RESEARCH ARTICLE

Network Pharmacology and Molecular Docking Technology-based Strategy to Explore the Potential Mechanism of Diabecon Formulation Botanicals

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ABSTRACT

This study presents network pharmacology and a molecular docking-centered approach to elucidate the possible mechanism of action underlying the therapeutic effects of diabecon, a formulation containing *Gymnema sylvestre*, *Pterocarpus marsupium*, and *Asphaltum punjabinum* botanicals. Through comprehensive bioinformatics analysis, a collection of bioactive compounds present in these botanicals was identified, and their potential targets were forecasted using Swiss Target Prediction and STITCH. Disease-related genes were retrieved from Genecards and OMIM, and common genes between potential targets and disease-related genes were determined. Pathway analysis using the DAVID database revealed significant enrichment in pathways related to metabolic processes, xenobiotic metabolism, and signaling pathways, such as the insulin signaling pathway and pathways in cancer. Network construction using cytoscape highlighted interactions among identified genes, providing insights into the molecular pathways modulated by diabecon. Molecular docking analysis further elucidated the possible connections amongst biologically active compounds and target proteins, with (2S)-7-hydroxyflavanone exhibiting strong binding affinity with DPP-IV enzyme. Overall, this integrated approach offers valuable insights into the potential mechanisms of action of diabecon, contributing to our understanding of its therapeutic effects in the management of diabetes mellitus.

Keywords: Network pharmacology, Molecular docking, Diabecon formulation, *Gymnema sylvestre*, *Pterocarpus marsupium*, *Asphaltum punjabinum*, Bioactive compounds, Pathway analysis, Target prediction, Disease-related genes, Insulin signaling pathway, Diabetes mellitus.

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INTRODUCTION

The rising prevalence of diabetes mellitus presents a significant global health challenge, underscoring the urgent need for effective therapeutic interventions[1]. Traditional medicinal systems, particularly herbal formulations, have long been recognized for their potential in managing various ailments, including diabetes. Diabecon, a formulation comprising *Gymnema sylvestre*, *Pterocarpus marsupium*, and *Asphaltum punjabinum* botanicals, has gained attention for its purported antidiabetic properties.[2,3] However, despite the empirical evidence supporting the efficacy of diabecon, the precise molecular mechanisms underlying its therapeutic effects remain poorly understood.[4] Traditional experimental approaches often fall short in revealing the complex connections among multiple biologically active compounds within herbal formulations and their targets in biological systems.[5]

In recent years, the combination of network pharmacology and molecular docking techniques has come out as a powerful strategy for deciphering the complex mechanisms of action of multifaceted herbal remedies. Network pharmacology provides a holistic view of drug actions by mapping the interactions between drugs, targets, and diseases within biological networks, offering valuable insights into the polypharmacological nature of herbal formulations.[6,7] Meanwhile, molecular docking serves as a computational tool to predict the binding affinities and modes of interaction between small molecules and their target proteins, facilitating the rational design of novel therapeutics.[8]

In this context, our efforts plan to employ a network pharmacology and molecular docking-based approach to unravel the probable mechanism of action underlying the antidiabetic effects of diabecon. By systematically exploring

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the interactions between the bioactive constituents of *G. sylvestre*, *P. marsupium*, and *A. punjabinum* and their putative targets implicated in diabetes mellitus, we seek to provide a comprehensive understanding of the synergistic effects of these botanicals in mitigating diabetic pathology. Through the integration of computational predictions with experimental validation, we endeavor to bridge the gap between traditional herbal medicine and modern pharmacology, offering valuable insights that may inform the development of novel therapeutic strategies for diabetes management.

