Published online in http://ijam.co.in ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 15 (2), 2024; 444-451

Insilico Studies Unveiling the Hepatoprotective Potential of *Morus alba Linn*: Docking and ADMET Analysis

Research Article

Abha Lichade[1], Aayushi Deshmukh[1],Yashwant Nakhate[2*], Pranali Kalambe[3]

1. Student, 3. Assistant Professor,
Dr. ArunMotghare College of Pharmacy, Konda-Kosra, Maharashtra, India.
2. Assistant Professor, School of Pharmacy, G.H. Raisoni University, Amravati, Maharashtra. India.

Abstract

The goal of the drug discovery process is to search for new drug molecules which can bind to a specific target known to be involved in causing a disease. This study aims to identify potential inhibitors against the TGF-β-type-I receptor (PDB Id-1VJY) by developing ligands through molecular docking and ADMET-based virtual screening. The plant-based nature product database of *Morus alba Linn* is utilized for this purpose. The resultants hits, identified as actives were evaluated by molecular docking studies to get insight into their potential binding interaction with the target protein. 1-deoxynojirimycin (A1), Catechin (A2), Cyanidine-3-rutinoside (A3), Cyclomulberrin (A4), Kaempferol (A5), Kuwanon-G (A6), Morusin (A7), Mulberrin (A8), Mulberrofuran-G (A9), Quercetin-3-(6-malonylglucoside) (A10), Quercitrin (A11), Rutin (A12), were selected for the molecular docking.ADMET based virtual screening ligand/Compound (A1, A2, A4, A5, A7, A8, A9) passes the lipinski's rule. Compound A4 (-10.7 kcal/mol), A5 (-10.4 kcal/mol) and A8 (-9.9 kcal/mol) had the highest binding affinity to the active site in TGF-β-type-I receptor. In conclusion, based on docking score and ADMET virtual screening, Cyclomulberrine (A4) (-10.7 kcal/mol) more affinity toward the TGF-β-type-I receptor that could be investigated further in the search for Hepatoprotective agent.

Keywords: *Morus alba Linn,* Hepatoprotective activity, Insilico studies, Docking, ADMET analysis.

Introduction

The search for novel therapeutic agents has led researchers to explore the field of in-silico studies, enabling the rapid identification and development of potential drugs. In silico methods like molecular docking are one type of solution to current problems in drug development.

Computer-aided drug design (CADD) comprises a set of techniques that provide a cost-efficient approach to In silico methods like molecular docking are one type of solution to current problems in drug development identifying potential drug candidates.

Among the extensive array of natural resources available, plants have long been recognized for their diverse pharmacological properties. One such plant is *Morus alba Linn.* commonly known as mulberry, is a plant rich in both medicinal and nutritional benefits. *Morus alba Linn* has shown a variety of pharmacological activities that make it an attractive subject for further research in medicine. These activities include antimicrobial, anti-inflammatory, antioxidant, anti-cancer, and cardiovascular effects, as well as hypoglycemic, hypolipidemic, liver-protective, anti-tumor, and immunoregulatory effects. The root bark of *Morus alba Linn* also contains compounds with antioxidant, anti-α-glucosidase, antityrosinase, and anti-inflammatory properties.

Additionally, *Morus alba Linn* has demonstrated immunostimulatory, antibacterial, and anticancer properties, as well as the ability to inhibit acetylcholine esterase. Other pharmacological activities of *Morus alba Linn* include antiplatelet, anxiolytic, anti-asthmatic, anthelmintic, antidepressant, immune-modulatory, and cardioprotective effects. Together, these diverse pharmacological properties suggest that *Morus alba Linn* may hold promise as a source of therapeutic agents(1-7). Ancient Chinese medicinal texts have documented the health advantages of mulberry, highlighting its primary functions such as nourishing the liver and kidneys, replenishing yin and blood, and enhancing vision. According to authoritative work, "Indian Medicinal Plants," *Morus alba Linn* has been recognized for its potential hepatoprotective activity.

