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Research Article

MOLECULAR DOCKING ANALYSIS OF *THIRIKANDAGATHI KIYAAZHAM* AGAINST TAMM–HORSFALL PROTEIN FOR ANTI-UROLITHIATIC ACTIVITY

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ABSTRACT

Urolithiasis is a common renal disorder characterized by the formation and aggregation of urinary crystals. Tamm- Horsfall protein (THP) plays a crucial role in modulating crystal nucleation and aggregation. This study evaluates the anti-urolithiatic potential of phytocompounds derived from a Siddha herbal decoction, *Thirikandagathi kiyaazham* (TKK) **Objective:** To identify and characterize phytocomponents from the Siddha formulation TKK that can bind to the Tamm–Horsfall protein (PDB-4WRN) and inhibit calcium oxalate crystallization. **Methods:** Seven phytocompounds were selected from TKK-Terminalia Chebula (gallic acid, maslinic acid), Emblica officinalis (ellagic acid, lupeol, quercetin), and Aerva lanata (rutin, ferulic acid)- and subjected to molecular docking analysis. Docking simulations were performed using auto dock tools with the Lamarckian genetic algorithm, focusing on interactions with core active-site residues (Cys527, Pro528, His529, Gly534, Arg583, Thr585, and Arg586) of the target protein. **Results:** Maslinic acid demonstrated the strongest interaction, forming contacts with three core residues (Cys527, Pro528, and Gly534), while ellagic acid and quercetin showed moderate interactions with two residues (Cys527 and Pro528). Gallic acid, lupeol, and ferulic acid exhibited limited interactions with single core residues, whereas rutin did not interact with any defined core active-site residues. **Conclusion:** Phytocompounds from TKK demonstrating multiple interactions with THP residues shows potential inhibition of calcium oxalate crystallization, suggesting their therapeutic profile for urolithiasis management and prevention of renal complications.

INTRODUCTION

Urolithiasis represents a significant global health burden, with prevalence rates fluctuating between 1% and 20% depending on geographic location and diagnostic methodology.[1] While the condition is a pervasive public health concern worldwide, it disproportionately affects middle-aged and older male populations.[2] Within the Indian context, the lifetime prevalence is estimated at approximately 7.9% with some rural pockets much higher.[3] Siddha medicine is a traditional system that employs herbs, metals, and minerals in its therapeutic formulations.

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Several therapeutic formulations are described in the Siddha texts for the treatment of urolithiasis *(Kalladaippu*). As documented in the traditional text *Anubava Vaithiya Deva Ragasiyam*, the herbal decoction *Thirikandagathi Kiyaazham* is specifically indicated for the clinical management of *Kalladaippu* (urolithiasis).[4] Modern approaches such as molecular docking and network pharmacology play a crucial role in validating these formulations scientifically and clarifying their mechanisms of action. These techniques help in bridging the traditional knowledge with contemporary biomedical science by identifying active compounds, their molecular targets, and the biological pathways they influence. This integrative analysis highlights the multi-component and multi-target nature of Siddha remedies, supporting their effectiveness as well as their safety profile. Such methodologies are essential for promoting the

integration of Siddha medicine into modern healthcare systems.

AIM AND OBJECTIVES

The objective of the study is to identify and characterize the phytochemical constituents of the herbal decoction TKK that exhibit binding affinity to the Tamm–Horsfall protein (PDB-4WRN).

