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Comparative analysis of the secondary metabolites of *Dendrobium officinale* from different growing origins by UPLC-Q/TOF-MS

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Abstract

Dendrobium officinale is a famous traditional Chinese medicine and nourishing food in China. The active constituents in *D. officinale* include a variety of chemical components such as polysaccharides, bibenzyl, phenanthrenes, and flavonoids etc. Among them, polysaccharide was selected as the quality control marker for *D. officinale* in the Chinese Pharmacopoeia. The previous studies found that the content of polysaccharide constituents in *D. officinale* from different growing origins had significant differences. To the best of our knowledge, whether the secondary metabolites other than polysaccharides are similarly different in *D. officinale* from different origins has not been reported. In the present continuing study, UPLC-Q/TOF-MS coupled with multivariate analysis were employed for comparative analysis of the secondary metabolites of *D. officinale* from different growing origins. At last, 12 differential secondary metabolites of *D. officinale* from different origins were identified. Network pharmacological analysis results indicated that these differential secondary metabolites of *D. officinale* from different origins are mainly involved in neuropsychiatric related disorder diseases. This investigation will provide a valuable information for doctors and consumers in clinical practice.

Keywords: *Dendrobium officinale*; chemical constituents; secondary metabolites; network pharmacology; neuropsychiatric diseases.

Practical Application: This investigation provides a valuable information for consumers and researchers to understand *D. officinale*.

1 Introduction

In recent years, the R&D of natural functional products from natural plants has attracted increasing attention in the world (Wang et al., 2022a, b). The genus *Dendrobium* contains approximately 1100 species, which is one of the largest genera in the family Orchidacea, and mainly distributed in southwestern Asia, Europe and Australia, such as China, Thailand, Myanmar and Vietnam (Yu et al., 2015). In traditional medicine, several *Dendrobium* species are used for various diseases or as beverages (Xu et al., 2013). Among them, the stems of *Dendrobium officinale* is the most dominant sources of Shihu, a well-known famous traditional Chinese medicine and nourishing food with thousands of years of history in China (Chinese Pharmacopoeia Commission, 2020), which is widely distributed throughout the world (Tang et al., 2017). In particular, *D. officinale* is widely grown in various regions of China, including Zhejiang, Guizhou, Fujian, Anhui, Hunan, Guangxi, Yunnan and other provinces (Liu et al., 2020; Yan et al., 2015; Yang et al., 2020). In traditional medicine, *D. officinale* was as a tonic to nourish Yin, clear heat, nourish stomach, and replenish body fluid (Cakova et al., 2017; Shin et al., 2017) and used for various diseases or as beverages (Cakova et al., 2017; Tan et al., 2023a, b). According to modern pharmacological effects, *D. officinale* exhibits various pharmacological effects such as antioxidant, enhancing immunity, anti-fatigue, hypotension, hypoglycemia, and others (He et al., 2022; Huang et al., 2019; Lv et al., 2020).

Phytochemical investigations showed that more than 190 compounds were found in *D. officinale*, such as polysaccharides, bibenzyl, phenanthrenes, flavonoids, alkaloids, amino acids, and other nutritional components (He et al., 2022). Among them, polysaccharides was selected as the quality control marker for *D. officinale* in the *Chinese Pharmacopoeia* (Ch.P., 2020 edition) (Chinese Pharmacopoeia Commission, 2020). In our previous studies, it was found that the polysaccharide content of *D. officinale* could be affected by its growing origins (Tan et al., 2020, 2023a; Zeng et al., 2020). To the best of our knowledge, whether the secondary metabolites other than polysaccharides are similarly different in *D. officinale* from different origins has not been reported. Due to the superiorities of high resolution, good selectivity, and shorter analysis time of ultra-high performance liquid chromatography coupled with Q/TOF-MS (UPLC-Q/TOF-MS), the method has been widely used as a powerful tool for qualitative analysis of secondary metabolites in traditional Chinese medicine (Lu et al., 2022). In the present continuing study, UPLC-Q/TOF-MS coupled with multivariate analysis were employed for comparative analysis of the secondary metabolites of *D. officinale* from different growing origins.

