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Hepatoprotective Efficacy of Selegiline: Molecular Insight

Megha Mishra[1*], Sunil Kumar[1], Jitender K Malik[1]
[1]Institutes of Pharmacy, P. K. University, Shivpuri (M. P.), India

Abstract: Liver fibrosis is a form of wound healing that develops in response to persistent liver injury brought on by viruses, poisons, and medicines that are harmful to the liver. Inflammation is a hallmark of the condition, which is then followed by the formation of scar tissue via the deposition of extracellular matrix proteins. Hepatitis C virus (HCV) entrance has been linked to the host cofactor ephrin receptor A2 (EphA2). Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l-deprenyl. Selegiline (deprenyl) is a selective inhibitor of cerebral monoamine oxidase type B at the dosage (10 mg/day) used in patients with Parkinson's disease. Through this activity, the drug increases nigrostriatal dopamine levels, and may protect neurons against damage by free radicals and possibly exogenous neurotoxins.The exact mechanism of action for the hepatoprotective action of Selegiline was still not revealed. With intent to propose the most probable mechanism of action of Selegiline the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme.

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

Review Paper

***Corresponding Author:**
Megha Mishra
Institutes of Pharmacy, P. K. University, Shivpuri (M. P.), India

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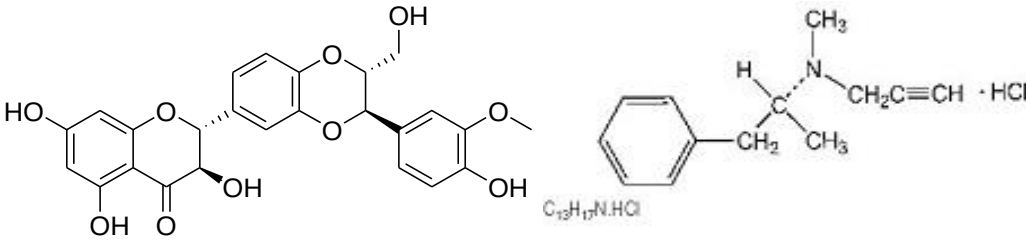
INTRODUCTION

Liver conditions include viral hepatitis, fatty liver, liver fibrosis, cirrhosis, and liver cancer pose major health risks to people and are among the world's biggest killers. Although there have been notable improvements in the last few decades, the majority of treatments still result in dismal patient outcomes. New preventative and therapeutic agents for liver disease are urgently needed due to the lack of available treatments and the severe side effects of current chemicals [1, 2]. The liver serves a variety of crucial roles as the body's primary metabolic organ. Reactive oxygen species (ROS) are activated by CCl4, xenobiotics, and other toxins, which are produced by cytochrome P450-dependent processes as a result of the creation of covalent bonds with lipoproteins and nucleic acids [3]. At a dosage of 10 mg per day, selegiline (deprenyl) is a selective inhibitor of cerebral monoamine oxidase type B used to treat Parkinson's disease. By increasing dopamine levels in the nigrostriatum, the medication also has the potential to shield neurons against damage caused by free radicals and perhaps exogenous neurotoxins [4, 5]. Additionally, selegiline prevents dopamine reuptake from synaptic clefts. Selegiline 10mg daily has no "cheese" effect because of its selectivity; it does not impede the breakdown of dietary amines like tyramine or enhance their indirect pressor effects. Selegiline is rapidly converted into L-methamphetamine and L-amphetamine after oral administration, which may explain the euphoria and insomnia experienced by many patients, while it seems more likely that selegiline's potentiation of dopaminergic activity with levodopa is to blame [6]. The medication is a helpful auxiliary. The exact mechanism of action for the hepatoprotective action of Selegiline was still not revealed. With intent to propose the most probable mechanism of action of Selegiline the docking based computational analysis has been performed against the hepatoprotective drug targets like PPARα enzyme [7-9].

