Molecular docking studies of natural compounds of Ipomoea carnea Jacq. and Lumasiran with target protein glycolate oxidase a novel in-silico insights into hyperoxaluria and urolithiasis management.

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Abstract

Urolithiasis is a prevalent and painful disorder characterized by kidney stone formation which poses significant health and economic challenges worldwide. This research explores the anti-urolithiatic property of various phytoconstituents of Ipomoea carnea jacq. using molecular docking by taking Lumasiran as a standard. A total of sixty-one phytoconstituents were analyzed, among which five compounds- 4'-Hydroxy-3'-methylacetophenone, Campesterol, Lup-20(29)-en-3-one, Salicylaldehyde hydrazine, and Spirosta-5,7-dien-3-yl acetate demonstrated the highest binding affinities toward glycolate oxidase, a key enzyme involved in oxalate metabolism. ADMET analysis highlights compound 4'-Hydroxy-3'-methylacetophenone due to its favorable GI absorption and drug likeness profiles. PASS analysis further indicated significant inhibitory activities against oxidoreductase and peroxidase enzymes, implicated in oxidative stress mediated urinary stone formation. Structural modifications in Campesterol and Lup-20(29)-en-3-one recommended to enhance their therapeutic efficacy. These findings suggest that the identified phytoconstituents have the potential to serve as lead compounds in the development of novel therapeutics for managing hyperoxaluria-induced urolithiasis.

1. Introduction

Recent change in dietary habits and lifestyle choices have significantly contribute to rise global health prevalence of kidney stones, making it an increasingly worldwide health issue (1). The treatments now used to break these painful stones are linked to different side effects, and the recurrent kidney stones have caused a concerning rise in the incidence of bleeding among the afflicted population (2). This disorder results from a high concentration of oxalate, calcium, urate, and cystine that finally crystallizes and grows over time to produce kidney stones. The consequent structural and functional damage to the kidneys might cause renal cell damage and finally cell death, hence aggravating the clinical problems. The development of kidney stones is closely associated with metabolic syndrome disorders, which might exacerbate the overall health of persons predisposed to urolithiasis (3). In recent years, both conventional and contemporary medical approaches have been utilized to address kidney stone disorders, seeking efficient solutions to manage this prevalent condition (4). Advancements in nanotechnology and biotechnology have positioned herbal medicines as prospective therapeutic agents that can reduce kidney stone formation and potentially eradicate existing stones. Despite these advancements, a comprehensive review indicates that various plant species remain underexplored concerning their antiurolithiatic potential. Moreover, it is crucial to acknowledge that all now marketed antiurolithiatic drugs remain deficient in adequate safety and efficacy data, underscoring the necessity for continued research (5). Urolithiasis, defined by the existence of urinary calculi or stones, is an indisputably painful ailment that impacts over an array of individuals. This health condition is among the most common kidney disorders globally, representing a major health challenge in both developed and developing countries, ultimately leading to a substantial cost strain on patients and healthcare systems (3). Epidemiological studies indicate that around 1 to 15% of individuals in industrialized areas may form a kidney stone, with the highest prevalence often observed between the ages of 20 and 55 (6). Alarmingly, over 75% of persons diagnosed with radioactive stones will encounter or have already encountered a recurrence, frequently within the initial year, despite implementing preventive measures (7). The pathophysiology of urolithiasis arises from the supersaturation of solutes or a decrease in solute inhibitors in the urine. This imbalance contributes to the precipitation of crystals, which can subsequently aggregate and grow into larger stones (3). Taking appropriate actions to reduce urinary supersaturation of the ions that form these stones, in addition to increasing the likelihood of spontaneous passage, will undoubtedly aid in expediting symptomatic relief for patients suffering from this distressing condition (8).

Urolithiasis is the formation of urinary calculi at any location along the urinary tract, which has clinical relevance and an increasing special focus. The majority of stone formers develop calcium-containing stones (9). Without adequate preventive protocols, the probability of stone recurrence over time exceeds 50%. Sometimes, calculi precipitate acute urinary retention, risk of pyelonephritis, and sepsis (10). Due to this clinical importance, the different methods to deal with urinary stones, like extracorporeal shock wave lithotripsy, endoscopic procedures such as ureterorenoscopic lithotripsy, percutaneous nephrolithotripsy, and laparoscopic stone removal, have occurred and been improved over time (11). Nowadays, scientific research increasingly contributes to defining different molecules involved in the etiopathogenesis and potential new biomarkers of stone disease, as well as new preventive medical treatments (12).

