Global Academic Journal of Pharmacy and Drug Research

Available online at https://www.gajrc.com
DOI: 10.36348/gajpdr.2023.v05i02.001

OPEN ACCESS

ISSN (P): 2706-9044
ISSN (O): 2707-255X

Original Research Article

Potential of Hepatoprotective Activity of *Abelmoschus Moschatus* Seed: *In-Silico* Validation

Rizwan Mirza[1*], Sunil Kumar[1], Jitender K Malik[1]
[1]Faculty of Pharmacy, P.K. University, Shivpuri (M.P.), India

***Corresponding Author**
Rizwan Mirza
Faculty of Pharmacy, P.K. University, Shivpuri (M.P.), India

Article History
Received: 11.03.2023
Accepted: 23.04.2023
Published: 29.04.2023

Abstract: A type of wound healing known as hepatic fibrosis arises in response to chronic liver damage brought on by viruses, toxins, and medications that are detrimental to the liver. The syndrome is characterized by inflammation, which is followed by the deposition of extracellular matrix proteins and the development of scar tissue. Ephrin receptor A2 is a host cofactor that has been associated to Hepatitis C virus (HCV) entry (EphA2). The *Abelmoschus moschatus* seed belong to family Malvaceae. It contains sitosterol b. total phenol, flavonoids which are responsible for antioxidant, antimicrobial and free radical scavenging activity. The exact mechanism of action for the hepatoprotective action of Myricetin was still not revealed. With intent to propose the most probable mechanism of action of Myricetin the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme.

Keywords: Myricetin, hepatoprotective, PPARα enzyme and molecular docking.

INTRODUCTION

Liver diseases such as viral hepatitis, fatty liver, liver fibrosis, cirrhosis, and liver cancer are among the leading causes of death worldwide. Despite significant advancements over the past few decades, the bulk of treatments continue to have poor patient outcomes. Due to the absence of effective treatments and the severe side effects of present chemicals, new preventative and therapeutic agents for liver disease are urgently needed [1-2]. As the body's main metabolic organ, the liver performs a number of vital functions. CCl4, xenobiotics, and other toxins that are created by cytochrome P450-dependent activities as a result of the formation of covalent bonds with lipoproteins and nucleic acids trigger reactive oxygen species (ROS) [3]. Researchers have thoroughly investigated the biological activity and therapeutic potential of *A. moschatus*. diuretic, antioxidant action and free-radical scavenging, antiproliferative, antimicrobial, antilithiatic, hepatoprotective, memory-boosting, antidiabetic, hemagglutinating, anti-ageing, antidepressant, anxiolytic, anticonvulsant, hypnotic, and muscle relaxant activities are a few examples [4]. As per literature survey myricetin (flavonoid) present in the seed of *Abelmoschus moschatus* [5].

Abelmoschus moschatus

Thus myricetin taken as lead molecule for elucidation of proposed mechanism of hepto-protective potential. The exact mechanism of action for the hepatoprotective action of Myricetin *Abelmoschus moschatus* seed present in was still not revealed. With intent to propose the most probable mechanism of action of Myricetin the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme. The docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the Myricetin is executing its hepatoprotective action *via* inhibiting PPARα enzyme. Molecular docking analysis has been one of the most basic and important strategy for drug discovery. It allows prediction of molecular interactions that hold together a protein and a ligand in the bound state. Molecular docking and MD simulations are very important techniques to understand the binding interaction of a ligand molecule with a drug target.

EXPERIMENTAL WORK

Molecular docking studies

Ligand Preparation:

2D Structure of ligands myricetin was drawn by using ChemDraw [6]. The two-dimensional structures of ligand was converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [7-8].

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is given in table 1. [5-9].

Table 1: The grid-coordinates of the grid-box used in the current study

Proteins	x-D	y-D	z-D	Spacing (Å)	x center	y center	z center
2znn	40	40	40	0.375	11.98	4.435	-7.653

