Middle East Research Journal of Pharmaceutical Sciences
ISSN: **2789-7702 (Print & Open Access)**
Frequency: Bi-Monthly
DOI: 10.36348/merjps.2022.v02i02.002

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Hepatoprotective Potential of *Caesalpinia bonducella*: Molecular Insight

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ABSTRACT: Liver fibrosis is a wound healing process initiated in response to chronic liver damage caused by viruses, toxins, and hepatotoxic drugs. The disease is characterized by inflammation followed by deposition of extracellular matrix proteins to form scar tissue. Ephrin receptor A2 (EphA2) has been identified as a host cofactor for hepatitis C virus (HCV) entry. The plant *Caesalpinia bonducella* is used in a variety of systems a traditional medicine used to treat human ailments and affiliation prickly shrub belonging to the Caesalpiniaceae family found throughout the world, especially tropical region. It is a very valuable medicinal plant because all parts of the plant have medicinal properties. It was like traditional Indian herbal medicine considered an important therapeutic modality for the treatment of various diseases. As per literature survey the plants containing kaempferol and quercetin-3-methylether are traditionally utilized for the cure of cancer and liver related disorders from the immortal time. The exact mechanism of action for the hepatoprotective action of kaempferol and quercetin-3-methylether was still not revealed. With intent to propose the most probable mechanism of action of kaempferol and quercetin-3-methylether the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme.

Keywords: *Caesalpinia bonducella*, hepatoprotective, PPARα enzyme and molecular docking.

RESEARCH PAPER

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How to cite this paper:
Mahesh Bhatt & J K Malik.; "Hepatoprotective Potential of *Caesalpinia bonducella*: Molecular Insight". Middle East Res J. Pharm. Sci., 2022 May-June 2(2): 28-34.

Article History:
| Submit: 10.04.2022 |
| Accepted: 29.04.2022 |
| Published: 01.06.2022 |

INTRODUCTION

Liver diseases such as viral hepatitis, fatty liver, liver fibrosis, cirrhosis and liver cancer are serious threats to human health and leading causes of death worldwide. Although there have been remarkable advances in the treatment of liver disease over the past decades, most treatments still provide unsatisfactory patient outcomes. Given the scarcity of treatment options and the serious side effects of conventional chemicals, new preventive and therapeutic agents for liver disease are urgently needed[1-2]. As the most important metabolic organ in the body, the liver performs many important functions. Damage to hepatocytes occurs through activation of reactive oxygen species (ROS) by CCl4, xenobiotics, and other toxicants generated by cytochrome P450-dependent steps resulting from the formation of covalent bonds with lipoproteins and nucleic acids [3]. Plants have played an important role in maintaining human health and improving food quality for thousands of years, it has supported human life and has been useful to people as a valuable ingredient, pharmaceuticals, spices, beverages, cosmetics and dyes. Herbal medicine is hypothesized that plants contain natural substances that promote health and reduce disease. In the recently, attention to plant research has been increasing all over the world, and many studies are being conducted. Evidence has been collected showing the immense potential of medicinal plants used in various field traditional systems. Today we have a lot of interest in using herbs therapy [4]. *Caesalpinia bonducella* is an Indian herb mentioned in Ayurveda, the ancient Hindi system of medicine in India. Caesalpinia bonducella belongs to the family Caesalpiniaceae and is found worldwide, especially in India, Sri Lanka, the Andaman and Nicobar Islands, India, especially in the tropics. The species name "Bonducella" comes from the Arabic word "Bonduce", which means "small sphere", indicating the spherical shape of the seeds. It is used for various diseases. It effectively relieves vata dosha, making it the perfect panacea for stomach pains caused by bloating. Roasted seeds powdered with ghee soothe the condition and relieve pain. During the postpartum period, roasted seed powder, asafoetida, ghee and a little salt relieve tummy ache. Seed powder taken with milk controls diarrhea. The astringent bark of the seeds is beneficial as a medicine for diarrhea, dysentery and colitis. Some reported pharmacological activities are antidiabetic activity, abortive activity, antioxidant activity, antibacterial activity, antidiarrheal activity, antifilarial activity, antispermatogenic activity,

antitumor activity and antiulcer potential [5-8]. As per literature survey the plants containing kaempferol and quercetin-3-methylether are traditionally utilized for the cure of cancer and liver related disorders from the immortal time [9]. The exact mechanism of action for the hepatoprotective action of kaempferol and quercetin-3-methylether was still not revealed. With intent to propose the most probable mechanism of action of kaempferol and quercetin-3-methylether the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme.

