ❖ Hypaconitine

Objective:

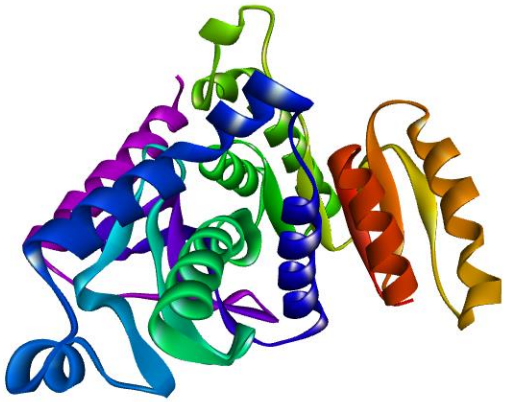
The objective of the present study is to find the potential drug candidate that can inhibit typhoid 1, 3 dehydroquinate dehydratase enzyme from certain alkaloids present in *Aconitum*

heterophyllum plant in the treatment of enteric fever caused by *Salmonella Typhi* by molecular docking.

Binding of phytocomponents with the core amino acids (His 143 and Lys-170) of the target Typhoid- 1, 3- dehydroquinate dehydratase by forming hydrogen bond will hinder the function of the enzyme and thereby inhibits biosynthesis of aromatic amino acids essential for the survival of the pathogen *Salmonella Typhi*. Thereby phytocomponents which inhibit the target Typhoid-1, 3-dehydroquinate dehydratase may act as a potential therapeutic agent for treatment of enteric fever.

PDB	**Name of the Target**
1GQN	Typhoid- 1,3- dehydroquinate dehydratase

Typhoid- 1, 3- dehydroquinate dehydratase -PDB 1GQN



RECEPTOR STRUCTURE

Crystalline structure of the target protein Typhoid- 1,3- dehydroquinate dehydratase 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 [12].

Protein preparation [13]

Three-dimensional protein structure of the target protein Typhoid- 1, 3-dehydroquinate dehydratase with PDB 1GQN were retrieved from the online repository of Protein Data Bank and subjected to protein clean prior to docking simulation.

Ligand Preparation

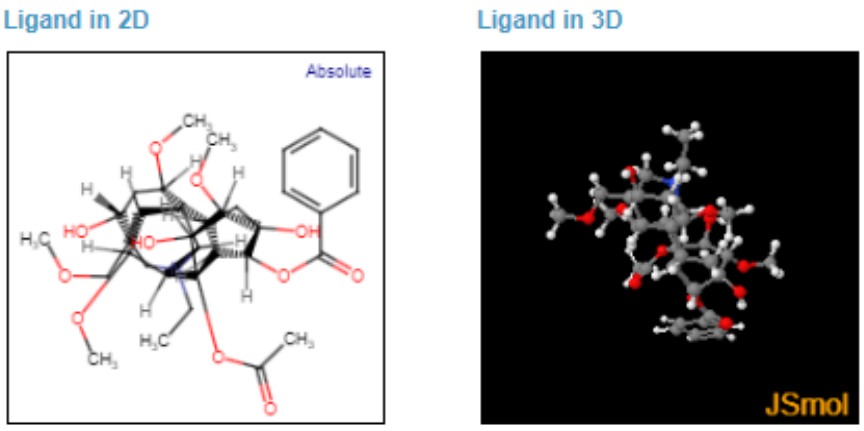
Phytochemical subjected to the investigation were retrieved from the herbs listed in the table based on the literature survey and 3D structure of the same were built using Chem Draw prof online tool version 12.0. Ligands prepared through geometry optimization method (MMFF94).

MATERIALS AND METHODS[14, 15]

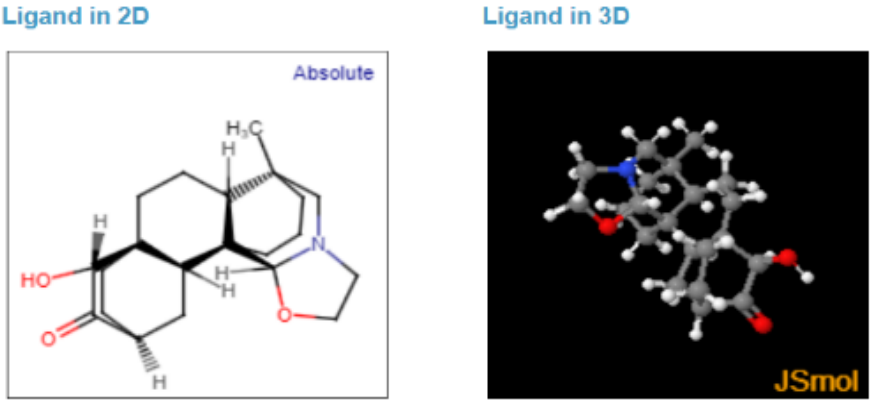
Docking calculations were carried out for retrieved phytocomponents against target protein. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (*Morris, Goodsell et al., 1998*). Affinity (grid) maps of 60×60×60 Å grid points 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.

