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Potentiation of myricetin against alcohol-induced hepatotoxicity: *In-silico* molecular docking validation

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Abstract
Background: Alcohol-associated liver disease (ALD) and liver-related mortality constitute a significant worldwide health burden, resulting from acute or chronic alcohol usage. Chronic alcohol intake impairs the liver's natural defence mechanisms and likely disrupts the intestinal barrier system and mucosal immune cells, resulting in diminished nutritional absorption. Flavonoid intake, characterised by liver-protective, antioxidant, and anti-inflammatory properties, is a crucial dietary element for improving liver function.
Purpose: The present study was conducted to evaluate the efficacy of Myricetin for their hepatoprotective potential.
Methodology: The scientific validation of the present work was conducted using a computational molecular docking analysis of the lead compounds myricetin against the *CYP2E1* enzyme.
Result: The results of the current analysis indicate that the myricetin are efficient hepatoprotective agent, demonstrating binding affinities to the target protein *CYP2E1* with binding energy of -8.26 kcal/mol.
Conclusion: The results demonstrated that chosen lead compound for further study exhibited substantial inhibitory efficacy against *CYP2E1* hence indicating its potential role in alcohol induced liver toxicity.

Keywords: Myricetin, *CYP2E1*, alcohol induced liver toxicity & molecular docking

Introduction
Alcoholic fatty liver disease (AFLD) is a potentially pathological condition that may advance to steatohepatitis, fibrosis, and cirrhosis, resulting in an elevated risk of hepatic failure and mortality. Alcohol promotes fatty liver by elevating the ratio of reduced nicotinamide adenine dinucleotide to oxidised nicotinamide adenine dinucleotide in hepatocytes; enhancing the activity of hepatic sterol regulatory element-binding protein (SREBP)-1, plasminogen activator inhibitor (PAI)-1, and early growth response-1; and diminishing hepatic peroxisome proliferator-activated receptor-α activity. Alcohol stimulates the innate immune system and disrupts the immunological response, leading to excessive production of tumour necrosis factor (TNF)-α by activated Kupffer cells, which subsequently alters hepatic SREBP-1 and PAI-1 activity. Alcohol misuse facilitates the translocation of bone marrow-derived cells (BMDCs) to the liver and subsequently alters TNF-α expression in BMDCs. Chronic alcohol use initiates a sympathetic hyperactivity-induced feedback loop that stimulates hepatic stellate cells (HSCs), leading to the overproduction of TNF-α by these cells. Carvedilol may inhibit this feedback loop by diminishing sympathetic activity, hence reducing the course of AFLD. Clinical trials assessing the combined therapy of carvedilol and a TNF-α inhibitor for the treatment of individuals with AFLD are necessary to avert the progression of alcoholic liver disease [1]. Toxic liver disease, or hepatotoxicity, comprises many distinct conditions that result in increasing liver damage, dysfunction, and potentially fatal outcomes. Environmental toxicity, alcoholic and non-alcoholic steatohepatitis, viral hepatitis, and cirrhosis are instances of liver illnesses that, while not mutually exclusive, can ultimately result in deadly liver disease. In young people, several variables contribute to the risk of liver injury, including increasing obesity rates, excessive alcohol intake, and the use of illicit drugs, either singularly or in conjunction with other substances. There is an immediate necessity to enhance comprehension of the factors contributing to the recent increase in lethal liver disease within a population that has not historically been at significant

risk [2]. Flavonoids, derived from natural sources, possess promising health benefits, particularly for human well-being. These natural compounds contain secondary metabolites derived from plants and possess the ability to influence biological processes in various ways. This activity forms the basis for cancer prevention and treatment [3]. Flavonoids are classified into several classes, including anthocyanidins, isoflavonoids, chalcones, flavonols, flavones, flavononols, and flavanones. Molecular mechanisms of Flavonoid in hepatoprotection [4]. Flavonoids can enhance the expression of SOD, HO-1, GSH and Nrf-2, Inhibiting the expression of pro apoptotic proteins such as caspase-3, caspase 7, caspase 9, cytochrome C and Bax as well as the expression of pro-inflammatory proteins like IL-1, IL-6, TNF, ROS and NF-κB, and production [5]. Growing evidence suggests that flavonoids positively influence lipid metabolism, oxidative stress, inflammation, insulin resistance, apoptosis, cellular proliferation, tumours, and hippocampal brain-derived neurotrophic factor, thereby aiding in non-alcoholic/alcoholic liver disease, type II diabetes, cardiovascular disease, cancer, memory, and cognitive function. Flavonoids are regarded as safe protectors due to their diverse functions. This investigation, informed by emerging research highlighting flavonoids as potential agents in the initiation, promotion, and progression of alcoholic liver disease (ALD), aimed to explore the hepatoprotective efficacy of myricetin targeting CYP2E1 through *In-silico* molecular docking.

