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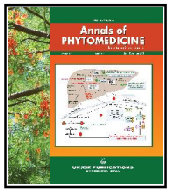

Original Article : Open Access

Theoretical exploration of *Momordica charantia* L. for the treatment of non-alcoholic fatty liver disease and liver sinusoidal endothelial cell dysfunction

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Abstract

Medicinal plants have been used from centuries for treating varieties of illnesses. *Momordica charantia* L. is a widespread medicine as well as vegetative food used traditionally for treating diabetes, bacterial infection, arthritis, malaria, cardiovascular diseases, *etc*. Due to the lack of biomolecular approaches to *M. charantia* in the alleviation of hepatitis associated with nonalcoholic fatty liver disease (NAFLD) and liver sinusoidal endothelial cell (LSEC) dysfunction, network pharmacology studies were conducted to determine and validate its biomolecular action. ADME and pharmacokinetics were studied to examine the pharmacokinetic action of its metabolites. The results revealed that *M. charantia* exhibits a multi-therapeutic effect *via* regulating numerous genes associated with the etiology of NAFLD and thus reducing inflammation, fibrosis, hypertension, obesity, fatty liver disease, diabetes mellitus, and other conditions are all improved. In the pharmacokinetic study, each metabolite of its demonstrated lipophilicity, good gastrointestinal (GI) absorption, and bioavailability. Thus, it is concluded that it also regulated various genomic expressions; namely, CASPs, ILs, MAPKs, AKTs, G6PD, NOs, IL1B, HIF1A, IL6, *etc*., responsible for hepatic pathophysiological alterations. Furthermore, the evidence signifies the biomolecular approach of *M. charantia* for alleviating NAFLD and liver sinusoidal endothelial cell dysfunction and provides impactful information for further biomolecular or clinical assessment to enhance the understanding and credibility of present findings.

1. Introduction

Due to their complex phytochemical composition and wide range of therapeutic actions, herbal medicines have historically played a significant role in the treatment of many ailments whether that may be acute or chronic. However, because of their few adverse effects, ease of accessibility, and affordability, medicinal plants and goods derived from them have seen exponential expansion in recent decades. This has helped to preserve sustainable growth in the nation's healthcare system (Gaurav *et al.,* 2020; Gautam *et al.,* 2021). More than half of all currently used medications and drugs are sourced from natural sources, making medicinal plants the primary source for novel drug discovery and development. Examining their countless therapeutic applications in the healthcare sector, even concerning their efficacy-based examination, quality, and safety, scientific data effectively influenced their regulatory features (Mallick *et al.,* 2015; Rasheed and Gupta, 2010). It is difficult to pinpoint the precise mechanism of phytochemicals that exhibit beneficial effects for the treatment of targeted or non-targeted bodily disorders from a pharmacological standpoint. We can gain actual data about the curative effects displayed by the specific chemicals in the plant's matrix using bioassay-guided fractionation or pharmacological evaluation of particular chemicals from the selected metabolites (Bhattacharya *et al.,* 2002; Nugroho *et al.,* 2017; Yang *et al.,* 2015).

NAFLD is quickly evolving into a severe global health issue. Specifically, among people who do not consume excessive amounts of alcohol, the term NAFLD refers to a spectrum of liver illnesses. NAFLD is the second most common cause of mortality in the general population, affecting all ages and ethnicities and occurring in millions of the population. This illness, NAFLD, is rapidly becoming a major global health issue. NAFLD affects people of all ages, ethnic groups, and up to one-third of the population, and it is one of the top two causes of death in the general population. NAFLD's high prevalence and detrimental clinical effects are currently a huge economic burden for many nations (Bernal-Reyes *et al.,* 2019; Cooper *et al.,* 2021; Golabi *et al.,* 2022; Hassen *et al.,* 2022; Konyn *et al.,* 2023; Lin *et al.,* 2022). However, there has not yet been a successful method for treating the condition. The main therapeutic strategy is to suggest healthy lifestyle practices, such as food and exercise regimens, which are aimed at lowering body weight and improving insulin sensitivity. Despite being successful in randomized controlled studies, these therapies have minimal effect on the frequency and severity of NAFLD at the community level due to limited patient compliance (Yao *et al.,* 2016). NAFLD is also considered to be a major contributor to liver metabolic syndrome, insulin resistance, hyperlipidemia, obesity, dyslipidemia, and hypertension. Although, plasma transaminase is an early sign of liver damage, NAFLD cannot be diagnosed by normal blood tests, liver biopsy, or histological staining (Bernal-Reyes *et al.,* 2019; Cheng *et al.,* 2022; Lin *et al.,* 2021; Yao *et al.,* 2016).

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To assess the relationship and compatibility between proteins or genomes of certain pathophysiology, *in silico* computational methods are becoming increasingly significant in drug design and development (Chandra *et al.,* 2018; Islam *et al.,* 2013). Network pharmacology represents one of the most sophisticated computational techniques used to assess the pharmacological aspects of the drug with genomes. Such computational techniques are used for assessing the biological effect of the substances and their biomolecular interaction. Network pharmacology identifies pharmacologically functional metabolites from large plant data sets of metabolites, including metabolomic data, and produces molecular-based evidence on their pharmacology applications (Yi *et al.,* 2018; Zhang *et al.,* 2019a).

The plant *Momordica charantia* L. belongs to the Cucurbitaceae family and is used for treating numerous diseases in traditional medicine (Fajinmi *et al.,* 2022; Mukherjee *et al.,* 2022). It is mostly found in tropical and subtropical regions of India. Its fruit has traditionally been cooked like a vegetable and used as a traditional medicine to treat diabetes mellitus. *M. charantia* contains a variety of phytochemicals, including triterpenes, polysaccharides, polyphenols, proteins, amino acids, and steroids (Karale *et al.,* 2022; Sharma and Yadav, 2022). Based on the evidence that is currently available, several *M. charantia* biological activities have also been reported, including antihyperglycemic, antiviral, antiulcer, antioxidant, antibacterial, antidiabetic, anticancer, anthelmintic, anti-inflammatory, and hepatoprotective activities (Bhagyalakshmi and Devaraja, 2023; Hussain *et al.,* 2022; Jia *et al.,* 2017; Krawczyk *et al.,* 2022; Mukherjee and Karati, 2023; Muribeca *et al.,* 2022; Oyelere *et al.,* 2022).