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The results indicated that 12 differential secondary metabolites of *D. officinale* from different origins are mainly involved in neuropsychiatric related disorder diseases. This investigation will provide a valuable information for consumers and researchers to understand *D. officinale*.

2 Materials and methods

2.1 Chemicals

LC-MS grade reagents such as acetonitrile, formic acid and water were purchased from Merck, Sigma-Aldrich, and Watsons, respectively. The other analytical reagents were purchased from Chengdu Kelong Chemical Reagent Factory.

2.2 Plant materials

All *D. officinale* samples were harvested from the Good Agricultural Practices (GAP) bases located in Zhejiang and Guizhou Province of China in 2019 as described previously (Tan et al., 2023a) (Table S1). All samples were authenticated by Associate Professor Daopeng Tan (pharmacognosy, Zunyi medical university).

2.3 Sample preparation

All samples were processed as described previously with some modifications (Lu et al., 2022). The fresh stems of *D. officinale* samples were dried at 60 °C and then grounded into powder for the assay. 75 mg *D. officinale* powder was precisely weighed, added with 70% methanol 1 mL, and then extracted by ultrasonication (400 W, 50 kHz) for 30 min. After cooling, the solution was centrifuged at 12000 rpm for 5 min, and the supernatant was loaded into the injection vial for UPLC-Q-TOF/MS analysis.

2.4 Instrument conditions

Instrument conditions were set as described previously with some modifications (Lu et al., 2022). Agilent 1290 Infinity II UPLC liquid chromatograph system was employed for the present secondary metabolites analysis. The separation was performed by the Waters CORTECS UPLC C18 (100 mm × 2.1 mm, 1.6 μm) chromatographic column with 0.1% formic acid water (A) - 0.1% formic acid acetonitrile (B) as the mobile phase, and the gradient elution conditions was set as: 0-2 min,0% B;2-4 min,5% B;4-8 min,20% B;8-15 min,30% B;15-22 min,60% B;22-30 min,84% B;30-35 min,90% B;35-40 min,5% B;40-45 min,5% B. Flow rate: 0.4 mL/min, column temperature: 40 °C, injection volume: 5 μL.

Mass spectrometry conditions: Agilent 6545 Q-TOF high-resolution mass spectrometry was used, with separate acquisition in positive and negative ion modes. Ion source parameters: capillary voltage (CV) of 4000 V, nozzle voltage (NV) of 1000 V, atomization gas pressure of 45 psi, dry gas flow rate of 10 L/min, sheath gas temperature of 350 °C, sheath gas flow rate of 11 L/min; ion source temperature (TEMP) of 350 °C, collision energy (Wang et al., 2016) of 10 V, mass scan range of m/z 50 ~ 1200. The secondary mass spectrometry information was acquired in Auto MS/MS mode with CEs of 20, 30, and 40 V, respectively.

2.5 Identification of secondary metabolites of D. officinale

The mass spectrometry data were imported into Agilent MassHunter Profinder 10.0 software for peak matching, peak alignment, ion fusion and deconvolution processing. Based on the peak area, retention time and molecular weight, the fragmented peaks with false positives were excluded. The corresponding molecular formulae were obtained by fitting and calculating with Qualitative Analysis B.07.00 software, and matched with the local database for preliminary structure inference. The chemical composition was further identified based on the secondary mass spectrometry data with the information provided by references, Scifinder database, etc.

2.6 Differential secondary metabolites mining

The mass spectrometry data after excluding false positives were analyzed by unsupervised Principal Component Analysis (PCA) and supervised Orthogonal projections on the latent structure-discrimination analysis (OPLS-DA) and Projections on the latent structure-discrimination analysis (PLS-DA) with SIMCA 14.1 software. The feasibility of the model was tested based on the Permutation test, and the threshold value of Variable importance in the projection (VIP) greater than 4 was used to screen the differential secondary metabolites.

