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"NETWORK PHARMACOLOGY-GUIDED DISCOVERY OF HERBAL ANTIDIABETIC AGENTS"

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and associated complications, necessitating the development of safer and more effective therapeutic strategies. Herbal medicines have gained considerable attention due to their multi-target actions, better safety profile, and long-standing traditional use. Network pharmacology, an emerging systems-level approach, integrates pharmacology, bioinformatics, and systems biology to elucidate the complex interactions between bioactive compounds, molecular targets, and disease pathways. In the present study, a network pharmacology-guided approach was employed to identify and analyze potential herbal anti-diabetic agents. Active phytoconstituents from selected medicinal plants were screened based on pharmacokinetic parameters, followed by target prediction and pathway enrichment analysis. Protein–protein interaction networks and compound–target–pathway networks were constructed to understand the underlying mechanisms of action. The analysis revealed that the identified phytoconstituents modulate key diabetes-related targets involved in insulin resistance, glucose metabolism, inflammation, and oxidative stress. These findings highlight the multi-component and multi-target nature of herbal anti-diabetic agents and provide a scientific basis for their therapeutic potential. Network pharmacology thus serves as a powerful tool for the systematic discovery and validation of herbal medicines in diabetes management.

Keywords: Diabetes mellitus, Network pharmacology, Neuroactive ligand-receptor interaction, Tembetarine, Tinospora cordifolia

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder due to insulin insensitivity/insulin resistance; modern pharmacotherapy utilizes synthetic oral hypoglycemic agents [1]. Although these molecules are effective in the management of elevated blood glucose level, they are not free from numerous side effects like genital mycosis, pancreatitis, ketoacidosis, nausea, vomiting, fractures, and neuropathy risk. GLP-1 agonists (p), like liraglutide, dulaglutide, and exenatide are contraindicated in multiple endocrine neoplasia (MEN) type 2 due to high risk of C cell tumor in thyroid and pancreatitis [2]. Further, T2DM is a polygenic condition; includes the collaborative task of multifarious pathogenic genes forming a labyrinthine dis ease network within the biological system [3]. Hence, blocking the task of one protein could trigger another pathway to earn the same response within the disease net work. This could be due to the collaborative function of multiple genes in a synergistic pattern to achieve a particular response.

The current synthetic oral hypoglycemic agents target a specific protein [2]; however, it is to be understood that a single drug can regulate multiple proteins as a "single master key unlocks multiple locks" [4], which could be dose-dependent i.e. minimization of dose may not achieve the desired pharmacological response and a higher dose may lead to adverse effects. Hence, for the management of complex disease like diabetes, it may not be advisable to target a single protein molecule; instead, target the multiple proteins with a low dose of multiple compounds and achieve the synergistic effect. Herbal medicines are reported to manage the diabetic condition followed by its symptomatic relief, also prevent the prob able complications; via the regeneration of beta-cells, minimization of insulin resistance [5] and lowering the elevated blood glucose level by restoring the liver glycogen level [6]. Multiple herbal medicines and their preparations have been reported to possess the anti-diabetic activity [7]. Further, isolated compounds from traditional folk medicines have also been identified to possess the anti-diabetic activity [8]. However, folk medicine lacks sufficient scientific data in the management of complex diseases like diabetes; be short of evidence in phytoconstituents composition, mechanism of action and ADMET profile.

Tinospora cordifolia, commonly identified as heart leaved moonseed, Guduchi, belongs to the family Menis permaceae is recorded as "Guduchi (St)" in the Ayurvedic Pharmacopoeia of India; utilized in the management of "Prameha" (an ayurvedic term that explains clinical conditions involved in obesity, prediabetes, diabetes mellitus, and metabolic syndrome). Further, Ayurvedic Pharmacopeia of India records terpenoids and alkaloids as a major phytoconstituents in the management of Jvara (Fever), Kustha (Skin disorders), Pandu (Anaemia), Vatarakta (Gout) and Kamala (Jaundice) [9]. Scientific reports have been made for T. cordifolia as an anti-diabetic agent in various experimental animal models [10, 11]. However, the probable mechanism of T. cordifolia in the manage ment of diabetes has not been illuminated yet. Hence, the present study aims to identify the potential phytoconstitu ents from T. cordifolia, identify their targets involved in diabetes mellitus (DM) and report the probable mechan ism in its management via the network pharmacology approach.

