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IN SILICO MOLECULAR DOCKING AND ADME PROFILING OF BIOACTIVE COMPOUNDS FROM HEMIDESMUS INDICUS (NANARI) AGAINST THE TARGETS OF URINARY TRACT INFECTION

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ABSTRACT

Background and Objective: Urinary tract infection (UTI) is one of the most prevalent bacterial infections affecting the urinary system and is predominantly caused by uropathogenic Escherichia coli. Bacterial adhesion mediated by FimH adhesin and inflammatory responses regulated by TNF-α play crucial roles in the establishment and progression of UTI. In Siddha literature, conditions characterized by painful, burning, and difficult urination is described under Neer Kadupu. Hemidesmus indicus (Nanari) is a medicinal plant traditionally used in Siddha medicine for the treatment of urinary disorders owing to its antimicrobial and anti-inflammatory properties. The present study aimed to evaluate the molecular docking interactions and ADME profiling of selected phytoconstituents of Hemidesmus indicus against FimH adhesin and TNF-α. **Materials and Methods:** Major phytoconstituents of Hemidesmus indicus, namely 2-Hydroxy-4-methoxybenzaldehyde, Lupeol, β-Sitosterol, Stigmasterol, Desmisine, and Hemidine, were subjected to molecular docking analysis using AutoDock Vina. The binding affinities of the selected compounds were compared with the standard drug Ciprofloxacin. Pharmacokinetic and drug-likeness properties were evaluated using SwissADME. **Results:** Molecular docking analysis demonstrated significant interactions between the selected phytoconstituents and TNF-α. Among the investigated compounds, β-Sitosterol exhibited the highest binding affinity with a docking score of −9.3 kcal/mol, followed by Stigmasterol (−8.7 kcal/mol), Hemidine (−7.6 kcal/mol), Lupeol (−7.0 kcal/mol), and 2-Hydroxy-4-methoxybenzaldehyde and Desmisine (−6.5 kcal/mol). The compounds formed stable hydrogen bonds and hydrophobic interactions with key amino acid residues of the target protein. ADME analysis revealed favorable pharmacokinetic characteristics, including acceptable gastrointestinal absorption, bioavailability, and compliance with drug-likeness criteria. **Conclusion:** The findings suggest that the phytoconstituents of Hemidesmus indicus possess promising anti-inflammatory and anti-UTI potential through modulation of TNF-α-mediated pathways. The significant docking interactions and favorable ADME properties provide scientific support for the traditional Siddha use of Nanari in the management of Neer Kadupu and related urinary disorders. Further in vitro, in vivo, and clinical studies are warranted to validate these computational findings.

KEYWORDS: Hemidesmus indicus, Nanari, Urinary Tract Infection, Neer Kadupu, FimH Adhesin, TNF-α, Molecular Docking, ADME Profiling, Ciprofloxacin, Siddha Medicine.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common infectious diseases affecting individuals of all age groups and is a significant public health concern worldwide. It involves infection of any part of the urinary system, including the kidneys, ureters, bladder, and urethra. Among the causative pathogens, Escherichia coli is responsible for nearly 80–90% of community-acquired UTIs. The pathogenesis of UTI involves bacterial adhesion to the urothelial surface, colonization, invasion, and subsequent inflammatory responses. FimH adhesin, a mannose-specific adhesin located at the tip of type 1

fimbriae of uropathogenic E. coli, plays a crucial role in bacterial attachment and establishment of infection. In addition, Tumor Necrosis Factor-alpha (TNF-α), a pro-inflammatory cytokine, contributes to the inflammatory cascade associated with urinary tract infections, resulting in tissue damage and clinical symptoms.

Although antibiotics such as Ciprofloxacin are commonly used for the treatment of UTIs, the emergence of antimicrobial resistance, recurrent infections, and adverse drug reactions have limited their long-term effectiveness. Consequently, there is an increasing interest in exploring medicinal plants as alternative therapeutic agents for the management of urinary tract infections.

According to Siddha literature, urinary disorders characterized by painful, burning, difficult, and scanty urination are classified under Neer Kadupu. Siddha texts describe Neer Kadupu as a condition resulting from derangement of the three humors (Vali, Azhal, and Iyyam), leading to urinary discomfort, inflammation, and impaired urinary function. Traditional Siddha management focuses on correcting humor imbalance, reducing inflammation, eliminating infection, and restoring normal urinary function through herbal medicines and dietary regulation.

