RESEARCH ARTICLE

A Network Pharmacology-based Approach to Explore Potential Targets and Mechanism of *Berberis aristata* Focusing on its Implications for Diabetes Mellitus

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Received: 19th May, 2024; Revised: 02nd June, 2024; Accepted: 10th June, 2024; Available Online: 25th June, 2024

ABSTRACT

Berberis aristata, a revered medicinal shrub in traditional systems like Ayurveda, holds promise in managing diabetes mellitus, a burgeoning global health concern. Through a comprehensive analysis of its bioactive compounds and their interactions with potential targets, this study elucidates the molecular mechanisms underlying its anti-diabetic effects. Screening through databases yielded 17 bioactive compounds, including rutin, quercetin, and berberine. Protein-protein interaction analysis identified 44 potential targets, with 36 genes overlapping with disease-related genes, indicating pivotal pathways in diabetes mellitus treatment. Further, pathway analysis highlighted G-protein coupled receptor signaling, calcium signaling, and neurotransmitter receptor activity as significant, with adjusted *p-values*. Network analysis revealed key hub genes like DRD1 and MMP2, emphasizing their central role in *Berberis aristata*'s therapeutic action. The findings underscore *Berberis aristata*'s potential as a source of novel anti-diabetic agents and offer groundwork for potential research in this field.

Keywords: *Berberis aristata*, Bioactive compounds, Diabetes Mellitus, Network pharmacology, Gene ontology, Pathway analysis.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.2.40

How to cite this article: Bethi S, Patil J, Thube U, Patil K. A Network Pharmacology-based Approach to Explore Potential Targets and Mechanism of *Berberis aristata* Focusing on its Implications for Diabetes Mellitus. International Journal of Pharmaceutical Quality Assurance. 2024;15(2):803-809.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Diabetes mellitus (DM) is a persistent metabolic disorder distinguished by hyperglycemia resulting from defects in insulin secretion. The universal occurrence of diabetes has reached epidemic proportions, necessitating the exploration of novel therapeutic approaches to manage and mitigate its complications. Conventional anti-diabetic medications, while effective, are often associated with adverse effects and limitations in long-term efficacy. This underscores the need for alternative treatments, particularly those derived from natural products with multi-target therapeutic potential.[1]

Berberis aristata, normally recognized as Indian barberry or tree turmeric, is a medicinal plant traditionally used in Ayurveda and other indigenous medical systems for its diverse pharmacological properties.[2] The bioactive compound berberine, isolated from *B. aristata*, has garnered significant attention due to its broad spectrum of biological activities, including anti-diabetic,[3] anti-inflammatory,[4] and antioxidant effects.[5] However, the precise molecular mechanisms and potential therapeutic targets through which *B. aristata* exerts its anti-diabetic effects remain inadequately understood.

Network pharmacology, an promising field that integrates systems biology and polypharmacology, offers a comprehensive approach to unravel the multifaceted relations among bioactive compounds and multiple biological targets.[6] By constructing and analyzing networks of relations, network pharmacology can identify key nodes and pathways that underpin the therapeutic effects of medicinal plants. This holistic approach

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aligns well with the multi-component and multi-target nature of herbal medicines, providing deeper insights into their mechanisms of action.[7]

We employ a network pharmacology-based approach to discover the probable targets and mechanisms of *B. aristata* in the context of diabetes mellitus. We aim to create a bioactive target network to identify key bioactive constituents and their interacting protein targets. Furthermore, we seek to elucidate the biological pathways and processes modulated by these interactions, thereby providing a mechanistic origin for the anti-diabetic effects of *B. aristata*.

Through this integrative approach, we aim to bridge the gap among traditional knowledge and modern biomedical research, contributing to the development of effective and safe natural therapies for diabetes management. The result of this examination have the prospective to enhance our perceptive of *Berberis aristata*'s pharmacological profile and pave the way for its incorporation into contemporary anti-diabetic treatment strategies.

