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REVIEW ARTICLE

Integrating Network Pharmacology in The Treatment of Diabetes Mellitus – A Review

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ABSTRACT
Diabetes mellitus (DM) is a chronic metabolic disorder characterized by insulin dysfunction, leading to elevated blood glucose levels. It is a global health crisis, with more than 422 million cases reported in 2014, and projections suggest this number will rise to 642 million by 2040. DM is generally divided into three types: Type-1, Type-2, and gestational diabetes. Type-1 DM occurs due to the autoimmune destruction of the pancreatic β-cells, on the other hand Type-2 DM happens because of insulin resistance and it makes up around 90% of the cases. Recently, network pharmacology (NP) has gained attention as a contemporary tool for studying how drugs interact with biological systems. This approach offers a chance to discover drugs that target multiple aspects of a disease, especially in traditional medicine. By using NP, researchers can identify natural products like polysaccharides and polyphenols for their potential benefits in treating diabetes. These natural compounds have shown encouraging results in controlling blood sugar levels, enhancing insulin sensitivity, and affecting related molecular pathways positively. NP brings together computational models and biological data effectively, creating an all-encompassing platform for identifying active compounds and new therapeutic targets. This review underscores the significance of NP in exploring fresh treatment methods for diabetes. It presents a structured way to merge natural remedies & traditional medicine into current healthcare practices.
Keywords: *Diabetes Mellitus, Network Pharmacology, Traditional Medicine, Drug Discovery*.

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INTRODUCTION

DM is a type of chronic noncommunicable disease (CNCD) (1) characterized by problems in the synthesis and action of the pancreatic hormone insulin, that eventually leads to abnormally high blood sugar levels(2). It is a category of metabolic illness and is regarded as the main issue affecting world health(3). As per the International Diabetes Federation, DM has emerged as a significant health hazard, ranking third in mortality rates, behind cancer and cardiovascular disorders. Currently, DM hurts both high- and low-income nations, with low-income nations suffering from severe damage. According to the most recent WHO figures, approximately 422 million people globally have diabetes (4). Based on the etiology and clinical characteristics, DM is commonly classified into three categories: Type-1, Type-2, and Gestational diabetes mellitus (GDM) (5). Type-1 diabetes or insulin-dependent diabetes is a disorder in which T lymphocytes destroy pancreatic β-cells, leading to total insulin insufficiency (6)(7) and this form of diabetes affects approximately 5-10% of people with this condition (8). Type-2 diabetes, sometimes known as adult-onset diabetes or non-insulin-dependent diabetes, is the most common type of the disease and accounts for at least 90% of all cases of diabetes (9). It is characterized by insulin resistance and a relative insulin shortage (10). Additionally, some women may develop gestational diabetes mellitus (GDM) during pregnancy, which is a temporary condition influenced by similar insulin dynamics (11). The reality underlying this form of diabetes is that women who have gestational diabetes have a greater

chance of developing type-2 diabetes in the future (12). A mix of additional environmental variables and genetic predispositions are though to be the primary reason behind type-1 diabetes (13). Insulin resistance is the main cause of type-2 diabetes (14) and obesity is a major contributing factor to diabetes(15). Approximately 90% of the population with type-2 diabetes is obese (16). Diabetes may also result from uncommon genetic variants and pancreatic injuries(17,18). Diabetes problems can be avoided or postponed with early diagnosis and effective blood pressure, cholesterol, and blood sugar management (19). In Asian nations, diabetes is more common, especially in China and India(20). These two nations were found to have the highest numbers of diabetic patient—109.6M and 69.2M, respectively (21). Treatment for diabetes accounts for almost 10% of the total health care expenditure in affluent nations (22). By 2040, there are up to 642 million cases of diabetes mellitus worldwide, according to predictions(23). Research on diabetes management and treatment is currently one of the most sought-after topics of study since this disease poses a major danger to an individual's health and places an expensive burden on society(24). Network pharmacology (NP) is a recently developed field that aims to understand pharmacological effects and interactions with many targets. Computational power is used to systematically catalog the chemical interactions between a drug molecule and a living cell. The NP seems to be a key instrument for comprehending the intricate interactions underlying the effects of botanical formulas on the entire body. By permitting an objective examination of possible target spaces, researchers also seek to identify novel therapeutic leads and targets as well as to repurpose already existing pharmacological molecules for various therapeutic situations. As they combine information science and systematic medicine, NPs are developing as a new area of drug discovery and development (25). As is often the case with new technologies in their early phases, network pharmacology has an unclear early understanding of drug development and may have overhyped its potential(26,27). Network pharmacology is beginning to gain traction and is a widely employed strategy in the contemporary drug development process (28). An integrated in silico method called network pharmacology aims to create a "protein–compound/disease–gene" network to uncover the processes underlying the complementary therapeutic effects of conventional drugs (29). As a result, the paradigm has changed from one of "one target, one drug" to one of "network target, multiple component therapeutics." From the standpoint of network pharmacology, this study clarified the possible relationships between target genes and the active components of medicinal plants. The current investigation focuses on the gap in the literature. A comprehensive strategy for investigating drug-target interactions is needed to more clearly define the new inhibitors and their mode of action for a given target. This review of the literature offers a thorough summary of the relevance, technique, and applications of network pharmacology in the treatment of several complex conditions, including diabetes.

