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NETWORK PHARMACOLOGY APPROACH TO STUDY POLY HERBAL FORMULATIONS IN DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (OM) is one of the most prominent metabolic disorders globally. exerting a massive burden on healthcare systems. While conventional single-target synthetic drugs are prevalent, they often present adverse side effects and loss of efficacy over time. Traditional medicine systems, particularly Ayurveda, have long utilized polyherbal formulations (PHFs) to manage complex diseases like diabetes. PHFs operate on the principle of synergy, where multiple phytoconstituents target varied physiological pathways concurrently. However, standardizing and validating the mechanistic actions of these complex mixtures using classical pharmacological methods has been exceedingly difficult. Network pharmacology. an emerging interdisciplinary field combining systems biology, bioinformatics, and computational pharmacology, provides a transfor- mative approach to deciphering the multi-component, multi-target, and multi- pathway mechanisms of PHFs. This comprehensive review and project report details the application of network pharmacology in investigating anti-diabetic polyherbal formulations. It outlines the complete methodology-from compound screening and target prediction to network construction and pathway enrichment analysis.

1 INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic condition characterized by per- sistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both [31. 20). With the global prevalence of diabetes reaching epidemic pro- portions, the long-term microvascular and macrovascular complications-such as nephropathy, neuropathy, retinopathy, and cardiovascular diseases-pose severe challenges to patients and healthcare

systerns worldwide. The current conventional pharmacotherapy for Type 2 Diabetes Mellitus (T2DM) includes sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, and DPP-4 inhibitors [21]. While effective in acute glycemic control, prolonged use of these single-target synthetic agents is frequently associated with undesirable side effects, including hypoglycemia, weight gain, gastrointestinal disturbances, and hepatic toxicity. Furthermore, drug resistance and declining beta-cell function often require patients to transition to insulin therapy or combination therapies, highlighting the limitations of the traditional "one-drug, one-target" discovery paradigm [1]. In contrast to conventional monotherapy, traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani have utilized Poly- herbal Formulations (PHFs) for centuries [22]. PHFs combine multiple medicinal plants. leveraging the inherent synergy among their diverse phytochemicals to achieve enhanced therapeutic efficacy with minimized toxicity. This multi component approach aligns perfectly with the complex, multifactorial pathophysiology of diabetes, as the combined phytochemicals can simultaneously modulate multiple targets across various metabolic pathways. Despite their clinical success in traditional settings, the global acceptance of PHFs has been hindered by a lack of rigorous scientific validation regarding their molecular mechanisms of action. Evaluating a complex mixture containing hun dreds of chemical compounds using classical reductionist pharmacological methods is virtually impossible. This bottleneck has necessitated a paradigm shift towards systems biology and computational techniques. Network pharmacology, first conceptualized by Andrew L. Hopkins in 2007 [1], has emerged as a revolutionary tool to address this challenge. It updates the drug discovery framework from a "one-target, one-drug approach to a "network-target, multiple-component strategy 2]. By integrating bioinformatics, chem- informatics, and network biology, network pharmacology enables researchers to systematically construct and analyze complex interactions between the multiple active compounds of a PHF, their corresponding human gene targets, and the interconnected disease pathways [3]. This report explores the systematic application of network pharmacology in validating the efficacy and deciphering the complex molecular mechanisms of poly- herbal formulations in the management of diabetes. It details the step-by-step computational methodology, major computational tools and databases, and pro- vides in-depth case studies on prominent anti-diabetic herbs.

2 Pathophysiologyof Diabetes Mellitusandthe Need for Multi-Target Therapy

2.1 The Multifactorial Nature of Diabetes Type 2 Diabetes Mellitus (T2DM) constitutes over 90% of all diabetes cases. Its pathophysiology is highly complex, extending far beyond simple insulin deficiency. It is fundamentally characterized by peripheral insulin resistance-where cells in muscle, fat, and liver fail to respond adequatety to insulin-and a progressive decline in pancreatic beta-cell function (32) Over time, researchers have identified several concurrent pathophysiological defects contributing to T2DM, famously termed the "Ominous Octet" by DeFronzo 33 . These include: 1. Decreased insulin secretion by pancreatic beta cells. 2. Decreased incretin effect in the gastrointestinal tract. 3. Increased lipolysis in adipocytes. 4. Increased glucose reabsorption in the kidneys. 5. Decreased glucose uptake by peripheral muscles. 6. Neurotransmitter dysfunction in the brain. 7. Increased hepatic glucose production. 8. Increased glucagon secretion by pancreatic alpha cells. 2.2 Limitations of Monotherapy Given this multifactorial etiology, treating T2DM by intervening at a single molec ular target (e.g.. stimulating insulin release via sulfonylureas) is inherently limited. The human body is a robust biological network, and perturbations at a single node are often compensated by alternative pathways, leading to drug resistance over time. A multi-target approach is essential to address the multiple underly ing defects simultaneously. This requirement naturally aligns with the philosophy of polyherbal medicine, where multiple compounds target different nodes in the disease network [5].