EXPERIMENTAL WORK

Ligand Preparation:

2D Structure of ligands kaempferol and quercetin-3-methylether was drawn by using ChemDraw [10].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 [11].

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.[12].

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

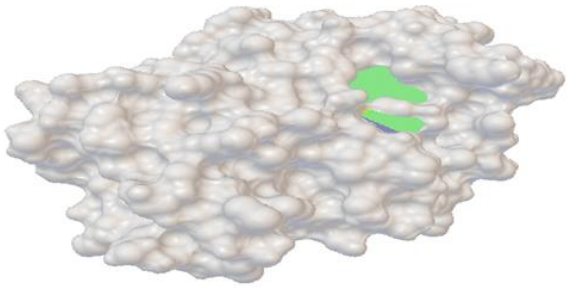


Figure 1: Grid box covering all active sites in PPARα enzyme (2znn).

Preparation of the docking file

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [13].

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 [14].

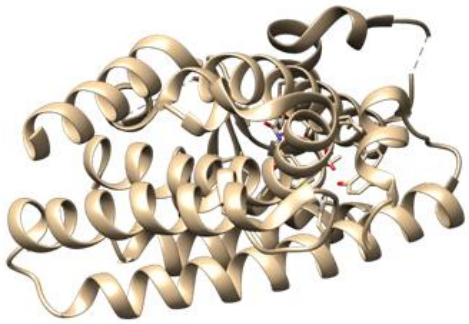


Figure 2: Crystal structure of PPARα enzyme. (PDB ID-2znn)

Molecular Docking Simulation Studies

Docking of ligand kaempferol and quercetin-3-methylether was performed against PPARα enzyme was performed by Autodock to establish its probable mechanism of action for their hepatoprotective effect. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible[15].

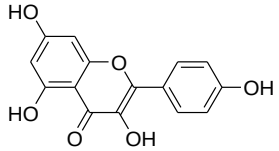
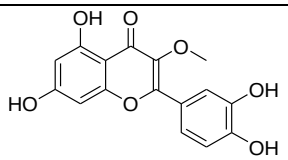
Toxicity & ADME-T Studies

The pharmacokinetics of kaempferol and quercetin-3-methylether 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[16].

RESULTS AND DISCUSSION

Liver is one of the most vital organs in the human body which is involved in the regulation of various biochemical functions. It bears noting that the lack of proper management of liver disorders by regular medicinal system gives more relevance for the development of effective and safe naturally derived hepatoprotective drugs. A plethora of studies suggest that the consumption of fruits and vegetables rich in natural antioxidants reduce the risk of chronic hepatic diseases. *Caesalpinia bonduc* seeds have been used in the folklore medicine since long time. The use of this plant has been quoted in the Ayurvedic and traditional scriptures. Plant is reported to have multiple restorative properties like anthelmintic, antibacterial, antidiuretic and recently it has received considerable attention to treat liver disorder. As per literature survey three compounds including, quercetin-3-methyl ether, kaempferol and kaempferol-3-O-α-L-rhamnopyranosyl-1→2)-β-D-xylopyranoside were isolated from EtOAc fraction, and out of these two compounds were evaluated for their hepatoprotective activity *via* molecular docking approach. Molecular docking has become an increasingly important tool for drug discovery. Flexible receptor molecular docking approaches, especially that including backbone flexibility in receptors, are a challenge for available docking methods. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity. For screening of hepatoprotective efficacy of phytoceuticals present in *Caesalpinia bonduc* seeds the PPARα receptors was targeted. The molecular docking of kaempferol and quercetin-3-methyl ether with PPARα showed binding energy (Kcal/mol) -7.43 & -6.63 having molecular interaction Tyr314, Ser280, Lys358, Met330, Met355, His440, Cys276, Cys278, Ile354, Phe273 and Val332, Met330, Cys276, Leu321, Lys358, Met355 respectively. The result was tabulated in table 2 and fig.1-8.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 kaempferol was shown in figure 9. The pharmacokinetic profiling of the quercetin-3-methylether ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, mutagenic and tumorogenic properties. The pharmacokinetic and toxicity profiling results of quercetin-3-methylether was shown in figure 10.