The current study is related to examining the biological significance of *M. charantia* chemical compounds in treating NAFLD and producing scientific evidence which would lay an adequate basis for additional research on examining its pharmacological applications.

2. Materials and Methods

2.1 Selection of compounds

The metabolite *M. charantia* was screened for the reported literature. The selected metabolites of *M. charantia* were apiole, gallic acid, quercetin, linalool, caffeic acid, ferulic acid, limonene as well as catechin (Ahamad *et al.,* 2017; Alam *et al.,* 2015).

2.2 Selection of potential targets or genes

From the gene card platform, several gene targets were chosen using the UniPort database of genes (https://www.uniprot.org/), which are included in the pathophysiology of liver disease and accompanying pathophysiological alterations. The screening of the genes was performed using the keywords such as hepatitis, liver disease, and NAFLD-associated targets (Casas *et al.,* 2019; Zhang *et al.,* 2019b).

2.3 Network pharmacology analysis

The incorporation analysis of the compound-gene network was used to investigate potentially discovered genes that related to one another in this study. Cytoscape (version 3.8.2) was used to perform this study. The interaction profile of the metabolites was determined with each protein. A network of protein and protein interaction and protein and compound interaction was developed. For each developed network, the no. of nodes, edges, the usual node degree, and local grouping coefficient were examined during data interpretation. During this analysis, the genes that were not found with the interaction were excluded from the network while the proteins, and chemicals with essentially functional connections were included in the analysis (Li *et al.,* 2021; Yi *et al.,* 2018).

2.4 Gene ontology (GO) analysis

Multiple genes involved in NAFLD's pathophysiology were evaluated using a gene ontology (GO) study. The analysis was carried out using Network Analyst and Metascape tools. The genes that were found with significant interaction with the active metabolites were subjected to analysis. Each gene was included in the Metascape and network analysis platform's search toolbar. In this study, the top improved results were included as the study's conclusion (Gautam, 2022).

2.5 ADME analysis

The ADME as well as the toxicological study of selected metabolites was carried out using SwissADME and ProTox-II-Prediction device for the noxiousness of chemicals. Topological Polar Surface Area (TPSA) for Log K_p (skin permeability), drug integrity. Furthermore, consensus Log Po/w for drug-likeness and drug lipophilicity was examined to determine ADME responses of metabolites (Daina *et al.,* 2017).

3. Results

Based on the proteins that interact or ligate with the compounds, 8 metabolites were chosen to determine the multi-mechanistic action of metabolites in liver disease. In this analysis, 41 genes were chosen from the pre-screening study of targeted genes that were even poorly associated with the active metabolite and other genes. The affinity of interaction and degree of betweenness, the interactions of each gene were determined (Figure 1). Out of 84 genes, the research revealed that 41 genes had significant interactions with each target and active metabolite, while 9 and 34 genes had little or no interactions (Table 1).

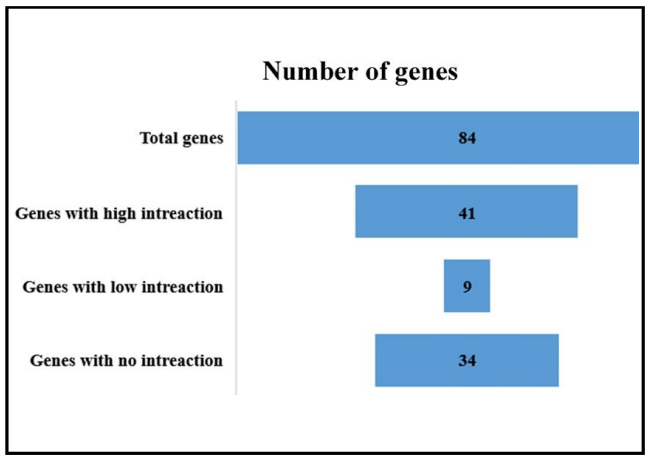


Figure 1: Graphical representation of selected genes depending on the interaction with each target and active metabolite.

Table 1: Selected genes for NAFLD from different databases (http://www.genecards.org)

S. No.	UniProt ID	Protein names	Gene names	Degree
1	O95477	Phospholipid-transporting ATPase ABCA1	ABCA1	14
2	O00763	Acetyl-CoA carboxylase 2	ACACB	4
3	P12821	Angiotensin-converting enzyme	ACE	28
4	P30542	Adenosine receptor A1	ADORA1	4
5	P30556	Type-1 angiotensin II receptor	AGTR1	20
6	P15121	Aldo-keto reductase family 1 member B1	AKR1B1	11
7	P05091	Aldehyde dehydrogenase, mitochondrial	ALDH2	1
8	P18054	Polyunsaturated fatty acid lipoxygenase ALOX12	ALOX12	4
9	P10415	Apoptosis regulator Bcl-2	BCL2	10
10	P42574	Caspase-3	CASP3	45
11	Q14790	Caspase-8	CASP8	25
12	P55211	Caspase-9	CASP9	22
13	P32246	C-C chemokine receptor type 1	CCR1	8
14	P11597	Cholesteryl ester transfer protein	CETP	5
15	P21554	Cannabinoid receptor 1	CNR1	11
16	P08123	Collagen alpha-2	COL1A2	8
17	P11511	Aromatase	CYP19A1	16
18	Q07973	1,25-Dihydroxyvitamin D	CYP24A1	4
19	P25101	Endothelin-1 receptor	EDNRA	13
20	P01133	Proepidermal growth factor	EGF	45
21	P00533	Epidermal growth factor receptor	EGFR	45
22	Q99814	Endothelial PAS domain-containing protein 1	EPAS1	10
23	P03372	Estrogen receptor	ESR1	31
24	P25116	Proteinase-activated receptor 1	F2R	15
25	P07148	Fatty acid-binding protein, liver	FABP1	15
26	P12104	Fatty acid-binding protein, intestinal	FABP2	6
27	P15090	Fatty acid-binding protein, adipocyte	FABP4	15
28	P49327	Fatty acid synthase	FASN	16
29	P11413	Glucose-6-phosphate 1-dehydrogenase	G6PD	8
30	P41235	Hepatocyte nuclear factor 4-alpha	HNF4A	20
31	P80365	Corticosteroid 11-beta-dehydrogenase isozyme 2	HSD11B2	3
32	P28223	5-Hydroxytryptamine receptor 2A	HTR2A	6
33	O14920	Inhibitor of nuclear factor kappa-B kinase subunit beta	IKBKB	16
34	P05412	Transcription factor AP-1	JUN	40
35	P35968	Vascular endothelial growth factor receptor 2	KDR	33
36	P28482	Mitogen-activated protein kinase 1	MAPK1	45
37	Q16539	Mitogen-activated protein kinase 14	MAPK14	33
38	P45983	Mitogen-activated protein kinase 8	MAPK8	36
39	Q00987	E3 ubiquitin-protein ligase Mdm2	MDM2	23
40	P39900	Macrophage metalloelastase	MMP12	5

