

Original Research Article

In silico Molecular Docking-Based Evaluation of the Antinephrolithiatic Potential of *Schleichera oleosa* (Lour.) Oken Phytoconstituents

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Abstract: **Background:** Nephrolithiasis is a common urinary tract disorder characterized by the formation and accumulation of mineral-based calculi within the urinary system. Calcium-containing stones, particularly calcium oxalate stones, represent the major type of urinary calculi. Despite the availability of several therapeutic approaches, recurrence of urinary stones remains a significant clinical concern. Medicinal plants containing biologically active phytoconstituents may provide a valuable source of potential lead molecules for the development of novel antinephrolithiatic agents. **Objective:** The present study aimed to investigate the potential antinephrolithiatic activity of selected phytoconstituents of *Schleichera oleosa* (Lour.) Oken using an in silico molecular docking approach against selected proteins associated with urinary stone formation and oxalate metabolism. **Methods:** Selected phytoconstituents of *S. oleosa*, namely linolelaidic acid and scopoletin, were evaluated against adenine phosphoribosyl transferase (APRT; PDB ID: 5ZNQ), glycolate oxidase (PDB ID: 1GOX), oxalate oxidase (PDB ID: 1FI2), and Tamm-Horsfall protein (PDB ID: 4WRN). Protein structures were obtained from the Protein Data Bank, while ligand structures were obtained from PubChem. Protein and ligand preparation was followed by molecular docking using PyRx based on the AutoDock Vina docking algorithm. Predicted ligand-protein interactions were subsequently examined using BIOVIA Discovery Studio Visualizer. **Results:** Both investigated phytoconstituents demonstrated favourable predicted binding energies toward the selected protein targets. Linolelaidic acid showed docking scores of -5.6, -5.2, -5.5, and -6.2 kcal/mol against APRT, oxalate oxidase, glycolate oxidase, and Tamm-Horsfall protein, respectively. Scopoletin exhibited docking scores of -6.2, -5.5, -6.9, and -7.3 kcal/mol against the corresponding targets. Among the evaluated ligand-target combinations, scopoletin showed the most negative predicted binding energy (-7.3 kcal/mol) with Tamm-Horsfall protein, whereas its interaction with glycolate oxidase also demonstrated a comparatively favourable docking score (-6.9 kcal/mol). **Conclusion:** The docking results indicate that linolelaidic acid and scopoletin may interact favourably with proteins potentially involved in pathways associated with urinary stone formation. In particular, scopoletin demonstrated comparatively stronger predicted binding across several of the investigated targets. These findings provide preliminary computational evidence supporting further investigation of *S. oleosa* phytoconstituents as potential antinephrolithiatic lead molecules. However, experimental validation through in vitro, in vivo, pharmacokinetic, toxicity, and ultimately clinical studies is necessary before therapeutic conclusions can be established.

Keywords: *Schleichera Oleosa*, Nephrolithiasis; Urolithiasis, Molecular Docking, Pyrx, Autodock Vina, Scopoletin, Linolelaidic Acid, Phytoconstituents, Antinephrolithiatic Activity.

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1. INTRODUCTION

Nephrolithiasis, commonly referred to as kidney stone disease, is a urinary tract disorder characterized by the formation of solid crystalline

deposits within the urinary system. Depending on their anatomical location, urinary calculi may occur in the kidneys, ureters, urinary bladder, or urethra and are collectively referred to as urolithiasis. The development

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of urinary stones is a multifactorial process involving urinary supersaturation, nucleation, crystal growth, aggregation, retention, and subsequent accumulation of mineral deposits within the urinary tract [1, 2].

Urinary calculi may contain a variety of chemical constituents, including calcium, oxalate, phosphate, uric acid, magnesium, ammonium, and cystine. Among the different types, calcium-containing stones are the most frequently encountered, with calcium oxalate representing a major component. Other clinically important stone types include uric acid, struvite, and cystine stones [2, 3]. The disease may produce severe renal colic, hematuria, urinary obstruction, infection, and, in complicated or recurrent cases, impairment of renal function [1-4].

A major challenge associated with nephrolithiasis is its tendency to recur. Even after successful removal or passage of a urinary stone, patients may remain susceptible to subsequent episodes. Current management strategies include increased fluid intake, dietary modification, pharmacological therapy, extracorporeal shock-wave lithotripsy, ureteroscopy, and other surgical interventions depending on stone characteristics and patient condition. Consequently, identification of safer and effective preventive or therapeutic agents remains an important area of research [5].