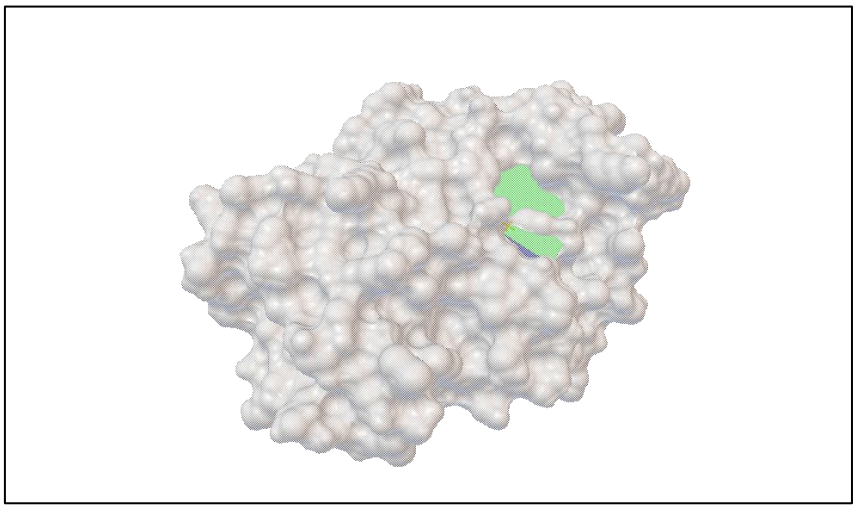


Figure 1: Grid box covering all active sites in PPARα enzyme (2znn).

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [10-11].

Macromolecular Structure

Peroxisome Proliferator Activated Receptors-α (PPARα)

The crystal structure of the PPARα enzyme consisting of macromolecular receptor is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (2znn.pdb) registered in the Protein data bank was used [12-14].

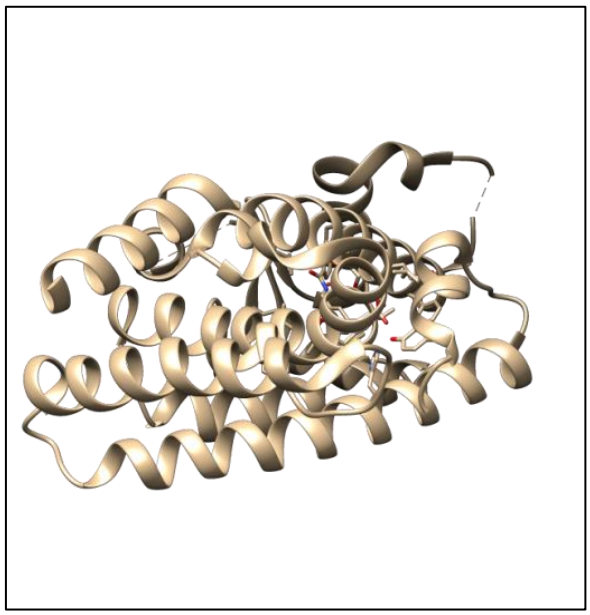


Figure 2: Crystal structure of PPARα enzyme. (PDB ID-2znn)

Molecular Docking Simulation Studies

Docking of ligand myricetin was performed against PPARα enzyme was performed by Autodock to establish its probable mechanism of action for their hepatoprotective effect. All the bonds of ligands were kept flexible, while no residues in receptor were made flexible [15-16].

Toxicity & ADME-T Studies

The pharmacokinetics of myricetin ligand molecules was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME-T properties [17-18].

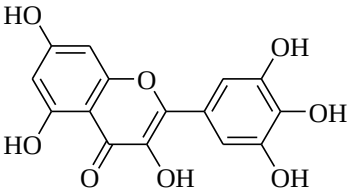
RESULTS AND DISCUSSION

As per literature survey myricetin (flavonoid) present in the seed of *Abelmoschus moschatus* by Pawar etal., 2017.Thus myricetin taken as lead molecule for elucidation of proposed mechanism of hepto-protective potential. The exact mechanism of action for the hepatoprotective action of Myricetin *Abelmoschus moschatus* seed present in was still not revealed. With intent to propose the most probable mechanism of action of Myricetin the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme. The docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the Myricetin is executing its hepatoprotective action *via* inhibiting PPARα enzyme. Molecular docking analysis has been one of the most basic and important strategy for drug discovery. It allows prediction of molecular interactions that hold together a protein and a ligand in the bound state. Molecular docking and MD simulations are very important techniques to understand the binding interaction of a ligand molecule with a drug target.

The most significant regulator of lipid peroxidation in ALD and NAFLD was identified as peroxisome proliferator-activated receptor alpha (PPAR), which had the greatest number of chemical interactions in our network investigation. According to earlier research, PPAR may mediate NAFLD via a periostin-dependent mechanism. It can activate the periostin-dependent JNK signalling pathway to control fatty acid oxidation and further activate hepatosteatosis both in vivo and in vitro. Moreover, increased liver mitochondrial glutathione (GSH) and lower levels of circulating fatty acyl-carnitines are linked to PPAR activation. Moreover, PPAR exerts a protective effect by activating adaptive transcription in response to persistent alcohol use, enhancing mitochondrial function. Molecular docking result revealed that the binding energy of Myricetin with PPARα is -6.8kcal/mol(table 2). The binding interaction showed Cys276, Thr279, Ala333, Leu331, Met330, Leu321, and Met355(table 2 & 3-5). The pharmacokinetic profiling of the kaempferol ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, and tumorogenic properties, but shows the presence of some mutagenicity. The pharmacokinetic and toxicity profiling results of myricetin was shown in figure 6.