Most chronic liver diseases are marked by an excess buildup of extracellular matrix (ECM) components, particularly fibrillar collagen, a condition known as liver fibrosis (8). Liver fibrosis is a dynamic condition that typically develops as a consequence of liver injuries, including chronic inflammation, viral hepatitis, alcohol abuse, metabolic liver diseases, and

*** Corresponding Author:**
Yashwant Nakhate
Assistant Professor,
Department of Pharmacognosy,
School of Pharmacy, G.H. Raisoni University,
Amravati, Maharashtra, India-444701.
Email Id: yashwant6nakhate@gmail.com

other factors(9). When liver injuries persist, the accumulation of fibrillar collagen leads to fibrosis, which can eventually impair liver function. In advanced stages, liver fibrosis can result in cirrhosis, hepatocellular carcinoma, liver failure, and portal hypertension (10,11). Despite significant advances in understanding the mechanisms that cause liver fibrosis, there are limited treatment options available for this condition (12-16). The hepatoprotective activity of certain agents such as *Morus alba Linn.* has the potential to impede the progression of liver fibrosis.

Morus alba Linn. is a tree or shrub that grows quickly and has a cylindrical trunk measuring 1.8m in circumference. The bark is rough and dark grayish-brown with longitudinal cracks and the latex is white or yellowish-white.

Figure 1: Morus alba Linn tree

Figure 2: A pictorial description of *Morus alba Linn.*

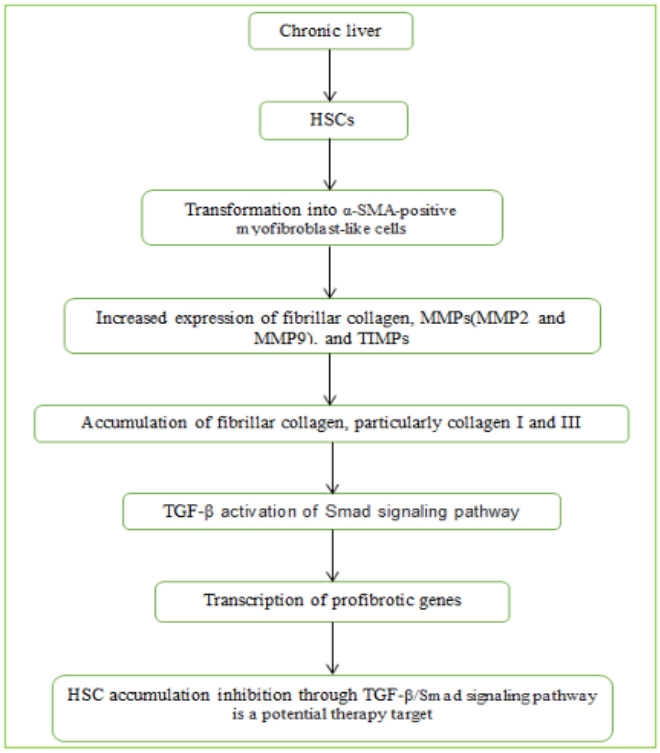
The stem is lateral, scaly, and coral, with two rows of oval or nearly oval leaves that are simple trilobal, dentate, and palm-shaped with three veins at the base. The flowers are greenish in colour and have four free scale-like petals, four stamens, and a pistil shape. The male flowers are loose and raceme-like catkins, while the female flowers have long or short spikes with an ovary obstruction, 1-(2-) chamber, single ovule, two styles, and a fan shape that contains the ovaries and has one ovule. The fruit is an ovarian syncarpous with some drupes surrounded by fleshy perianths up to 5 cm in length(17,18).The leaves of *Morus alba* Linn, which belong to the family Moraceae and genus *Morus*, are widely used in Asian countries as ethnomedicine and functional foods, such as tea, beverages, and noodles, due to their biological and nutritional value. Mulberry leaves are considered a medical-food homologous plant that is rich in protein, vitamins, and functional components. They are primarily used as raw materials for silkworm rearing, traditional Chinese medicine, and animal feed. The crude protein content of mulberry leaves is approximately 17-25% (nitrogen content is about 2.72-4%), indicating that they have significant nutritional value (19,20). Also the root and bark extracts of *Morus alba* Linn have gained significant attention for their hepatoprotective activity. Various studies have demonstrated the ability of these extracts to protect hepatocytes against injury, reduce liver inflammation, and modulate key cellular signaling pathways involved in liver fibrosis.The phytoconstituents found in *Morus alba* Linn, including 1-deoxynojirimycin, catechin, cyanidin-3-rutinoside, cyclomulberrin, kaempferol, kuwanon G, morusin, mulberrin, mulberrofuran G, quercetin 3-(6-malonylglucoside), quercitrin, and rutin. Have been demonstrated to exhibit hepatoprotective activity(21).