Experimental Work

Ligand Preparation:

2D Structure of ligand (silibinin and Selegiline) was drawn using ChemSketch, the two-dimensional structure of was converted into 3-D structure and optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility 10]. The basic structure of ligand (silibinin and Selegiline) is given below:



2D structure of silibinin 2D structure of Selegiline

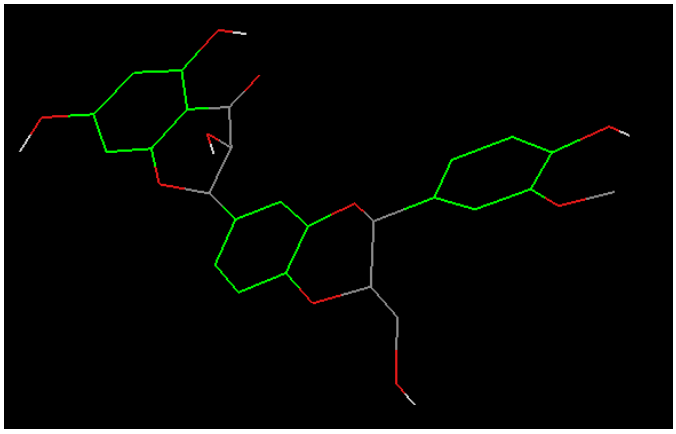


Figure 1: 2D and 3D conformer of Selegiline

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 0.419 Å and No. of points considered are 40, 54 and 40 points in the x, y, and z dimensions and -9.732, 11.403 and68.925 as x, y, z centers [11].

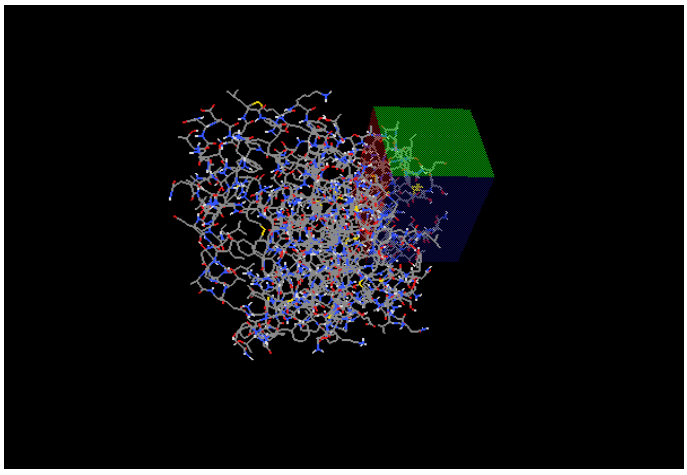


Figure 2: Grid box covering all active sites in receptor

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 [12].

Docking of PPARα enzyme with Silibinin and Selegiline

Crystal structure

The crystal structure of the protein consisting of receptor associated with bound ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (6LU7.pdb) registered in the Protein data bank was

used. The bound ligand peptide like inhibitors found within the receptor [13].

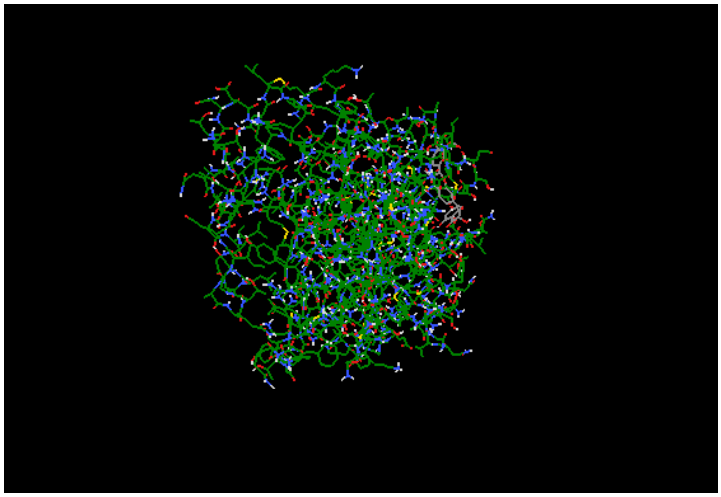


Figure 3: Crystal structure of PPARα enzyme with bound peptide like inhibitor ligand (PDB ID-6LU7)

Processing of Protein

The downloaded receptor protein is having two chains A and C, and both the chains have been used for experimental purpose. The bound ligand peptide like inhibitor was separated from the macromolecular complex by using software Chimera [14].

