

# Application of Network Pharmacology for Evaluating the Protein-Protein Interaction Network and Mechanisms for *Polygonum cuspidatum* in Treating Diabetes Mellitus

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## Abstract

Diabetes mellitus is currently the fastest growing chronic disease in the world, its serious complications have caused substantial amount of financial burden in the healthcare sector. *Polygonum cuspidatum* has been commonly used for medical treatment among the Asian population. The stem and root has been known to exhibit anti-cancer property and the ability to attenuate diabetes related complications. Nonetheless, the active compounds of *P. cuspidatum* are still yet to be identified; thus, the objective of this study is to apply the principles of network pharmacology to promptly identify the most promising candidates from *P. cuspidatum* as well as understanding their functions respectively. Network pharmacology is an approach to determine the process of disease development through understanding the system biology and bionetwork of the disease. Furthermore, by understanding the signal transduction pathways and how the compounds modulate the system, this will help to restore the balance in the affected biological processes, improve the efficacy of the compound and reduce its side effects. Using the Traditional Chinese Medicine Integrative Database, 46 compounds were identified in *P. cuspidatum* and bibliometrics was applied to measure the correlation between the compounds and diabetes. Among the 46 compounds, there were six compounds that showed clear correlation with diabetes, namely resveratrol, gallic acid, catechin, quercetin, rhein, and apigenin. These compounds will be evaluated in the later stage to fully understand the active compounds from *P. cuspidatum* that could potentially improve the complications of diabetes, and ultimately be used clinically on diabetic patients.