Activated hepatic stellate cells (HSCs) are the primary source of fibrillar collagen in the injured liver. In a healthy liver, HSCs are quiescent and serve as the primary storage site for vitamin A in the space of Disse. However, following chronic injury, HSCs undergo a significant transformation into α-smooth muscle actin (α-SMA)-positive myofibroblast-like cells that increase their expression of fibrillar collagen, matrix metalloproteinases (MMPs) such as MMP2 and MMP9, and tissue inhibitors of metalloproteinases (TIMPs). As a result, fibrillar collagen accumulates in the liver, particularly collagen I and III. Studies suggest that transforming growth factor beta 1 (TGF-β1) plays a crucial role in this pathogenesis by activating its downstream Smad signalling pathway. Smads are categorized into three groups based on their structure and function: receptor-activated Smads (R-Smads) include Smad2/3, common Smad (Co-Smad) is Smad4, and inhibitory Smads (I-Smad) include Smads 6, 7, and 8. When TGF-β1 binds to its receptor, Smad2/3 becomes phosphorylated and binds with Smad4. These complexes then translocate into the nucleus where they activate transcription of profibrotic genes. Therefore, inhibiting the accumulation of activated HSCs by modulating either their activation and/or proliferation or promoting their apoptosis through the TGF-β/Smad signalling pathway is a potential target for therapy (22-28).

In addition to its key role in hepatic fibrogenesis, the immune system also plays a significant part in the pathogenesis of liver fibrosis. This occurs through the infiltration of immune cells, including lymphocytes and monocytes, into the liver, leading to inflammation and fibrosis. Moreover, an imbalance between pro-inflammatory and anti-inflammatory cytokines can worsen the fibrotic process. By delving into these supplementary aspects of liver fibrosis within the context of the immune system, we can uncover valuable

insights regarding potential therapeutic targets for the advancement of hepatoprotective interventions (29).

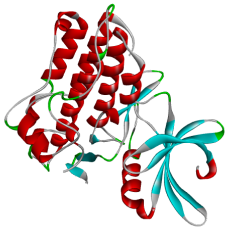
Figure 3 : A chart representing the pathophysiology of activated hepatic stellate cells (HSCs) in the injured liver



Materials and methods

1) Protein/Macromolecule

Figure 4: The crystal structure of the TGF beta type 1 receptor (PDB ID: 1VJY)

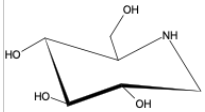
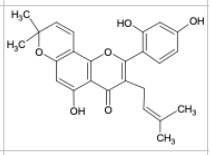
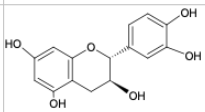
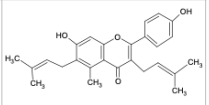
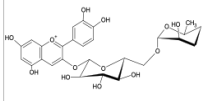
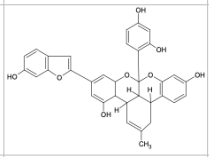
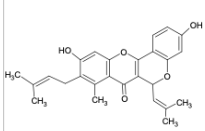
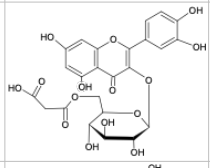
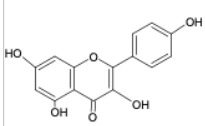
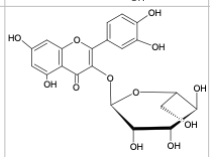
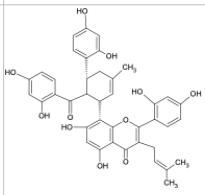
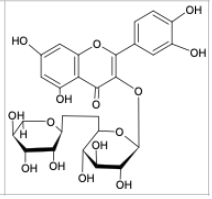


The TGF-beta is involved in a number of disease processes in the liver. In particular, TGF-beta has been shown to play a key role in the development of liver fibrosis, which is characterised by the excessive accumulation of extracellular matrix proteins and the activation of hepatic stellate cells.

As such, targeting TGF-beta signaling pathways has emerged as a potential therapeutic strategy for the treatment of liver fibrosis and other fibrotic diseases (30).

The crystal structure of the TGF beta type 1 receptor (PDB ID: 1VJY) was selected for docking studies based on a literature review. Prior to the interaction study with the ligands, the macromolecule was prepared by removing water molecules and het atoms to ensure a clean and focused analysis.