METHODS

Mining of phytoconstituents and proteins involved in diabetes

Phytoconstituents of T. cordifolia were mined from the available literature; scientific journals and traditional me dicinal books. The database was constructed for the phytoconstituents, their types, SMILES and PubChem CID. The duplication of phytoconstituents was eliminated during the construction of the database. The canonical SMILES and PubChem CID of each phytoconstituents were retrieved from the PubChem Database [12]. SMILES were queried for the prediction of the target in BindingDB [13] at the percentage similarity of 70% with known ligand molecules. The proteins involved in diabetes were identified with reference to the known targets of diabetes reported in Therapeutic Target Database (TTD) [14]. Gene ID of each protein molecule identified as the target of diabetes mellitus was retrieved from the UniProt [15]

Druglikeness prediction and ADMET profile

Phytoconstituents were predicted for the druglikeness score via the utilization of "Lipinski's rule of five" model by using MolSoft (http://www.molsoft.com/). Similarly, admetSAR2.0 [16] was used to predict ADMET profile of individual phytoconstituents.

Prediction of side effects

ADVERpred [17] was used to predict the probable side effects by querying the SMILES of each phytoconstituent. The mol charge of the phytoconstituents was removed (if present) during the prediction of side effects. The side effects were considered if the probable activity (Pa) is higher than probable inactivity (Pi) and Pa value greater than 0.7.

Pathway and network analysis

Set of proteins involved in DM was queried in STRING [18] and gene enrichment analysis was performed to identify the pathways that are modulated by the phytoconstituents. Further, the KEGG pathway(https://www.genome.jp/ kegg/) analysis was performed to identify the pathways in volved in DM. Cytoscape [19]3.5.1wasusedtoconstruct the network between phytoconstituents, protein molecules, and identified pathways. The color and node size scale were used to interpret the whole network which is based on the number of edges (edge count). The node with the maximum number of edge count was indicated with colossal node.

Docking studies

Three-dimensional structure of tembetarine was re trieved from PubChem database and minimized using MMFF94 forcefield [20]. The target molecule beta 1 adrenergic receptor was retrieved from the RCSB (https:// www.rcsb.org/) database. Discovery Studio [21] was used to remove water molecules and heteroatoms from the protein molecule. Similarly, SWISS-MODEL [22] was used for the homology modeling of beta 1 adrenergic re ceptor by using accession number: NP_000675.1 as a query sequence and PDB ID: 4BVN as a template. Auto Dock4.0 [23] was used to predict the binding affinity of tembetarine with beta 1 adrenergic receptor. After docking, the pose scoring the lowest binding energy was chosen to visualize the ligand-protein interaction.

RESULTS

Mining of phytoconstituents and proteins involved in diabetes

Thirty-one different phytoconstituents were identified in Tinospora cordifolia from different databases and other open-source records; nine of them were predicted to modulate the diabetic protein molecules (Table 1). These phytoconstituents were identified as alkaloids, ter penes, and steroids. Similarly, the majority of the targeted diabetic protein molecules were surface proteins and enzymes (Fig. 1).