Hemidesmus indicus R.Br. (Nanari), belonging to the family Apocynaceae, is an important medicinal plant extensively used in Siddha medicine for the treatment of Neer Kadupu, urinary tract disorders, dysuria, burning micturition, and inflammatory diseases. The roots of Nanari are rich in bioactive phytoconstituents such as 2-Hydroxy-4-methoxybenzaldehyde, Lupeol, β-Sitosterol, Stigmasterol, Desmisine, and Hemidine, which possess antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory activities. These pharmacological properties suggest that Nanari may exert protective effects against UTIs by inhibiting bacterial adhesion and modulating inflammatory pathways.

Recent advances in computer-aided drug discovery have enabled the use of molecular docking and ADME profiling for the identification of potential therapeutic agents. Molecular docking predicts the binding affinity and interactions of bioactive compounds with disease-associated molecular targets, whereas ADME analysis evaluates pharmacokinetic properties such as absorption, distribution, metabolism, and excretion. These approaches provide valuable insights into the therapeutic potential of phytocompounds prior to experimental validation.

Therefore, the present study was undertaken to investigate the molecular docking interactions and ADME profiling of selected phytoconstituents from Hemidesmus indicus against the key UTI-associated targets FimH adhesin and TNF-α. The docking performance of the phytoconstituents was compared with the standard drug Ciprofloxacin to scientifically validate the traditional Siddha use of Nanari in the management of Neer Kadupu and related urinary tract disorders.

MATERIALS AND METHODS

Collection and Selection of Phytoconstituents

The phytoconstituents of Hemidesmus indicus (Nanari) were identified through an extensive review of published literature and phytochemical databases. The major bioactive compounds selected for the study included 2-Hydroxy-4-methoxybenzaldehyde, Lupeol, β-Sitosterol, Stigmasterol, Desmisine, and Hemidine. The three-dimensional (3D) structures of the selected compounds were retrieved from the pubchem.ncbi.nlm.nih.gov in Structure Data File (SDF) format.