However, it is notably more prevalent in men, with studies indicating that the incidence is two to three times higher in male populations compared to their female counterparts (13). Recent statistics reveal that the prevalence of urolithiasis in Western societies currently ranges from 5–12%. This issue not only impacts individual health but also has considerable economic repercussions, particularly due to the high recurrence rates associated with this condition (14). The financial burden varies significantly among different countries, attributed to varying costs of endourologic procedures that are performed on men. As the global population continues to grow, the costs associated with endourologic management are projected to escalate rapidly. Although these therapies may assist in managing the illness, they do not reinstate kidney functioning to their baseline state (15). Alarmingly, 30–70% of patients with urolithiasis will encounter a recurrence, so complicating their medical therapy. As a direct result of recurring recurrences, individuals necessitate different drugs to alleviate various stone-related symptoms (16). Notwithstanding the wide array of pharmaceutical alternatives for symptom management, the concerning trend from 2015 to 2024 reveals a rise in patients having chronic kidney disease or advancing to end-stage renal disease. This highlights the pressing necessity for more efficacious preventive measures and therapeutic solutions to address the challenges presented by urolithiasis (17).

Mostly due to bad eating habits, inadequate water intake, too much soft drink consumption, and growing obesity rates, the young people are prone to a notable increase in prevalence rates (18). Moreover, individuals affected by urolithiasis frequently experience recurrent episodes of the disorder, highlighting a concerning clinical trial. One particular kind of kidney illness, kidney-only hyperoxaluria, is known for its chronic character and usually recurring episodes (19). Moreover, it is important to recognize that access to and utilization of various surgical treatments can influence significantly by an individual's financial level. Under surgical treatment possibilities for urolithiasis, this covers treatments include shock wave therapy, ureteroscopy, and other forms of medication therapy (20). Furthermore, important is the fact that every surgical operation involves intrinsic hazards that can decrease renal capacity and hence raise the probability of major medical problems. These problems could cover disorders including diabetes, hypertension, and cardiovascular disease, all of which add to a greater burden of health (21).

Ipomoea carnea Jacq. also known as Bush Morning Glory or Besharam (family: Convolvulaceae) is widely distributed across various regions of India, Pakistan, Nepal, Bangladesh, Sri Lanka and some parts of South America (22). Due to its diverse pharmacological properties like antimicrobial, anti-inflammatory, antioxidant, antifungal, hepatoprotective activities it is utilized in various traditional medicines (23). Ethanolic extracts of Ipomoea carnea leaves and flowers contain various phytochemical constituents such as alkaloids, flavonoids, glycosides, steroids, tannins, saponins and these phytoconstituents (24) were identified with the help of GC-MS analysis. Recently molecular docking studies investigated these phytochemicals and these pinpoint the medical efficacy of these phytochemicals specifically in reducing oxidative stress and inflammation.

In conclusion, it is imperative to provide top priority to initiatives aimed at properly managing this medical illness and its consequences on health systems and public well-being given the great cost burden and the possible negative health outcomes connected with urolithiasis.

2. Pathophysiology of Urolithiasis

Urinary stones formed by the deposition of minerals components; a process known as urolithiasis. These stones can develop in various parts of urinary tract, including kidneys, bladder, and urethra (25). Renal calculi primarily result from the supersaturation of phosphate and oxalate ions, which is strongly associated with kidney dysfunction. These supersaturation ions can precipitate and form a solid concretion, leading to obstruction within the urinary system. As those deposits grow, they take on a crystalline, stone-loke appearance (26). Both animal models and human patients frequently suffer from stone-related disorders, prompting extensive research into their pathogenesis and treatment. Recent genetic studies have identified hereditary factors contributing to urolithiasis, suggesting a complex genetic predisposition to the disease (27). The formation of stone involves the interaction of supersaturated ions through enzymatic and molecular mechanisms, which are believed to play a key role in the initiation and progression of crystal aggregation (28). Additionally, several physiological and biochemical processes contribute to intrarenal crystal sorting and deposition, including deficiencies in natural urinary inhibitors that normally prevent stone formation (29). Current research continues to explore diverse therapeutic strategies, yet managing kidney stones remains challenging due to the limitations and potential side effects of existing treatment options. Emerging molecular data increasingly highlights the intricate interactions between renal crystals and the body’s inflammatory response, offering new insights into the underlying mechanisms of urolithiasis (Fig. 1).