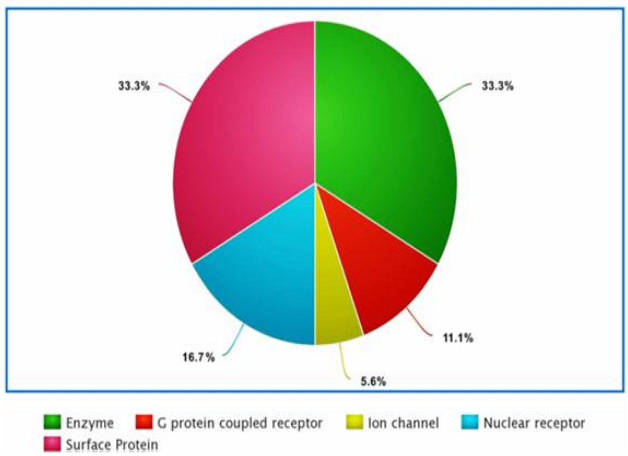


Fig. 1 Types of protein molecules involved in diabetes

Predictive side effects, ADMET profile, and druglikeness of compounds

Except for N-E-feruloyl tyramine, all the eight phytoconstituents were predicted for their probable side effects. The probability of side effects for arrhythmia, myocardial infarction, and nephrotoxicity of predicted compounds is shown in (Fig. 2). Phytochemicals were predicted for their probability for absorptivity, blood-brain barrier permeability, isoenzyme inhibitory activity, mutagenicity, plasma protein binding affinity, and fish aquatic toxicity. The ADMET profile of each phytoconstituent is represented in heat map (Fig. 3). Similarly, all nine phytoconstituents were predicted for their druglikeness score; the highest was scored by tembetarine (Table 2)

Table1Typesofcompoundsandtheirtargets

Compounds	CompoundType	PubChemCID	TargetedProteins
Tembetarine	Benzyl-iso-quinolinealkaloid	167718	HTR2A,HTR2C,ACACB,ADRB1,ADRA2C,ADRA1D,ESR1,DPP4,DRD1,DRD1B, PARP1,KCNA4
Magnoflorine	Aporphine alkaloid	73337	HTR2A,HTR2C,ADRA1D,ADRA2C,ADRB1,DRD1,DRD1B
Tinocordiside	Cadinane sesquiterpene glycoside	177384	HSD11B2,NR3C1
Tinocordifolioside	Daucane-typesesquiterpene glucoside	100926541	BACE1,ESR1,HSD11B2,HTR2A,HTR2C,NR3C1,NR3C2
MakisteroneA	Steroid	12312690	BACE1,ESR1,HSD11B2,HTR2A,HTR2C,NR3C1,NR3C2
Tetrahydropalmatine	Iso-quinolinealkaloid	72301	ACACB,ADRA1D,ADRA2C,ADRB1,DPP4,DRD1,ESR1,HTR2A,HTR2C,KCNA4, PARP1
N-E-feruloyltyramine	Alkaloid	5280537	CNR2