Preparation of Ligand

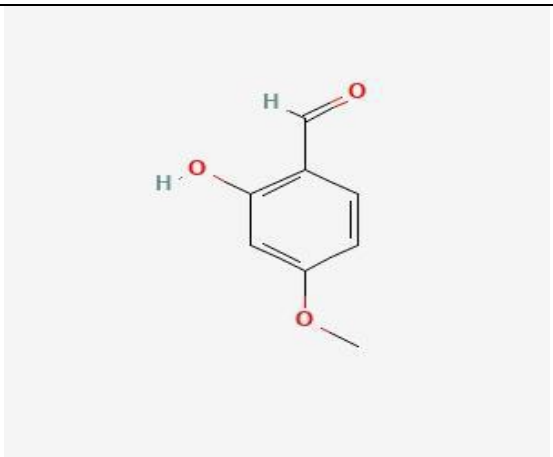
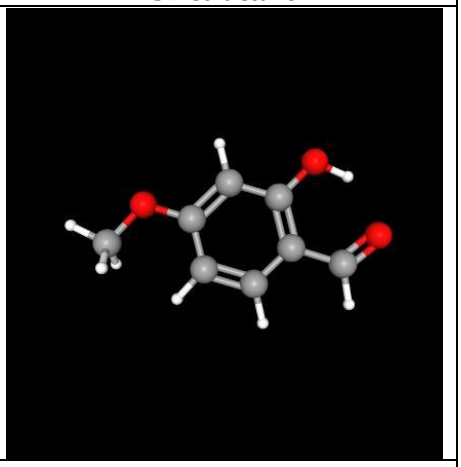
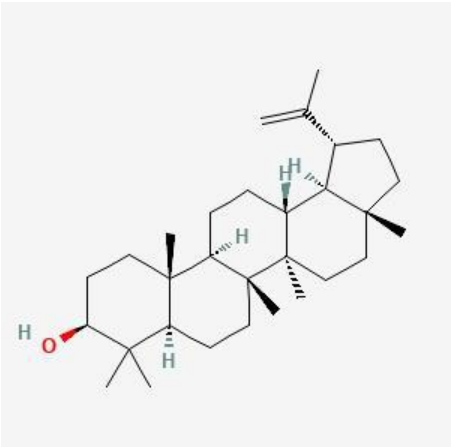
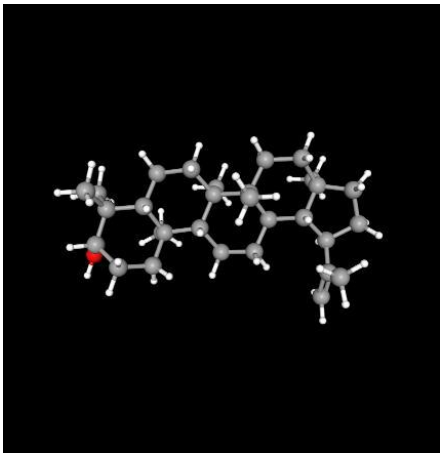
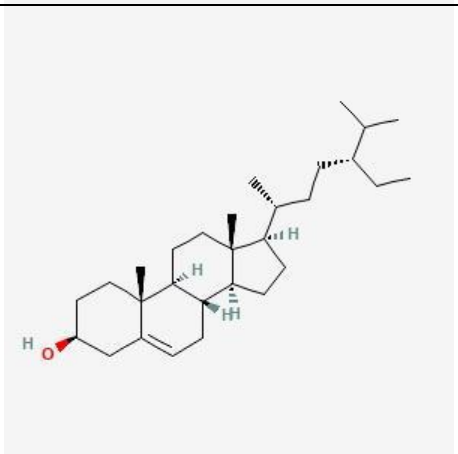
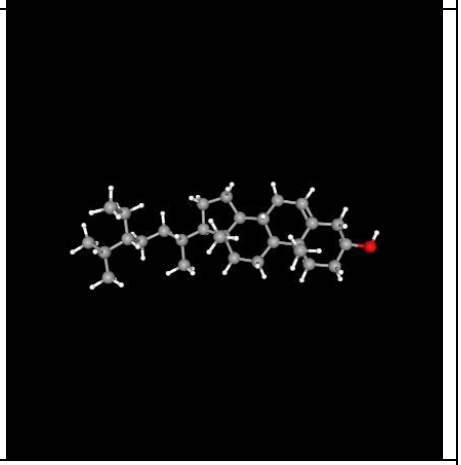
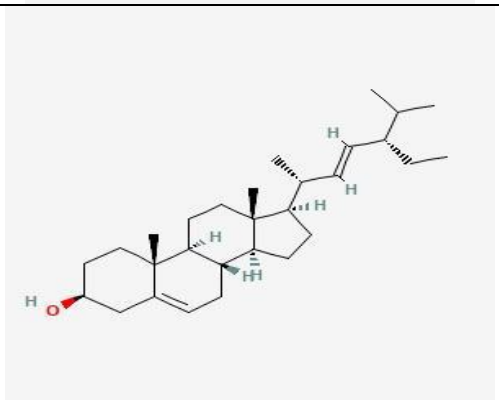
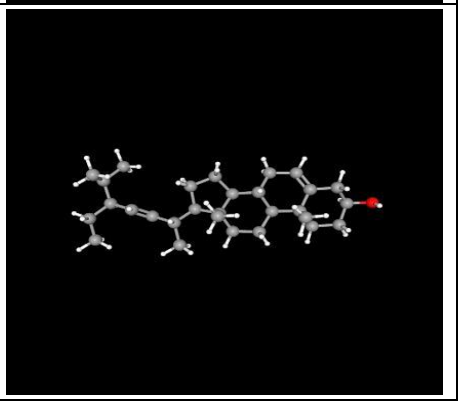
The identified phytochemicals along with their Molecular weight, Molecular formula, H-bond donor, H-bond acceptor, Rotatable bonds were listed in table 1.