## Results

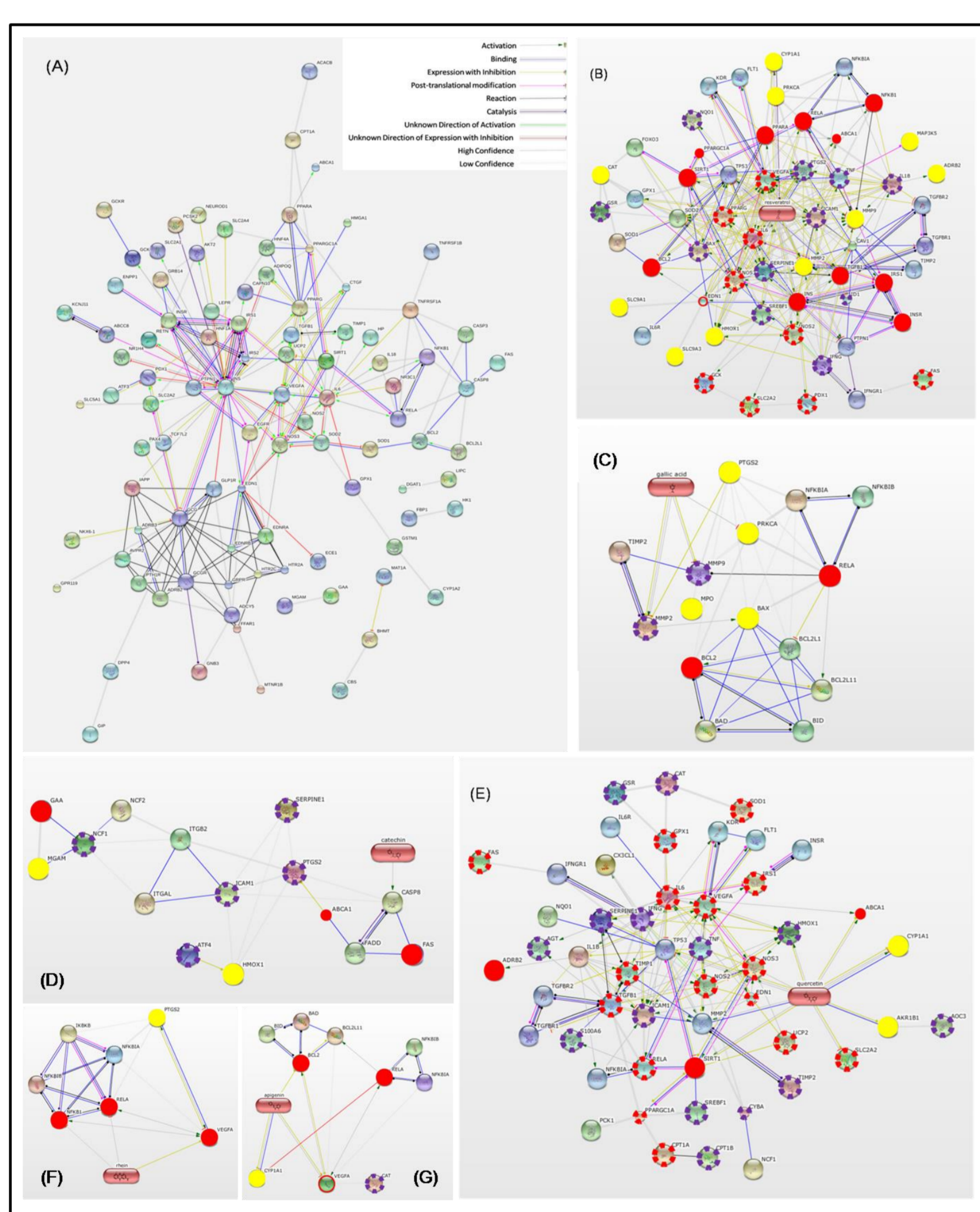


Figure 1. Total protein-protein interaction of DM related proteins created by using STRING 10 shown as (A). Different ingredient related regulatory sub-pathway created by using STITCH 4.0, where (B)-(G) resveratrol, gallic acid, catechin, quercetin, rhein and apigenin respectively.

