Indian Journal of Biochemistry & Biophysics
Vol. 63, February 2026, pp. 153-162
DOI: 10.56042/ijbb.v63i2.19947

Phytochemical investigation and integrating network pharmacology of *Trigonella foenum graecum* Linn., for antidiabetic potential

Kumar P, and Tiwari SB*

Department of Pharmacy, MJP Rohilkhand University, Bareilly-243 006, Uttar Pradesh, India

Received 22 May 2025; *revised 08 July 2025*

In this present work, we have investigated phytochemicals and therapeutic action of *Trigonella foenum graecum* Linn., in diabetic mellitus condition by network pharmacology. In this study, we employed identified active compounds from *Trigonella foenum graecum* Linn., leaves extract were identify by HPLC and SwissADME, STRING, Cytoscape, KEGG and GO software used for purpose of protein-protein interaction, protein compound interaction and pathways enrichment analysis. These approach to elucidate the therapeutic mechanisms of *Trigonella foenum graecum* Linn., specifically targeting the advanced glycation end products PI3K-Akt signaling pathway implicated in DM pathogenesis. In the present study, we identified key diosgenin, trigonelline and quercetin bioactive compounds in *Trigonella foenum graecum* Linn., A total of 259 compound related targets and 17738 diabetic mellitus related targets with 224 interacting targets between them. PI3K, AKT, GSK3, mTOR, CDK, MDM2, CREB, IKK and Mcl-1 highly expressed targets. Out of the 224 targets that intersected, 40 targets were directly linked to PI3K-Akt signaling pathway. This work underscores importance of network pharmacology in unravelling complex mechanisms underlying the therapeutic effects of natural products, offering insights for the development of innovative treatments for DM and related complications. *Trigonella foenum graecum* Linn., might exert an antidiabetic effect by regulating PI3K-Akt signaling pathway.

Keywords: Diabetes mellitus, PI3K-Akt signaling pathway, Diosgenin, Trigonelline

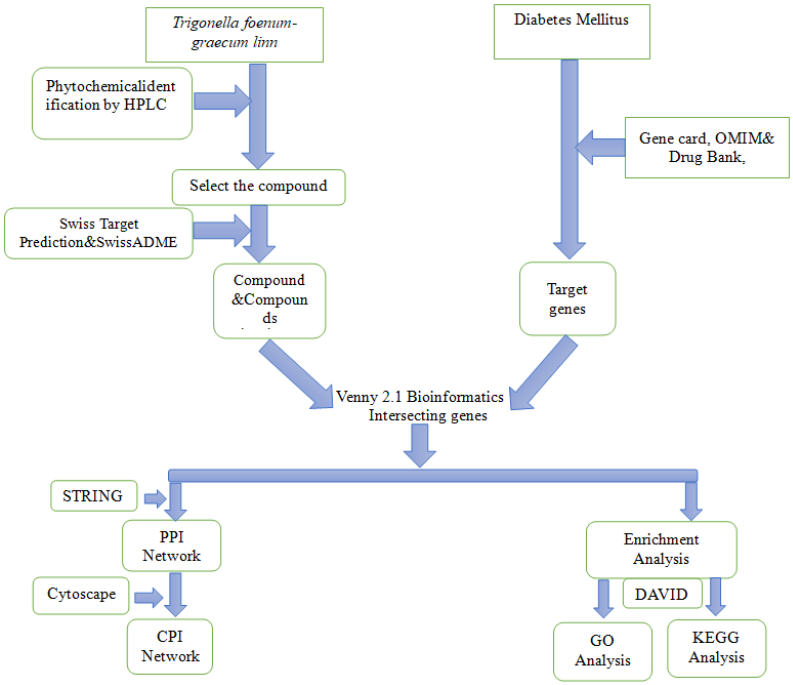
Diabetes mellitus (DM) is a situation in which the human body's capacity to regulate blood glucose levels is impaired, leading to a deficiency of the body's capacity to properly digest carbohydrates, proteins and fats. This is caused by a complete or partial suppression of insulin activity[1]. It is a situation indicated by excess plasma glucose concentration that does not respond to treatment. In the long term, this can lead to a variety of problems, such as retinopathy and nephropathy. Furthermore, individuals with diabetes are more similarly to create other health issues, mainly heart disease, peripheral artery and cerebral vascular disorder, blindness, and non-alcoholic fatty liver disease. Additionally, these are more likely to contract certain infectious diseases, including tuberculosis[2].

Type 1 diabetes mellitus is a situation in which the pancreas is unable to synthesize insulin, resulting in the death of β-cells. This is typically due to autoimmune damage, but can also be caused by genetic predisposition, environmental factors, viral agents, and infections[3]. Type 2 diabetes results from a complex arrangement of genetic predisposition to decreased release of insulin and resistance; as well as environmental factors, including obesity, excessive consumption, lack of physical activity, stress, and the natural aging process. Patients with T2DM experience chronic hyperglycaemia as an outcome of the progressive degeneration of pancreatic beta-cells and development of insulin tolerance[4]. DM, a potentially life-threatening endocrine disorder interferes with the body's regulation of blood glucose levels. The primary pathogenic cause of DM is an elevation of oxidative damage, resulting in a buildup of reactive oxidants (ROS) that ultimately impede the body's antioxidant defence system[5].

Diabetes is a prevalent health issue in India, with an estimated forty million individuals suffering from the condition in 2007, representing approximately twenty percent of the global diabetic population[6,7]. Heterogeneous Aetio-Pathology Insulin secretion disorders Insulin action disorders Carbohydrate, fat, and protein metabolism disorders[8].

