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In silico investigation of various Phytoconstituents present in *Schleichera oleosa* (Koshamra) Fruits as Hepatoprotective agents

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ABSTRACT

Different parts of *Schleichera oleosa* such as fruits, leaves, bark and seeds are used as tribal food, animal feed, seed-oil, and timber. The tree serves as important source for traditional medicines for curing pruritus, malaria, inflammation, and ulcers. The past researches have studied the properties of *S. oleosa* extracts from the bark and stem and it was found to reduce the free radicals that cause the death of cancer cells. However, hepatoprotective perspective of *S. oleosa* fruit extract was not yet studied. The main objective of this study was to explore the potential of various phytoconstituents [Protocatechuic acid, *p*-hydroxy benzoic acid, Vanillic acid, Caffeic acid, Syringic acid, *p*-coumaric acid, etc.] as hepatoprotective agent by using *in-silico* approaches with the help of published literature on downregulation of enzyme/molecular component expression and combining this information in order to recognize drug target High-mobility group AT-hook 2 (PDB ID: 3UXW, Crystal Structures of an A-T-hook/DNA complex); https://doi.org/10.2210/pdb3UXW/pdb]. The *in silico* studies revealed that the phytoconstituents successfully inhibited the biological target at varied degree which suggested plausible utilization as hepatoprotectives.

Keywords: Hepatoprotective, Phytoconstituents, Phytochemicals, Docking, *In silico*, *Schleichera oleosa*

INTRODUCTION

The rising global prevalence of liver diseases, including hepatitis, cirrhosis, and hepatocellular carcinoma, necessitates the urgent development of effective therapeutic strategies. Among these, hepatoprotective agents play a critical role in preventing and mitigating liver damage. Traditionally, synthetic drugs have dominated this space; however, they are often associated with adverse side effects and limited efficacy. This has sparked considerable interest in the exploration of natural products, particularly phytoconstituents, as safer and more effective alternatives for liver protection [1].

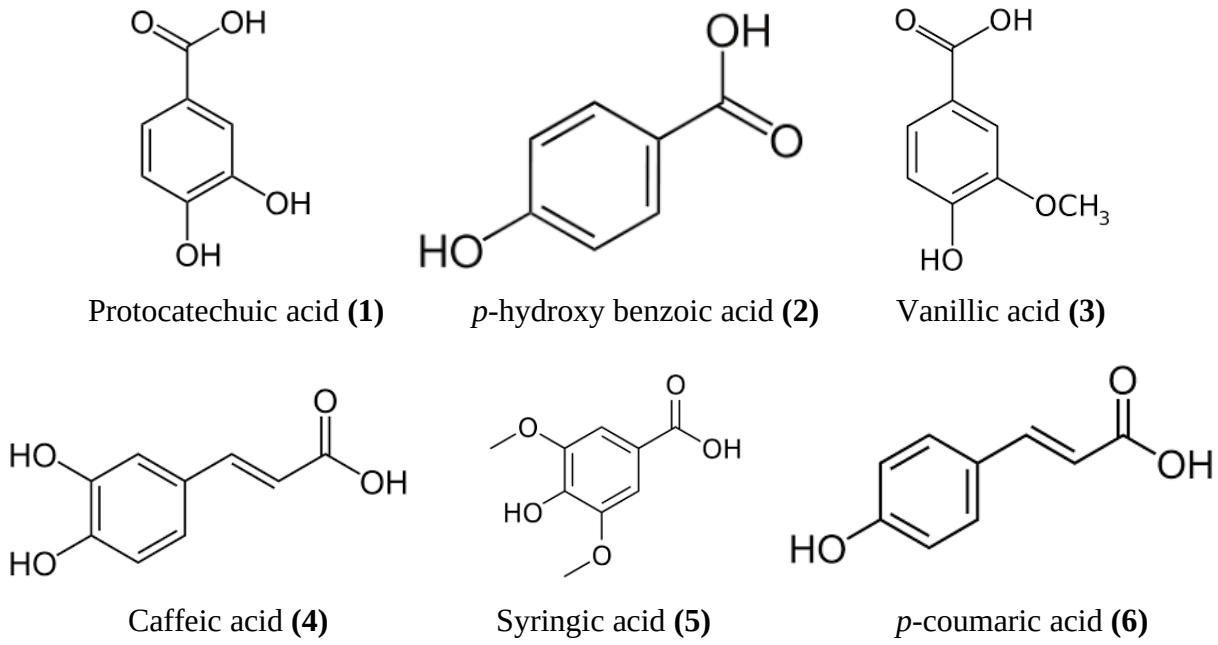
Schleichera oleosa, commonly known as Koshamra, is a medicinal plant extensively used in traditional medicine for its diverse therapeutic properties, including its reputed hepatoprotective effects. The fruits of *S. oleosa* are rich in various bioactive compounds that have been reported to exhibit antioxidant, anti-inflammatory, and hepatoprotective activities. The fruits of *Schleichera oleosa*, commonly known as Koshamra, are renowned in traditional medicine for their diverse pharmacological potentials, attributed to a rich array of bioactive compounds. These fruits have been traditionally utilized for their medicinal properties, including their roles in treating various ailments and promoting overall health. Modern pharmacological studies have begun to uncover the scientific basis for these traditional uses, highlighting the potential of *Schleichera oleosa* fruits in several therapeutic areas [2].