Natural products have historically contributed significantly to pharmaceutical discovery. Medicinal plants contain diverse secondary metabolites capable of interacting with multiple molecular pathways. Flavonoids, phenolic compounds, coumarins, terpenoids, tannins, alkaloids, and other phytochemicals have been investigated for antioxidant, anti-inflammatory, antimicrobial, and nephroprotective properties. Such biological activities may be relevant to the pathophysiological processes associated with urinary stone development [6, 7].

Schleichera oleosa (Lour.) Oken, commonly known as the Kusum tree, belongs to the family Sapindaceae [8]. The species is widely distributed throughout the Indian subcontinent and parts of Southeast Asia. In India, it occurs in several regions including Madhya Pradesh, Chhattisgarh, Jharkhand,

Odisha, Maharashtra, West Bengal, and parts of southern India. Various parts of the plant, including the leaves, bark, seeds, and seed oil, have traditionally been used for different medicinal purposes [9, 10].

Phytochemical investigations of *S. oleosa* have reported the presence of several classes of bioactive constituents. These compounds have been associated with antioxidant, anti-inflammatory, antimicrobial, and other pharmacological activities. Such properties provide a rationale for exploring the plant as a potential source of molecules relevant to renal and urinary disorders [9-11].

Molecular docking is a widely used computer-aided drug-design technique for investigating the possible interaction of small molecules with biological macromolecules. It provides an estimate of ligand binding affinity and helps predict the orientation of a ligand within a potential binding site. Although docking scores cannot independently establish pharmacological efficacy, they can be useful for prioritizing compounds for subsequent experimental investigation [12, 13].

In the present study, selected phytoconstituents of *S. oleosa*, namely linolelaidic acid and scopoletin, were evaluated against four selected protein targets associated with biochemical processes relevant to nephrolithiasis. The objective was to assess their predicted binding affinities and ligand-protein interaction profiles using molecular docking.

2. MATERIALS AND METHODS

2.1 Computational Resources

The present investigation was performed using publicly available biological databases and molecular modelling software. The principal resources used were the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB-PDB), PubChem, PyRx, Molegro Molecular Viewer, and BIOVIA Discovery Studio Visualizer [14-17].

2.2 Selection of Target Proteins

Four protein structures were selected to represent molecular targets of interest to processes relevant to nephrolithiasis, oxalate metabolism, and urinary tract biology.

Table 1: Selection of Target Proteins

S. No.	Target protein	PDB ID
1	Adenine phosphoribosyl transferase (APRT)	5ZNQ
2	Oxalate oxidase	1FI2
3	Glycolate oxidase	1GOX
4	Tamm-Horsfall protein	4WRN

The three-dimensional structures of the selected proteins were obtained from the RCSB Protein Data Bank in PDB format [14].

2.3 Selection and Retrieval of Ligands

Two phytoconstituents reported/selected from *Schleichera oleosa* were considered for the present computational investigation:

1. **Linolelaidic acid**
2. **Scopoletin**

The chemical structures of the selected compounds were retrieved from PubChem [15]. The ligand structures were converted into suitable molecular formats for subsequent preparation and docking.

2.4 Protein Preparation

The downloaded protein structures were initially inspected and prepared for docking. The structures were imported into molecular visualization software, and unnecessary molecules or heteroatom components were removed as appropriate for docking preparation.

The prepared protein structures were subsequently saved in PDB format. Polar hydrogen atoms were considered during receptor preparation to facilitate appropriate hydrogen-bonding interactions during docking. The prepared receptors were then imported into PyRx for molecular docking [12-16].

2.5 Ligand Preparation

The selected ligand structures were imported into the molecular visualization environment and converted into the required molecular format. The structures were subjected to energy minimization to obtain energetically favourable conformations. Following preparation, the ligand structures were converted into PDBQT format for docking using the AutoDock Vina module available through PyRx.

2.6 Molecular Docking

Molecular docking was performed using PyRx, a virtual screening platform that incorporates AutoDock Vina for ligand-protein docking [13-16].

The prepared protein was designated as the macromolecular receptor, while each phytoconstituent

was treated as an individual ligand. A separate docking experiment was conducted for each ligand-protein combination.

