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Network Pharmacology and Molecular Docking-based Analysis of *Berberis aristata* DC. (*Daruharidra*): Elucidating Multitarget Mechanisms and Therapeutic Pathways in Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) accounts for approximately 90% of diabetes cases and is projected to rise to 783.2 million by 2045. This escalating prevalence underscores the urgent need for novel therapeutic agents with improved efficacy and minimal side effects. *Berberis aristata* DC., commonly known as *Daruharidra*, or Indian Barberry, has been extensively referenced in *Ayurvedic* texts for its use in managing diabetes. **Aim:** The present study aimed to employ a network pharmacology and molecular docking approach to identify potential molecular targets, pathways, and mechanisms underlying the anti-diabetic effects of *B. aristata*. **Methods:** Bioactive compounds of *B. aristata* were retrieved from the IMPPAT 2.0 database and screened for drug-likeness. Network pharmacology, protein-protein interaction analyses, functional enrichment, and pathway analyses were conducted using tools such as Cytoscape, Metascape and STRING. Molecular docking was performed using the Glide module from Schrodinger Suite 40. **Results:** The study identified six bioactive compounds, 282 target genes, and 26 disease terms associated with T2DM and its major complications. Key target genes were found to be linked to conditions such as fatty liver disease, diabetes mellitus, hypercholesterolemia, and hyperlipidaemia. Functional enrichment analysis highlighted involvement of target genes in critical pathways, including lipid metabolism, responses to hormones like insulin, glucagon, and incretins, cellular lipid responses, oxidative stress, and the AGE-RAGE signalling pathway. The docking study revealed that Berberine, Rutin, Jatrorrhizine, Palmatine and Quercetin have a high affinity with 6THA (Human sugar transporter 1 protein), 4NO7 (Human Glucokinase) and 7WSM (Human sugar transporter 4 protein). **Conclusion:** This study elucidates the anti-diabetic potential of *B. aristata* and demonstrates its ability to modulate multiple target genes and pathways central to metabolic dysfunction and the progression of T2DM, providing a scientific basis for its therapeutic applications in type 2 diabetes management.

Major Findings: The study reveals that *B. aristata* targets are involved in key T2DM pathways, including insulin signalling, lipid transport, and glucose homeostasis. Target regulatory hubs highlight their role in modulating insulin resistance and β-cell dysfunction. Its major phytoconstituents exhibited strong binding affinity toward key glucose regulatory proteins (GLUT1, GLUT4, and GCK).

Keywords: *Berberis aristata*, *Daruharidra*, Diabetes Mellitus, Network Pharmacology, Molecular Docking, *Prameha*

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1. Introduction

Type 2 diabetes mellitus (T2DM) is characterised by dysregulation of carbohydrate, lipid and protein metabolism, which results from impaired insulin secretion, insulin resistance in skeletal muscle, liver and adipose tissue or a combination of both, and may lead to the numerous complications[1]. Globally, the prevalence of diabetes within the adult demography is currently 10.5%, affecting around 536.6 million individuals, and is projected to surge to 12.2% (783.2 million adults) by 2045. T2DM accounts for 90% of these cases and has emerged as a global pandemic in recent decades[2]. A cross-sectional research study reports that approximately 101 million individuals in India are currently living with diabetes, and an additional 136 million are pre-diabetic[3]. *Ayurveda* describes a condition known as *Prameha*, which parallels type 2 diabetes mellitus (T2DM), characterised by clinical symptoms such as *Prabhootavila mutrata* (excessive and turbid urine production) and *Baram-baram mehati* (frequent urination), *etc.*[4,5]. Moreover, managing T2DM with current conventional drugs has been associated with significant side effects[6]. This situation highlights the urgent need for new therapeutic agents that can optimise diabetes management and improve health outcomes with fewer or no side effects. *Berberis aristata DC* (BA) is commonly known as *Daru Haldi, Daruharidra,* Indian barberry, Tree turmeric and Chitra, *etc*. It is a hard, spinous, yellowish herb belonging to Berbedaceae family. It grows majorly in the sub- Himalayan region, Nilgiri hills of southern India and hilly areas of Nepal up to an altitude of 2000 to 3500 meters[7]. This significant herb is mentioned in ancient books of *Ayurveda,* such as Charaka and Sushruta, for its various medicinal properties to treat a variety of diseases[8] viz. dysentery, diabetes, wound healing, skin disease, inflammation, diarrhoea, jaundice, menorrhagia and eye diseases, *etc*.[9]. Various conventional studies have reported anti-hyperglycaemic and anti-diabetic activity of *Darvi*[10-13]. Further, berberine, berbamine, rutin, jatrrhozine and palmitine, *etc.,* are reported as major chemical constituents of BA and proven to possess anti-diabetic, anti-inflammatory and antioxidant activities[14]. Proteins such as GLUT 1 (6THA), GLUT 4 (7WSM) and GCK (4NO7) are the well-studied primary targets in the management of T2DM as they are involved in glucose transport in muscle and adipose tissue, glucose sensing and insulin secretion in pancreatic β-cells, as well as glycogen synthesis in the liver and insulin-regulated glucose uptake into fat and muscle cells respectively[15,16]. Network pharmacology has shifted the research approaches from a "one-target, one-drug" mode to a "network-targeted multiple-component mode[17] and *Berberis aristata DC.* has been widely reported for its antidiabetic potential. Existing studies are predominantly limited to single-compound and single-target approaches, particularly focusing on berberine. T2DM management requires a comprehensive systems-level understanding involving multiple targets and pathways, which remains inadequately addressed. Furthermore, several studies have been conducted on different *Ayurveda* drugs to explore their molecular mechanism[18,19] but there is a lack of integrated network pharmacology-based analyses, interaction profiling, and comparative evaluation of multiple phytoconstituents against key glucose regulatory proteins such as glucokinase, GLUT1, and GLUT4. Therefore, the present study aims to bridge these gaps by employing an integrated network pharmacology and molecular docking approach to elucidate the multi-target mechanisms of *B. aristata* in the management of T2DM. It addresses the break in literature by presenting an integrated approach exploring drug-target interactions to better identify the novel inhibitors for a particular target and their mode of action.

