Network Pharmacological Analysis of the Anti-Type 2 Diabetes Mellitus Mechanisms of *Pterocarpus marsupium* Heartwood

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Abstract

Type 2 diabetes mellitus (T2DM) is a progressive, multi-pathological and multifactorial disease. Recently, network pharmacology has emerged as a new approach to explore natural product actions and interactions with the multiple targets underlying diseases. Hence, the present study attempted to explore the molecular mechanism of Pterocarpups marsupium heartwood (PMH) in T2DM using the network pharmacology approach. The bioactive present in PMH was extracted from Indian medicinal plants, phytochemistry and therapeutics 2.0 (IMPPAT) database. Their protein targets were predicted using the SwissTargetPrediction web tool. The proteins involved in the pathogenesis of T2DM were retrieved from the TherapeuticTargetDisease database. Out of twenty-one bioactives of PMH, 17 were found to modulate 28 potential PMH-T2DM-related targets. Out of the 17 bioactive compounds in PMH, oleanolic acid, liquiritigenin, 7,4'-dihydroxyflavone, naringetol, (2S)-7-hydroxyflavanone and pterostilbene showed interaction with five or more target proteins associated with T2DM.

In the protein-protein interaction (PPI) study, PPARG, PPARA, NR3C1, PPARD, NR1H4, PTGS2, GPBAR1, PTGS1, NR3C2 and INSR were identified as the top ten targets. 28 potential targets associated with T2DM were linked to 11 signaling pathways. Notably, lipolysis in adipocytes and the PPAR signaling pathway were identified as having the lowest false discovery rate among the target proteins. In conclusion, we have identified 17 bioactive compounds in PMH and 28 potential target proteins that can affect 11 signaling pathways. This study demonstrated PMH's multicomponent, multitarget and multi-pathway characteristics used for further research on its mechanism in the treatment of T2DM.

Keywords: Network pharmacology, *Pterocarpus marsupium*, Protein-protein interaction, KEGG pathways.

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused by the dysfunction of pancreatic cells that secrete insulin and/or insulin resistance in peripheral organs[3,4,12]. According to the International Diabetes Federation, it is estimated that 439 million people may suffer from T2DM by 2030 and by 2050, a 33% increase is expected[41]. In the last 30 years, the number of diabetics worldwide has increased fourfold[47]. Insulin resistance is a common condition in T2DM that affects the liver, skeletal muscle and adipose tissue cells, making them less responsive to insulin. As a result, the body cannot efficiently metabolize glucose, leading to high blood sugar levels[6]. This chronic hyperglycemia causes inflammation and oxidative stress, harming the cardiovascular, endocrine, nervous and excretory systems[28,38].

Studies have shown that T2DM increases the risk of myocardial infarction by 2-6 times compared to healthy individuals[2]. Additionally, T2DM patients are more likely to develop colon, pancreas, endometrial and liver cancer[3,14,40]. T2DM is not a recently discovered ailment. Its existence dates back to ancient India, where it was known as "Madhumeha," a term coined by the Ayurveda physician Sushruta. He noticed flies and ants attracted to the urine of people suffering from Madhumeha[15]. Over time, traditional remedies, including herbal plants, have been employed to manage the condition[30].

Over 800 plants with antidiabetic properties have been identified and used for this purpose [30]. One of the significant antidiabetic plants is *Pterocarpus marsupium* Roxb. (PM). PM belongs to the genus Pterocarpus and the family Fabaceae (legumes). More than 20 species of this genus are distributed in tropical Asia, Africa and South America[16,22]. The tree grows in moist, well-drained soils in areas of moderate rainfall in the tropical regions of India, Sri Lanka and Myanmar. In India, PM grows in the areas of mixed deciduous forests of the central and peninsular regions. In various places, PM is known by different names like Indian Kino, Bijayasal, Bijasar, Pitasala, Venga, or Asana and Gammalu, due to the widespread distribution over regions with different languages and cultures[10,11,16,31].