Table 2: Result of docking of PPARα enzyme

S.No	Compound Name	Structure	Binding Energy (kcal/mol)	Interacting Residues
1	kaempferol		-7.43	Tyr314, Ser280, Lys358, Met330, Met355, His440, Cys276, Cys278, Ile354, and Phe273
2	quercetin-3-methylether		-6.63	Val332, Met330, Cys276, Leu321, Lys358, and Met355

Interactions

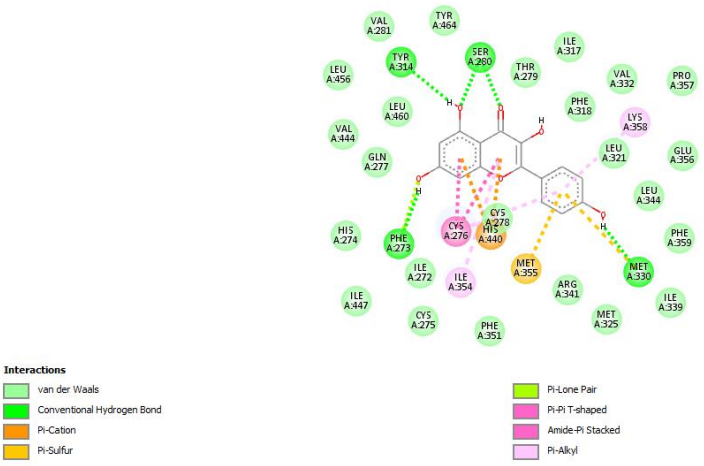


Figure 3: Two-dimensional binding interaction of kaempferol with PPARα enzyme

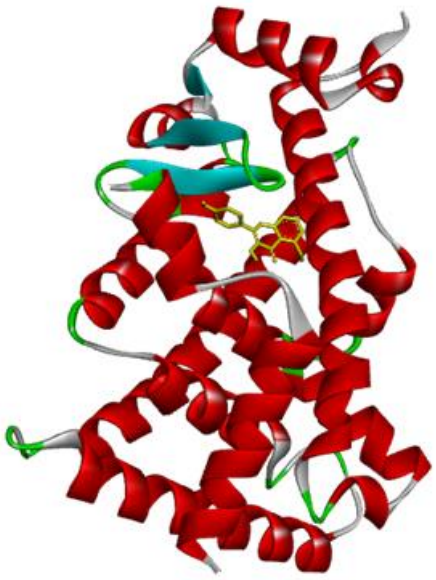


Figure 4: Three-dimensional binding interaction of kaempferol with PPARα enzyme