METHODOLOGY

Collection of Bioactive Compounds

To comprehensively gather information on the bioactive constituents of *Berberis aristata*, extensive investigations were conducted in the PubMed database using both the botanical name "*Berberis aristata*" and associated substance terms. This method ensured a thorough collection of relevant scientific literature. Additionally, data on bioactive compounds were sourced from specialized phytochemistry databases, namely the IMPPAT database[8] and the KnapSack[9] database. These databases provided a wealth of information on the variety of bioactive compounds present in *Berberis aristata*, which are essential for understanding its medicinal properties.

Identification of Potential Targets and Genes Associated with Disease

To identify potential targets for the bioactive compounds found in *Berberis aristata*, we employed the Swiss Target Prediction[10] and STITCH[11] databases. These resources are instrumental in predicting the connections among bioactive compounds and their potential protein targets in the human body. Concurrently, disease-related genes were acquired from the OMIM[12] and Gene Cards databases.[13] OMIM provides comprehensive information on genetic disorders and the genes involved, while Gene Cards offers a detailed compilation of human genes and their functions. To determine the intersection between potential targets of the bioactive compounds and disease-related genes, venn diagram analysis was used.[14] This approach helped identify common targets that could be crucial for therapeutic interventions.

Pathway Analysis using DAVID Database

A pathway analysis was conducted to determine the biological processes affected by the discovered genes. The evaluation was conducted utilizing the DAVID database,[15] which consolidates many bioinformatics tools for the functional study of extensive gene lists. The pathways linked to the discovered genes were retrieved from various databases, such as KEGG, biological processes, molecular functions, and cellular components. The importance of these pathways was evaluated utilizing adjusted *p-values*, which offered a statistical indication of the pathways that are most likely affected by the bioactive components of *B. aristata*.

Network Construction using Cytoscape

A network was created employing Cytoscape version 3.10.1, a robust bioinformatics software platform designed for visualizing intricate networks, in order to depict the connections between genes and their corresponding pathways. Within this network, the source nodes were designated to represent bioactive substances, whereas the target nodes were designated to represent genes and proteins. Hub genes, characterized by their extensive interconnectedness, were found through the STRING database. The created network not only yielded valuable insights into the complex gene relationships but also enabled future investigation of possibilities for molecular pathways and biological targets for the treatment of diabetes mellitus.[16]

RESULTS AND DISCUSSION

Identification of Bioactive Compounds in *B. aristata*

Bioactive compounds shown in Table 1 presents in *B. aristata* botanicals

B. aristata, an endangered high-value medicinal shrub, has been used by Ayurveda practitioners for thousands of years to treat various health conditions, including wounds, diabetes, urinary tract infections and cancer. It has also been found to help manage diabetes by improving lipid profile and insulin resistance in overweight patients. *Berberis aristata*'s edible

Table 1: Botanical – Bioactive

S. No.	*Botanicals*	*NAME*	*PubChem CID*
1	*B. aristata*	Tetrahydropalmatine	5417
2	*B. aristata*	Rutin	5280805
3	*B. aristata*	Quercetin	5280343
4	*B. aristata*	Promoline	362574
5	*B. aristata*	Palmatine	19009
6	*B. aristata*	Pakistanine	193239
7	*B. aristata*	Oxyacanthine	11066
8	*B. aristata*	Meratin	122361330
9	*B. aristata*	Jatrorrhizine	72323
10	*B. aristata*	Chlorogenic acid	1794427
11	*B. aristata*	Chitraline	157105
12	*B. aristata*	beta-Hydrastine	197835
13	*B. aristata*	Berberine	2353
14	*B. aristata*	Berbamine	275182
15	*B. aristata*	Berberine	2353
16	*B. aristata*	1-O-Methylpakistanine	181478
17	*B. aristata*	(+/-)-Karachine	630739

fruits are rich in vitamin C, and have a bitter taste. *B. aristata* is also used for non-culinary purposes, such as making yellow tannin dye from the root and stem, using the wood as fuel, and making fencing. Despite its endangered status, *B. aristata* has significant traditional uses in treating inflammation, wound healing, skin diseases, jaundice, and eye infections.