Basically, it's pretty much agreed that the thing that sets all types of diabetes apart is the fact that the

*Correspondence:
Phone: +91-9451325149 (Mob)
E-mail: s.tiwari@mjpru.ac.in



Graphical abstract

pancreas' β-cells don't work properly or are damaged[9,10]. The mechanism of the β-cells may be impaired by a variety of mechanisms, or they may be destroyed. These cells are not regenerated, as it appears that the pancreas is not able to regenerate them after 30 years of age[11]. Genetic predisposition and abnormality, as well as epigenetic processes and insulin resistance, as well as autoimmunity and concurrent illnesses, as well as inflammation and external factors, can all play an essential part in the growth of glucose tolerance[12]. Determining the status of the β-cells in the body can assist in the delineation of distinct subtypes of diabetes and guide treatment[13].

The annual, herbaceous, and fragrant plant *Trigonella foenum graecum* Linn., well-known as fenugreek, is a member of the Fabaceae family. It comes from Northern Africa and India, making it one of the oldest medicinal herbs. Medicinal extracts or powders are made from the leaves and seeds, which develop into long pods. The seeds of fenugreek are widely used as a condiment in India[14].

Additionally, the seeds are high in oils, mucilage, and the amino acids (lysine, argenine, tryptophan, threonin, valin, and methionin). The plant's most common product, galactomannan, is known to calm and relax irritated tissues. It also contains calcium, iron, and zinc, as well as vitamins A, C, D, and B1. In addition to being high in fiber, 4-hydroyisoleucine, and fenugreekine, a substance that may have low blood sugar properties, fenugreek seeds also having alkaloids such as trigonelline, gentianine and carpine chemicals[15]. *T. foenum-graecum* leaves and seeds are commonly utilized to create powder and extracts for medicinal uses in a variety of studies. Fenugreek has been shown to produce hypoglycaemic, hypolipidemic, and hypocholesterolaemia effects in a number of early studies on humans and animals. Additionally, *T. foenum-graecum* has been shown to have antibacterial, anticancer, anti-parasitic, and antifertility properties[16].

Materials and Methods

Chemicals

Methanol, distilled water and formic acid.

Collection, authentication and Extraction of plant material

It is possible to identify the plant needed for this investigation by looking for them in their natural habitat. In this work *Trigonella foenum graecum* Linn., plants were used. Collection, authentication and drying of material prior to being pounded into powder, the plant parts should be air-dried and preferably harvested in the Rohilkhand Bareilly region. This can be confirmed with a botanist Dr. Alok Shrivastava at MJP Rohilkhand University, Campus Bareilly (UP), India with the serial no.

RU/B1/2024/12. Making extracts Using a Soxhlet apparatus with methanol as solvent systems, plants of *Trigonella foenum graecum* Linn., was processed sequentially. A 100 g of crushed *Trigonella foenum graecum* Linn., leaves was extracted using methanol (600 mL) and a Soxhlet extractor for 3 h at (65–70°C). The solvent combination was then filtered using a Whatman No. 1 paper filter, the extract was moved into a round flask, and the solvent was evaporated at 400°C using a rotary evaporator. Lastly, the oil extract was stored at 40°C to avoid the compounds degrading for additional analysis.

Phytochemical screening of extract[17]

Test for Tannin

There were 5 drops of 10% lead acetate added to 5 mL of plant extract. Tannin is present when a pale-yellow precipitate forms.

Test for Saponin

The extract was diluted by boiling 1 mL in 10 mL of water before being filtered using Whatman filter paper. There was a vigorous shaking of 5 mL of filtrate and 2 mL of regular distilled water. The presence of saponins is indicated by the appearance of steady, persistent foam.

Test for Flavonoids

To only 1 mL of the extract, some diluted sodium hydroxide was added. The plant extract became a vivid yellow, but when a few drops of diluted acid were added, the colour quickly faded (50% concentration).

Test for Terpenoid

Two milliliters of chloroform were added to half a gram of plant extract, and the same amount of strong sulphuric acid was added. The presence of terpenoids is indicated by an interface coloration of reddish brown.

Test for Phenolic compounds

Two milliliters of plant extract, five drops of 1% ferric chloride, and one milliliter of potassium ferro cyanide were mixed to produce a bluish-green solution, demonstrating the presence of a phenolic component.

Test for Reducing sugar

Filtered distilled water was used to dissolve 0.5 g of plant extract. For 5 min, the filtrate was boiled with 2 drops each of Fehling's solutions A and B. When reducing sugar is present, a bright orange precipitate form.

Test for Steroid

To a solution of two milliliters of plant extract in 5 mL of chloroform, strong sulphuric acid was added. A two-stage change in density is diagnostic of steroid use.

Identification and draggability of phytocompounds

The potential phytochemical constituents of TFG plant identify by the High-Performance Liquid Chromatography technique. Pub chem (https://pubchem.ncbi.nlm.nih.gov/) and SWISS ADME (http://www.swiss adme.ch/) were used for extract and calculate drug similarity properties of the obtained compounds by the IR and HPLC. The active components about TFC leaves were evaluated for drug-likeness qualities (according to lipinski's rule of five) using compounds canonical SMILES, or derived from the Pub Chem databases by SWISS ADME. The database was created by compiling specific attributes such as cononical smiles, molecular weight, chemical formula, number of acceptors and donors for bonds of hydrogen, and logP value of particular phytoconstituents from the Pub Chem chemical compounds data library. During database creation, plant compound duplication was removed. Using "Model of Lipinski's Rule of Five," the Mol-Soft (https://molsoft.com/mprop/) was used to estimate the phytocompounds' drug matching score.