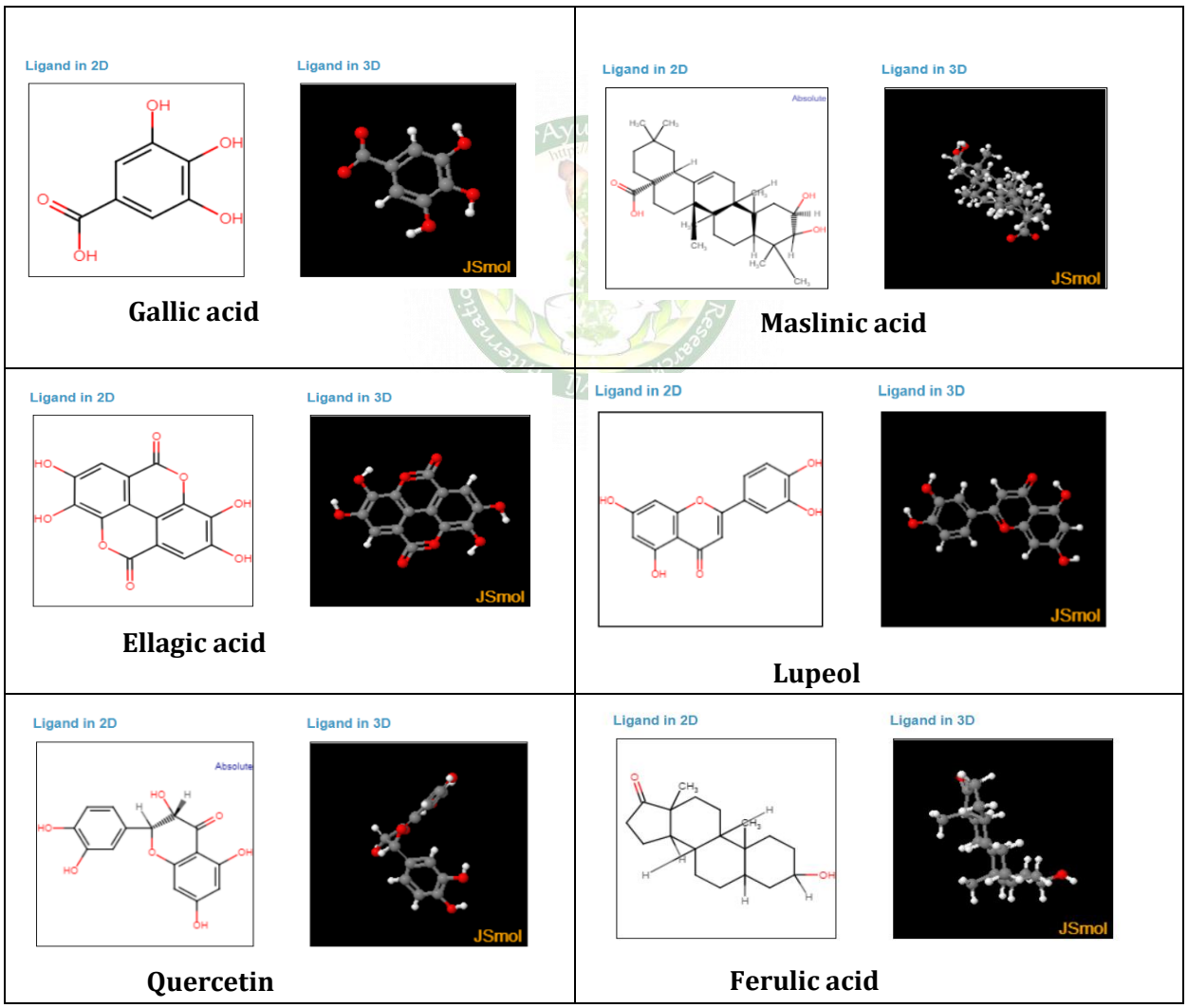
MATERIALS AND METHODS

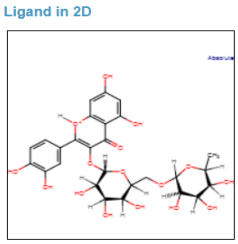
Selection of phytocompounds from TKK

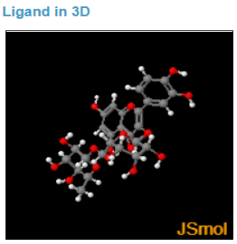
Seven phytocompounds (Table 1 & Fig 1) were selected from TKK for docking analysis such as gallic acid, maslinic acid, ellagic acid, lupeol, quercetin, ferulic acid, rutin against target protein and its ligand properties mentioned in Table 2.