With the endeavor of molecular docking result Myricetin is effectively used as therapeutic strategy for liver disorder. Thus outcome studied proven the efficacy of Myricetin present in *Abelmoschus moschatus* for hepatoprotective potential.

Table 2: Results of docking of PPARα enzyme

S. No	Compound Name	Structure	Binding Energy (kcal/mol)	Interacting Residues
1	Myricetin		-6.28	Cys276, Thr279, Ala333, Leu331, Met330, Leu321, and Met355

Interactions

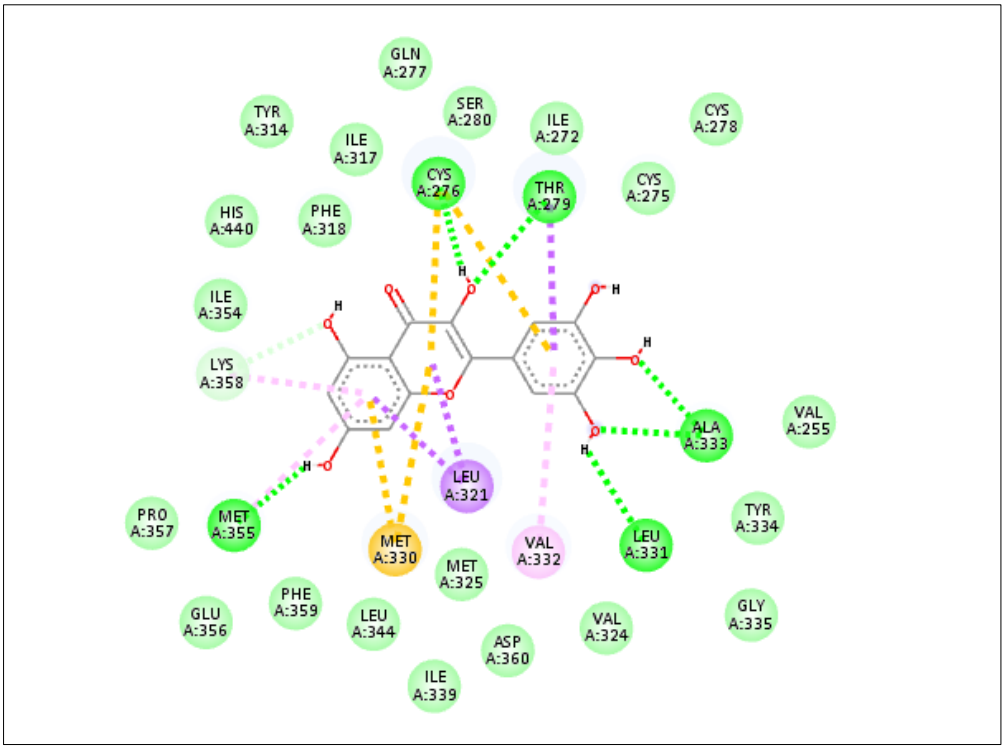


Figure 3: Two-dimensional binding interaction of myricetin with PPARα enzyme

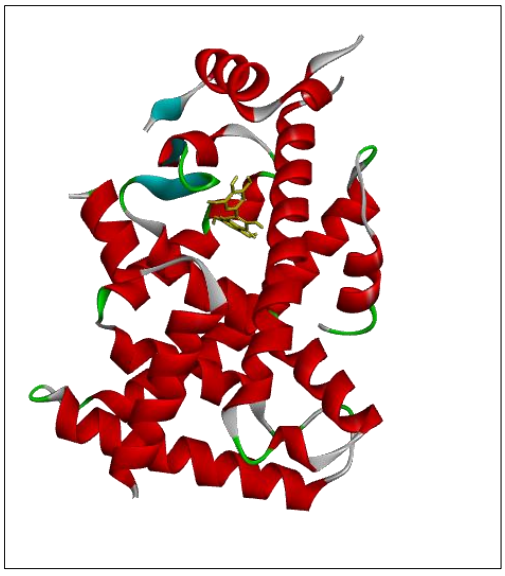


Figure 4: Three-dimensional binding interaction of myricetin with PPARα enzyme

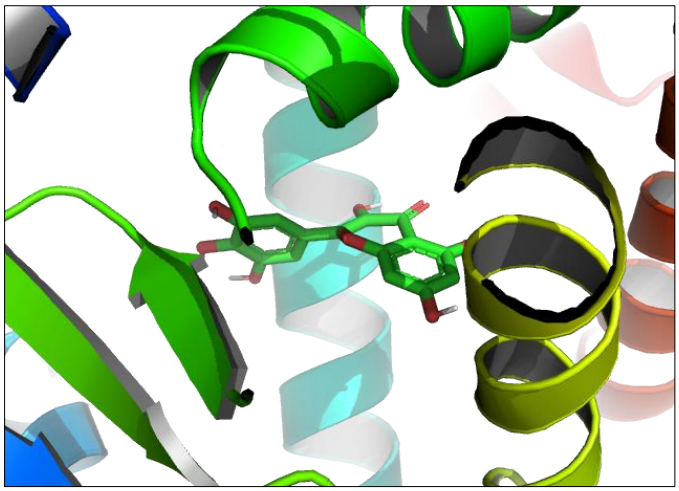


Figure 5: Binding conformation of ligand myricetin with PPARα enzyme

Toxicity & ADME-T Studies

