Potential Molecular Mechanisms of JTW in the Treatment of Diabetes Mellitus and Depression Based on Network Pharmacology

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Research

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Abstract

Background: The incidence of diabetes mellitus (DM) and depression is increasing year by year around the world, bringing a serious burden to patients and their families. As a well-known traditional Chinese medicine (TCM), Jiao-tai-wan (JTW) has obvious hypoglycemic and antidepressant effects, but its specific targets and mechanisms are still unclear.

Methods: The active compounds and corresponding targets of JTW were screened by the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) and the Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM). The GeneCards, the Online Mendelian Inheritance in Man (OMIM), the DrugBank and the Therapeutic Target Database (TTD) were used to collect targets of DM and depression. After sorting out the intersection targets of drugs and diseases, the Cytoscape software was used to perform a "Drug-Compounds-Targets-Disease (D-C-T-D)" network to analyze the active compounds of JTW, and the protein-protein interaction (PPI) network was constructed by the STRING database to screen and analyze the key target proteins. Finally, the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the intersection targets were carried out by the database for annotation, visualization and integrated discovery (DAVID).

Results: 28 active compounds and 484 corresponding targets of JTW, 1407 DM targets and 1842 depression targets were collected by screening the above databases, and a total of 117 targets were obtained after taking the intersection. JTW plays a role in reducing blood glucose level and antidepressant mainly through active compounds such as quercetin, styrene, cinnamic acid, ethyl cinnamate, (R)-Canadine, palmatine and berberine, etc., the key targets of its therapeutic effect include insulin (INS), protein kinase B1 (AKT1), interleukin-6 (IL-6), vascular endothelial growth factor A (VEGF-A), tumor necrosis factor (TNF) and so on, mainly involved in HIF-1 signal pathway, pathways in cancer, Hepatitis B, TNF signal pathway, PI3K-Akt signal pathway and MAPK signaling pathway, etc.

Conclusion: In this paper, the possible mechanism of JTW on DM and depression was explored by network pharmacology, reflecting the characteristics of multi-component, multi-target and multi-pathway, which provides a theoretical basis for the experimental research and clinical application of JTW in the future.

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia with a rapidly increasing prevalence. According to the International Diabetes Federation (IDF), about 463 million adults worldwide suffered from DM in 2019, and the number is expected to reach 700 million in 2045 [1]. China has the largest number of DM patients in the world, with an incidence of 11.2% [2]. Not only DM itself is seriously harmful to human health, but also the complications will bring a heavy burden to the family and society. Depression, one of the most prevalent disorders of mental health that limits psychosocial functioning

and diminishes quality of life, is a common psychological complication of diabetes [3]. A meta-analysis showed that 14.5% of patients with type 2 diabetes mellitus (T2DM) were complicated with depression [4], and depression is twice as common in people with DM as in the general population [5]. Long-term depression not only affects patients' compliance with treatment, but also causes neuroendocrine dysfunction and increases blood glucose level, and poor blood glucose control will aggravate patients' depression. Therefore, it is urgent to strengthen early identification and give corresponding psychological or drug intervention.

At present, the commonly used antidepressants are selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). According to reports, psychopharmacological treatment with SSRIs medications has a moderate-to-large effect on depression with lesser effects on glycemic control [6]. Another cohort study showed that antidepressant use is associated with the risk of diabetes onset in a time- and dose-dependent manner, the adjusted hazard ratio is 3.95 for long-term high-dose antidepressant use [7]. Hence in-depth exploration of the pathogenesis and development of drugs with the dual effects of improving of DM and depression is imminent.

Traditional Chinese medicine (TCM) is a holistic medical system for diagnosis, prevention and treatment of diseases which uses experience-based therapies such as acupuncture and herbal medicine [8]. Jiao-tai-wan (JTW), originated from the "*Han Shi Yi Tong*" in the Ming Dynasty, is composed of two herbal medicines: Huanglian (*Rhizoma Coptidis*) and Rougui (*Cinnamon*), and it has been used to treat insomnia since ancient times. With the development of science and technology and the verification of experiments, the therapeutic effect of JTW on DM has been discovered [9–11]. Since insomnia and depression are closely related, in recent years, more and more studies have confirmed that JTW have obvious antidepressant effects in addition to reducing blood glucose level and improving sleep quality. Experimental research results showed that JTW can significantly alleviate the depressive-like behavior of mice, such as shortening the immobility time of the tail suspension test (TST) and forced swimming test (FST) [12, 13]. Therefore, JTW may have dual effects in the treatment of DM and depression. However, the mechanism of JTW to treat DM and depression is not yet clear, especially the molecular target mechanisms of its effective components, which needs to be further explored.