NETWORK PHARMACOLOGY

Evolution of network pharmacology

For the first time, Shao Li's 1999 discovery of "Syndrome," was rooted in the NP, which is a connection between TCM and biomolecular networks(30). A few years later, he proposed that the "multicausal and micro-functional" effects of herbal formulas may regulate the disease gene network (31). The first biomolecular network of cold/hot syndrome in TCM was constructed by Li et al. in 2007 using bioinformatics, and they discovered the network regulatory effects of cold/hot syndrome formulas (32). The same year, the UK pharmacologist Andrew L. Hopkins of Dundee University presented "Network Pharmacology" (33). Specifically, this technique has recently gained traction and is anticipated to develop into a viable paradigm for the upcoming generation of medication creation (34). In 2009, Pan Jiahu used network pharmacology to create a novel drug discovery model (35). Due to the significant overlap between the core concepts of network pharmacology and TCM, network pharmacology has recently gained popularity as a topic of study in systematic pharmacological research, particularly in the field of research on the pharmacodynamic mechanism of TCM. In the same year, Li created a paradigm for TCM prescription research and TCM evidence called the "phenotypic network-biological network-Chinese medicine network"(36). Two years later (37), he first presented the concept of "network targets" and developed a cooperative method for medication combination prediction using network targets. Li's group created and released the first international standard for network pharmacology in 2021 with the goal of standardizing data feasibility and boosting the trustworthiness of outcomes for Network Pharmacology Evaluation Techniques"(38)

Network pharmacology and traditional medicine

Without performing scientific research, local populations have utilized therapeutic herbs for more than ten years (39,40). Traditional treatments involve the use of a variety of species of medicinal plants(41,42). The loss of valuable value for various plant species has resulted from the unsustainable use

and traditional methods of gathering and applying medicinal plants, even though these plants improve people's lives by offering inexpensive and natural remedies (43,44). Conventional medical care, which provides encouraging promise for managing the complex nature of illnesses and is characterized by holistic philosophy and substantial experimentation in multicomponent therapies (45–47). One distinctive feature of traditional medicine is the use of herbal formulas (48). By comprehending the combined nature of herbal formulations and their mechanisms of action, ancient medicines can be reengineered in this era of big data(49,50). Modern network pharmacology offers a unique opportunity to examine in a methodical way both the molecular complexity of herbal formulas and the associations that exist between herbal formulas and complex illnesses (51,52). The use of plants in conventional medicine has suggested the use of a best molecular match, which might cause a network reaction that is more reliable than a single medication (53–55). In the field of developing novel drugs, network-based approaches are becoming increasingly common research instruments. By employing natural products as the main compound accountable for medication synergism and cumulative action, they aid in the understanding of novel remedies. These methods have been shown to be effective for a range of herbal formulations utilized in conventional medicine (56–58). Network pharmacology is regarded as a cutting-edge method for identifying possible molecular targets and active chemicals in a range of herbal formulations or basic plants(59–61). This comprehensive strategy serves as a benchmark for the preliminary screening of pharmaceutical bioactive substances found in plants and a novel therapeutic idea for investigating the mechanisms of action of active molecules for the treatment of illness(62,63). Consequently, the integration of network pharmacology into conventional medicine presents distinctive and innovative approaches for identifying active ingredients, biomarkers, and scientific underpinnings of traditional medicine, which are based on intricate biological systems of the human body(64,65).