Identification of Potential Targets and Disease-Related Genes

A total of 44 targets were discovered represented in Table 2. 15888 Genes linked with diseases were gathered from the Gene card and OMIM databases. Figure 1, the Venn diagram analysis, helped identify shared genes between possible targets and disease-related genes, offering insights into the molecular pathways that contribute to the treatment effects of diabetes mellitus. Analysis revealed the presence of 36 genes that are often shared. MMP2 XDH SLC22A2 MAOA DRD3 CHRM1 ADRA1A HTR1A MMP13 AKR1B10 SLC47A1 ACHE HTR2B HTR6 CYP2C19 CYP2C9 CDK4 HTR5A MMP12 AKR1B1 DRD1 NOX4 AVPR2 ADRA2B SLC18A2 OPRM1 BCHE CDK2 SIGMAR1 MAOB F3 APP ADRA2A HTR2A ADRA2C DRD2.

B. aristata contains compounds that interact with various receptors, enzymes, and proteins in the body, potentially contributing to its therapeutic effects. These compounds include tetrahydropalmatine, rutin, quercetin, promoline, palmatine, pakistanine, oxyacanthine, chlorogenic acid, chitraline, beta-hydroxydrastine, and (+/-)-karachine. While traditional knowledge supports many of these uses, scientific research continues to explore the full potential of *B. aristata*. It is important to consult a healthcare professional before using any herbal remedies or supplements.

The venn diagram illustrates the relationship between targets and genes, with targets consisting of 8 elements and genes consisting of 15,888 elements. The overlapping section between the circles contains 36 common elements, highlighting the uniqueness of each category and what they share in common.[17]

GO Enrichment and Pathway Analysis

The top 10 pathways with the highest relevance for all data in Tables 3, 4, 5, and 6 were chosen using corrected *p-values*. This selection offers a thorough insight into the molecular mechanisms behind the pharmacological effects of diabetes mellitus.[18]

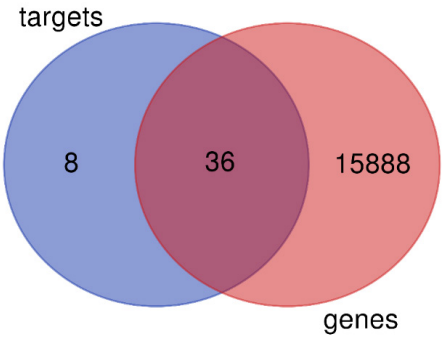

Figure 1: Venn diagram

Table 2: Bioactives and identified targets

S. No.	*Bioactive*	*Targets*
1	Tetrahydropalmatine	DRD1
2	Tetrahydropalmatine	DRD2
3	Tetrahydropalmatine	SIGMAR1
4	Tetrahydropalmatine	F3
5	Rutin	NMUR2
6	Rutin	ADRA2A
7	Rutin	ADRA2C
8	Rutin	ACHE
9	Quercetin	NOX4
10	Quercetin	AVPR2
11	Quercetin	AKR1B1
12	Quercetin	XDH
13	Quercetin	MAOA
14	Promoline	SLC47A1
15	Promoline	CHRNA4 CHRNB2
16	Promoline	CHRNA3 CHRNB4
17	Promoline	CHRNB4 CHRNA2
18	Promoline	CHRNA3 CHRNB2
19	Promoline	SLC6A3
20	Palmatine	HTR2B
21	Palmatine	BCHE
22	Pakistanine	ADRA1A
23	Pakistanine	HTR1A
24	Oxyacanthine	ADRA2B
25	Oxyacanthine	CHRM1
26	Chlorogenic acid	MMP13
27	Chlorogenic acid	MMP2
28	Chlorogenic acid	APP
29	Chlorogenic acid	MMP12
30	Chlorogenic acid	AKR1B10
31	Chitraline	HTR7
32	Chitraline	HTR2A
33	Chitraline	DRD3
34	Chitraline	HTR6
35	Chitraline	OPRM1
36	Chitraline	HTR5A
37	beta-Hydrastine	CYP2C19
38	beta-Hydrastine	SLC22A2
39	beta-Hydrastine	CDK2
40	beta-Hydrastine	CDK4
41	beta-Hydrastine	MAOB
42	beta-Hydrastine	CYP2C9
43	(+-)-Karachine	SLC18A2
44	(+-)-Karachine	CHRM4