Network pharmacology is a new discipline based on the theories of systems biology, bioinformatics and classical pharmacology. The new method for analyzing the targets and mechanisms of drug treatment of diseases from multiple angles provides the possibility to reveal the mechanism of TCM, which is booming in recent years and has been widely used in the field of TCM [14]. Network pharmacology, as a useful tool, can help us to further understand the role of drugs and how we can improve drug discovery for complex diseases [15]. Thus, this paper used the method of network pharmacological analysis to construct the network of "Drug-Compounds-Targets-Disease (D-C-T-D) " to explore the targets and mechanisms of JTW in the treatment of DM and depression, in order to provide ideas and theoretical basis for the later experimental research and future clinical application. The workflow is shown in Fig. 1.

2. Materials And Methods

2.1 Screening of active compounds and targets of JTW

The active compounds and corresponding targets of JTW were screened using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, <https://tcmbspw.com/tcmssp.php>), a unique systems pharmacology platform of Chinese herbal medicines that captures the relationships between drugs, targets and diseases [16]. The oral bioavailability (OB) and drug-likeness (DL) contained in this database are important indicators for evaluating ADME (absorption, distribution, metabolism, and excretion) attributes. OB represents the percentage of an orally administered dose of unchanged drug that reaches the systemic circulation [17], and DL represents the similarity of a compound to the drug [18]. Therefore, the OB and DL are often used as the key factors to screen active compounds of drugs ($OB \geq 30\%$ and $DL \geq 0.18$) [19, 20]. We also chose those two indicators as the screening criteria in our study.

The Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM, <http://bionet.ncpsb.org.cn/batman-tcm/>) was also used to screen the active compounds and potential targets. The BATMAN-TCM database is the first online bioinformatics analysis tool specially designed for the research of molecular mechanism of TCM, which is aimed at accelerating the elucidation of TCM's molecular mechanism [21]. According to the parameter information given by the BATMAN-TCM database, the Score cutoff ≥ 30 and P value ≤ 0.05 were considered as indicators when screening the active compounds of JTW.

In addition, we also searched the relevant literature on the compounds of JTW and completed the data collection to avoid omitting some important active compounds and corresponding target information due to the setting of screening criteria.

2.2 Collection of targets of DM and depression

The targets of DM and depression were also obtained by searching the databases, namely the GeneCards (<https://www.genecards.org/>, version 5.1), the Online Mendelian Inheritance in Man (OMIM, <https://omim.org/>), the DrugBank (<https://go.drugbank.com/>, version 5.1.8) and the Therapeutic Target Database (TTD, <http://db.idrblab.net/ttd/>). The GeneCards is a database that integrates gene-centric data from about 150 web sources, including genomic, transcriptomic, proteomic, genetic, clinical and functional information [22]. The OMIM database focuses on the relationship between phenotype and genotype and contains information on all known mendelian disorders and over 15,000 genes [23]. The DrugBank is a web-enabled database containing comprehensive molecular information about drugs, their mechanisms, their interactions and their targets, which combines detailed drug data with comprehensive drug target information [24]. The TTD database provides information about the known and explored therapeutic protein and nucleic acid targets, the targeted disease, pathway information and the corresponding drugs directed at each of these targets [25]. With the key words including "depression", "depressive", "depressive disorder", "depressive illness", "diabetes" and "diabetes mellitus", targets related to DM and depression were founded in the above databases.

2.3 Construction and analysis of the "D-C-T-D" network

The targets of active compounds and diseases were collected and sorted out to obtain the intersection targets of JTW, DM and depression. According to these intersection targets, the Venn diagram was obtained by using jvenn platform (<http://jvenn.toulouse.inra.fr/app/example.html>) [26]. Afterwards, we integrated the information of the intersection targets and input them into Cytoscape software (<https://cytoscape.org/>, version 3.8.2) to construct a "D-C-T-D" network and complete the subsequent analysis. Cytoscape is a software platform for the large-scale integration of molecular interaction network data, and can integrate these networks with annotations, gene expression profiles and other state data [27].

