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Research Article

In-silico Characterization of the Phytochemicals of *Phyllanthus Niruri* Against Nephrolithiasis

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Abstract

Nephrolithiasis, which is also known as kidney stone disease, is a regular urological disorder that came with the formation of crystalline deposits within the renal system. It is very significant that the regular and convention procedures for the prevention and treatment of kidney stone diseases including lithotripsy and pharmacotherapy have limitations ranging from recurrence, expensive and great adverse effects, which necessitate the search for safer and highly effective alternatives in phytochemicals with proven biological activities. *Phyllanthus niruri* is locally and traditionally recognized and active for its antiurolithiatic and nephroprotective effects, with its various diverse bioactive constituents such as flavonoids, alkaloids, tannins, and phenolic compounds. In this work we employed molecular docking and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analyses to screen phytochemicals generated from *Phyllanthus niruri* as potential inhibitors of nephrolithiasis associated proteins. 64 phytochemicals were retrieved from literature and was used to perform docking against the 7KLL protein target using AutoDock and AutoDock Vina integrated in PyRx. Binding affinities, inhibition constants as well as protein-ligands interactions were analyzed using Biovia Discovery Studio and PyMOL. ADMET predictions were performed using online softweb Admetsar2 to assess pharmacokinetic and safety profiles. Amariin (−8.8 kcal/mol), Ellagitannin (8.5 kcal/mol), Miquelianin (-8.6 kcal/mol) Nirurin (-8.5 kcal/mol), Quercetin 3-0-beta-D-glucuronopyranoside (-8.6 kcal/mol) demonstrated strong binding affinities comparable to or higher than standard drugs allopurinol (−5.9 kcal/mol), levofloxacin (−.6.7 kcal/mol), and nifedipine (−5. kcal/mol). used for comparison. The ADMET evaluation shown that the top ligands possess favorable drug-likeness, oral bioavailability, and non-toxicity. The results suggest that *Phyllanthus niruri* phytochemicals possess promising inhibitory potential against nephrolithiasis targets and may serve as leads for the development of safe, plant-based therapeutics.

Keywords

Phyllanthus Niruri, Nephrolithiasis, Molecular Docking, ADMET Analysis, Phytochemicals, Autodock Vina

1. Introduction

Nephrolithiasis, which is also known as kidney stone disease is a regular metabolical and urological disorder that came with the formation of crystalline deposits of insoluble salts, majorly calcium oxalate within the renal system. Over recent

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decades, kidney stone disease has been increased significantly globally with an estimated lifetime risk of 10–12% in men and 7–9% in women [1]. The disease causes considerable economic and healthcare burdens, most especially in the regions with very hot climates and inadequate access to medical facilities that can aid the prevention and treatment. Patho-physiologically, the formation of stone develops from the supersaturation of urinary tract with crystalline insoluble substances such as uric acid, calcium, oxalate and phosphate usually aggravated by metabolic disorders, dehydration as well as dietary factors [2].

The existing management procedures not excluding pharmacological interventions like thiazide diuretics, allopurinol, and citrate therapy as well as minimally invasive surgical techniques like extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy [3] With all their efficacy and potentiality towards inhibiting the disease, they are frequently resulted to high recurrence rates, postoperative pain, infection risks, and drugs induced toxicity [4] Consequent on the aforementioned there is need to explore the natural bioactive compounds as alternative or adjunct therapeutic agent to diminish the existence of this disease and it has gained enormous and increasing attention.

Phyllanthus niruri (Figure 1) belong to the family of Phyllanthaceae and it is commonly referred to as "stone breaker" or "chanca piedra," has been reported that it is widely employed in traditional medicine systems in some area of the world such as Ayurveda and Chinese medicine for exhibiting hepatoprotective, antiviral, and nephroprotective properties [6,]. Studies on the Phytochemicals that are made up of the Phyllanthus niruri have revealed the presence of flavonoids, lignans, tannins, and alkaloids which possess diverse pharmacological activities including antioxidant, anti-inflammatory, and antiurolithiatic effects [5].

Figure 1. *The Phillanthus niruri (extracted from [6]).*

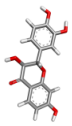
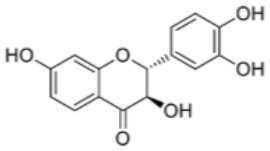
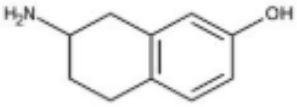
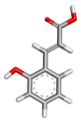
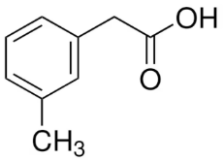
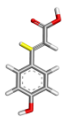
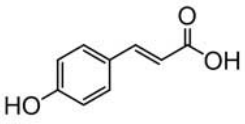
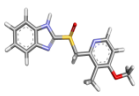
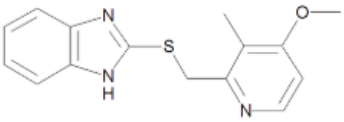
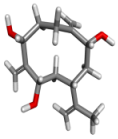
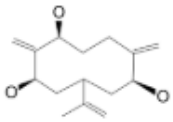
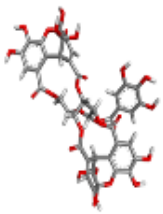
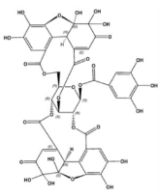
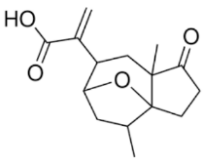
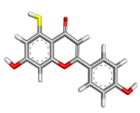
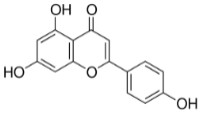
Computational chemistry has made it easier and possible to screen and predict bioactive compounds with high precision through in-silico methods such as molecular docking and ADMET analysis etc [7] These tools enable us to identify the potential inhibitors through modeling interactions between ligands and target proteins while also predicting pharmacokinetic properties through the available computational tools. This study, therefore, aims to investigate the molecular dockings and pharmacokinetic potential of phytochemicals derived from Phyllanthus niruri against nephrolithiasis-associated targets.