The docking workflow consisted of the following general steps:

1. Importing the prepared receptor into PyRx.
2. Defining the receptor as a macromolecule.
3. Importing the prepared ligand.
4. Defining the ligand for docking.
5. Selecting the Vina docking procedure.
6. Defining the appropriate grid/search space around the target region.
7. Performing the docking calculation.
8. Recording the predicted binding affinity values.

The docking score was expressed in kcal/mol [13]. In general, a more negative predicted binding energy indicates a more favourable calculated ligand-receptor interaction under the assumptions of the docking model.

2.7 Analysis of Ligand-Protein Interactions

The docked complexes were further analysed using BIOVIA Discovery Studio Visualizer 2.0. Two-dimensional interaction diagrams were generated to visualize potential hydrogen bonds, hydrophobic interactions, and other ligand-residue contacts.

The interaction profiles were used to support interpretation of the docking scores and to identify residues potentially contributing to ligand binding.

3. RESULTS

3.1 Molecular Docking Results

The docking analysis demonstrated favourable predicted interactions between both selected phytoconstituents and the four target proteins.

The calculated binding energies are presented in Table 1.

Table 1: Predicted binding affinities of selected *Schleichera oleosa* phytoconstituents against nephrolithiasis-associated protein targets

S. No.	Phytoconstituent	APRT (5ZNQ)	Oxalate oxidase (1FI2)	Glycolate oxidase (1GOX)	Tamm-Horsfall protein (4WRN)
1	Linolelaidic acid	-5.6	-5.2	-5.5	-6.2
2	Scopoletin	-6.2	-5.5	-6.9	-7.3

Binding Affinity is expressed as Kcal/Mol.

Among all investigated ligand-target combinations, scopoletin showed the most negative predicted binding energy (-7.3 kcal/mol) against Tamm-Horsfall protein (PDB ID: 4WRN). Scopoletin also demonstrated a comparatively favourable predicted affinity toward glycolate oxidase (-6.9 kcal/mol).

Linolelaidic acid showed its most favourable docking score against Tamm-Horsfall protein (-6.2 kcal/mol), followed by glycolate oxidase (-5.5 kcal/mol), APRT (-5.6 kcal/mol), and oxalate oxidase (-5.2 kcal/mol).

For scopoletin, the predicted binding energies were -6.2 kcal/mol for APRT, -5.5 kcal/mol for oxalate

oxidase, -6.9 kcal/mol for glycolate oxidase, and -7.3 kcal/mol for Tamm-Horsfall protein.

3.2 Ligand-Protein Interaction Analysis

Two-dimensional interaction analysis was performed to investigate the potential interactions between the selected phytoconstituents and the target proteins.

