Co-administration of herbal inhibitors of P-glycoprotein with renal drugs enhance their bioavailability – *In silico* approach

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**Abstract**

**Introduction:** Multidrug resistance (MDR) is primarily associated with reduced intracellular drug accumulation owing to overexpression of p-glycoprotein, an active efflux transporter. Competitive inhibition or allosteric modulation of p-glycoprotein may alter the pharmacokinetics of the drugs that serve as substrates, resulting in enhanced drug bioavailability and tissue penetration. This study endeavors to assess the efficacy of the components of reno-protective herbs in the inhibition of p-glycoprotein activity thereby enhancing the possibility of the retention of co-administered renal medications inside the target cells.

**Methods:** Drug-likeness and pharmacokinetic properties were determined to ensure the safety and efficacy of herbal constituents. Molecular docking employing the CDOCKER module of Discovery Studio was performed to investigate the binding affinity between the active constituents and the p-glycoprotein receptor (6C0V). Molecular dynamics simulation was utilized to further assess the stability of the complex of receptors with the component bearing its maximal affinity.

**Results:** The analyses suggested that the inhibitors viz., atisine, kutkin, and embelin from *Aconitum heterophyllum*, phylloquinone from *Calendula officinalis*, stigmasterol from *Paederia foetida*, and convallamarogenin from *Convallaria majalis* demonstrated maximum binding affinity towards p-glycoprotein.

**Conclusion:** Atisine may thus be identified as the lead compound in the augmentation of drug bioavailability inside the cell, along with its reno-protective efficacy.

**Keywords:** Multidrug resistance, Efflux transporter, Biological availability, Herbs, Docking

**Introduction**

Drug efflux transporters such as p-glycoprotein play a major role in the maintenance of cellular homeostasis and are primarily responsible for multidrug resistance (MDR). P-glycoprotein is ubiquitously expressed in the epithelial cells of the small intestine, liver, kidney, and endothelial cells of the blood-brain barrier to expel the toxic compounds but in the process also modulates the pharmacodynamics of the drugs. So, the identification and formulation of p-glycoprotein inhibitors, which when co-administered with such drugs, is a strategy that would enhance drug bioavailability inside the target cells (1).

The beneficial effects of medicinal plants on kidney dysfunction are often attributed to their antioxidant defense mechanisms with additive benefits on inflammation and fibrosis (2). Furthermore, some plants and their active metabolites are known to ameliorate kidney ailments such as interstitial nephritis, altered intraglomerular hemodynamics, and glomerulonephritis (3). These bioactive ingredients have functional scaffolds to revert p-glycoprotein-mediated MDR (4). The majority of renal drugs viz., cyclosporine (5), mycophenolate (6), tacrolimus (7), dapagliflozin (8), and valsartan (9) are substrates of p-glycoprotein and are thus effluxed by the cells.

Materials and Methods

Protein preparation
The 3D crystal structure of p-glycoprotein (PDB code: 6C0V) used for the docking evaluation was downloaded from the protein data bank (http://www.rcsb.org) at a resolution of about 3.4 Å (37). The protein was energetically minimized using the protein preparation wizard of Discovery Studio. This involved the cleaning of protein and optimization of side-chain conformations using the ChiRotor algorithm. The potential binding pockets were detected using Dogsitescorer server (https://proteins.plus/#dogsite).

Ligand preparation
3D structures and canonical smiles of 376 ligand molecules (Table S1) and control drugs doxycycline and elacridar, were obtained for molecular docking from PubChem (https://pubchem.ncbi.nlm.nih.gov/), chEMBL (https://www.ebi.ac.uk/chembl/), and ChemSpider (http://www.chemspider.com/) databases. The canonical SMILES were translated into SDF files employing the online SMILE translator (https://cactus.nci.nih.gov/translate/). The prepare ligands protocol of discovery studio was used to perform tasks such as the removal of duplicates and computing isomers and tautomers.

Drug likeness and ADMET analysis
Druggability of the components were examined with Molinspiration tool (http://www.molinspiration.com). Pharmacokinetic study was performed with the pKCSM tool to examine the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) property of the small molecules (http://biosig.unimelb.edu.au/pkcsm/prediction).