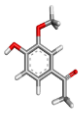
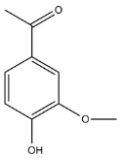
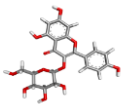
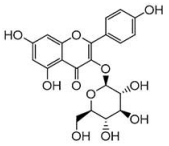
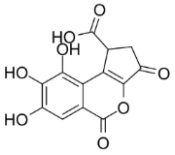
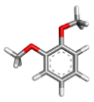
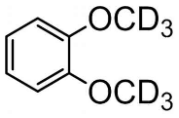
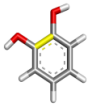
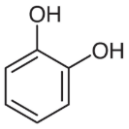
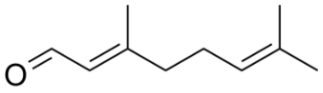
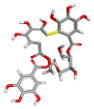
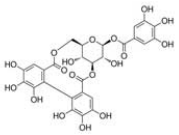
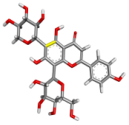
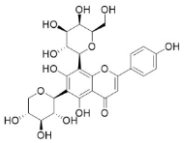
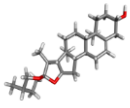
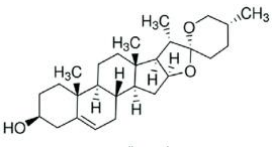
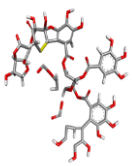
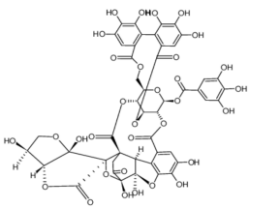
2. Materials and Methods

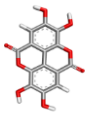
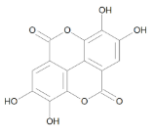
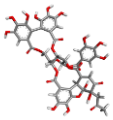
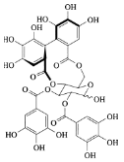
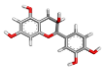
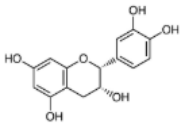
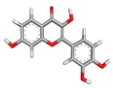
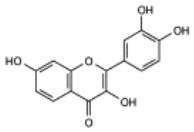
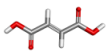
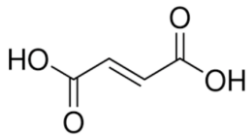
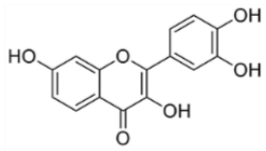
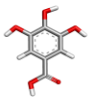
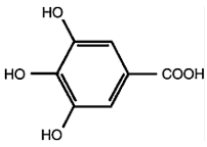
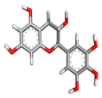
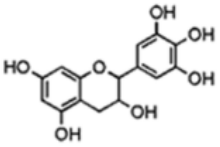
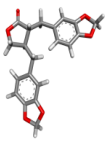
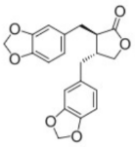
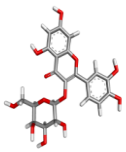
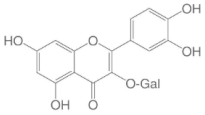
2.1. Ligand Preparation

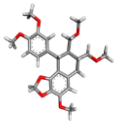
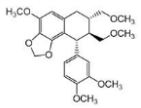
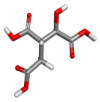
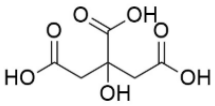
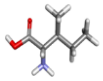
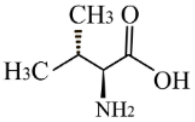
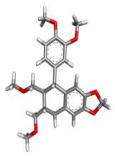
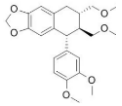
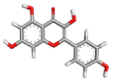
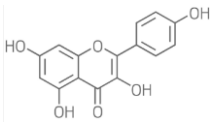
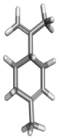
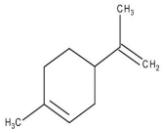
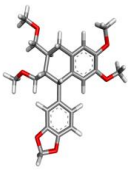
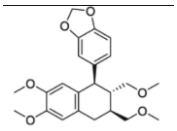
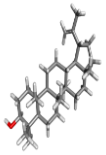
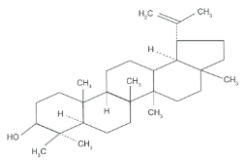
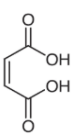
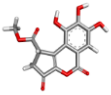
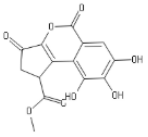
A total of sixty-four phytochemicals (Table 1) previously reported in Phyllanthus niruri were selected from literature databases alongside some standard pharmaceutical drugs used for the treatment of nephrolithiasis. The 3D structures of all ligands were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov) [8] in SDF format and converted to PDB using the SMILES Online Translator (https://cactus.nci.nih.gov/translate/). Energy minimization was performed to obtain the most stable conformers. The phytochemicals identified and examined include (-)-Fustin, (S)-2-Amino-7-Hydroxytetralin, 2-Hydroxycinnamic acid, 4-Coumaric acid, 4-Desmethoxypropoxyl-4-methoxy Rabeprazole, Ageratriol, Amariin, Ambrosic acid, Apigenin, Apocynin, Astragalin, Brevifolincarboxylic acid, Catechol Dimethylether-d6, Catechol, Citral, Corilagin, Corymboside, Diosgenin, Elaeocarpusin, Ellagic acid, Ellagitannin, Epicatechin, Fisetin, Fumaric acid, Fustin, Gallic acid, Gallocatechin, Hinokinin, Hyperoside, Hypophyllanthin, Isocitric acid, Isoleucine, Isolintetralin, Kaempferol, Limonene, Lintetralin, Lupeol, Maleic acid, Methyl brevifolincarboxylate, Miquelianin, Myricitrin, Niranthin, Nirphyllin, Nirtetralin, Nirurin, Norsecurinine, Orientin, P-Cymene, Phyllanthin, Phyllnirurin, Phyllochrysine, Phyltetralin, Protocatechuic acid, Pyrogallol, Quercetin, Quercetin-3-O-beta-D-glucuronopyranoside, Quercetol, Quercitrin, Repandusinic acid A, Repandusinic acid B, Rutin, Trifolin, Urinatetralin and Vitexin and three standard drugs Allopurinol, Levofloxacin and Nifedipine were employed for comparison in this study. Each of these compounds was evaluated based on its molecular weight, molecular formula, 2D structure, and molecular structure to assess their potential efficacy in treating nephrolithiasis.