2.4 Construction of the protein-protein interaction (PPI) network

The intersection targets of JTW, DM and depression were uploaded to the STRING database (<https://www.string-db.org/>, version 11.0) to construct the PPI network of protein-protein interaction and the key targets were screened and analyzed subsequently. The STRING is a database which aims to achieve a comprehensive and objective global network, including direct (physical) as well as indirect (functional) interactions. We set the scoring condition to > 0.90 , and the selected target proteins were limited to "*Homo sapiens*". In the PPI network, the edges represent protein-protein associations, and the more lines, the greater the correlation [28].

2.5 Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses

The database for annotation, visualization and integrated discovery (DAVID) (<https://david.ncifcrf.gov/>, version 6.8) was used to carry out GO enrichment analysis and KEGG enrichment analysis on the intersection targets. The DAVID database is a web-based online bioinformatics resource that can be used to explain the functions of large lists of genes/proteins [29]. The GO enrichment analysis includes three different biological aspects: biological process (BP), molecular function (MF) and cellular component (CC) [30]. KEGG is a knowledge base for systematic analysis of gene functions [31].

3. Results

3.1 Screening of active compounds and targets of JTW

After searching the TCMSP database and the BATMAN-TCM database and screening with the criteria of $OB \geq 30\%$, $DL \geq 0.18$, and Score cutoff ≥ 30 , combined with the results of related literature [32–34], a total of 28 active compounds of JTW were initially obtained, namely 14 of Huanglian and 14 of Rougui. The relevant information of these 28 active compounds can be found in the Supplementary Table 1. What's more, 526 corresponding targets were collected from the two databases, including 179 of

Huanglian and 347 of Rougui. After standardizing and unifying target names and deleting duplicate targets, a total of 484 drug targets were obtained.

3.2 Collection of therapeutic targets of DM and depression

The key words such as "depression", "depressive", "depressive disorder" and "depressive illness" were used to search for the therapeutic targets of depression in the GeneCards, OMIM, DrugBank, and TTD databases. After simplifying the results of each database and screening and removing duplicate targets, a total of 1842 targets of depression were obtained. Similarly, 1407 targets of DM were obtained by using "diabetes" and "diabetes mellitus" as the key words to search in the databases.

3.3 Screening of the intersection targets and constructing the D-C-T-D network

Through taking the intersection of 484 drug targets, 1842 depression targets and 1407 DM targets, we obtained a total of 117 targets (Fig. 2A), which correspond to 17 active compounds (Table 1). Subsequently, we input the information of the intersection targets into Cytoscape software for analysis in order to explore the possible mechanism of the therapeutic effect of JTW. Figure 2B shows the D-C-T-D network constructed by the Cytoscape, which fully reveals the multi-component and multi-target mechanism of JTW in the treatment of DM and depression. In addition, the analyzer tool that comes with the software was used to analyze the active compounds. The results showed that the active compounds with the highest number of targets included quercetin, styrene, cinnamic acid, ethyl-cinnamate, (R)-Canadine, palmatine, berberine, etc., indicating that the above compounds may be the main components of JTW in treating DM and depression.

3.4 Construction and analysis of the PPI Network

117 intersection targets were uploaded to the STRING database to obtain the PPI network. There are 117 nodes and 1907 edges in the PPI network (Fig. 3A), which suggests that there may be a complex relationship between these targets, and JTW may regulate these targets in a variety of ways. Since the more lines in the PPI network, the greater the correlation, we analyzed each node and screened out the top 10 targets (Fig. 3B). Therefore, we speculate that the active compounds of JTW may play a role in the treatment of DM and depression through targets such as insulin (INS), protein kinase B1 (AKT1), interleukin-6 (IL-6), vascular endothelial growth factor A (VEGF-A), tumor necrosis factor (TNF) and so on.

3.5 GO enrichment analysis

The DAVID database was used to perform GO enrichment analysis of 117 intersection targets to explore the relationship between these targets and diseases, including three aspects of BP, MF and CC. The top ten results were output after ranking according to the *P* value from small to large (Fig. 4). It can be seen that the occurrence of DM and depression involves many biological processes, and JTW can achieve the purpose of treatment by regulating multiple biological processes, among which the most closely related

biological processes include positive regulation of nitric oxide biosynthetic process (GO:0045429), response to drug (GO:0042493), aging (GO:0007568), positive regulation of transcription, DNA-templated (GO:0045893), regulation of blood pressure (GO:0008217) and so on. In the classification of cellular components, the top five are extracellular space (GO:0005615), extracellular region (GO:0005576), plasma membrane (GO:0005886), membrane raft (GO:0045121) and cell surface (GO:0009986). The results of molecular functional enrichment analysis indicated that the active compounds of JTW may regulate enzyme binding (GO:0019899), identical protein binding (GO:0042802), cytokine activity (GO:0005125), protein homodimerization activity (GO:0042803) on DM and depression. Supplementary Fig. 1 shows the bubble chart results of the top 20 in the GO enrichment analysis.