2.7 Mining for potential targets of differential secondary metabolites

The 3D structures of the differential chemical components of *D. officinale* were searched through the PubChem Compound (National Center for Biotechnology, 2022) database in the National Center for Biotechnology Information (NCBI) or the 2D structures were drawn using ChemBioDraw Ultra 14.0. The Swiss Target Prediction database (Swiss Institute of Bioinformatics, 2022a) and SEA database (Shoichet Lab, 2022) were used to predict the targets of the Dendrobium components, and the biological sources of the targets were set to " homo sapiens". The targets with probability values greater than 0 in the Swiss Target Prediction database and $P < 0.05$ in the SEA database were selected as the potential targets of the differential secondary metabolites. All targets were normalized to Gene symbols by BioDBnet database (https://biodbnet-abcc.ncifcrf.gov/db/db2db.php), and duplicate values were removed.

2.8 KEGG and disease enrichment analysis of potential targets of differential secondary metabolites

KEGG pathway enrichment analysis was performed by STRING database (Swiss Institute of Bioinformatics, 2022b), with FDR < 0.05 as the screening condition, and sorted by FDR value from smallest to largest. Disease enrichment analysis of potential targets of action was performed by using the bioinformatics platform tool WebGestalt (2022), selecting the Over-Representation Analysis (Ruiz-Cisneros et al.) method, with the Funtional Database set to "Disgenet", confidence interval for BH statistics was FDR<0.05, and minimum protein number was 5 (Nmin=5).

3 Results and discussion

3.1 Identification of secondary metabolites of D. officinale

The data of secondary metabolites of *D. officinale* collected by LC-MS were fitted and calculated by Qualitative Analysis B.07.00 software to obtain the corresponding molecular formulae and matched with the local database for preliminary structure inference. The identification was based on the secondary mass spectrometry data, the retention time of the control, the precise molecular weight and the fragmentation pattern of the high-energy secondary fragments of the existing controls, as well as the information provided by the reported references and the Scifinder database. At last, 95 small molecule compounds were initially identified (Figure S1, Table S2), including flavonoid glycosides, bibenzyl, alkaloids, organic acids, sugars, etc.

3.2 Profile difference analysis of secondary metabolites of D. officinale from different origins

In order to compare the effects of different origins on the secondary metabolites of *D. officinale*, unsupervised pattern recognition principal component analysis (PCA) was first applied to Dendrobium samples from Dushan, Danzhai, Xinyi, Taizhou and Yueqing. As shown in Figure 1A, in the PCA plots, the secondary metabolite profiles of Dendrobium samples from the five origins were not clearly distinguished, but the samples from Xinyi, showed a separation trend in the PC1 direction. Further analyzed by the least partial squares analysis (PLS-DA), it can be found that the samples from Xingyi are obviously independent from the other origins (Figure 1B). These results indicated that the secondary metabolites of *D. officinale* from Xingyi are obviously different from the other origins.

3.3 Differential secondary metabolites of D. officinale from different origins

To investigate the differential secondary metabolites of *D. officinale* from different origins, in this study, Xingyi samples was used as the model samples and compared with Dushan, Danzhai, Taizhou and Yueqing samples by the OPLS-DA method, respectively. As shown in Figure 2, the fitted parameters were R2X=0.494, RY2=0.956, and Q2=0.879 for Xingyi *vs* Dushan at 95% confidence interval (Figure 2A); R2X=0.454, RY2=0.946, and Q2=0.911 for Xingyi *vs* Denzhai at 95% confidence interval (Figure 2B); R2X=0.356, RY2=0.835, Q2=0.711 for Xingyi *vs* Taizhou at 95% confidence interval (Figure 2C); Xingyi *vs* Yueqing, at 95% confidence interval, the fitted parameters are R2X=0.526, RY2=0.955, Q2=0.868 (Figure 2D).