NETWORK PHARMACOLOGY ON DIABETES MELLITUS

Databases of natural products

Natural products have been important sources of lead for drug discovery, contributing to the production of approximately 64% of all pharmaceuticals(66). Natural product databases are crucial for drug discovery and screening. As a result, several databases were created to offer relevant data on natural items. Super Natural II[3](67) is a publicly accessible database that contains more than 326,000 natural goods and incorporates several search features. Approximately 170,000 chemicals were included in the database, which also included detailed information about the items, such as their two-dimensional structures, associated structural and physicochemical attributes, anticipated toxicity class, and vendor information. One of the source databases used was NAPRALERT (68). The database gathered information about natural items by using textual numeric data. Approximately 105,000 organism names, 195,000 pharmacological data points, and 190,000 identified chemicals were gathered. Additionally, this approach offered a method for accurately identifying the source of potential biological processes. Another publicly accessible lexicon centered on biological entities was Chemical Entities of Biological Interest (ChEBI)[4](69), which focuses on tiny chemical components found in both manmade and natural items. More than 12,000 molecular entities, classes, and groupings were represented in the database. The ChEBI ID, ChEBI name, definition, structural diagram, formula, synonym, and registration number were among the crucial details that were supplied. DrugBank is an enhanced drug database (70). Approximately, 1,467 FDA-approved medications were among the approximately 4,900 drug listings that the 2.0 edition of DrugBank offered. Furthermore, the database had shared connections with almost all major bioinformatics and biological databases, including PubChem, GenBank and PubMed. Additional natural product-related databases were also created, including the UPND (Universal Natural Products Database) (71), PubChem (72), the Chinese Natural Product Database (CNPD) (73), the Dictionary of Natural Products (DNPs)[5], the CHDD (74), the Herb BioMap database (China Copyright of Computer Software, 2011SR076502), the Traditional Chinese Medicines Database (TCMD)(75), and ChemBank(76).

For research including virtual screening and the identification of novel substances from naturally occurring chemicals, any of the databases can be helpful. The details regarding the buildings and the study of physicochemical qualities are beneficial and may aid in the creation of new drugs.

[3]http://bioinformatics.charite.de/supernatural

[4]http://dnp.chemnetbase.com/

[5]http://dnp.chemnetbase.com/

Natural remedies for dm treatment

Natural ingredients have long been used to treat diabetes mellitus, particularly in Asia, India, and Africa. Numerous investigations have been conducted with an emphasis on herbal remedies for the development

of diabetes medication. The hypoglycaemic effects of numerous extract types and bioactive ingredients have been investigated.

Extract

Worldwide, prescriptions for the treatment of diabetes have been heavily reliant on extracts from natural items. A few of them underwent rigorous, scientific evaluation to determine their characteristics (77). Traditionally, many plant extracts have been utilized to treat diabetes. In a long-term research, diabetic rats were given an aqueous extract of *Annona muricata* daily or for 28 days which resulted in a reduction in blood sugar and serum creatinine levels as well as decreased malondialdehyde (MDA), aspartate transaminase (AST), alanine transaminase (ALT) activity, and nitrite levels of low-density lipoprotein cholesterol (LDL-C) (78). According to Khanra et al.(79), leaf extract from *Abroma augusta* L. (*Malvaceae*) may be used as a preventive measure against type 2 diabetes and the renal and heart damage it causes. By modifying PPARα/SREBP-1, chicory seed extract was able to target hyperglycaemia, hyperlipidaemia, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). According to Ziamajidi et al. (80). Other extracts, such as the flavonoid-rich extract from Sophora tonkinensis Gagnep(81), the extracts from grape seeds and skin(82), and the Hypericum perforatum extract (83) have also been employed for DM therapy. Thus, the use of herbal extracts for T2DM therapy at a systematic level is possible.

Polysaccharides

One of the primary constituents of natural sources is polysaccharides, which are composed of more than ten monomeric sugar units joined by glycosidic linkages. Primary bioactive polysaccharides, which are portions of natural products, have garnered increased interest recently (84). Polysaccharides derived from natural sources were used to treat diabetes mellitus between 2010 and 2016, as **Table 1** illustrates. Earlier (2015) reported that tea polysaccharides (TPSs) increase body weight and reduce blood glucose levels. The TG (Triglyceride) and HDL-c levels returned to nearly normal, whereas the TC (Total Cholesterol) and LDL-c levels were reduced. Additionally, by upregulating the expression of the GLUT4 target protein, p-Akt, and PI3K target protein in the PI3K/Akt signalling pathway, TPS may play an efficient role in low blood sugar. TPS was suggested to be a potentially effective therapeutic option for T2DM(85). By upregulating both mRNA transcription and the production of the PDX1 protein, a water-loving TPS increased insulin release which was imitated by glucose through the cAMP-PKA pathway(86).The antidiabetic properties of corn silk polysaccharides (POCS) were tested in rats with diabetes caused by streptozocin (STZ). According to Zhao W. et al.(87), these findings demonstrated that POCS might considerably lower blood glucose levels, total cholesterol (TC) and total triglycerides (TG) levels. It has been observed that mulberry leaf polysaccharides successfully restore normal levels of IR and hepatic glucose metabolism. Preventing polysaccharides was shown to be a preventive measure for type 2 diabetes by expressing protein-tyrosine phosphatase 1B, triggering the PI3K/AKT signalling pathway, and reducing oxidative stress(88). Furthermore, polysaccharides from *Cynomorium songaricum* (89)and *Lachnum calyculiforme* (90) have shown clear hypoglycaemic effects. Several signalling pathways can be targeted by polysaccharides to treat diabetes mellitus.