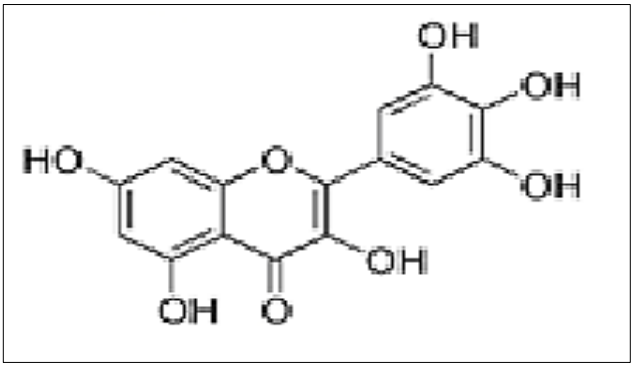
Experimental Work

Selection Lead Molecule

Flavonoids are a category of polyphenolic bioactive chemicals derived from plants, characterised by diverse chemical structures and characteristics. Over 9,000 unique flavonoid molecules have been discovered, demonstrating their regulation of several developmental processes and their significant biological significance in living creatures. The progress in phytochemical research demonstrates that flavonoids possess several health advantages, including antioxidant properties, free radical scavenging abilities, and anticancer effects. The fundamental structures consist of C6-C3-C6 rings with diverse substitution patterns, leading to a series of subclass compounds, and the correlations between chemical structures and bioactivity have been examined. Numerous studies have extensively associated the hepatoprotective effects of bioactive flavonoids from plants with their antioxidant properties, anti-inflammatory activities, interactions with Sterol Regulatory Element-binding Proteins (SREBP), Peroxisome Proliferator-activated Receptor gamma (PPARγ) receptors, and inflammatory mediator cytokines [6].

Myricetin

Myricetin scientifically designated as 3,3′,4′,5,5′,7-Hexahydroxyflavon, is a flavonoid compound prevalent in numerous natural plants. Myr has demonstrated several biological roles, including immunomodulatory and anti-inflammatory properties. Myr has demonstrated an inhibitory effect on LPS-induced inflammation in RAW 264.7 macrophages and TNF-α-induced A549 cells via the NF-κB signaling pathway [7]. Myricetin has been found as free molecule or glycosidically bound such as myricetin-3-*O*-β-d-galactopyranoside, myricetin-3-*O*-(4”-acetyl)-α-l-arabinopyranoside, myricetin-3-*O*-(3”-acetyl)-α-L-arabinopyranoside, myricetin-3-*O*-α-l-rhamnopyranoside, myricetin-3-*O*-β-d xylopyranoside, myricetin-3-*O*-(6”-galloyl)-β-d-galactopyranoside, myricetin 3-*O*-α-l-arabinofuranoside, myricetin-3-*O*-(2”-*O*-galloyl)-α-l-rhamnoside, myricetin-3-*O*-(3”-*O*-galloyl)-α-l-rhamnoside, and myricetin-3-*O*-α-l-rhamnoside [8].



Selection of Target protein

Cytochrome P450 2E1 (CYP2E1) is essential in hepatotoxicity caused by alcohol use and several xenobiotics. CYP2E1 produces reactive metabolites that provoke oxidative stress, mitochondrial malfunction, and cellular apoptosis. This enzyme seems to contribute to the advancement of obesity-related fatty liver to non-alcoholic steatohepatitis. Increased CYP2E1 activity in non-alcoholic fatty liver disease (NAFLD) is considered to cause the overproduction of reactive oxygen species, leading to oxidative stress, necroinflammation, and fibrosis [9]. Hepatic cytochrome P450 2E1 (CYP2E1, also known as P450j) has a distinctive role in liver pathophysiology. CYP2E1 is pivotal in the development of several acute and chronic liver disorders caused by pharmaceuticals, toxic substances, and alcohol use [10-11].

Designing of current investigation

This study aimed to assess the hepatoprotective effect of myricetin utilising Autodock 4.2 software. Phyto-constituents were obtained from the PubChem database. The three-dimensional structure was obtained from the Protein Data Bank (PDB). The active region of the target protein was identified using CASTP (Computed Atlas of Surface Topography of Proteins). Information on protein-ligand interactions is acquired using the Protein Ligand Interaction Profiler.