The VIP value distribution map in the OPLS-DA model was used to screen the points with VIP values greater than 4 as the differential components between the two groups, respectively (Figure 3), and the black dashed line represents the differential components between the two groups with VIP values greater than 4. The intersection of the four groups A, B, C and D was taken, at last, 16 differential secondary metabolic components were screened (Figure 4).

Based on the results of the identification of Dendrobium secondary metabolites described as Table S1, 12 chemical components were finally identified among the 16 differential secondary metabolites, including: L-tert-Leucine (**83**), 4-[(5-Hydroxy-3-methyl-1-oxo-2-penten-1-yl)amino]-butanoic acid methyl ester or isomer (**62**), Methyl N-acetyl-sibirosaminide or isomer (**64**), Verpacamide A or isomer (**65**), N-tert-Butoxycarbonyl-L-glutamic acid dimethyl ester or isomer (**69**), 2-Methyl-1H-indol-7-yl-β-D-mannopyranoside or isomer (**73**), D-Ribo-Phytosphingosine or isomer (**74**), Adenophoraside A or isomer (**75**), Pinellic acid (**88**), N-(2,4,10,17-Tetrahydroxyheptadecyl)-acetamide or isomer (**77**), 2-Propen-1-yl 2-(acetylamino)-2-deoxy-3-O-β-D-galactopyranosyl-6-O-methyl-α-D-galactopyranoside (**79**), and 6-O-L-isoleucyl-sucrose (**80**). By comparing the abundance of these 12 differential chemical components in different origins, the results showed that their abundance in the Xingyi sample was significantly higher than that in the other four origins, $P<0.05$ (Figure 5).

3.4 Network pharmacological analysis of differential secondary metabolites of D. officinale from different origins

The Swiss Target Prediction database was used for target prediction of 12 differential secondary metabolic components,

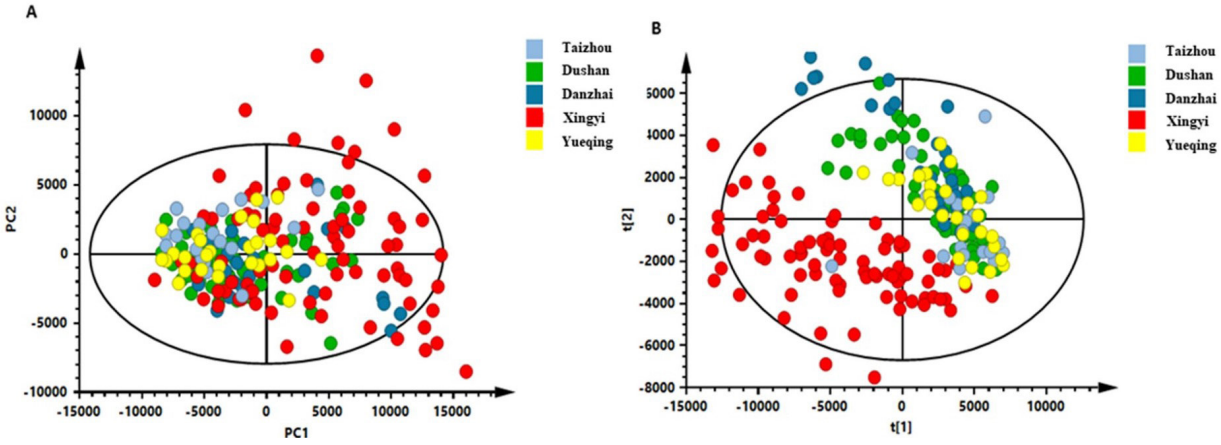

Figure 1. The effect of origins on spectrum of secondary metabolites in *D. officinale* (A) PCA maps of five origins; (B) PLS-DA maps of five origins.