Table 1: Ligands

S.No.	Compound Name	Pubchem ID	Compound structure	S.No.	Compound Name	Pubchem ID	Compound structure
1	1-deoxynojirimycin	29435		7	Morusin	5281671	
2	Catechin	9064		8	Mulberrin	5481958	
3	Cyanidin-3-rutinoside	441674		9	Mulberrofuran G	196583	
4	Cyclomulberrin	11742872		10	Quercetin 3-(6-malonylglucosid)	14730813	
5	Kaempferol	5280863		11	Quercitrin	5280459	
6	Kuwanon G	5281667		12	Rutin	5280805	

3) ADMET analysis

To conduct in silico ADME screening and drug likeness evaluation, we utilized two free web tools: Swiss ADME and pkCSM. SwissADME is a free web tool developed by the Swiss Institute of Bioinformatics, which can be accessed at www.swissadme (31-32). pkCSM, on the other hand, is a web server that predicts pharmacokinetic and toxicity properties of small molecules and can be accessed at www.pkcsm.org (33). These toolutilized physicochemical properties and structural features to assess different ADMET parameters. The bioavailability radar was particularly utilized to analyze the ligands potential in biological systems.

Table 2: Lipinski's rule of 5

Parameters	Threshold
H-bond donors	≤ 5
H-bond acceptors	≤ 10
Molecular weight(MWT)	≤ 500
Calculated Log P (CLog P)	≤ 5 (or MlogP ≤ 4.15)

4) Molecular docking

To investigate the interactions between ligands and the active site of the TGF beta type 1 receptor, molecular docking studies were conducted using Pyrx (Version 0.9). The grid box was defined around the active site of the receptor, ensuring that all potential binding sites were included in the analysis. Default parameter settings were applied. To validate the docking procedure, rigorous redocking experiments were performed, in which the native ligand was redocked into the active site. Visualizations were then carried out to analyse the interactions between the ligands and the receptor.

Results and Discussion

1) ADMET Analysis

The ADMET analysis played a crucial role in evaluating the pharmacokinetic properties of the selected ligands derived from *Morus alba Linn* . Using the swissadme tool and pkCSM tool, we predicted various ADMET parameters, including absorption, distribution, metabolism, excretion, and toxicity. These parameters are pivotal in determining the viability of a compound for further drug development. The results indicated that the study revealed that among the 12 ligands exhibiting hepatoprotective activity, 7 ligands were found to comply with Lipinski's rules. Notably, 6 of these ligands exhibited zero violations, while only one ligand showed a single violation.

Table 3: Lipinski's parameter

Lipinski's rules	1-deoxynoji-rimycin	Catechin	Cyclomul-berrin	Kaempferol	Morusin	Mulberrin	Mulberro-furan G
Formula	C6H13NO4	C15H14O6	C26H26O5	C15H10O6	C25H24O6	C26H28O4	C34H28O8
Molecular Weight	163.17	290.27	418.48	286.24	420.45	404.50	564.58
LogP	-2.9668	1.5461	6.08802	2.2824	5.2697	6.19702	6.7207
TPSA	92.95	110.38	79.90	111.13	100.13	70.67	132.75
HB donor	5	5	2	4	3	2	5
HB acceptor	5	6	5	6	6	4	8
Lipinski's rules violations	0	0	0	0	0	0	1

Table 4: Absorption properties

Absorption Properties	1-deoxynoji-rimycin	Catechin	Cyclomul-berrin	Kaempferol	Morusin	Mulberrin	Mulberro-furan G
Aqueous Solubility (log mol/L)	-0.747	-3.117	-3.78	-3.04	-4.056	-3.327	-2.899
$CaCO_2$ Permeability (log Papp in 10 cm/s)	-0.287	-0.283	0.131	0.032	0.048	-0.199	-0.43
Intestinal Absorption (% absorbed)	42.869	68.829	95.088	74.29	93.485	84.917	100
Skin permeability (log Kp)	-3.086	-2.735	-2.735	-2.735	-2.736	-2.735	-2.735
P-glycoprotein Substrate	No	Yes	Yes	Yes	Yes	Yes	Yes
P-glycoprotein I inhibitor	No	No	Yes	No	Yes	Yes	Yes
P-glycoprotein II inhibitor	No	No	Yes	No	Yes	Yes	Yes

Table 5: Distribution properties

Distribution properties	1-deoxynoji-rimycin	Catechin	Cyclomul-berrin	Kaempferol	Morusin	Mulberrin	Mulberro-furan G
VDss (log L/kg)	-0.567	1.027	-0.651	1.274	0.079	-0.835	-1.846
Fraction unbound (Fu)	0.935	0.235	0	0.178	0.002	0	0.227
BBB permeability (log BB)	-1.256	-1.054	-1.187	-0.939	-1.16	-1.308	-1.269
CNS permeability (log PS)	-4.737	-3.298	-1.859	-2.228	-1.838	-2.056	-2.949