Scientific Validation of Hepatoprotective Efficacy of selected flavanol derivatives by *In-silico* molecular docking

Molecular docking studies

Ligand Preparation:

2D Structure of genkwanin and myricetin were drawn using ChemSketch [12], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

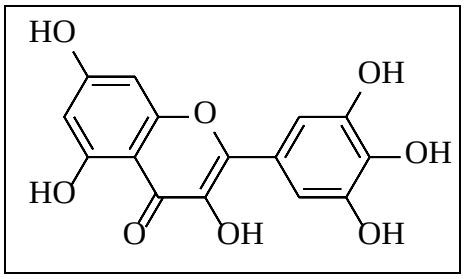


Fig 1: 2D structure of Myricetin

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 and grid points for the considered receptor in the current study are given in table 1 [13-15].

Table 1: Grid parameters used in current docking analysis

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	CYP2E1	50	50	50	0.392	5.697	-8.543	14.228

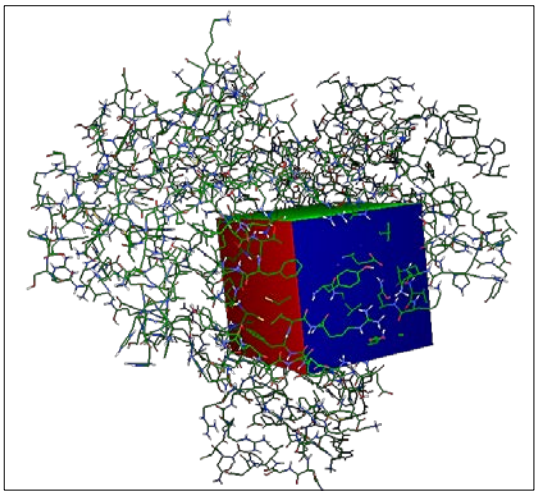


Fig 2: Grid box covering all active sites in CYP2E1 receptor

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 [16-19].

Docking Study

Crystal structure

The crystal structure of the protein consisting of CYP2E1 receptor was downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [20-23]. The complex ligand was separated by using Chimera software for all the target receptors.

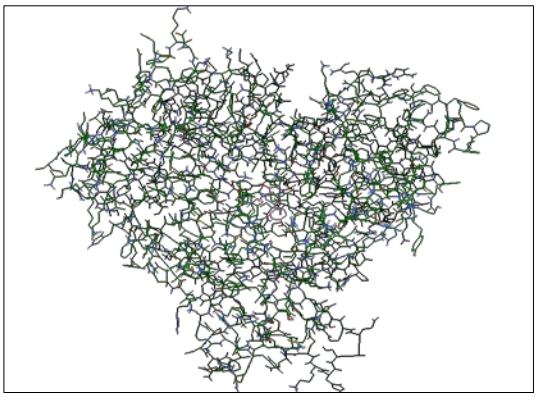


Fig 3: Crystal structure of CYP2E1 receptor (PDB ID-3lc4)

Processing of Protein

The downloaded receptor protein is having two chains, i.e. chain A and B, out of which has chain A has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [24-25].

Molecular Docking Simulation Studies

Docking of ligand genkwanin and myricetin against CYP2E1 receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [26].

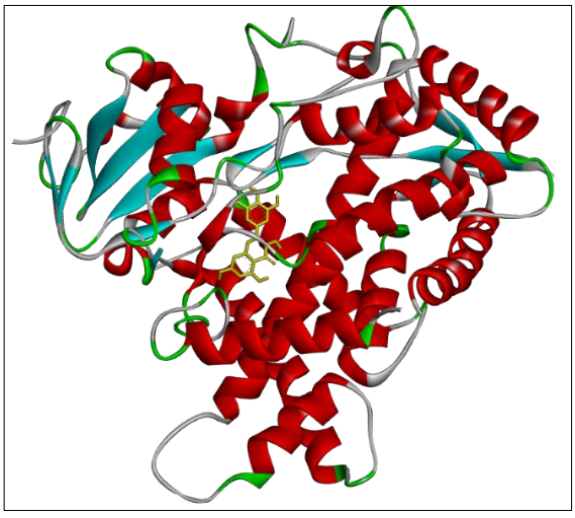


Fig 4: Binding mode of myricetin within the active site of CYP2E1 receptor

Toxicity & ADME-T Studies

The ligand molecules *viz*. genkwanin and myricetin 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 [27].