Polyphenols

Table 2 highlights the antidiabetic polyphenols that were derived from natural sources between 2010 and 2016. The flavour and color of fruit, as well as other plant-based products, are mostly attributed to polyphenols, which are secondary metabolites of plants. According to Quideau et al.(91), these compounds may be found in a variety of natural drinks such as red wines, tea, and chocolate, as well as fresh fruits and vegetables. The polyphenol categories used in DM therapy were evaluated by Solayman et al.(92) These categories included anthocyanin, ellagitannin, luteolin, rosmarinic acids, catechin, resberatrol, rutin, quercetin, diosimin, and myricetin.

Anthocyanins and polyphenols from the black soybean seed coat were shown to enhance insulin sensitivity and hyperglycaemia by modulating the AMPK signalling pathway both in vivo and in vitro. Procyanidins (PCs) and cyanidin 3-glucoside (C3G) are the primary antidiabetic polyphenols that also improve glucose absorption (93). According to previous reports, Vernonia amygdalina polyphenols have antihyperglycemic properties. These effects are most likely caused by GLUT4 translocation inhibition and hepatic G6Pase inhibition (94). One kind of green tea polyphenol EGCG may aid in liver and skeletal muscle metabolic IR and endothelial dysfunction. Furthermore, EGCG might decrease IR, boost insulin-induced glucose secretion, and lessen β-cell death in db/db animals(95).

Other constituents

In addition to polysaccharides and polyphenols, various components of natural products have been linked to the prevention of DM. The natural ingredients for DM management, including terpenoids, tannins,

saponins, alkaloids, and lignans(96–98), have been described in a number of publications. For many years, DM has been treated using traditional herbal treatments. This category includes investigations on antidiabetic drugs conducted between 2010 and 2016. The structure-activity connection suggests that the mechanisms of action of natural items differ significantly from those of the antidiabetic medications used today. Natural products may be a viable source of novel DM treatments with several targets and components.

APPLICATION OF NETWORK PHARMACOLOGY

The sharp decline in new treatment alternatives begs the question of whether drug discovery focusing on single-targets is a successful approach, even with the continuous research efforts of the pharmaceutical industry. Network pharmacology offers a different perspective than traditional drug development methods and allows discussions on how drugs can specifically target proteins or networks involved in diseases(99). Furthermore, use of bioinformatics methods in combination with high-throughput screening plays a crucial role. These tools help create models that link drugs, targets, and disease networks. By comparing how a drug interacts with its specific target model, researchers can explore the basic mechanisms through which drugs affect biological networks. Recently, advancements in network biology have greatly improved our understanding of complex connections within these systems. As a result, network pharmacology (NP) is becoming increasingly relevant in treating severe diseases and conditions. This approach uncovers the connections between proteins that correlate with clinical outcomes for particular ailments. Currently, scientists are leveraging computer technology and multiomics techniques to better capture the integrated metabolic responses of humans. This effort helps them explore a growing variety of intricate illnesses. Below, we will discuss some specific applications of network pharmacology within biology. Key applications of network pharmacology are given in **Table 3**.

Table-1. Polysaccharides used in the management of DM.