MATERIAL AND METHODS

Collection of Bioactive Compounds of Diabecon Botanicals

Pharmacology networks must be built using the bioactive substances found in the botanical sources *G. sylvestre*, *P. marsupium*, and *A. punjabinum* in order to clarify the possible mechanism of diabecon. Searches were performed in the PubMed database using the botanical names and chemical phrases connected with them to obtain information on bioactive ingredients.[9] To identify potential active compounds within the diabecon formulation containing *G. sylvestre*, *P. marsupium*, and *A. punjabinum* botanicals, we employed a multi-step approach utilizing various bioinformatics online tools and databases. Initially, we utilized the MPPAT (Molecular Property Prediction and Analysis Tools) database[10] and the KNapSAcK database (http://www.knapsackfamily.com/knapsac).[11]

Identification of Potential Targets and Disease-Related Genes

Bioinformatics repositories like Swiss Target Prediction (http://www.swisstargetprediction.ch/) and STITCH (http://stitch.embl.de/) used to unearth potential targets of active compounds. The genes associated with ailments were sourced from OMIM (https://www.omim.org/) and Genecards (https://www.genecards.org/). The process of pinpointing common genes between potential targets and disease-associated genes was facilitated through Venn diagram analysis.

Pathway Analysis using DAVID Database

The DAVID (Database for Annotation, Visualization, and Integrated Discovery) repository (https://david.ncifcrf.gov/tools.jsp) was used to perform the pathway assessment. We used it to extract pathways associated with the identified genes from the Kyoto Encyclopedia of Genes and Genomes (KEGG), biological process (BP), molecular function (MF), and cellular component (CC) databases. Adjusted *p-values* were used to determine which paths, numbered between 10 and 15, were the most relevant.[12-14]

Network Construction using Cytoscape

Cytoscape version 3.9.1 was utilized for network construction, with installation of necessary apps/plugins. Source nodes and target nodes were defined, and hub genes were identified using the STRING database. The constructed network provided insights into the interactions among the identified genes, facilitating a deeper investigation of the molecular mechanisms involved in the diabecon formulation.[15,16]

Molecular Docking

In our study, we employed a systematic approach combining network pharmacology and molecular docking tools to discover the prospective mechanism of the diabecon formulation containing *G. sylvestre*, *P. marsupium*, and *A. punjabinum* botanicals. The most gene and its related targets were identified from the hub gene. Protein structures of human dipeptidyl peptidase-IV (DPP-IV) implicated in were obtained from Protein Data Bank (PDB)databases and underwent thorough preparation and quality assessment to ensure reliability for subsequent molecular docking studies by using https://pdb-redo.eu/ online server.[17] Molecular docking simulations were performed using CB-Dock, focusing on cavity detection, docking center, box size determination, and evaluation of binding poses.[18] This integrated approach offers a comprehensive strategy to explicate the potential molecular mechanisms involved in the therapeutic effects of the diabecon formulation.

RESULTS

Identification of Bioactive Compounds in Diabecon Botanicals

A comprehensive search conducted in the PubMed database yielded a collection of bioactive compounds (Table 1) present in *G. sylvestre*, *P. marsupium*, and *A. punjabinum* botanicals, key components of the diabecon formulation. We identified a range of bioactive substances with potential therapeutic relevance using chemical phrases and botanical names associated with these sources.

Identification of Potential Targets and Disease-Related Genes

Bioinformatics databases, including Swiss Target Prediction and STITCH were employed to identify potential targets of the active compounds identified in diabecon. About 38 targets were identified from these databases and details of that are provided in Table 2. 19033 Disease-related genes were collected from Gene card and OMIM databases. Venn diagram (Figure 1) analysis facilitated the identification of common genes between potential targets and disease-related genes, providing insights into the molecular pathways underlying the therapeutic effects of diabecon. About 41 common genes were found after analysis namely MMP2, UGT1A8, SNCA, F10, ABCB1, ACHE, CA7, PTPN1, PRODH, SLCO1B1, IP6K3, EPHX2, CA2, BCL2, CYP19A1, ALPL, F3, AR, DHCR24, DPP4, PTPRS, UGT1A9, CA1, CISD3, STAT3, HSD11B2, PTGES, ESR1, AKR1B1, SLCO1B3, GSK3B, UGT1A7, IL6, ABCG2, IGF1R, AKR1C3, CES1, CA4, SIRT1, ESR2 and PLAU.