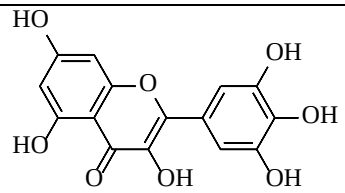
Result and Discussion: Medicinal plants are a natural boon to humanity, playing a vital role in the protection, maintenance, and enhancement of our health. Traditional medicines serve as alternative therapies due to their pharmacological advantages, little or absent adverse effects, and abundant availability in nature. Phytochemicals are vital plant compounds that mitigate necrotic cell death, rejuvenate the antioxidant defence system, curtail oxidative stress, and inhibit tissue inflammation and mitochondrial malfunction. Alcohol is recognised for causing liver damage and fibrosis via oxidative stress, formation of acetaldehyde, alterations in CYP2E1 function, and lipid accumulation. According to the existing scientific evidence, flavonoids exhibit many pathways that contribute to their established hepatoprotective benefits, including anti-inflammatory, antioxidant, antiapoptotic, antihyperlipidemic, anticancer, antiviral, and antifibrotic properties.

The result of molecular docking of myricetin was tabulated in table 2, showing binding energy -8.26 kcal/mol against *CYP2 E1 protein* respectively. The binding mode showed in fig.4 whereas 3D &2D binding interaction was shown in fig.5-6. The selected lead molecule showed good interaction with selected ligand. The binding interaction of lead molecules are as follows:

Compound	Vander waal's	H bond	Unfavourable Donar-Donar	π-cation	π-Donar H bond	π-Alkyl
Myricetin	Ala299 Thr303 Gly439 Ile114 Trp122 Ser431 Leu393 Phe430	Pro429 Cys437 Arg100 Arg435 Asn367	Leu368	Arg126	Ala438	Val364 Ile115

The pharmacokinetic profiling of the *Myricetin* 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 lead molecule was shown in fig.7 & table. 3-5. Myricetin follows strictly Lipinski rule. The results of the current inquiry indicated that Myricetin had significant inhibitory effects on the CYP2E1 protein, consequently mitigating oxidative stress, the generation of reactive oxygen species (ROS), inflammation, the deactivation of hepatic stellate cells, liver fibrosis, and hepatotoxic damage. They also induce the deactivation of hepatic stellate cells and inhibit liver fibrosis.

Table 2: Results of docking of Myricetin against CYP2E1 receptor

S. No	Compound Name	Structure	Binding Energy CYP2E1
1	*Myricetin*		-8.26 (ki: 1.52)

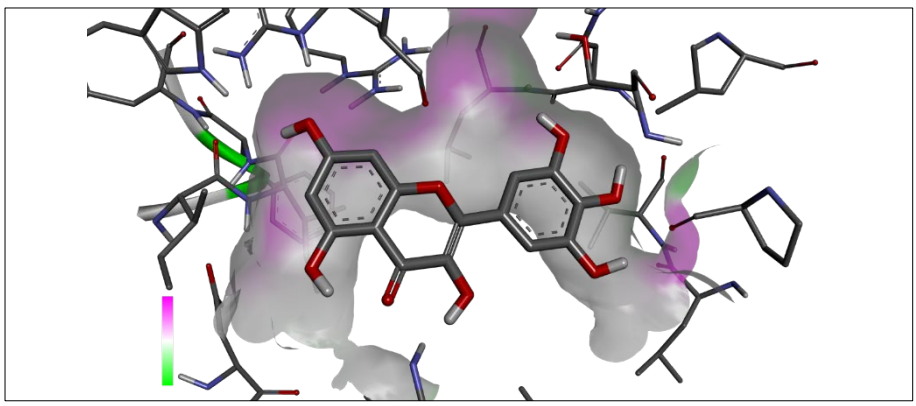


Fig 5: Three-dimensional binding mode of myricetin within the active site of CYP2E1 receptor