3 Polyherbal Formulations (PHFs) in Traditional Medicine

3.1 The Principle of Synergy The foundational principle of PHFs is pharmacological synergy. Synergy occurs when the combined therapeutic effect of two or more compounds is greater than the sum of their individual effects. In Ayurvedic medicine, formulations are meticulously designed to include primary therapeutic herbs alongside complementary herbs that enhance-bloavailability, reduce toxicity, or target secondary complica- tions [23]. 3.2 AdvantagesofPHFsin Diabetes 1. Multi-target Action: The diverse phytochemicals (flavonoids, alkaloids, saponins, tannins) interact with multiple receptors, enzymes, and ion channels concurrently. 2. Fewer Side Effects: Because each active constituent is present in a relatively low concentration, the risk of target-specific toxicity is minimized. 3. Management of Complications: PHFs often contain antioxidant and anti- inflammatory compounds that do not just lower blood sugar but also protect against diabetic nephropathy and neuropathy [24]. Traditional formulations like Triphala, Balarishta, and modern equivalents like Diabecon represent standard examples of combining herbs to achieve superior anti- diabetic activity,

4 Introduction to Network Pharmacology

Network pharmacology is rooted in the concepts of systems biology and polyphar- macology. It uses computational techniques to map the complex interactions be- tween drugs, targets, and diseases in a network format, usually represented as graphs with nodes (representing compounds, genes, or diseases) and edges (repre- senting interactions) [34]. 4.1 Core Concepts 1. Polypharmacology: The realization that many effective drugs act not on a single target, but on multiple targets [11]. 2. Network Robustness: Biological networks are scale-free and robust. Attacking a single central node might cause toxicity, while gently modulating several interconnected peripheral nodes can restore the network to a healthy state without severe side effects [8 . 3. Drug Repurposing: Finding new targets for existing herbal compounds. 4.2 Applicationin Herbal Medicine Herbal medicines are natural combinatorial chemical libraries. Network phar- macology allows us to filter these libraries, identify the most "druggable" active compounds, predict their human targets, and understand how they alter diabetic pathways 16). This scientific translation bridge is vital for modernizing traditional medicine.

5 Methodology of Network Pharmacology for Poly- herbal Formulations

The standard workflow of a network pharmacology study for a polyherbal formula- tion involves several rigorous computational steps, integrating data from multiple specialized databases [4]. 5.1 Step 1: Chemical Constituent Database Construction The first step is retrieving all known chemical constituents of the plants in the formulation. This is achieved using specialized botanical and chemical databases. -TCMSP (Traditional Chinese Medicine Systems Pharmacology): A major database for herbal compounds, providing comprehensive ADME properties [12]. -IMPPAT (Indian Medicinal Plants, Phytochemistry And Thera-peutics): A curated database specifically for Indian medicinal plants. PubChem & ChemSpider: Used for obtaining 2D/3D chemical struc- tures and canonical SMILES strings. 5.2 Step 2: ADME Screening (Oral Bioavailability and Drug-likeness) Not all plant compounds can be absorbed by the human body. To filter out inactive compounds, in silico ADME (Absorption, Distribution, Metabolism, and Excretion) screening is performed 18). The two most critical parameters are: - Oral Bioavailability (08): Usually, compounds with OB 230% are se lected. Drug-Likeness (DL): Evaluates structural similarity to existing drugs. Compounds with DL 2 0.18 are typically retained. Tools like SwissADME and the TCMSP server are extensively utilized for this screening phase. 5.3 Step 3: Target Prediction (Target Fishing) Once the active compounds are identified, their potential human protein targets must