Gene Ontology Enrichment and Pathway Analysis using DAVID Database

We performed pathway analysis using the DAVID database to identify the biological pathways associated with the discovered genes. In addition to KEGG pathways, we also retrieved BP, MF, and CC pathways. The top 10 most relevant pathways in Tables 3-6 were selected based on adjusted *p-values*, providing

Table 1: Botanical - bioactive

Botanical	*Name*	*PubChem CID*
	Gymmnemic_ acid- II	91617872
	Gymmnemic _acid- III	14264066
	Gymmnemic _acid- IV	14264063
	Gymmnemic _acid- IX	91617808
	Gymmnemic _acid -V	14683206
	Gymmnemic_ acid- VI	91617894
	Gymmnemic _acid -VII	91617592
	Gymmnemic _acid -VIII	91617623
	Gymmnemic_ acid -X	15674686
	Gymmnemic _acid- XI	15674687
	Gymmnemic_ acid- XII	91826975
	Gymmnestrogenine	15560302
	Gynosaponin TN-2	319538106
G. sylvestre	Gypenosides -II	53232197
	Gypenosides- LV	53581228
	Gypenosides -LXIII	52669293
	Gypenosides- LXXIV	50155152
	Gypenosides -V	53730223
	Gypenosides XVII	44584555
	Gypenoside XXVIII	274140052
	Gypenoside XXXVII	274140053
	Lupeol	259846
	Methyl alpha-D-galactopyranoside	76935
	Methyleugenol	7127
	Resiniferonol	162824
	Stigmasterol	5280794
	(-)-Epicatechin	72276
	(2S)-7-hydroxyflavanone	688857
	Abscisic acid	5280896
	Pterosupin	133775
	3,7,4'-Trihydroxyflavone	5281611
	Propterol	185124
	7,4'-Dihydroxyflavone	5282073
	LMPK12050339	44257328
	beta-Eudesmol	91457
P. marsupium	Ebanol	6504499
	Garbanzol	442410
	Isoliquiritigenin	638278
	Liquiritigenin	114829
	Marsupsin	134369
	Naringetol	439246
	Propterol-b	185124
	Pseudobaptigenin	5281805
	Pterostilbene	5281727
	pterosupin	23498438
	fulvic acid	5359407
	Coumarin	323
A. punjabinum	humic acid	90472028
	Pyrocatechol	289

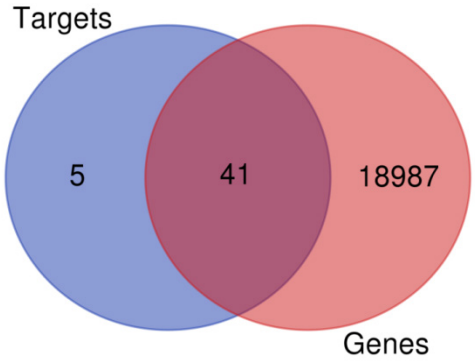

Figure 1: Venn diagram showing common genes between potential targets and disease-related genes

a comprehensive understanding of the molecular mechanisms involved in diabecon's pharmacological effects.

Network Construction using Cytoscape

Cytoscape version 3.9.1 was used for network construction in Figures 2-5, with necessary apps/plugins installed. Source nodes and target nodes were defined, and hub genes were identified using the STRING database. The constructed network revealed interactions among the identified genes, offering insights into the complex molecular pathways modulated by Diabecon.

Molecular Docking Analysis

In molecular docking analysis, crystal structure of human DPP-4 protein structures implicated in the molecular mechanisms targeted by diabecon were obtained from the PDB and underwent thorough preparation and quality assessment using https://pdb-redo.eu/ online server. Molecular docking simulations were performed using CB-Dock, focusing on