2. Materials and Methods

2.1 Retrieval of Bio-actives of BA, their Targets and Associated Diseases

Reported bio-actives of BA were obtained from IMPPAT 2.0 database and checked for drug likeness through the Lipinski rule. The compounds having bioavailability score of 0.55, gastro-intestinal solubility level of at least moderately soluble and which have qualified the Lipinski rule of five, *i.e.*, molecular weight lower than 500 Da, number of donor hydrogen bonds less than 5, number of acceptor hydrogen bonds less than 10, fat water partition coefficient LogP lower than 5 and molar refractivity should be between 40-130 were employed in further network construction[20]. These bio-actives were again searched in the Binding DB to validate their

targets. The search was filtered for "Homo sapiens" in organisms[21]. In similarity search, to ensure accuracy, compounds with a similarity score greater than or equal to 0.7 and Affinity filter (nM, default maximum = 1000) were considered. Further, their structures were obtained from PubChem and the target protein name of the active component was converted to the standard target gene name using the UniProt database[22] was utilised to determine the diseases associated with each drug target gene. After that, the obtained terms were filtered for the term T2DM.

2.2 Network Construction

The Compound-Protein/gene-Disease (CPD) network was constructed using Cytoscape 3.10.2, and other analyses were performed in Metascape to show the molecular-level correlation between chemical constituents of BA, target proteins, T2DM and its major complications, along with pathway analysis.

2.3 Protein-protein Interaction (PPI) and Enrichment Analysis

Protein-protein interaction enrichment analysis has been carried out for the obtained set with the help of Metascape, which has used the physical interactions detected in STRING (physical score > 0.132) and BioGrid databases. Further, the Molecular Complex Detection (MCODE) algorithm has been applied to identify densely connected network components. Enrichment analysis for Cell Type Signatures and Disease target involved was performed through DisGeNET, and tissue/organ specificity enrichment was performed using PaGenBase. Transcriptional Regulatory Relationships and Transcription factor targets enrichment were executed in TRRUST (Transcriptional Regulatory Relationships Unravelled by Sentence-based Text mining) software. It is followed by pathway and process enrichment analysis to find pathways involved in diabetes and the top three best-scoring terms by p-value, as the functional description of the corresponding components.

2.4 Functional Enrichment and Pathways Analysis

For the obtained gene data set, pathway and process enrichment analysis have been carried out in the Metascape that incorporated ontology sources such as KEGG Pathway, GO Biological Processes, Reactome Gene Sets, and WikiPathways. All genes in the dataset have been used as the enrichment background. Terms with a pvalue < 0.01, a minimum count of 3, and an enrichment factor > 1.5 are collected and grouped into clusters based on their membership similarities. The most statistically significant term within a cluster is chosen to represent the cluster. Biological Process (BP), Molecular Function (MF), Cellular Component (CC) and pathway enrichment were also performed with GO-process.

2.5 Molecular Docking

2.5.1 Protein Preparation

Crystallographic structures of the target proteins were downloaded from the Protein Data Bank (PDB). The Receptor Binding Domains (RBDs) viz. 4NO7, 6THA and 7WSM structures were extracted from the PDB database as these structures have no mutations and have high resolution. Further, protein preparation was performed using the Protein Preparation Wizard tool of the Schrödinger suite 38. The preparation involved the removal of water molecules and cofactors, correcting mislabelled elements, adding hydrogen atoms, assigning bond orders, optimising hydrogen bonds, and minimising restrained energy using the OPLS4 force field. The prepared proteins were then utilised for grid generation using the Glide module within the Schrodinger suite.

2.5.2 Ligand Preparation

The ligands used in this study were prepared using the Schrödinger suite and the PubChem database as the source for phytochemical 3D sdf. structures. The downloaded structures were then imported into the Schrödinger suite, where they were processed using the LigPrep module 39. Phytochemicals optimisation was performed at a pH of 7±2 using the Epik tool. The optimised structures were then subjected to energy minimisation using the OPLS4 force field to ensure accurate molecular conformations for subsequent docking studies. The prepared ligand library was subsequently used for molecular docking to assess its potential as modulators of the target proteins.

2.5.3 Docking

Molecular docking studies were performed using the Glide module from Schrödinger Suite 40. For

ligand docking, the Standard Precision (SP) mode was employed to assess the binding interactions between the ligand and the target protein. Flexible ligand docking was carried out, where the ligand conformational flexibility was considered during the docking process, allowing for the exploration of various possible binding modes. The docking process utilised the default settings of the SP mode, which balances computational efficiency and accuracy. Glide's scoring function was used to rank the ligand poses based on their predicted binding affinity to the protein. The results were analysed to identify the most favourable binding conformations and interactions.

3. Results

3.1 Bio-actives of BA, Putative Targets and Associated Diseases

A total of 15 bio-actives related to *B. aristata* bark were found in the IMPPAT database, and 6 bio-actives, such as Berberine, Berbamine, Palmatine, Rutin, Quercetin and Jatrorrhizine, were found suitable for the network construction. The chemical structures of selected compounds are depicted in Figure 1.

These six bio-actives were then searched for reported targets in the STITCH (Search Tool for Interacting Chemicals) database and 282 targets were retrieved. The genes for the respective targets were obtained from the UniProt database. Among 282 putative targets, there were 65 for Berberine, 4 for Berbamine and Palmatine each, 22 for Rutin, 186 for Quercetin and 1 for Jatrorrhizine. The details, such as chemical formula, PubChem Id, biosynthetic class, canonical smiles, and target gene names pertaining to bio-actives have been provided in Supplementary file (Table 1). Initially, 72 pathological conditions related to diabetes were obtained from DisGeNET. Further, these terms were narrow down to T2DM and its major complications, by eliminating the terms like Diabetes insipidus, Insulin dependent diabetes, Type 1 diabetes, Neonatal diabetes, Gestational diabetes, Autoimmune diabetes, Post transplant diabetes, Monogenic diabetes, Brittle diabetes, Lipoatrophic diabetes, Fibrocalculous diabetes, Maturity onset diabetes, Phosphate diabetes, Autosomal diabetes, Congenital diabetes, Cystic fibrosis diabetes, Fulminant diabetes, Mitochondrial diabetes, Children diabetes, Transient diabetes, *etc*. Finally, 26 disease terms pertaining to T2DM and its major complications were obtained and used for network construction.

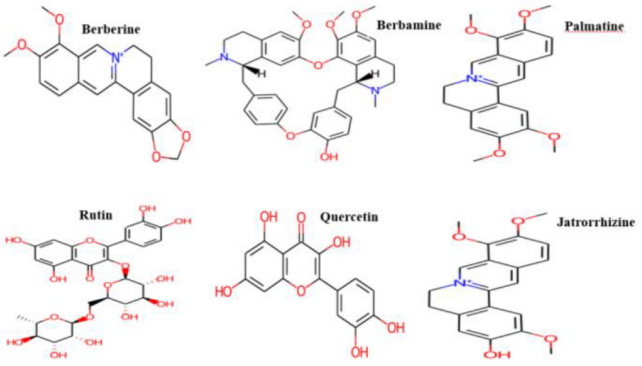


Figure 1. Chemical structure of bio-actives of *B. aristata*.