Table 6: Metabolism properties

Metabolism Properties	1-deoxynoji-rimycin	Catechin	Cyclomul-berrin	Kaempferol	Morusin	Mulberrin	Mulberro-furan G
CYP2D6 Substrate	No	No	No	No	No	No	No
CYP3A4 substrate	No	No	Yes	No	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	Yes	Yes	Yes	Yes	No
CYP2C19 Inhibitor	No	No	Yes	No	Yes	Yes	No
CYP2C9 Inhibitor	No	No	Yes	No	Yes	Yes	No
CYP2D6 Inhibitor	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	Yes	No	No	Yes	No

Table 7: Excretion properties

Excretion Properties	1-deoxynoji-rimycin	Catechin	Cyclomul-berrin	Kaempferol	Morusin	Mulberrin	Mulberro-furan G
Total Clearance	0.935	0.183	0.278	0.477	0.224	0.436	0.236
Renal OCT2 substrate	No	No	No	No	No	No	No

Table 8: Toxicity properties

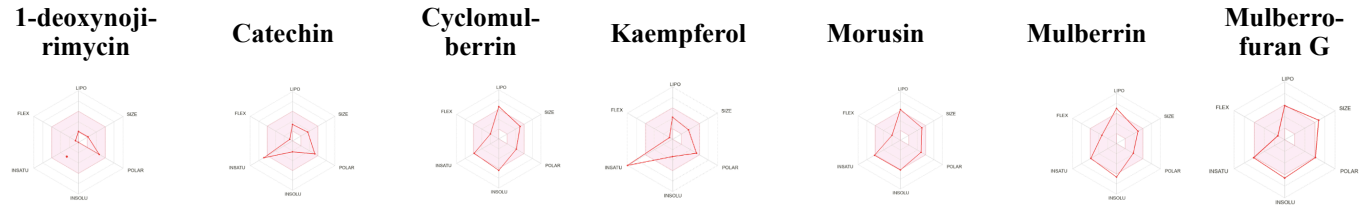
Toxicity properties	1-deoxynoji-rimycin	Catechin	Cyclomul-berrin	Kaempferol	Morusin	Mulberrin	Mulberro-furan G
AMES toxicity	No	No	No	No	No	No	No
Max. tolerated dose (log mg/kg/day)	2.362	0.438	0.067	0.531	0.231	0.369	0.43
hERG I inhibitor	No	No	No	No	No	No	No
hERG II inhibitor	No	No	Yes	No	Yes	Yes	Yes
Oral Rat Acute Toxicity LD50 (mol/kg)	1.879	2.428	2.226	2.449	2.361	2.535	2.549
Oral Rat Chronic Toxicity LOAEL (mol/kg_bw/day)	3.602	2.5	1.347	2.505	2.017	1.417	2.578
Hepatotoxicity	No	No	No	No	No	No	No
Skin sensitisation	No	No	No	No	No	No	No
T.pyriformis toxicity	0.267	0.347	0.294	0.312	0.334	0.289	0.285
Minnow toxicity	4.937	3.585	0.095	2.885	-0.135	0.479	0.137

1.1) Bioavailability radar

We employed the online tool SwissADME to assess the bioavailability radar of phytochemicals. The predictions provided us with valuable insights into the potential bioavailability of the phytochemicals under investigation. Data on characteristics such as solubility, polarity, size, flexibility, saturation, and lipophilicity were gathered. However, it is crucial to note that these computational predictions should be validated through in vitro and in vivo experiments to ensure their accuracy

and reliability. If a compound significantly deviates from the factors represented by the pink region, it suggests that the compound may not be bioavailable. Conversely, adherence to all the factors in the pink region indicates that the compound is bioavailable (34, 35). The results of this analysis are presented below:

Figure 5: Bioavailability radars of ligands



2) Molecular docking

Molecular docking was conducted on ligands known for their hepatoprotective activity. Among these ligands, the active hits were further evaluated through molecular docking studies to gain insights into their potential binding interactions with the target protein.

The binding affinities were carefully interpreted, with lower docking scores and more negative binding energies indicating stronger interactions.

The obtained binding affinities were compared with Silymarin which was chosen as standard.