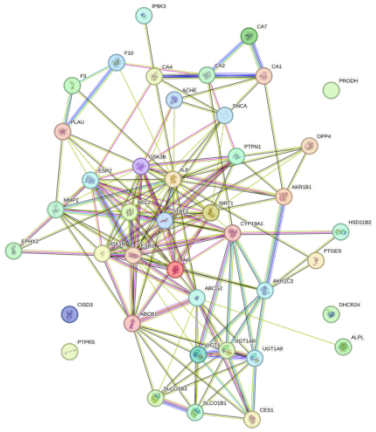

Figure 2: Protein-protein interaction analysis by STING

Table 2: Bioactives and identified targets

S. No.	*Bioactive*	*Target*
1	beta-Amyrin acetate	Coagulation factor X
2	beta-Amyrin acetate	Delta(24)-sterol reductase
3	beta-Amyrin acetate	Prostaglandin E synthase
4	Deacylgymnemic acid	11-beta-hydroxysteroid dehydrogenase 1
5	Deacylgymnemic acid	11-beta-hydroxysteroid dehydrogenase type 2
6	Gymnemasaponin II	Bifunctional epoxide hydrolase 2
7	Gymnemasaponin II	Tissue factor
8	Gymnemaside II	STAT-3
9	Gymnemic acid I	SCOATFM-1B1
10	Gymnemic acid I	SCOATFM-1B3
11	(-)-Epicatechin	72 kDa type IV collagenase
12	(-)-Epicatechin	Alpha-synuclein
13	(-)-Epicatechin	Apoptosis regulator Bcl-2
14	(-)-Epicatechin	Carbonic anhydrase 7
15	(-)-Epicatechin	Alkaline phosphatase, tissue-nonspecific isozyme
16	(2S)-7-hydroxyflavanone	A_KRFM-C3
17	(2S)-7-hydroxyflavanone	Androgen receptor
18	(2S)-7-hydroxyflavanone	Carbonic anhydrase 1
19	(2S)-7-hydroxyflavanone	Carbonic anhydrase 12
20	(2S)-7-hydroxyflavanone	Carbonic anhydrase 2
21	(2S)-7-hydroxyflavanone	Carbonic anhydrase 4
22	(2S)-7-hydroxyflavanone	Dipeptidyl peptidase 4
23	(2S)-7-hydroxyflavanone	Estrogen receptor
24	(2S)-7-hydroxyflavanone	Estrogen receptor beta
25	3,7,4'-Trihydroxyflavone	17-beta-hydroxysteroid dehydrogenase type 2
26	3,7,4'-Trihydroxyflavone	CK- II-α 3
27	3,7,4'-Trihydroxyflavone	CD-GSH ISD protein 1
28	3,7,4'-Trihydroxyflavone	Glycogen synthase kinase-3 beta
29	3,7,4'-Trihydroxyflavone	Inositol hexakisphosphate kinase 2
30	3,7,4'-Trihydroxyflavone	Insulin-like growth factor 1 receptor
31	beta-Eudesmol	Liver carboxylesterase 1
32	beta-Eudesmol	Tyrosine-protein phosphatase non-receptor type 1
33	Garbanzol	Aromatase
34	Isoliquiritigenin	Aldo-ketoreductase family 1 member B1
35	Pseudobaptigenin	Receptor-type tyrosine-protein phosphatase S
36	Pterostilbene	ATP-dependent translocase ABCB1
37	Pterostilbene	ATP-binding cassette transporter ABCG2
38	Pyrocatechol	Acetylcholinesterase

Table 3: Results of biological process (BP) pathways analysis

Rank	*Biological process*	*p-values*
1	- regulation of the apoptotic process	0.00008
2	Signal transduction	0.01406
3	+ Regulation of cell proliferation	0.00070
4	Xenobiotic metabolism route	0.00000
5	+ Regulation of cell migration	0.00018
6	+ Regulation of gene expression	0.00361
7	+ Regulation of protein kinase B signaling	0.00050
8	Reply to xenobiotic stimulation	0.00224
9	+ Regulation of the apoptotic process	0.00447
10	Proteolysis	0.01301

Table 4: Results of molecular function pathways analysis

Rank	*Molecular function*	*p-values*
1	Zinc ion binding	0.00008
2	Enzyme binding	0.00000
3	Protein homodimerization activity	0.00014
4	Steroid binding	0.00000
5	Serine-type endopeptidase activity	0.00063
6	Carbonate dehydratase activity	0.00001
7	Hydro-lyase activity	0.00001
8	RNA polymerase II transcription factor action	0.00020
9	Protease binding	0.00173
10	Sequence-specific DNA binding	0.03565

Table 5: Results of cellular component pathways analysis

Rank	*Cellular component*	*p-values*
1	Integral component of membrane	0.0004
2	Plasma membrane	0.001205
3	Cytosol	0.026775
4	Membrane	0.017951
5	Extracellular exosome	0.008869
6	Endoplasmic reticulum	0.001617
7	Endoplasmic reticulum membrane	0.005559
8	Mitochondrion	0.021175
9	Cell surface	0.008421
10	Macromolecular complex	0.045096

cavity detection, docking center, box size determination, and evaluation of binding poses. Cavities and potential interactions between the bioactive compounds of diabecon and DPP-IV are Illustrated in Figures 6 and 7, respectively.