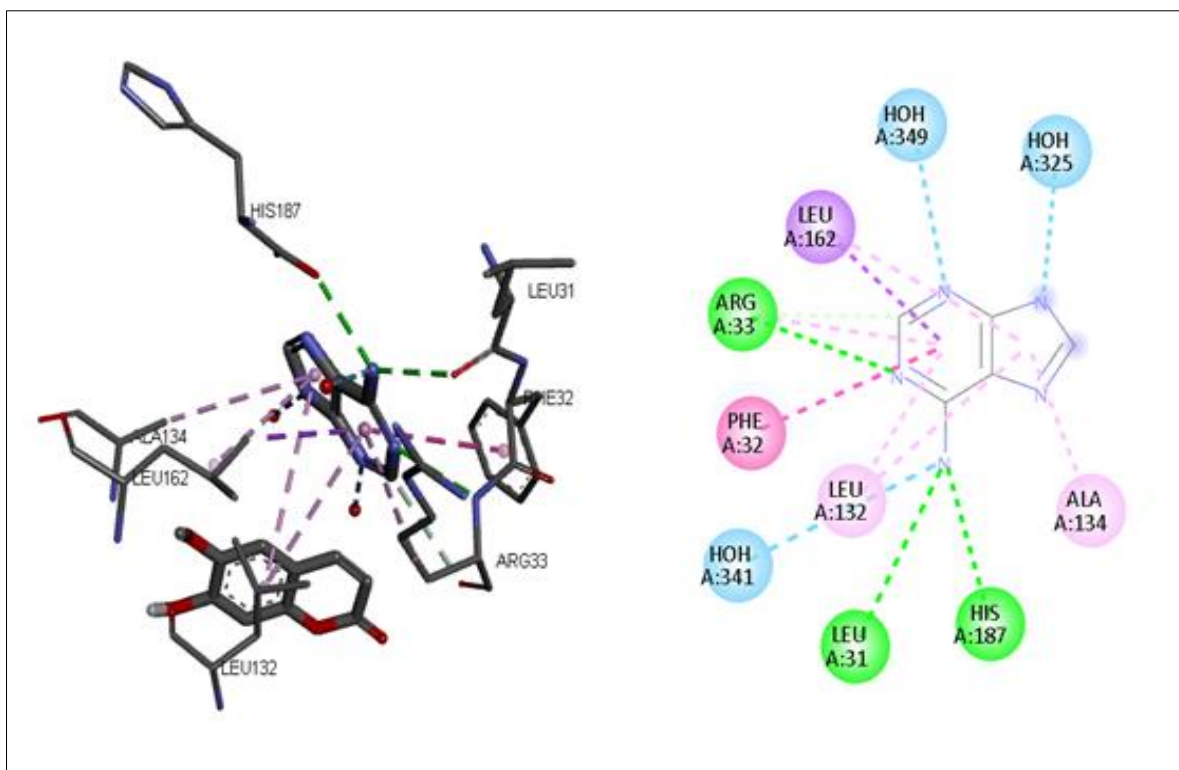


Figure 1: 2D interaction diagram of scopoletin with APRT (PDB ID: 5ZNQ)

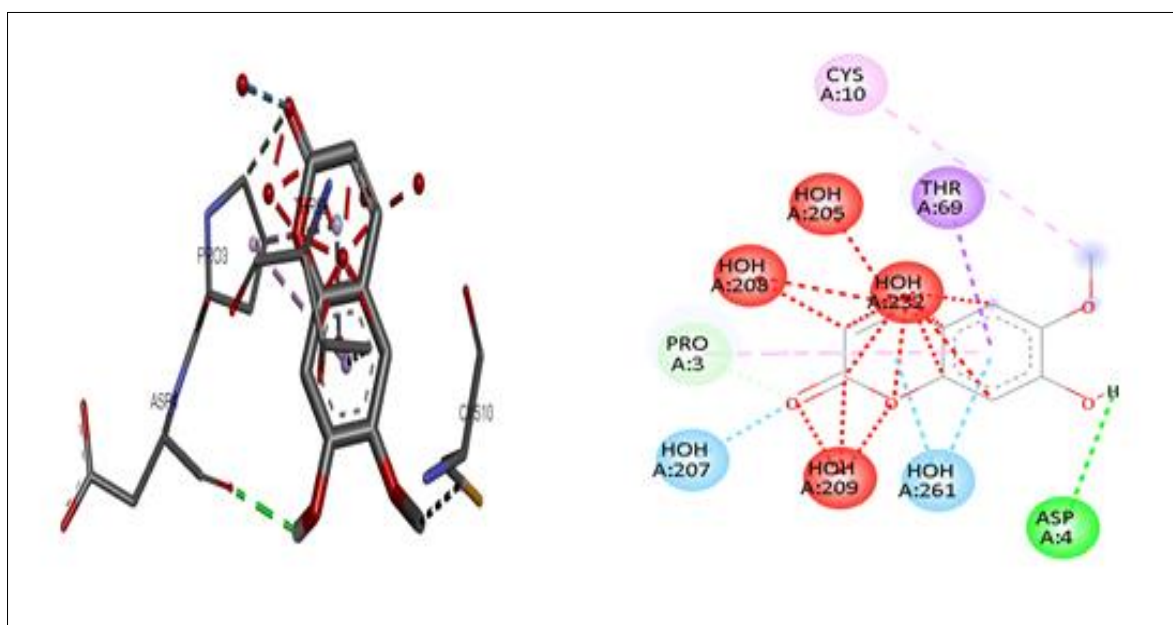


Figure 2: 2D interaction diagram of scopoletin with oxalate oxidase (PDB ID: 1FI2)