41	P0825372	kDa type IV collagenase	MMP2	32
42	P08254	Stromelysin-1	MMP3	25
43	P22894	Neutrophil collagenase	MMP8	11
44	P14780	Matrix metalloproteinase-9	MMP9	40
45	P42345	Serine/threonine-protein kinase mTOR	MTOR	32
46	P35228	Nitric oxide synthase, inducible	NOS2	16
47	P29474	Nitric oxide synthase, endothelial	NOS3	40
48	Q13133	Oxysterols receptor LXR-alpha	NR1H3	8
49	O75469	Nuclear receptor subfamily 1 Group I member 2	NR1I2	6
50	P08235	Mineralocorticoid receptor	NR3C2	5
51	P04629	High-affinity nerve growth factor receptor	NTRK1	11
52	P09619	Platelet-derived growth factor receptor beta	PDGFRB	23
53	P16284	Platelet endothelial cell adhesion molecule	PECAM1	27
54	P42336	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	PIK3CA	26
55	P48736	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	PIK3CG	12
56	P27169	Serum paraoxonase/arylesterase 1	PON1	7
57	Q07869	Peroxisome proliferator-activated receptor alpha	PPARA	20
58	Q03181	Peroxisome proliferator-activated receptor delta	PPARD	7
59	P37231	Peroxisome proliferator-activated receptor gamma	PPARG	37
60	P17252	Protein kinase C alpha type	PRKCA	15
61	P05771	Protein kinase C beta type	PRKCB	12
62	P07477	Trypsin-1	PRSS1	4
63	P25105	Platelet-activating factor receptor	PTAFR	7
64	P60484	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	PTEN	37
65	P23219	Prostaglandin G/H synthase 1	PTGS1	8
66	P35354	Prostaglandin G/H synthase 2	PTGS2	41
67	Q06124	Tyrosine-protein phosphatase nonreceptor type 11	PTPN11	22
68	P17706	Tyrosine-protein phosphatase nonreceptor type 2	PTPN2	7
69	P29350	Tyrosine-protein phosphatase nonreceptor type 6	PTPN6	14
70	P02753	Retinol-binding protein 4	RBP4	5
71	Q04206	Transcription factor p65	RELA	35
72	Q13464	Rho-associated protein kinase 1	ROCK1	12
73	O75116	Rho-associated protein kinase 2	ROCK2	8
74	P16109	P-selectin	SELP	14
75	P04278	Sex hormone-binding globulin	SHBG	3
76	P13866	Sodium/glucose cotransporter 1	SLC5A1	2
77	P35610	Sterol O-acyltransferase 1	SOAT1	1
78	P01137	Transforming growth factor beta-1 proprotein	TGFB1	27
79	P01375	Tumor necrosis factor	TNF	51
80	P19438	Tumor necrosis factor receptor superfamily member 1A	TNFRSF1A	23
81	P20333	Tumor necrosis factor receptor superfamily member 1B	TNFRSF1B	12
82	P04637	Cellular tumor antigen p53	TP53	44
83	P55851	Mitochondrial uncoupling protein 2	UCP2	12
84	P11473	Vitamin D3 receptor	VDR	14

3.1 Network pharmacology analysis

3.1.1 Active metabolites target genes network

M. charantia metabolite and their interaction profile with each gene were examined. According to the results of the study, metabolites, and gene networks were developed and evaluated for their significant interaction. In the developed network of compounds and proteins, a total of 84 proteins (Table 1) were analyzed to determine the interaction with metabolites of *M. charantia*. Edges interacting with compounds in the network were left to be visible, whereas edges that did not exhibit any interaction with compounds vanished from the network (Figure 2). Several targets, such as ILs, NOS, MAPKs, CASPs, and others, were found to interact strongly with quercetin. These targets are associated with several pathophysiologies such as inflammation, oxidative stress, as well as inflammation induced by oxidative stress. Ferulic acid was set up to interact with G6PD, MAPK3, MAPK1, and other proteins. Caffeine was discovered to interact with MAPKs, G6PD, and MMPs. Catechin interacts with PTGS2, NOS, ILs, PON1, and other molecules. Gallic acid interacts with AKT1, CASPs, MMPs, JUN, and other proteins. Apiole was shown to interact with the TP53 while linalool and limonene were found to interact with PPARG, NOS, and other molecules. Figure 2 shows the established network of active metabolites and targets proteins.