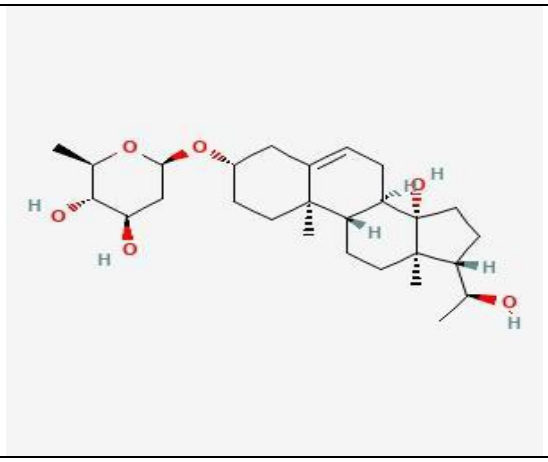
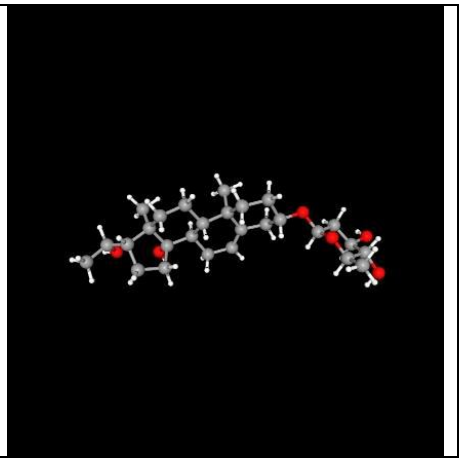
Table 1: Chemical properties of selected Ligands.

Compound	Molecular Weight g/mol	Molecular formula	H- bond donor	H- bond acceptor	Rotatable bonds
2-Hydroxy-4-methoxybenzaldehyde	152.15	$C_8H_8O_3$	1	3	2
Lupeol	426.7	$C_{30}H_{50}O$	1	1	1
β-Sitosterol	414.7	$C_{20}H_{50}O$	1	1	6
Stigmasterol	412.7	$C_{29}H_{48}O$	1	1	5
Hemidine	464.6	$C_{27}H_{44}O_6$	4	6	3

Each selected phytochemical was prepared for docking by obtaining its 2D and 3D structures from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format and converted to PDB format, followed by energy minimization to ensure stable conformations and reduced steric hindrance. Each ligand was then parameterized with appropriate partial charges and rotatable bonds to enable flexible interactions with the target protein. The structures of the ligands are shown in Table 3.

Table 2: 2D and 3D structure of the selected Ligands.

Compound	2D Structure	3D structure
2-Hydroxy-4-methoxybenzaldehyde		
Lupeol		
β-Sitosterol		
Stigmasterol		

Hemidine		

Preparation of Target

The protein targets selected for the study were FimH adhesin and Tumor Necrosis Factor-alpha (TNF-α), which play important roles in bacterial adhesion and inflammatory responses during urinary tract infection. The three-dimensional crystal structures of the target proteins were obtained from the rcsb.org. Water molecules, co-crystallized ligands, and unwanted heteroatoms were removed from the protein structures. Polar hydrogen atoms and Kollman charges were added using AutoDock Tools, and the prepared proteins were saved in PDBQT format.

Table 3: Selected targets and their action.

Target protein	PDB ID	Structure	Role in UTI
FimH adhesin	4XO8		FimH is a bacterial adhesin located at the tip of type 1 fimbriae of uropathogenic Escherichia coli. It mediates bacterial attachment to mannose receptors on urinary epithelial cells, initiating colonization and infection.
TNF-α	2AZ5		TNF-α is a pro-inflammatory cytokine released during bacterial infection. It promotes inflammation, recruitment of immune cells, tissue injury, and urinary tract symptoms

Molecular Docking

Docking simulations were conducted using MGL AutoDock tools to evaluate the binding interactions between the target protein and each ligand. Molecular interaction analysis was performed using AutoDock 1.5.7 (Morris et al.2009) by following steps: Gasteiger partial charges were added to the ligand atoms. Nonpolar hydrogen atoms were merged, and rotatable bonds were defined. A grid box was centered on key active site residues to confine docking to relevant regions. Parameters, including binding affinity (ΔG), inhibition constant (Ki) and interaction surface, were calculated for each ligand. Docking was repeated using SwissDock Vina platform.