Table 3: Findings from the research of biological process pathways

S. No.	*Term*	*p-value*
1	GPCR signal	0.0000378
2	response to xenobiotic stimulus	0.0000000125
3	GPCR signal pathway with cAMP messenger	0.00000000000577
4	Adrenaline receptor signaling	0.000000000000419
5	+ ERK1 and ERK2 flow	0.00000284
6	chemical synaptic transmission	0.00000314
7	- regulation of cell propagation	0.000114
8	+ regulation of cell propagation	0.000266
9	GPCR with PL-C messenger signaling pathway	0.000000799
10	behavioral response to cocaine	0.00000198

Table 4: Findings from the research of molecular function pathways

S. No.	*Term*	*p-value*
1	Protein binding	0.032309226
2	Oxidoreductase activity	0.00000244
3	GPCR activity	0.00231573
4	GPCR serotonin receptor activity	0.000000000418
5	Neurotransmitter receptor activity	0.000000343
6	Serotonin binding	0.000000953
7	G-protein alpha-subunit binding	0.0000229
8	Flavin adenine dinucleotide binding	0.000269
9	Serine-type endopeptidase activity	0.004955232
10	Alpha2-adrenergic receptor activity	0.00001

Table 5: Findings from the research of cellular component pathways

S. No.	*Term*	*p-value*
1	Plasma membrane	3.00E-08
2	Membrane	0.014676
3	Dendrite	3.88E-08
4	Synapse	1.69E-06
5	Extracellular space	0.01418
6	Endosome	0.001849
7	Axon	0.002959
8	Glutamatergic synapse	0.005259
9	Presynaptic membrane	0.001562
10	Perikaryon	0.002446

Table 6: Findings from the research of KEGG path examination

S. No.	*Term*	*p-value*
1	Neuroactive ligand-receptor interaction	1.11E-11
2	Serotonergic synapse	5.78E-12
3	Calcium signaling pathway	2.80E-04
4	Dopaminergic synapse	1.10E-04
5	Cocaine addiction	2.89E-05
6	Alcoholism	0.004804622
7	cAMP signaling pathway	0.009007861
8	Parkinson disease	0.015898706
9	Amphetamine addiction	0.002033794
10	Drug metabolism - cytochrome P450	0.002297756

They have a common structure and can be bind to ligands, allowing them to interact with G-proteins. GPCRs respond to xenobiotic stimuli, adenylate cyclase-activating adrenergic receptors, ERK1 and ERK2 cascades, chemical synaptic transmission, cell proliferation, phospholipase C-activating GPCRs, and the behavioral response to cocaine. These pathways play a crucial role in cellular responses to foreign substances, xenobiotics, and drug exposure. *B. aristata*'s bioactive compounds have various effects on various physiological processes. G-protein-coupled receptor signaling pathway (GPCRs) is crucial for cellular communication, triggering downstream signaling cascades that affect various physiological processes. Xenobiotic stimuli, such as drugs and toxins, can be influenced by the plant's compounds. The GPCR pathway, coupled to cyclic nucleotide second messenger, regulates cell growth, neurotransmission, and hormone signaling. Adrenergic receptors respond to adrenaline and noradrenaline, affecting heart rate, blood pressure, and metabolism. The ERK1/2 pathway is essential for cell proliferation, differentiation, and survival. Chemical synaptic transmission involves neurotransmitters transmitting signals between neurons. The plant's compounds may impact neuronal communication. Cell proliferation can be inhibited or promoted, depending on the context. Phospholipase C (PLC) activation leads to intracellular calcium release, influencing cellular responses. The behavioral response to cocaine suggests an impact on behavior related to exposure and potential effects on the nervous system. It is important to consult a healthcare professional before using any herbal remedies or supplements.[19]