One of the most prominent pharmacological potentials of *Schleichera oleosa* fruits is their hepatoprotective activity. The fruits are rich in antioxidants, which play a crucial role in protecting liver cells from oxidative stress, a major contributor to liver diseases such as hepatitis, cirrhosis, and hepatocellular carcinoma [3]. The antioxidants in *Schleichera oleosa* scavenge free radicals and reduce lipid peroxidation, thereby preventing cellular damage and enhancing liver function. In addition to hepatoprotection, *Schleichera oleosa* fruits exhibit significant anti-inflammatory properties. The bioactive compounds present in the fruits, such as flavonoids and tannins, inhibit the production of pro-inflammatory cytokines and enzymes, thereby reducing inflammation. This anti-inflammatory potential makes *Schleichera oleosa* fruits a promising candidate for the treatment of inflammatory conditions, including arthritis and inflammatory bowel disease [4]. The fruits of *Schleichera oleosa* also demonstrate antimicrobial activity, which is particularly valuable in combating bacterial and fungal infections. Studies have shown that the extracts from these fruits can inhibit the growth of various pathogenic microorganisms,

making them useful in the treatment of infections and in preserving food and herbal formulations. Furthermore, *Schleichera oleosa* fruits have been reported to possess anticancer properties. The bioactive compounds in the fruits induce apoptosis in cancer cells, inhibit cell proliferation, and disrupt the signaling pathways involved in tumor growth [5]. These anticancer effects, combined with the antioxidant and anti-inflammatory activities, suggest that *Schleichera oleosa* fruits could be a valuable resource in cancer prevention and therapy. The fruits also exhibit potential as antidiabetic agents. They have been found to regulate blood glucose levels and enhance insulin sensitivity, making them beneficial in managing diabetes and preventing its complications. Additionally, the fruits have shown hypolipidemic effects, which can help in reducing cholesterol levels and preventing cardiovascular diseases [6].

In recent years, the advent of *in silico* approaches has revolutionized drug discovery and development, enabling the efficient screening and evaluation of bioactive compounds for their therapeutic potential. These computational methods, including molecular docking and pharmacokinetic predictions, allow for the rapid identification of potential drug candidates and their mechanisms of action, thereby accelerating the drug development process while reducing the need for extensive *in vitro* and *in vivo* testing. In the context of hepatoprotection, *in silico* tools offer a powerful means to investigate the interactions of phytoconstituents with key molecular targets involved in liver injury and repair, providing valuable insights into their potential efficacy as hepatoprotective agents [7].

The present study aims to leverage *in silico* techniques to investigate the hepatoprotective potential of various phytoconstituents [Protocatechuic acid **(1)**, *p*-hydroxy benzoic acid **(2)**, Vanillic acid **(3)**, Caffeic acid **(4)**, Syringic acid **(5)**, and *p*-coumaric acid **(6)**] present in the fruits of *S. oleosa*. By employing molecular docking studies, this research seeks to identify and evaluate the key bioactive compounds within *S. oleosa* that could serve as promising candidates for the development of hepatoprotective agents. The findings of this study are expected to contribute to the growing body of knowledge on natural hepatoprotective agents and provide a scientific basis for the traditional use of *S. oleosa* in liver-related ailments.



Protocatechuic acid **(1)** *p*-hydroxy benzoic acid **(2)** Vanillic acid **(3)**

Caffeic acid **(4)** Syringic acid **(5)** *p*-coumaric acid **(6)**

Figure 1. Structure of phytoconstituents.

MATERIALS AND METHODS

Preparation of Ligand

Cambridge Soft ChemDraw Ultra v.8.0 was used to draw up the phytochemicals. Using the Open Babel software, the.cdx files that were generated were transformed into.mol2 files. Molecular mechanics as a force field (MM2) was used to optimize and minimize energy for the compounds that were drawn, with the root-mean-square (RMS) cut-off maintained at 0.100 [8,9].