Evaluating the target gene of active constituent and pathological gene of diabetes mellitus

The homo sapiens mode of SMILES was used to retrieve related genes for chemicals from swiss target prediction (STP) (http://www.swisstargetprediction.ch/) and similarity ensemble (SEA) (http://sea.bkslab.org/). Utilizing Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/), it was possible to identify potential genes that overlapped between the two datasets. On the other hand, using the species "Homo sapiens" constraint, genes associated with DM were also discovered utilizing the DisGeNET library (https://www.disgenet.org/), OMIM database (https://omim.org/), and the GenCLiP3, database (http://ci.smu.edu.cn/genclip3/analysis.php). After that, the potential target from all 3 previously mentioned databases were merged and eliminated duplication to get a set of targets that were pertinent to DM. Ultimately, genes between the chosen compound-associated gene and the DM target gene were found and intersected by Venny 2.1[18].

PPI-Network building of an intersecting gene

The genes that overlapped in compound-associated gene and the target genes were placed into the STRING gene database structure, Version 11.0b, (https://strin g-db.org/) to be searched for proteins as human organism, with the strongest likelihood foundation for interactions between proteins being a score for >0.4[19]. Subsequently, the network was loaded into cytoscape 3.8.2 software and whole network was further classified through the cytohubba plugin combined into cytoscape, utilizing the maximum clique centrality (MCC) technique to identify the network's core genes[20].

Developing compound-target networks

A compound-target genes network was built utilizing the outcomes of *TFG* and DM, and cytoscape 3.8.2 was used to view the network. In the network, chemicals and genes are shown as nodes, and the relationships in between them are shown as edges[21,22]. Next, the network analyzer application, which was coupled with cytoscape, was used to study the entire network. A node size scale was used to depict the network, and nodes were sorted according to their degree value, with the largest node being the node with the greatest degree count.

Analyses of pathway enhancement for primary targets

The Kyoto encyclopedia of genes and genomes (KEGG) analysis of pathway enrichment on overlapping genes was carried out utilizing an online server STRING V 11.0b in Homo sapiens mode. P-value <0.001 was used as the cutoff point to identify pathways implicated in diabetes. The FDR errors control method was used to correct the p-value, and the outcome was known as the Q values. KEGG-based enrichment pathway results were used to infer possible molecular mechanisms of *TFG* on DM. The bubble map of pathways was mapped using Origin Pro 2021 software.

Results

Phytochemical screening of extract

On the basis of phytochemical screening, leaves extract of *Trigonella foenum-graecum* Linn., was found that this extract shows the presence of phytoconstituents such as saponin, reducing sugar, tannins, flavonoids, phenolic compounds, steroids and terpenoids.

Phytochemical constituents of *Trigonella foenum-graecum* Linn.

Phytochemical identification of *Trigonella foenum-graecum* Linn., by the HPLC methods in (Fig. 1), the major peak at 30.546 min (77.20%) suggests Diosgenin, a well-known steroidal saponin in *Trigonella foenum graecum* Linn., Secondary peaks at 27.017 min & 27.570 min could be trigonelline, a key alkaloid found in *Trigonella foenum graecum* Linn., The small peaks at 24.323 min & 25.327 min might correspond to flavonoids like quercetin, which are known minor components of *Trigonella foenum graecum* Linn., extract in (Table 1).

Compound chemical analysis and screening for drug likeness

As shown in Table 2, Using lipinski's rule of five, an evaluation the pharmacokinetics or drug-likeness parameters of the identified compounds. This was done by using the Swiss ADME online application. Two out of three compounds, according to Lipinski's role, showed drug-like characteristics without breaking any one of the following rules: (i) molecular

Table 1 — Possible identify Compounds of *Trigonella foenum-graecum* Linn., by the HPLC

Sr. no.	Compound	Retention Time (RT)	UV- Absorbance (nm)	Category
1	Diosgenin	30-31 min.	250-277 nm	Steroidal Saponin
2	Trigonelline	27-28 min	250-277 nm	Alkaloid
3	Quercetin	24-25 min	250-277 nm	Flavonoid

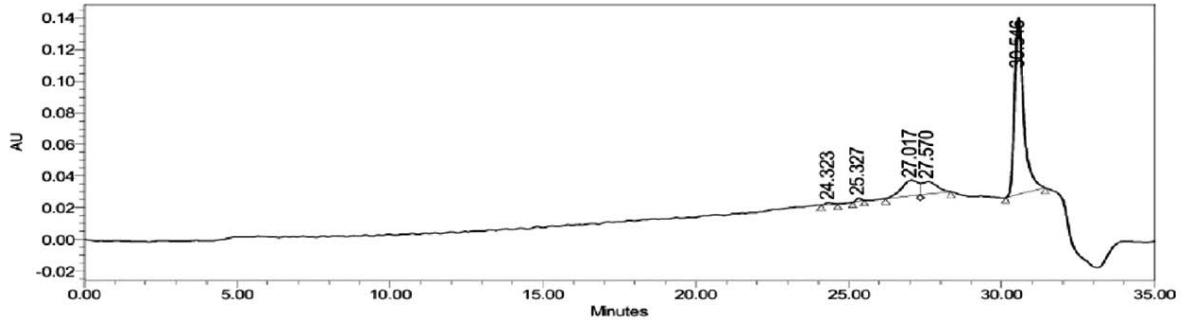


Fig. 1 — HPLC Chromatograph of *Trigonella foenum-graecum* Linn.

mass not to more than five hundred; (ii) a hydrogen bond donor not to more than five; (iii) a hydrogen bond acceptor not to more than ten; along with (iv) MLogP not to exceed four and a half with a nornal the bioavailability score about >0.1. The components that were breached were as follows diosgenin, trigonelline and quercetin. To determine if compounds contain TPSA 140 & nRot 10 or not, Veber's filter was taken into consideration.