3.2 Network Construction

The CPD target network was constructed for the selected bio-actives that consisted of 262 nodes and 942 edges. In the constructed network, the average number of neighbours to a node was found to be 7.218 with a path length, network diameter and centralisation value of 2.352, 5 and 0.685, respectively. The constructed network has been depicted in Figure 2, in which yellow triangles, light green circles, oval shapes and inverted arrows represent the herbal drug, bio-actives, target genes and associated diseases, respectively.

3.3 PPI Network Analysis

The resultant network (Figure 3A) contains the interaction subset of the target proteins. Further, densely connected network components were identified by MCODE and shown in Figure 3B. Pathway and process enrichment analysis has been applied to each MCODE component independently, and the best-scoring terms by p-value have been retained as the functional description of the corresponding components and shown in Table 1.

3.4 Enrichment Analysis in Cell Type Signature, PaGenBase, DisGeNET, and TRRUST

Enrichment analysis by Cell type Signatures and PaGenBase for the top 20 cell/tissue types (arranged

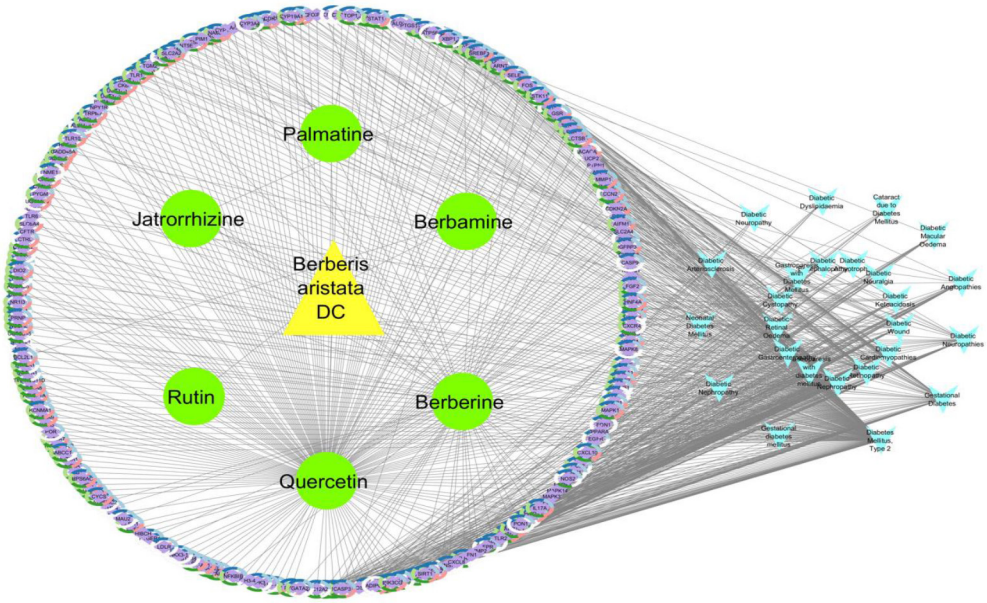


Figure 2. Compound-target-disease network of *B. aristata*.

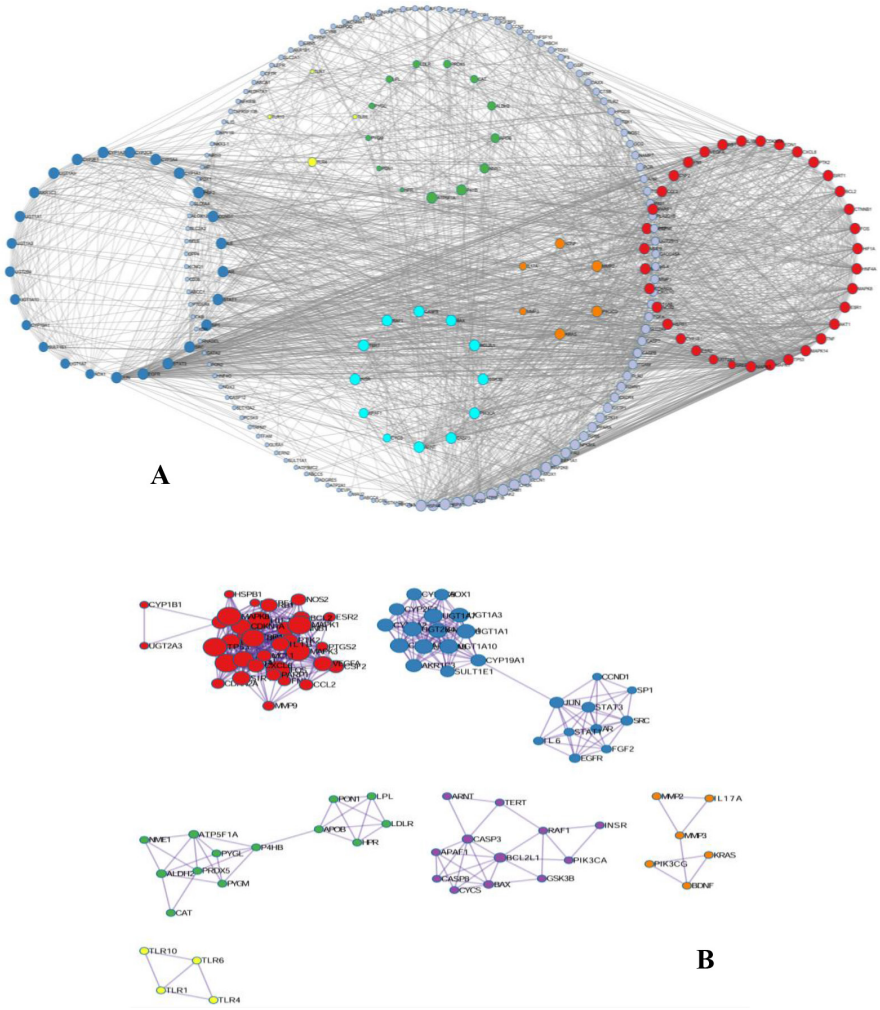


Figure 3. **(A).** PPI network, **(B).** MCODE cluster enrichment of target proteins.

as per log p value) in which target genes have significant expression and perform tissue-specific functions is shown in Figures 4A B, respectively. Diseases associated with the target genes have been depicted in Figure 5. The top 20 Transcription Factors (TFs) as per their log p value and number of target genes (highest to lowest) using TRRUST are depicted in Figure 6, and the regulated gene percentage along with log p values for all enrichment analyses are provided in Supplementary file (Table 2).

