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Mechanisms underlying the therapeutic effects of *Dendrobium officinale* in treating metabolic syndrome based on clinical datasets, network pharmacology, molecular docking and enzyme kinetic assay

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Abstract: **Background**: Metabolic syndrome (MetS) significantly increases risks for diabetes and cardiovascular diseases. Dendrobium officinale, a Traditional Chinese Medicine (TCM), shows potential in treating MetS, yet its active components and mechanisms remain unclear. **Objectives**: To identify the key active constituents of D. officinale and elucidate their mechanisms against MetS using integrated clinical and experimental approaches. **Methods**: A clinical trial (n=37) evaluated D. officinale powder efficacy in MetS patients. Network pharmacology predicted active compounds and targets. Molecular docking assessed compound-target interactions. Enzyme kinetic assay measured inhibition of protein tyrosine phosphatase 1B (PTP1B). **Results**: Clinical results showed significant improvements in triglycerides (TG), fasting blood glucose (FBG), body mass index (BMI), and waist circumference. Network pharmacology and molecular docking identified Vicenin II and Schaftoside as key compounds targeting PTP1B. Enzyme assays confirmed both potently inhibited PTP1B activity (IC50 values: Vicenin II 6.94±0.22 μM; Schaftoside 6.33±0.21 μM), stronger than positive control NaVO4 (IC50 12.65±1.60 μM). Kinetic analysis indicated Vicenin II as a competitive inhibitor and Schaftoside as mixed-type. **Conclusion**: Dendrobium officinale effectively improves MetS parameters. Vicenin II and Schaftoside are identified as key active constituents, likely exerting therapeutic effects through potent PTP1B inhibition.

Keywords: Active constituents; *Dendrobium officine*; Metabolic syndrome; Network pharmacology; Protein tyrosine phosphatase 1B

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INTRODUCTION

Metabolic syndrome (MetS) is characterized as an ailment affecting the metabolism of proteins, lipids, carbohydrates and various other substances within the human body, which is a risk factor for diabetes and cardiovascular diseases(Ramírez-Vélez *et al*., 2019). MetS is usually diagnosed by the coexistence of three or more of the following health issues: central obesity, high blood pressure, elevated blood sugar and dyslipidemia (characterized by low levels of high-density lipoprotein (HDL) cholesterol or elevated triglyceride levels) (Wu *et al*., 2020). Treatment of MetS involves an all-encompassing approach and multi-targeted modulation aimed at slowing down weight gain, ameliorating insulin resistance and dyslipidemia, as well as controlling glucose and blood pressure (Dommermuth *et al*., 2018; Tang *et al*., 2015). Whereas single interventions, such as lowering hyperglycemia or hypertension alone, is ineffective in modulating multiple metabolic disorders (Di *et al*., 2019; Tan *et al*., 2023a). In addressing MetS, traditional Chinese medicine (TCM) has irreplaceable advantages due to its holistic concept and multi-target regulation (Tan *et al*., 2020; Wu *et al*., 2020). Several studies have shown that TCM is effective in obesity-related hypertension as an add-on therapy exerts compared with conventional drug therapy (Tan *et al*., 2023b; Wang *et al*., 2014; Yu *et al*., 2018; Zhang *et al*., 2018). *Dendrobium officinale* is a well-known TCM and tonic food, which was used as a tonic for treating disease symptoms by nourishing yin, clearing heat, nourishing the stomach and replenishing fluids for thousands of years in China (Cakova *et al*., 2017; Shin *et al*., 2017). *D. officinale* has many pharmacological effects such as hypoglycemia, antioxidant, anti-insulin resistance, hypotension, etc (Huang *et al*., 2019; Lv *et al*., 2020; Ye *et al*., 2017). Phytochemical investigations have revealed that *D. officinale* have more than 300 compounds including polysaccharides, flavonoids, bibenzyl, alkaloids, phenanthrenes and other components (Lai *et al*., 2024; Li *et al*., 2023; Ye *et al*., 2017; Zhou *et al*., 2023). However, it is not yet known which are the most relevant chemical constituents for the treatment of MetS with *D. officinale*. Considering these limitations, we evaluated the efficacy and mechanism of *D. officine* in healing MetS by utilizing clinical datasets, network pharmacology, molecular docking and enzyme kinetics.

MATERIALS AND METHODS

Materials and chemicals

D. officinale samples were obtained from Guizhou Province of China in 2020 and Identified by Professor

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Daopeng Tan (Pharmacognosy, Zunyi Medical University). Acetonitrile and formic acid, both of LC-MS grade, were obtained from Merck Co., Ltd. Others analytical chemicals were obtained from Chengdu Kelong Chemical Reagent Factory. Recombinant human PTP1B protein (ab51277) was obtained from Laibo Chemicals Industries, Ltd. Vicenin II (purity ≥98.0%) and Schaftoside (purity ≥98.0%) were purchased from Chengdu Aifa Biotechnology Co., Ltd.

Population of the study

MetS patients were enrolled in this study at Longhua Hospital, which is affiliated with Shanghai University of Traditional Chinese Medicine, from May 2020 to May 2021, as ratified by the Medical Ethics Committee of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (Approval number: 2020LCSY021) and Clinical Trial Code: ChiCTR2000034550 (Link: https://www.chictr.org.cn/showproj.html?proj=55914).