ADME and Drug-Likeness Prediction

The pharmacokinetic properties of the selected phytocompounds were evaluated using the SwissADME web server to determine their drug-likeness, absorption, distribution, metabolism, and excretion characteristics. Parameters including gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 inhibition, P-glycoprotein interaction, skin permeation, Lipinski's rule of five, bioavailability score, and medicinal chemistry properties were analyzed.

RESULTS AND DISCUSSION

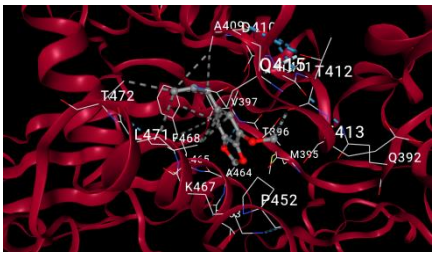
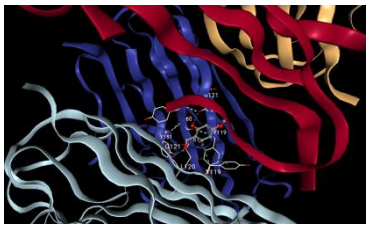
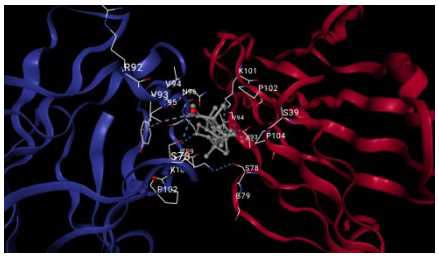
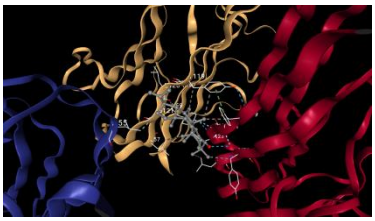
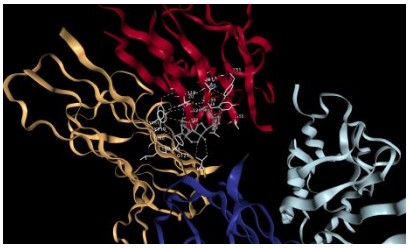
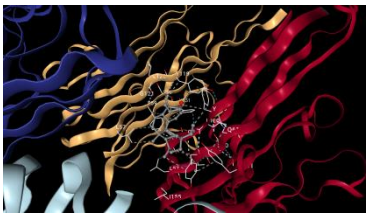
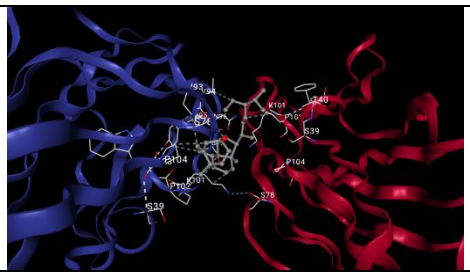
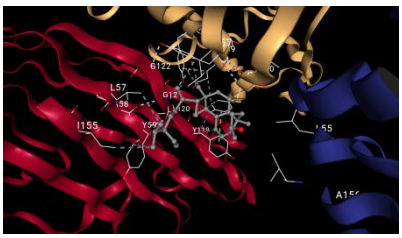
The molecular docking analysis performed in the present study demonstrated significant binding interactions between the selected phytoconstituents of Gowthamar