3.5 Pathway and Process Enrichment Analysis

The top 20 clusters with their representative enriched terms (one per cluster) and pathway are shown in Figure 7. The gene count, percentage, log p and log q values pertaining to detected pathways are provided in Supplementary file (Table 6). The network for pathways associated with the target genes is presented in Figure 8. BP, CC, MF enrichment networks and their comparative score are shown in Figures 9(a-d), respectively.

3.6. Docking Analysis

Molecular docking analysis revealed that several phytochemical constituents exhibited high affinity toward specific target proteins. Descriptions of the bio-actives and corresponding dock score are shown in Table 2. The H-bonds and other interactions between the protein-ligand complex are represented in Figure 10 (a-o).

Table 1. Functional description of GO terms with MCODE enrichment

MCODE	GO terms	Description	Log_{10}(P) value
MCODE 1	WP5353	Macrophage-stimulating protein MSP signalling	-37.7
MCODE 1	R-HSA-6785807	Interleukin-4 and Interleukin-13 signalling	-30.1
MCODE 2	hsa00140	Steroid hormone biosynthesis	-28.8
MCODE 2	WP702	Meta-pathway biotransformation Phase I and II	-24.6
MCODE 3	WP3601	Lipid particles composition	-8.1
MCODE 3	GO:0044248	Cellular catabolic process	-7.9
MCODE 3	R-HSA-174824	Plasma lipoprotein assembly, remodelling and clearance	-7.6
MCODE 4	hsa05200	Pathways in cancer	-18.3
MCODE 4	hsa04210	Apoptosis	-16.2
MCODE 5	WP3676	BDNF TrkB signalling	-7.6
MCODE 5	WP4565	Neural crest cell migration in cancer	-7.3
MCODE 6	WP3877	MYD88 distinct input-output pathway	-13.1
MCODE 6	R-HSA-5602358	TLR signalling cascade	-12.0

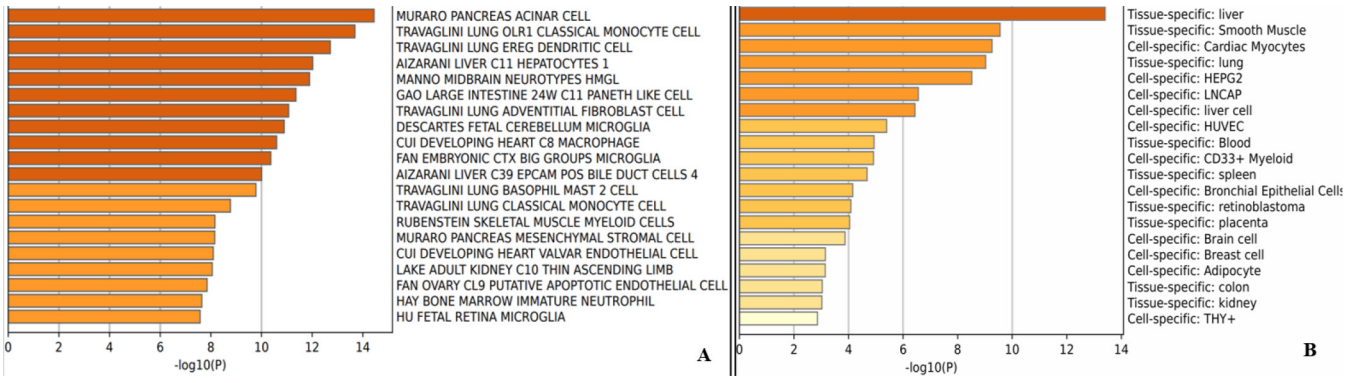


Figure 4. Top 20 cell/tissue types having significant representation of target genes.

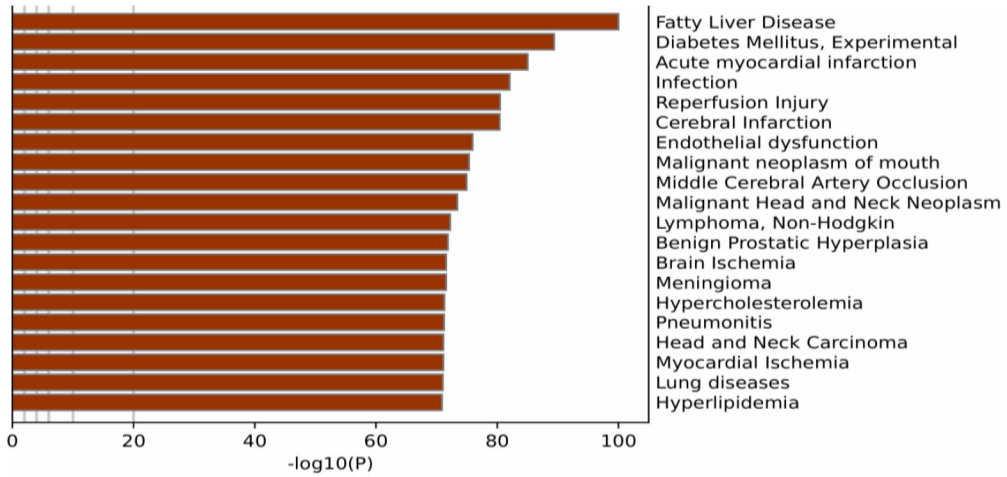


Figure 5. Top 20 associated diseases for target genes.

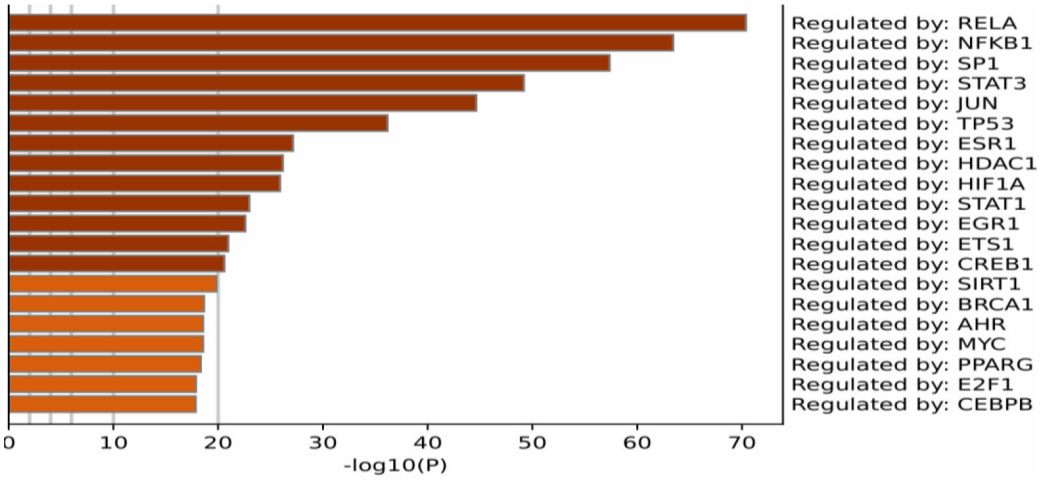


Figure 6. Top 20 TFs for the target genes.