Inclusion criteria were: (1) Age 18 to 65 years old, both male and female; (2) Meets MetS diagnostic criteria(Wu *et al*., 2020); (3) Voluntarily sign an informed consent form and agree to participate in this clinical study and all visits and examinations as required by the study protocol. Exclusion criteria were: (1) Pregnant women and nursing mothers; (2) Comorbid serious primary disease, including but not limited to cardiac, hepatic, renal insufficiency, tumors and other serious cerebrovascular disease. Shedding criteria were: (1) Patients who must discontinue medication due to serious adverse drug reactions; (2) Ineffective treatment, patients abandon the trial on their own; (3) Patients with poor compliance, unwilling to comply with treatment or unable to complete follow-up visits; (4) Those who have no adverse reactions during the course of treatment but whose treatment is interrupted for other reasons (e.g., moving out of the country, missing a visit, etc.). Termination criteria were: (1) Patients withdrew informed consent and asked to be withdrawn from the study; (2) Patients had a pregnancy event during the trial; (3) Side effects of medication or therapeutic manipulation that remain intolerable; (4) Circumstances in which the researcher finds it necessary to withdraw from the study.

Methods of clinical treatment

This trial utilized a single-arm exploratory clinical research method. *D. officinale* was crushed into a fine powder and then given to MetS patients for treatment, 6 g/dose, 2 times/day, orally for 4 weeks. Participants who quit the trial due to untolerable reactions or uncontrollable conditions will enter into a follow-up period after the last treatment. All participants will enter into a follow-up period for 4 weeks after the last treatment. Adverse events will be recorded during the whole study. The flowchart is shown as fig. 1. *D. officinale* is in accordance with the standards of the Chinese Pharmacopoeia (2020 edition).

Related clinical indicators

Throughout the trial, the primary focus of patient observation was the alteration in lipid levels and blood sugar, with the key clinical parameters being: triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and fasting blood glucose (FBG). In addition to this, The patient's body mass index (BMI) and waist circumference measurements were documented. Waistline and weight were recorded at each visit (i.e., every 2 weeks) and BMI was calculated (kg/m^2). Safety indicators: vital signs, including blood pressure, respiration, heart rate and temperature, need to be recorded routinely at each visit; electrocardiogram (using a standard 12-lead electrocardiogram), at baseline, at the end of 4 weeks after taking the drug; blood counts and hepatic and renal functions, at baseline, assessed at the end of 4 weeks after taking the drug; adverse event observation and recording: detailed monitoring and recording throughout the clinical study.

Network pharmacology analysis

Collection of active ingredients in D. officinale

The active chemical constituents of *D. officinale* obtained from by the TCMSP database (http://lsp.nwu.edu.cn/tcmsp.php), a systems TCM pharmacology platform(Ru *et al*., 2014). The active ingredients were selected according to the oral bioavailability being greater than or equal to 30% and a drug-likeness (DL) score of at least 0.18 for subsequent analyses (Zhang *et al*.).

Prediction of potential active ingredients and MetS-related targets

The online docking simulation tools Swiss Target Prediction (http:// www. swisstargetprediction. ch/) (probability ＞0), SEA (http:// sea. bkslab. org /) ($P < 0.05$) were employed to forecast the targets of the active compounds found in *D. officinale*, respectively. In addition, the search terms of "MetS" and "Metabolic syndrome" were used in TTD (http: // db. idrblab. net /ttd /), DisGeNET (http:// www. disgenet. org/) to collect disease-associated proteins. The intersection targets of MetS-related proteins and predicted targets of *D. officinale* were acquired utilizing Venny version 2.1.1 (http://bioinfo.cnb. csic.es/tools/venny/index.html).

PPI network construction

The ingredient-disease targets were submitted to the STRING database (http://string-db.org),(Szklarczyk *et al*., 2015) with the biological species restricted to "Homo sapiens" in order to acquire information regarding protein-protein interactions (PPI). Cytoscape 3.8.0 software (https://www.cytoscape.org/) was employed to perform a systematic topological analysis of the network parameters and potential key targets.

Gene ontology and pathway enrichment analysis

The Gene Ontology (GO) database (https://geneontology.org/) was utilized to investigate the potential biological and molecular mechanisms, encompassing details on cellular components (Balli *et al*.), biological processes (BP) and molecular functions (MF). The KEGG database (https://www.genome.jp/kegg/) was employed to identify the candidate targets and their biological functions.

ADME analysis

ADME defines the concentration, distribution within tissues and metabolic pathways of a drug in vivo, serving as a crucial reference for estimating the bioavailability and biological activity of pharmaceutical compounds. SwissADME was employed to forecast the ADME parameters, pharmacokinetic characteristics and pharmacological properties of the key components of *D. Officinale* (Daina *et al*., 2017).

Molecular docking

For molecular docking validation of potentially active ingredients in *D. officinale* and their candidate key targets, the AutoDock Vina software was employed to evaluate the binding activity of the constituents, using a docking score threshold of ≤ -7 kcal/mol. The molecular structures of all potential ingredients were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov), while the structure of the candidate protein was retrieved from the Protein Data Bank (PDB, http://www.rcsb.org).

Inhibition of protein tyrosine phosphatase 1B assay

The PTP1B inhibition experiment was performed as our previous method referred (Zhou *et al*., 2021). The candidate compounds, along with the positive control ($NaVO_4$), were individually solubilized in dimethyl sulfoxide (DMSO) and subsequently diluted to achieve a range of concentrations in a 100 μL MOPS solution, which consisted of 25 mM MOPS, 1 mM EDTA, 2 mM dl-dithiothreitol and 0.1 M NaCl, followed by the addition of 25 nM PTP1B and 2 mM disodium 4-nitrophenyl phosphate (pNPP) catalyzing 0.5 h at 37 °C and terminated with the introduction of 1.0 M NaOH. The effectiveness of the inhibition was evaluated by measuring the quantity of the hydrolyzed product at a wavelength of 405 nm. The inhibitory activity of PTP1B was quantified as a percentage of inhibition, as represented in equation (1):

$$\text{Inhibition (\%)} = (1 - \Delta A_{sample} / \Delta A_{control}) \times 100\% \quad .....(1)$$

The kinetic behavior and associated inhibition constants (*K*i values) were examined using Lineweaver-Burk and Dixon plots. Various concentrations of active compounds were analyzed through enzymatic reactions utilizing 100 nM PTP1B and different concentrations p-NPP substrates in 96-well plates. The absorbance measurements were taken at a wavelength of 405 nm at three-minute intervals. The enzymatic rate was determined using a time-Δabs plot. All tests were conducted in triplicate.