Class	Origin	Effect and Mechanism	Reference
Plant	*Astragalus membranaceus*	Increasing insulin responsiveness; lowering the expression of myostatin; and inhibiting the ROS-ERK/NF-κB pathway	(100)
	Liriope spicata	Enhancing the PPARγ protein expression, enhancing the PI3K signalling pathway, and enhancing glucose metabolism	(101)
	Lycium barbarum	Lowering the postprandial blood glucose level and delaying the absorption of carbohydrates	(102)
	Ophiopogon japonucus	Controlling the GSK-3, Glut-4, InsR/IRS-1/PI3K/Akt signalling pathway	(103)
	Cucurbita moschata	Lowering TG, TC, LDL, and cholesterol levels while raising fecal fat and HDL values	(104)
	Panax ginseng	Reducing oxidative damage and promoting higher insulin secretion	(105)
Mushroom	*Ganoderma Lucidum*	Upregulating mRNA transcripts of Bcl-2 and PDX-1; downregulating those of Bax, iNOS, and Casp-3	(106)
	Ganoderma atrum	Activating PI3K/Akt/Enos signal pathway	(107)
	Grifola frondosa	Enhancing glucose metabolism and controlling the Akt/GSK-3 signalling pathway	(108)
Seaweed	*Enteromorpha prolifera*	Controlling the GLUT-4, GCK, APN, and InsR mRNA levels in adipose and hepatic tissue	(109)
Bacterial	*Trametes gibbosa*	Lowering the LDL-C levels TG, TC, and BG; increasing HDL-C levels	(110)
Anima	*Misgurnus anguillicaudatus*	Boosting PEPCK mRNA expression, lowering glycogen levels, and raising insulin levels	(111)

Table-2. Polyphenols used in the management of DM.

Origin	Effect & Mechanism	Reference
Ecklonia cava	Enhancing the management of blood sugar; controlling the hepatic glucose metabolism; and increasing Akt protein	(112)
Folium Mor	Increasing Glut-4IRS-1/PI3K/Glut-4 signalling pathway and IRS-1 of PI3K-p85α mRNA and protein expression	(113)
Litchi chinensis Sonn	Enhancing lipid metabolism, enhancing insulin resistance and glucose tolerance, and raising NF-κB and Bax mRNA levels	(114)
Corchorus olitorius	Inhibit α-amylase and α-glucosidase; strong antioxidant potential	(115)
Theobroma cacao L.	Modulating the MAPK signalling pathway to improve glucose absorption, adiponectin secretion, and insulin sensitivity	(116)
Grape seed	Regulating MFG-E8, IL-1β and NLRP3	(117)
Curcuma longa	Reducing the SphK1-S1P signalling pathway's activation	(118)

Table-3. Applications of Network Pharmacology.

Pharmacology	● **To create fresh leads from natural products** ● **Recognizing the way that medications work** ● **Identifying potential medication adverse effects** ● **Forecasting new symptoms** ● **Predicting toxicity** ● **Estimating potential interactions between drugs** ● **Rational design of medications based on a collection of interrelated proteins** ● **Utilizing drug for other purposes**
Traditional Medicine	● Scientific evidence in favor of Ayurvedic medication ● Recognizing the reasoning behind conventional compositions ● Recognizing the way in which Ayurvedic medications work ● Safety and effectiveness of Ayurvedic medication ● Potential replacements for threatened plant species ● Network-oriented designing and formulating plant prescription ● Examining the synergistic effect of several bioactives ● Botanical indicators to ensure quality
Drug Research	● Finding novel targets for drugs ● Decreased time and expenses through virtual testing ● Knowing the signaling pathways associated with various diseases ● Designing experiments based on drugs and targets ● Treatments for illnesses depending on many genes ● Identification of the genes responsible for illness ● Diagnostic biomarkers ● Investigating antibiotic or medication resistance

CONCLUSION

This work highlights the significance of network pharmacology in enhancing the understanding of diabetes management, particularly through the exploration of natural compounds. By using multi-target method in conjugation with NPs, we can identify key bioactive elements such as polysaccharides and polyphenols, that potentially have therapeutic effects on diabetes, such as improving glucose regulation and insulin sensitivity. Combining traditional medicine with modern healthcare strategies via NPs not only provides new perspectives for drug discovery but also leads to safer, more effective and sustainable

diabetes treatments. Network pharmacology can connect ancient wisdom with current biomedical research and is an exciting pathway that could offer innovative solutions for tackling this global health challenge.

FUTURE DIRECTION

Future research in network pharmacology should focus on integrating advanced computational models and multi-omics approaches to better understand the mechanisms of diabetes mellitus and related diseases. The application of machine learning and artificial intelligence can enhance the analysis of large-scale datasets, aiding in the prediction of therapeutic targets and drug interactions. Collaboration between traditional medicine practitioners and modern biomedical researchers is essential to translate network pharmacology findings into clinically viable therapies. This synergy can lead to innovative strategies that address the complexities of diabetes management. Furthermore, broadening the application of network pharmacology to other chronic diseases will highlight its potential in drug discovery, ultimately contributing to the development of safer and more effective treatment options.

AUTHOR CONTRIBUTIONS

Dr. Snigdha Das Mandal conceptualized the study and provided supervision. Prasan Das conducted the literature review and drafted the manuscript. S.P. Nayak contributed to the data analysis and interpretation. Kinjal Patel assisted in manuscript revision. All the authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

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