Table 1: List of phytocompounds from TKK selected for docking studies

S.No	Scientific name	Phytocompounds
1	*Terminalia Chebula* Fruit rind	Maslinic acid [5]
		Gallic acid [6]
2	*Emblica officinalis* Dried fruit	Ellagic acid [7]
		Lupeol [7]
		Quercetin [7]
3	*Aerva lanata* Whole plant	Ferulic acid [8]
		Rutin [9]







Rutin

Fig 1: 2D and 3D Structure of Phytocomponents from TKK

Table 2: Ligand properties of the phytocompounds from TKK selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Gallic acid	170.12g/mol	$C_7H_6O_5$	4	5	1
Maslinic acid	472.7 g/mol	$C_{30}H_{48}O_4$	3	4	1
Ellagic acid	302.19 g/mol	$C_{14}H_6O_8$	4	8	0
Lupeol	426.7 g/mol	$C_{30}H_{50}O$	1	1	1
Quercetin	302.23 g/mol	$C_{15}H_{10}O_7$	5	7	1
Rutin	610.5 g/mol	$C_{27}H_{30}O_{16}$	10	16	6
Ferulic acid	194.186 g/mol	$C_{10}H_{10}O_4$	2	4	3

Target Protein Preparation

The crystalline structure of the target protein Tamm–Horsfall protein (PDB-4WRN) was retrieved from the protein data bank and subjected to protein clean-up procedures illustrated in Fig 2. Essential missing hydrogen atoms were added to the structure prior to docking calculations. Different orientations of the lead molecules with respect to the target protein were evaluated using the AutoDock program, and the best dock pose was selected based on interaction study analysis.

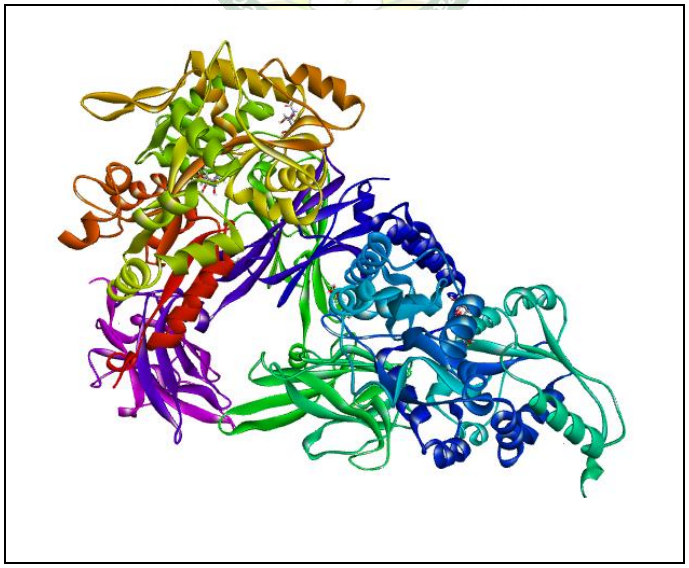


Fig 2: 3D- Structure of Tamm–Horsfall protein (PDB) - 4WRN

Methodology

Docking calculations were carried out for retrieved phytocomponents against target protein Tamm–Horsfall protein. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. Affinity (grid) maps of 60×60×60 Å grid points and 0.375 Å spacing were generated using the Autogrid program.[10] 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.[11] 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.

RESULTS

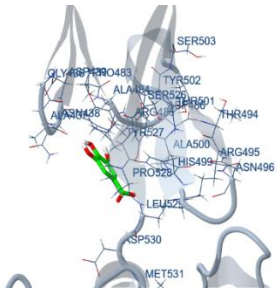
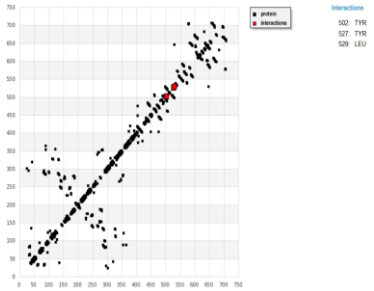
Interactions between the phytoconstituents of TKK and Tamm-Horsfall protein mentioned in Table 3 & 4.