Table 1. *Shows the Identified compounds in PHYLLANTHUS NIRURI and three pharmaceutical drugs used to cure NEPHROLITHIASIS with their respective molecular weight, 2D structure and molecular structure.*

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular For-mular	3D Structure	Molecular Structure
L1	(-)-Fustin (12310641)	288.25	$C_{15}H_{12}O_6$		
L2	(S)-2-Amino-7-Hy-droxytetralin (14750918)	163.22	$C_{10}H_{13}NO$		
L3	2-Hydroxycinnamic acid (637540)	164.16	$C_9H_8O_3$		
L4	4-Coumaric acid (637542)	164.16	$C_9H_8O_3$		
L5	4-Desmethoxypro-poxyl-4-methoxy Rabeprazole (11558510)	301.4	$C_{15}H_{15}N_3O_2S$		
L6	Ageratriol (181557)	252.35	$C_{15}H_{24}O_3$		
L7	Amariin (5482103)	968.6	$C_{41}H_{28}O_{28}$		
L8	Ambrosic acid (75368818)	264.32	$C_{15}H_{20}O_4$		
L9	Apigenin (5280443)	270.24	$C_{15}H_{10}O_5$		

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular For-mular	3D Structure	Molecular Structure
L10	Apocynin (2214)	166.17	$C_9H_{10}O_3$		
L11	Astragalin (5282102)	448.4	$C_{21}H_{20}O_{11}$		
L12	Brevifolincarboxylic acid (9838995)	292.2	$C_{13}H_8O_8$		
L13	Catechol Di-methylether-d6 (12209214)	144.2	$C_8H_{10}O_2$		
L14	Catechol (289)	110.11	$C_6H_6O_2$		
L15	Citral (638011)	152.23	$C_{10}H_{16}O$		
L16	Corilagin (73568)	634.5	$C_{27}H_{22}O_{18}$		
L17	Corymboside (13644660)	564.5	$C_{26}H_{28}O_{14}$		
L18	Diosgenin (99474)	414.6	$C_{27}H_{42}O_3$		
L19	Elaeocarpusin (3086477)	1110.8	$C_{47}H_{34}O_{32}$		

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular For-mular	3D Structure	Molecular Structure
L20	Ellagic acid (5281855)	302.18	$C_{14}H_6O_8$		
L21	Ellagitannin (10033935	992.7	$C_{44}H_{32}O_{27}$		
L22	Epicatechin (72276)	290.27	$C_{15}H_{14}O_6$		
L23	Fisetin (5281614)	286.24	$C_{15}H_{10}O_6$		
L24	Fumaric acid (444972)	116.07	$C_4H_4O_4$		
L25	Fustin (5317435)	288.25	$C_{15}H_{12}O_6$		
L26	Gallic acid (370)	170.12	$C_7H_6O_5$		
L27	Gallocatechin (65084)	306.27	$C_{15}H_{14}O_7$		
L28	Hinokinin (442879)	354.4	$C_{20}H_{18}O_6$		
L29	Hyperoside (5281643)	464.4	$C_{21}H_{20}O_{12}$		

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular For-mular	3D Structure	Molecular Structure
L30	Hypophyllanthin (182140)	430.5	$C_{24}H_{30}O_7$		
L31	Isocitric acid (1198)	192.12	$C_6H_8O_7$		
L32	Isoleucine (6306)	131.17	$C_6H_{13}NO_2$		
L33	Isolintetralin (101241675)	400.5	$C_{23}H_{28}O_6$		
L34	Kaempferol (5280863)	286.24	$C_{15}H_{10}O_6$		
L35	Limonene (2231)	136.23	$C_{10}H_{16}$		
L36	Lintetralin (11361584)	400.5	$C_{23}H_{28}O_6$		
L37	Lupeol (259846)	426.7	$C_{30}H_{50}O$		
L38	Maleic acid (444266)	116.07	$C_4H_4O_4$		
L39	Methyl brevifolin-carboxylate (5319518)	306.22	$C_{14}H_{10}O_8$		