3.6 KEGG enrichment analysis

We also conducted KEGG enrichment analysis of the 117 intersection targets through the DAVID database, and the results showed that these targets involved 124 pathways. We selected the top 20 according to the *P* value from small to large for further analysis (Fig. 5). It can be seen that JTW mainly regulates Chagas disease (American trypanosomiasis) (hsa05142), HIF-1 signaling pathway (hsa04066), pathways in cancer (hsa05200), Hepatitis B (hsa05161) and so on to treat DM and depression. In addition, there are also many targets enriched in pathways such as TNF signaling pathway (hsa04668), PI3K-Akt signaling pathway (hsa04151) and MAPK signaling pathway (hsa04010), indicating that they may also play an important role in the treatment.

Afterwards, in order to explore the relationship between the top 20 pathways, drugs and intersection targets, we integrated the collected information and conducted a network by using the Cytoscape (Fig. 6). It is obvious from the network that each pathway can correspond to multiple targets, and each target can also connect to multiple pathways. Different pathways can be connected to each other through the intersection targets, which fully reflects the multi-component, multi-target, and multi-pathway mechanism of JTW in treating DM and depression.

4. Discussion

Both DM and depression are serious chronic diseases, which can lead to a serious decline in the quality of life, increase functional disability and costs of care than many other chronic diseases [35]. The bidirectional link between DM and depression has been confirmed. An epidemiological study has shown that the prevalence rate of depression is more than three times higher in people with type 1 diabetes mellitus (T1DM) and nearly twice as high in people with T2DM than those without [36]. Another research also indicated that the presence of diabetes doubles the odds of comorbid depression [37]. The results of a meta-analysis carried out by Mezuk et al. showed that compared with people without diabetes, people with T2DM had a 15% increased risk of depression, while those with depression had a 60% increased risk of developing T2DM [38]. However, the current treatments for these two diseases are relatively single and there is a lack of the comprehensive treatment needed to improve clinical outcomes [39].

JTW, one of the most classical Chinese prescription, has been used to treat insomnia for hundreds of years. In recent years, more and more experiments have confirmed that JTW can not only improve the quality of sleep, but also has the dual effects of hypoglycemic and antidepressant [40–42]. In the traditional theories of TCM, different diseases may have similar etiology, pathogenesis, symptoms, and disease location during the occurrence and development, so that different diseases can be cured with the same prescription, which fully reflects the advantages of TCM in syndrome differentiation, holistic treatment and comprehensive treatment [43]. Our study is to explore the targets and mechanisms of the dual effects of JTW through the novel analysis method called network pharmacology.

The results of analysis using Cytoscape software showed that the active compounds with the highest number of targets included quercetin, styrene, cinnamic acid, ethyl-cinnamate, (R)-Canadine, palmatine, berberine and so on. First of all, quercetin, a naturally occurring flavonoid, is one of the active compounds of Huanglian. A number of research results have confirmed that quercetin has multiple pharmacological effects such as antioxidant, anti-tumor, anti-inflammatory, antimicrobial, regulating immune function, and protecting cardiovascular function, etc. [44–47]. The study conducted by Roslan et al. demonstrated that quercetin can ameliorate metabolic derangements in diabetes, including near normal final body weight, fasting blood glucose (FBG) and insulin levels [48]. Jeong et al. also found that quercetin could effectively improve hyperglycemia and dyslipidemia in T2DM and may be useful in the management of DM and prevention of diabetic complications [49]. Not only that, quercetin has also been found to alleviate LPS-induced depression-like behaviors in rats [50], and can dose-dependently decrease the immobility time of diabetic mice in FST and this effect is comparable to that of fluoxetine, a traditional antidepressant [51, 52].