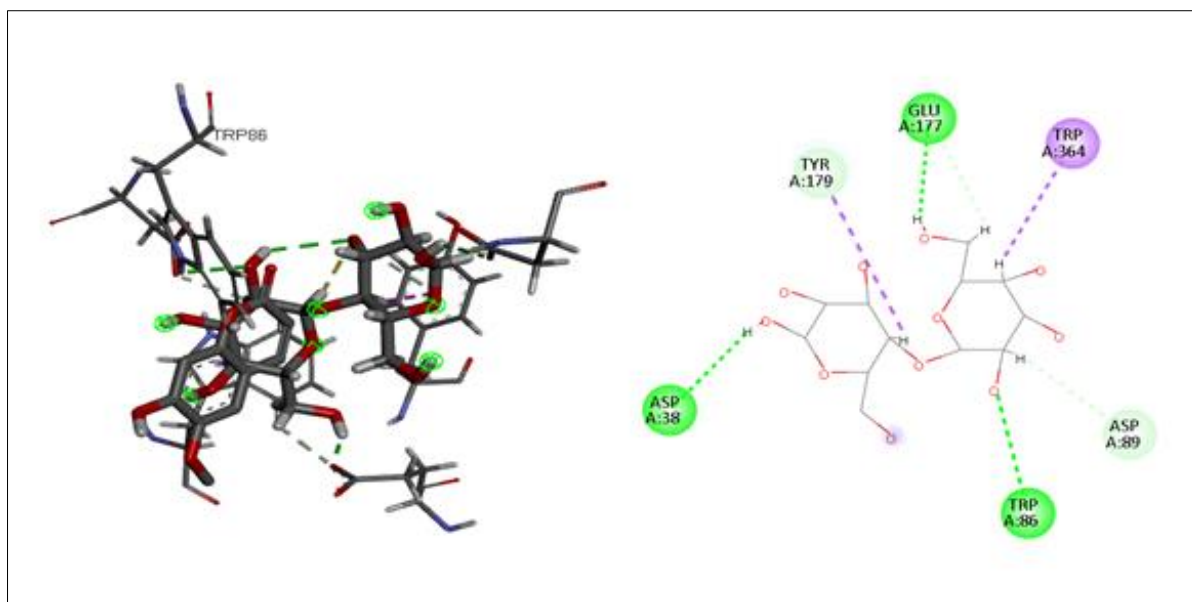


Figure 3: 2D interaction diagram of scopoletin with Tamm-Horsfall protein (PDB ID: 4WRN)

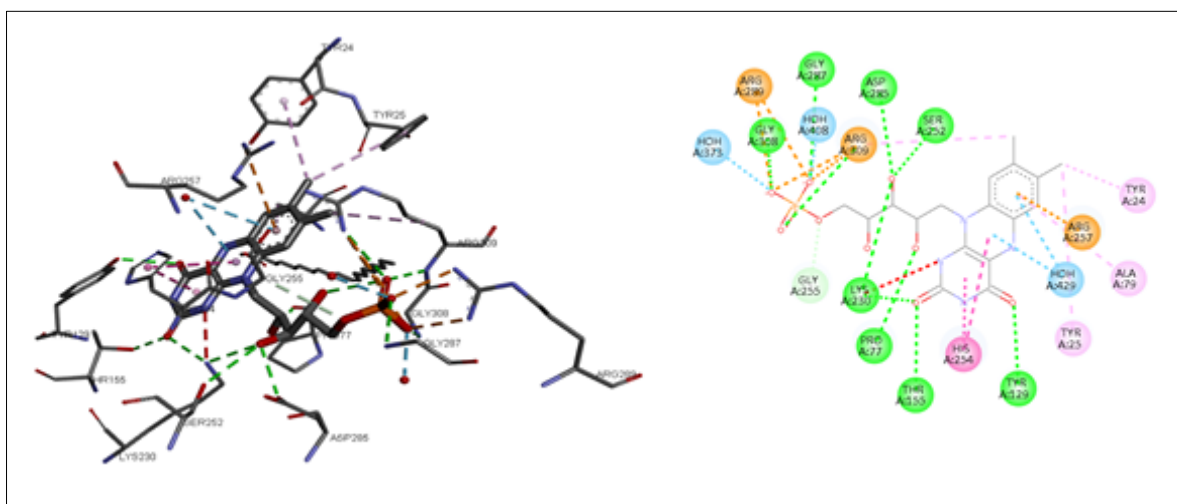


Figure 4: 2D interaction diagram of scopoletin with glycolate oxidase (PDB ID: 1GOX)