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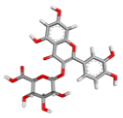
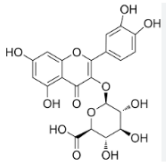
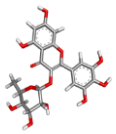
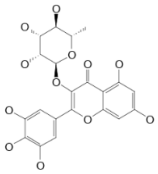
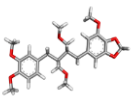
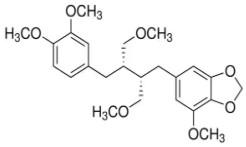
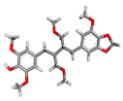
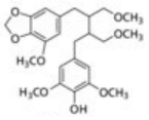
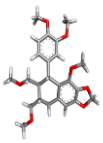
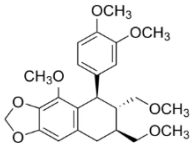
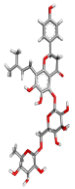
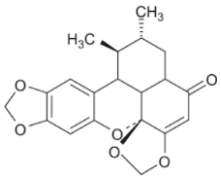
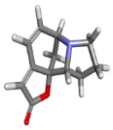
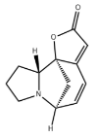
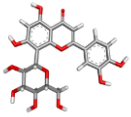
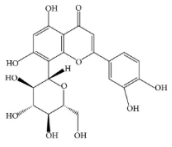
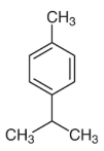
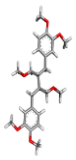
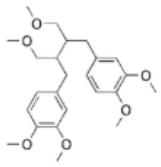
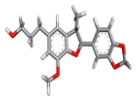
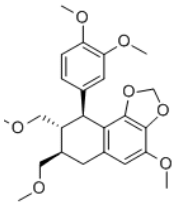
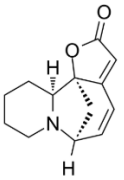
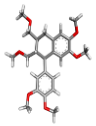
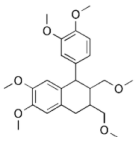
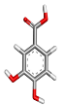
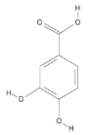
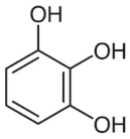
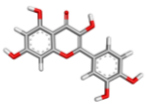
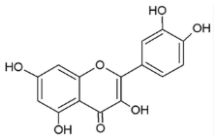
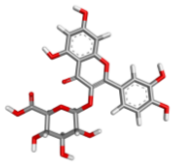
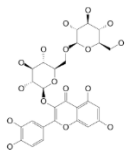
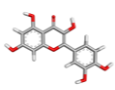
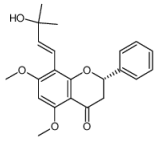
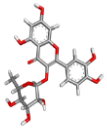
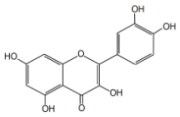
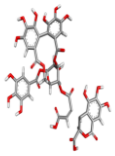
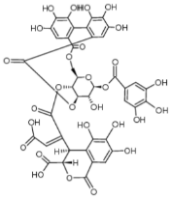
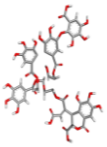
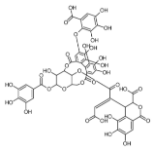
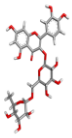
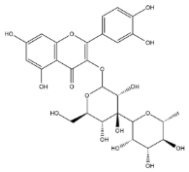
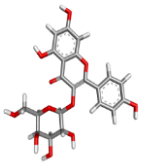
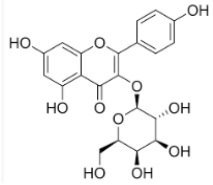
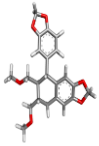
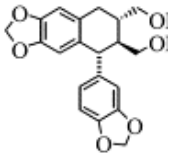
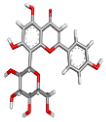
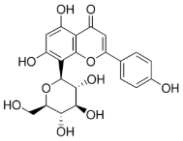
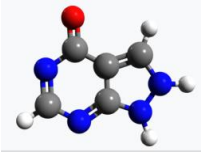
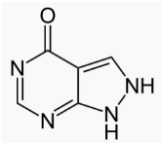
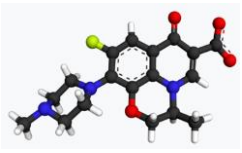
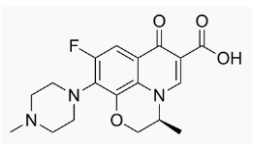
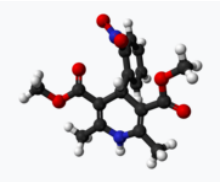
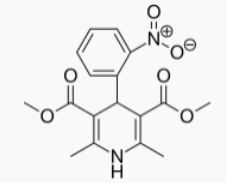
L40	Miquelianin (5274585)	478.4	$C_{21}H_{18}O_{13}$		
L41	Myricitrin (5281673)	464.4	$C_{21}H_{20}O_{12}$		
L42	Niranthin (13989915)	432.5	$C_{24}H_{32}O_7$		
L43	Nirphyllin (5491556)	448.5	$C_{24}H_{32}O_8$		
L44	Nirtetralin (182644)	430.5	$C_{24}H_{30}O_7$		
L45	Nirurin (125896)	664.6	$C_{32}H_{40}O_{15}$		
L46	Norsecurinine (11106439)	203.24	$C_{12}H_{13}NO_2$		
L47	Orientin (5281675)	448.4	$C_{21}H_{20}O_{11}$		
L48	P-Cymene (7463)	134.22	$C_{10}H_{14}$		

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular Formular	3D Structure	Molecular Structure
L49	Phyllanthin (358901)	418.5	$C_{24}H_{34}O_6$		
L50	Phyllnirurin (179963)	342.4	$C_{20}H_{22}O_5$		
L51	Phyllochrysine (267769)	217.26	$C_{13}H_{15}NO_2$		
L52	Phyltetralin (11223782)	416.5	$C_{24}H_{32}O_6$		
L53	Protocatechuic acid (72)	154.12	$C_7H_6O_4$		
L54	Pyrogallol (1057)	126.11	$C_6H_6O_3$		
L55	Quercetin (5280343)	302.23	$C_{15}H_{10}O_7$		
L56	Quercetin-3-O-beta-D-glucuronopyranoside (5274585)	478.4	$C_{21}H_{18}O_{13}$		
L57	Quercetol (5280343)	302.23	$C_{15}H_{10}O_7$		

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular For-mular	3D Structure	Molecular Structure
L58	Quercitrin (5280459)	448.4	$C_{21}H_{20}O_{11}$		
L59	Repandusinic acid A (147900)	970.7	$C_{41}H_{30}O_{28}$		
L60	Repandusinic acid B (16131091)	1138.8	$C_{48}H_{34}O_{33}$		
L61	Rutin (5280805)	610.5	$C_{27}H_{30}O_{16}$		
L62	Trifolin (5282149)	448.4	$C_{21}H_{20}O_{11}$		
L63	Urinatetralin (11760779)	384.4	$C_{22}H_{24}O_6$		
L64	Vitexin (5280441)	432.4	$C_{21}H_{20}O_{10}$		
L65	Allopurinol (135401907)	136.11	$C_5H_4N_4O$		
L66	Levofloxacin (149096)	361.4	$C_{18}H_{20}FN_3O_4$		

S/N	Ligands/ Pubchem Cid	Molecular Weight (G/Mol)	Molecular Formular	3D Structure	Molecular Structure
L67	Nifedipine (4485)	346.3	$C_{17}H_{18}N_2O_6$		

2.2. Target Protein Selection

We obtained the crystal structure of the nephrolithiasis associated receptor (PDB ID: 7KLL) (Figure 2) [9] from the Protein Data Bank (https://www.rcsb.org) [10, 11]. It was subjected to thorough cleaning and treatment by removing all water molecules, ligand and heteroatoms using Biovia Discovery Studio 4.5 to make the receptor ready and suitable for docking. The active site of the receptor was clearly defined based on the literature reported binding residues.