2D and 3D Structure of Phytocomponents

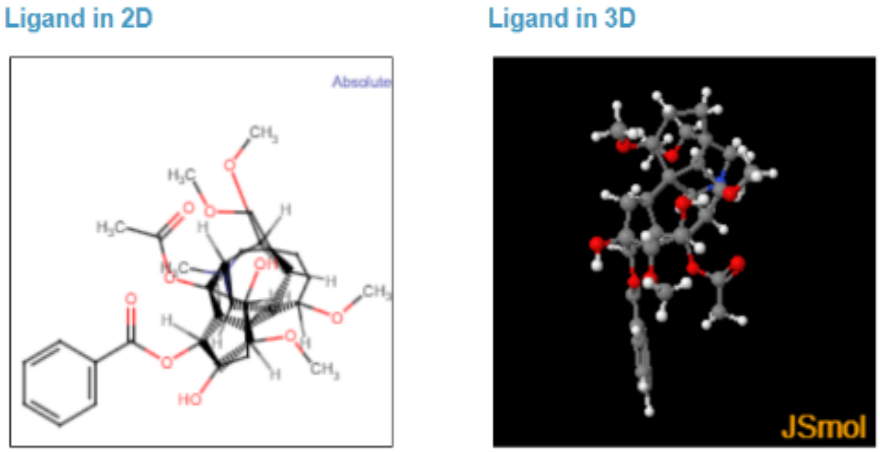
Aconitine



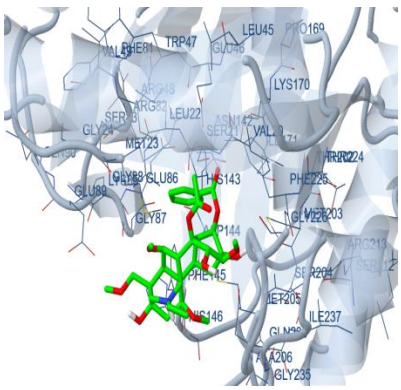
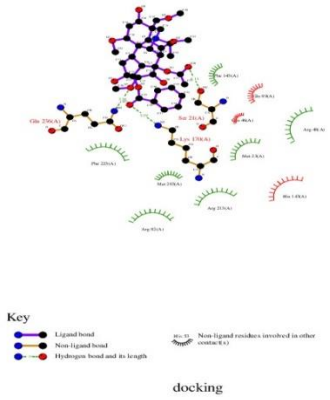
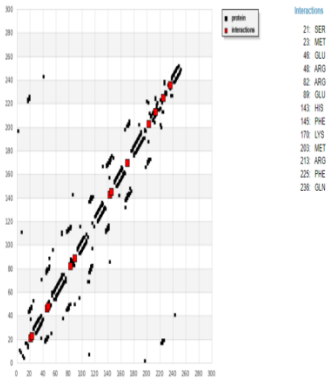
Anthorine

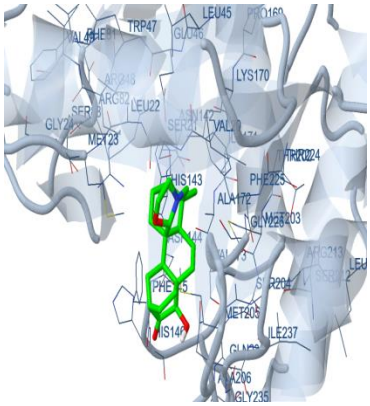
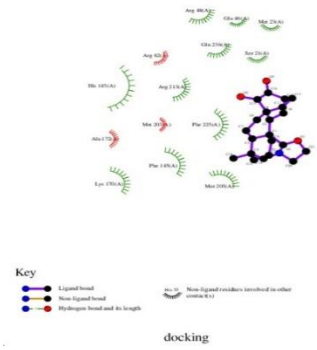
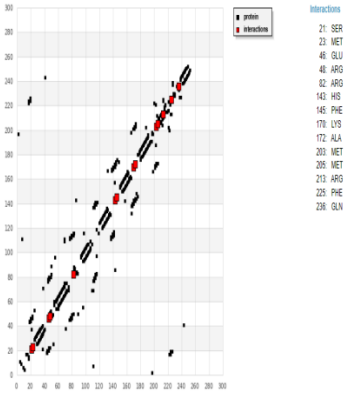
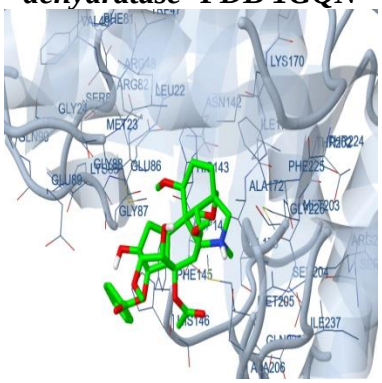
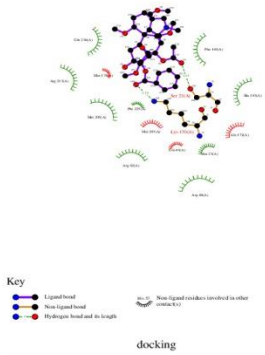
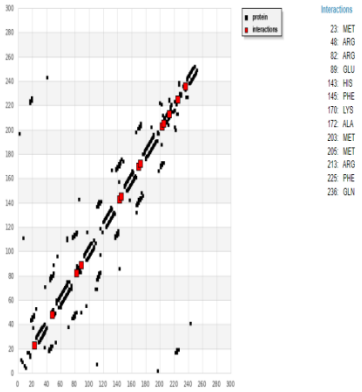