Molecular Docking Simulation Studies

Docking of Silibinin and Selegiline ligand on PPARα enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [15].

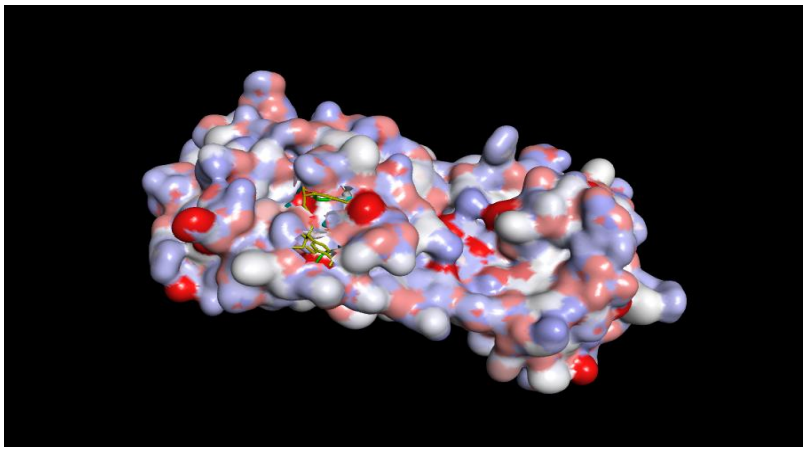


Figure 4: Binding mode of Silibinin within the active site of Receptor

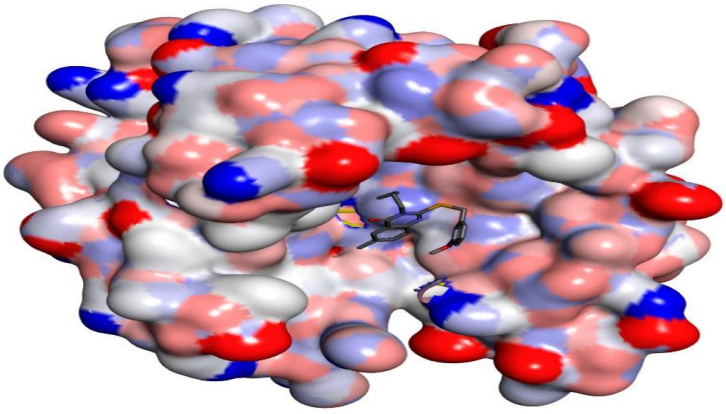


Figure 5: Binding mode of Selegiline within the active site of Receptor

Toxicity & ADME-T Studies

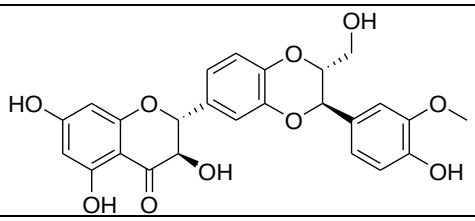
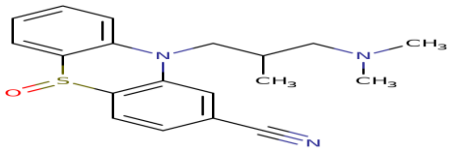
The modified lead molecules are studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [16].

RESULTS AND DISCUSSION

The liver is one of the most important organs in the human body involved in regulating various biochemical functions. It should be noted that the lack of adequate treatment of liver disease by the usual medical system makes the development of effective and safe natural-derived hepatoprotective agents more important. A number of studies suggest that eating fruits and vegetables rich in natural antioxidants may reduce the risk of chronic liver. Selegiline is an inhibitor of monamine oxidase used in the treatment of depression and as adjunctive therapy in combination with levodopa and carbidopa in the therapy of Parkinson disease. Selegiline has been associated with a low rate of serum enzyme elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury.