Berberine, a natural isoquinoline alkaloid, is also an active compound of Huanglian. Berberine has a wide range of pharmacological effects, such as antimicrobial, anti-inflammatory, anti-tumor, antioxidant, neuroprotective, etc. [53, 54], and can be used to treat many gastrointestinal disorders [55, 56]. The results of a clinical trial showed that berberine can significantly reduce FBG and hemoglobin A1c (HbA1c) in patients with diabetes, and its hypoglycemic effect was similar to that of metformin [57]. A randomized controlled trial (RCT) completed by Zhang et al. indicated that the hypoglycemic effect of berberine is mediated by gut microbiome [58]. The therapeutic effect of berberine on depression has also been confirmed by numerous experiments. Studies have found that berberine can exert antidepressant effect by regulating brain biogenic amines such as norepinephrine (NE), serotonin (5-HT) and dopamine (DA), etc. [59], it can also inhibit neuroinflammation to prevent depression-like behavior [60]. In animal experiments, berberine can greatly shorten the immobility time of mice in FST and TST, which also supports the view that berberine plays an antidepressant effect [61, 62].

Cinnamic acid, one of the effective compounds of Rougui, is a natural aromatic carboxylic acid. Studies have reported that cinnamic acid also has multiple pharmacological effects such as antioxidant, anti-tumor, anti-inflammatory, neuroprotective, and antimicrobial [63–65]. As one of the fundamental herbs in traditional Chinese medicine, cinnamic acid has been widely used to treat many disorders for a long time [65]. Research results show that cinnamic acid can regulate glycogen production and gluconeogenesis

[66], and can also significantly enhance insulin secretion in isolated islets [67], thereby exerting anti-diabetic activity. In addition, Hemmati et al. found that the administration of cinnamic acid can inhibit the FBG level in diabetic mice [68]. Although there are few researches on the therapeutic effect of cinnamic acid in depression, derivatives of cinnamic acid and other natural products can exert antidepressant effects and have potential applicability as candidates for antidepressant drugs [69].

In addition, other active compounds of JTW are also considered to have the effect of improving DM and depression. For example, palmatine can protect cells against reactive oxygen species and endoplasmic stress, thus exhibiting antidiabetic properties [70]. The results of behavioral tests such as sucrose preference test (SPT), FST and open-field test (OFT) in rats also confirmed the antidepressant effect of it [71].

Inflammatory mediators have always been considered to be important factors in promoting the development of insulin resistance (IR), which will lead to the occurrence of T2DM. The results of our PPI network analysis that IL-6 and TNF are the top five targets also confirmed this view, indicating that they may play an important role in the treatment of DM and depression. It was found that the levels of cytokines such as TNF- α and IL-6 were highest in non-treated diabetic rats, and decreased significantly following quercetin or glibenclamide treatments [48]. The systematic review conducted by Esser et al. directly showed that immune system activation and chronic low-grade inflammation are involved in the pathogenesis of IR and diabetes [72]. Inflammation is also thought to have a bidirectional relationship with depression [73]. A meta-analysis demonstrated that there was a significant correlation between depression and C-reactive protein (CRP) and IL-6 in children and adolescents [74]. IL-6 knockout mice exhibit resistance to stress-induced depression-like behavior and showed reduced despair in FST and TST [75]. Vascular endothelial growth factor (VEGF) is a key driver of neovascularization and vascular permeability [76, 77]. Prakash et al. revealed that diabetes-induced cerebral neovascularization is accompanied by increased expression of VEGF-A and activation of VEGF receptor-2 (VEGFR-2) [78]. A case-control study showed that altered VEGF secretion, caused by genetic variation in VEGF-A gene, is involved in T2DM pathogenesis [79]. VEGF is also related to other diabetic complications such as diabetic retinopathy (DR) and diabetic foot ulcer (DFU) [80, 81], and has been considered as a therapeutic target for anti-angiogenesis in DR [82, 83]. In addition, VEGF exerts effective neurotrophic effects. In both major depressive disorder (MDD) subjects and rat depression models, the hippocampal VEGF and other growth factors are abnormally regulated [84]. Increasing VEGF expression in the hippocampus of rats can improve depression-like behaviors in rats after myocardial infarction (MI) [85]. Deyama et al. confirmed that VEGF signaling plays a crucial role in the antidepressant effects of brain-derived neurotrophic factor (BDNF) and ketamine [86, 87]. The genome-wide association study (GWAS) also proved the role of VEGF in the development of depression [88]. It can be seen that VEGF is closely related to DM and depression. The correlation between INS and DM has long been recognized worldwide, and AKT1, as a key factor in the PI3K-Akt signaling pathway, has been confirmed by many researches on its relationship with DM and depression, which will be discussed in detail below.