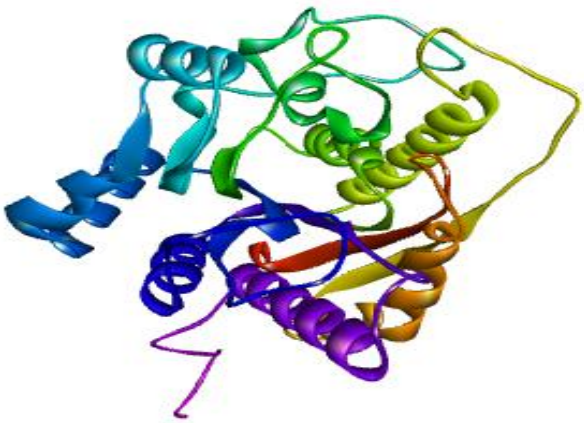


Figure 2. *Crystal structure of the nephrolithiasis receptor (PDB ID: 7KLL).*

2.3. Docking Simulation

Molecular docking simulations is an essential tool in computational chemistry for exploring ligand-receptor interactions in computer aided drug discovery, using specialized software tools, softwebs, and protocols to predict binding affinities and optimize molecular interactions. In this study, the molecular docking was carried out using the AutoDock and AutoDock Vina integrated inside the PyRx virtual screening platform [12] The grid box dimensions were set to 86.3271 × 97.6678 × 89.3663 Å in the X, Y, and Z axes while the grid center coordinates set to 9.1266, −2.2417, and 9.1787 Å. The exhaustiveness parameter was maintained at the default value of 8 to maintain speed and accuracy. Binding affinities were recorded in kcal/mol, the inhibition constant was calculated, and the docked complexes were visualized using PyMOL and Biovia Discovery Studio to identify hydrogen bonds, hydrophobic interactions, and π-π stacking.

2.4. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Prediction

The top-ranking ligands were subjected to ADMET property prediction using SwissADME (http://www.swissadme.ch) and AdmetSar2, Key pharmacokinetic parameters; absorption (GIT permeability, P-gp substrate), distribution (BBB permeability, plasma protein binding), metabolism (CYP450 inhibition), excretion, and toxicity (hepatotoxicity, carcinogenicity, AMES mutagenicity) were evaluated and identified. Drug-likeness was assessed according to Lipinski's rule of five criteria.

2.5. Data

Docking scores were analyzed to determine ligand–protein affinities, with more negative binding energy values indicating stronger binding. Compounds were ranked and compared to standard drugs. ADMET parameters were used to identify the most promising candidates with optimal bioavailability and safety profiles.

3. Results

3.1. Molecular Docking Analysis

Molecular docking was conducted to predict the binding affinities and interaction profiles of 64 phytochemicals from Phyllanthus niruri against the nephrolithiasis-associated protein target (PDB ID: 7KLL). The docking results, Table 2 revealed that several compounds exhibited strong binding energies, suggesting favorable interactions within the active site of the receptor. Among the phytochemicals, Amariin (−8.8 kcal/mol), Ellagitannin (8.5 kcal/mol), Miquelianin (-8.6

kcal/mol) Nirurin (-8.5 kcal/mol), Quercetin 3-0-beta-D-glucuronopyranoside (-8.6 kcal/mol) demonstrated the lowest (most favorable) binding energies, outperforming standard drugs such as allopurinol (−5.9 kcal/mol), levofloxacin (−.6.7 kcal/mol), and nifedipine (−5.0 kcal/mol).

Table 2. *Shows the ligands, their binding affinity values and their respective Inhibition Constant.*

S/N	LIGANDS	BINDING AFFINITY (Kcal/Mol)	Inhibition Constant K_I (µM)
1	(-)-Fustin	-7	7.43
2	(S)-2-Amino-7-Hydroxytetralin	-6.1	33.92
3	2-Hydroxycinnamic acid	-6.9	8.80
4	4-Coumaric acid	-6.2	28.65
5	4-Desmethoxypropoxyl-4-methoxy Rabeprazole	-6.2	28.65
6	Ageratriol	-6.3	24.20
7	Amariin	-8.8	0.36
8	Ambrosic acid	-6.4	20.45
9	Apigenin	-7.9	1.63
10	Apocynin	-5.8	56.27
11	Astragalin	-7.8	1.93
12	Brevifolincarboxylic acid	-7.5	3.20
13	Catechol Dimethylether-d6	-4.9	256.86
14	Catechol	-4.8	304.07
15	Citral	-5.1	183.30
16	Corilagin	-7.9	1.63
17	Corymboside	-7.7	2.28
18	Diosgenin	-7.6	2.70
19	Elaeocarpusin	-7.3	4.48
20	Ellagic acid	-7.7	2.28
21	Ellagitannin	-8.5	0.59
22	Epicatechin	-7.4	3.78
23	Fisetin	-7.2	5.30
24	Fumaric acid	-5.3	130.80
25	Fustin	-7	7.43
26	Gallic acid	-6.8	10.41
27	Gallocatechin	-7.2	5.30
28	Hinokinin	-6.3	24.20
29	Hyperoside	-7.6	2.70
30	Hypophyllanthin	-5.8	56.27
31	Isocitric acid	-6	40.15
32	Isoleucine	-4.8	304.07
33	Isolintetralin	-5.9	47.53
34	Kaempferol	-7.6	2.70