The following table shows the binding affinities of ligands that were obtained from Pyrx (Version 0.9) by means of virtual screening:

Ligands	Binding affinities
Silymarin	-9.5
A1	-6.6
A2	-9.4
A3	-10.8
A4	-10.7
A5	-10.1
A6	-6.7
A7	-9.2
A8	-9.9
A9	-9.4
A10	-9.2
A11	-9.7
A12	-10.5

Figure 6: Molecular docking visualization, 3D representation and H-bond interaction between 1VJY and Silymarin

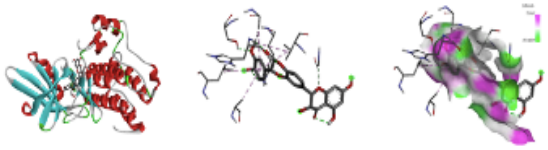


Figure 7: Molecular docking visualization, 3D representation and H-bond interaction between 1VJY and Cyclomulberine

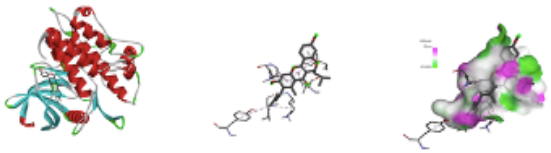


Figure 8: Molecular docking visualization, 3D representation and H-bond interaction between 1VJY and Kaemferol

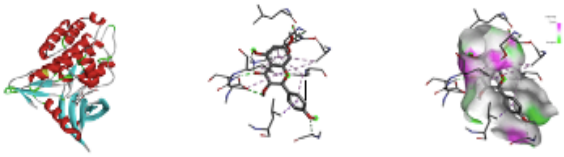
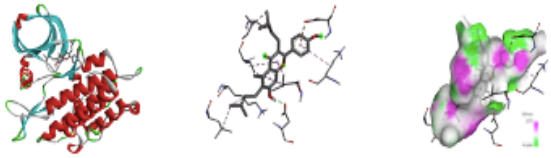


Figure 9: Molecular docking visualization, 3D representation and H-bond interaction between 1VJY and Mulberrin



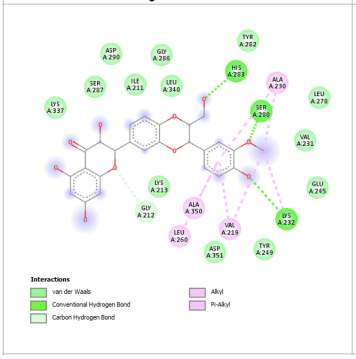
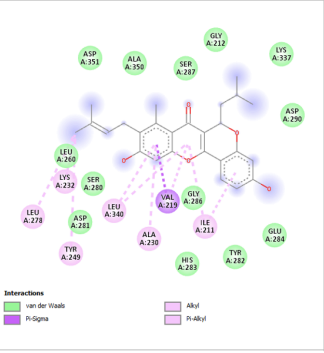
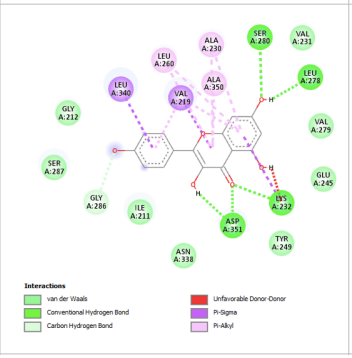
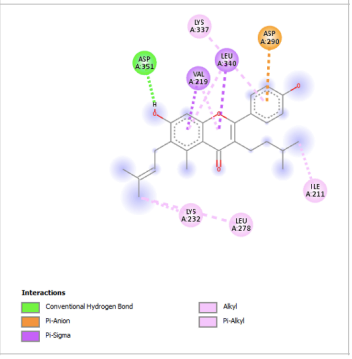
1-deoxynojirimycin (A1), Catechin (A2), Cyanidine-3-rutinoside (A3), Cyclomulberin (A4), Kaempferol (A5), Kuwanon-G (A6), Morusin (A7), Mulberrin (A8), Mulberrofuran-G (A9), Quercetin-3-(6-malonylglucoside) (A10), Quercitrin (A11), and Rutin (A12) were selected for molecular docking analysis. Amongthem, from compounds that followed Lipinski's rules A4 (-10.7 kcal/mol), A5 (-10.4 kcal/mol), and A8 (-9.9 kcal/mol) exhibited the highest binding affinity to the active site in the TGF-β-type-I receptor.In this study Silymarin (-9.5 kcal/mol) was used as a standard for comparison.