Statistical analysis

The data were presented as mean ± standard deviation (X± SD) and analyzed by box plots using R 4.1.4 software. Group comparisons were conducted using a one-way analysis of variance (ANOVA). Differences in the relevant indicators before and after treatment of the patients were compared using the paired samples t-test.

RESULTS

Clinical efficacy of D. officinale in the treatment of MetS

Thirty-nine patients with a diagnosis of MetS were enrolled from Longhua Hospital affiliated with Shanghai University of Traditional Chinese Medicine, of which two fell into the shedding criteria and were excluded. A total of 37 patients were eligible for inclusion and completed the treatment course. The study included 18 male subjects with an average age of 57 ± 8 years and 19 female subjects with an average age of 58 ± 7 years (fig. 2). The overall distribution was homogeneous.

After a two-month course of applying *D. officinale* to treat MetS, the results of the main efficacy evaluation indexes of the enrolled patients showed that, compared with the pre-treatment period, the TC, TG, HDL-C and FBG of the patients treated with oral *D. officinale* powder showed a tendency to improve, with a significant difference in the improvement of TG and FBG (fig. 2) and the mean value of FBG also reached the range of the expected target (The target value range of FBG < 6.1 mmol/L). The above results suggest that *D. officinale* can improve MetS by significantly regulating the TG and FBG levels of patients. And no adverse effects were observed during the treatment period.

The secondary efficacy evaluation indexes of the MetS patients, including BMI and waistline, were monitored every two weeks during the above treatment. As shown in fig. 2, the BMI and waistline of MetS patients were significantly improved after every two weeks of oral *D. officinale* powder.

Network pharmacology analysis

A total of 313 secondary metabolic constituents in *D. officinale* were collected from the literature. These chemical components belonged to alkaloids, flavonoids, bibenzyls, amides, phenolic glycosides, phenanthrenes, anthraquinones, organic acids and other types of compounds. Next, these secondary metabolites were imported into Swiss Target Prediction database and SEA database for docking simulation and 1446 potential therapeutic targets were predicted. On the other hand, the DisGeNET and TTD databases were employed to search with the keywords "Metabolic syndrome" and "MetS" and 18753 MetS-related targets were identified.

Table 1: ADME profile of the key components of *D. officinale* as forecasted by SwissADME

Compounds	Physicochemical properties					Solubility			Pharmacokinetics		Medicinal Chemistry	
	MW	HB donors	HB acceptors	Rotatable bonds	Consensus log P	Log S (ESOL)	Log S (Hussain et al.)	Log S (SILICOS-IT)	GI absorption	CYP enzymes inhibitors	P-gp substrate	Pains alert
Vicenin II	594	11	15	5	-1.98	Soluble	Soluble	Soluble	Low	No	Yes	0
Schaftoside	564	10	14	4	-1.68	Very soluble	Soluble	Soluble	Low	No	Yes	0
Isoschaftoside	564	10	14	4	-1.64	Very soluble	Soluble	Soluble	Low	No	Yes	0
Apigenin 6,8-di-C-arabinoside	534	9	13	3	-1.30	Very soluble	Soluble	Soluble	Low	No	No	0
Vicenin III	564	10	14	4	-1.71	Very soluble	Soluble	Soluble	Low	No	Yes	0
Vicenin II	594	11	15	5	-1.98	Soluble	Soluble	Soluble	Low	No	Yes	0

The intersection of the targets was used to identify 1385 potential targets of *D. officinale* for intervening in MetS by using the Venn diagram (fig. 3). These 1385 intersection targets were input into STING 11.0, the minimum intersection score was set ≥ 0.7, to obtain 226 targets. Among them, EGFR, FGFR1, MAPK1, PIK3CA, PTP1B were the top 5 targets with node degree. Next, the 226 targets obtained and the 135 components of *D. officinale* associated with them were topologically analyzed using Cytoscape 3.8.0 software to create a network of component-target, which was classified based on the magnitude of the degree and the main components of *D. officinale* were identified and the top 5 ranked components were Isoschaftoside, Vicenin II, Schaftoside, Apigenin 6,8-di-C-arabinoside, Vicenin III (fig. 3).

GO functional enrichment and KEGG pathway analysis were conducted for 226 PPI network targets. The top 5 were then visualized as bar charts. In biological processes (BP), *D. officinale* has a great influence on protein phosphorylation, protein autophosphorylation, phosphorylation of peptidyl-serine, the negative regulation of apoptotic processes and the positive regulation of transcription from RNA polymerase II promoters. At the molecular level, the functions of *D. officinale* constituents are mainly primarily associated with activities such as protein serine, threonine and tyrosine kinase, ATP binding, enzyme binding and protein kinase functions. The targets in cellular components are closely related to cytosol, nucleus, cytoplasm, nucleoplasm, macromolecular complex activities (fig. 4A).