Preparation of Protein

3D crystalline target structure; High-mobility group AT-hook 2 (PDB ID: 3UXW, Crystal Structures of an A-T-hook/DNA complex) was downloaded from the Protein Data Bank (PDB). The target was created by removing all water molecules beyond 5A°, assigning disulfide links, bond order, and formal charges, and removing metal ions, co-factors, and heterogroup from the useable preprocessed and studied structure. With the assistance of the H-bond assignment technique, the hydrogen atoms as well as the hydrogen-bonding network were optimized. Molecular docking was used to estimate receptor grids for protein targets where the ligand would mix within the predicted active site. The grids (cubic boxes with defined dimensions) encompass the whole ligand and were built at the ligand's centroid (crystallized with the target structure).

The grid box size was increased to 126 A°, 126 A° and 126 A° (x, y, and z, respectively) to include all of the amino acid residues present in stiff macromolecules. The Auto Grid 4.2, which came with Auto Dock 4.2, was used to generate grid maps. The grid points were 0.375° apart. The Van der Waals scale factor was set to 1.0, while the charge cutoff was set at 0.25. Induced-fit docking (IFD) was conducted on each ligand, and the lowest resulting score for the best-docked posture was confirmed [10,11].

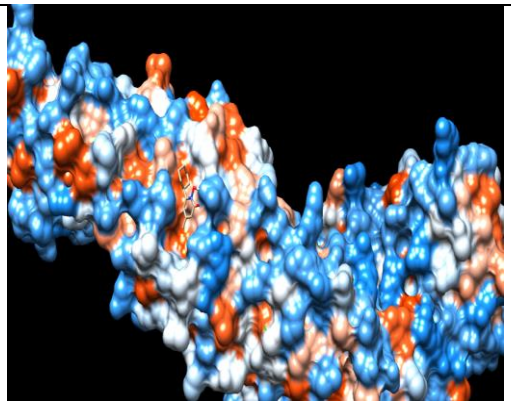
Docking Procedure

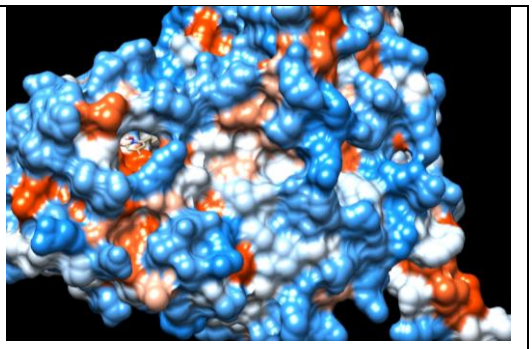
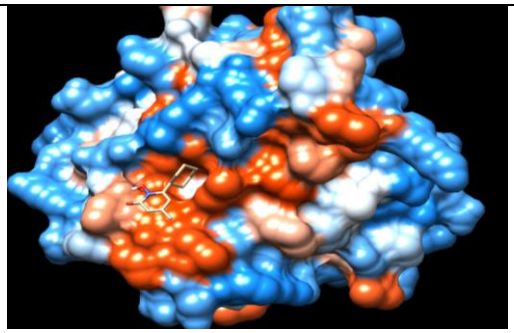
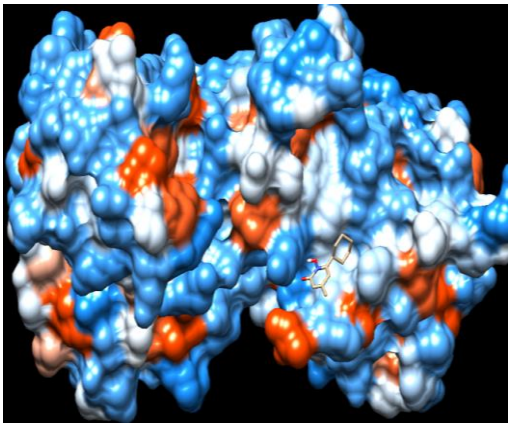
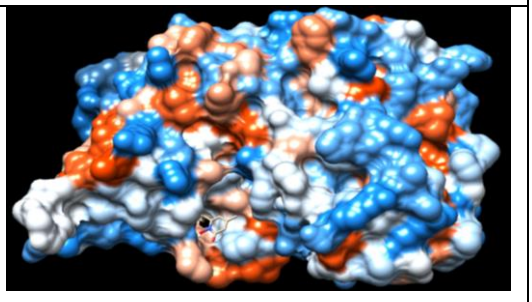
The IFD was created utilizing the structure-based drug design technique, which involves rendering precise geometry ligands to dock with a biological target's defined structure. The free-state ligands are docked into the rigid state receptor's active site, enzyme, tube, etc., resulting in a predicted binding mode and the strength of the fit being evaluated. In receptor-based computational techniques, the attachment of a low-molecular-weight ligand to a macromolecular protein has its own significance since the most suitable connection with low energy values and possible steric conflicts is found. To investigate a particular docking issue, Auto Dock provides a number of search methods. In this study, the Lamarckian Genetic Algorithm (LGA) was employed to identify the best conformers. During the docking process, a maximum of 10 conformers were evaluated. The population was limited to 150 individuals, who were selected at random. The mutation rate was set to 0.02 and the crossover rate was set to 0.8. The maximum number of energy evaluations was set to 500000, the maximum number of generations was set to 1000, the maximum number of top individuals that automatically survived was set to 1. Translations had a 0.2 step size, quaternions had a 5.0° step size, and torsions had a 5.0° step size. Cluster tolerance was set to 0.5, external grid energy to 1000.0, maximum binding energy to 0.0, maximum number of retries to 10000, and 10 LGA runs were performed. The interactions and binding energy of the docked structure were studied using the Auto Dock findings. It was performed many times to get different docked conformations as well as to assess anticipated docking energy. The optimal ligand-receptor structure was selected among the docked structures based on the ligand's lowest energy and minimum solvent accessibility. The Accelrys Visualizer discovery studio tool was used to visualize the docking findings [12,13].