During the last 50 years, preclinical studies performed on this plant have reported hypoglycemic[1,10,20,31,35,42], antidiabetic[10,11,23,29,31] hepatoprotective[9,18] anti-ulcer[21], antioxidant[24,29,31], antimicrobial[29], antidyslipidaemic[31], anti-inflammatory[29] and analgesic[29] activities. PM is a traditional Ayurvedic medicine[25] used in folk medicine to treat fever, diarrhea, worm infection, leprosy, diabetes, anemia, obesity and skin diseases[11,22,29]. In some places, wooden drinking cups carved from the heartwood pieces of this tree serve as containers for storing water and medicinal components enter

the water stored in these cups[16].

In recent years, there has been a shift from the "single-agent-single-target" approach in drug development to the "single-drug, multi-target" approach. This change was driven by the discovery that multiple proteins are involved in the pathogenesis of various diseases. Medicinal plants enriched with chemically diverse phytoconstituents have shown promise in contributing antioxidant and anti-inflammatory effects and interacting with targets involved in lowering blood glucose[39]. Although there are few scientific reports on the anti-T2DM properties of PMH, the molecular mechanism of PMH heartwood in treating T2DM based on a "multicomponent-multi-target and multi-pathways" mechanism is still unexplored[19].

To address this gap, the present study aims to investigate the molecular mechanism of PMH heartwood in treating T2DM using a network pharmacology approach. This approach involves the use of bioinformatics, cheminformatics, computational biology, systems biology and network-based mathematical tools[46]. It is based on the concept of systems pharmacology that helps us to understand a holistic and systemic view of traditional medicines and to take into consideration the interactions between multiple molecules and targets in the body to unfold several avenues of mechanistic understanding of disease state and herbal medicine[45,46,48].

Material and Methods

Data Mining for Bioactive of PMH: The information on bioactive compounds present in PMH was extracted from the IMPPAT database (https://cb.imsc.res.in/imppat/). The canonical SMILES of each compound was obtained from the PubChem database.

Predicting Potential Targets of Bioactives of PMH and T2DM: The SMILES codes of each plant compound in PMH were used to predict their protein targets using the SwissTargetPrediction web tool[7]. The proteins involved in the development of T2DM were obtained from the Therapeutic Target Database (TTD)[32]. The targets of PMH bioactive compounds that overlapped with the T2DM (PMH-T2DM) targets were used for network analysis.

Network Construction and Analysis: The candidate targets considered as PMH-T2DM intersecting targets, were uploaded into the Search Tool of STRING database (Version 11.5, available at https://string-db.org/) to generate a protein-protein interaction (PPI) network[37]. Further, KEGG pathway enrichment analysis[17] was carried out to identify pathways associated with candidate targets using the DAVID database[8]. Moreover, the other networks between the bioactive present in PMH, the targets of these bioactive intersecting with T2DM targets and a network between PMH-T2DM intersecting targets and the KEGG pathway were constructed using an open-source software Cytoscape v3.10.1[36]. The network analyzer tool added in Cytoscape was used to analyze and interpret the network.

Results

PMH bioactive compounds and target prediction: Using the IMPPAT database, 21 bioactive components were identified in PMH's heartwood. Table 1 lists these phytochemicals, their class/subclass, natural product likeness, target proteins and the number of target proteins obtained. The prominent interacting compounds included PMH17 (oleanolic acid), PMH13 (liquiritigenin), PMH6 (7,4'-dihydroxyflavone), PMH16 (naringetol) and PMH1 ((2S)-7-hydroxyflavanone).

Protein-protein interaction network, PMH Phytochemical-target and target-pathway networks: The protein-protein interaction network generated using the STRING database comprised of 28 interacting proteins with 80 edges and an average node degree of 5.74 (Figure 2). The network when imported to Cytoscape version 3.10.1, illustrates the relationships between PMH-T2DM-intersecting targets. The PPI shows that among the targets, PPARG has the highest number of interactions, followed by PPARA, PPARD, PTGS2 and PTGS1. In humans, PPARG has been associated with partial lipodystrophy and severe insulin resistance[34]. Moreover, PPARA and PPARD primarily stimulate oxidative lipid metabolism. PPARG is principally involved in the cellular assimilation of lipids through anabolic pathways[34]. The other target proteins that are highly involved in the PPI, were PTGS2 and PTGS1. PTGS2 is involved in blood glucose regulation.