Fig. 4B showed the top 20 enriched results obtained from KEGG pathway analysis. Pathways unrelated to MetS, such as "Pathways in cancer", were excluded. Finally, the pathways primarily pertain to lipids and atherosclerosis, thyroid hormone signaling pathway, PI3K-Akt signaling pathway, mechanisms of endocrine resistance, AGE-RAGE signaling pathway associated with diabetic complications, neurotrophin signaling pathway, chemokine signaling pathway, resistance to EGFR tyrosine kinase inhibitor, the synthesis, secretion and action of growth hormone, T cell receptor signaling pathway, as well as the signaling pathway related to fluid shear stress and atherosclerosis (fig. 4B). Thus, the results indicated that the active ingredients of *D. officinale* might treat MetS by acting on these pathways.

ADME analysis

Drug-likeness was analyzed to check whether the top 5 key components of *D. officinale* (Isoschaftoside, Vicenin II, Schaftoside, Apigenin 6,8-di-C-arabinoside, Vicenin III) possess favorable ADME properties. An effective oral medication should exhibit favorable aqueous solubility, which can be estimated using models such as ESOL, ALI logS and SILICOS-IT logS.

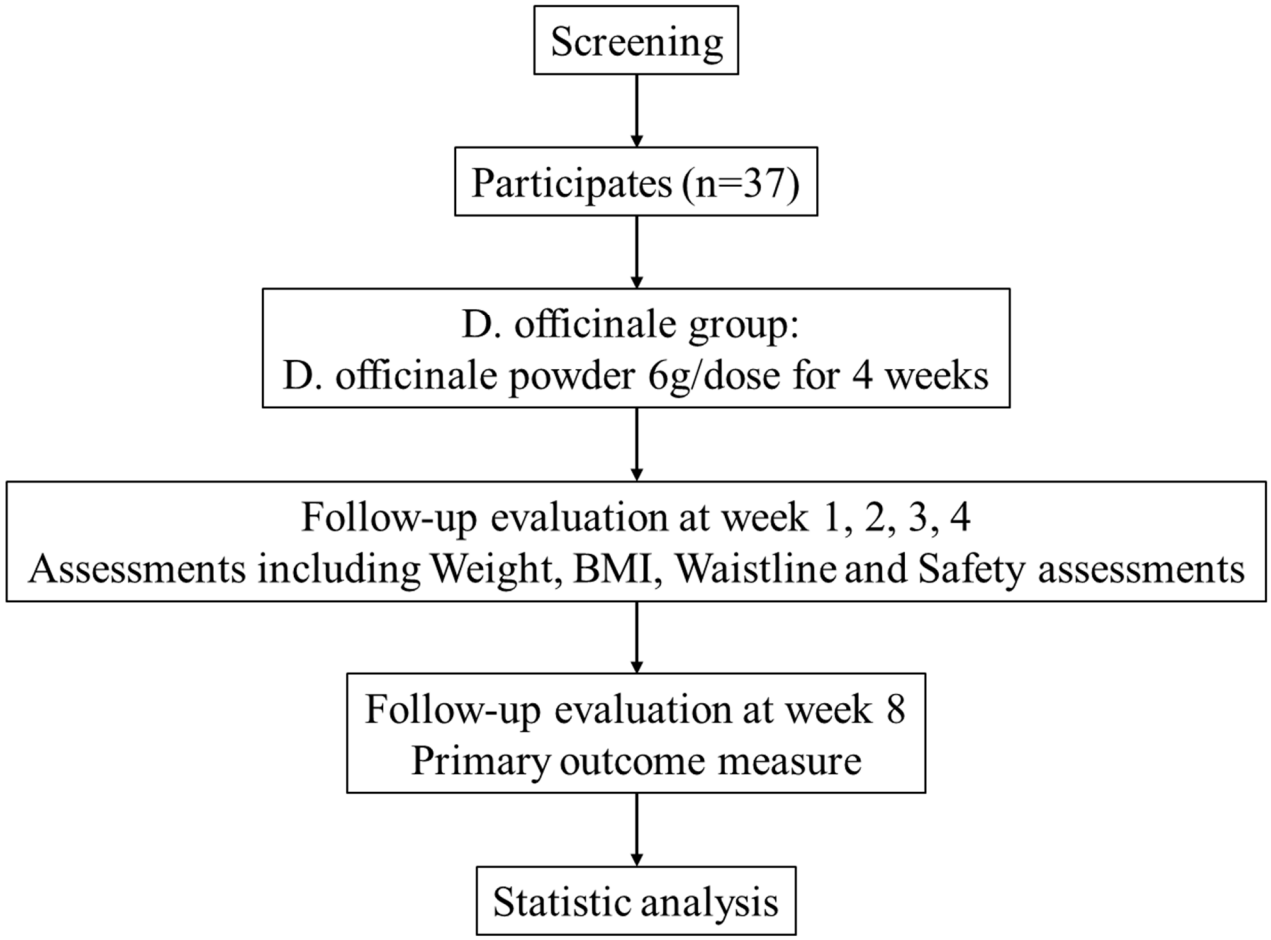

Fig. 1: The clinical flowchart.

Table 2: Molecular docking binding ability of active ingredients and potential targets of *D. officinale* (kcal/mol)

Chemical name	EGFR	FGFR1	MAPK1	PIK3CA	PTP1B
Vicenin II	-7.0	-8.4	-9.6	-9.5	-7.4
Schaftoside	-7.3	-8.1	-9.3	-9.4	-8.0
Isoschaftoside	-7.3	-8.5	-9.4	-9.0	-7.3
Apigenin 6,8-di-C-arabinoside	-7.2	-8.4	-9.2	-9.6	-7.2
Vicenin III	-7.9	-8.9	-9.7	-9.4	-7.1

Furthermore, it is essential for the drug to adhere to Lipinski's five rules, which stipulate that the molecular weight should not exceed 500 g/mol, the number of HBA should be limited to 10 or fewer, the number of HBD should be 5 or fewer, the LogP value should be 5 or less and the total number of rotatable bonds should not exceed 10(Lipinski *et al*., 2001). Drug-likeness analysis of the top 5 components of *D. officinale* was listed in table 1.