Amongst the bioactive mentioned table 7 (2S)-7-hydroxy flavanone was found to be intact with DPP-IV at pocket C5 in chain D with score -8.9. compound interact with following amino acids namely TYR48, GLN505, GLN527, ASP545, VAL546, TYR547, LYS554, ASP556, THR557, VAL558, PHE559, ARG560, LEU561, THR565, VAL575, TRP627, GLY628, TRP629, SER630 and GLY632.

Table 6: Results of pathways by KEGG examination

Rank	*Pathway*	*p-values*
1	Metabolic pathways	0.00060
2	Chemical carcinogenesis - receptor activation	0.00000
3	Pathways in cancer	0.00217
4	Bile secretion	0.00000
5	Steroid hormone biosynthesis	0.00001
6	EGFR tyrosine kinase inhibitor resistance	0.00042
7	Prostate cancer	0.00091
8	Endocrine resistance	0.00094
9	advanced glycation end products - receptor for advanced glycation endproducts signaling path in diabetic	0.00102
10	Proteo-glycans in cancer	0.01321

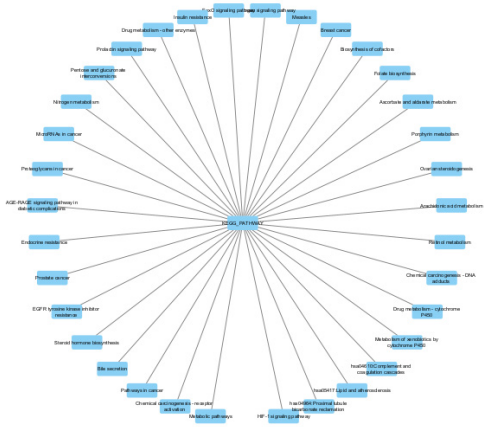

Figure 5: Network of KEGG pathways associated with GO

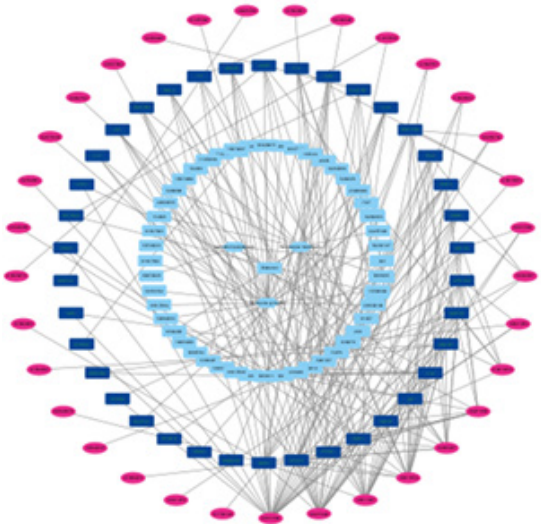

Figure 3: Diabecon-disease network

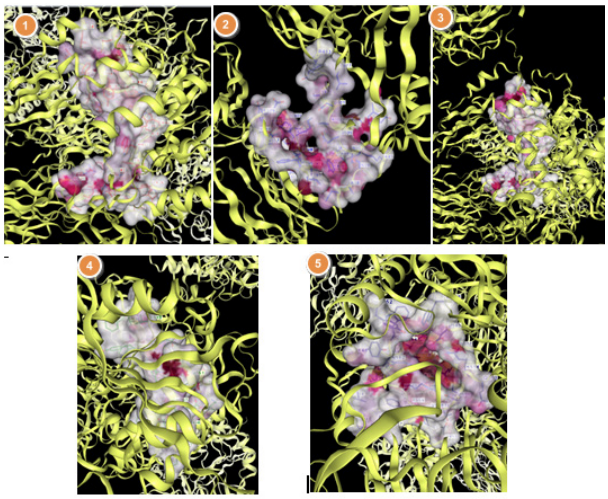

Figure 6: Cavities detected in DPP-IV enzyme by Cb-dock server

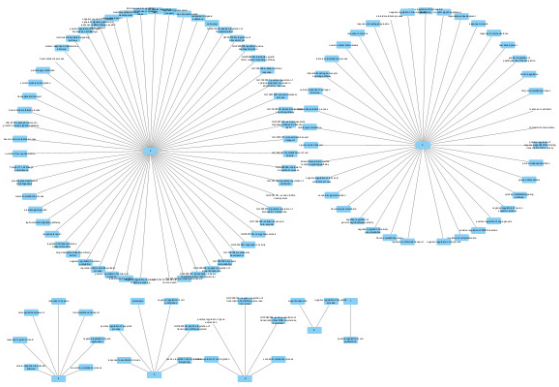

Figure 4: Network of biological process pathways

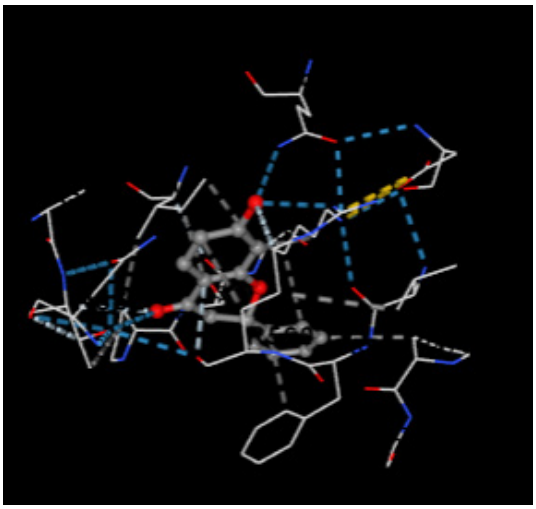

Figure 7: Binding of (2S)-7-hydroxy flavanone with DPP-IV enzyme

Table 7: Docking results with autodock vina socking score

S. No.	*Bioactive*	*Docking score*
1	beta-Amyrin acetate	-8.8
2	Deacylgymnemic acid	-8.2
3	Gymnemasaponin II	-7.0
4	Gymnemaside II	-8.8
5	Gymnemic acid I	-7.9
6	(-)-Epicatechin	-8.2
7	(2S)-7-hydroxy flavanone	-8.9
8	3,7,4'-Trihydroxy flavone	-8.0
9	beta-Eudesmol	-7.8