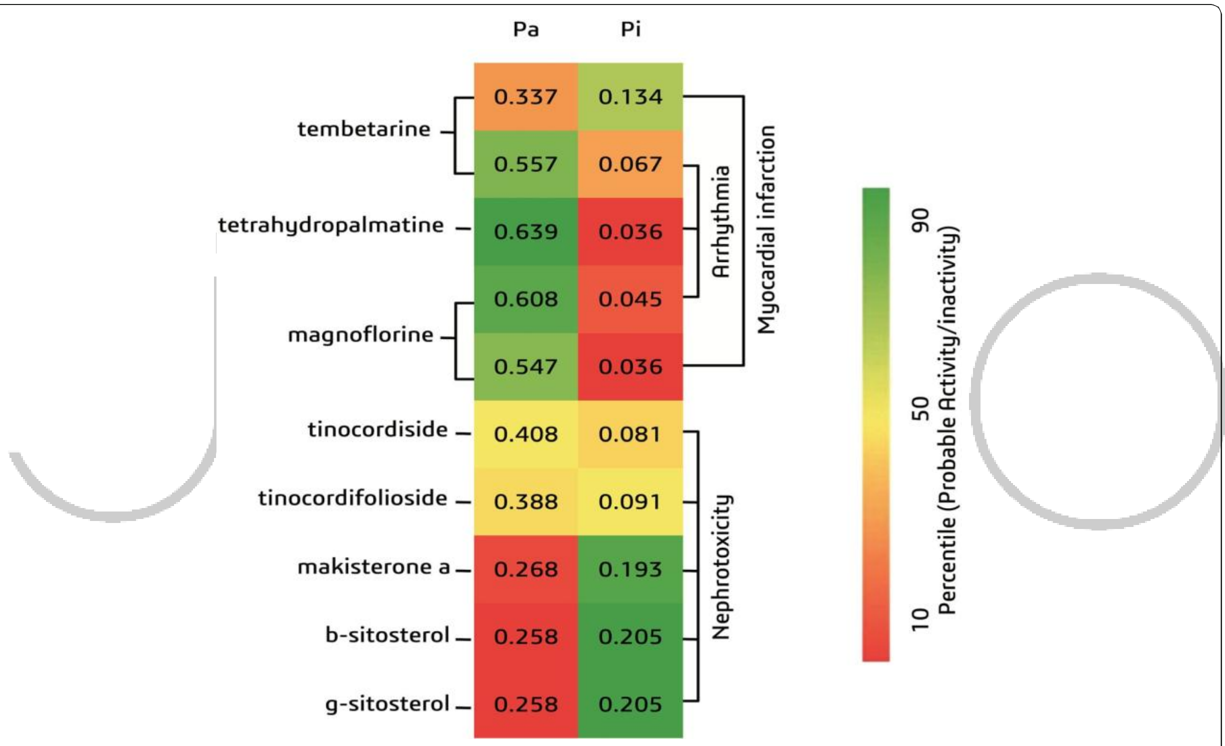
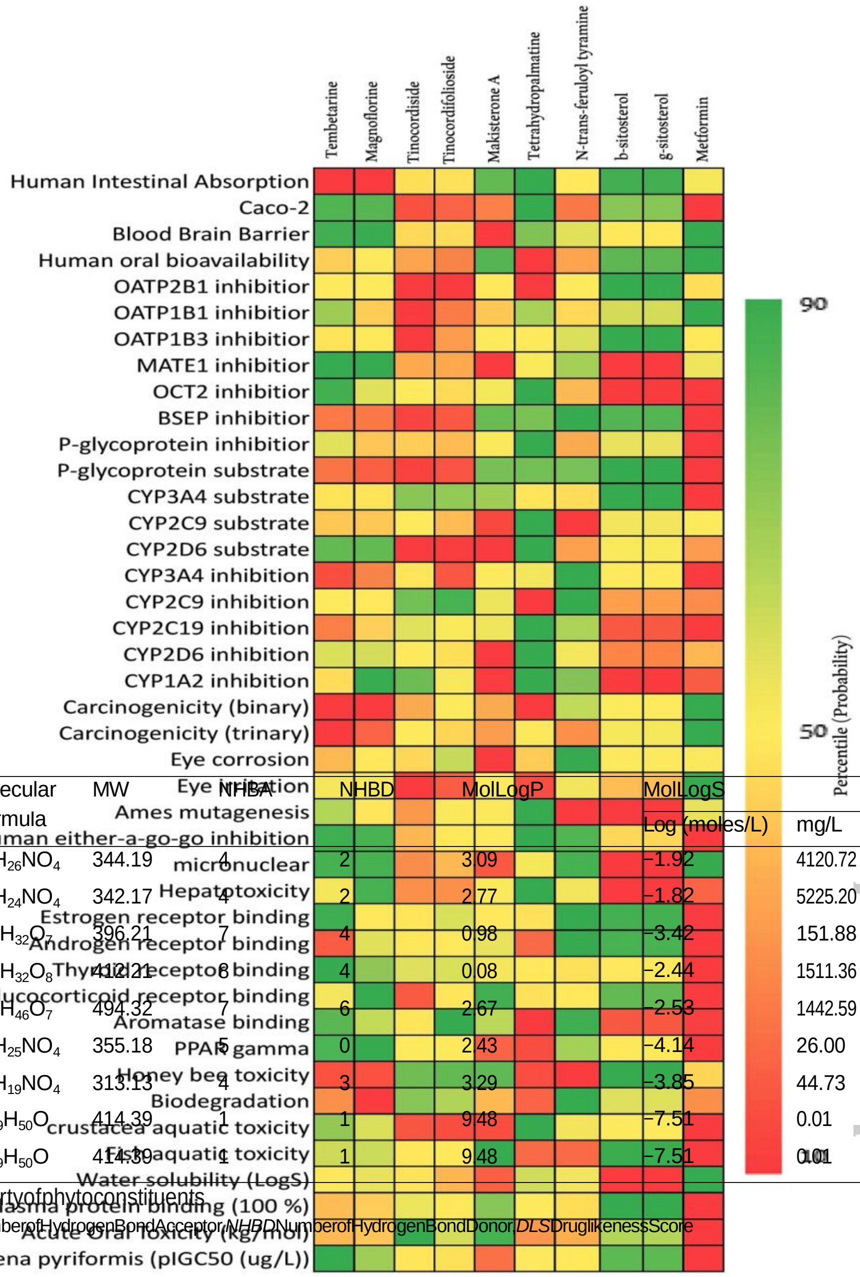