2.1. Normal glyoxylate metabolism

Glyoxylate is a small but biologically significant molecule that is commonly detected using high-performance liquid chromatography (HPLC) techniques. This compound is formed during a variety of metabolic reactions, one of the key processes being the oxidative deamination of glycine that occurs within the mitochondria (30). Despite the fact that glyoxylate can be detoxified by an enzyme known as glyoxylate reductase (GR), which converts it into the readily metabolizable form of glycine, this process relies heavily on the existence of putative cytosolic GR found within the mouse or the cytosolic mitochondrial GR that is present in liver and kidney tissues (31). Nonetheless, the primary metabolic pathway responsible for the detoxification of glyoxylate is notably active within the liver's peroxisomes (32). This toxicity is exacerbated by the rigid intracellular uptake mechanisms, likely occurring through aquaporin channels, which result in the rapid precipitation of calcium oxalate monohydrate (COM) (33). The reduction in dietary proteins and amino acids triggers a metabolic response that produces four key mitochondrial enzymes along with a multitude of peroxisomal enzymes. These biochemical processes enable the concentration of glyoxylate to increase to levels that exceed its solubility limits, resulting in potential pathologies (34). It is important to note that there is a significant gap in understanding regarding the genetic regulation of the conversion from aldehyde to glyoxylate, especially within uterine tissue. This lack of regulation leads to a concerning inability to effectively convert hormonal stress into glycine throughout the ovulatory cycle (35). Furthermore, the accumulation of glyoxylate is particularly detrimental as it fuels the formation of oxalate stones, especially during episodes of hyperoxaluria. Therefore, investigating the biochemical mechanisms and genetic factors that play a role in preventing such chronic elevations of glyoxylate is crucial for understanding its etiology and the associated health implications (36).

2.2. Glyoxylate metabolism in PH1

The role of AGT in PH1 disease has centered primarily on its significant connection with glyoxylate metabolism, which is crucial for understanding the overall biochemical processes involved (37). Glyoxylate is predominantly produced by the enzyme 2-hydroxy-3-oxoadipate aldolase, which serves as an important intermediate in both the catabolism of tyrosine and phenylalanine, two essential amino acids in human metabolism (38). As a result, the balanced and well-regulated metabolism of glyoxylate emerges as a paramount concern for preventing the deposition of harmful calcium oxalate and its associated compounds in the kidneys as well as in other vital organs throughout the body (39). The enzymes alanine-glyoxylate transaminases 1 and 2 play a pivotal role, catalyzing the conversion of glyoxylate into glycine in both the cytoplasm and in the mitochondrial matrix of hepatocytes. This conversion is critical, as glycine is subsequently transformed into glyoxylic acid, which is an important compound in various metabolic pathways (40).

Subsequently, glyoxylic acid undergoes further metabolic processes converting into glycine through a series of biochemical reactions that are essential for the reduction of glyoxylic acid to glyoxal. The enzyme glyoxylate reductase facilitates this transition, playing a crucial part in several pathways (41). Glyoxal is subsequently converted to glyceric acid, which serves as an antioxidant produced by the testis. In oxidative stress situations, glyoxylate and glycerate may activate glyoxylate knockout 2, a process facilitated by the enzyme glyoxal reductase (42). Furthermore, glycerate metabolized into either pyruvate or oxaloacetate through the enzymatic actions of glycerate kinase or 6-phosphoglycerate dehydrogenase, both of which play critical roles in cellular metabolic pathway. These transformations elucidate the complex metabolic routes linking these molecular entities and their significance in cellular metabolism (43).

3. Mechanism of stone formation

Urolithiasis is a heterogenic disorder characterized by the formation of stones within the renal or urinary excretory tracts. It is the result of an imbalance between urinary solutes, urinary crystallization inhibitors, and the ability of the kidney to excrete these compounds through the urine (44). Urolithiasis is a major healthcare problem affecting more than 12% of the population worldwide. The location and the type of stone primarily depend on the anatomy and

function of the renal tract (3, 45). In most of the cases, these stones can be flushed out spontaneously, however this is not always the case. When this happens, additional intervention is necessary, and this involves hospital treatment, so the chances of hospital admission and treatment costs increase (46).