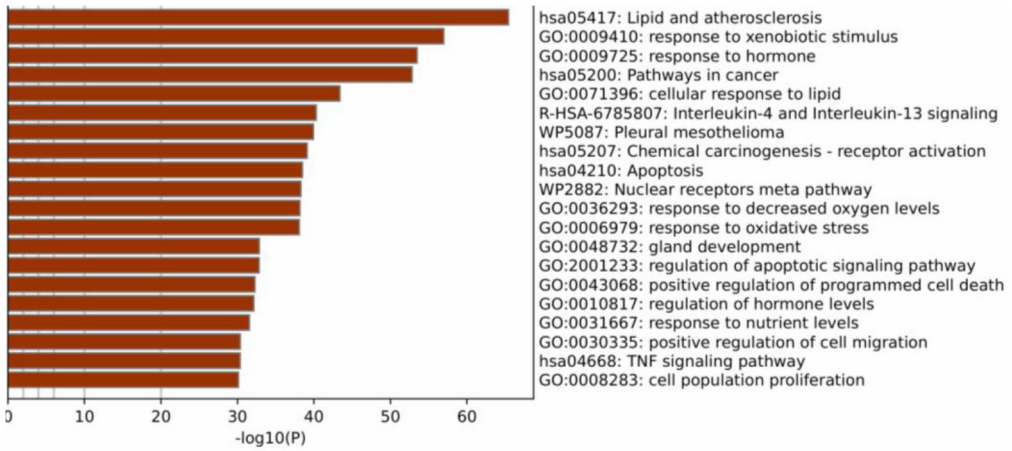


Figure 7. Top 20 pathway clusters for the target genes.

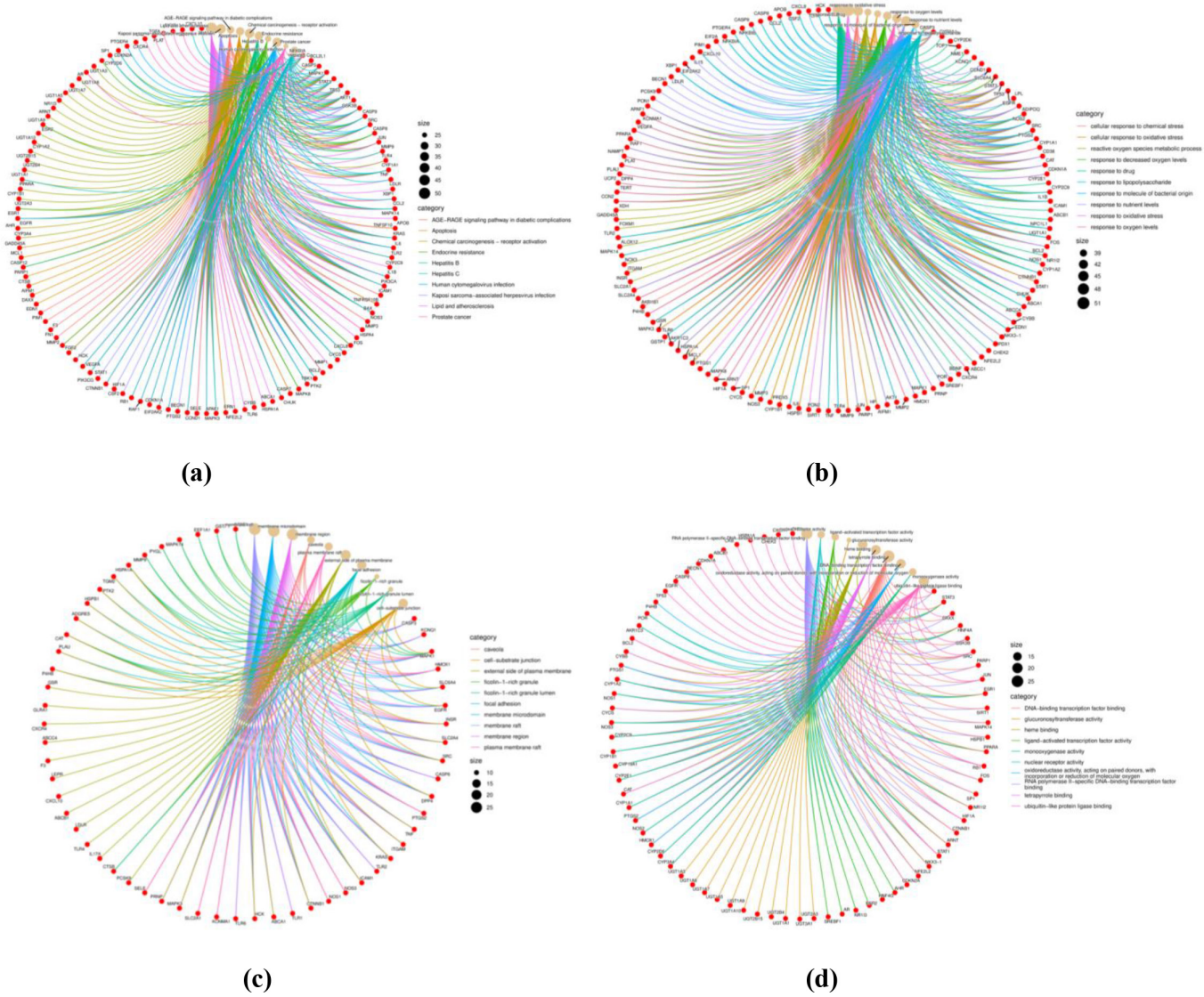


Figure 8. Gene-pathways network of B.A.