be predicted. This is achieved through pharmacophore mapping, molecular similarity searches, and machine learning models. Swiss TargetPrediction: Predicts targets based on a combination of 20 and 30 similarity with known ligands [19]. SEA (Similarity Ensemble Approach): Uses chemoinformatics to relate proteins based on the set-wise chemical similarity among their ligands. TargetNet & STITCH: Databases connecting chemicals to biological tar- gets. 5.4 Step 4: Disease Target Acquisition Simultaneously, genes associated with Diabetes Mellitus are collected from clinical and genetic databases: -GeneCards: A comprehensive database of human genes associated with diseases. OMIM (Online Mendelian Inheritance in Man): Catalog of human genes and genetic disorders. -DisGeNET: Platform integrating gene-disease associations. The intersection of the "Compound-Target genes" and "Diabetes-associated genes" yields the Common Target Genes, representing the potential therapeutic targets of the PHF. 5.5 Step 5: Protein-Protein Interaction (PPI) Network Construction Proteins do not act in isolation; they interact in complex networks. The common target genes are mapped onto a PPI database, most commonly STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) (14). The resulting PPI network is visualized using Cytoscape [13]. 5.6 Step 6: Network Topological Analysis Cytoscape plugins like NetworkAnalyzer or CytoNCA are used to identify the "hub" genes-the most critical targets in the network, Metrics include: Degree Centrality: The number of direct connections a node has. Betweenness Centrality: The number of shortest paths passing through a node. Closeness Contrality: How close a node is to all other nodes in the net- work. 5.7 Step 7: Gene Ontology (GO) and KEGG Pathway En- richment Analysis To understand the biological meaning behind the hub genes, enrichment analysis is performed using tools like DAVID or Cytoscape's ClueGO (15). GO Analysis: Categonzes targets into Biological Processes (BP), Cellular Components (CC), and Molecular Functions (MF) (16). KEGG Analysis: Maps targets to specific metabolic and signaling path- ways (Kyoto Encyclopedia of Genes and Genomes) [1.7].

6 Major Signaling Pathways Implicated in Diabetes Management

Network pharmacology studies consistently reveal that anti-diabetic polyherbal formulations modulate multiple highly conserved signaling pathways [7]. The most prominent pathways identified through KEGG enrichment include: 6.1 1. PI3K/Akt Signaling Pathway The Phosphoinositide 3-kinase (PI3K)/Protein Kinase B (Akt) pathway is central to insulin signaling. Upon insulin receptor activation. PI3K phosphorylates PIP2 to PIP3, activating Akt. Activated Akt stimulates the translocation of GLUT4 transporters to the cell membrane,

facilitating glucose uptake into muscle and adipose tissues. Impairment of this pathway is a hallmark of insulin resistance. Polyherbal compounds like curcumin and quercetin heavily target nodes in this pathway to restore insulin sensitivity [9]. 6.2 2. AMPK Signaling Pathway AMP-activated protein kinase (AMPK) is a critical cellular energy sensor. Activation of AMPK stimulates glucose uptake, fatty acid oxidation, and mitochondrial biogenesis, while inhibiting gluconeogenesis in the liver. Many herbal compounds. such as berberine (from Coptis chinensis) and charantin (from Momordica cha rantia), act as potent AMPK activators, mimicking the effects of exercise and metformin [10] 6.3 3. AGE-RAGE Signaling Pathway in Diabetic Com- plications Advanced Glycation End-products (AGEs) form due to chronic hyperglycemia. Their interaction with the Receptor for AGES (RAGE) triggers a cascade of ox idative stress and inflammation, leading to diabetic nephropathy and retinopathy. Network analysis frequently identifies the AGE-RAGE pathway as a key target for the protective effects of antioxidant-rich polyherbal formulations. 6.4 4. TNF and NF-KB Inflammatory Pathways Chronic low-grade inflammation is a major driver of insulin resistance. Adipose tissue in diabetic patients secretes pro-inflammatory cytokines like TNF-a and IL-6. which activate the NF-KB pathway, leading to serine phosphorylation of the Insulin Receptor Substrate (IRS-1) and blunting insulin signaling.

7 Key Medicinal Plants in Polyherbal Formulations: A Network Perspective

This section explores the specific plants commonly used in antidiabetic formula- tions, their active compounds, and network targets [25, 26). 7.1 Momordica charantia (Bitter Melon) Active Compounds: Charantin, Vicine, Polypeptide-p (plant insulin), Momordicin. Network Targets: AMPK. PESK AKTI. INSR (Insulin Receptor). Mechanism: Network pharmacology studies show that M. charantia exerts a multi-target effect by simultaneously activating AMPK to suppress hepatic gluconeogenesis and enhancing PI3K/Akt signaling to promote peripheral glucose uptake. Polypeptide-p directly interacts with insulin receptors [28 . 7.2 Gymnema sylvestre (Gudmar) Active Compounds: Gymnemic acids, Gymnemasaponins. Network Targets: GLP-1R, KCN311 (ATP-sensitive potassium channel), CASP3. Mechanism: Known as the "sugar destroyer," it acts on the pancreas to stimulate insulin secretion by interacting with ATP-sensitive potassium channels. Network analysis also reveals its role in preventing beta-cell apoptosis via caspase-3 inhibi tion and promoting beta-cell regeneration 27] 7.3 Trigonella foenum-graecum (Fenugreek) Active Compounds: Trigonelline, Diosgenin, 4-Hydroxyisoleucine. Network Targets: PPAR-Y. IRS1, TNF. Mechanism: The soluble dietary fiber delays carbohydrate absorption. Com- putationally,