Fig.2Probablesideeffectsofphytoconstituents.Pa:Probableactivity,Pi:Probable inactivity



Phytoconstituents	Molecular formula	MW	NHBA	NHBD	MolLogP	MolLogS Log (moles/L)	mg/L	DLS
Tembetarine	$C_{20}H_{26}NO_4$	344.19	4	2	3.09	−1.92	4120.72	1.41
Magnoflorine	$C_{20}H_{24}NO_4$	342.17	4	2	2.77	−1.82	5225.20	0.8
Tinocordiside	$C_{21}H_{32}O_7$	396.21	7	4	0.98	−3.42	151.88	0.47
Tinocordifolioside	$C_{21}H_{32}O_8$	412.21	8	4	0.08	−2.44	1511.36	0.23
MakisteroneA	$C_{28}H_{46}O_7$	494.32	7	6	2.67	−2.53	1442.59	1.38
Tetrahydropalmatine	$C_{21}H_{25}NO_4$	355.18	5	0	2.43	−4.14	26.00	1.24
N-E-feruloyltyramine	$C_{18}H_{19}NO_4$	313.13	4	3	3.29	−3.85	44.73	0.24
β-sitosterol	$C_{29}H_{50}O$	414.39	1	1	9.48	−7.51	0.01	0.88
γ-sitosterol	$C_{29}H_{50}O$	414.39	1	1	9.48	−7.51	0.01	0.88

Table2Druglikenesspropertyofphytoconstituents

*MW*Molecularweight,*NHBA*NumberofHydrogenBondAcceptor,*NHBD*NumberofHydrogenBondDonor,*DLS*DruglikenessScore

Pathway and network analysis

Gene set enrichment analysis identified thirteen different pathways; modulated by proteins involved in the DM. The peer interpretation of protein interaction under the KEGG pathway analysis identified four different pathways which are directly linked in the pathogenesis of DM. Among them, neuroactive ligand-receptor interaction was identified to score the highest count of gene sets with the lowest false discovery rate (Table 3). Sixty-seven edges were identified in the drug-protein-pathway network in which fifty-two were target-phytoconstituents interactions and fifteen were target-pathway interaction. The constructed network included thirty-four nodes representing four pathways, twenty-one targets and nine phytoconstituents. Tembetarine scored highest edge count; interaction was found with twelve protein molecules i.e. ACACB, ADRA1D, ADRA2C, ADRB1, DPP4, DRD1, DRD1B, ESR1, HTR2A, HTR2C, KCNA4, and PARP1. Similarly, neuroactive ligand-receptor interaction modulated the highest number of protein molecules i.e. DRD5, ADRB1, DRD1, CNR2, ADRA2C, NR3C1, HTR2A, ADRA1D, and HTR2C. Tembetarine majorly modulated proteins which are involved in neuroactive ligand-receptor interaction pathway i.e. ADRA1D, ADRA2C, ADRB1, DRD1, HTR2A, and HTR2C (Fig. 4). Further, ADRA1D, ADRA2C, ADRB1, CNR2, DRD1, HTR2A, HTR2C, and NR3C1 proteins from neuroactive ligand-receptor interaction path way were also modulated by other phytoconstituents to show the synergistic effect for anti-diabetic activity.