The mechanism of stone formation is complex and multifaceted, having three phases: nucleation, growth, and aggregation. However, in recent years, uric nephrolithiasis has emerged as an independent disease entity in patients with insulin resistance (28). To prevent or decrease stone-associated symptoms and complications, such as hydronephrosis and kidney function loss, and to avoid stone recurrence in patients, the exact mechanism of stone lithogenesis should be understood (47). Many factors play roles in regulating the ability of urine to prevent microscopic nuclei from growing to clinically important sizes and to inhibit these small crystals from adhering to renal epithelial cells (48).

4. Role of Lumasiran in Urolithiasis

Lumasiran is an RNA interference (RNAi)-based treatment that targets hepatic HAO1 mRNA, which encodes glycolate oxidase (GO), a major enzyme involved in oxalate production (49). It is effective in urolithiasis associated with primary hyperoxaluria type 1 (PH1). Renal impairment, urolithiasis, and nephrocalcinosis are symptoms of PH1, an uncommon autosomal recessive disorder caused by AGXT gene mutations that cause the liver to produce too much oxalate and then deposit it in the kidneys (50). By inhibiting the expression of HAO1 mRNA, Lumasiran gets rid of this pathophysiological process. Glycolate oxidase is responsible for transforming glycolate into glyoxylate, the first step in making oxalate (51). Hepatocytes selectively absorb Lumasiran via the asialoglycoprotein receptors (ASGPR), allowing for targeted hepatic administration through conjugation to a triantennary N-acetylgalactosamine (GalNAc) ligand. The surface of hepatocytes is covered with ASGPRs, which are involved in the receptor-mediated endocytosis of GalNAc-conjugated siRNAs (52). This process enables the siRNAs to be transported throughout the cell and eventually incorporated into the RNA-induced silencing complex (RISC). Degradation of HAO1 mRNA occurs when the antisense strand of Lumasiran binds to its complementary sequence within the RISC (53). By halting glycolate oxidase translation, this breakdown eliminates the metabolic route that leads to excessive oxalate formation. Recurrent calcium oxalate stone formation, nephrocalcinosis, and increasing renal impairment in PH1 patients can be reduced with Lumasiran because it efficiently lowers systemic oxalate levels by lowering hepatic oxalate production (54).

5. Material and methods

5.1 Literature survey and Gas Chromatography-Mass Spectrometry

61 phytochemicals were screened out based on GCMS analysis on *Ipomoea carnea jacq*. plant and literature survey was also done for the phytoconstituents (Table 1). Docking studies were performed on those phytochemicals and Lumasiran was used as a standard for those studies. Literature survey was done for the selection of protein and crystal structure of protein was retrieved from the protein data bank (PDB Id -7M2O) and the protein consist of one chain which have resolution 2.07 Å.

5.2 Molecular Docking

5.2.1 Protein Preparation

The crystal of Human Glycolate Oxidase was retrieved from Protein Data bank (PDB Id- 7M2O). Auto Dock Tools were used in protein preparation which include water molecule removal, addition of polar hydrogen and assignment of Kollman charges to standardize the atomic charge distribution. The prepared protein was then saved in .pdbqt format for further docking simulations (55).

5.2.2 Ligand Preparation: The ligands were prepared using ChemDraw software. Initially 2D structure was prepared and Chem 3D was used to convert it into its 3D conformation after that energy was minimized and converted into pdbqt Open Babel was used to convert it into .pdbqt format (56).

5.2.3 Grid Generation: After protein and ligand were prepared both were imported and a grid box was generated around the active site of ligand to ensure encapsulation of key residue which involved in ligand interaction. The grid box parameter which includes center parameter (x, y, z) and dimensions (length, width height) were optimized to cover the binding pocked and which helps to provide sufficient flexibility for ligand movement. This step ensured the docking calculations (57).

5.2.4 Docking: The Docking runs were carried out for each ligand allowing flexibility in ligand orientation and binding energy (kcal/mol) was calculated for each ligand-protein interaction which provides the binding affinity of ligand with protein. More the negative value more is the binding affinity (58).