Molecular docking

For molecular docking validation of potentially important active ingredients of *D. officinale* and their candidate key targets, the above 5 key ingredients (Vicenin II, Schaftoside, Isoschaftoside, Apigenin 6,8-di-C-arabinoside, Vicenin III) and 5 potential target proteins (EGFR, FGFR1, MAPK1, PIK3CA, PTP1B) screened by network pharmacology were selected as ligands and receptors, respectively, to validate their interactions. The affinity < -7 kcal/mol represents good binding between the ingredients and targets. The results of molecular docking showed strong binding between these ingredients and targets (table 2, fig. 5).

Verification of results by biological evaluation

The results of PTP1B inhibition indicated that Vicenin II and Schaftoside exhibited inhibitory activitiy against PTP1B, with IC_{50} values of 6.94±0.22 μM (Vicenin II) and 6.33±0.21 μM (Schaftoside). Correspondingly, the outcomes were below the standards set by the positive control ($NaVO_4$, 12.65±1.60 μM).

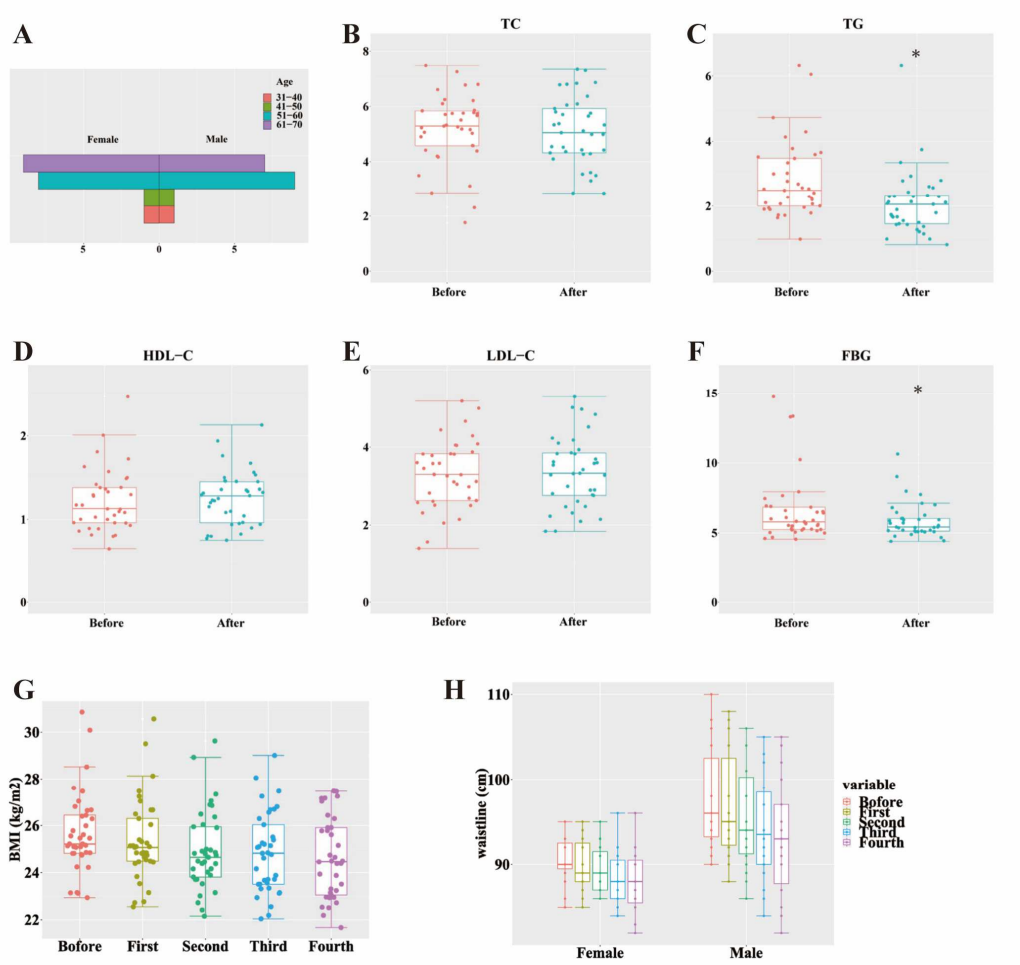

Fig. 2: Clinical efficacy of D. officinale in treating MetS. (A) Changes in serum triglyceride (TG) levels before and after treatment. (B) Changes in fasting blood glucose (FBG) levels before and after treatment. (C) Dynamic changes in body mass index (BMI) during the 4-week treatment period. (D) Dynamic changes in waist circumference during the 4-week treatment period. (E) Changes in total cholesterol (TC) levels before and after treatment. (F) Changes in high-density lipoprotein cholesterol (HDL-C) levels before and after treatment. (G) Schematic diagram of the participant inclusion and exclusion criteria process. (H) Demographic characteristics of the enrolled MetS patients.
Data in subfigures A-F and H are presented as mean ± SD. Statistical significance is indicated as $*P < 0.05$ vs. baseline (pre-treatment).