10	Garbanzol	-7.9
11	Isoliquiritigenin	-7.8
12	Pseudobaptigenin	-8.8
13	Pterostilbene	-5.8

CONCLUSION

In conclusion, our study utilized a network pharmacology and molecular docking approach to investigate the potential mechanism of action underlying the therapeutic effects of diabecon, a formulation containing *G. sylvestre*, *P. marsupium*, and *A. punjabinum* botanicals. Through a comprehensive analysis of bioactive compounds present in these botanical sources, we identified a range of molecules with potential therapeutic relevance. Subsequent identification of potential targets and disease-related genes revealed a network of interactions that may contribute to the pharmacological effects of diabecon. Notably, our pathway analysis highlighted several key biological processes and signaling pathways associated with diabetes and cancer, including metabolic pathways, estrogen signaling, and proteoglycans in cancer. Furthermore, molecular docking simulations provided insights into the potential connections among biologically active compounds and target proteins, elucidating the molecular mechanisms underlying diabecon's therapeutic effects. The identification of high-affinity interactions, such as that observed between (2S)-7-hydroxyflavanone and DPP-IV enzyme, underscores the potential of diabecon to modulate key biological processes implicated in diabetes management. Overall, our findings contribute to a better understanding of the pharmacological properties of diabecon and provide a basis for further exploration of its therapeutic potential in the management of diabetes and related complications.

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