5.2.5 Analysis of Docking Result: Ligand-protein interaction show various interactions such as hydrogen bond, hydrophobic interaction, π-π stacking and these interactions were analyzed using visualization tool Biovia Discovery Studio (59).

5.3 ADMET analysis

This study employed SwissADME to assess the pharmacokinetic characteristics, drug-likeness, and ADME profile of chosen substances through the analysis of essential physicochemical and pharmacokinetic parameters. The molecular weight (M.W.) of each chemical was evaluated to confirm it remained within the optimal range of < 500 g/mol, in compliance with Lipinski's Rule of Five. The counts of hydrogen bond donors (HBD) and acceptors (HBA) were evaluated, confirming they were ≤ 5 and ≤ 10, respectively, to ensure adequate membrane permeability. Lipophilicity (Log P o/w) was assessed, with an optimal range of 0–5, as excessive lipophilicity can result in inadequate solubility and elevated toxicity hazards. Water solubility was assessed using Log S (ESOL), with values over − 4 signifying favorable solubility. The gastrointestinal (GI) absorption was forecasted, with higher absorption regarded as a favorable attribute for oral

bioavailability. The permeability of the blood-brain barrier (BBB) was assessed, with positive permeability suggesting possible activity in the central nervous system (CNS). The inhibition of cytochrome P450 (CYP) enzymes CYP1A2, CYP2C19, CYP2C9, and CYP3A4 was evaluated to forecast potential drug-drug interactions and metabolic stability, with a preference for the non-inhibition of key CYP enzymes to ensure metabolic clearance. Drug-likeness was assessed according to Lipinski's Rule of Five, confirming that compounds exhibited ≤ 1 violation for optimal oral bioavailability. The PAINS (Pan-Assay Interference Compounds) filter was ultimately employed to identify potential assay interference, with PAINS-free compounds being preferable for drug development. The most promising compounds were chosen based on their ideal molecular weight, lipophilicity, solubility, gastrointestinal absorption, blood-brain barrier permeability, and little CYP inhibition, confirming their appropriateness as drug-like candidates for subsequent in silico and experimental validation (60).

5.4 Prediction of Activity Spectra for Biologically Active Substances (PASS)

PASS (Prediction of Activity Spectra for Substances) software was used to forecast the biological activity profiles of chosen substances. Based on structural similarity to known bioactive chemicals, the in-silico tool PASS can predict more than 4000 types of biological activities. These activities include therapeutic effects, mechanisms of action, metabolic pathways, and toxicological hazards. The compounds' molecular structures were fed into the PASS online server for analysis after being produced in SMILES format. Pa > 0.7 indicates a high likelihood of biological activity, Pa between 0.5–0.7 suggests moderate activity requiring further validation, and Pa < 0.5 implies low confidence in biological function. The software presents these results in terms of Pa and Pi, respectively, where Pa is the probability of activity and Pi is the probability of inactivity. Predicted action mechanisms, enzyme targets, receptor interactions, and potential toxicological issues were used to assess each compound's therapeutic potential.

6. Result and discussion

Among 61 phytoconstituents, 20 phytoconstituents (1, 9, 11, 15, 16, 18, 27, 25, 33, 35, 37, 41, 42, 44, 52, 53, 56, 57, 58, and 59) show better docking score than that of standard and these compounds show various interactions like conventional hydrogen bonding, alkyl interaction, Pi-alkyl interaction, pi-sigma interaction, carbon-hydrogen interaction, covalent bonding with various amino acids.