Furtherly, the kinetic behavior of Vicenin II and Schaftoside in relation to PTP1B was analyzed utilizing Lineweaver-Burk and Dixon plots. As illustrated in fig. 5 A, the maximum rate of the reaction catalyzed by PTP1B remained constant despite an increase in substrate concentration, while the K_m was increased. Therefore, Vicenin II is a competitive inhibitor against PTP1B. Whereas, the K_m value of Schaftoside increased with increasing inhibitor concentration and the reaction rate decreases. So, Schaftoside is a mixed-type inhibitor against PTP1B (fig. 6 C). In Dixon plot (fig. 6 B-D), The K_i values for Vicenin II and Schaftoside were established at 6.37 µM and 5.31 µM, respectively, indicating their potential as natural inhibitors of PTP1B.

DISCUSSION

MetS is a multifaceted metabolic disorder which can damage multiple organs. For the treatment of metabolic syndrome, TCM has unique advantages due to its holistic concept and Regulation involving multiple targets. In the present work, we explored the potential effective components and their modes of action in treating MetS with *D. officinale* based on clinical datasets, network pharmacology, molecular docking, ADME analysis and in vitro enzyme activity assessment. First, the clinical trial results indicated that TG, FBG, BMI and waistline indexes of MetS patients were significantly improved after the intervention of *D. officinale*. To the best of our knowledge, this is the first report of clinical trial data on *D. officinale* for MetS.

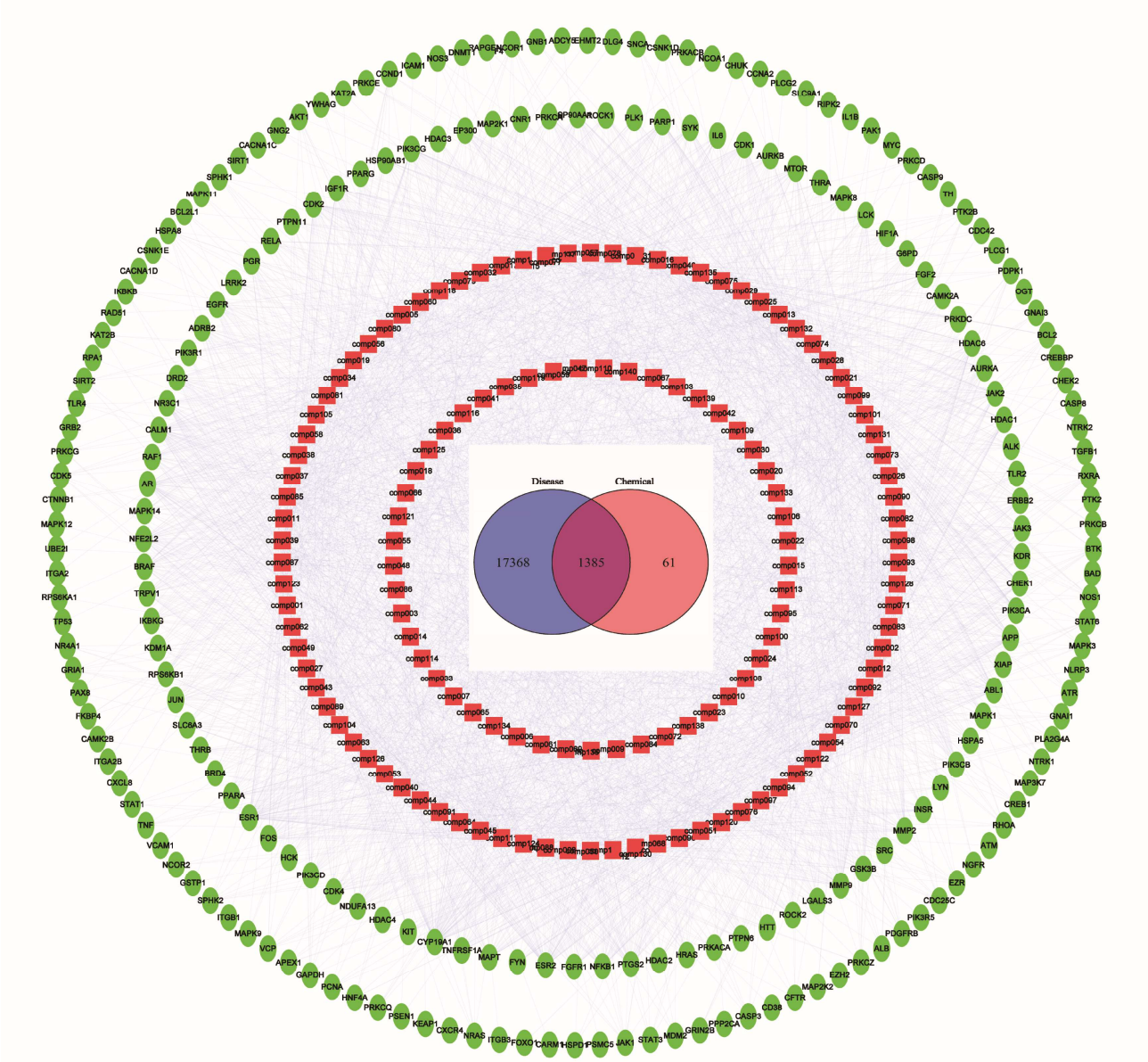

Fig. 3: Active Ingredients-Target Network Analysis of *D. officinale*

Next, the results of the network pharmacology analysis showed that EGFR, FGFR1, MAPK1, PIK3CA, PTP1B were the 5 main targets of MetS being intervened by *D. officinale.* And compounds of Isoschaftoside, Vicenin II, Schaftoside, Apigenin 6,8-di-C-arabinoside and Vicenin III were likely to be the top 5 that play a key role in this process. To test this conjecture, we modeled the interactions between these compounds and their targets by molecular docking and the results showed that they have a good affinity for each other.