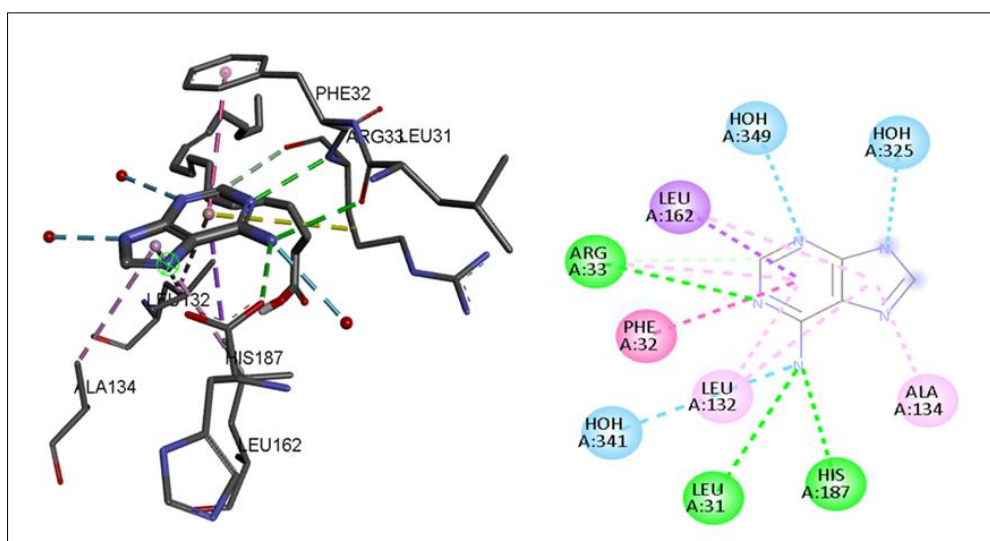


Figure 5: 2D interaction diagram of linolelaidic acid with APRT (PDB ID: 5ZNQ)

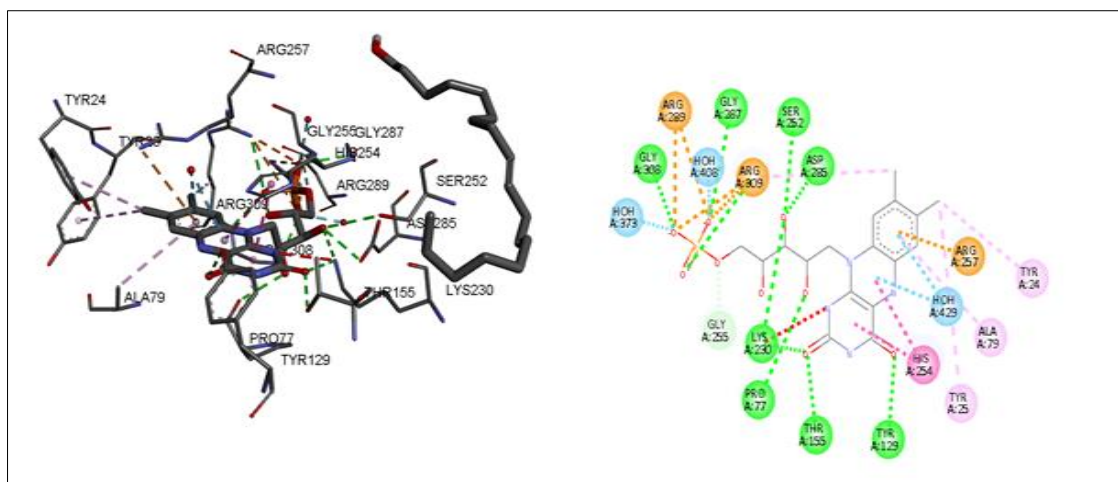


Figure 6: 2D interaction diagram of linolelaidic acid with glycolate oxidase (PDB ID: 1GOX)