3) Study of interactions

The ligands with the most favourable binding energies, which also meet Lipinski's rule of five, were shortlisted for further analysis. Among the ligands that passed Lipinski's rule of five, the top three with the highest binding affinities were selected for the interaction study. These ligands are Cyclomulberrin, Kaempferol, and Mulberrin.

Cyclomulberrin showed the highest binding affinity to the TGF beta type 1 receptor.

In the study of the interactions between 1VJY and Cyclomulberrin, four different interactions were observed. For the interactions between 1VJY and Kaempferol, six different interactions were observed. Five different interactions were observed in the study of the interactions between 1VJY and Mulberrin and for the standard Silymarin five different interactions were observed. Displayed below are the images that illustrate these interactions.

Figure 10: Interaction between 1VJY and Silymarin	Figure 11: Interaction between 1VJY and Cyclomulberrin	Figure 12: Interaction between 1VJY and Kaemferol	Figure 13: Interaction between 1VJY and Mulberrin
			

Conclusion

This research study focused on evaluating the potential of phytochemicals derived from *Morus alba Linn* plant native to China and India as hepatoprotective drugs. A total of 12 phytochemicals were selected and subjected to filtration based on Lipinski's rule of 5 parameters. Out of these, 7 phytochemicals successfully passed the filtration and underwent docking studies. During the docking process, the native inhibitor silymarin was used as a reference. Our findings revealed that three ligands, namely Cyclomulberrin, Kaempferol, and Mulberrin, exhibited higher potency compared to the reference inhibitor Silymarin. These three phytochemicals, obtained from the White mulberry (*Morus alba Linn*), demonstrated the best docking results and showed promising oral availability.Based on the docking score and ADMET virtual screening, Cyclomulberrin (A4) displayed a notable affinity (-10.7 kcal/mol) towards the TGF-β-type-I receptor. This suggests that Cyclomulberrin has the potential to be further investigated as a hepatoprotective agent. In conclusion, our research highlights the significance of these three phytochemicals derived from White mulberry (*Morus alba Linn*) in terms of their docking results and oral availability. Specifically, Cyclomulberrin (A4) exhibits a strong affinity towards the TGF-β-type-I receptor, indicating its potential as a promising candidate for further exploration in the search for effective hepatoprotective agents.

References

1. Batiha GE, Al-Snafi AE, Thuwaini MM, Teibo JO, Shaheen HM, Akomolafe AP, Teibo TK, Al-Kuraishy HM, Al-Garbeeb AI, Alexiou A, Papadakis M. Morus alba: a comprehensive phytochemical and pharmacological review. Naunyn-schmiedeberg's Archives of Pharmacology. 2023 Jul;396(7):1399-413.
2. Zhong X, Yang H, Ke XX, Cui HJ. Research progress on chemical constituents and pharmacological activities of Morus alba. Zhongguo Zhong yao za zhi Zhongguo Zhongyao Zazhi China Journal of Chinese Materia Medica. 2022 May 1;47(9):2373-91.
3. Hsu JH, Yang CS, Chen JJ. Antioxidant, anti-α-glucosidase, antityrosinase, and anti-inflammatory activities of bioactive components from Morus alba. Antioxidants. 2022 Nov 11;11(11):2222.
4. Chang BY, Koo BS, Kim SY. Pharmacological activities for Morus alba L., focusing on the immunostimulatory property from the fruit aqueous extract. Foods. 2021 Aug 23;10(8):1966.
5. Dubey V, Shah KW, Raghuwanshi RK. Comprehensive Notes on Phytochemical and Pharmacological Activity of Morus alba. Pharmaceutical and Biosciences Journal. 2020 Sep 1:01-6.
6. Chan EW, Phui-Yan LY, Siu-Kuin WO. Phytochemistry, pharmacology, and clinical trials of Morus alba. Chinese journal of natural medicines. 2016 Jan 1;14(1):17-30.
7. Yang S, Wang BL, Li Y. Advances in the pharmacological study of Morus alba L. Yao Xue Xue Bao Acta Pharmaceutica Sinica. 2014 Jun 1;49(6):824-31.
8. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. Annual review of pathology: mechanisms of disease. 2011 Feb 28;6:425-56.
9. Bataller R, Brenner DA. Liver fibrosis. The Journal of clinical investigation. 2005 Feb 1;115(2):209-18.
10. Kisseleva T, Brenner DA. Fibrogenesis of parenchymal organs. Proceedings of the American Thoracic Society. 2008 Apr 15;5(3):338-42.
11. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. The Lancet. 2014 May 17;383(9930):1749-61.
12. Schuppan D, Kim YO. Evolving therapies for liver fibrosis. The Journal of clinical investigation. 2013 May 1;123(5):1887-901.
13. Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. Hepatology. 2012 Aug;56(2):769-75.
14. Trautwein C, Friedman SL, Schuppan D, Pinzani M. Hepatic fibrosis: concept to treatment. Journal of hepatology. 2015 Apr 1;62(1):S15-24.
15. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology. 2008 May 1;134(6):1655-69.
16. Lee YA, Wallace MC, Friedman SL. Pathobiology of liver fibrosis: a translational success story. Gut. 2015 May 1;64(5):830-41.