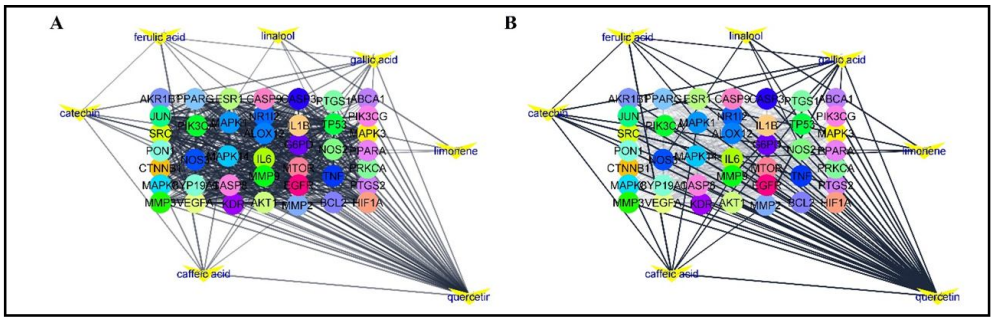
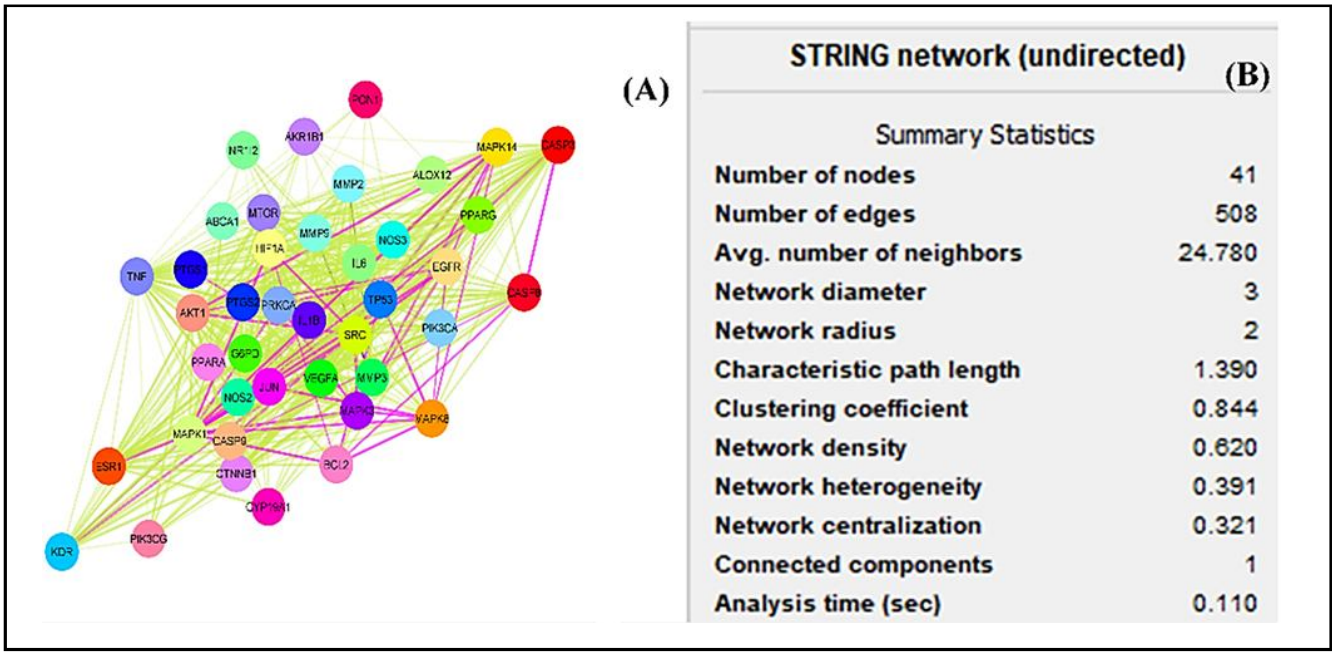


Figure 2: The active components with targets are shown by the compound and protein interaction (CPI) network, with quercetin demonstrating the most prominent interaction. (A) common network with an interconnection of protein-protein and compounds. (B) protein-compound interaction.

3.1.2 Protein-protein interaction

The links between proteins and diseases in 41 putative target genes linked to NAFLD pathogenesis were also assessed. The investigation was made *via* STRING as well as Network Analyst online tool. Furthermore, the PPI analysis was used to identify the protein interaction with other proteins with a mean score of 0.400. The developed network contains 41 nodes, 508 edges, average local clustering coefficient, and node degree was found as 0.844 and 24.8, respectively. In the developed network, 182 predicted edges, as well as PPI enrichment *p*-value, were found as 182 and 1.0e-16. The developed PPI had several more interactions than anticipated. In this study, each gene was found partially even significantly connected and exhibited strong interaction with metabolites. The edges of each node represent protein and compound interaction. The interaction of each gene with metabolites represents their pathophysiological involvement in hepatitis or NAFLD. The PPI network has been plotted in Figure 3.