The molecular docking of silibinin and selegiline with PPARα enzyme revealed that (Table 1), it has exhibited the chemical interaction with the amino acids in the active pockets which is showed in Figure 3 & 4. Theoretically, the ligand molecule has shown encouraging docking score. The docking result of silibinin and selegline revealed that their docking scores was -7.92 kcal mol^{-1} & -7.01 kcal mol^{-1} (Table 1 & Fig 6 & 7) and it can predicted as a very good inhibitor of PPARα enzyme. The pharmacokinetic profile of silibinin and Selegiline reveals that it is having good pharmacokinetic profile without presence of any major toxic effects. The pharmacokinetic and toxicity profiling results of silibinin and Selegiline were shown in Figure 8 & 9.

Table 1: Results of docking of silibinin and Selegiline against PPARα enzyme

S. No	CompoundName	Structure	Binding Energy (Kcal/mole)	Ki (µM)
1	Silibinin(Std)		-7.92	1.56
2	Selegiline		-7.01	1.72

Interactions

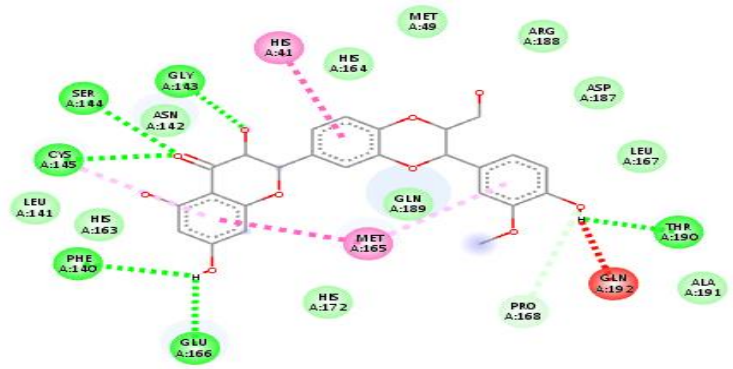


Figure 6: Binding interaction of Silibinin with PPARα enzyme

The silibinin interacts with the His41, Ser144, Phe140, Glu166, Pro168, Met165, Thr190 and Gly143 residues of PPARα enzyme to form a complex structure.