Molecular docking analysis
The receptor-ligand docking evaluation was performed by the CDOCKER module of Discovery Studio (version 2019 onwards) which is based on CHARMM-based docking algorithm. The ligands were flexed with the rigid receptor during the refinement and high-temperature dynamics generated random ligand conformations which were refined by grid-based (GRID1) simulated annealing and forcefield minimization. A set of refined ligand poses for each component was generated and the best pose was selected on the basis of the lowest binding free energy.

The design of the experiment was aimed towards a ligand-based approach, thus allowing the incorporation of all the binding poses for all the ligands used in the study. This maximized the pool of proposed hits which could develop into lead compounds.

Molecular dynamics simulation
The top-scoring conformation identified through docking analyses was used for molecular dynamics (MD) simulation. The ligand-receptor complex was subjected to CHARMM36 force-field and the solvation was performed under Explicit Periodic Boundary conditions. The system was relaxed by two rounds of energy minimization (500 steps of steepest descent and 500 steps of conjugate gradient) with the final RMS gradient of 0.1. The temperature of the system was raised from 50 K to 300 K (heating) for 4ps and equilibration was performed for 10ps. The simulation (production) was executed for 10ps with a time step of 2fs at a constant temperature of 300 K. The electrostatic calculation was set to particle mesh Ewald (PME) and Verlet leapfrog integrator (LEAP) was used to perform numerical integration of the equation of motion. The analyze trajectory protocol was employed to calculate geometric properties such as distance, angle, torsion, and the number of non-bond interactions for each simulation frame. Root mean square fluctuation (RMSF) from the average structure in the trajectory and interaction energy between two sets of atoms were also computed. The stability of the conformation was assessed through binding free energy calculation using Poisson-Boltzmann with non-polar surface area (PBSA) method and radius of gyration (Rg).

Results
A total of 376 components of 27 reno-protective herbs were initially screened on the basis of druggability and ADMET properties. These were then docked against outward facing p-glycoprotein transporter, 6C0V. Considering substrate expulsion from an inward V-shaped transmembrane receptor, the outward-facing conformation is necessary for the study of the more exposed inhibitor-binding and substrate-binding domains. P-glycoprotein uses the energy from ATP hydrolysis to extrude drug substrates out of the cell, locking it in outward V conformation when another ATP hydrolysis reverses it to the unbound inward V conformation.

Drug likeness
Drug likeness result was computed based on Lipinski's
The rule of five (38), which showed that 331 compounds had acceptable drug-like properties indicating a good oral bioavailability (Table 1).

**ADMET prediction**

The ADMET properties were computed using pkCSM revealing that 39 components served as p-glycoprotein inhibitors and their ADMET values were within an acceptable range (Table 2). ADMET features affect oral bioavailability and metabolism of small molecules (39).

**Molecular docking analysis**

To understand the binding interaction of herbal components with p-glycoprotein, molecular docking analysis was conducted using Discovery Studio. The p-glycoprotein inhibitors were sequentially analyzed in order of their best (maximally negative) binding energy viz., atisine, kutkin, phylloquinone, embelin, stigmasterol, convallamarogenin, spinasterol, furostanol, dehydrocostus–lactone, β-sitosterol, amyrin acetate, 4-alpha-Methylcholest-7-en-3beta-ol (4AMC), lanosterol, erythrodil, D-friedoolean-14-en-3-one, 6-acetonyldihydrochelerythrine, lupeol, verazine, protopine, nuciferine, dihydrosanguinarine, cadienol, picrinine, 1H-Indole-2,3-dione, 5-pentyl-1-(trimethylsilyl)-3-(O-methyloxime)(1H-ID), maritinone, 6-acetonyldihydroavicine, azadirone,1,2,4-Cyclopentanetrione,3,3-bis(3-methyl-2-butanyl)-5-(3-methyl-1-oxobutyl) (1,2,4-CPT), β-amyrin, epifriedelinol, taraxerol, lonicresinol, taraxasterol, alschomine, adenanthin, and podophyllotoxin.