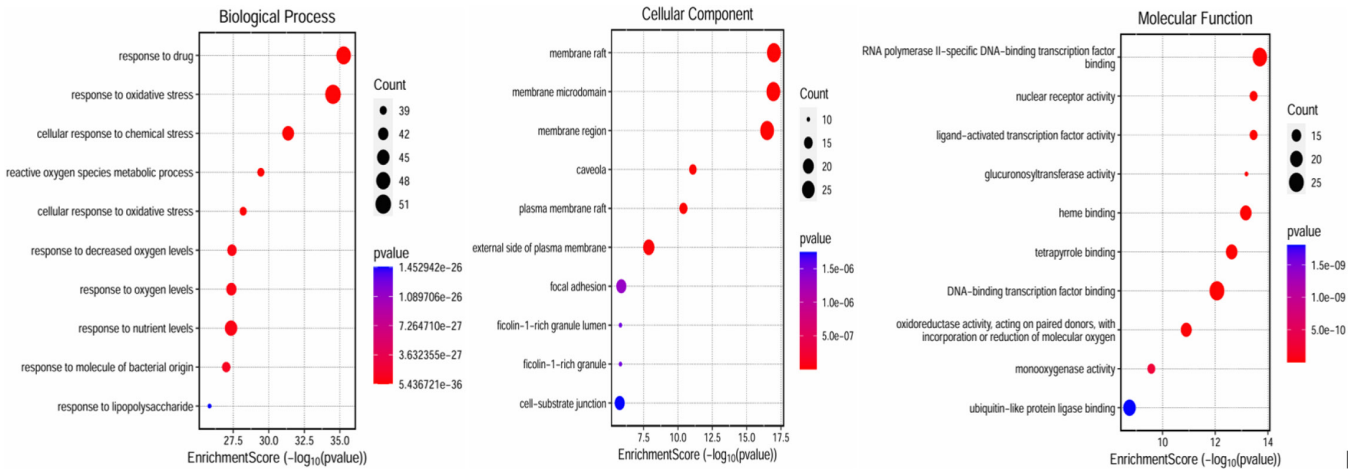


Figure 9. **(a).** BP analysis of therapeutic targets, **(b).** CC analysis of therapeutic targets. (**c).** MF analysis of therapeutic targets. **(d).** Comparative enrichment score of BP, CC and MF.

4. Discussion

Berberis aristata has widely been used in India as well as other traditional systems of medicine due to its diverse pharmacological activity against various diseases such as diabetes and metabolic disorders[23], dysregulated redox process[24] and inflammatory conditions[25]. A recent study reported that, its therapeutic potential is specifically attributed to presence of various secondary metabolites including berberine, berbamine, quercetin, jatrorrhizine, columbamine, palmatine, oxycanthine, *etc*.[26]. Although 282 putative targets were initially retrieved from six bioactive compounds, the compound-target network comprised 262 nodes due to the merging of overlapping targets shared among multiple compounds and merging of isoforms gene nodes into parent gene nodes. A higher number of nodes and edges may provide a more detailed understanding of the drug-target interactions, protein-protein interactions, disease gene networks and potential therapeutic targets. Such networks often exhibit modularity, enabling identification of pathway-specific modules and druggable regions, thereby supporting multi-target and polypharmacological drug design effectively[27]. A

Table 2. Binding energy of BA bioactive and its predictive targets

Ligands	PubChem Id.	Target		
		GCK-4NO7	GLUT1-6THA	GLUT4-7WSM
		Binding energy (KCal/Mol)		
Berberine	2353	-7.852	-9.027	-7.407
Jatrorrhizine	72323	-7.786	-8.236	-6.872
Quercetin	5280343	-7.584	-8.076	-7.058
Palmatine	19009	-5.542	-9.205	-7.842
Rutin	5280805	-4.817	-8.421	-9.615

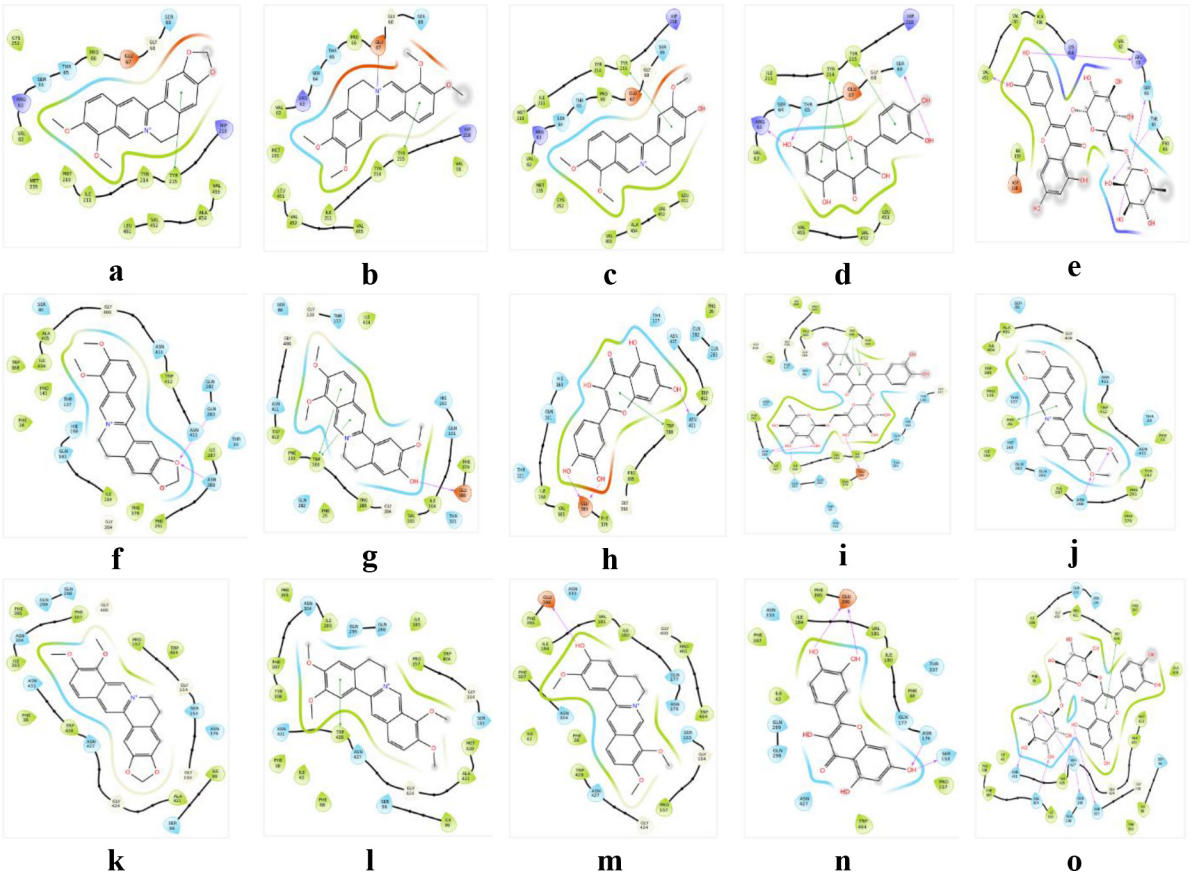


Figure 10. Docking analysis showing H-bonds and other interactions between protein-ligand complex of **(a).** 4NO7- Berberine; **(b).** 4NO7- Jatrorrhizine; **(c).** 4NO7- Quercetin; **(d).** 4NO7- Palmatine; **(e).** 4NO7- Rutin; **(f).** 6THA-Palmatine; **(g).** 6THA- Berberine; **(h).** 6THA- Rutin; **(i).** 6THA- Jatrorrhizine; **(j).** 6THA- Quercetin; **(k).** 7WSM- Rutin; **(l).** 7WSM- Palmatine; **(m).** 7WSM- Berberine; **(n).** 7WSM- Quercetin; **(o).** 7WSM- Jatrorrhizine.