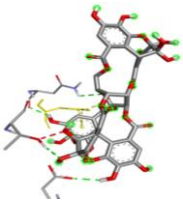
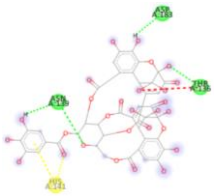
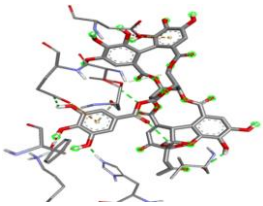
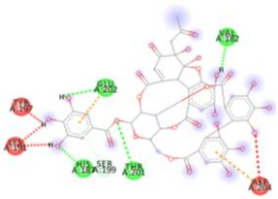
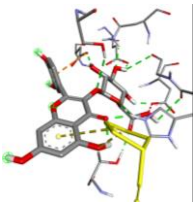
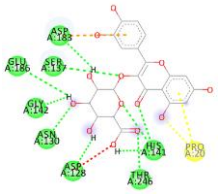
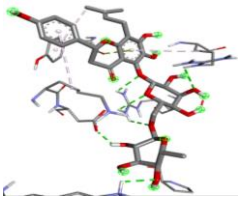
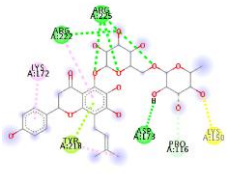
S/N	LIGANDS	BINDING AFFINITY (Kcal/Mol)	Inhibition Constant K_I (μM)
35	Limonene	-5.5	93.34
36	Lintetralin	-6.4	20.45
37	Lupeol	-8.1	1.16
38	Maleic acid	-5.1	183.30
39	Methyl brevifolincarboxylate	-7.4	3.78
40	Miquelianin	-8.6	0.50
41	Myricitrin	-7.6	2.70
42	Niranthin	-4.7	359.95
43	Nirphyllin	-6	40.15
44	Nirtetralin	-5.9	47.53
45	Nirurin	-8.5	0.59
46	Norsecurinine	-7.1	6.28
47	Orientin	-7.6	2.70
48	P-Cymene	-5.7	66.61
49	Phyllanthin	-5.2	154.84
50	Phyllnirurin	-6.9	8.80
51	Phyllochrysine	-7.2	5.30
52	Phyltetralin	-6	40.15
53	Protocatechuic acid	-6.4	20.45
54	Pyrogallol	-5.2	154.84
55	Quercetin	-7.5	3.20
56	Quercetin-3-O-beta-D-glucuronopyranoside	-8.6	0.50
57	Quercetol	7.5	3.20
58	Quercitrin	-8.1	1.16
59	Repandusinic acid A	-7.5	3.20
60	Repandusinic acid B	-7.8	1.93
61	Rutin	-7.9	1.63
62	Trifolin	-7.2	5.30
63	Urinatetralin	-6.7	12.33
64	Vitexin	-7.6	2.70
65	Allopurinol	-5.9	47.53
66	Levofloxacin	-6.7	12.33
67	Nefedipine	-5.9	47.53

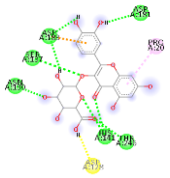
The top ligands were stabilized through multiple hydrogen bonds, π–π stacking, and hydrophobic interactions with key active site residues of the 7KLL protein Table 3. For example, Amariin and Miquelianin formed hydrogen bonds with residues ASP 183 and HIS 141, which are critical for ligand anchorage and enzyme inhibition. Visualization in Biovia Discovery Studio confirmed well-defined hydrogen bond networks and aromatic stacking interactions, Table 4 that contribute to enhanced binding stability.

Table 3. *The docking scores, inhibition constant and amino acids residues of Interaction between the selected Phytochemicals and standard drug against 7KLL based on their binding affinity and inhibition constant compare to the standard drug.*

Ligands	Name	Binding Affinity ΔG (kcal/mol)	Inhibition constant K1 (μM)	Residue involved in the interaction
L7	Amariin	-8.8	0.36	ASP: 183, ASN: 139, THR: 136, HIS: 141
L21	Ellagitannin	-8.5	0.59	VAL: 182, GLU: 202, TYR: 197, LYS: 191, HIS: 187, SER: 199, THR: 201, ASP: 204
L40	Miquelianin	-8.6	0.50	ASP: 183, GLU: 186, SER: 137, GLY: 142, ASN: 130, ASP: 128, THR: 246, HIS: 141, PRO: 20
L45	Nirurin	-8.5	0.59	ARG: 222, ARG: 225, LYS: 172, TYR: 218, ASP: 173, PRO: 116, LYS: 150
L56	Quercetin 3-0-beta-D-glucuronopyranoside	-8.6	0.50	ASP: 181, ASP: 183, PRO: 20, SER: 137, ASN: 130, HIS: 141, THR: 246, ASP: 128
L65	Allopurinol (standard drug)	-5.9	47.53	GLU: 186, ASP: 183, ASP: 128
L66	Levofloxacin (standard drug)	-6.7	12.33	PRO: 20, ASN: 139, HIS: 141, SER: 137
L67	Nefedipine (standard drug)	-5.9	47.53	LYS: 17, SER: 16, PHE: 15, GLU: 25, PHE: 55

Table 4. *3D and 2D of bonded and non-bonded interaction with the receptors and ligand.*

Receptor + Ligand	3D STRUCTURE	2D STRUCTURE
7KLL + L7		
7KLL + L21		
7KLL + L40		
7KLL + L45		

Receptor + Ligand	3D STRUCTURE	2D STRUCTURE
7KLL + L56		

These findings indicate that the phytochemicals possess structural and functional complementarity to the nephrolithiasis-associated target, implying potential inhibitory activity relevant to the prevention or dissolution of kidney stones.