The binding energy parameter is one of the most established parameters for evaluating docking complexes, specifically, protein-small molecule complexes. Since the calculation of binding energy is dependent on the interacting partners, it is difficult to predict an optimum threshold value that can be used as a reference standard universally as the interactions vary based on the partners. The established inhibitors of p-glycoprotein have been used and the binding energies obtained in those interactions have been used to construct the reference range to evaluate the efficacy of the other molecules that have been analyzed.

The lowest binding energy of interaction was observed to be with atisine (-100.76 kcal/mol) and kutkin (-90.8 kcal/mol), components present in *A. heterophyllum*, followed by phylloquinone (-83.13 kcal/mol), a component present in *C. officinalis* (Figure 1).

**Table 1. Drug-likeness properties of potential inhibitors**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MW</th>
<th>LogP</th>
<th>nOHNH</th>
<th>nON</th>
<th>nViolations</th>
</tr>
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<tbody>
<tr>
<td>Atisine</td>
<td>343.51</td>
<td>3.67</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Kutkin</td>
<td>460.44</td>
<td>1.07</td>
<td>4</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Phylloquinone</td>
<td>450.71</td>
<td>8.80</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Embelin</td>
<td>294.39</td>
<td>6.62</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Stigmasterol</td>
<td>412.70</td>
<td>7.87</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Convallamarogenin</td>
<td>430.63</td>
<td>5.04</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Spinasterol</td>
<td>412.70</td>
<td>7.87</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Furostanol</td>
<td>402.66</td>
<td>6.96</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dehydrocostus lactone</td>
<td>230.31</td>
<td>2.29</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Beta-sitosterol</td>
<td>414.72</td>
<td>8.62</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

MW: Molecular weight; LogP: Log of octanol/water partition coefficient; nON: Number of hydrogen bond acceptors; nOHNH: Number of hydrogen bond donors; nViolations: Number of rule of five violations.

**Table 2. Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of potential inhibitors**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Water solubility (log mol/L)</th>
<th>CYP P450 2D6 inhibition</th>
<th>Intestinal absorption (% absorbed)</th>
<th>BBB permeability (log BB)</th>
<th>Fraction unbound (Fu)</th>
<th>P-glycoprotein inhibitor</th>
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</thead>
<tbody>
<tr>
<td>Atisine</td>
<td>-3.096</td>
<td>Yes</td>
<td>91.76</td>
<td>-0.102</td>
<td>0.322</td>
<td>Yes</td>
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<tr>
<td>Kutkin</td>
<td>-3.639</td>
<td>No</td>
<td>65.029</td>
<td>-1.323</td>
<td>0.1</td>
<td>Yes</td>
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<tr>
<td>Phylloquinone</td>
<td>-6.911</td>
<td>No</td>
<td>96.834</td>
<td>-0.281</td>
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<td>Embelin</td>
<td>-4.511</td>
<td>Yes</td>
<td>89.155</td>
<td>-0.06</td>
<td>0.232</td>
<td>Yes</td>
</tr>
<tr>
<td>Stigmasterol</td>
<td>-6.682</td>
<td>No</td>
<td>94.97</td>
<td>0.771</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Convallamarogenin</td>
<td>-5.23</td>
<td>No</td>
<td>96.482</td>
<td>-0.227</td>
<td>0.02</td>
<td>Yes</td>
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<tr>
<td>Spinasterol</td>
<td>-6.682</td>
<td>No</td>
<td>94.97</td>
<td>0.771</td>
<td>0</td>
<td>Yes</td>
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<tr>
<td>Furostanol</td>
<td>-5.196</td>
<td>No</td>
<td>98.657</td>
<td>0.721</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Dehydrocostus lactone</td>
<td>-3.846</td>
<td>No</td>
<td>98.917</td>
<td>0.566</td>
<td>0.268</td>
<td>Yes</td>
</tr>
<tr>
<td>Beta-sitosterol</td>
<td>-6.773</td>
<td>No</td>
<td>94.464</td>
<td>0.781</td>
<td>0</td>
<td>Yes</td>
</tr>
</tbody>
</table>