Among the 20 phytoconstituents, five (27, 37, 44, 56, 58) show the best docking scores (Table 2). Compound 27 shows conventional hydrogen bonding, hydrogen bonding, alkyl interaction, pi-alkyl interaction and pi-cation interaction with HIS260, LYS236, ARG263, TYR26, TYR27, VAL318, and ALA79 amino acid residues; hydrogen bonding is important for strong and specific binding, pi-cation interaction helps in electrostatic stabilization and hydrophobic interactions like alkyl and pi-alkyl helps in stabilizing the ligand in binding site. Compound 37 shows conventional hydrogen bonding and alkyl interaction with GLN 146, ALA212, VAL139, and TYR134 amino acid residue; glutamine act as H-donor/acceptor to stabilize the ligand through electrostatic interactions, and hydrophobic or aromatic interaction helps to maintain the ligand in energetically favorable conformation within the active site of protein. Compound 44 shows conventional hydrogen bonding and carbon-hydrogen bonding with amino acid residue ARG240; Arginine has a guanidinium group which is mainly involved in hydrogen bonding and this bonding suggests that this interaction is important for anchoring the ligand with active site and helps in functional activity of ligand. Compound 56 shows conventional hydrogen bonding, pi-cation interaction, and pi-alkyl interaction with TRP110, ARG263, ALA79, VAL318, and ARG315 amino acid residues; tryptophan residue engage in hydrogen bonding due to the side chain which help in enhancing the specificity and affinity, pi-cation interaction with the aromatic ring of ligand which helps to stabilize the complex via electrostatic attraction and van der Waals forces, hydrophobic interaction helps in stabilizing the ligand. Compound 58 shows conventional hydrogen bonding, and alkyl interaction with ARG240, TYR163, and PRO215 amino acid residues; hydrogen bonding between ligand and ARG240 stabilize the ligand within the active site of protein, the guanidinium group in arginine makes it more specific and stable toward the target protein. Pi-alkyl interaction (hydrophobic interaction) increases the hydrophobic stabilization of ligand within the active site.

ADMET Analysis

Important factors influencing oral bioavailability and pharmacokinetics, such as drug-likeness, solubility, absorption, and metabolism, are revealed by the SwissADME analysis of the chosen compounds. Because of its good solubility (Log S = -1.71, categorized as soluble), moderate lipophilicity (Log P = 1.59), and high gastrointestinal (GI) absorption, compound 27 (MW 150.17 g/mol) stands out as a suitable option for oral administration. Its capacity to pass through the blood-brain barrier (BBB) also raises the possibility of CNS activation. Its status as a CYP1A2 inhibitor, however, raises questions about possible toxicity and altered drug clearance due to metabolic interactions.

When taken orally, Compound 37 (MW 400.68 g/mol) may have limited bioavailability due to its low GI absorption. Although its high lipophilicity (Log P = 6.89) indicates low aqueous solubility and possible buildup in fatty tissues, which could impact medication distribution and clearance, it has a moderate solubility profile (Log S = -7.54, categorized as moderately soluble). It's one Lipinski rule violation (probably from too much Log P) indicates that it would need structural changes to increase its oral bioavailability and solubility even if it has neither CYP inhibition nor PAINS alarms.

Compound 44 (MW 424.7 g/mol) is not suited for successful oral medication formulation without augmentation techniques like prodrugs or Nanoformulations since it has even lower GI absorption, comparable to Compound 37. Its high lipophilicity (Log P = 7.31) and poor solubility (Log S = -8.43) both point to serious problems with bioavailability. It reduces the likelihood of drug-drug interactions by not inhibiting any CYP enzymes, just like Compound 37. However, unless formulation tactics are used to promote medication absorption and systemic distribution, its low solubility and high Log P make it less acceptable.

One of the most promising compounds is compound 56 (MW 136.15 g/mol), which exhibits high GI absorption, optimal lipophilicity (Log P = 1.02), and high solubility (Log S = -2.23, categorized as soluble), all of which point to good oral bioavailability and advantageous pharmacokinetics. Crucially, it doesn't penetrate the blood-brain barrier, which could restrict CNS function but could work in favor of medications meant to act peripherally. It causes a PAINS alarm (Hzone_phenol) but does not inhibit any CYP enzymes, indicating that it might be vulnerable to assay interference in biological screens. Before this is taken into consideration as a lead compound, it must be empirically verified.

Compound 58 (MW 454.64 g/mol) is an excellent option for oral medications because it also exhibits strong GI absorption. Though it is still below ideal levels, its moderate solubility (Log S = -6.09) is better than that of Compounds 37 and 44. Although it may have some solubility problems, the lipophilicity (Log P = 5.28) is still somewhat above the optimal threshold, making it easier to handle than Compound 44. It lowers the danger of metabolic interactions because, like Compounds 37 and 44, it does not inhibit CYP enzymes. It does, however, break one Lipinski rule, most likely because of its Log P value, which indicates that slight structural changes could improve its drug-like qualities (Table 3).