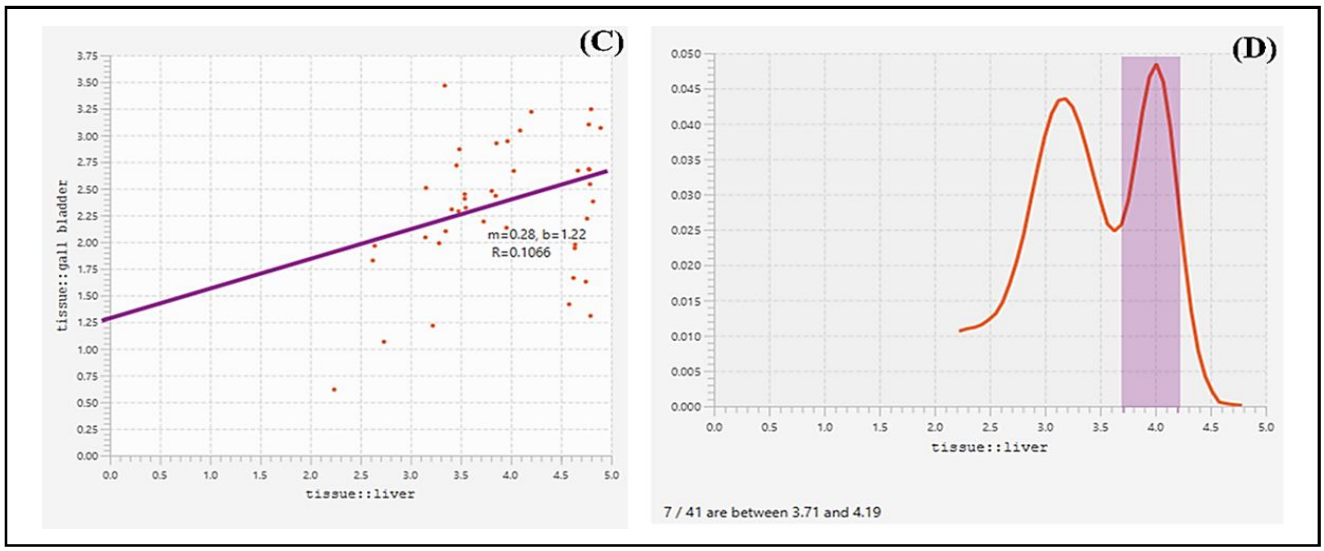
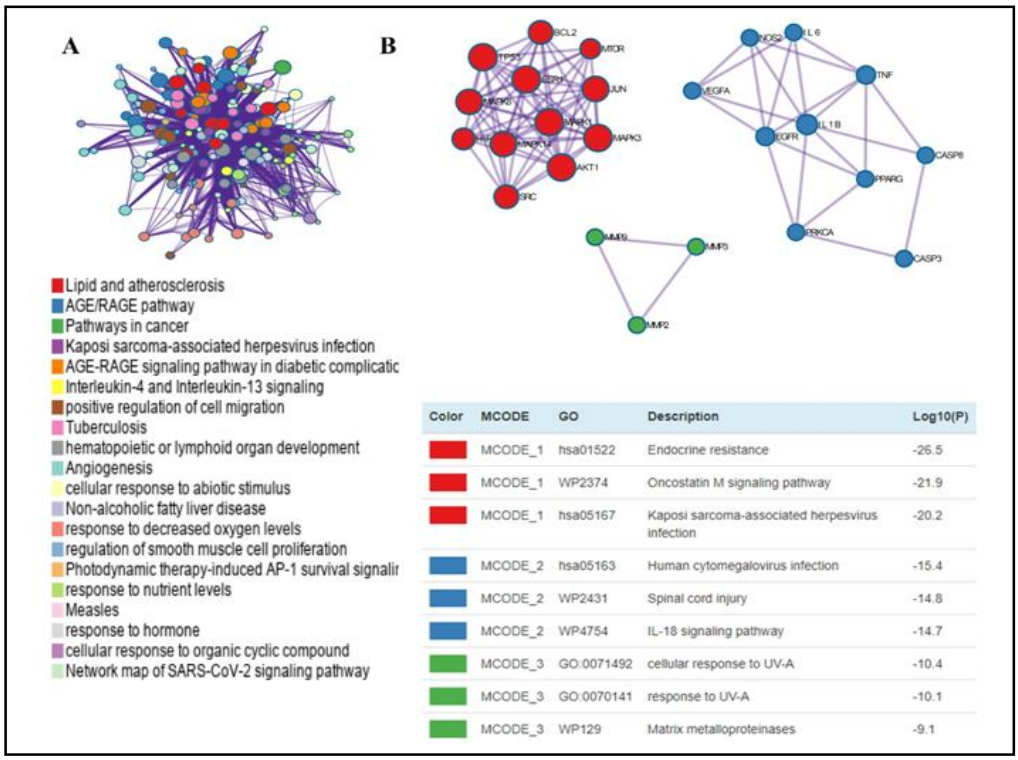


Figure 3: PPI network created *via* STRING tool and Cytoscape. (A) and (B) depicts PPI created by Cytoscape, and the pink line stand represents edges and nodes interaction alongwith the summary statistics. (C) represents the correlation of genes based on their pathophysiological role in the liver and gall bladder. (D) represents gene enrichment through gene histogram analysis.

3.1.3 Gene ontology (GO) analysis

This study was conducted to assess the role of genes in the pathophysiological of NAFLD and to determine the possible therapeutic pathways involved in the treatment of the disease. The results depicted that the metabolites of *M. charantia* exhibited multi-therapeutic action *via* regulating gene expression involved in NAFLD or hepatocyte dysfunction. The possible pathways involved in the treatment of disease by metabolites of *M. charantia;* namely, lowering endothelial dysfunction, diabetes mellitus, fatty liver disease, hypertension, fibrosis, *etc.* Furthermore, it was found that each target had different physiological functions in the regulation of NAFLD and was important for sinking oxidative stress, inflammation, and oxidative stress induced by inflammatory cytokines. An overview of the analysis' findings is shown in Figures 4 and 5.



Color	MCODE	GO	Description	Log10(P)
	MCODE_1	hsa01522	Endocrine resistance	-26.5
	MCODE_1	WP2374	Oncostatin M signaling pathway	-21.9
	MCODE_1	hsa05167	Kaposi sarcoma-associated herpesvirus infection	-20.2
	MCODE_2	hsa05163	Human cytomegalovirus infection	-15.4
	MCODE_2	WP2431	Spinal cord injury	-14.8
	MCODE_2	WP4754	IL-18 signaling pathway	-14.7
	MCODE_3	GO:0071492	cellular response to UV-A	-10.4
	MCODE_3	GO:0070141	response to UV-A	-10.1
	MCODE_3	WP129	Matrix metalloproteinases	-9.1

Figure 4: Gene ontology (GO) of genes that reveals the interaction of active compounds of *M. charantia*. A and B represent the enrichment of genes and their role in different pathways, respectively.