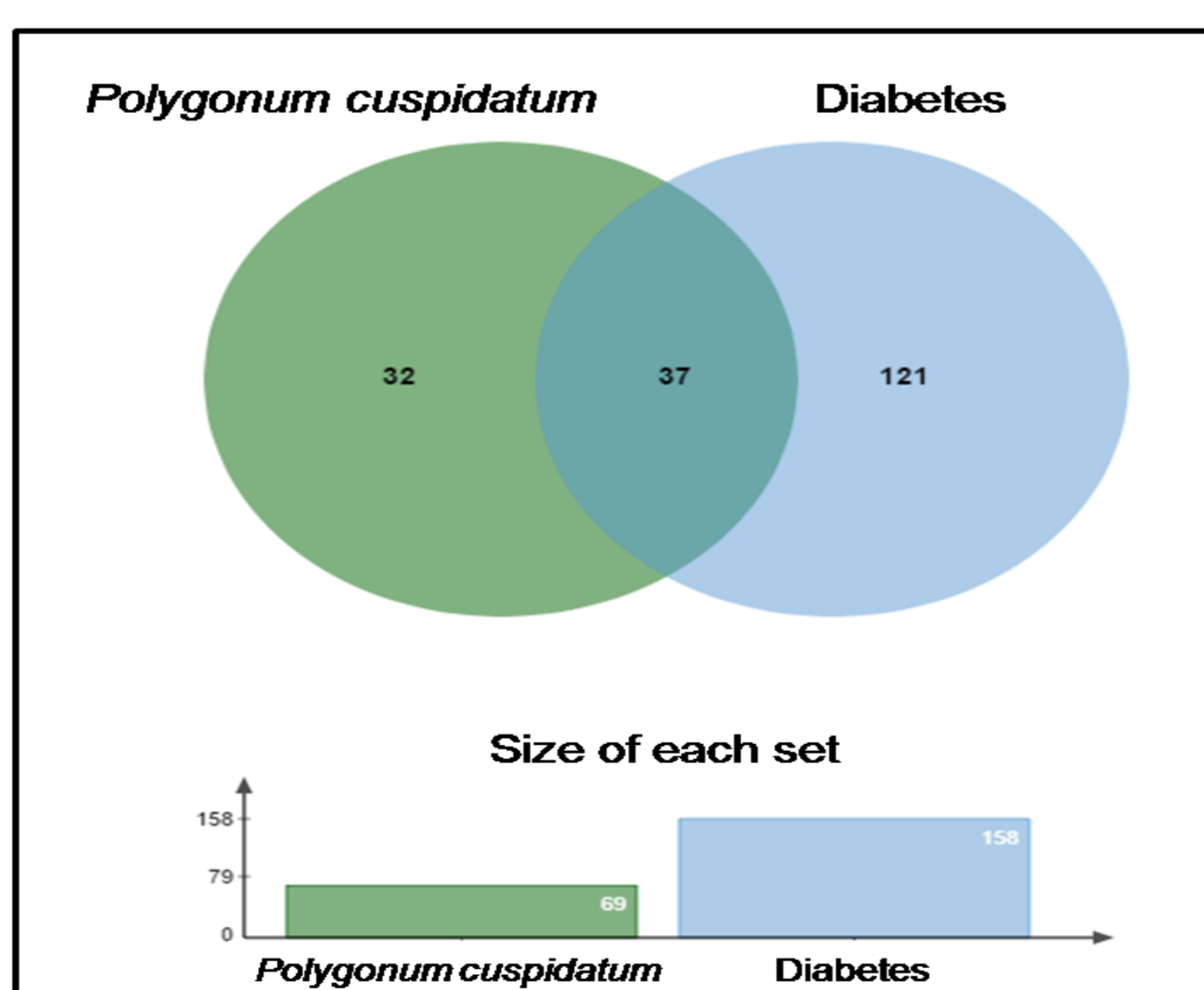


Figure 2. Venn diagram of *P. cuspidatum* targeted proteins and DM disease network proteins.