moderate range of neighbours (5-15) suggests multi-target activity with a balanced efficacy-safety profile. In *B. aristata*, an average of 7.2 neighbours indicates safe polypharmacological potential. The network path length indicates the efficiency of biological interactions, where shorter path lengths (2-4) and diameters (3-5) signify well-connected networks that enable rapid communication and multi-pathway modulation. In the present study, the average path length (2.352) and diameter (5) fall within the optimal range, suggesting efficient network dynamics and potential for rapid therapeutic effects of *B. aristata*[28]. Network centralisation reflects the presence of hub genes critical to disease regulation. A moderate centralisation value indicates optimal target connectivity. The observed centralisation of 0.685 indicates that *B. aristata* can effectively target multiple nodes, supporting improved therapeutic outcomes T2DM[29]. The constructed PPI network revealed the interconnection of 218 nodes, 1946 edges, 17.85 neighbours with a diameter of 8 and a path length of 2.509. It reflects the extensive interconnection of proteins and their influence on one another. The major pathways with the number of their corresponding genes, which are implicated in T2DM, are shown in Figure 11.

Apart, gene enrichment also revealed their influence on other crucial pathways such as Lipid transport (25 genes), Response to lipopolysaccharide (38 genes), AGE-RAGE signalling pathway in diabetic complications (29 genes), Insulin secretion (14 genes), Response to insulin resistance (18 genes), Insulin signalling pathway (16 genes), Carbohydrate and Glucose homeostasis (32 genes), Carbohydrate derivative metabolic process (28 genes) and Response to Reactive oxygen species (31genes), *etc*. and description pertaining to all 30 major pathways is provided in Supplementary file (Table 7). The enrichment revealed that a significant number of target genes of B. aristata are involved in the pathophysiology of T2DM and can potentially influence the therapeutic outcome. MCODE enrichment highlights clusters of target genes involved in key T2DM-related pathways, including MSP, IL-4, and IL-13 signalling, which promote anti-inflammatory M2 macrophage polarisation and counter insulin resistance-associated inflammation seen in T2DM[30,31]. Additional pathways such as steroid hormone biosynthesis, xenobiotic biotransformation, and mitochondrial energy metabolism influence glucose homeostasis and insulin sensitivity[32], oxidative stress and inflammation[33], and cellular dysfunction lead to dyslipidaemia in T2DM[34], respectively. Dysregulation of lipid metabolism and lipoprotein assembly contributes to diabetic dyslipidaemia[35], while impaired β-cell apoptosis accelerates hyperglycaemia that accelerates T2DM progression[36]. Furthermore, reduced Brain-Derived Neurotrophic Factor (BDNF) levels[37], and overactivation of MYD88/TLR signalling exacerbate insulin resistance and chronic inflammation[38], collectively driving T2DM progression. Therefore, regulation of target genes by *B. aristata* may contribute to the optimal management of T2DM. Cell type signature analysis identified dominant expression

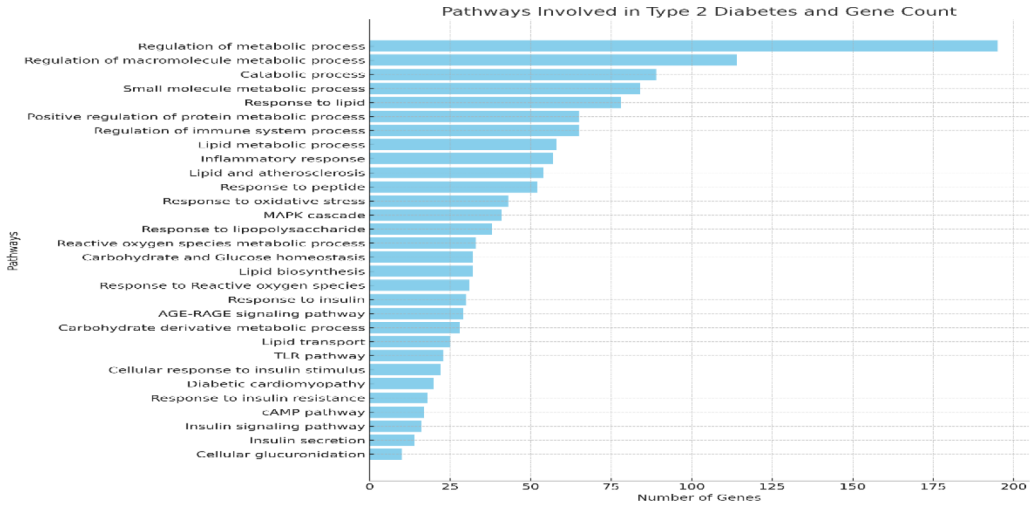


Figure 11. Gene enrichment for the PPI network.