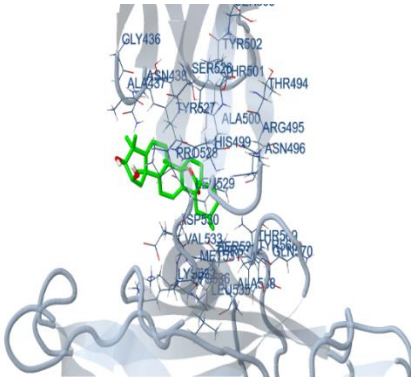
Table 3: Summary of the molecular docking studies of phytocompounds against Tamm–Horsfall protein (PDB) - 4WRN

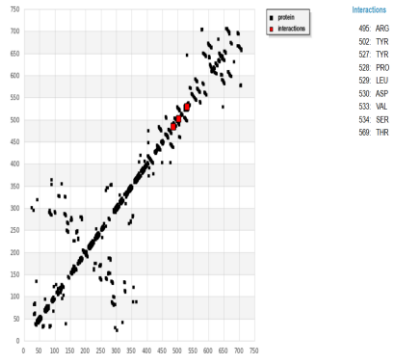
Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact Surface
Gallic acid	-4.39 kcal/mol	608.40 uM	-0.27 kcal/mol	-3.93 kcal/mol	385.878
Maslinic acid	-8.56 kcal/mol	532.73 nM	-0.04 kcal/mol	-8.44 kcal/mol	767.917
Ellagic acid	-5.39 kcal/mol	111.66 uM	-0.18 kcal/mol	-4.26 kcal/mol	522.756
Lupeol	-7.14 kcal/mol	5.86 uM	-0.16 kcal/mol	-7.87 kcal/mol	730.928
Quercetin	-5.85 kcal/mol	51.51 uM	-0.11 kcal/mol	-5.22 kcal/mol	510.962
Rutin	-10.08 kcal/mol	40.79 nM	-0.26 kcal/mol	-4.99 kcal/mol	632.864
Ferulic acid	-4.47 kcal/mol	532.23 uM	-0.58 kcal/mol	-4.92 kcal/mol	482.271

Table 4: Amino acid Residue Interaction of Lead against Tamm–Horsfall protein (PDB) - 4WRN

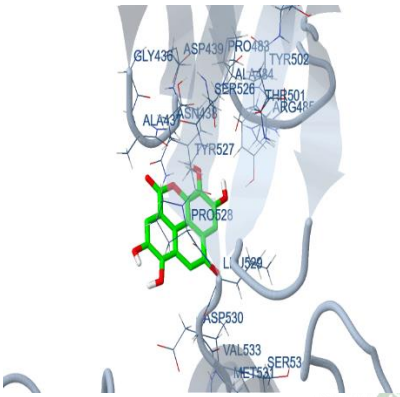
No. of inter actions	Phyto compounds	Amino acid Residues listed from docking Interactions (Target residues only)									
1	Gallic acid	Tyr502	Cys527	His529							
3	Maslinic acid	Arg495	Tyr502	Cys527	Pro528	His529	Asp530	Val533	Gly534	Thr569	
2	Ellagic acid	Tyr502	Cys527	Pro528	Asp530						
1	Lupeol	Thr498	His499	Pro528	Asp530	Glu639	Ser643	Ser644	Gln645	Arg647	Glu642
2	Quercetin	Ala484	Tyr502	Cys527	Pro528	Asp530					
0	Rutin	Thr498	His499	Ser526	Val638	Glu642					
1	Ferulic acid	Arg495	Ala500	Tyr502	Cys527	His529	Asp530	Val533	Thr569		

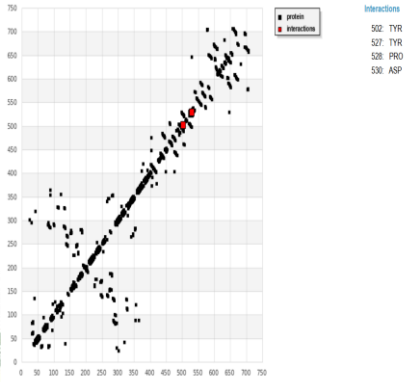
Lead with THP interaction	**Hydrogen bond plotting with core amino acid Analysis**
	