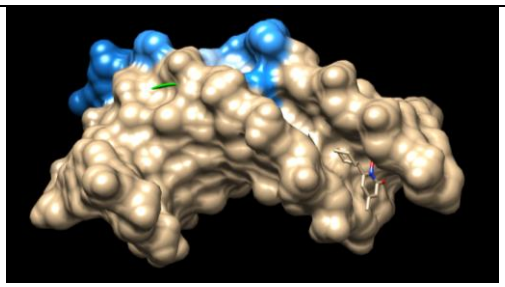
RESULTS

The docking study revealed that compound named Caffeic acid **(4)**, present in *S. oleosa* demonstrated the highest inhibition of the hepatoprotective target High-mobility group AT-hook 2 with docking score of -6.63 Kcal/mol (**Table 1**) by interacting with amino acid residues TRP:383 (H1), CYS:419 (H2), ARG:386 (H3), THR:418 (H4), ASN:415 (H5), ASP:459, ARG:457 by forming 5 hydrogen bonds whereas the well-known compound Protocatechuic acid **(1)** presented the lowest inhibition of the hepatoprotective target High-mobility group AT-hook 2 with docking score of -4.90 Kcal/mol by interacting with amino acid residue GLN322 (H1) by forming 1 hydrogen bond (H1: Distance = 2.07 Å). *p*-hydroxy benzoic acid **(2)** (-4.96 Kcal/mol; ASP:339 (H1), LEU:457 (H2), PRO:460, VAL:424, HIS:458, ILE:416) by forming 2 hydrogen bonds (H1: Distance = 2.76 Å, H2: Distance = 3.26 Å), Vanillic acid **(3)** (-5.22 Kcal/mol; CYS53 (H1), VAL50) by forming 1 hydrogen bond (H1: Distance = 2.88 Å), Syringic acid **(5)** (-6.03 Kcal/mol; ASP:492, GLU:491), and *p*-coumaric acid **(6)** (-4.85 Kcal/mol; LYS:122, GLY:120 (H1), ASP:149) by forming 1 hydrogen bond (H1: Distance = 2.53 Å) showed moderate to good inhibition of the target.

Table 1. Docking scores, Interaction behaviors, and Docking poses of phytochemicals against High-mobility group AT-hook 2.

Compound	**Binding Energy (kcal/mol)**	**No. of H Bonds / Bond Distance**	**Interacting residues**	**Docking pose**
1	-4.90	01 (H1: Distance = 2.07 Å)	GLN322 (H1)	

2	-4.96	02 (H1: Distance = 2.76 Å, H2: Distance = 3.26 Å)	ASP:339 (H1), LEU:457 (H2), PRO:460, VAL:424, HIS:458, ILE:416	
3	-5.22	01 (H1: Distance = 2.88 Å)	CYS53 (H1), VAL50	
4	-6.63	05 (H1: Distance = 2.4 Å, H2: Distance = 3.30 Å, H3: Distance= 1.86 Å, H4: Distance = 2.00 Å, H5: Distance = 1.83 Å)	TRP:383 (H1), CYS:419 (H2), ARG:386 (H3), THR:418 (H4), ASN:415 (H5), ASP:459, ARG:457	
5	-6.03	00	ASP:492, GLU:491	