17. Batiha GE, Al-Snafi AE, Thuwaini MM, Teibo JO, Shaheen HM, Akomolafe AP, Teibo TK, Al-Kuraishy HM, Al-Garbeeb AI, Alexiou A, Papadakis M. Morus alba: a comprehensive phytochemical and pharmacological review. Naunyn-schmiedeberg's Archives of Pharmacology. 2023 Jul;396(7):1399-413.
18. Orwa C. Agroforestree Database: a tree reference and selection guide, version 4.0. http://www.worldagroforestry.org/sites/treedbs/treedatabases. asp. 2009.
19. Zhang R, Zhang Q, Zhu S, Liu B, Liu F, Xu Y. Mulberry leaf (Morus alba L.): A review of its potential influences in mechanisms of action on metabolic diseases. Pharmacological Research. 2022 Jan 1;175:106029.
20. Zhou R, Chen C, Hu J, Liao X, Hu H, Tong Z, Liang J, Huang F. The self-nitrogen-doped carbon quantum dots derived from Morus alba L. leaves for the rapid determination of tetracycline. Industrial Crops and Products. 2022 Nov 15;188:115705.
21. https://www.way2drug.com dated 02-10-2023 time 16:20 IST
22. Bataller R, Brenner DA. Hepatic stellate cells as a target for the treatment of liver fibrosis. InSeminars in liver disease 2001 (Vol. 21, No. 03, pp. 437-452). Copyright© 2001 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.:+ 1 (212) 584-4662.
23. Border WA, Noble NA. Transforming growth factor β in tissue fibrosis. New England journal of medicine. 1994 Nov 10;331(19):1286-92.
24. Gressner AM, Weiskirchen R, Breitkopf K, Dooley S. Roles of TGF-beta in hepatic fibrosis. Front Biosci. 2002 Apr 1;7(1):d793-807.
25. Breitkopf K, Godoy P, Ciuclan L, Singer MV, Dooley S. TGF-β/Smad signaling in the injured liver. Zeitschrift für Gastroenterologie. 2006 Jan;44(01):57-66.
26. Schuppan D, Kim YO. Evolving therapies for liver fibrosis. The Journal of clinical investigation. 2013 May 1;123(5):1887-901.
27. Fabregat I, Moreno-Càceres J, Sánchez A, Dooley S, Dewidar B, Giannelli G, Ten Dijke P, IT-LIVER Consortium. TGF-β signalling and liver disease. The FEBS journal. 2016 Jun;283(12):2219-32.
28. Cales P. Apoptosis and liver fibrosis: antifibrotic strategies. Biomedicine & pharmacotherapy. 1998 Jul 1;52(6):259-63.
29. Torre P, Motta BM, Sciorio R, Masarone M, Persico M. Inflammation and fibrogenesis in MAFLD: role of the hepatic immune system. Frontiers in medicine. 2021 Dec 9;8:781567.
30. Gressner AM, Weiskirchen R, Breitkopf K, Dooley S. Roles of TGF-beta in hepatic fibrosis. Front Biosci. 2002 Apr 1;7(1):d793-807.
31. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017 Mar 3;7(1):42717.
32. http://www.swissadme.ch dated 16-11-2023 time 14:08 IST
33. https://biosig.lab.uq.edu.au/pkcsm dated 22-11-2023 time 13:50 IST
34. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017 Mar 3;7(1):42717.
35. Lu J, Xie L, Liu K, Zhang X, Wang X, Dai X, Liang Y, Cao Y, Li X. Bilobalide: A review of its pharmacology, pharmacokinetics, toxicity, and safety. Phytotherapy Research. 2021 Nov;35(11):6114-30.

*****