After analyzing these criteria for 3 different chemicals, it was discovered inside the permissible range. The second step was studying the pharmacokinetics of these drugs based on their suppression of cytochrome P450 (CYP), gastrointestinal absorption and blood brain barrier permeability. These gastrointestinal (GI) absorption, and blood-brain barrier (BBB) permeability. These factors aid in identifying a compound's drug-like qualities. We chose compounds with high Gastrointestinal absorption, BBB permeability, P-gp non-substrates, & no CYP inhibitors. Since the focus of this study is neurodegenerative disease, the medication needs to pass across the blood-brain barrier in order to attach to the target and reach the brain cells. the P-gp non-substrate constituents were selected to ensure compounds had excellent absorption and bioavailability and that P-gp drug efflux would not become a problem. Since CYPs are in charge of drug metabolism and their suppression could lead to a protracted drug-drug interaction that could be fatal, CYP non-inhibitor constituents were chosen. The acceptable range contained only three compounds, having CIDs 99474, 5570 and 5280343 were found in the permissible range.

Targets prediction genes of *TFG* leaves or pathological genes of DM results

Using the TFG with DM database, grater targets particular to the filter 224 substances were created. From screened bioactive chemicals, 17738 genes from DM and 259 from TFG were found. The two databases' 224 shared genes were enhanced by the Venny 2.1 programs (Fig. 2). Targets of TFG unique to DM were obtained from several databases, including GeneCards, Swiss Target Prediction, and STITCH, based around SMILES. Applying GeneCards and the NCBI Gene database, the known current treatment targets for neurodegenerative disorders were obtained. They built their network using the visualization program Gephi 0.9.2 in order to provide a more accurate depiction of the target network.

Analysis of target proteins in Protein-protein interaction network

In a manner to produce the PPI network and provide a comprehensive explanation of how TFG functions on diabetic mellitus, the last 224 typical goals of drugs and DM were added to STRING database. In the database of string network 2 genes GPR35 and HAAO interact with each other weren't interacting with any additional gene. According to the string network investigation, STK17B, KCNA3 and

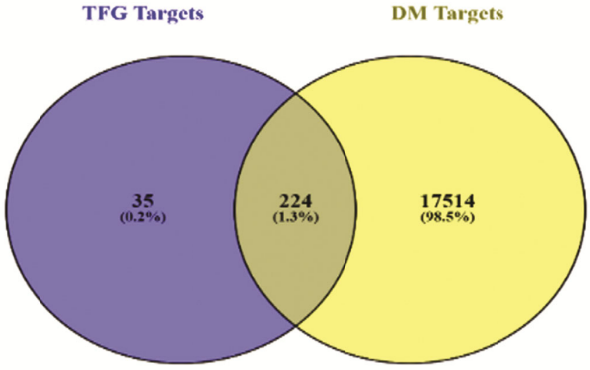
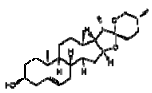
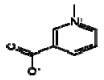
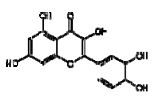


Fig. 2 — A Venn diagram showing the 224 shared target genes between the targets of diabetes mellitus and TFG chemical

Table 2 — Compound names and drug-like characteristics of three compounds derived from *TFG*

Sr. No.	Compounds	Chemical Formula	Pub Chem/ CD C ID	Blood Brain Barrier (BBB)	GI Absorption	MW <500	HBA <10	HBD <5	MlogP ≤4.15	Lipinski's Violations ≤1	Bioavailability score > 0.1	Chemical structure
1	Diosgenin	C27H4203	99474	Yes	High	414.62 g/mol	3	1	4.94	1	0.55	
2	Trigonelline	C7H7NO2	5570	No	High	137.14 g/mol	2	0	0.33	0	0.55	
3	Quercetin	C15H10O7	5280343	No	High	302.24 g/mol	7	5	0.56	0	0.55	

HCRTR2 weren't interacting with any additional gene and each gene had an interest in adjacent genes byconstructing 224 nodes linked by 2236 edges, expected number of edges 1012 and average node degree 20 (Fig. 3a). The protein–protein interaction (PPI) enrichment p-value was found to be less than 1.0×10^{-16}, indicating a highly significant enrichment.

By identifying important proteins in the network using the MCC method, we were able to increase both the specificity and sensitivity of nodes. According to recent studies, MCC also identified high- & low-degree proteins to determine which proteins are necessary on the list of the highest-ranking proteins[23]. Consequently, we systematically pruned the