Certain PTGS2 inhibitors have been reported to alter glucose homeostasis *in vivo* by stimulating glucose uptake in skeletal muscles that express PTGS2[29]. PMH has been reported to have antidiabetic, anti-inflammatory and analgesic activities[29], suggesting that the interaction between PMH and PTGS2 could be a potential mechanism involved, since eight PMH compounds showed interaction with PTGS2.

Table 1
Data mining for Phytoconstituents/ bioactives

Phytochemical Code	Bioactives	Classy Fire Class/Subclass	NP-Likeness score	Target Protein	Count
PMH1	(2S)-7-hydroxyflavanone	Flavonoids/Flavans	1.293	SLC5A2, PTGS1, PTGS2, PPARG, FGFR1	5
PMH2	1-[2,4-dihydroxy-3-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-	Linear 1,3-diarylpropanoids/	1.676	SLC5A2	1

	(hydroxymethyl) oxan-2-yl] phenyl]-3-hydroxy-3	Chalcones and dihydrochalcones			
PMH3	3,7,4'-Trihydroxyflavone	Flavonoids/Cinnamylphenols	1.038	ESRRA, PARP1, PTGS2, F2	4
PMH4	4-[2-Hydroxy-3-(4-hydroxyphenyl) propyl] phenol (propterol)	Linear 1,3-diarylpropanoids/ Cinnamylphenols	0.582	PTGS2, NR3C1, T2DMRB3	3
PMH5	4-Hydroxybenzaldehyde	Organooxygen compounds/ Carbonyl compounds	0.823	COMT	1
PMH6	7,4'-Dihydroxyflavone	Flavonoids/ Flavones	0.847	ESRRA, PARP1, PTGS2, PTPN1, INSR, F2, TBXAS1	7
PMH7	7-Hydroxy-5,4'-dimethoxy-8-methylisoflavone 7-O-rhamnoside	Isoflavonoids/Isoflavonoid o-glycosides	1.455	SLC5A2, T2DMORA2B	2
PMH8	beta-Eudesmol	Prenol lipids/Sesquiterpenoids	2.801	SLC10A, PTGS1, HSD11B, GCGR	4
PMH9	(-)-Epicatechin	Flavonoids/ Flavan-3-ols	2.304	SLC5A2, ADORA2B	2
PMH10	Ebanol	Prenol lipids/ Monoterpenoids	2.377	SLC10A, PTGS2, GCGR, NR3C2	4
PMH11	Garbanzol	Flavonoids	1.838	-	-
PMH12	Isoliquiritigenin	Linear 1,3-diarylpropanoids/ Chalcones and dihydrochalcones	0.7	MGAM, PTGS2, PTPN1	3
PMH13	Liquiritigenin	Flavonoids	1.366	SLC5A2, ESRRA, PTGS1, PTPN1, PPARG, FGFR1, INSR	7
PMH14	Lupeol	Prenol lipids/ Triterpenoids	3.054	GPBAR1, PTGS1, PTPN1, HSD11B1	4
PMH15	Marsupsin	Aurone flavonoids/ Auronols	1.735	-	
PMH16	Naringetol	Flavonoids/ Flavans	1.76	SLC5A2, ESRRA, PTGS1, PPARG, FGFR1, INSR	6
PMH17	Oleanolic acid	Prenol lipids ClassyFire Subclass: Triterpenoids	3.272	GPBAR1, FFAR1, NR1H4, PTGS1, PTGS2, PTPN1, PPARG, HSD11B, NR3C1, NR3C2, PPARA, SCD, PPARD, HSD11B2	14
PMH18	Propterol-b	Linear 1,3-diarylpropanoids/Cinnamylphenols	1.03	-	-
PMH19	Pseudobaptigenin	Isoflavonoids/ Isoflav-2-enes	0.82	ESRRA, MGAM, PTGS1, TBXAS1, PPARA	5
PMH20	Pterostilbene	Stilbenes/	0.376	PTGS1, PTGS2, HSD11B1, GCGR, HDAC1	5
PMH21	trans-Stilbene	Stilbenes/ Shikimates and Phenylpropanoids	0.038	-	-