Table.3 ADME analysis of better compounds

S.No.	Compound	M.W (g/mol)	Donor HB	Acceptor HB	Lipophilicity (Log P o/w)	Log S (ESOL)	Water Solubility	GI Absorption	BBB Permeation	CYP Inhibitor (1A2, 2C19, 2C9, 3A4)	Lipinski Rule	PAIN
1	1	416.68	0	2	7.86	-8.2	Poorly Soluble	Low	No	No	Yes, 1 Violation	0 ale
2	9	120.15	0	1	2	-2.43	Soluble	High	Yes	No	Yes, 0 violation	0 ale
3	11	144.13	2	4	0.03	-0.68	Soluble	High	No	No	Yes, 0 violation	0 ale
4	15	180.2	1	3	1.51	-1.83	Soluble	High	Yes	CYP1A2 - Yes	Yes, 0 violation	0 ale
5	16	150.17	1	2	2.14	-2.81	Soluble	High	Yes	No	Yes, 0 violation	0 ale
6	18	120.15	0	1	1.99	-2.44	Soluble	High	Yes	CYP1A2 - Yes	Yes, 0 violation	0 ale
7	25	150.17	1	2	1.73	-2.13	Soluble	High	Yes	No	Yes, 0 Violation	0 ale
8	27	150.17	1	2	1.59	-1.71	Soluble	High	Yes	CYP1A2-Yes	Yes, 0 Violation	0 ale
9	33	426.72	1	1	7.39	-8.02	Poorly Soluble	Low	No	No	Yes, 1 Violation	0 ale
10	35	592.85	4	7	6.55	-8.23	Poorly Soluble	Low	No	No	Yes, 1 Violation	0 ale
11	37	400.68	1	1	6.89	-7.54	Moderately Soluble	Low	No	No	Yes, 1 Violation	0 ale
12	41	222.19	1	5	1.51	-2.49	Soluble	High	Yes	No	Yes, 0 Violation	0 ale
13	42	412.69	1	1	7.05	-7.64	Moderately Soluble	Low	No	No	Yes, 1 Violation	0 ale
14	44	424.7	0	1	7.31	-8.43	Poorly Soluble	Low	No	No	Yes, 1 Violation	0 ale
15	52	372.41	1	6	2.7	-3.79	Moderately Soluble	High	Yes	No	Yes, 0 Violation	0 ale
16	53	358.39	2	6	2.26	-3.58	Moderately Soluble	High	Yes	No	Yes, 0 Violation	0 ale
17	56	136.15	2	2	1.02	-2.23	Soluble	High	No	No	Yes, 0 Violation	1 ale Hzor
18	57	354.35	0	6	2.79	-3.96	Moderately Soluble	High	Yes	No	Yes, 0 Violation	0 ale
19	58	454.64	0	4	5.28	-6.09	Moderately Soluble	High	No	No	Yes, 1 Violation	0 ale
20	59	454.73	0	2	7.4	-7.95	Poorly Soluble	Low	No	No	Yes, 1 Violation	0 ale

PASS Analysis-

The data shows the pass prediction values of phytoconstituents with respect to their ability to inhibit oxidoreductase and peroxidase. Oxidoreductase plays significant role in redox reaction and oxidative stress as oxidative stress can lead to renal injury and promote stone formation whereas peroxidase involved in breakdown of hydrogen peroxide, a reactive oxygen species (ROS), excessive ROS can cause renal tubular damage and contribute to crystal formation. Compound 37 inhibit both oxidoreductase and peroxidase (Pa = 0.884 and Pa = 0.835) suggest it could effectively reduce oxidative stress. Compound 27 have moderate oxidoreductase inhibition activity and peroxidase activity which might still contribute to prevention of stone formation. Compound 56 has

moderate inhibition activity against oxidoreductase and strong inhibition activity against peroxidase. Compounds 44 and 58 have moderate inhibition activity against oxidoreductase but no data on peroxidase inhibition indicates their role in preventing urolithiasis may be limited to one aspect (Table 4).

Table.4 PASS analysis of better compounds.