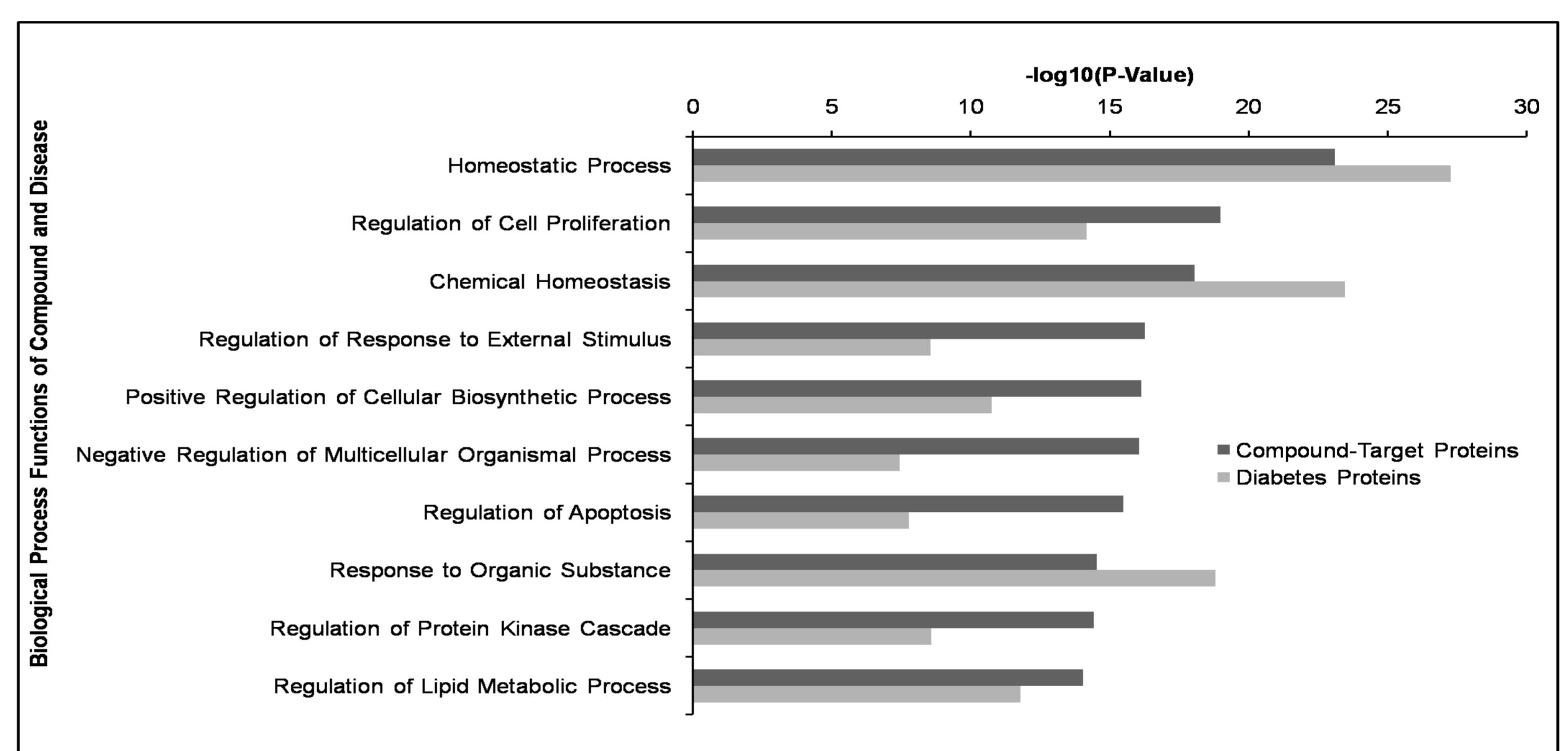


Figure 3. GO enrichments of the biological process function are between *P. cuspidatum* targeted proteins and DM disease network proteins.

Table 1. Correlation between the compounds from *P. cuspidatum* and DM

Compound	Compound Ref.	Compound and Diabetes Ref. <sup>a</sup>	Probability <sup>b</sup>	H <sub>i</sub> Score
Resveratrol	7246	444	3.47E-33	324.60
Gallic acid	6887	155	3.95E-33	324.04
Catechin	8733	271	8.38E-33	320.77
Quercetin	11880	342	1.17E-32	319.30
Rhein	1718	52	7.78E-29	281.09
Apigenin	2783	56	2.04E-22	216.89
Emodin	1336	23	7.07E-09	81.51
3,4-Dihydroxybenzoic acid	1180	21	1.78E-08	77.49
Desoxyrhaponticin	14	3	1.26E-05	48.99
Cinaroside	4	2	9.04E-05	40.44
Anthraquinone	11900	73	1.69E-04	37.72
Torachryson-8-o-beta-d-glu copyranoside	7	1	2.69E-02	15.70
Polydatin	207	3	4.79E-02	13.20
Piceatannol	521	5	5.48E-02	12.61
Guaijaverin	22	1	8.22E-02	10.85
Piceid	326	3	1.35E-01	8.68
Chrysophanol	365	3	1.71E-01	7.67
Physcion	275	2	2.90E-01	5.38

a. Number of references listed when compound and DM were searched in PubMed

b. Probability of dissociation between compounds and DM

Table 2. Ten significant GO clusters with the highest number of counts from the enrichment analysis of the curated and inferred proteins associated with *P. cuspidatum*

GO#	Category	Description	Count	PValue
GO:0042592	BP	Homeostatic process	34	7.62E-24
GO:0042127	BP	Regulation of cell proliferation	31	1.03E-19
GO:0005886	CC	Plasma membrane	29	0.008468
GO:0042981	BP	Regulation of apoptosis	28	3.12E-16
GO:0031328	BP	Positive regulation of cellular biosynthetic process	27	6.99E-17
GO:0009891	BP	Positive regulation of biosynthetic process	27	9.93E-17
GO:0000267	CC	Cell fraction	26	1.28E-11
GO:0010033	BP	Response to organic substance	26	2.90E-15
GO:0010604	BP	Positive regulation of macromolecule metabolic process	26	1.52E-13
GO:0045449	BP	Regulation of transcription	26	5.32E-04

GO, Gene Ontology; Curated target proteins, genes from CTD; Inferred target proteins, genes from TTD; CC, cellular compartment; BP, biological process; There are a total of 69 proteins in this analysis.

## Conclusion

The use of network pharmacology may provide a cost-effective way of identifying herbal medicines that might be highly effective against DM or those containing minimal side effects. On the other hand, utilizing more data sources and statistical software/methods is essential in assisting the identification of active compounds and their predicted functions against targeted diseases. Lastly, inclusion of in vitro and in vivo experiments could also help to verify the effectiveness of the compounds against the target proteins of each disease; hence, achieving the aim of increasing efficiency in drug development.