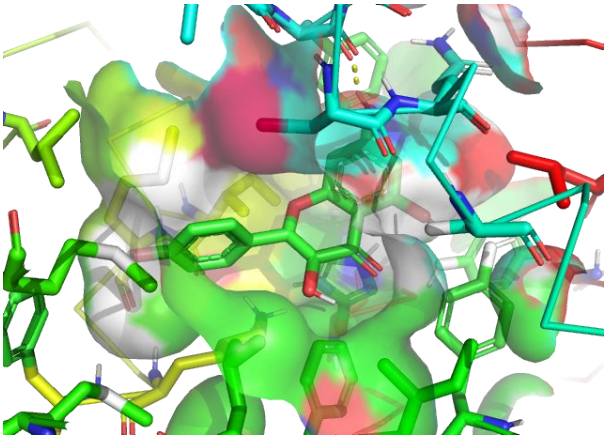


Figure 5: Binding conformation of ligand kaempferol with PPARα enzyme

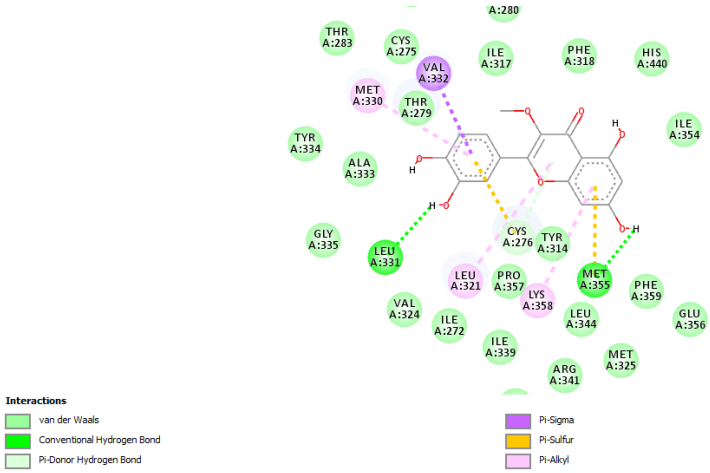


Figure 6: Two-dimensional binding interaction of quercetin-3-methylether with PPARα enzyme

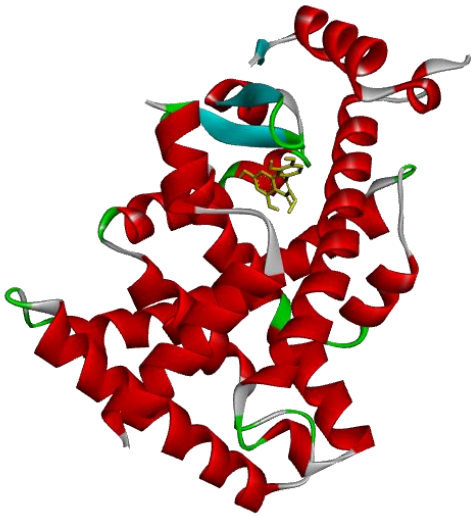


Figure 7: Three-dimensional binding interaction of quercetin-3-methylether with PPARα enzyme

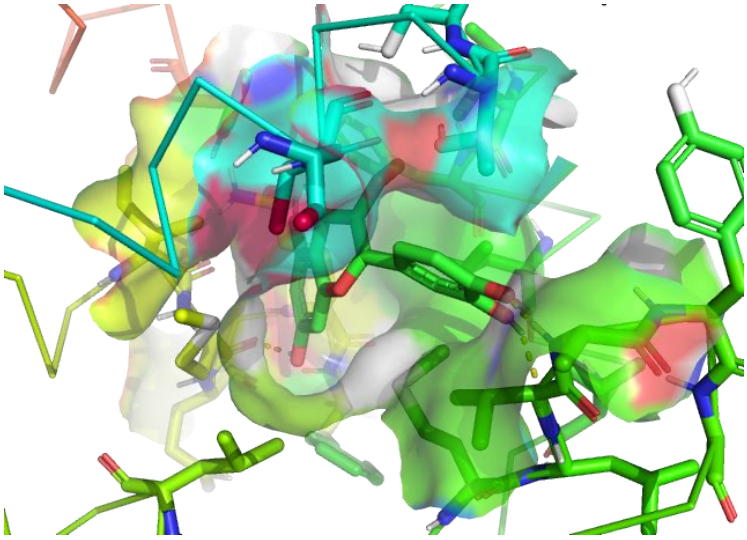


Figure 8: Binding conformation of ligand quercetin-3-methylether with PPARα enzyme