They act as guanine nucleotide exchange factors (GEFs) when a ligand binds, activating an connected G protein by substitute bound GDP for a GTP. GPCRs also play a role in redox reactions, acting as signal transducers. They regulate cellular communication, modulating intracellular signaling pathways and coordinating responses to extracellular stimuli. GPCRs also play a crucial role in neurotransmission, detecting neurotransmitters and initiating downstream signaling events. They interact with G proteins, specifically binding to the α subunit, and are involved in redox reactions. Serine-type endopeptidase activity and alpha2-adrenergic receptor activity are also important in cellular processes. *B. aristata*'s molecular function (MF) pathways provide insights into the plant's bioactive compounds. Protein binding is essential for signaling, enzymatic activity, and structural stability. Oxidoreductases are enzymes involved in redox reactions, playing a role in metabolism, energy production, and detoxification. G-protein coupled receptor (GPCR) activity regulates processes like neurotransmission, hormone response, and immune function. G-protein coupled serotonin receptor activity mediates serotonin's effects on mood, behavior, and other physiological functions. Neurotransmitter receptor activity

binds neurotransmitters, modulating neuronal communication and influencing behavior. Serotonin binding affects mood, appetite, and sleep. G-protein alpha-subunit binding is crucial for GPCR signaling. Flavin adenine dinucleotide (FAD) binding is involved in redox reactions and energy metabolism. Serine-type endopeptidase activity cleaves peptide bonds within proteins, regulating blood clotting, digestion, and immune responses. Alpha2-adrenergic receptor activity responds to norepinephrine and regulates sympathetic nervous system activity, affecting blood pressure, blood flow, and stress responses. These molecular functions highlight the diverse roles of *B. aristata*'s bioactive compounds.[20]

GPCRs are receptors found in various cellular compartments, including the plasma membrane, dendrites, synapses, extracellular space, endosomes, axons, glutamatergic synapses, presynaptic membrane, and perikaryon. They detect extracellular signals and initiate intracellular responses, affecting neuronal communication, synaptic function, and overall cellular physiology. GPCRs on dendrites can respond to neurotransmitters, while synapses detect neurotransmitters released from presynaptic neurons. They can also be internalized into endosomes, affecting signaling duration and desensitization. Their diverse roles extend beyond the plasma membrane. The cellular components (CC) pathways analysis provides a comprehensive understanding of the cell's organization and function. The plasma membrane, a cellular component that surrounds the cell and regulates molecule movement, is crucial for maintaining cell integrity. Membranes, including the plasma membrane, organelle membranes, and vesicle membranes, are essential for compartmentalization and transport within cells. Dendrites, specialized extensions of nerve cells, receive signals from other neurons and play a key role in transmitting information within the nervous system. Synapses are junctions between neurons or target cells, where neurotransmitters are released to transmit signals. Extracellular space, the area outside cells, is essential for communication and exchange between cells. Endosomes are membrane-bound compartments involved in sorting and trafficking molecules, and axons are long projections of neurons that carry electrical impulses away from the cell body. Glutamatergic synapses use the neurotransmitter glutamate, involved in excitatory signaling in the brain and playing a role in learning, memory, and neural plasticity. The presynaptic membrane, a specialized region of the axon terminal, releases neurotransmitters into the synapse, essential for communication between neurons.[21]