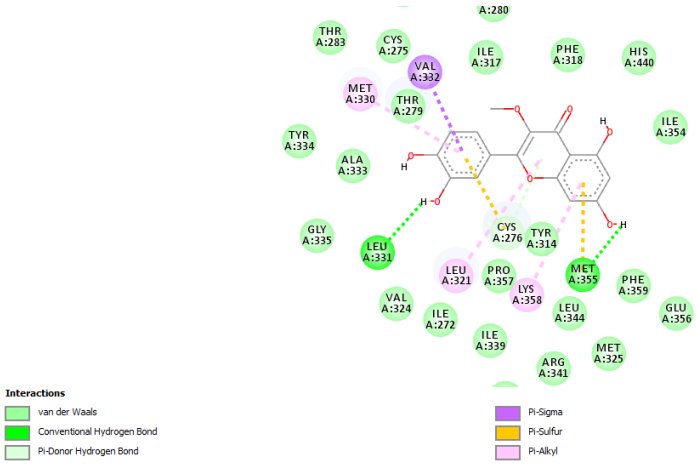


Figure 7: Two-dimensional binding interaction of Selegiline with PPARα enzyme

Toxicity & ADME-T Studies

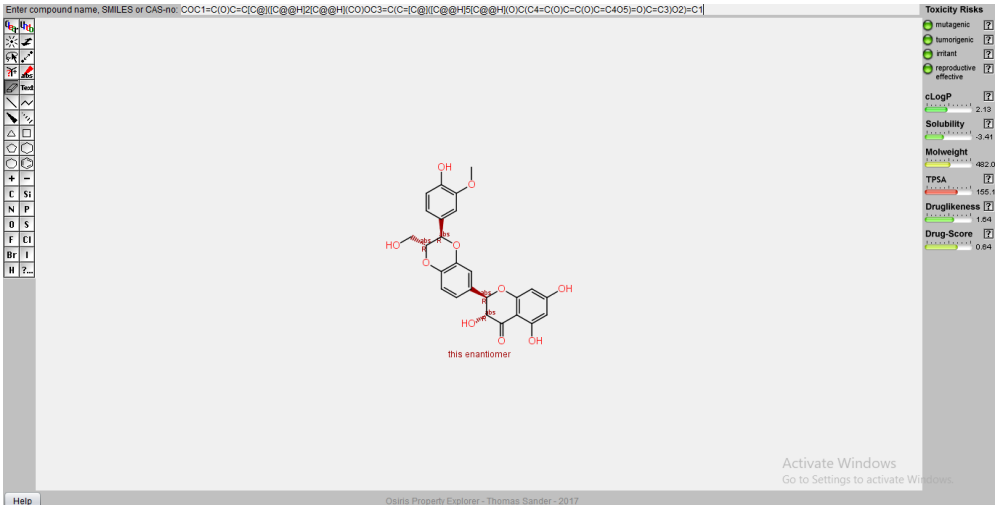


Figure 8: Pharmacokinetic and toxicity profiling of silibinin

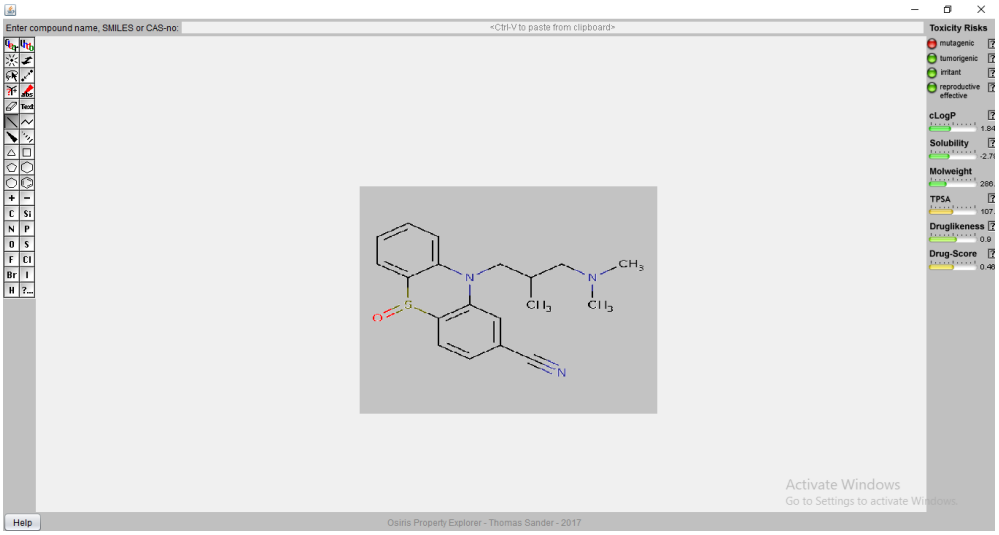


Figure 9: Pharmacokinetic and toxicity profiling of Selegiline

CONCLUSION

A literature review indicates that selegiline treats neural and liver alignments with dose dependent action. The exact mechanism of action of its hepatoprotective effects has not yet been elucidated. With the intention of proposing the most likely mechanism of action of selegiline, a docking-based computational analysis was performed on hepatoprotective drug targets such as the PPARα enzyme using silibilinin as a standard molecule. Docking analysis, chemical interactions, and subsequent physicochemical pharmacokinetic profiling revealed that selegiline exerts hepatoprotective effects via inhibition of his PPARα enzyme. Molecular docking analysis is one of the most basic and important strategies in drug discovery. This allows prediction of the molecular interactions that hold the protein and ligand together in the bound state. Molecular docking and MD simulations are very important techniques for understanding the binding interactions between ligand molecules and drug targets. Peroxisome proliferator-activated receptor alpha (PPARα), which has shown the majority of compound interactions in network studies, has been implicated as a 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 Selegiline 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 Selegiline are effectively used as therapeutic strategy for liver disorder. Thus outcome studied proven the efficacy of Selegiline for hepatoprotective efficacy.

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