Gallic acid with Tamm Horsfall protein (PDB)- 4WRN	



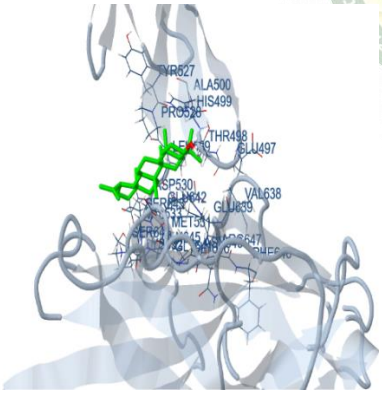


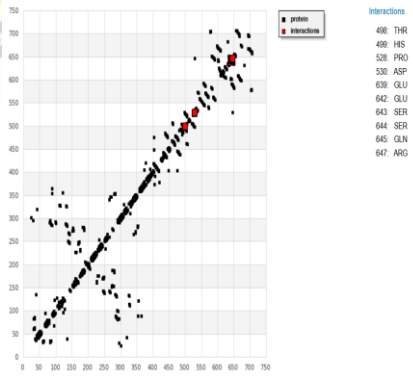
Maslinic acid with Tamm–Horsfall protein (PDB) - 4WRN



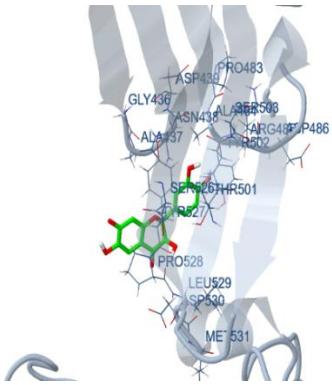


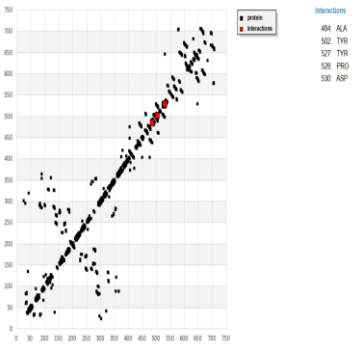
Ellagic acid with Tamm–Horsfall protein (PDB) - 4WRN