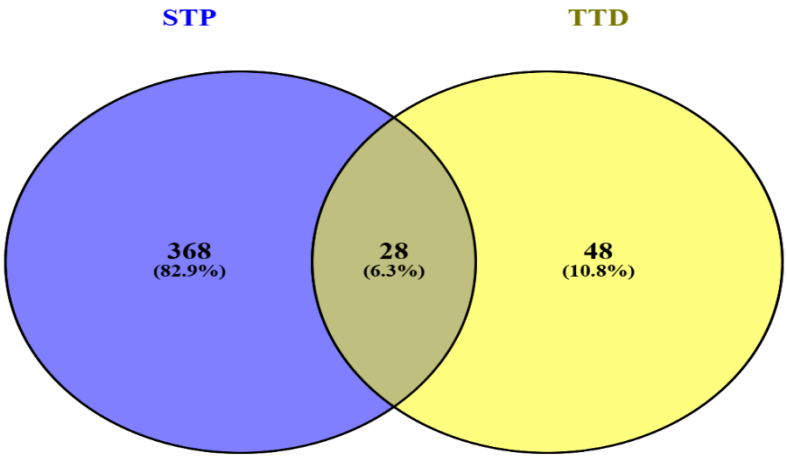

Figure 1: Potential targets of PMH heartwood in T2DM

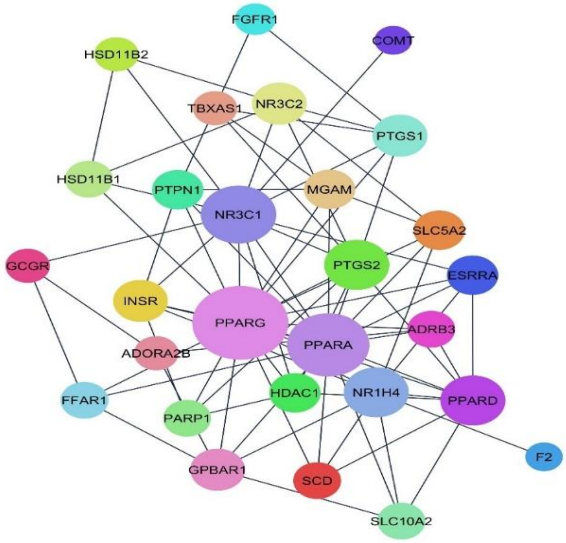

Figure 2: Protein-protein interaction network of PMH-T2DM intersecting targets using STRING database