The pharmacokinetic profiling of the kaempferol ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, and tumorogenic properties, but shows the presence of some mutagenicity. The pharmacokinetic and toxicity profiling results of myricetin was shown in figure 6.

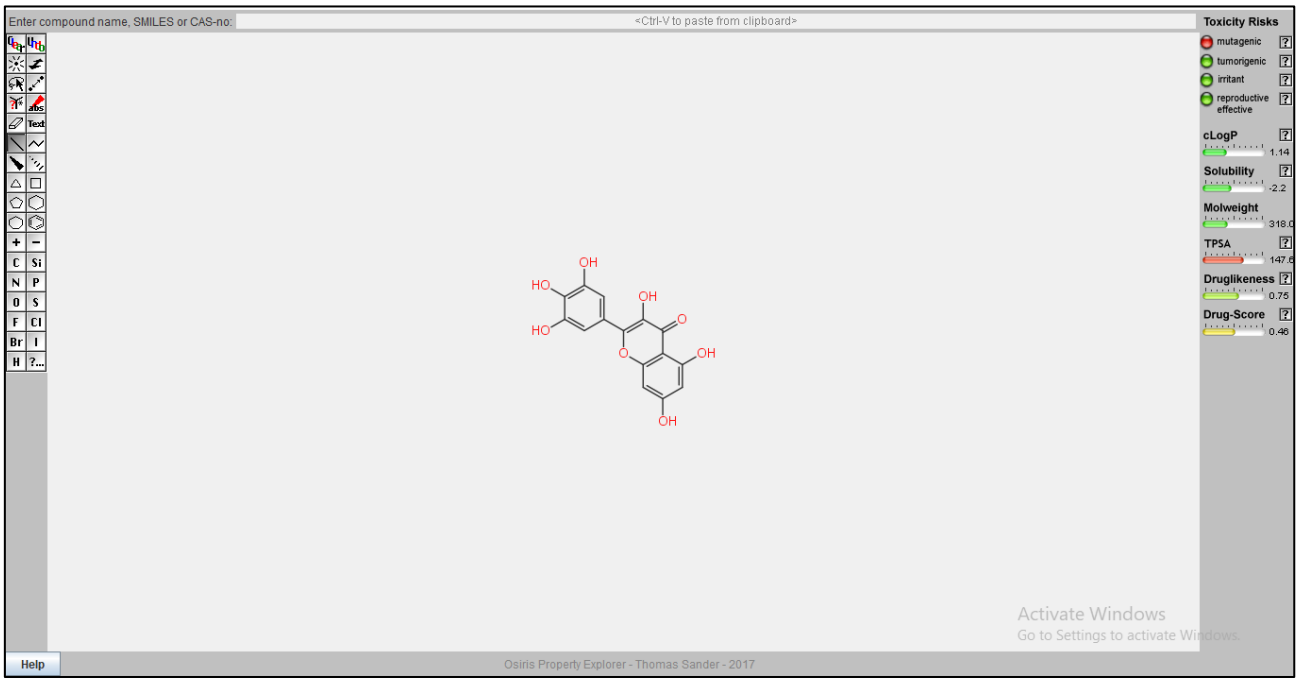


Figure 6: Pharmacokinetic and toxicity profiling of myricetin

CONCLUSION

The outcome of present study showed the Myricetin present in *Abelmoschus moschatus* seed is executing its hepatoprotective action *via* inhibiting PPARα enzyme thereby it alters regulate fatty acid oxidation by activating the periostin-dependent JNK signaling pathway. They also prevent activation of PPARα so that decreased mitochondrial glutathione (GSH) in the liver and increased levels of circulating fatty acyl-carnitines. The docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the myricetin is executing its hepatoprotective action via inhibiting PPARα enzyme.