Hypaconitine



Docking Pose

Aconitine with Typhoid- 1,3-dehydroquinate dehydratase - PDB 1GQN	*2D Interaction Plot Analysis*	*Hydrogen bond plotting with core amino acid Analysis*
		

Anthorine with Typhoid- 1,3-dehydroquinate dehydratase - PDB 1GQN 	***2D Interaction Plot Analysis*** 	***Hydrogen bond plotting with core amino acid Analysis*** 
Hypaconitine with Typhoid- 1,3- dehydroquinate dehydratase -PDB 1GQN 	***2D Interaction Plot Analysis*** 	***Hydrogen bond plotting with core amino acid Analysis*** 

Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Aconitine	645.7 g/mol	$C_{34}H_{47}NO_{11}$	3	12	11
Anthorine	343.5 g/mol	$C_{22}H_{33}NO_2$	1	3	0
Hypaconitine	615.7 g/mol	$C_{33}H_{45}NO_{10}$	2	11	10

Summary of the molecular docking studies of compounds against Typhoid- 1, 3-dehydroquinate dehydratase -PDB 1GQN

Compounds	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Aconitine	-4.04 kcal/mol	1.09 mM	-7.21 kcal/mol	-0.29 kcal/mol	936.287
Anthorine	-6.04 kcal/mol	37.08 uM	-6.28 kcal/mol	-0.07 kcal/mol	653.529
Hypaconitine	-5.67 kcal/mol	69.70 uM	-7.73 kcal/mol	-0.31 kcal/mol	918.539

Amino acid Residue Interaction of Lead against Typhoid- 1, 3- dehydroquinate dehydratase – PDB 1GQN

Compounds	Interactions	Amino acid Residues													
Aconitine	2	21	23	46	48	82	89	143	145	170	203	213	225	236	
		SER	MET	GLU	ARG	ARG	GLU	HIS	PHE	LYS	MET	ARG	PHE	GLN	
Anthorine	2	21	23	46	48	82	143	145	170	172	203	205	213	225	236
		SER	MET	GLU	ARG	ARG	HIS	PHE	LYS	ALA	MET	MET	ARG	PHE	GLN
Hypaconitine	2	23	48	82	89	143	145	170	172	203	205	213	225	236	
		MET	ARG	ARG	GLU	HIS	PHE	LYS	ALA	MET	MET	ARG	PHE	GLN	

RESULTS AND DISCUSSION

Total of 3 bioactive lead compounds were retrieved from the herb *Aconitum heterophyllum* the phytochemicals such as Aconitine, Anthorine and Hypaconitine possess 2 interactions with the core active amino acid residues present on the target Typhoid-1, 3-dehydroquinate dehydratase. It is of interest to design inhibitors for typhoid target Typhoid- 1, 3-dehydroquinate dehydratase by using molecular docking based virtual screening. Binding of phytocomponents with the core amino acids (His 143 and Lys-170) of the target Typhoid- 1,

3- dehydroquinate dehydratase by forming hydrogen bond will hinder the function of the enzyme and thereby inhibits biosynthesis of aromatic amino acids essential for the survival of the pathogen *S. Typhi*.

The enzyme "Typhoid-1, 3-dehydroquinate dehydratase" plays a vital role in the biosynthesis of aromatic amino acids, particularly in the shikimate pathway. The shikimate pathway is important for the biosynthesis of aromatic amino acids, namely tyrosine, phenylalanine, and tryptophan. *Salmonella typhi* utilizes the shikimate pathway for synthesizing essential aromatic compounds [16]. So this research has focused on identifying and characterizing the enzymes of the shikimate pathway to develop inhibitors.

CONCLUSION

Based on the results of the computational analysis it was concluded that all the bio-active compound's like Aconitine, Anthorine and Hypaconitine significant binding affinity against the target Typhoid- 1, 3- dehydroquinate dehydratase by interacting with active amino acid present on the active site thereby it was concluded that these compounds may inhibits biosynthesis of aromatic amino acids essential for the survival of the pathogen *S. Typhi*. The present study concludes that the phytochemicals of *Aconitum heterophyllum* which inhibit the target Typhoid-1, 3-dehydroquinate dehydratase and can be exploited to identify a potential drug candidate in the treatment of enteric fever.

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AUTHOR'S CONTRIBUTION

Conceptualization Dr.Tamil muhil, Validation and formal analysis Dr.Chithra, Writing original draft preparation Dr.Ramani, Writing, editing and methodology Dr.Malarvizhi, Visualization and supervision Dr.Meenakshi. Publication assistance done by Dr.S. Selvakumar. All authors have read and agreed to the publish the version of the manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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