http://www.herbmedpharmacol.com
To assess the selectivity and strength of the receptor-ligand interactions, the hydrogen bonds, and hydrophobic interactions were computed. The analyzed inhibitory components in order of their maximum hydrogen bonded interactions were found to be lyoniresinol, podophyllotoxin, alschomine, atisine, embelin, convallamarogenin, nuciferine, protopine, erythrodiol, picrinine, 6-acetonyldihydroavicine, phylloquinone, 1H-Indole-2,3-dione, 5-pentyl-1-((trimethylsilyl)-3-o-methyloxime)(1H-ID), 1,2,4-cyclopentanetrione, 3,3-bis(3-methyl-2-butenyl)-5-(3-methyl-1-oxobutyl)(1,2,4-CPT), dehydrocostus–lactone, 4alpha-Methylcholesta-8,24-dien-3beta-ol (4AMC), cadienyl, maritinone, verazine, spinasterol, and furostanol. Maximal hydrogen bond interactions observed was four, as found in the case of lyoniresinol from *Toona sinensis*. Atisine, a component present in *A. heterophyllum* displayed two hydrogen bond interactions (Figure 2).

The analyzed inhibitory components in order of their maximum hydrophobic interactions were found to be epifriedelinol, friedelanol, amyrin acetate, β-sitosterol, convallamarogenin, D-friedoolean-14-en-3-one, cadienyl, maritinone, taraxasterol, furostanol, 1,2,4-cyclopentanetrione, 3,3-bis(3-methyl-2-butenyl)-5-(3-methyl-1-oxobutyl)(1,2,4-CPT), erythrodiol, phylloquinone, spinasterol, 4alpha-Methylcholesta-8,24-dien-3beta-ol (4AMC), verazine, picrinine, dihydrosanguinarine, alschomine, dehydrocostus–lactone, protopine, β-amyrin, 6-acetonyldihydrochelerythrine, azadirone, atisine, kutkin, 1H-indole-2,3-dione, 5-pentyl-1-((trimethylsilyl)-3-o-methyloxime)(1H-ID), taraxasterol, lyoniresinol, podophyllotoxin, stigmasterol, lupeol, nuciferine, adenanthin, embelin, and lanosterol. Maximal hydrophobic interaction detected was 10 in epifriedelinol and friedelanol from *Paederia foetida* and *Ficus bengalensis*, respectively. Atisine, a component present in *A. heterophyllum* displayed 6 hydrophobic interactions (Figure S1).

Molecular docking with Discovery Studio (version 2019 onwards) showed that atisine, kutkin, and phylloquinone might serve as the best inhibitors of the efflux transporter. For p-glycoprotein and atisine interaction, two hydrogen bonds were identified with amino acid residues SER979, GLU972, and six hydrophobic (alkyl and pi-alkyl) interactions were observed with PHE72, PHE336, LEU332, LEU975, LEU976, and ILE736. Kutkin, on the other hand, showed six hydrophobic interactions (pi-alkyl, pi-pi T-shaped, pi-pi stacked, and pi-sigma) with PHE72, PHE336, PHE732, PHE72, LEU975, LEU976, ILE736 at the distance of 5.14 Å, 3.41 Å, 2.83 Å, 5.44 Å, 5.16 Å, and 5.21 Å, respectively. Phylloquinone was involved in one hydrogen bond interaction with LEU332 at the distance of 2.56 Å and eight hydrophobic (pi-pi T-shaped, pi-pi stacked, pi-alkyl, and alkyl) interactions with PHE72, PHE336, PHE732, LEU332, LEU339, LEU975, LEU976, and ILE736 at the distance of 4.43 Å, 5.37 Å, 4.14 Å, 3.41 Å, 5.45 Å, 5.17 Å, 5.43 Å, and 4.71 Å, respectively (Figure 3). Atisine was found to be the best compound among the 376
components studied, largely based on binding free energy, along with hydrogen and hydrophobic interactions.