PTP1B serves as a critical regulator of insulin signaling pathways(He *et al*., 2022), inhibition of PTP1B has been reported to be effective in managing MetS(Hussain *et al*., 2019; Nandi *et al*., 2020; Tan *et al*., 2023c; Teimouri *et al*., 2022). Considering the availability of compounds and enzymes, in the present study, the bioactivity verification was performed by using the pNPP method to detect the inhibitory activity of two flavonoid-carbon glycoside components (Vicenin II, Schaftoside) of *D. officinale* against PTP1B. The results indicated that Vicenin II, Schaftoside possessed stronger PTP1B inhibitory activity than the positive control and is a potential natural PTP1B inhibitor. This result is consistent with the fact that Schaftoside has been reported in the literature to inhibit PTP1B(Balli *et al*., 2019).

CONSLUSION

D. officinale is effective in improving MetS in patients.

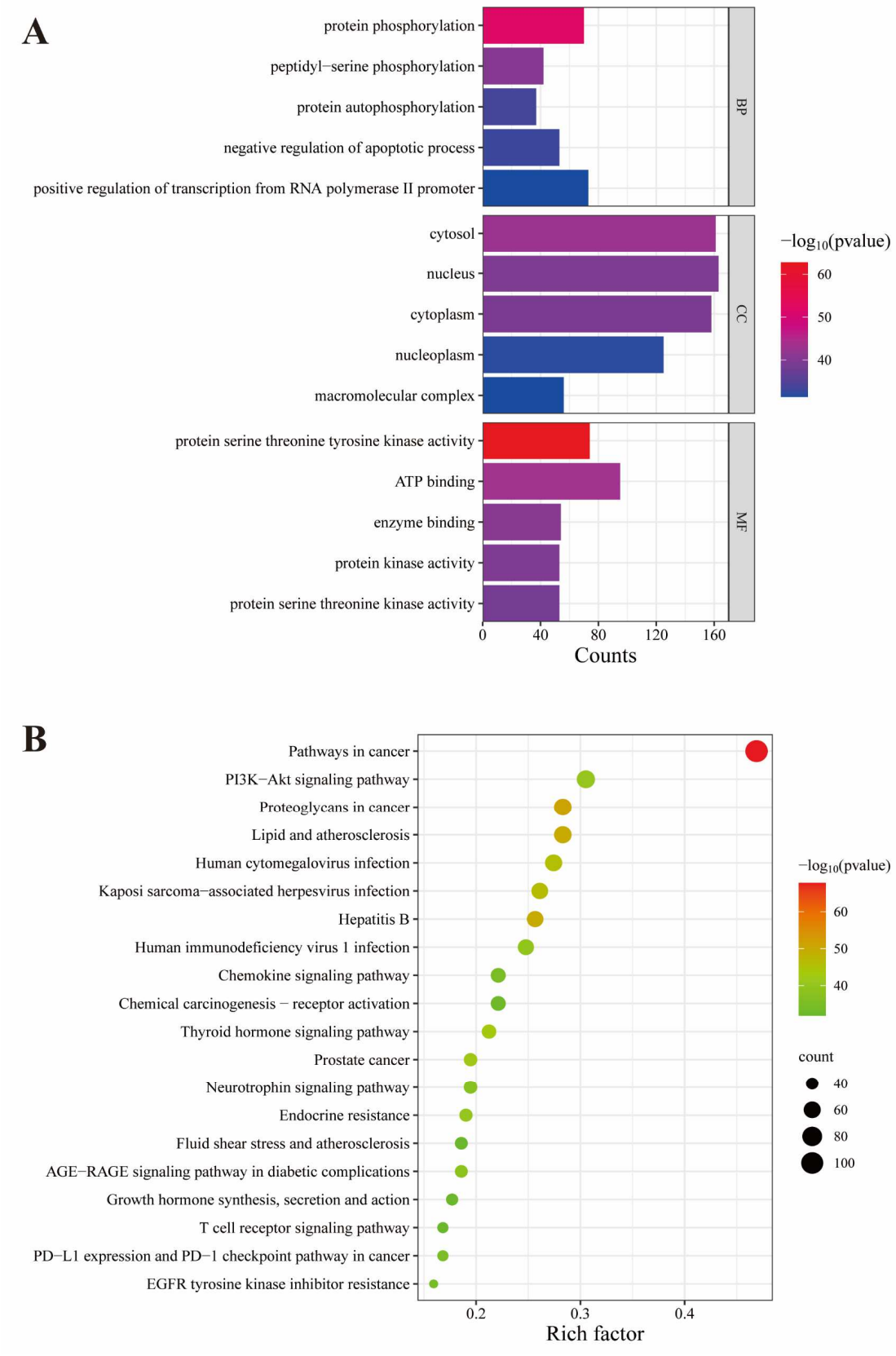

Fig. 4: GO function (A) and KEGG (B) enrichment analysis of potential targets of *D. officinale*