They transmit signals from extracellular ligands to intracellular effectors, modulating synaptic transmission and behavior. GPCRs also respond to serotonin, a neurotransmitter involved in mood regulation and sleep. They can activate calcium signaling pathways, leading to changes in intracellular calcium levels and downstream effects. GPCRs also play a role in Parkinson's disease, amphetamine addiction, and drug metabolism.The neuroactive ligand-receptor interaction pathway is a crucial part of cell signaling and communication within the nervous system. It examines the interactions between various ligands and their receptors, such as neurotransmitters and hormones. The serotonergic synapse pathway examines serotonin receptors and their downstream effects. The calcium signaling pathway investigates how calcium levels are regulated and their impact on cell function. The dopaminergic synapse pathway delves into dopamine receptors and their signaling pathways. The alcoholism pathway examines the impact of alcohol consumption on the brain and other organs, including processes related to alcohol metabolism, oxidative stress, and addiction. The cAMP signaling pathway covers cAMP production, downstream targets, and their effects on cell function. Parkinson's disease, a neurodegenerative disorder, explores factors related to dopamine dysfunction and neuronal degeneration. Amphetamine addiction relates to the effects of amphetamines on the brain, including altered neurotransmitter release, receptor activation, and addiction-related changes. The drug metabolism - cytochrome P450 pathway covers drug metabolism and detoxification processes. These pathways offer valuable insights into cellular mechanisms, disease processes, and drug interactions.[22]

Network Construction using Cytoscape

Hub genes identified using the STRING database.

The protein-protein interaction (PPI) analysis conducted *via* STRING unveiled a network of interactions among the potential protein targets identified for the bioactive compounds of *B. aristata* in the context of diabetes mellitus. The analysis elucidated the complex interplay and connectivity among these proteins, highlighting key nodes with high degrees of interaction. By exploring the PPI network, several densely connected clusters of proteins were identified, indicating potential functional modules or pathways involved in the anti-diabetic mechanisms of *B. aristata*. Moreover, the analysis provided insights into the protein associations and their relevance to diabetes-related processes such as glucose homeostasis, insulin signaling, and inflammation.

The Cytoscape analysis revealed a comprehensive botanical-targets-diabetes mellitus disease network, highlighting the intricate relationships between the bioactive compounds of *B. aristata* and their potential protein targets involved in diabetes mellitus. The constructed network identified several key hub genes, which are highly interconnected and likely play pivotal roles in mediating the anti-diabetic effects of *B. aristata*. Notably, the analysis pinpointed critical pathways such as the insulin signaling pathway, the AMPK signaling pathway, and the PPAR signaling pathway. These pathways are essential for glucose metabolism, insulin sensitivity, and overall metabolic regulation. The identification of these hub genes and pathways provides valuable insights into the molecular mechanisms through which *B. aristata* exerts its therapeutic effects, paving the way for further validation and potential development of targeted anti-diabetic therapies.[23]

CONCLUSION

In conclusion, the current examination offers a ample understanding of the potential therapeutic effects of *B. aristata* in the management of diabetes mellitus. Through the

identification of bioactive compounds and their interaction with specific protein targets, as well as the elucidation of relevant molecular pathways, our results give emphasis on the mechanisms underlying the anti-diabetic properties of *B. aristata*.

The analysis exposed a miscellaneous collection of bioactive compounds present in *B. aristata*, including tetrahydropalmatine, rutin, quercetin, and berberine, among others, each with the potential to modulate key molecular targets implicated in diabetes mellitus. By targeting receptors, enzymes, and signaling pathways involved in glucose homeostasis, insulin sensitivity, and inflammatory processes, these bioactive compounds offer promising avenues for the development of novel anti-diabetic therapies.

Furthermore, the network analysis highlighted the interconnectedness of these molecular targets, emphasizing the complex but orchestrated nature of *B. aristata*'s pharmacological effects. Hub genes identified within the network, such as DRD1, NOX4, and MMP2, provide valuable insights into the central nodes governing the biological responses to *B. aristata* compounds.

Additionally, pathway analysis uncovered the involvement of crucial biological processes and signaling pathways, including GPCR signaling, calcium signaling, and neurotransmitter receptor activity, further elucidating the mechanisms through which *B. aristata* exerts its therapeutic effects on diabetes mellitus.

Overall, our study bridges traditional knowledge with modern scientific approaches, providing a molecular basis for the traditional use of *B. aristata* in diabetes management. These findings underscore the potential of *B. aristata* as a source of novel anti-diabetic agents and lay the groundwork for future research and development in this field. However, further experimental validation and clinical studies are warranted to fully harness the therapeutic potential of *B. aristata* in the treatment of diabetes mellitus.

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