**Molecular dynamics simulation**

The MD simulation study was conducted using Discovery Studio to predict the efficacy of atisine as possible novel inhibitor. The best pose was obtained from the molecular docking experiment by CDOCKER. The Standard Dynamics Cascade (SDC) performed a series of minimization and equilibration steps followed by molecular dynamics using CHARMm algorithm. SDC summary was acquired from minimization and equilibration steps followed by steepest descent and conjugate gradient, followed by heating, equilibration and production dynamics. The total energy was found to decrease and the temperature was stable at 301°K±4.

The stability of the conformation was evaluated by a root mean square fluctuation (RMSF) graph. These values were computed to evaluate the effect of the binding of ligands on protein flexibility. The RMSF of a structure is the time average of the RMSD. RMSD quantifies the divergence of a structure from a reference over time while the RMSF is calculated to an average structure of the simulation. An area of the structure with high RMSF values frequently diverges from the average, indicating high mobility. Thus, RMSF evaluates the binding poses effectively. In Figure 4, the RMSF graph shows that the structure is not much fluctuating. The key residues viz., SER979, GLU972, LEU332, PHE336, PHE732, LEU975, LEU976, and ILE736 involved in various interactions were found without any abnormal fluctuation and had relatively low RMSF values (0.3–0.6 Å²). These findings suggest that the critical interactions of the ligand in the binding pocket might maintain protein stability.

Figure 5 depicts the nature of the binding surface of the protein. The hydrogen bonds are shown by dashed lines. From the figure it can be concluded that one part of the inner pocket is slightly electronegative (Figure 5a) indicated by the small red segment at the base of the surface representation; this can have a positive impact on transient interactions as documented by Pocketome data (40) and acidic (Figure 5c) with a predominance of aromatic residues predominating the core and outer extremities of the pocket (Figure 5b). The binding surface is filled with aromatic residues which contribute to edge interaction and hydrophobicity (Figure 5d). Aromatic stacking has long been recognized as one of the key constituents of ligand–protein interfaces and thus this predominance of aromatic residues indicates that the ligand has found a good fit in the protein neighborhood (41). Several hydrogen bond acceptors and two donors are clearly visible around the bound ligand (Figure 5c). H-bonds are crucial for binding and specificity and other interactions make the structure stable and compact. In biological systems, it has been observed that H-bond competing process is always present with water. Since bulk water interferes with reversible biological processes, enthalpy-entropy compensation occurs during H-bond formation (42). In this study we found that hydrogen bonding was present due to the presence of residues which were potentially hydrophobic in nature and thus this interference was not present here.
The interaction energy was calculated between sets of atoms across all conformations using CHARMM and was found to be stable. The radius of gyration (Rg) of a protein is computed as the average distance of all atoms to its geometric center: \( R_g = \left( \frac{\sum r^2}{N} \right)^{1/2} \), where \( r \) is the distance between an atom and the geometric center and \( N \) is the total number of atoms. The radius of gyration is stable around 47.95 Å which shows that the complex structure was compact during simulation.

MM-PBSA method was used to calculate the binding free energy of p-glycoprotein-atisine complex. The binding energy of the protein with the ligand (\( \Delta G_{\text{binding}} \)) was calculated for each frame using equation: \( \Delta G_{\text{binding}} = G(a) - G(b) - G(c) \) where, \( G(a) \) is the free energy of the protein-ligand complex and \( G(b) \) and \( G(c) \) are free energies of the protein and ligand, respectively. Then, the average of \( \Delta G_{\text{binding}} \) was calculated over all frames and reported as the DeltaG Average. Average binding free energy (DeltaG Average) was found to be -19.7126 kcal/mol (Table 3). The results of this simulation study showed the stability of the protein-ligand complex and suggested that atisine could likely inhibit p-glycoprotein better than kutkin and phylloquinone.

**Discussion**

Renal drugs would be partially excreted from the target cells owing to overexpression of the efflux transporter p-glycoprotein. Inhibiting the expulsion by p-glycoprotein would enhance the bioavailability of the desired drugs as there would be retention in the reno-cytes.