3.2. Admet Analysis and Pharmacokinetics

ADMET analysis of the top 5 ligands was conducted using SwissADME [13] and AdmeSar2 [14] to predict their pharmacokinetic properties. The results, Table 5 showed that compounds such as Amariin,, Ellagitannin, Miquelianin, Nirurin, Quercetin-3-O-beta-D-glucuronopyranoside complied with Lipinski's Rule of Five, indicating good oral bioavailability. All the top ligands demonstrated high gastrointestinal (GIT) absorption, non-inhibition of CYP2D6 and CYP3A4 enzymes, and non-hepatotoxic properties. None of the compounds exhibited AMES mutagenicity or carcinogenic potential. Furthermore, the compounds showed moderate plasma protein binding and low blood-brain barrier (BBB) permeability, which are desirable for drugs targeting renal tissues.

Table 5. *Shows the ligands and their drug-like parameters.*

Ligands	Compound	Molecular weight (g/mol)	Hydrogen Bond acceptor (HBA)	Hydrogen bond donor (HBD)	Log P	Rule of five violation	Heavy atom
L1	(-)-Fustin	288.25	6	4	-0.10	0	21
L2	(S)-2-Amino-7-Hydroxytetralin	163.22	2	2	1.21	0	12
L3	2-Hydroxycinnamic acid	164.16	3	2	1.22	0	12
L4	4-Coumaric acid	164.16	3	2	0.96	0	12
L5	4-Desmethoxypropoxyl-4-methoxy Rabeprazole	301.4	4	1	0.96	0	21
L6	Ageratriol	252.35	3	3	1.24	0	18
L7	Amariin	968.6	28	13	-1.67	3	69
L8	Ambrosic acid	264.32	4	1	1.51	0	19
L9	Apigenin	270.24	5	3	0.52	0	20
L10	Apocynin	166.17	3	1	0.51	0	12
L11	Astragalin	448.4	11	7	-0.09	2	32
L12	Brevifolincarboxylic acid	292.2	8	4	-0.11	0	21
L13	Catechol Dimethylether-d6	144.2	2	0	1.48	0	10
L14	Catechol	110.11	2	2	0.79	0	8
L15	Citral	152.23	1	0	2.49	0	11
L16	Corilagin	634.5	18	11	-0.30	3	45
L17	Corymboside	564.5	14	10	-1.32	3	40

Ligands	Compound	Molecular weight (g/mol)	Hydrogen Bond acceptor (HBA)	Hydrogen bond donor (HBD)	Log P	Rule of five violation	Heavy atom
L18	Diosgenin	414.6	3	1	4.29	1	30
L19	Elaeocarpusin	1110.8	32	15	-2.59	3	79
L20	Ellagic acid	302.18	8	4	0.14	0	22
L21	Ellagitannin	992.7	27	13	-0.07	3	71
L22	Epicatechin	290.27	6	5	0.24	0	21
L23	Fisetin	286.24	6	4	-0.03	0	21
L24	Fumaric acid	116.07	4	2	-0.29	0	8
L25	Fustin	288.25	6	4	-0.10	0	21
L26	Gallic acid	170.12	5	4	-0.16	0	12
L27	Gallocatechin	306.27	7	6	-0.29	1	22
L28	Hinokinin	354.4	6	0	2.71	0	26
L29	Hyperoside	464.4	12	8	-0.38	2	33
L30	Hypophyllanthin	430.5	7	0	1.91	0	31
L31	Isocitric acid	192.12	7	4	-0.06	0	13
L32	Isoleucine	131.17	3	2	-0.15	0	9
L33	Isolintetralin	400.5	6	0	2.23	0	29
L34	Kaempferol	286.24	6	4	-0.03	0	21
L35	Limonene	136.23	0	0	2.72	0	10
L36	Lintetralin	400.5	6	0	2.23	0	29
L37	Lupeol	426.7	1	1	4.72	1	31
L38	Maleic acid	116.07	4	2	-0.29	0	8
L39	Methyl brevifolincarbox-ylate	306.22	8	3	-0.09	0	22
L40	Miquelianin	478.4	13	8	-0.45	2	34
L41	Myricitrin	464.4	12	8	-0.07	2	33
L42	Niranthin	432.5	7	0	1.91	0	31
L43	Nirphyllin	448.5	8	1	1.39	0	32
L44	Nirtetralin	430.5	7	0	1.91	0	31
L45	Nirurin	664.6	15	9	-0.04	3	47
L46	Norsecurinine	203.24	3	0	0.63	0	15
L47	Orientin	448.4	11	8	-0.14	2	32
L48	P-Cymene	134.22	0	0	2.51	1	10
L49	Phyllanthin	418.5	6	0	2.43	0	30
L50	Phyllnirurin	342.4	5	1	2.38	0	25
L51	Phyllochrysine	217.26	3	0	1.02	0	16
L52	Phyltetralin	416.5	6	0	2.03	0	30
L53	Protocatechuic acid	154.12	4	3	0.26	0	11
L54	Pyrogallol	126.11	3	3	0.18	0	9

Ligands	Compound	Molecular weight (g/mol)	Hydrogen Bond acceptor (HBA)	Hydrogen bond donor (HBD)	Log P	Rule of five violation	Heavy atom
L55	Quercetin	302.23	7	5	-0.56	0	22
L56	Quercetin-3-O-beta-D-glucuronopyranoside	478.4	13	8	-0.45	2	34
L57	Quercetol	302.23	7	5	-0.56	0	22
L58	Quercitrin	448.4	11	7	-1.84	2	32
L59	Repandusinic acid A	970.7	28	15	-0.21	3	69
L60	Repandusinic acid B	1138.8	33	18	-1.39	3	81
L61	Rutin	610.5	16	10	-0.33	3	43
L62	Trifolin	448.4	11	7	-0.06	2	32
L63	Urinatetralin	384.4	6	0	2.42	0	28
L64	Vitexin	432.4	10	7	-0.02	1	31
L65	Allopurinol	136.11	3	2	-0.35	0	10
L66	Levofloxacin	361.4	6	1	-0.39	0	26
L67	Nifedipine	346.3	6	1	0.52	0	25

Amariin, Ellagitannin and Miquelianin demonstrated superior pharmacokinetic behavior, exhibiting optimal solubility and permeability profiles, while phyllanthin displayed higher lipophilicity (LogP 3.9), suggesting effective membrane permeability. Collectively, the ADMET results, Table 6 confirmed the suitability of these compounds as drug-like candidates with minimal predicted toxicity and acceptable absorption and metabolism parameters.