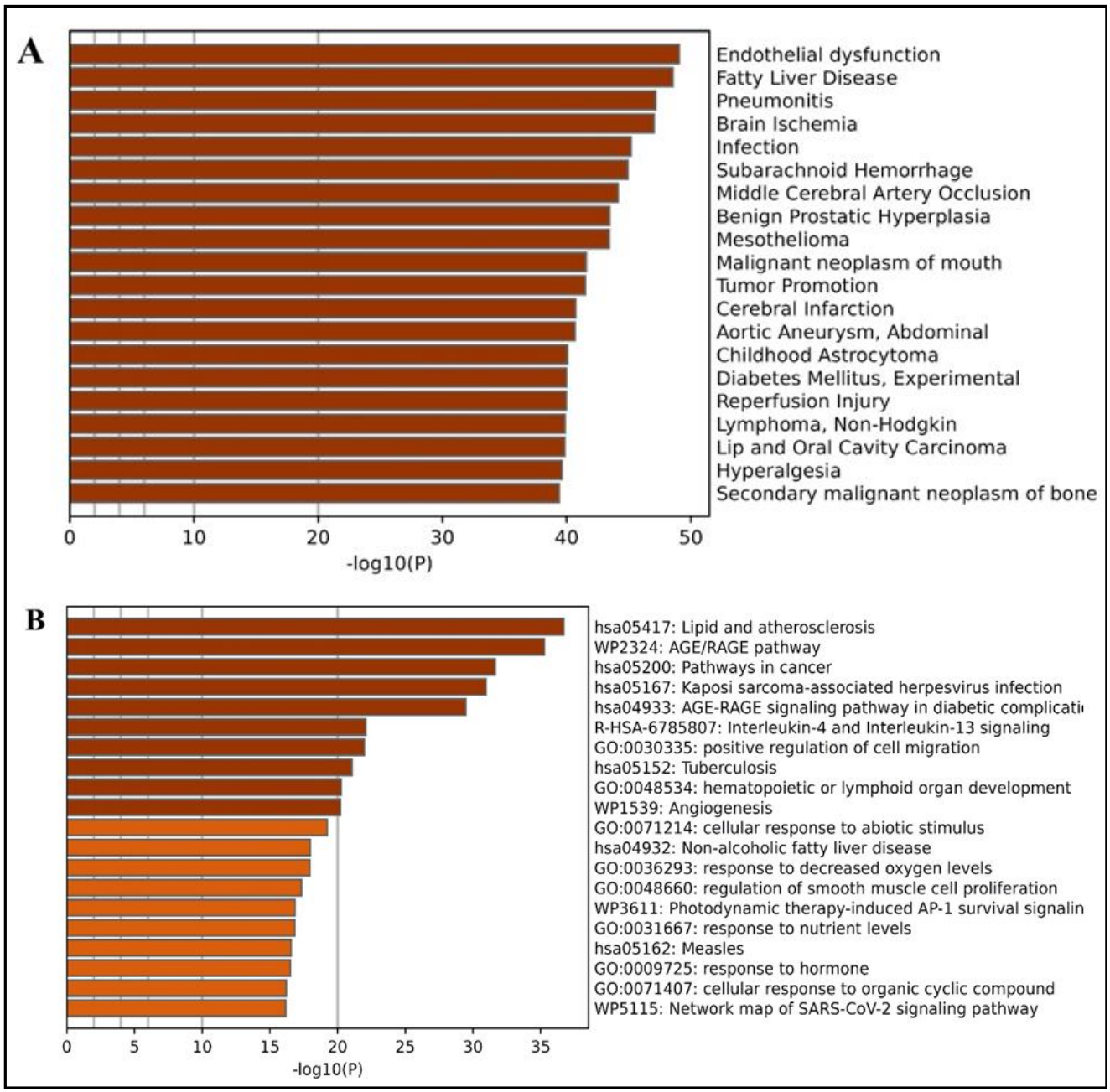


Figure 5: Gene ontology (GO) and gene-disease association analysis of genes reveal the interaction of active compounds of *M. charantia*. A and B represent multi-targeted action of genes involved in disease and pathways, respectively.

3.2 ADME analysis

The computational analysis "Swiss ADME" was successfully used to conduct ADME profiling of each selected metabolite. In this analysis, drug-like response, lipophilicity, TPSA value, ESOL Log S values, consent Log Po/w, GI absorption, log K_p (cm/s), and BBB permeant efficacy of each potential metabolite was determined. The approach for the determination of TPSA was determined by calculating the polar surface area (PSA) of components. TPSA value of metabolites helps as a descriptor to estimate ADME features of components, particularly those relating to permeability, bioavailability as well as brain access (Daina and Zoete, 2016).

Furthermore, the arithmetic means of 5 determined factors of lipophilicity correspond to the characteristic of lipophilicity as well as consensus log Po/w. The log Po/w as the coefficient of partition between two known solvents represents the solubility nature in n-octanol and water and is considered a standard parameter for lipophilicity. Through consensus log Po/w, the models increase the physicochemical properties' prediction accuracy (Mannhold *et al.,* 2009). The findings of the analysis demonstrate that a negative logP value of metabolite indicates the component has strong hydrophilic characteristics positive logP worth demonstrates the lipophilic of the compound. A similar model that was developed by Potts and

Guy, demonstrates skin coefficient of permeability or skin permeability (K_p) of molecules represents more negative the log K_p (with K_p in cm/s) when they exhibit low skin permeation (Daina *et al.,* 2017). Based on the conclusions, the log K_p values of each metabolite of *M. charantia* were found to be less than -8.00. Hence, our investigation implies that they all have high skin permeability. Table 2 and Figures 6-7 provide a summary of the results of the ADME analysis. Moreover, TPSA and Consensus log Po/w stand for physicochemical parameters that examine the ability of molecules to reach out beyond the blood-brain barrier. If, the molecule is covered over the yellow yolk of the egg-shaped plot and represents the molecule's probability to reach the BBB permeability. In case, the molecules that fall under the white region represent the molecule's hydrophilic characteristic. Additionally, the chemical does not force the two compartments to be mutually exclusive and they both remain outside the grey area, indicating little minimal brain penetration and absorption (Daina *et al.,* 2017). Findings of the investigation indicate that apiole, ferulic acid, linalool, as well as limonene had a high affinity for permeating the BBB while excluding other substances. Figure 6 provides a summary of the ADME analysis's "boiled egg plot".

Table 2: *M. charantia* metabolites' ADME analysis

Molecule	Formula	MW	TPSA	iLOGP	Consensus Log P	log Kp (cm/s)	Bioavailability score	BBB permeant
Caffeic acid	$C_9H_8O_4$	180.16	77.76	0.97	0.93	-6.58	0.56	No
Catechin	$C_{15}H_{14}O_6$	290.27	110.38	1.33	0.83	-7.82	0.55	No
Ferulic acid	$C_{10}H_{10}O_4$	194.18	66.76	1.62	1.36	-6.41	0.85	Yes
Gallic acid	$C_7H_6O_5$	170.12	97.99	0.21	0.21	-6.84	0.56	No
Limonene	$C_{10}H_{16}$	136.23	0	2.72	3.37	-3.89	0.55	Yes
Linalool	$C_{10}H_{18}O$	154.25	20.23	2.7	2.66	-5.13	0.55	Yes
Quercetin	$C_{15}H_{10}O_7$	302.24	131.36	1.63	1.23	-7.05	0.55	No