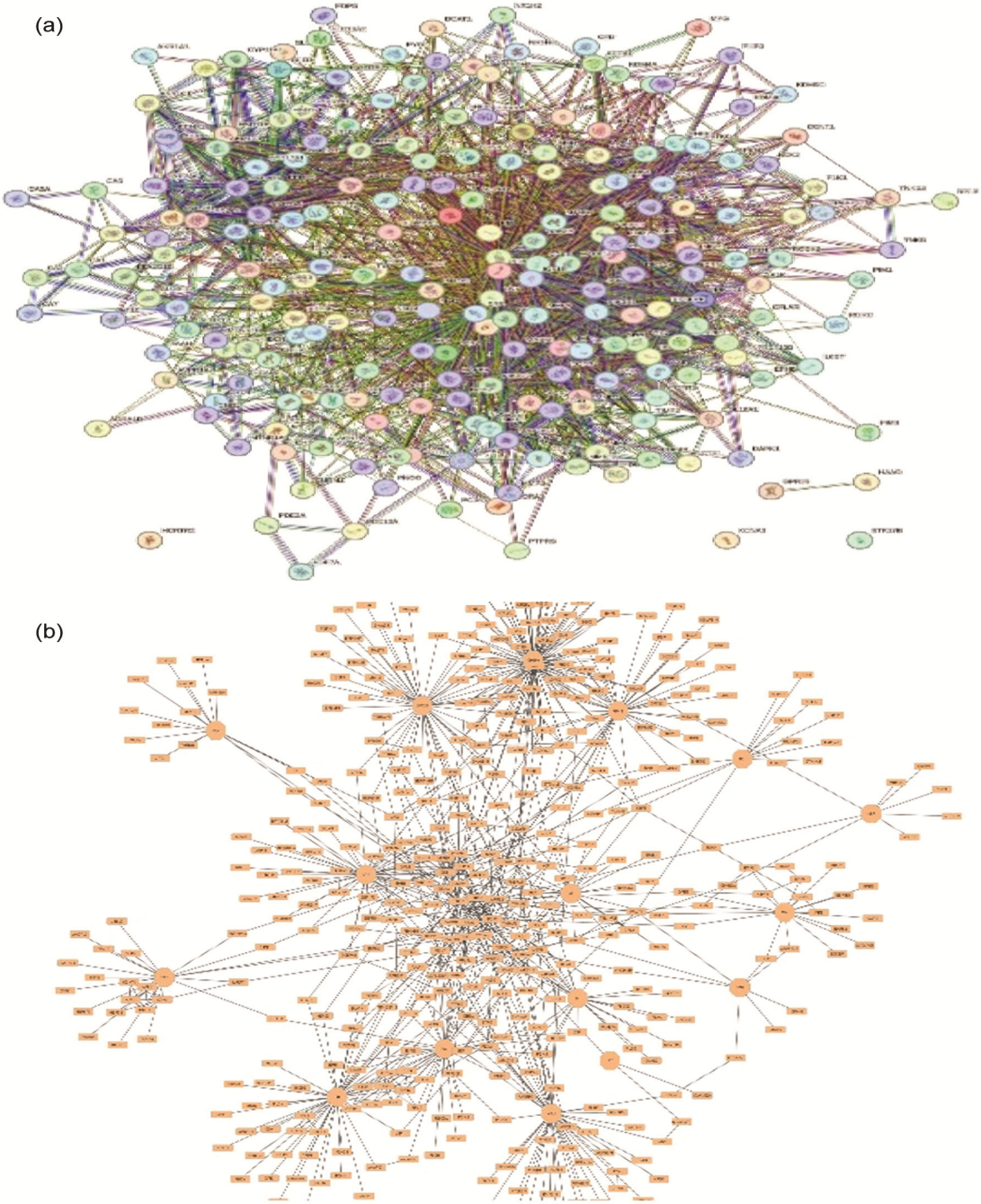


Fig. 3 — (a) The STRING-related protein-protein interaction (PPI) network includes 224 genes associated with TFG and DM; and (b) Target Protein interaction network by Cytoscape v3.7.2