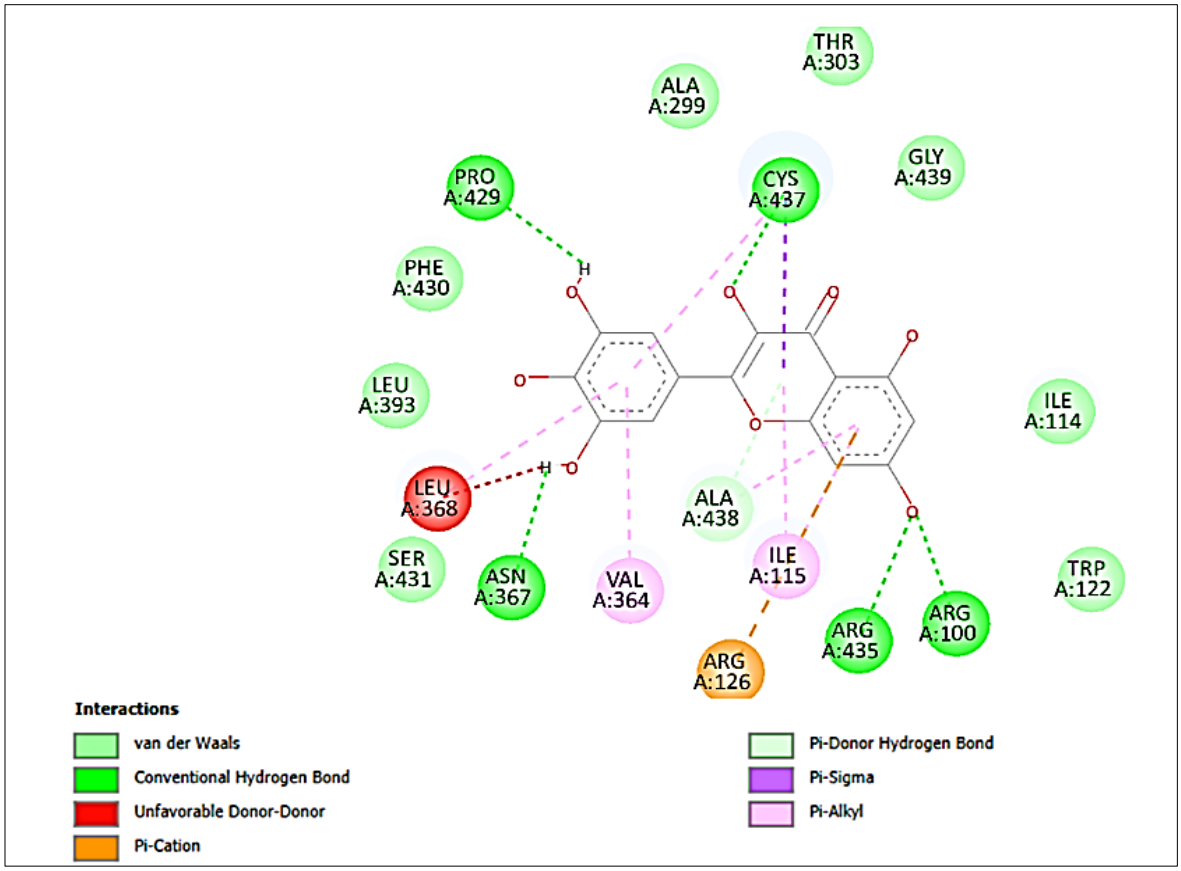


Fig 6: Two-dimensional binding mode of myricetin within the active site of CYP2E1 receptor