The results of KEGG enrichment analysis showed that the active compounds of JTW may play a therapeutic effect on DM and depression by regulating multiple pathways. The intersection targets are mainly enriched in HIF-1 signaling pathway, pathways in cancer, TNF signaling pathway, PI3K-Akt signaling pathway and MAPK signaling pathway, etc. Many studies have shown that HIF-1 signaling pathway is associated with DM and depression. Hypoxia-inducible factor 1-alpha (HIF-1 α) is important for maintaining the function and survival of pancreatic β cells [89] and the expression of hypoxia-inducible factor 1-beta (HIF-1 β) mRNA in patients with T2DM is decreased [90]. Glucose-induced inhibition of HIF-1 α protein stability may also accelerate the deterioration of β cell function and speed progression to diabetes [91]. Myocyte HIF-1 α is necessary for normal muscle glucose uptake and insulin sensitivity [92]. Furthermore, HIF-1 is also associated with diabetic complications such as DR and diabetes kidney disease (DKD) [82, 93, 94]. In conclusion, HIFs play a role in the pathogenesis of β cell dysfunction and diabetes [92]. In terms of depression, Li et al. established a depression model using chronic unpredictable mild stress (CUMS) and found that FG-4592 can reverse depressive behaviors by activating HIF-1 signaling pathway [95]. The study conducted by Shibata et al. indicated that the altered expression of HIF-1 and its target genes mRNA in peripheral blood cells are associated with mood disorders, especially with MDD [96]. Kang et al. also proposed that interventions including the intermittent hypoxia conditioning and hyperbaric oxygen therapy to elevate the level of HIF-1 in the brain might be considered as new additional treatments for depression [97].

PI3K-Akt signaling pathway is the main downstream molecular pathway of insulin, which plays a crucial role in regulating glucose and lipid metabolism. PI3K-Akt signaling pathway block and abnormal function of downstream target proteins can cause IR [98]. Lots of studies have confirmed that the IR of diabetic mice can be improved by regulating the PI3K-Akt signaling pathway [99–101]. AKT1 has been considered as a key mediator of insulin-stimulated glucose uptake, suppression of apoptosis, stimulation of glycolysis and the activation of glycogen and protein synthesis [102]. The activation of PI3K-Akt pathway can protect pancreatic β cells from the influence of different apoptotic stimuli [103]. What's more, Cao et al. found that the expression of PI3K in depressed rats were attenuated significantly [104]. The study of Xie et al. showed that Crocin can ameliorate depression via PI3K-Akt mediated suppression of inflammation [105], these studies illustrate the close connection between PI3K-Akt signaling pathway and depression.

In mammalian cells, MAPK families has been divided into three categories, including p38, extracellular signal-related kinase (ERK) and c-Jun N-terminal kinase (JNK) [106]. Among them, ERK1/2 play a pivotal role in various neuropsychiatric disorders, including depression [107]. Regulating the CUMS-induced MAPK pathway and NF- κ B protein complex activation can alleviate depression-like behavior in mice [108]. Paroxetine combined with fluorouracil, ketamine and ghrelin and other drugs can show antidepressant-like effects via the MAPK signaling pathway [109–111]. In addition, resveratrol can attenuate cardiac dysfunction caused by diabetes, and the effects are related to down-regulation of AT1R-ERK/p38 MAPK signaling pathway [112]. Cui et al. found that Huanglian can alleviate inflammation by regulating the expression of pro-inflammatory cytokines through MAPK signaling pathway, thereby

inhibiting the occurrence and development of IR and diabetes [113]. Gelidium elegans extract can ameliorate T2DM via regulation of MAPK and PI3K-Akt signaling pathways [114].

5. Conclusion

In summary, this study based on network pharmacological analysis revealed the active compounds and corresponding targets and pathways of JTW, a classic TCM, in the treatment of DM and depression. The multi-component, multi-target, and multi-pathway mechanism of JTW provides a reference for in-depth study of the pharmacological effects. However, the pathogenesis of DM and depression is more complicated, and the targets and pathways are interrelated and regulate each other, in addition, due to the limitations of some databases, we cannot collect all the active compounds and targets of JTW. In the future, more in-depth and comprehensive study is still needed, and *in vivo* and *in vitro* experiments are necessary for exploring and verifying more extensive pharmacological effects and mechanisms of JTW.