Table 6. *ADME analysis and Pharmacokinetics of the derivatives.*

Parameter	Amariin	Ellagitannin	Miquelianin	Nirurin	Quercetin-3-O-beta-D-glucuronopyranoside
Molecular Weight (g/mol)	968.64	992.71	478.36	664.65	478.36
LogP (Lipophilicity)	-1.67	-0.07	-0.45	-0.04	-0.45
Hydrogen Bond Donors (HBD)	13	13	8	9	8
Hydrogen Bond Acceptors (HBA)	28	27	13	15	13
Topological Polar Surface Area (TPSA) (Å²)	456.32	447.09	227.58	245.29	227.58
Number of Rotatable Bonds	3	5	4	8	4
Lipinski's Rule of Five Violations	3	3	2	3	2
Veber's Rule Compliance (Yes/No)	No	No	No	No	No
Gastrointestinal (GI) Absorption (High/Low)	Low	Low	Low	Low	Low
Blood-Brain Barrier (BBB)	No	No	No	No	No

Parameter	Amariin	Ellagitannin	Miquelianin	Nirurin	Quercetin-3-O-beta-D-glucuronopyranoside
Permeability (Yes/No)					
P-glycoprotein (P-gp) Substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes
CYP450 Enzyme Inhibition	CYP3A4, CYP1A2	CYP3A4, CYP1A2	CYP3A4	CYP3A4, CYP2D6	CYP3A4
Bioavailability Score	0.17	0.17	0.11	0.17	0.11
Water Solubility (Good/Poor)	Good	Poor	Good	Good	Good
LogS (Solubility Index)	-3.24	-5.95	-3.09	-3.11	-3.09
Human Intestinal Absorption (HIA) (%)	18%	22%	35%	27%	38%
Renal Clearance (Yes/No)	No	No	Yes	No	Yes
Hepatotoxicity	Inactive (0.98)	Inactive (0.75)	Inactive (0.75)	Inactive (0.98)	Inactive
Mutagenicity	Inactive (0.82)	Inactive (0.60)	Inactive (0.68)	Inactive (0.82)	Inactive (0.82)
Respiratory Toxicity	Inactive (0.99)	Active (0.71)	Active (0.83)	Inactive (0.77)	Inactive
Cardiotoxicity	Inactive (0.91)	Inactive (0.57)	Inactive (0.61)	Inactive (0.91)	Inactive
Immunotoxicity	Inactive (0.99)	Active (0.97)	Active (0.58)	Inactive (0.99)	Inactive (0.99)

4. Discussion

The integration of in-silico docking and ADMET evaluation in this study provided mechanistic insights into the potential antiurolithiatic properties of Phyllanthus niruri phytochemicals. The strong binding affinities exhibited by Amarin, Ellagitannin, and Miquelianin suggest their ability to interact effectively with the nephrolithiasis-related protein (7KLL). These interactions are likely to inhibit crystal formation or aggregation processes that underline renal stone development. Ellagitannin, a hydrolyzable tannin, has been reported in earlier studies to exhibit significant antioxidant and calcium oxalate crystal inhibitory activity [15]. Its multiple hydroxyl groups contribute to strong hydrogen bonding and chelating capacity, which may underlie its binding to active site residues of 7KLL. Similarly, Amarin and Miquelianin possess polyphenolic structures capable of modulating oxidative stress pathways and preventing lipid peroxidation, both implicated in nephrolithiasis progression [16]. The observed binding energies of the phytochemicals surpass those of standard drugs such as allopurinol, indicating that natural compounds could serve as competitive or adjunct inhibitors with lower toxicity risk. Furthermore, ADMET profiling confirmed that these phytochemicals possess favorable pharmacokinetic properties and meet key criteria for oral bioavailability and safety, this supports previous findings where *Phyllanthus niruri* extracts demonstrated renal protective, diuretic, and antioxidant activities [13, 17] Collectively, the study reinforces the ethnopharmacological use of *Phyllanthus niruri* as a natural remedy for kidney stones and validates the application of computational screening in identifying plant-derived lead compounds with therapeutic potential. Nevertheless, while molecular docking provides predictive insights, in vitro and in vivo validation remains necessary to establish precise inhibitory mechanisms, bioavailability, and efficacy in biological systems.

5. Conclusions

This study explored the molecular interactions and pharmacokinetic potential of phytochemicals derived from *Phyllanthus niruri* for the prevention and treatment of nephrolithiasis using in silico methods. The docking analysis revealed that compounds such as Amarin, Ellagitannin, Miquelianin, Nirurin, Quercetin-3-O-beta-D-glucuronopyranoside exhibited superior binding affinities compared with standard nephrolithiasis drugs. ADMET evaluations further confirmed their drug-likeness, safety, and favorable absorption and metabolism characteristics. The findings highlight Phyllanthus niruri as a promising natural source of bioactive compounds capable of modulating nephrolithiasis-associated targets. These results provide a foundation for subsequent experimental validation and potential drug development aimed at safer, cost-effective, and plant-based interventions for kidney stone disease.

Abbreviations

ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity

Author Contributions

Adeboye Omolara Olubunmi: Conceptualization, Resources, Supervision, Writing – review & editing

Agboluaje Saheed Alabi: Formal Analysis, Investigation, Methodology, Software, Validation

Salami Leke Peter: Data Curation, Project Administration, Visualization, Writing – original draft

Conflicts of Interest

There are no conflicts of interest.

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