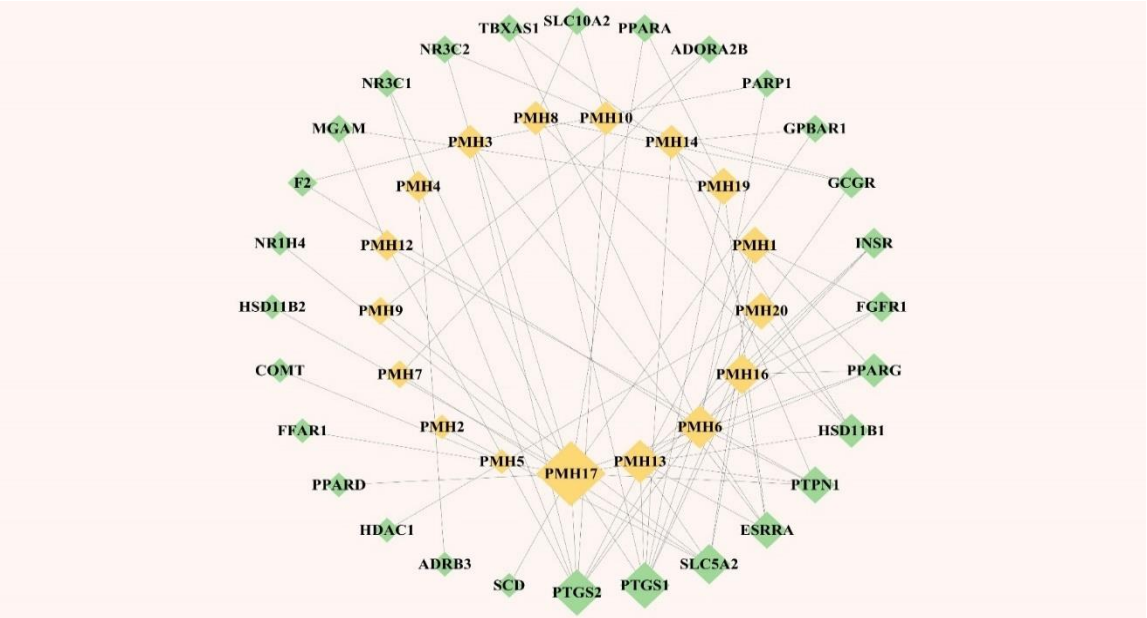

Figure 3: PMH phytochemicals and PMH-T2DM common targets network constructed using Cytoscape 3.10.1. The network represents interactions between PMH-bioactives (orange diamonds), PMH-T2DM intersecting targets (green diamonds)

The network between the bioactive compounds present in the heartwood of PMH and intersecting PMH-T2DM targets consisted of 45 nodes and 77 edges. Here, nodes include PMH heartwood bioactive (17 nodes) and T2DM-related targets (28 nodes), while edges indicate the interaction between these nodes. Many bioactive PMH compounds were found to interact with several targets in the network as shown by the degree numbers (Table 3). The phytochemical with the highest number of interactions is PMH17, which interacts with 14 targets including GPBAR1, FFAR1, NR1H4, PTGS1, PTGS2, PTPN1, PPARG, HSD11B1, NR3C1, NR3C2, PPARA, SCD, PPARD and HSD11B2. Another phytochemical with a significant number of interactions is PMH13 (liquiritigenin), a flavonoid that interacts with seven protein targets: SLC5A2, ESRRA, PTGS1, PTPN1, PPARG, FGFR1 and INSR.

The third phytochemical, PMH6, identified as 7,4'-dihydroxyflavone and belonging to the flavonoids/flavones class, also shows seven interactions with the following targets: ESRRA, PARP1, PTGS2, PTPN1, INSR, F2 and TBXAS1. The fourth phytochemical, PMH16, known as naringetol and classified as a flavonoid/flavan, exhibits six interactions with targets including SLC5A2, ESRRA, PTGS1, PPARG, FGFR1 and INSR. Another phytochemical, PMH19, identified as pseudobaptigenin which is an isoflavonoids/isoflavone-2-enes, is associated with five interacting targets: ESRRA, MGAM, PTGS1, TBXAS1 and PPARA. Another phytochemical, PMH20, identified as pterostilbene, a stilbene, is associated with five interacting targets: PTGS1, PTGS2, HSD11B1, GCGR and HDAC1. These are the top interacting PMH phytochemicals interacting with five or more targets. Other PMH phytochemicals also showed interaction with four or more targets which are shown in table 1 and figure 3.

KEGG enrichment analysis was performed to determine the signaling pathway involved in T2DM. A network was prepared between the PMH-T2DM common targets and the associated KEGG signaling pathways, providing insights into the enriched pathways. The network consisted of 31 nodes and 40 edges. Here, nodes include PMH-T2DM-related targets (20 nodes) and KEGG paths (11 nodes) while edges indicate the interaction between these nodes.