Abbreviations

DM diabetes mellitus

TCM traditional Chinese medicine

JTW Jiao-tai-wan

TCMSP Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform

BATMAN-TCM Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine

OMIM Online Mendelian Inheritance in Man

TTD Therapeutic Target Database

D-C-T-D Drug-Compounds-Targets-Disease

PPI protein-protein interaction

GO Gene Ontology

KEGG Kyoto Encyclopedia of Genes and Genomes

DAVID database for annotation, visualization and integrated discovery

INS insulin

AKT1 protein kinase B1

IL-6 interleukin-6

VEGF-A vascular endothelial growth factor A

TNF tumor necrosis factor

IDF International Diabetes Federation

T2DM type 2 diabetes mellitus

SSRIs selective serotonin reuptake inhibitors

SNRIs serotonin and noradrenaline reuptake inhibitors

OB oral bioavailability

DL drug-likeness

ADME absorption, distribution, metabolism, and excretion

BP biological process

MF molecular function

CC cellular component

FBG fasting blood glucose

HbA1c hemoglobin A1c

RCT randomized controlled trial

NE norepinephrine

5-HT serotonin

DA dopamine

SPT sucrose preference test

OFT open-field test

IR insulin resistance

CRP C-reactive protein

VEGF vascular endothelial growth factor

VEGFR-2 VEGF receptor-2

DR diabetic retinopathy

DFU diabetic foot ulcer

MDD major depressive disorder

MI myocardial infarction

BDNF brain-derived neurotrophic factor

GWAS genome-wide association study

HIF-1 α hypoxia-inducible factor 1-alpha

HIF-1 β hypoxia-inducible factor 1-beta

DKD diabetes kidney disease

CUMS chronic unpredictable mild stress

ERK extracellular signal-related kinase

JNK c-Jun N-terminal kinase

Declarations

Authors' Contributions

TYH, SH, HWY and DH designed this work, and wrote and revised the whole manuscript. LFE and NKX searched the databases and collected the data. WZ and WHZ analyzed the data.

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Availability of data and materials

All data are available in the manuscript and they are showed in figures and tables.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1. Seventeen active compounds of Jiao-tai-wan and their corresponding oral bioavailability (OB) and drug-likeness (DL)

Mol ID	Molecule Name	OB (%)	DL
MOL000098	quercetin	46.43	0.28
MOL000105	Protocatechuic Acid	25.37	0.04
MOL000475	Anethole	32.49	0.03
MOL000704	Styrene	29.55	0.01
MOL000785	palmatine	64.6	0.65
MOL000991	Cinnamaldehyde	31.99	0.02
MOL001454	berberine	36.86	0.78
MOL001458	coptisine	30.67	0.86
MOL002295	Cinnamic Acid	19.68	0.03
MOL002668	Worenine	45.83	0.87
MOL002834	Ethylcinnamate	20.54	0.04
MOL002894	berberrubine	35.74	0.73
MOL002897	epiberberine	43.09	0.78
MOL002903	(R)-Canadine	55.37	0.77
MOL002904	Berlambine	36.68	0.82
MOL002907	Corchoroside A qt	104.95	0.78
MOL003526	Cinnamyl Acetate	21.15	0.04

Figures

Figure 1

Workflow of this network pharmacology analysis. TCMSP= Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; BATMAN-TCM= Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine; OMIM= Online Mendelian Inheritance in Man; TTD= Therapeutic Target Database; JTW=Jiao-tai-wan; PPI=protein-protein interaction; D-C-T-D= Drug-Compounds-Targets-Disease; GO= Gene Ontology; KEGG= Kyoto Encyclopedia of Genes and Genomes.

Figure 2

(A) The 117 intersection targets of Jiao-tai-wan, diabetes mellitus and depression. (B) The Drug-Compounds-Targets-Disease (D-C-T-D) network.

Figure 3

(A) The protein-protein interaction (PPI) network of 117 intersection targets. (B) The bar plot of the top 10 targets in the PPI network.

Figure 4

The top 10 biological process (BP), molecular function (MF) and cellular component (CC) in GO analysis of 117 intersection targets.

Figure 5

The top 20 signaling pathways in KEGG enrichment analysis of 117 intersection targets.

Figure 6

Drug-intersection targets-signaling pathways network of Jiao-tai-wan in the treatment of diabetes mellitus and depression.

Supplementary Files

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- [SupplementaryFigure1.pdf](#)
- [SupplementaryTable1.docx](#)