Docking studies

The binding affinity and inhibitory constant of tembetarine with beta 1 adrenergic receptor was found to be − 6.25 kcal/mol and 36.45μM respectively. Two hydrogen bond interactions were found in ligand-protein complex i.e. ASN:94 and THR:93 with "H" atom (hydroxyl group attached to carbon 19) and "O" atom (hydroxyl group attached to carbon 4) respectively (Fig. 5)

DISCUSSION

Exploration of folk medicines for the management of complex diseases like diabetes via the utilization of net work pharmacology is a well-accepted approach. Many attempts have been made to understand the molecular mechanisms of folk medicines in the management of the disease by using network pharmacology [24–26]. The utilization of T. cordifolia has been demon started for the management of DM [10]. However, the molecular mechanism of T. cordifolia in the management of diabetes has not been illuminated clearly. Hence, the current study utilizes the network pharmacology approach to understand the probable molecularmechanismsofT. cordifolia inthemanagementofDM. We constructed the network interaction between phytoconstituents, their targets, and probable path ways. The result reflects terpenes, steroids, and alkaloids as apotential phytoconstituents to interactwith multiple proteinmolecules involved in the pathogenesis of DM. Among them, tembetarine, a benzyl-iso quinoline alkaloid possesses the potential role in the pharmacotherapy of DMby targeting the numerous protein molecules within the network.

Ayurvedic Pharmacopoeia of India records terpenoids and alkaloids asmajor phytoconstituents inT. cordifolia [9]; were involved tomodulate the multiple pathogenic proteinmoleculeswhichareassociatedwithDM.

One of the clinical trials of T. cordifolia reports the alkaloids as a potential phytoconstituents in the management of diabetes inT2DMpatients [27]. Further, the reports have been found to explain the beneficial roleof alkaloids inthemanagement of diabetes and associated complications [28]. This could be due to the prime role of tembetarinewith other phytoconstituents by targeting the numerous protein molecules involved in the pathogenesis of DM to work in a synergistic way as demonstrated in the current findings

Targetingdopamineandserotoninreceptorsare identifiedasoneof theapproaches inthepharmacotherapy ofDM[29, 30].Thepresent studypredicts tembetarine for itsmaximumdruglikeness score(Table2)andprobability to cross the blood-brain barrier (Fig. 3). This suggests the probability of tembetarine to act on the dopamine and serotonin receptors andmodulate the glucosehomeostasis via the participation innoradrenalineoutput,appetitecontrolandperpetuatingbiological clockwhichdirectlyrespondstothepancreaticbeta-cell secretion.

Thecontrol intheappetite isalsooneof the import ant approaches in diabetes management [31]. The current study identifies tembetarine and tetrahydropalmatetoinhibitDPP4(Table1)andincreasethelevelof incretins suggestingtheir important role intheappetite control andparticipation inglucose homeostasis. Further, T. cordifolia is reported for its protective effect against insulin resistance andoxidative stress [32] and contribute in improving glucose tolerance in diabetic rats[33];demonstrated in the current study by modulatingESR1andPTPN1proteinsbysteroids.

KEGG pathway records neuroactive ligand- receptor interaction as one of the major pathways for leptin deficiency (KEGG Entry: H02059), leptin receptor deficiency (KEGG Entry: H02060), and genetic obesity (KEGG Entry: H02106, [34]). Leptin deficiency is one of the major reasons due to the uncontrolled diabetic con- dition [35] leading to unregulated appetite, thermo- genesis, elevated hepatic gluconeogenesis and lowered glucose uptake expounding the shape of insulin resist- ance [36]. Aldosterone-regulated sodium reabsorption is associated with insulin-resistant diabetes mellitus with acanthosis nigricans (KEGG Entry: H01228) [37]. In the current study, two genes i.e. PTPN1 and ACACB were identified to be regulated which are involved in the insulin resistance/signaling. PTPN1 is identified to eradicate phosphate groups from phosphorylated tyrosine residues and is involved in T2DM and insulin resistance [38]. ACACB inhibits glucose and fatty acid oxidation and enhancesthestorageoffat.Italsoregulatestheoxidation of fatty acid in mitochondria via the inhibition of carnitine palmitoyltransferase 1; proves imperative characterin diabetic and obese conditions [39]. Theinvitroandinvivostudiesreflectthepotencyofal- kaloids and steroids from *T. cordifolia* play a crucial role in the management of diabetes [40]. The previous report suggeststheinsulinsensitivityefficacyof*T.cordifolia*[41, 42] which could be due to the interaction of β/γ-sitosterol withPTPN1andACACB (Table1).Further,alkaloid rich fraction has been reported to minimize the elevated blood glucose level via the insulin mimicking and insulin- releasing effect [40]. The current study identifies modula- tion of neuroactive ligand-receptor interaction (KEGG Entry:hsa04080)viathemajorityofthephytoconstituents including tembetarine; modulates secretins e.g. glucagon and glucagon-like peptide (GLP) which are well-acknowledgedforinsulinsensitization.Thissuggestsalkaloidsfrom*T.cordifolia*modulatetheinsulinsensitivity via neuroactive ligand-receptor interaction.