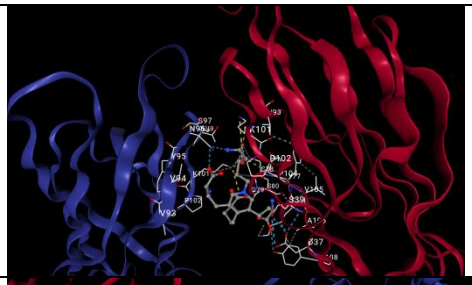
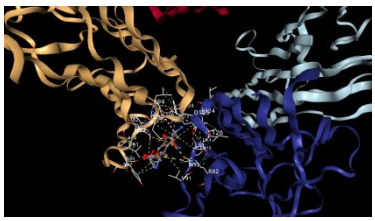
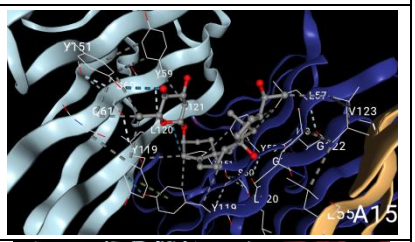
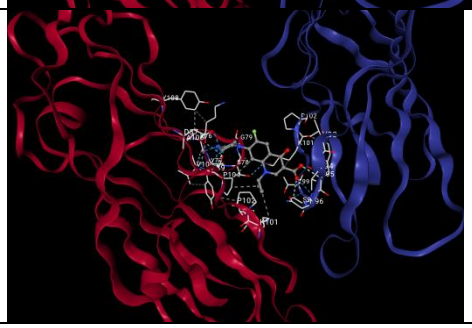
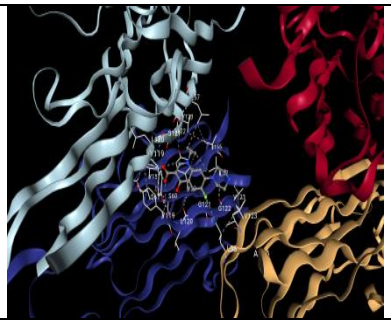
Chooranam and the inflammatory target proteins TNF-α (PDB ID: 2AZ5) and COX-2 (PDB ID: 5IKR), which play a major role in the pathogenesis of UTI.

Table 4: Binding energies of different compounds.

Compounds	FimH adhesin		TNF-α	
	No. of Interactions	Highest Binding Free Energy (Kcal/ mol)	No. of Interactions	Highest Binding Free Energy Kcal/ mol
2-Hydroxy-4-methoxybenzaldehyde	16	-6.5	10	-5.1
Lupeol	20	-7.0	20	-9.4
β-Sitosterol	20	-9.3	20	-9.3
Stigmasterol	20	-8.7	18	-9.2
Desmisine	20	-6.5	19	-7.6
Hemidine	19	-7.6	20	-8.7
Ciprofloxacin	20	-7.7	20	-8.6

Table 5: Docking interactions of Different compounds.

Compound	FimH adhesin	TNF-α
2-Hydroxy-4-methoxybenzaldehyde		
Lupeol		
β-Sitosterol		
Stigmasterol		

Desmisine		
Hemidine		
Ciprofloxacin (Standard)		

Molecular docking was performed to evaluate the interaction of the selected phytoconstituents of Hemidesmus indicus with TNF-α and to compare their binding affinity with the standard drug Ciprofloxacin. Binding affinity is expressed as docking energy (kcal/mol), where more negative values indicate stronger and more stable ligand–protein interactions.

Among all the compounds studied, β-Sitosterol exhibited the strongest binding affinity towards TNF-α with a docking score of −9.3 kcal/mol, which was substantially higher than that of Ciprofloxacin (−7.7 kcal/mol). This result suggests that β-Sitosterol possesses a greater binding stability towards TNF-α and may effectively inhibit inflammatory signaling associated with urinary tract infection.

Similarly, Stigmasterol demonstrated a docking score of −8.7 kcal/mol, which was also superior to Ciprofloxacin. The strong interaction observed for Stigmasterol indicates its potential role in suppressing TNF-α-mediated inflammatory responses.

Hemidine showed a docking score of −7.6 kcal/mol, which was nearly comparable to Ciprofloxacin (−7.7 kcal/mol), indicating similar binding behavior and potential anti-inflammatory activity. Lupeol exhibited a docking score of −7.0 kcal/mol, while Desmisine and 2-Hydroxy-4-methoxybenzaldehyde demonstrated docking scores of −6.5 kcal/mol. Although these values were slightly lower than that of Ciprofloxacin, they still indicate appreciable interaction with the target protein and may contribute to the overall therapeutic efficacy of the plant.

The docking results revealed that β-Sitosterol and Stigmasterol exhibited stronger binding affinities than Ciprofloxacin, suggesting that these phytosterols may possess significant anti-inflammatory potential through effective interaction with TNF-α. Hemidine showed binding affinity nearly equal to the standard drug, indicating its potential contribution to the therapeutic activity of Nanari.