Table 3 — Study of target enhancement influenced by TFG phytocompounds

S. No.	KEGG ID	Pathway Description	Genes ID
1	has01521	EGFR tyrosine kinase inhibitor resistance	EGFR AKT1 FGFR3 FGFR2 MTOR GSK3B HGF IGF1R JAK2 KDR MET PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 AXL MAP2K1 RAF1 SRC VEGFA
2	hsa05230	Central carbon metabolism in cancer	EGFR AKT1 FGFR1 FGFR3 FGFR2 FLT3 SIRT3 MTOR KIT MET PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 MAPK2K1 RAF1 SLC2A2
3	hsa04917	Prolactin signaling pathway	MAPK14 CYP17A1 AKT1 ESR2 GSK3B JAK2 PIK3CA PIK3CB PIK3CD PIK3R1 MAPK8 MAPK9 MAPK10BMAP2K1 RAF1 SLC2A2 SRC
4	hsa05218	Melanoma	CDK4 CDK6 EGFR AKT1 FGFR1 HGF IGF1R MDM2 MET PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 MAP2K1 RAF1
5	hsa01522	Endocrine resistance	CDK4 MAPK14 EGFR AKT1 ESR2 MTOR IGF1R MDM2 MMP2 MMP9 PIK3CA PIK3CB PIK3CD PIK3R1 MAPK8 MAPK9 MAPK10 MAP2K1 PTK2 RAF1 SRC
6	hsa05215	Prostate cancer	CDK2 EGFR AKT1 FGFR1 FGFR2 MTOR GSK3B IGF1R IKBKB AR MDM2 MMP3 MMP9 PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 MAP2K1 RAF1
7	hsa05206	MicroRNAs in cancer	CDK6 CYP1B1 CYP24A1 EGFR FGFR3 MTOR ABL1 HDAC1 IKBKB MCL1 MDM2 MDM4 MET MMP9 PDGFRA PDGFRB ABCB1 PIK3CA PIK3CB PIM1 PIK3CD PIK3R1 MAP2K1 PTGS2 RAF1 ROCK1 VEGFA
8	has04926	Relaxing signaling pathway	MAPK14 EGFR AKT1 MMP1 MMP2 MMP9 MMP13 NOS1 NOS2 NOS3 PIK3CA PIK3CB PIK3CD PIK3R1 MAPK8 MAPK9 MAPK10 MAPK2K1 RAF1 SRC VEGFA
9	hsa04072	Phospholipase D signaling pathway	EGFR AKT1 F2 F2R MTOR GRM1 GRM5 CXCR1 INSR KIT PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3CG PIK3R1 AVPR1A AVPR2 MAP2K1 RAF1 SYK
10	has05208	Chemical carcinogenesis-reactive oxygen species	AKR1A1 MAPK14 CYP1A1 CYP1B1 AKR1C1 EGFR AHR EPHX1 EPHX2 AKT1 ABL1 HGF IKBKB MET NOX4 PIK3CA PIK3CB PIK3CD PIK3R1 MAPK8 MAPK9 MAPK10 MAPK2K1 PTK2 PTPN1 RAF1 SRC VEGFA AKR1C3 MAP3K14
11	hsa05205	Proteoglycans in cancer	MAPK14 CTSL EGFR AKT1 FGFR1 MTOR HGF IGF1R KDR5 MDM2 MET MMP2 MMP9 PIK3CA PIK3CB PIK3CD PIK3R1 MAP2K1 PTK2 RAF1 ROCK1 SHH SMO SRC VEGFA CAMK2B ROCK2
12	has05167	Kaposi sarcoma-associated herpesvirus infection	CDK4 CDK6 CCR1 MAPK14 AKT1 MTOR GSK3B IKBKB IL6ST JAK2 PIK3CA PIK3CB PIK3CD PIK3CG PIK3R1 MAPK8 MAPK9 MAPK10 MAP2K1 PTGS2 RAF1 SRC SYK VEGFA
13	has05417	Lipid and atherosclerosis	MAPK14 CYP1A1 CYP2A6 CYP2C8 CYP2C9 AKT1 ERN1 GSK3B IKBKB JAK2 MMP1 MMP3 MMP9 NOS3 PIK3CA PIK3CB PIK3CD PIK3R1 MMPK8 MMPK9 MMPK10 PTK2 SRC CAMK2B TNFRSF10B ROCK2
14	hsa04510	Focal adhesion	EGFR AKT1 GSK3B HGF IGF1R KDR MET MYLK PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 MAPK8 MAPK9 MAPK10 MAP2K1 PTK2 RAF1 ROCK1 SRC VEGFR ROCK2
15	has04015	Rap1 signaling pathway	CNR1 ADORA2A MAPK14 EGFR AKT1 F2R FGFR1 FGFR3 FGFR2 HGF IGF1R INSR KDR KIT MET PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 MAP2K1 RAF1 SRC VEGFA
16	has 04014	Ras signaling pathway	EGFR AKTI FGFR1 FGFR3 FGFR2 FLT3 ABL1 HGF IGF1R IKBKB INSR KDR KIT MET PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3R1 PLA2G1B MAPK8 MAPK9 MAPK10 MAPK2K1 RAF1 VEGFA
17	hsa04151	PI3K-Akt signaling pathway	CDK2 CDK4 CDK6 CHRM1 CHRM2 EGFR AKT1 F2R FGFR1 FGFR3 FGFR2 FLT3 MTOR GSK3B HGF NR4A1 IGF1R IKBKB IL2 INSR JAK2 KDR KIT MCL1 MDM2 MET NOS3 PDGFRA PDGFRB PIK3CA PIK3CB PIK3CD PIK3CG PIK3R1 PKN1 MAP2K1 PTK2 RAF1 SYK VEGFA
18	hsa04020	Calcium signaling pathway	CHRM1 CHRM2 ADORA2A ADRA1D EGFR F2R FGFR1 FGFR3 FGFR2 GRM1 GRM5 HGF KDR MET MYLK NOS1 NOS2 NOS3 OXTR PDGFRA PDGFRB AVPR1A TACR1 VEGFA CAMK2B CD38
19	hsa05200	Pathways in cancer	CDK2 CDK4 CDK6 DAPK1 EGFR AKT1 ESR2 F2 F2R FGFR1 FGFR3 FGFR2 FLT3 ALK MTOR ABL1 GSK3B HDAC1 HGF IGF1R IKBKB IL2 IL6ST AR JAK2 KIT MDM2 MET MMP1 MMP2 MMP9 NOS2 PDGFRA PDGFRB PIK3CA PIK3CB PIM1 PIK3CD PIK3R1 MAPK8 MAPK9 MAPK10 MAPK2K1 PTGS2 PTK2 RAF1 ROCK1 SHH SMO TERT VEGFA CAMK2B ROCK2
20	hsa01100	Metabolic pathways	AKR1A1 PDE10A CYP1A1 CYP2A6 CYP2C8 CYP2C9 CYP3A4 CYP11B1 CYP11B2 CYP17A1 CYP19A1 CYP24A1 CYP51A1 AKR1C1 DHFR EPHX2 FASN FDPS AKR1B1 SIRT3 HAAO ALOX12 ALOX15 HIBCH HPGDS GLO1 HSD11B1 HSD17B1 IMPDH2 ARG1 MAOA NOS1 NOS2 NOS3 PDE2A PDE3A PDE3B PDE4B PDE7A PGK1 PIK3CA PIK3CB PIK3CD PIK3CG PLA2G1B AKR1B10 PTGS1 PTGS2 PYGL SCD TYR XDH CA1 CA2 CA3 CA4 CA5A CA6 CA7 CA9 AKR1C3 CD38