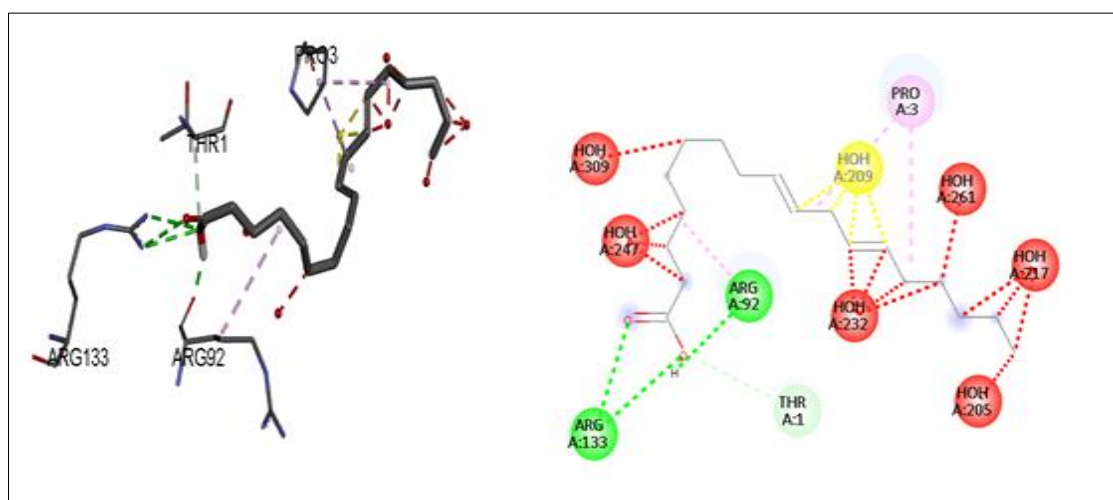


Figure 7: 2D interaction diagram of linolelaidic acid with oxalate oxidase (PDB ID: 1F12)

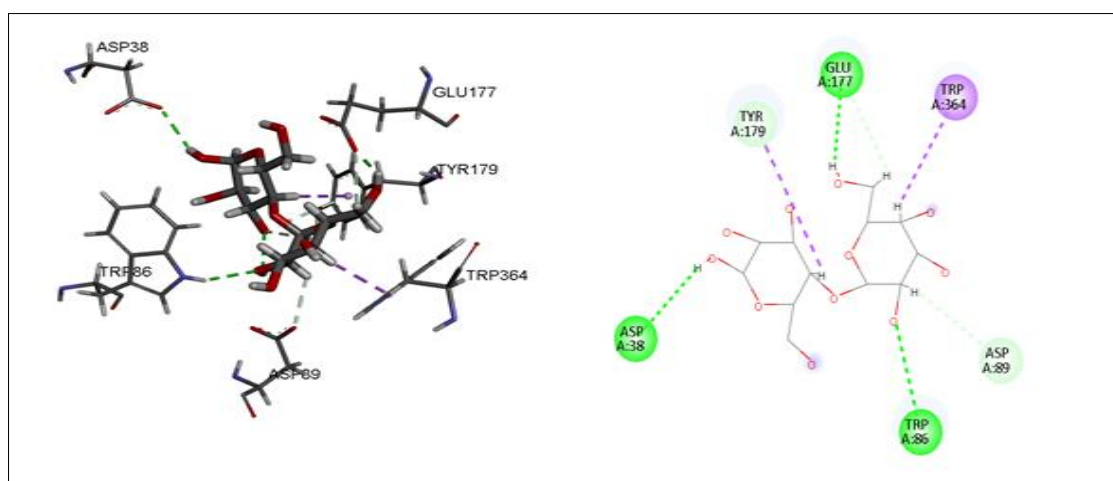


Figure 8: 2D interaction diagram of linolelaidic acid with Tamm-Horsfall protein (PDB ID: 4WRN).

4. DISCUSSION

Nephrolithiasis is a multifactorial condition in which urinary supersaturation, crystal nucleation, growth, aggregation, and retention contribute to stone development. Calcium oxalate is particularly important in the pathogenesis of urinary stone disease. Consequently, proteins involved in oxalate metabolism

and urinary crystal-related processes represent potential molecular targets for computational investigation [1-3].

The present study evaluated two selected phytoconstituents of *Schleichera oleosa*, linolelaidic acid and scopoletin, against APRT, oxalate oxidase, glycolate oxidase, and Tamm-Horsfall protein. The

molecular docking results demonstrated that both compounds were capable of producing negative predicted binding-energy values with all investigated targets.

The docking score of a ligand provides an estimate of its predicted binding affinity within the selected receptor environment. More negative values generally indicate a more favourable predicted interaction; however, docking scores should not be interpreted as direct measurements of biological efficacy. They are dependent on the docking algorithm, receptor preparation, ligand conformation, search space, and scoring function [12, 13].