Insulin resistance and T2DM are the major contributing factors in the cardiomyopathy [43] which is one ofthe risk factors in diabetic complications. Beta 1 adrenergic receptor is reported to activate phospholamban in myocytes and eNOS in myocytes [44]; phospholamban decreasesmusclerelaxationandcardiaccontractility [45]; decreases heart rate and stroke volume respectively and eNOS maintains vascular tone [46]. The role of neuroactive ligand-receptor interaction in the cardioprotection has been reported [47]. In the current finding, three different phytoconstituents i.e. tembetarine, tetrahydro-palmatine, and magnoflorine were identified to interact with ADRB1; one of the protein molecules from neuro- active ligand-receptor interaction. Hence, the reported cardioprotective effects of *T. cordifolia* [48, 49] could be duetotheinteractionwithADRB1andneuroactiveligand-receptor interaction. This finding is further sup- ported by the mining of protein targets which identified ADRB1 as a potential target for tembetarine.

In conclusion, we identified tembetarine as one of the major alkaloids to interact with the maximum number of protein molecules that are involved in the pathogenesis of DM. Further, neuroactive ligand-receptor interaction was identified as a major pathway in the management of dia- betes and cardio-protection which is one of the major risks in insulin resistance and diabetes. However, the current findings are only based on processor simulations which need to be demonstrated via wet-lab protocols.

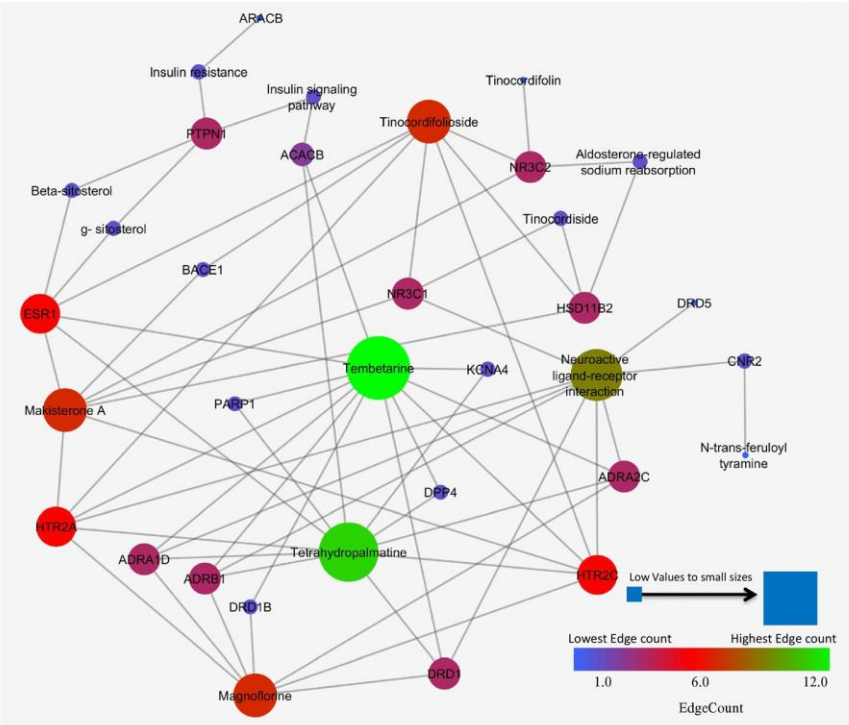


Fig.4Networkrepresentationofinteractionbetweenphytoconstituents,targetsandpathways

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