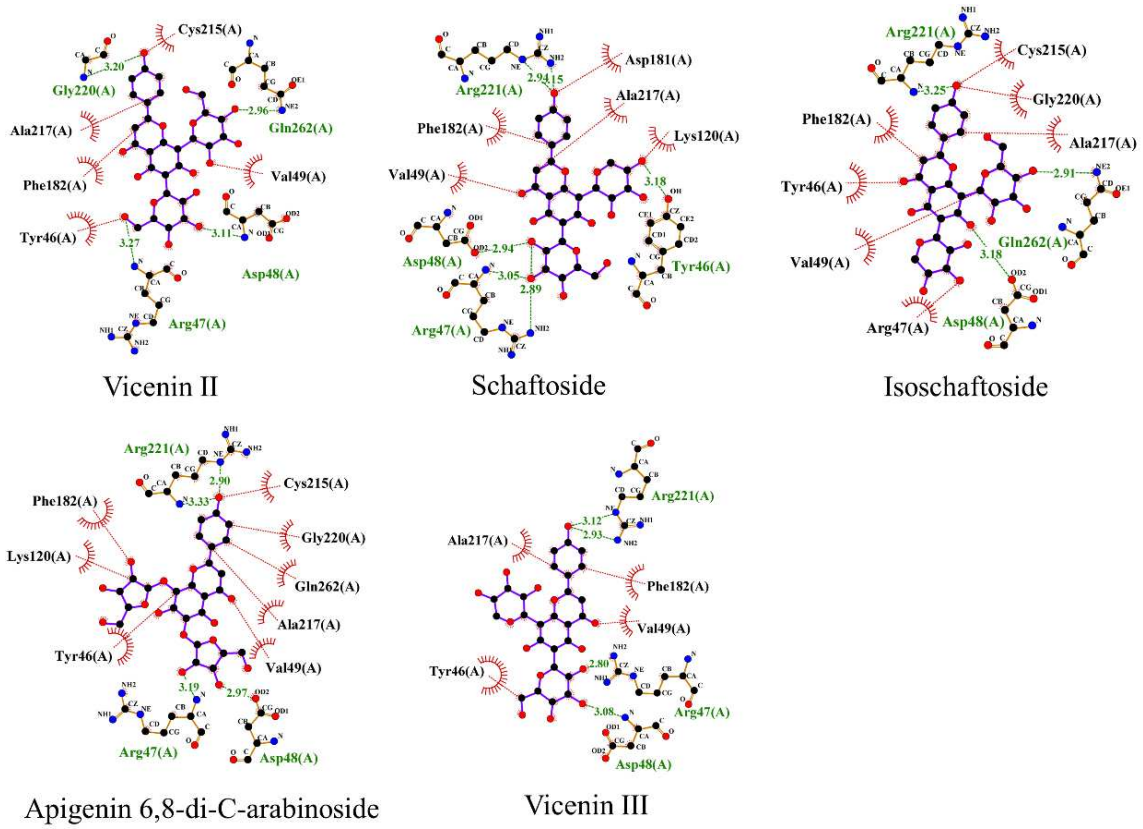

Fig. 5: Docking pose of potential active instituents of *D. officinale* with PTP1B target.

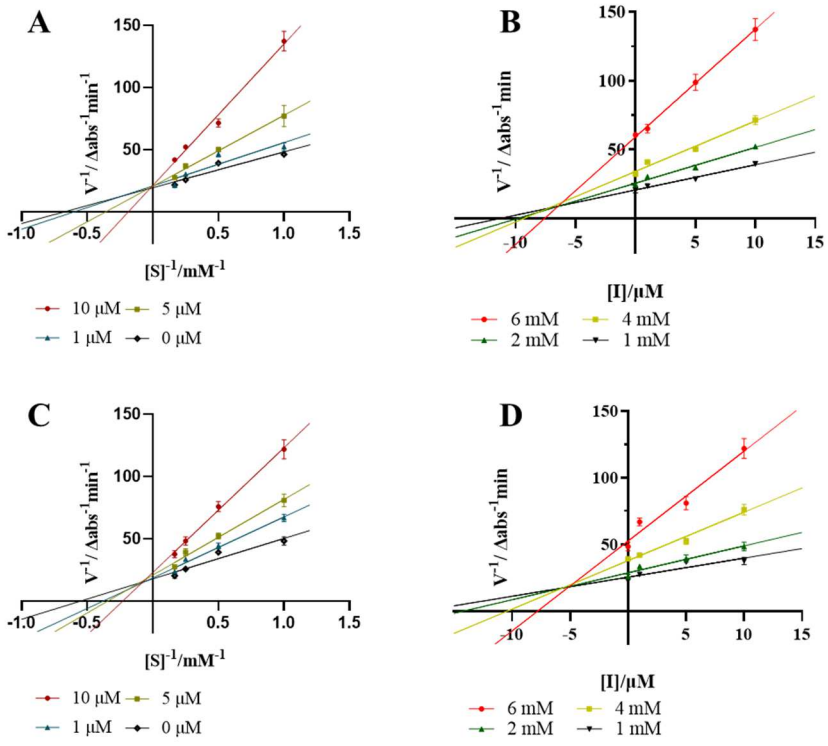

Fig. 6: Lineweaver-Burk plots for PTP1B inhibition of Vicenin II (A), and Schaftoside (C). Dixon plots for PTP1B inhibition of Vicenin II (B), Schaftoside (D). Each value was expressed as means±SD of three replications.

This may be mainly due to the action of Vicenin II and Schaftoside contained in *D. officinale* by inhibiting the activity of PTP1B enzyme.

Acknowledgement
Not applicable.

Authors' contributions
J. W.: wrote the manuscripts and analyzed the data. Q. H. and L. Q.: conducted experiments and assisted in the writing of the article. X. W. and M. W.: involved in analysis of the data, reviewed and revised the paper. Y. H. and D. T.: provided direct design of the experiment and funding acquisition. All authors have approved the final version of the manuscript and agreed to be accountable for all aspects of work.

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Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article.

Ethical approval
The clinical trial was approved by the Medical Ethics Committee of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (Approval number: 2020LCSY021) and registered (ChiCTR2000034550). Informed consent was obtained from all participants.

Conflict of interest
The authors declare no competing financial interest.

Supporting information
Supporting information may be found in the online version of this article.

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