Among the investigated combinations, scopoletin showed the strongest predicted interaction with Tamm-Horsfall protein, with a docking score of -7.3 kcal/mol. Scopoletin also displayed a relatively favourable score of -6.9 kcal/mol against glycolate oxidase. These findings indicate that scopoletin may have a comparatively favourable interaction profile among the compounds investigated in this study.

Linolelaidic acid demonstrated docking scores ranging from -5.2 to -6.2 kcal/mol across the four targets. Its most favourable predicted interaction was observed with Tamm-Horsfall protein, followed by APRT and glycolate oxidase. Although these results suggest potential interactions with the selected targets, they should be interpreted as computational predictions rather than evidence of direct inhibition.

Tamm-Horsfall protein, also known as uromodulin, is a major urinary glycoprotein produced by the kidney and has been associated with urinary tract physiology and interactions with urinary crystals. Therefore, interaction of phytoconstituents with this protein is of potential interest in the context of urolithiasis. Nevertheless, the biological consequence of the predicted binding requires experimental confirmation [21, 22].

Glycolate oxidase is involved in hepatic glyoxylate metabolism and contributes to the generation of oxalate through metabolic pathways. Because excessive oxalate availability can promote calcium oxalate crystallization, molecular targets associated with oxalate metabolism have attracted attention in research related to calcium oxalate nephrolithiasis. The comparatively favourable docking score obtained for scopoletin against glycolate oxidase therefore provides a rationale for further experimental investigation [18-20].

The predicted interaction with oxalate oxidase was comparatively weaker than some of the other ligand–target combinations investigated in the present work. Linolelaidic acid showed a docking score of -5.2 kcal/mol, while scopoletin showed -5.5 kcal/mol against this target. These values indicate favourable calculated

interactions according to the docking model, although their biological relevance cannot be established solely from these scores [8-11].

The phytochemical composition of *S. oleosa* provides a possible basis for investigating its medicinal potential. The plant has traditionally been used for various ailments, and reported phytochemicals may contribute to antioxidant and other biological activities. Oxidative stress and inflammation have been implicated in renal injury and stone-associated processes; therefore, compounds possessing antioxidant or anti-inflammatory characteristics may be of interest in the broader context of nephroprotection.

An important aspect of the present findings is that molecular docking can help prioritize candidate compounds for subsequent experimental research. The relatively favourable docking profile of scopoletin, particularly against Tamm-Horsfall protein and glycolate oxidase [22], suggests that this compound warrants further investigation. However, computational affinity alone cannot demonstrate enzyme inhibition, reduction of calcium oxalate crystallization, prevention of stone formation, or clinical efficacy.

Further studies should therefore include in vitro calcium oxalate nucleation, growth and aggregation assays, enzyme inhibition studies, cellular models, appropriate animal models, pharmacokinetic evaluation, toxicity assessment, and eventually controlled clinical investigations. Such studies would help determine whether the computational interactions observed in the present investigation translate into measurable antinephrolithiatic activity.

5. CONCLUSION

The present in silico investigation explored the potential interactions of two selected phytoconstituents of *Schleichera oleosa*, namely linolelaidic acid and scopoletin, with four protein targets associated with pathways relevant to nephrolithiasis.

Both compounds demonstrated negative predicted binding energies against APRT, oxalate oxidase, glycolate oxidase, and Tamm-Horsfall protein. Among the investigated ligand–target combinations, scopoletin exhibited the most favourable predicted binding energy of -7.3 kcal/mol against Tamm-Horsfall protein, followed by -6.9 kcal/mol against glycolate oxidase. Linolelaidic acid showed its most favourable interaction with Tamm-Horsfall protein, with a predicted binding energy of -6.2 kcal/mol.

These findings suggest that the selected *S. oleosa* phytoconstituents may possess molecular characteristics worthy of further investigation in the context of nephrolithiasis. However, the results represent preliminary computational evidence and should not be interpreted as proof of antinephrolithiatic efficacy.

Comprehensive in vitro and in vivo studies are required to establish the mechanisms of action, pharmacological efficacy, safety, and therapeutic relevance of these compounds.

7. DECLARATIONS

Ethics Approval: Not applicable, as the present study involved computational analysis and did not use human participants or experimental animals.

Consent for Publication: Not applicable.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: No external funding was received for the present study.

Data Availability

The protein structures used in this study were obtained from the publicly accessible Protein Data Bank, and ligand information was obtained from PubChem. The docking results generated during the present study are included in the manuscript.

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