6	-4.85	01 (H1: Distance = 2.53Å)	LYS:122, GLY:120 (H1), ASP:149	

DISCUSSION

The induced-fit molecular docking experiments validated and clarified the drugs' hepatoprotective activity. This approach has been around for a long and is still used to determine the binding sites of ligands to target proteins and the interactions between chemicals and these proteins. To create a model of the inhibitors' binding affinity, the molecular docking technique was used [14]. The main parameters used to forecast the results were docking score, hydrogen bonds, Van der Waal's interactions, π-cation interaction, and π-π stacking interactions. We calculated the ligand affinity for proteins using these parameters. A positive binding affinity is indicated by a negative docking score. According to the docking findings, there are a number of crucial features: Increased Van der Waals interactions and the presence of additional hydrogen bonding connections are indicators of ligands with many bulky groups and a high binding affinity for the molecular target, respectively, which is indicative of antagonist activity. Thus, inhibitor binding predictions may be made using the IFD module [15].

Both compounds were ringed by hydrophobic amino acid residues, as was clearly visible. It follows that neither chemical was able to penetrate the protein's active site binding cleft since they were both unable to evaporate into the surrounding solvent. It is possible that the ligands may access deeper regions of the cavity due to their small size. The ligand was completely obscured by amino acid residues when surface representation was applied, making it impossible to see it at the cavity. The stable fitting of ligands causes Van der Waals interactions, which attain maximum stability. Chemicals were able to access the active site of the protein as they did not expose it to solvent. In the target's active site, amino acid residues create a deep bent-shaped cleft that enables the ligand to make strong connections. One suggestion suggests that the amino function is mostly responsible for the improved target inhibition [16]. Research has shown that the placement of interacting oxygen groups is very important. Putting the hydroxyl group furthest from the scaffold and the keto group near it could improve interaction with the active

site, according to this theory. Steric, hydrophobic, electrostatic, and hydrophilic interactions may all have a role in the stability of the drug-target association. Molecular docking investigations, which successfully predicted the compounds' theoretical binding to the biological target, verified their interactions [17].

CONCLUSION

The *in silico* investigation of the phytoconstituents present in *S. oleosa* (Koshamra) fruits has provided valuable insights into their potential as hepatoprotective agents. This study has systematically explored the interaction of various bioactive compounds with key molecular targets implicated in liver diseases, revealing promising candidates for further exploration and potential therapeutic application. The computational docking studies have demonstrated that several phytoconstituents exhibit strong binding affinities to crucial proteins involved in oxidative stress, inflammation, and apoptosis—three pivotal pathways in the pathogenesis of liver disorders. Notably, compounds such as Protocatechuic acid **(1)**, *p*-hydroxy benzoic acid **(2)**, Vanillic acid **(3)**, Caffeic acid **(4)**, Syringic acid **(5)**, and *p*-coumaric acid **(6)** have shown remarkable potential in stabilizing these target proteins, thereby inhibiting the processes that lead to hepatic damage. The findings of this study underscore the significance of *S. oleosa* fruits as a reservoir of bioactive compounds with hepatoprotective properties. The predicted pharmacokinetic and toxicity profiles of the identified phytoconstituents further reinforce their suitability as candidates for drug development. These in silico results provide a strong foundation for subsequent *in vitro* and *in vivo* studies, which are necessary to validate the hepatoprotective effects of these compounds and to better understand their mechanisms of action. Moreover, the study highlights the importance of integrating computational approaches in the early stages of drug discovery, particularly in identifying and prioritizing bioactive compounds from natural sources. The potential of these phytoconstituents to mitigate liver damage through multiple mechanisms suggests that *S. oleosa* fruits could serve as a valuable natural therapeutic option or as a complementary treatment in managing liver diseases. Future research should focus on the experimental validation of these findings, including the isolation of individual phytoconstituents, detailed mechanistic studies, and evaluation of their therapeutic efficacy in animal models. Additionally, the exploration of synergistic effects between these compounds could reveal enhanced hepatoprotective activities, contributing to the development of more effective and safer

hepatoprotective agents. This study provides a comprehensive in silico analysis of the hepatoprotective potential of *S. oleosa* fruits, paving the way for further research and development in this area. The promising results obtained here highlight the potential of these fruits as a source of novel hepatoprotective agents and contribute to the growing body of evidence supporting the medicinal value of *S. oleosa*.

Conflict of Interest

Declared none

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Animal ethical permission

Not required

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