Table 2
Topological parameters of PPI network of PMH-T2DM-related targets

Name	Degree	Betweenness centrality	Closeness centrality
PPARG	18	0.294715	0.75
PPARA	14	0.144147	0.658537
NR3C1	12	0.205072	0.627907
PPARD	9	0.036491	0.55102
NR1H4	9	0.095876	0.54
PTGS2	9	0.062145	0.574468
GPBAR1	6	0.039067	0.509434
PTGS1	6	0.05482	0.529412
NR3C2	6	0.021544	0.482143
INSR	6	0.023827	0.54
ESRRA	5	0.008503	0.519231
PTPN1	5	0.034518	0.490909
HDAC1	5	0.005638	0.519231
MGAM	5	0.020204	0.5
SLC5A2	5	0.021606	0.509434
T2DMRB3	4	0.022347	0.482143
FFAR1	4	0.014008	0.482143
SLC10A2	4	0.001425	0.457627
PARP1	4	0.001978	0.473684
HSD11B1	4	0.010495	0.490909
SCD	4	7.12E-04	0.473684
T2DMORA2B	3	0.007241	0.385714
GCGR	3	0.020562	0.428571
HSD11B2	3	0	0.409091
TBXAS1	3	0.002374	0.402985
FGFR1	2	0.001684	0.380282
COMT	1	0	0.391304
F2	1	0	0.355263

It was found that 28 targets of T2DM were associated with 11 signaling pathways including regulation of lipolysis in adipocytes, PPAR signaling pathway, aldosterone-regulated sodium reabsorption, arachidonic acid metabolism, steroid hormone biosynthesis, pathways in cancer, neuroactive ligand-receptor interaction, adherens junction, insulin resistance, AMPK signaling pathway and platelet activation as shown in figure 4 and table 4. Of the 11 signaling pathways, the pathways in cancer have six genes: PPARD, HDAC1, PTGS2, FGFR1, PPARG and F2. The insulin resistance pathway includes three target proteins, namely INSR, PPARA and PTPN1. The pathways with the lowest FDR are the regulation of lipolysis in adipocytes and PPAR signaling pathways.

Table 3
Topological parameters of PMH bioactives

Name	Degree	Betweenness Centrallity	Closeness entrality
PMH17	14	0.384299239	0.461538
PMH13	7	0.115523113	0.407767
PMH6	7	0.112067292	0.392523
PMH16	6	0.079215668	0.392523
PMH1	5	0.107874597	0.415842
PMH20	5	0.081949867	0.385321
PMH19	5	0.06113449	0.365217
PMH10	4	0.042192803	0.352941
PMH8	4	0.039826838	0.336
PMH14	4	0.019395854	0.352941
PMH3	4	0.037604903	0.365217
PMH4	3	0.053810169	0.341463
PMH12	3	0.024222472	0.358974
PMH9	2	0.023228804	0.257669
PMH7	2	0.023228804	0.257669
PMH2	1	0	0.254545
PMH5	1	0	1
PTGS2	8	0.265863	0.488372
PTGS1	8	0.207035	0.456522
SLC5A2	6	0.182853	0.33871
ESRRA	5	0.049448	0.355932
PTPN1	5	0.078514	0.42
HSD11B1	4	0.030877	0.35
PPARG	4	0.046585	0.381818
FGFR1	3	0.002249	0.318182
INSR	3	0.012333	0.333333
GCGR	3	0.007184	0.295775
MGAM	2	0.00313	0.291667
GPBAR1	2	0.003382	0.323077
SLC10A2	2	0.002363	0.287671
PARP1	2	9.55E-04	0.287671
NR3C1	2	0.015242	0.328125
F2	2	9.55E-04	0.287671
ADORA2B	2	5.81E-04	0.207921
PPARA	2	0.012625	0.33871
TBXAS1	2	0.004098	0.304348
NR3C2	2	0.011011	0.333333
FFAR1	1	0	0.318182
NR1H4	1	0	0.318182
COMT	1	0	1
HDAC1	1	0	0.28
PPARD	1	0	0.318182
SCD	1	0	0.318182
T2DMRB3	1	0	0.256098
HSD11B2	1	0	0.318182