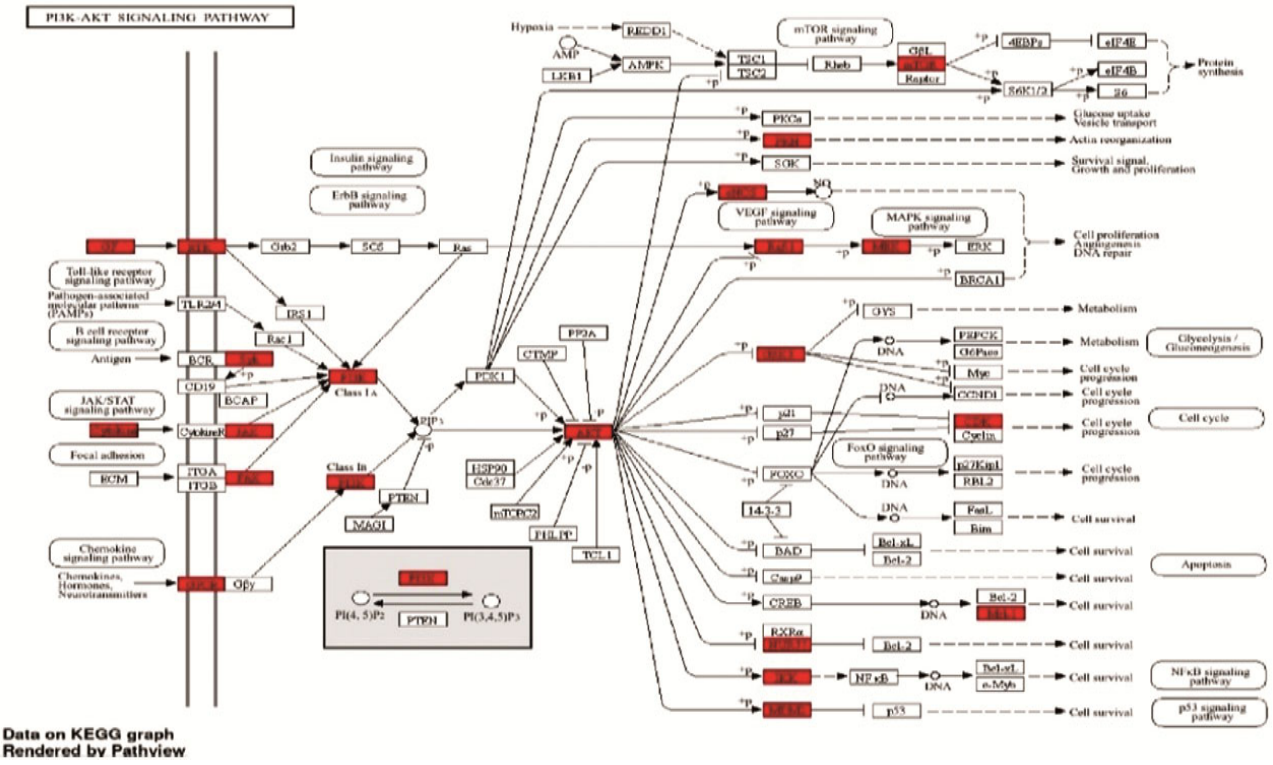


Fig. 4 — Illustration of the PI3K-Akt signaling pathway in diabetes mellitus complications, the red node represents the enriched gene in the present study

previously constructed networks down to the topmost 224 gene groups using the Cytoscape v3.7.2 program. According to the Cytoscape database in the hyperglycaemia condition AKT1, MAPK1, STAT3, SIRT1, PPARG, PIK3R1, IL6, TNF, TP53 and INS was found to be the most significant protein-coding gene in the newly created network, with a 6.27+ 10 score. The most important genes were represented by multiple blue nodes throughout the network. Central hub proteins include GP1, MA, GAG, REV, VPR, and TAT, suggesting they have many interactions and represented by the red nodes in the network (Fig. 3b). This type of network typically represents key regulators of diabetes mellitus related genes and their interaction.

This suggests that a random set of proteins with the same size and distribution chosen at random from the genome would not reveal as many connections between proteins as there are. This type of enhancement implies that the proteins have some biological relationships when taken together.

Assessment of pathway enrichment

Table 3 showed that, out of the 224 targets that intersected, 40 targets were directly associated with the signaling pathway PI3K-Akt which were eliminated at erroneous finding Rates of less than 0.001 and were therefore directly implicated in the advancement of DM. For route enrichment analysis, we employed a rich component and adjusted FDR value (Q-Value) analysis. With an increase in Rich factor comes an increase in the degree overall pathway enrichment. A lower value indicates a better enrichment pathway. Figure 4 provides comprehensive details on PI3K-Akt signaling pathway system. The target genes of the ongoing research are PI3K, AKT, GSK3, mTOR, CDK, MDM2, CREB, IKK and Mcl-1 highly expressed represented by the red node in the diagram. According to the pathway enrichment compensatory activation of certain elements such as AKT and PI3K can occur in response to metabolic disturbances. However, overactivity of GSK3 (glycogen synthase kinase 3) can impair glycogen synthesis, contributing to poor glucose storage. Additionally, dysregulation of transcription factors like CREB and FoxO can enhance gluconeogenesis, thereby exacerbating hyperglycaemia. Furthermore, the IKK complex plays a critical role in linking inflammation through NF-κB signaling to the development of insulin resistance, further complicating glucose metabolism.

Discussion

After the development of numerous treatment modalities, the rate of morbidity in diabetes patients continues to rise. Using network pharmacology and gene set enrichment as tools, the present research aimed to uncover the molecular mechanisms underlying the antidiabetic actions of phytoconstituents from TFG. Research on multi-target medications with great efficacy and minimal toxicity is also included. The creation of innovative multi-targeted medications that may be expanded upon evaluated in experimental and clinical settings is aided by the data gathered from these methods. In the current research, we looked into the molecular processes of the popular medicinal herb TFG in the management of diabetes mellitus by employing a variety of chemo-informatics and system biology techniques. Previous studies that indicated this kind of basil has sedative, anti-inflammatory, anti-stress, anti-mutagenic, anti-ulcerative, gastroprotective, liver protective, and anti-bacterial properties provide credence to its widespread usage in medicine[21].

Compounds-genes networking system revealed that three compounds shortlisted identify for the therapeutic impact of TFG against DM had relevant information gleaned from the PubChem chemistry database. This data was used to estimate the ADMET profile and potential druggability. After this process, the study sought to use BindingDB with a likelihood score of 0.7 to determine the likely protein targets. The experimental protein-small molecule interaction data are archived in the publicly accessible BindingDB (https://www.bindingdb.org) [22].