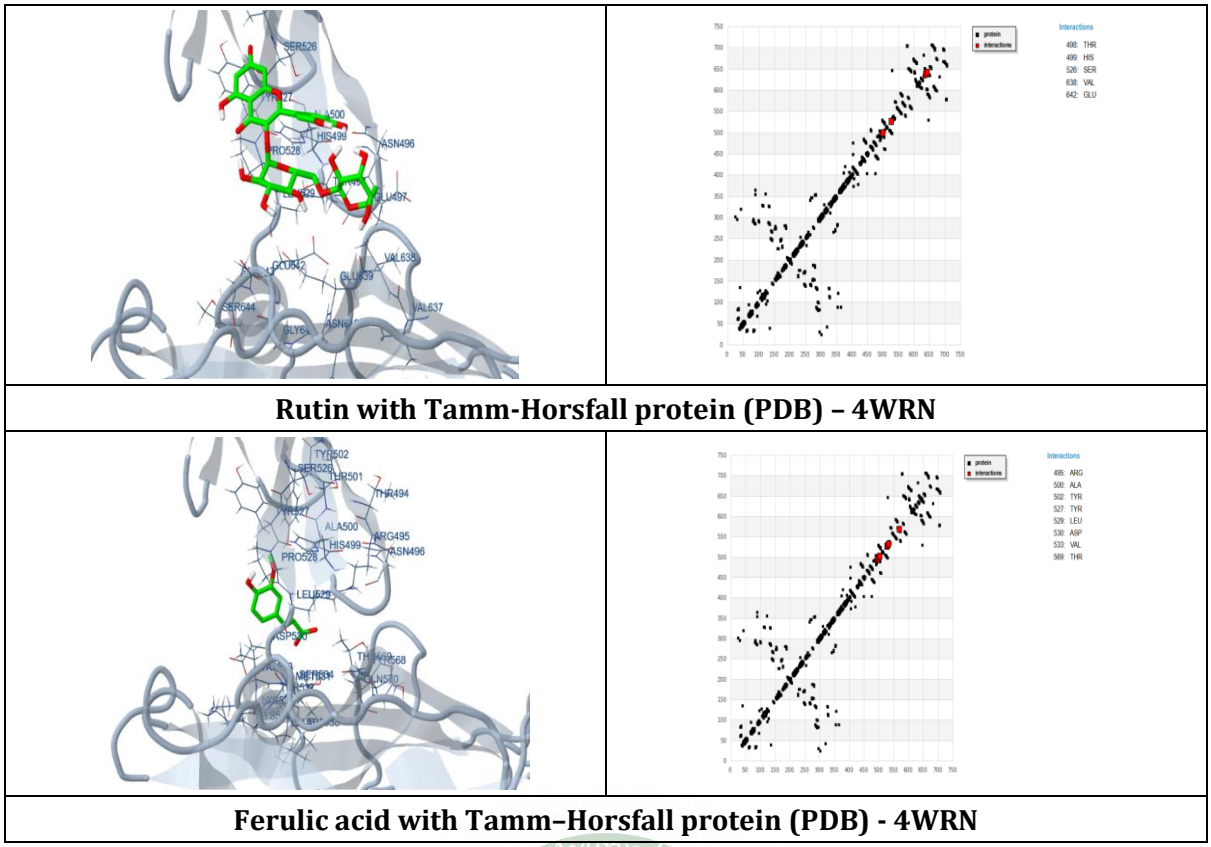


Lupeol with Tamm–Horsfall protein (PDB) - 4WRN





Quercetin with Tamm–Horsfall protein (PDB) - 4WRN



Rutin with Tamm-Horsfall protein (PDB) – 4WRN

Ferulic acid with Tamm–Horsfall protein (PDB) - 4WRN

Fig 3: Phytocompounds interaction with Tamm-Horsfall Protein

DISCUSSION

Thirikandagathi kiyaazham, indicated for urolithiasis, is a herbal decoction containing *Terminalia chebula, Emblica officinalis,* and *Aerva lanata*. Urolithiasis is common, recurrent, and closely tied to systemic metabolic health. THP/uromodulin is a central endogenous modulator of urolithiasis. Normal, properly glycosylated THP inhibits calcium oxalate/phosphate crystal growth, aggregation, and adhesion, and supports a protective response to urinary supersaturation.[12] Reduced levels, altered glycosylation/oxidation, abnormal polymerization, or impaired regulation convert THP from a guardian into a facilitator of crystal formation and retention, increasing kidney stone risk.[13] The formulation's therapeutic potential can be explored through molecular docking studies to predict interactions of its phytoconstituents with target proteins involved in urolithiasis. These in silico analyses provide preliminary insights into the mechanism of action and bioactivity. To establish scientific validation, further in vivo studies are essential.

The docking analysis demonstrated that several phytocompounds interact with the core active-site residues of the Tamm–Horsfall protein (Cys527, Pro528, His529, Gly534, Arg583, Thr585, and Arg586), which are associated with the calcium oxalate crystallization process involved in kidney stone formation. Among the screened compounds, Maslinic acid exhibited the highest interaction with the core residues, specifically binding to Cys527, Pro528, and Gly534, suggesting stronger engagement within the active-site region of the protein. Ellagic acid and Quercetin displayed moderate interaction profiles by forming contacts with Cys527 and Pro528, while gallic acid, lupeol, and ferulic acid showed limited interaction, each interacting with only one of the core residues. Rutin, in contrast, did not interact with any of the defined core active-site residues, indicating a comparatively weaker or peripheral binding orientation within the protein structure.

CONCLUSION

The findings indicate that phytocompounds of TKK exhibiting multiple interactions with key residues of the Tamm–Horsfall protein may have enhanced potential to inhibit calcium oxalate crystallization. Consequently, these compounds represent promising candidates for the therapeutic management of urolithiasis and associated renal disorders. Further in-vivo studies are essential to evaluate the efficacy and safety profile.

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