of target genes across key metabolic and immune cells. Notably, 31 genes were enriched in pancreatic acinar cells, which include the OLR1 cells (30 genes) helps to clear oxidised lipids, and EREG (26 genes) encodes epiregulin that modulates inflammatory responses and limits tissue damage[39]. Significant expression was also observed in C11 hepatocytes (19 genes) and intestinal Paneth-like cells (19 genes), highlighting roles in glucose and lipid metabolism[40] and incretin-mediated insulin regulation[41], respectively. PaGenBase analysis further confirmed tissue-specific enrichment in liver (29 genes), smooth muscle (11 genes), spleen (14 genes), and cell lines such as HEPG2 (14 genes) and HUVEC (13 genes), underscoring their involvement in glucose homeostasis, oxidative stress, and insulin signalling in T2DM, and their dysfunction contributes to the development of T2DM and its complications[42]. Moreover, details for other gene expression in different cell/tissue types with log P values are provided in Supplementary file (Table 3). Gene-disease association analysis revealed strong links with fatty liver disease (101 genes-45%), diabetes mellitus (85 genes-38%), hypercholesterolemia (72 genes-32%), and hyperlipidaemia (70 genes-31%). A detailed list can be found in Supplementary File (Table 4). Pathway enrichment indicated regulatory involvement of target genes in lipid metabolism (54 genes), hormonal regulation (insulin, glucagon, incretins, 69 genes), cellular response to lipid (53 genes), oxidative stress response (43 genes), AGE-RAGE (advanced glycation end-products (AGE)-receptor for AGE (RAGE)) pathway (24 genes) and regulation of apoptotic signalling pathway which regulates beta cell apoptosis (40 genes) along with gland development (endocrine glands that regulates insulin production and secretion), *etc.*[43,44] which are crucial for the glucose metabolism in the body and patho-physiology of T2DM. These findings were further validated through BP, MF and CC enrichment. Further, log P and log Q values are provided in Supplementary File (Table 6). Transcription factor analysis identified critical regulators, including RELA, NFKB1, PPARG, SP1, and JUN, associated with inflammation and oxidative stress (RELA, NFKB1, and STAT3), insulin sensitivity and resistance (ESR1, CEBPB, PPARG), β-cell dysfunction and apoptosis (JUN, TP53, STAT1, E2F1), Metabolic dysregulation (SP1, HDAC1, HIF1A, MYC) and Lipid Metabolism (CREB1, SIRT1)[45,46]. The details of TF with their log P value are provided in Supplementary File (Table 5). Collectively, these findings suggest that *B. aristata* may exert therapeutic effects in T2DM through multi-target modulation of genes, pathways, and transcriptional networks. Therefore, *B. aristata* can be a potential therapeutic agent to manage T2DM by modulating the target genes and associated pathways.

The molecular docking analysis demonstrated significant binding affinities between the selected bio-actives (berberine, jatrorrhizine, palmatine, quercetin and rutin) and the target proteins (GLUT1-6THA, GLUT4-7WSM and GCK-4NO7), which could potentially translate into therapeutic benefits in the management of T2DM. The GCK, GLUT1, and GLUT4 were selected for docking analysis as they represent key and complementary molecular nodes governing glucose sensing, insulin-independent glucose uptake, and insulin-responsive glucose transport, respectively. Moreover, these pathways are reported to be central to the development of T2DM pathophysiology[47,48]. Dysregulation of these targets is central to the pathophysiology of insulin resistance and Type 2 Diabetes Mellitus, making them rational and biologically relevant targets for evaluating therapeutic interactions. The more negative values of binding energy reflect the greater probability of binding at the site. In the present study, palmatine (- 9.205 KCal./Mol) showed the strongest binding affinity to 6THA, followed by berberine (-9.027 KCal./Mol), rutin (-8.421 KCal./Mol), jatrorrhizine (-8.236 KCal./Mol), and rutin (-8.076 1KCal./Mol). For 7WSM, the highest affinity was observed in rutin (-9.615 KCal./Mol), followed by palmatine (-7.842 KCal./Mol), berberine (-7.407 KCal./Mol), quercetin (-7.058 KCal./Mol) and jatrorrhizine (-6.872 KCal./Mol). Berberine has exhibited highest affinity with a docking score of -7.852 KCal./Mol followed by jatrorrhizine (-7.786 KCal./Mol), quercetin (-7.584 KCal./Mol), palmatine (-5.542 KCal./Mol) and rutin (-4.817 KCal./Mol) for 4NO7, while berbamine has exhibited significantly low docking score of -3.312, -4.101 and -4.117 KCal./Mol for 4NO7. 6THA and 7WSM respectively. Apart from the number of different types of bonds and the nature of protein ligand complex interaction, which have been presented in Table 3.

The robust network of interactions, including hydrogen bonds, π-π stacking, and hydrophobic alkyl

Table 3. Number of hydrogen bonds and interaction strength in protein-ligand complexes

Ligand	Targets	H-bonds	Hydrophobic	π-π /π-cation
Berberine	4NO7	1	10	Strong
	6THA	1	9	Strong
	7WSM	2	9	Strong
Jatrorrhizine	4NO7	2	9	Moderate
	6THA	3	8	Moderate
	7WSM	3	8	Moderate
Quercetin	4NO7	4	7	Moderate
	6THA	5	7	Moderate
	7WSM	5	7	Moderate
Palmatine	4NO7	1	11	Strong
	6THA	1	10	Strong
	7WSM	1	10	Strong
Rutin	4NO7	8	6	Weak
	6THA	9	5	Weak
	7WSM	10	6	Weak

interactions, underscores the strength and specificity of these compounds' binding. Docking analysis of phytoconstituents from *Berberis aristata* revealed that rutin exhibited the highest number of hydrogen bonds across all targets, indicating superior binding specificity and potential enzyme inhibition. Quercetin demonstrated a balanced interaction profile, supporting multi-target antidiabetic activity. Berberine and palmatine showed predominant hydrophobic and π-interactions, suggesting their role in metabolic pathway modulation, particularly AMPK activation[49]. This multifaceted binding profile not only marks *B. aristata* as a promising candidate for further investigation but also suggests that they could modulate several targets simultaneously[50,51] and may offer distinct advantages over conventional drugs being used in the management of T2DM[52].

5 Limitations and Future Scope

Although rigorous screening criteria and methodologies were applied, the present study is primarily based on in-silico methodologies that may not reflect the dynamic complexity of biological systems and may limit direct clinical translation of the findings. Future studies should therefore focus on validating the predicted targets and pathways through molecular dynamics simulations, complemented by *in vivo* studies and clinical trials, which are essential to support the evidence-based application of *Berberis aristata* in the management of Type 2 Diabetes Mellitus.

6. Conclusion

The alarming rise in cases of non-communicable diseases, specifically diabetes and public concerns pertaining to the safety of the currently available conventional medicine have raised the need for safe and efficacious treatment options. The present study has uncovered the anti-diabetic potential of *B. aristata* through network pharmacology and gene enrichment analysis that demonstrated its ability to modulate numerous target genes and pathways, which are central to metabolic dysfunction and progression of T2DM.

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Rohit Singh: contributed to the concept, design, literature search, experimental studies, data acquisition, data analysis, and manuscript preparation. Anjali Upadhyay: contributed to the literature search, experimental studies, data acquisition, and manuscript preparation. Pramod Yadav: contributed to the concept, experimental studies, statistical analysis, manuscript editing, and manuscript review. Ashok Patel: contributed to the statistical analysis, manuscript editing, and manuscript review. P.K. Prajapati.: contributed to the data analysis, manuscript editing, and manuscript review. All authors have read and agreed to the published version of the manuscript.