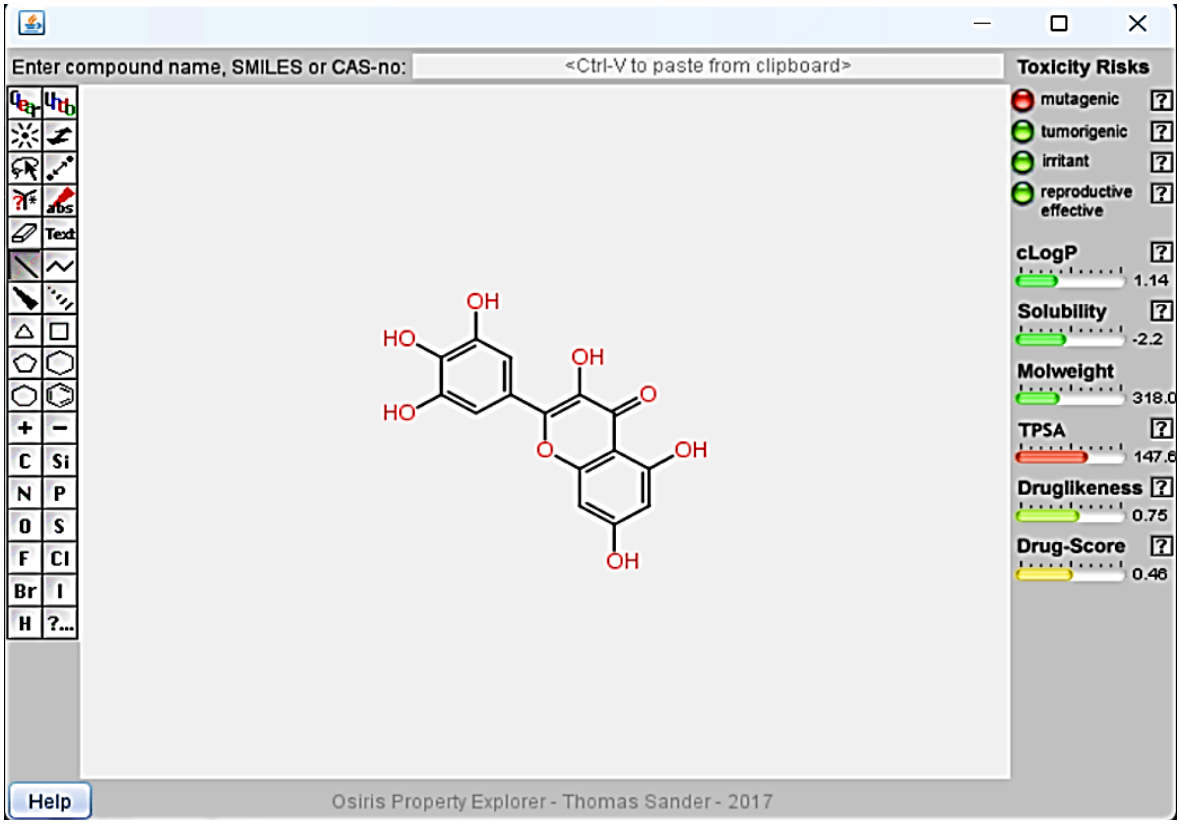


Fig 7: Pharmacokinetic and toxicity profiling of myricetin

Table 3: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	Tumorigenic	Irritant	Reproductive effectivity
Myricetin	NO	NO	Yes	NO

Table 4: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Myricetin	1.14	-2.2	318	14.76	0.75	0.46

Table 5: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar(<5)	H bond acceptor (<10)
Myricetin	Yes	6	8

Conclusion

Flavonoid intake, characterised by liver-protective, antioxidant, and anti-inflammatory properties, is a crucial dietary element for improving liver function. These compounds possess hepatoprotective, antioxidant, and anti-inflammatory properties. Flavonoids can protect the liver from toxins due to their pharmacological anti-inflammatory, antioxidant, anti-cancer, and antifibrogenic capabilities. The antioxidant properties of natural substances and their ability to stimulate the body's intrinsic antioxidant defence system are largely attributed to their hepatoprotective effects. *Cytochrome P450 2E1* (CYP2E1) is essential in hepatotoxicity caused by alcohol use and several xenobiotics. CYP2E1 produces reactive metabolites that cause oxidative stress, mitochondrial malfunction, and cellular apoptosis. This enzyme seems to contribute to the advancement of obesity-related fatty liver to non-alcoholic steatohepatitis. Increased CYP2E1 activity in non-alcoholic fatty liver disease (NAFLD) is considered to cause an overproduction of reactive oxygen species, subsequently leading to oxidative stress, necroinflammation, and fibrosis. This toxicity mostly arises via the generation of reactive metabolites, although CYP2E1 stimulation may also contribute independently through the synthesis of reactive oxygen species from molecular oxygen. Alcohol misuse exemplifies a scenario linked to CYP2E1 induction and the production of ROS by CYP2E1; nevertheless, there is growing evidence that several xenobiotics can similarly augment CYP2E1 expression and activity in hepatic or other tissues. The recent analysis revealed that Myricetin had significant binding energy. The structural unit of the identified compound played a significant influence in hepatoprotective action. Myricetin, with an extra hydroxyl group, exhibited higher activity; the presence of OH groups at the C-3, C-4, and C-5 positions strengthened its inhibitory capacity against reactive oxygen species, hence augmenting its antioxidant activity. The lack of a double bond enhances inhibitory potential, whereas the Pyrollol-B ring and hydroxyl group are accountable for biological action. The arrangement of hydroxyl groups has a significant effect in controlling biological activity. The results of the current experiment indicated that the chosen polyphenolic flavone derivative (myricetin) had substantial inhibitory effects on the CYP2E1 protein, hence preventing mitochondrial dysfunction and oxidative stress, and demonstrated a protective effect against liver toxicity.

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