The superior docking performance of β-Sitosterol and Stigmasterol may be attributed to their steroidal framework, which facilitates extensive hydrophobic interactions within the active binding pocket of TNF-α. The presence of multiple phytoconstituents with moderate to high binding affinity suggests a synergistic effect that may contribute to the overall efficacy of Hemidesmus indicus in managing urinary tract inflammation.

ADME PROPERTIES

Table 6: ADME properties of Different compounds.

Compound	GI absorption	BBB permeant	P-gp	CYP1A2 inhibitors	CYP2C19 inhibitors	CYP2C9 inhibitors	CYP2D6 inhibitors	CYP3A4 inhibitors	Log Kp (cm/s)
2-Hydroxy-4-methoxybenzaldehyde	High	Yes	No	No	No	No	No	Yes	-6. 61
Lupeol	Low	No	Yes	No	No	Yes	No	Yes	-1. 90
β-Sitosterol	Low	No	Yes	No	No	Yes	No	Yes	-2. 20
Stigmasterol	Low	No	Yes	No	No	Yes	No	Yes	-2.74
Hemidine	High	No	Yes	Yes	Yes	No	Yes	Yes	-7. 14

Drug-likeness

Table 7: Drug-likeness of the compounds.

Compounds	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability
2-Hydroxy-4-methoxybenzaldehyde	Yes 0 violations	No 2 violations	Yes	Yes	No 1 violation	0.55
Lupeol	Yes 1 violation	No 3 violations	Yes	No 1 violation	No 2 violations	0.55
β-Sitosterol	Yes 1 violation	No 3 violations	Yes	No 1 violation	No 2 violations	0.55
Stigmasterol	Yes 1 violation	No 3 violations	Yes	No 1 violation	No 2 violations	0.55
Hemidine	Yes 0 violation	No 1 violation	Yes	Yes	Yes	0.55

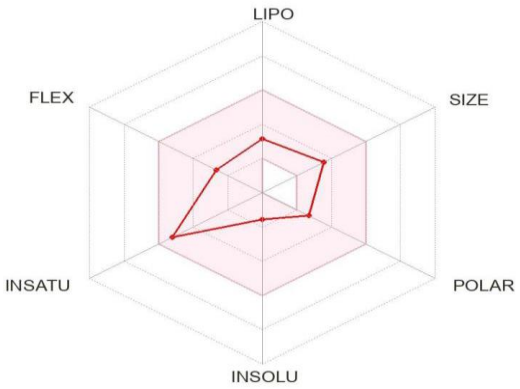
ADME profiling was performed to assess the pharmacokinetic suitability of the selected phytoconstituents. The analysis revealed that 2-Hydroxy-4-methoxybenzaldehyde and Hemidine possessed high gastrointestinal absorption, indicating favorable oral bioavailability. Most compounds demonstrated acceptable drug-likeness properties and complied with Lipinski's Rule of Five.

Although β-Sitosterol and Stigmasterol exhibited lower gastrointestinal absorption than some of the smaller molecules, they displayed excellent docking performance and acceptable bioavailability scores, supporting their potential as biologically active compounds.

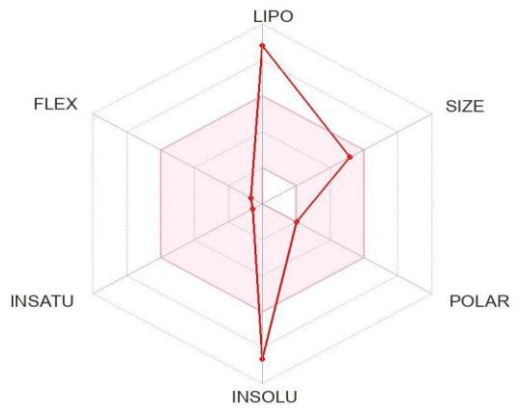
The docking and ADME analyses collectively indicate that the phytoconstituents of Hemidesmus indicus possess promising therapeutic potential against urinary tract infection. β-Sitosterol and Stigmasterol demonstrated stronger binding affinities than Ciprofloxacin, while Hemidine exhibited comparable activity to the standard drug. The favorable pharmacokinetic characteristics further support their suitability as potential oral therapeutic agents.