diosgenin is identified as potent agonist of PPAR similar to thiazolidinediones, enhancing insulin sensitivity in peripheral tissues without the severe side effects associated with synthetic PPAR-y agonists [29 . 7.4 Syzygium cumini (Jamun) Active Compounds: Jamboline, Ellagic acid, Quercetin. Network Targets: Alpha-glucosidase, Alpha-amylase, AKT1. Mechanism: Its primary network action involves the inhibition of carbohydrate-digesting enzymes in the gut, thereby reducing postprandial hyperglycemia. It also exhibits strong free-radical scavenging activity, mitigating oxidative stress associated with diabetes [30]. 7.5 Tinospora cordifolia (Giloy) Active Compounds: Berberine, Tinosporin, Magnoflorine. Network Targets: IL-6. TNF- , NF-KB. Mechanism: It acts predominantly as an immunomodulator and anti-inflammatory agent. By targeting the TNF and NF-KB pathways, it reduces systemic inflamma- tion. thereby indirectly alleviating insulin resistance in skeletal muscle and adipose tissue. 7.6 Curcuma longa (Turmeric) Active Compounds: Curcumin, Demethoxycurcumin. Network Targets: STAT3, MAPK, PPAR-Y. NOS2. Mechanism: Curcumin is one of the most widely studied pleiotropic compounds. Network pharmacology highlights its massive target profile, spanning metabolic regulation (PPAR-Y) and profound anti-inflammatory/antioxidant effects (MAPK. STAT3), making it vital in managing diabetic complications.

8 Extended Case Study: Network Pharmacol- ogy of a Composite Polyherbal Formulation

To understand the practical application, consider a hypothetical composite for- mulation consisting of Gymnema sylvestre, Momordica charantia, and Tinospora cordifolia. 8.1 Compound-TargetNetwork When the active constituents of these three herbs are pooled, an extensive compound- target network is formed. A typical network analysis might reveal over 50 active compounds mapping to 150 unique target genes related to diabetes. Network topology will show that flavonoids (like Quercetin and Kaempferol), common across many plants, occupy the highest degree nodes, acting as universal hubs. 8.2 Synergistic Mechanisms The combination of these herbs ensures that different pathophysiological axes of diabetes are addressed simultaneously: 1. Secretagogue Action: G. sylvestre stimulates insulin release. 2. Sensitizing Action: M. charantia enhances peripheral sensitivity and ac- tivates AMPK. 3. Protective Action: T. cordifolia suppresses the inflammatory cytokines that induce insulin resistance. This tripartite action computationally validates the traditional rationale behind combining these specific herbs.

9 Challenges and Limitations of Network Pharmacology

While network pharmacology has revolutionized herbal medicine research, several limitations must be acknowledged: 1. Data Dependency and Quality: The accuracy of the network is heavily dependent on the completeness and reliability of public databases. False positives in PPI networks or target predictions can skew results. 2. Dose and Concentration Ignorance: Current static network models of- ten fail to account for the concentration of the active compound reaching the target tissue. A compound might show an interaction in silico, but its bioavailability in vivo might be negligible. 3. Lack of Pharmacodynamic Synergy Modeling: While network phar macology identifies shared targets, quantifying true pharmacological synergy (eg., using isobologram analysis) computationally remains difficult. 4. Need for Experimental Validation: Network pharmacology generates hypotheses. These must invariably be validated using in vitro (e.g.. cell lines. Westem blotting, RT-qPCR) and in vivo (e.g., streptozotocin-induced diabetic rat models) experimental data.

10 Future Perspectives

The future of studying polyherbal formulations in diabetes lies in the integration of multi-omics data. Integration with Transcriptomics: Combining network pharmacology with RNA-seq data from diabetic patients treated with PHFs will provide dy- namic insights into gene expression changes, moving beyond static database mappings. - Artificial Intelligence and Machine Learning: Advanced deep learn- ing models (e.g., Graph Neural Networks) will improve target prediction accuracy and effectively model complex drug-drug interactions within the body. - Gut Microbiota Interactions: Many herbal compounds are metabolized by the gut microbiame before absorption. Future network models must in- corporate microbiome-herb interactions, which play a crucial role in diabetes metab olism.

11 CONCLUSION

The integration of polyherbal formulations into modern antidiabetic regimens holds immense promise due to their multi-target synergistic effects and superior safety profiles. Network pharmacology provides an elegant, systematic, and com prehensive methodology to demystify these complex botanical mixtures. By map- ping the intricate webs of active compounds, target genes, and signaling pathways (such as PI3K/Akt. AMPK, and AGE-RAGE), network pharmacology successfully bridges the gap between traditional Ayurvedic wisdom and modern molecular bi- ology. As computational tools evolve and integrate with experimental omics data network pharmacology will undoubtedly accelerate the discovery

and standardiza- tion of novel, highly effective polyherbal therapeutics for the holistic management of Diabetes Mellitus.

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