REFERENCES

1. Melo, A. P. S., França, E. B., Malta, D. C., Garcia, L. P., Mooney, M., & Naghavi, M. (2017). Mortality due to cirrhosis, liver cancer, and disorders attributed to alcohol use: Global Burden of Disease in Brazil, 1990 and 2015. *Revista Brasileira de Epidemiologia*, *20*, 61-74.
2. Rush, B., Walley, K. R., Celi, L. A., Rajoriya, N., & Brahmania, M. (2017). Palliative care access for

hospitalized patients with end-stage liver disease across the United States. *Hepatology*, *66*(5), 1585-1591.
3. Khare, C. P. (2004). *Encyclopedia of indian medicinal plants: rational western therapy, ayurvedic and other traditional usage, botany*. Springer.
4. Pullaiah, T. (2006). Encyclopaedia of World Medicinal plants Regency Publications. *University of Chicago*, *1*, 1377.
5. Pawar, A. T. (2017). Phytopharmacology of Abelmoschus moschatus medik.: A review. *International Journal of Green Pharmacy (IJGP)*, *11*(04).
6. Soni, H., & Malik, J. (2022). Isolation, characterization and radical scavenging activities of rutin isolated from leaves of Annona squamosa. *Journal of Pharmacognosy and Phytochemistry*, *11*(2), 222-228.
7. Fabbrini, G., Abbruzzese, G., Marconi, S., & Zappia, M. (2012). Selegiline: a reappraisal of its role in Parkinson disease. *Clinical neuropharmacology*, *35*(3), 134-140.
8. Pålhagen, S., Heinonen, E., Hägglund, J., Kaugesaar, T., Mäki-Ikola, O., Palm, R., & Swedish Parkinson Study Group. (2006). Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology*, *66*(8), 1200-1206.
9. Yang, L., Li, C. L., & Tsai, T. H. (2020). Preclinical Herb–Drug Pharmacokinetic Interaction of Panax ginseng Extract and Selegiline in Freely Moving Rats. *ACS omega*, *5*(9), 4682-4688.
10. Henchcliffe, C., Schumacher, H. C., & Burgut, F. T. (2005). Recent advances in Parkinson's disease therapy: use of monoamine oxidase inhibitors. *Expert review of neurotherapeutics*, *5*(6), 811-821.
11. Lew, M. F. (2005). Selegiline orally disintegrating tablets for the treatment of Parkinson's disease. *Expert Review of Neurotherapeutics*, *5*(6), 705-712.
12. Malik, J. K., Soni, H., Sharma, S., & Sarankar, S. (2020). Hydroxychloroquine as potent inhibitor of COVID-19 main protease: Grid based docking approach. *Eurasian Journal of Medicine and Oncology*, *4*(3), 219-226.
13. Soni, H., Gautam, D., Sharma, S., & Malik, J. (2020). Rifampicin as potent inhibitor of COVID-19 main protease: In-silico docking approach. *Saudi Journal of Medical and Pharmaceutical Sciences*, *6*(9), 588-593.
14. Soni, H., Mishra, S., Mishra, R. K., & Mishra, S. R. (2022). Silibin as Potent Inhibitor of COVID-19 Main Protease: In-Silico Docking Approach. *Journal of Molecular Pharmaceuticals and Regulatory Affairs*, 1-7.
15. Soni, S., Malik, J. K., Sarankar, S. K., & Soni, H. (2019). Rutin as a potent inhibitor of dihydrofolate reductase: A computational design and docking. *EAS J. Pharm. Pharmacol*, *1*, 130-134.
16. Soni, N. U. P. U. R., Pardasani, K. R., & Mujwar, S. O. M. D. U. T. T. (2015). In silico analysis of dietary agents as anticancer inhibitors of insulin like growth factor 1 receptor (IGF1R). *J Pharm Pharm Sci*, *7*(9), 191-196.
17. Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera—a visualization system for exploratory research and analysis. *Journal of computational chemistry*, *25*(13), 1605-1612.
18. Agrawal, N., Upadhyay, P. K., Mujwar, S., & Mishra, P. (2020). Analgesic, anti-inflammatory activity and docking study of 2-(substituted phenyl)-3-(naphthalen1-yl) thiazolidin-4-ones. *J. Indian Chem. Soc*, *97*, 39-46.