S.No.	Compound	Oxidoreductase Inhibitor		Peroxidase Inhibitor	
		Pa	Pi	Pa	Pi
1	1	0.432	0.097	0.888	0.003
2	9	0.566	0.049	0.528	0.035
3	11	0.320	0.148	0.561	0.030
4	15	0.378	0.117	0.628	0.021
5	16	0.558	0.040	0.661	0.016
6	18	0.463	0.087	0.471	0.043
7	25	0.619	0.031	0.725	0.009
8	27	0.678	0.018	0.604	0.024
9	33	0.879	0.003	0.701	0.003
10	35	0.561	0.051	0.720	0.010
11	37	0.884	0.003	0.835	0.002
12	41	0.725	0.012	0.829	0.004
13	42	0.849	0.004	0.746	0.003
14	44	0.718	0.013	-	-
15	52	0.624	0.029	0.578	0.028
16	53	0.624	0.029	0.578	0.028
17	56	0.317	0.150	0.709	0.011
18	57	0.405	0.107	0.432	0.090
19	58	0.718	0.013	-	-
20	59	0.933	0.001	0.414	0.018

7. Conclusion

Urolithiasis, a common and painful disorder marked by the development of kidney stones, presents considerable health and economic concerns worldwide. This study investigated several phytoconstituents for their ability to inhibit important enzymes such as oxidoreductase and peroxidase, which are implicated in oxidative stress and crystal formation in kidney stones. The docking studies indicated that compounds 27, 37, 44, 56, and 58 demonstrated robust binding affinities to the target protein, characterized by advantageous interactions including hydrogen bonding and hydrophobic interactions, positioning them as promising candidates for further development. PASS study verified that these compounds can efficiently inhibit both oxidoreductase and peroxidase, with compound 37 exhibiting the greatest inhibitory potential. ADMET study further corroborated the suitability of these compounds for oral delivery, emphasizing compound 27 for its superior solubility and gastrointestinal absorption. Compounds such as compound 37 and compound 44 necessitate changes to enhance bioavailability owing to their lipophilicity and solubility challenges. The findings highlight the promise of these phytoconstituents as lead molecules for developing safer and more effective therapies for urolithiasis, necessitating further research to enhance their pharmacokinetic profiles and therapeutic efficiency.

Declarations

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Data availability All data generated or analyzed during this study are included in this article.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

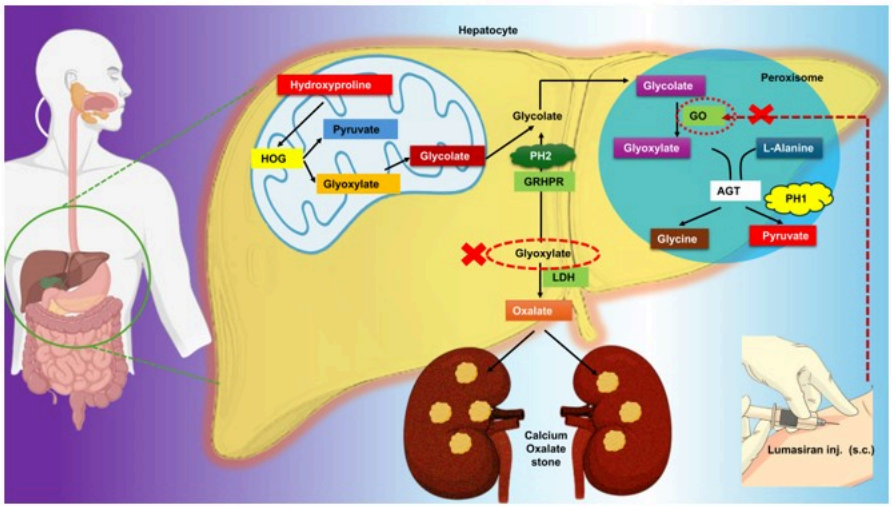

Figure 1

Pathophysiology and Role of Lumasiran in Urolithiasis

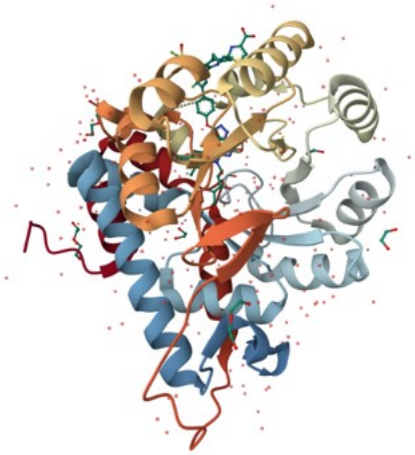

Figure 2

3D structure of protein (PDB Id -7M2O)

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