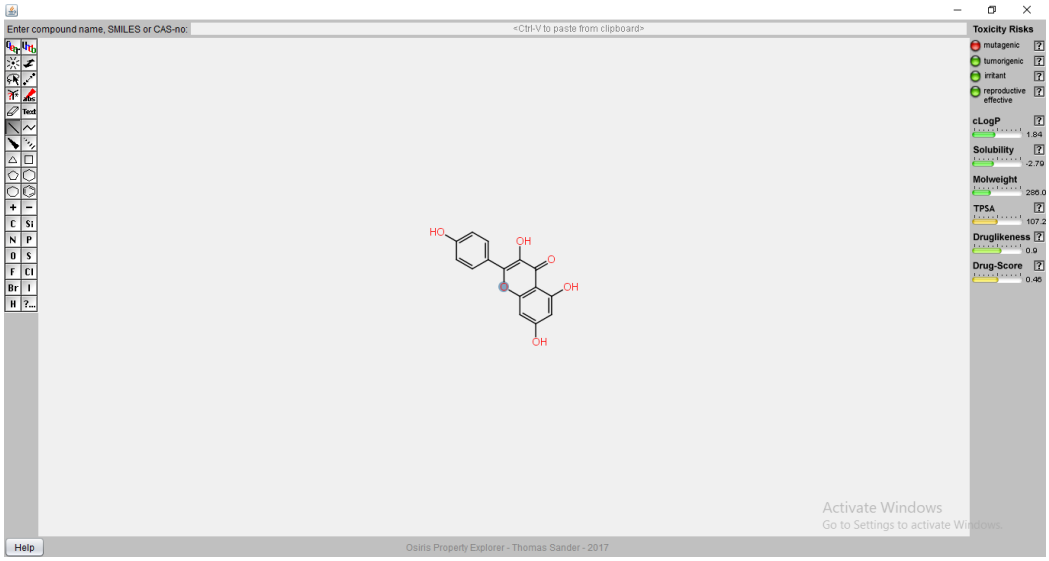


Figure 9: Pharmacokinetic and toxicity profiling of kaempferol

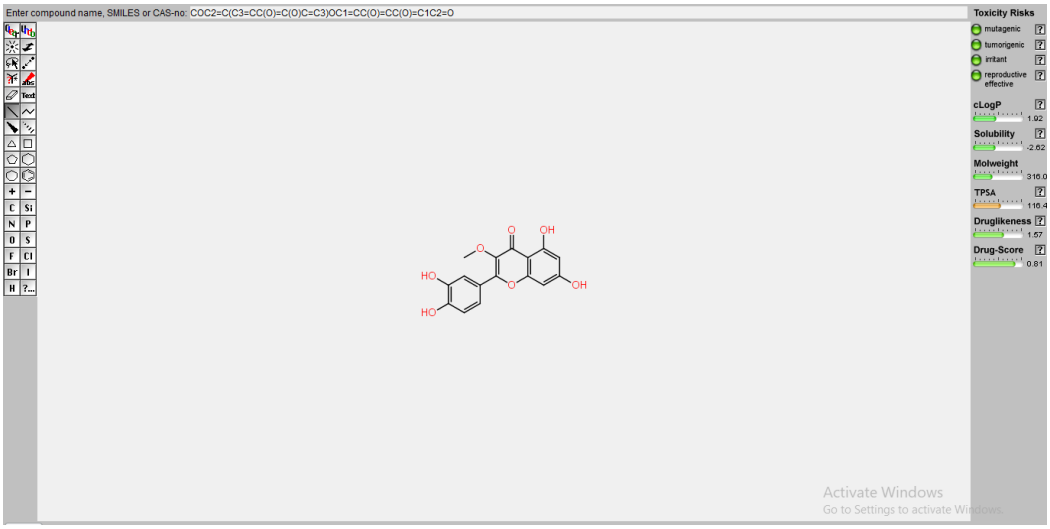


Figure 10: Pharmacokinetic and toxicity profiling of quercetin-3-methylether

CONCLUSION

Literature surveys show that plants containing kaempferol and quercetin-3-methyl ether have been traditionally used since time immemorial to treat cancer and liver disease. The exact mechanism of action of its hepatoprotective effect has not yet been elucidated. With intent to propose the most probable mechanism of action of kaempferol and quercetin-3-methylether 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 kaempferol and quercetin-3-methylether 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. Peroxisome proliferator-activated receptor alpha (PPARα), which had the largest number of compound interactions in our network study, was indicated as the key regulator of lipid peroxidation in ALD and NAFLD. In previous studies, PPARα may mediate NAFLD through a periostin-dependent pathway. It can regulate fatty acid oxidation by activating the periostin-dependent JNK signaling pathway and further activate hepatosteatosis in vivo and in vitro. Activation of

PPARα is also associated with increased mitochondrial glutathione (GSH) in the liver and decreased levels of circulating fatty acyl-carnitines. Furthermore, PPARα plays a protective role to enhance mitochondrial function in response to chronic alcohol consumption by adaptive transcriptional activation The outcome of present study showed the kaempferol and quercetin-3-methylether 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. With the endeavor of molecular docking result kaempferol and quercetin-3-methylether are effectively used as therapeutic strategy for liver disorder. Thus outcome studied proven the efficacy of *Caesalpinia bonduc* for hepatoprotective potential.

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