These findings provide scientific evidence supporting the traditional Siddha use of Nanari in the treatment of Neer Kadupu. The observed anti-inflammatory activity through TNF-α inhibition, together with acceptable ADME properties, suggests that Nanari may serve as a valuable source of lead compounds for the development of novel therapies against urinary tract infections

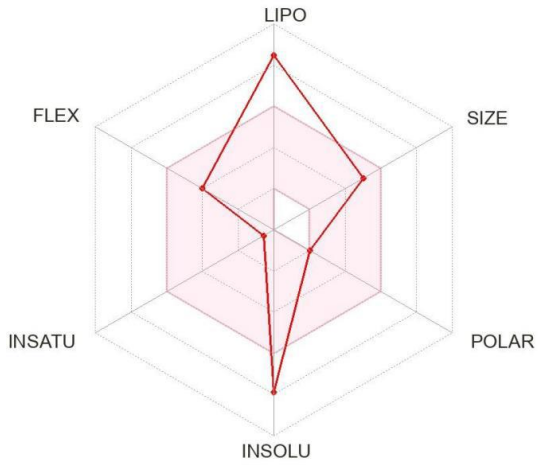
2-Hydroxy-4-methoxybenzaldehyde



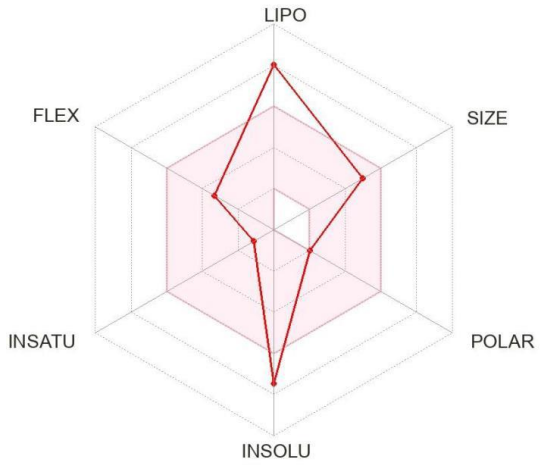
Lupeol



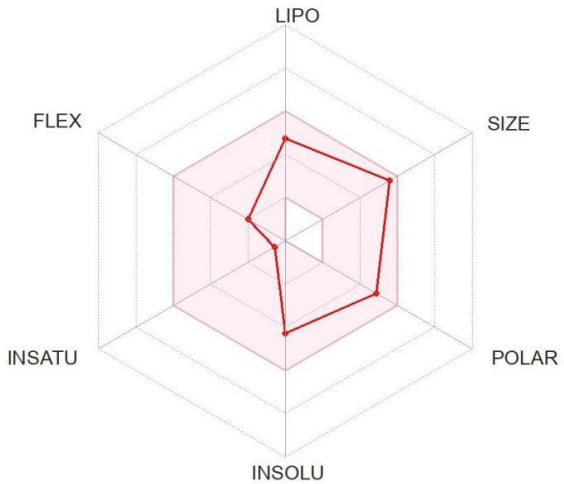
B-Sitosterol



Stigmasterol



Hemidine



CONCLUSION

The present in silico study highlights the therapeutic potential of Hemidesmus indicus (Nanari) against urinary tract infection (UTI) through its significant interactions with the inflammatory target TNF-α. Molecular docking analysis revealed that β-Sitosterol and Stigmasterol exhibited stronger binding affinities than the standard drug Ciprofloxacin, while Hemidine showed comparable binding activity. These findings indicate that the phytoconstituents of Nanari may effectively modulate inflammatory pathways associated with UTI.

Furthermore, ADME analysis demonstrated favorable pharmacokinetic properties, including acceptable gastrointestinal absorption, bioavailability, and drug-likeness characteristics for most of the selected compounds. The combined docking and ADME results suggest that the bioactive constituents of Nanari possess promising anti-inflammatory and therapeutic potential.

Overall, this study provides scientific support for the traditional Siddha use of Hemidesmus indicus in the management of Neer Kadupu and related urinary disorders. However, further in vitro, in vivo, and clinical investigations are required to validate the efficacy and safety of these phytocompounds and to establish their potential as novel therapeutic agents for urinary tract infections.

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