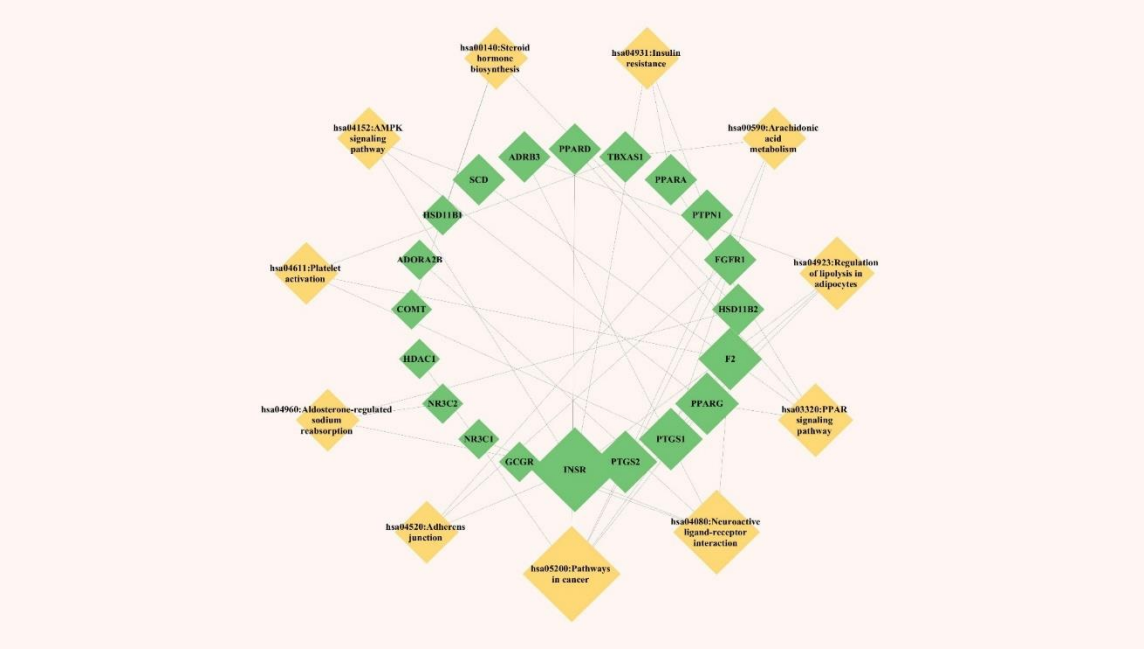

Figure 4: KEGG pathway network constructed using Cytoscape 3.10.1. The network represents pathways and interacting PMH-T2DM targets

Table 4
KEGG pathway analysis of 28 targets of PMH-T2DM intersecting target proteins

Term	Count	Fold Enrichment	FDR	Genes
hsa04923:Regulation of lipolysis in adipocytes	4	23.97288136	0.050185591	ADRB3, INSR, PTGS2, PTGS1
hsa03320:PPAR signaling pathway	4	18.61052632	0.052644961	SCD, PPARG, PPARA, PPARD
hsa04960:Aldosterone-regulated sodium reabsorption	3	27.91578947	0.151279105	HSD11B2, INSR, NR3C2
hsa00590:Arachidonic acid metabolism	3	17.39016393	0.206555411	TBXAS1, PTGS2, PTGS1
hsa00140:Steroid hormone biosynthesis	3	17.10967742	0.206555411	HSD11B1, HSD11B2, COMT
hsa05200:Pathway in cancer	6	3.980487805	0.206555411	HDAC1, PPARG, F2, PTGS2, FGFR1, PPARD
hsa04080:Neuroactive ligand-receptor interaction	5	4.804347826	0.224728167	ADRB3, ADORA2B, GCGR, F2, NR3C1
hsa04520:Adherens junction	3	11.40645161	0.315313576	PTPN1, INSR, FGFR1
hsa04931:Insulin resistance	3	9.732110092	0.375643865	PTPN1, INSR, PPARA
hsa04152:AMPK signaling pathway	3	8.695081967	0.39422095	SCD, INSR, PPARG
hsa04611:Platelet activation	3	8.4864	0.39422095	TBXAS1, F2, PTGS1

Discussion

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose levels caused by abnormal insulin secretion or action[27]. Inflammation and oxidative stress have been identified as major variables in the onset and progression of T2DM[43]. As a result, researchers have become interested in investigating the potential synergistic therapeutic effects of natural products that contain complex chemical mixtures. These natural products have a variety of bioactive compounds with diverse chemical structures that are suitable for interacting with multiple protein targets of therapeutic importance[33]. Network pharmacology has emerged as a promising discipline based on the concept of systems pharmacology and helps us to understand a holistic and systemic view of traditional medicines. Network pharmacology considers the interactions between multiple molecules and targets in the body[45,46,48].