More than a million entries of data are included in this database, most of which are taken from academic publications and steadily rising US patents. The 3D X-ray crystal arrangement of human alpha amylase is not yet available in a protein data library. Consequently, modeler 9.10 was used to build its homologous structure. Although protein structure can be revealed using homology modeling, the degree to that an arrangement matches a framework depends on its characters. The method is based on findings that mild to moderate changes in an amino acid sequence usually result in minimal modifications in the 3D structure, and that a protein's fundamental endorsement is higher stable than its amino acid chain. In order to get the protein - protein network and functional characterisation, the generated list of phytocompound protein targets was also uploaded to the STRING database[22].

An analogous online resource 224 common target genes were identified as a consequence of other researchers' use of STRING to visualize the regulatory structure and protein–protein interacting network among TFG and DM, the target genes. The mechanisms behind the therapy of diabetic mellitus were also determined by use of the bioactive substances derived from TFG. In order to better understand the compound target-pathway network, many genes were targeted, and DM-related signaling pathways were altered.

AKT1, MAPK1, STAT3, SIRT1, PPARG, PIK3R1, IL6, TNF, TP53 and INS were among key target in the PI3K-Akt signaling pathway that were shown to have enriched pathways by phytocompounds (diosgenin and trigonelline) to reduce the blood glucose level as per the KEGG Analysis. Hence, PI3K-Akt signaling pathway has been discovered as the major techniques for controlling hyperglycaemia.

Conclusion

TFG is thought to be a potential source for herbal antidiabetic medicines due to its abundance of advantageous phytoconstituents. However, the PI3K-Akt signaling system and its extensive beneficial substances for diabetes were first examined in this paper using network pharmacology. The results of HPLC data investigation show the three compounds are identify in the leaves extracts of TFG that were highly connected with PI3K-Akt signaling pathway are responsible for antidiabetic properties.

Acknowledgement

I am grateful to Department of Pharmacy, MJP Rohilkhand University, Bareilly, Uttar Pradesh, India for issue the required things to perform the present research work in a successful manner. I am also thanking other teaching and non-teaching staff for their valuable support to research work.

Conflict of interest

All authors declare no conflict of interest.

References

1 Puchulu FM, Definition, diagnosis and classification of diabetes mellitus. *Dermatol Diabetes*, (2018) 1.

2 Zimmet P, Alberti KG & Shaw J, Global and societal implications of the diabetes epidemic. *Nature*, 414 (2001) 782.

3 National Institute of Diabetes and Digestive and Kidney Diseases publication. 14 (2014) 51.

4 Lou J, Risk factors for diabetic nephropathy complications in community patients with type 2 diabetes mellitus in Shanghai: logistic regression and classification tree model analysis. *Int J Health Plann Manage*, (2019) 1.

5 Fahad A, Potential antidiabetic activity of barbigerone on glucose and inflammatory cytokine levels in streptozotocin activated diabetic rats. *J King Saud Univ Sci*, 34 (2022) 1.
6 Laakso M, Biomarkers for type 2 diabetes. *Mol Metab*. 27 (2019) 139.
7 Bansode B, Jungari DS, Economic burden of diabetic patients in India: a review. *Diabetes Metab Syndr*, 13 (2019) 2469.
8 Kahn SE, Cooper ME & Del Prato S, Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet*. 383 (2014) 1068.
9 Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L, The many faces of diabetes: a disease with increasing heterogeneity. *Lancet*, 383 (2014) 1084.
10 Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR & Aguilar RB, The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification schema. *Diabetes Care*, 39 (2016) 179.
11 Perl S, Significant human β cell turnover is limited to the first three decades of life as determined by in vivo thymidine analog incorporation and radiocarbon dating. *J Clin Endocrinol Metab*, 95 (2010) 234.
12 Ozel Y, Aktas HS, Kirmaci HK, Ahmad S, Tetik S, Sekerler T, Polat EB, Sayir N & Elcioglu HK, Evaluation of ischemia reperfusion injury in streptozotocine-induced diabetic rats and its amelioration by hazelnut. *Indian J Exp Biol*, 62 (2024) 795.
13 Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH & Groop L, Differentiation of diabetes by pathophysiology, natural history, and prognosis. *Diabetes*, 66 (2017) 241.
14 Ramya P, Lakshmidevi N, Jayashree K & Suresh RN, Evaluation of anti-diabetic effect of *Trigonella foenum graecum* Linn., Leaf extract in streptozotocin induced diabetic rats. *Int J Diabetes Dev Ctries*, 32 (2012) 138.
15 Nisha & Rao PB, Trigonella foenum-graecum: A Common Indian Spice with Medicinal Properties. *Res J Pharm Technol*, 9 (2016) 173.
16 Theysshana V, Leslie TLT, Johnson S, Shu YC & Shalini V, Revisiting *Trigonella foenum-graecum* L.: Pharmacology and Therapeutic Potentialities. *Plant*, 11 (2022) 1.
17 Adil M, Filimban FZ, Ambrin, Quddoos A, Sher AA & Naseer M, Phytochemical screening, HPLC analysis, antimicrobial and antioxidant effect of *Euphorbia parviflora* L. *Sci Rep*; 14 (2024) 1.
18 Stelzer G, The GeneCard Suite: From Gene Data mining to disease genome sequence analyses. *Current Protoc Bioinformatics,* 54 (2016) 01.
19 Szklarczyk D, The STRING data base quality-controlled protein- protein association network, made broadly accessible. *Nucleic Acids Res*, 45 (2017) 362.
20 Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B & Ideker T, Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res*, 13 (2003) 2498.
21 Lee AY, Park W, Kang TW, Cha MH & Chun JM, Network pharmacology-based prediction of active compounds and molecular targets in Yijin-Tang acting on hyperlipidaemia and atherosclerosis. *J Ethnopharmacol*, 22 (2018) 151.
22 Chin C, Chen S, Wu H, Ho C, Ko M & Lin, Cyto Hubba: identifying hub objects and sub- networks from complex interactome. *BMC Syst Biol*, 20148 (2014) 11.