Herbal constituents are known to modulate p-glycoprotein activity by directly interacting with the ATP-binding site or the substrate-binding site. Inhibition of the efflux of rhodamine 123 in the MDR human leukaemia cell line by stigmasterol (43) (\( \text{Paederia foetida} \)), the reversion of MDR in NCI/ADR-RES cells by \( \beta \)-Sitosterol (44) (\( \text{Abies webbiana} \)), inhibition of p-glycoprotein mediated efflux of \([3H]\)digoxin in LLCGA5-COL150 cells by lupeol (45) (\( \text{C. officinalis} \)), and p-glycoprotein inhibition in cultured bovine brain capillary endothelial cells by berberine (46) (\( \text{A. heterophyllum} \)) suggest the potency of the bioactive compounds in modulation of p-glycoprotein activity.

Herbal compounds have long been known to promote renal function and slow down the progression of kidney disease.
disease (47). Berberine (A. heterophyllum) has been known to exert reno-protection against gentamicin-induced nephrotoxicity in rats through the attenuation of oxidative stress, apoptosis, and mitochondrial dysfunction (48). Similar reno-conservation effect was observed on the administration of β-sitosterol (Paederia foetida) in nephrotoxicity induced in Wistar rats via the up-regulation of Nrf2 gene expression (49). Nuciferine from Nelumbo nucifera improved renal injury by the inhibition of TLR4/PI3K/NF-κB signaling pathway and NLRP3 inflammasome activation in rat renal cortex and HK-2 cells (50). So, the simultaneous administration of these natural compounds would not only enhance the accumulation of the renal treatment drugs inside the target cells but also impart additional reno-protection.

The inhibitors of the efflux carrier protein may be sequentially aligned on the basis of their magnitude of negative binding free energy along with hydrogen bonding and hydrophobic interactions, all of which play vital roles in stabilizing the appropriate conformation of the ligand at the target site of the protein. Hydrogen bonding provides directionality and specificity of interaction between the receptor and ligand. The energetics and kinetics of hydrogen bonding need to accredit the pharmacological significance of renal function. Further circumvention of drug efflux along with augmentation protective herbs which might play significant role in circumvention of p-glycoprotein mediated renal drug efflux.

Table 3. Radius of gyration, interaction energy and binding free energy of all conformations during molecular dynamics simulation

<table>
<thead>
<tr>
<th>Time</th>
<th>Radius of Gyration (Å)</th>
<th>VDW Interaction Energy</th>
<th>Electrostatic Interaction Energy</th>
<th>Interaction Energy</th>
<th>G_6C0V: complex</th>
<th>G_not_6C0V: B_2</th>
<th>DeltaG_6C0V</th>
</tr>
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<tbody>
<tr>
<td>Conformation 1</td>
<td>16</td>
<td>47.8989</td>
<td>-95.0946</td>
<td>-40.0492</td>
<td>-55.0454</td>
<td>-49739.6</td>
<td>89.0716</td>
</tr>
<tr>
<td>Conformation 2</td>
<td>18</td>
<td>47.8655</td>
<td>-81.6751</td>
<td>-41.0953</td>
<td>-40.5798</td>
<td>-49802.3</td>
<td>79.5228</td>
</tr>
<tr>
<td>Conformation 3</td>
<td>20</td>
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<td>-49716.5</td>
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Conclusion
The renoprotective natural compounds which are considered as p-glycoprotein inhibitors, exhibit drug-likeness and other pharmacokinetic attributes. The binding potency of these potential lead compounds promises increased drug bioavailability when co-administered during medical treatment. Hence, atisine is the lead inhibitory component, followed by kutkin and phylloquinine as analyzed from an array of renoprotective herbs which might play significant role in circumvention of drug efflux along with augmentation of renal function. Further in vitro and in vivo studies are needed to accredit the pharmacological significance of these lead molecules.

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Authors’ contribution
PG conceptualized; CR performed the data collection, analysis, validation, and preparation; PG and CR supported during the validation and preparation of the final manuscript. All authors read, reviewed, and approved the manuscript and edited English language.

Conflict of interest
The authors declare that there is no conflict of interest.
Ethical considerations

The manuscript is not submitted to or being considered by any other journal in part or full for publication. No part of the manuscript contains plagiarized portion from any other published material.

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Supplementary files

Supplementary file 1 contains Table S1 and Figure S1.

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Eflux of renal drugs by herbal inhibitors