Since network pharmacology can unfold several avenues of mechanistic understanding of disease state and herbal medicine, the present study applied network pharmacology to construct and to analyze PMH mechanisms in the

management of T2DM. The phytochemicals in PMH were obtained from the IMPPAT database, which is a manually curated database containing 1742 Indian medicinal plants, 9596 phytochemicals and 1124 therapeutic uses. It comprises a total of 27074 plant-phytochemical associations and 11514 plant-therapeutic associations[26]. From the database, 21 bioactive compounds belonging to different chemical classes were obtained for PMH.

Targets for these bioactive compounds were obtained from the SwissTargetPrediction database, which can predict the targets of bioactive molecules based on a combination of 2D and 3D similarity measures with known ligands[13]. Out of 21 target proteins, no target proteins were found for four PMH phytochemicals. These phytochemicals are garbanzol, marsupsin, propterol-b and trans-stilbene. As a result, 17 PMH bioactive compounds were used for the analysis. T2DM targets were obtained from the TTD database. The intersection targets (28) between the PMH-T2DM were used for the network pharmacological analysis.

Among the PMH bioactive compounds, oleanolic acid (PMH17) showed interaction with 14 target proteins associated with T2DM including GPBAR1, FFAR1, NR1H4, PTGS1, PTGS2, PTPN1, PPARG, HSD11B1, NR3C1, NR3C2, PPARA, SCD, PPARD, HSD11B2. Oleanolic acid is potentially useful for diabetes patients. Earlier studies have reported that oleanolic acid improves insulin response, preserves β-cell functionality and survival and protects against complications related to diabetes[5]. Additionally, it can directly modulate enzymes associated with insulin biosynthesis, secretion and signaling. Apart from oleanolic acid, five other PMH bioactive compounds that had five or more interactions are liquiritigenin, 7,4'-dihydroxyflavone, naringetol, (2S)-7-hydroxyflavanone and pterostilbene.

In order to determine the synergistic mechanism related to PMH-T2DM target proteins, KEGG pathway enrichment analysis was performed. The analysis further showed that the pathways related to the regulation of lipolysis in adipocytes, PPAR signaling pathway, aldosterone-regulated sodium reabsorption, arachidonic acid metabolism, steroid hormone biosynthesis, cancer pathways, neuroactive ligand-receptor interaction, adherens junctions, insulin resistance, AMPK signaling pathway and platelet activation could be regulated by bioactive compounds of PMH.

Based on the FDR value, regulation of lipolysis in adipocytes and the PPAR signaling pathway is the most significant pathways. Thus, it can be concluded that the potential mechanism of PMH could be regulating the expression or interaction with ADRB3, INSR, PTGS2, PTGS1, SCD, PPARG, PPARA and PPARD, as these are the targets involved in the regulation of lipolysis in adipocytes and the PPAR signaling pathway. Moreover, topological analysis showed that these targets had the highest interaction in protein-protein interaction and bioactive compound-protein target networks.

Conclusion

This study demonstrated PMH's multicomponent, multitarget and multi-pathway characteristics. It highlighted 17 PMH bioactive compounds, 28 target proteins and 11 signaling pathways that may play an important role in the anti-T2DM mechanism of PMH. Oleanolic acid, liquiritigenin, 7,4'-dihydroxyflavone, naringenol, (2S)-7-hydroxyflavanone and pterostilbene could be marker compounds that interact with five or more target proteins, contributing to the regulation of the PPAR signaling pathway and lipolysis in adipocytes.

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(Received 10th September 2024, accepted 22nd November 2024)