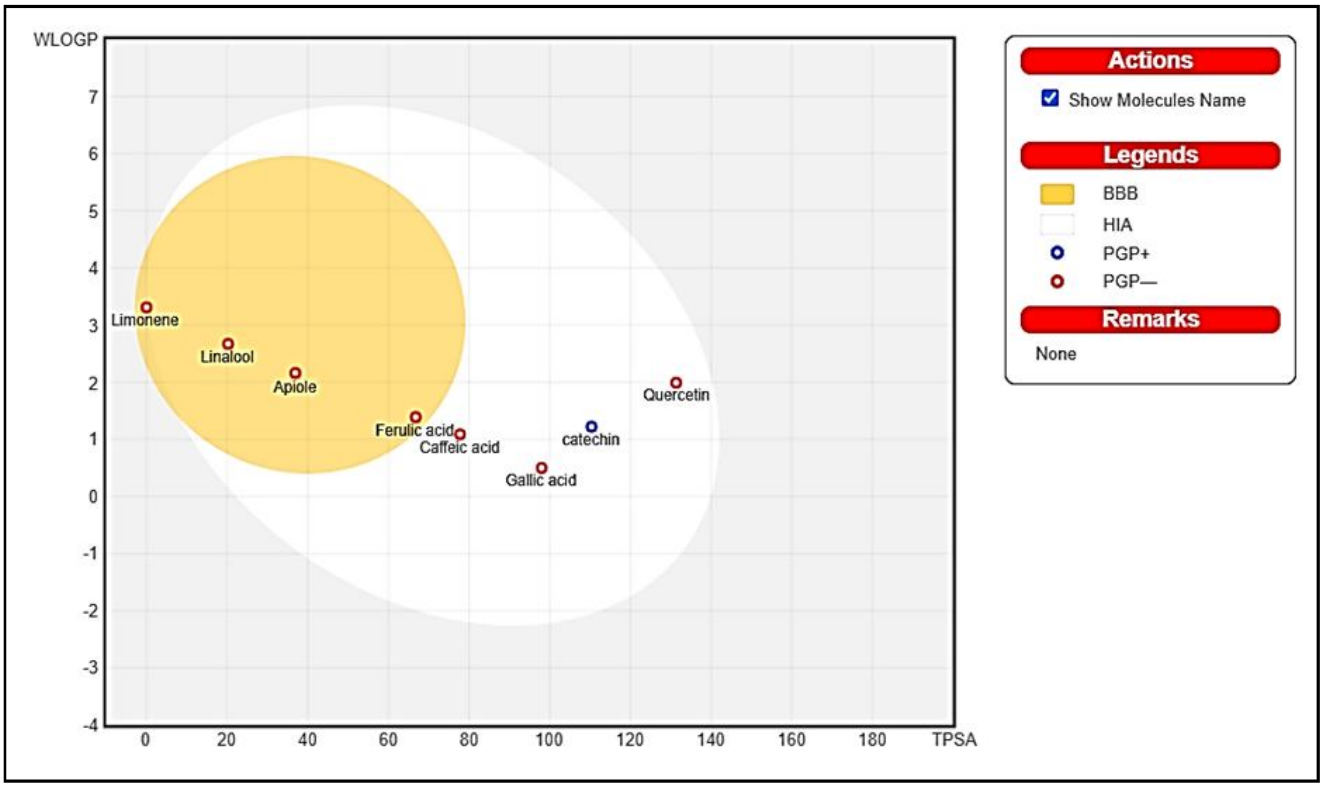


Figure 6: ADME egg plot of *M. charantia* metabolites.

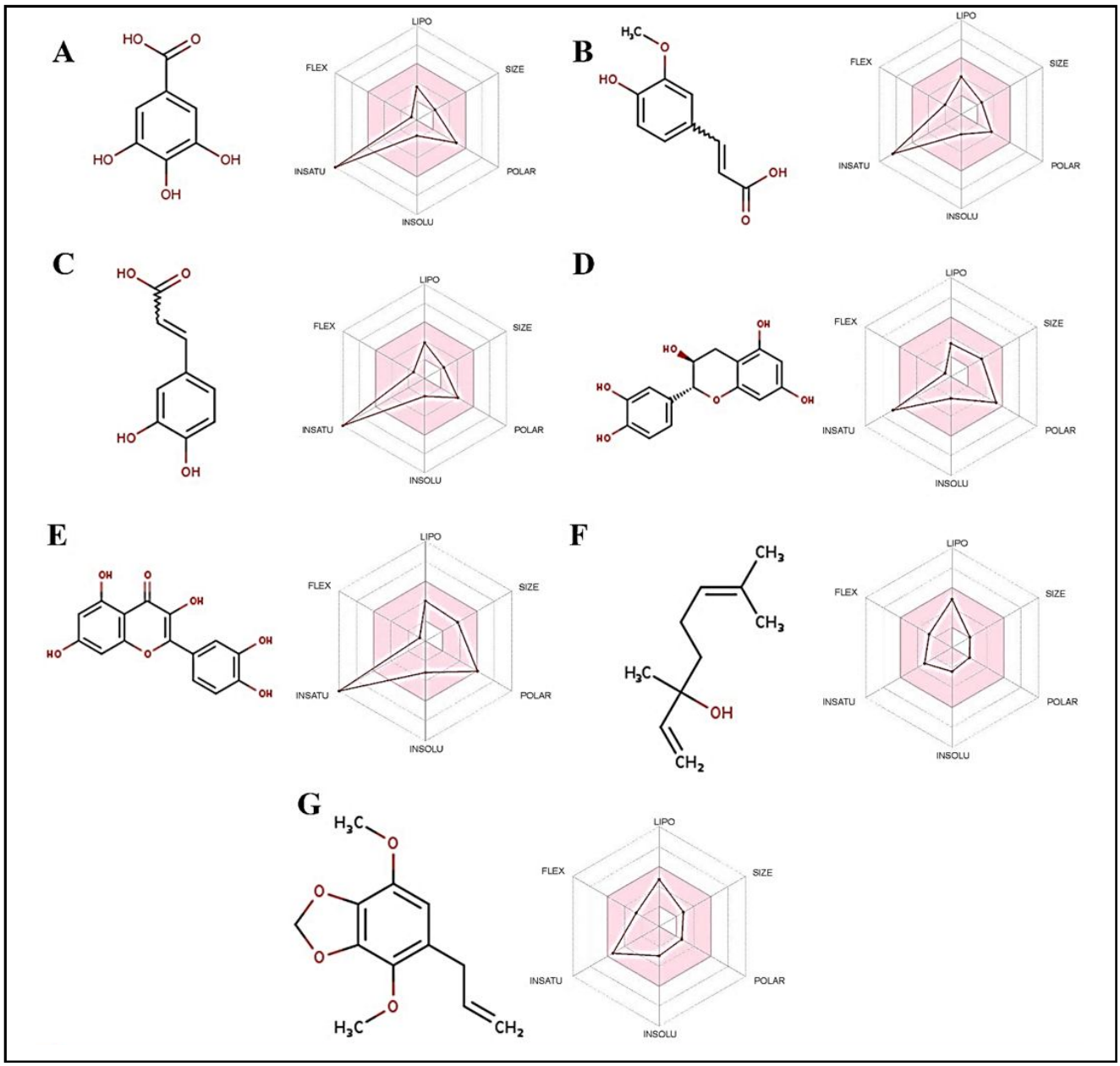


Figure 7: ***M. charantia*** **compounds ADME analysis. The chemical structure and ADME radar plot of (A) Gallic acid; (B) Ferulic acid; (C) Caffeic acid; (D) Catechin; (E) Quercetin; (F) Linalool, and (G) Limonene.**

4. Discussion

The multi-targeted and therapeutic effect of herbal medicinal plants in the treatment of disease enhances credibility, drug discovery, and development strategies in the promotion of the healthcare system. Medicinal plants or natural products are playing a significant role for ages in easing several acute and chronic disorders. *M. charantia* is an Indian herb that has historically been used to cure several illnesses, including diabetes. The current study is associated with developing the scientific evidence based on *M. charantia* traditional therapeutic claim in the alleviation of hepatitis, NAFLD, and associated complications using network biology as well as polypharmacology approaches. *M. charantia* possesses a variety of chemical constituents; namely, terpenoids, polyphenols, steroids, *etc.*

In the current study, various genes or proteins were chosen from several databases of genes and analyses for their biological roles in the alleviation of NAFLD. The analysis of a few selected metabolites, including gallic acid, quercetin, apiole, caffeic acid, and ferulic acid revealed that, out of eight metabolites, the phenolic compound as quercetin was found as the most significant biologically active compound of *M. charantia* in alleviation of liver disease and associated pathophysiological complications. Quercetin interacts with numerous genes or proteins like caspases, nitric-oxide-synthases (NOS), and mitogen-activated protein kinases (MAPKs). It is reported that CASPs, NOS, and MAPKs are crucial for controlling oxidative stress-induced inflammation (S, Prince 2018; Gautam *et al.,* 2021). Furthermore, it has been reported that quercetin acts against damaged

extracellular matrix (ECM) due to excessive inflammatory stress, distortion of cell migration, and capillary basement membrane even during the propagation phase, thus stimulating the healing of diabetic wounds (Ayuk *et al.,* 2016). Although, endogenous AKT improves insulin-stimulating response in glucose metabolism or absorption as well as increases glucose transport to the muscle and adipose tissue. AKT regulates glucose uptake by modulating the insulin-induced translocation of GLUT4 (Cong *et al.,* 1997).

Moreover, the anti-inflammatory effect of polyphenols is well exhibited *via* exerting their therapeutic potential *via* multi-mechanistic and therapeutic approaches. It is also demonstrated that phenols regulate the expression of NF-κB, IL-4, TNF, as well as MAPK activation (Shukla and Gupta 2010). Quercetin is also reported as an anti-inflammatory agent *via* regulations of inflammatory cytokines expression such as IL-6, IFN-α, IL-1α, and TNF-α secretion (Chen *et al.,* 2016). PONs expression is also regulated by quercetin and ameliorates dyslipidemia-induced CKD (Solati and Mahboobi, 2012). Gallic acid is acknowledged as the most effective antioxidant agent that exerts, anti-inflammatory, and hepatoprotective activity also *via* regulating CAT, TNF, SOD, CASP3, and IL-1B (Basist *et al.,* 2022; Ojeaburu and Oriakhi, 2021). Ferulic acid is also a phenolic compound that acts against oxidative stress, hepatotoxicity, and autophagy. The primary function of ferulic acid was discovered which shows that it significantly regulates MAPKs AGEs, NF-κB, CASPs, JNK, and ERK are the most structured proteins in renal pathophysiology (Bami *et al.,* 2017; Narasimhan *et al.,* 2015; Yang *et al.,* 2018).

Furthermore, it has demonstrated that oxidative insult levels, anti-oxidative responses, and serum aminotransferase activity were all greater in the cisplatin-induced group. A rise in the apoptotic shift, a concomitant increase in IL-1, COX-2, and mRNA levels, and a corresponding decrease in NF-B-p65 and caspase-1 enzyme activity were also observed. Treatment combined with the admin of ferulic acid has decreased the hepatotoxic result of cisplatin. Liver tissues' histological analysis supported these adjuvant treatments' ameliorative effects on cisplatin toxicity. It is conceivable to propose that the antioxidative, antiapoptotic, and anti-inflammatory properties of ferulic acid are responsible for the hepatoprotective benefits of co-administration against cisplatin-induced hepatotoxicity (Esmat *et al.,* 2022).

As per the findings, catechins also regulate several genes associated with fibrosis, albuminuria, and kidney damage brought on by diabetes to protect against oxidative and inflammatory stress and are acknowledged as the most effective substances for fighting NOS, IL-6, and cytokines induced in inflammation that also brought oxidative stress (Li *et al.,* 2015).

5. Conclusion

Based on the aforementioned information, *M. charantia* has a few metabolites, including polyphenols, which play a significant part in the treatment of NAFLD by regulating various genes responsible for its pathophysiology, *viz.*, AKTs, CASPs, MAPKs, ILs, and NOs. Additionally, the generated data supports the conventional assertion that *M. charantia* can be a promising agent for NAFLD and it alleviates liver sinusoidal endothelial cell dysfunction.

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Conflict of interest

The author declares no conflicts of interest relevant to this article.

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