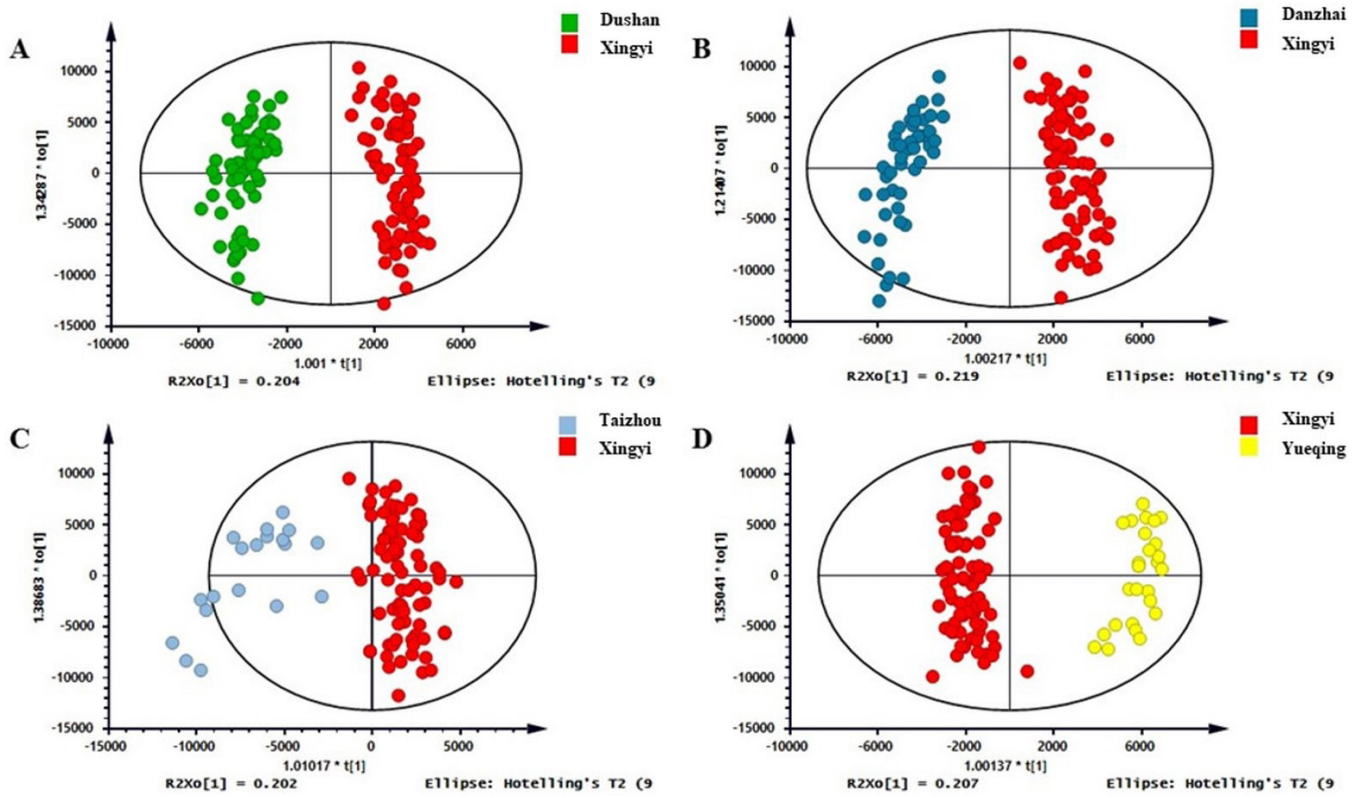

Figure 2. OPLS-DA of screening different metabolites of *D. officinale*; (A) Xingyi *vs* Dushan; (B) Xingyi *vs* Danzhai; (C) Xingyi *vs* Taizhou; (D) Xingyi *vs* Yueqing.

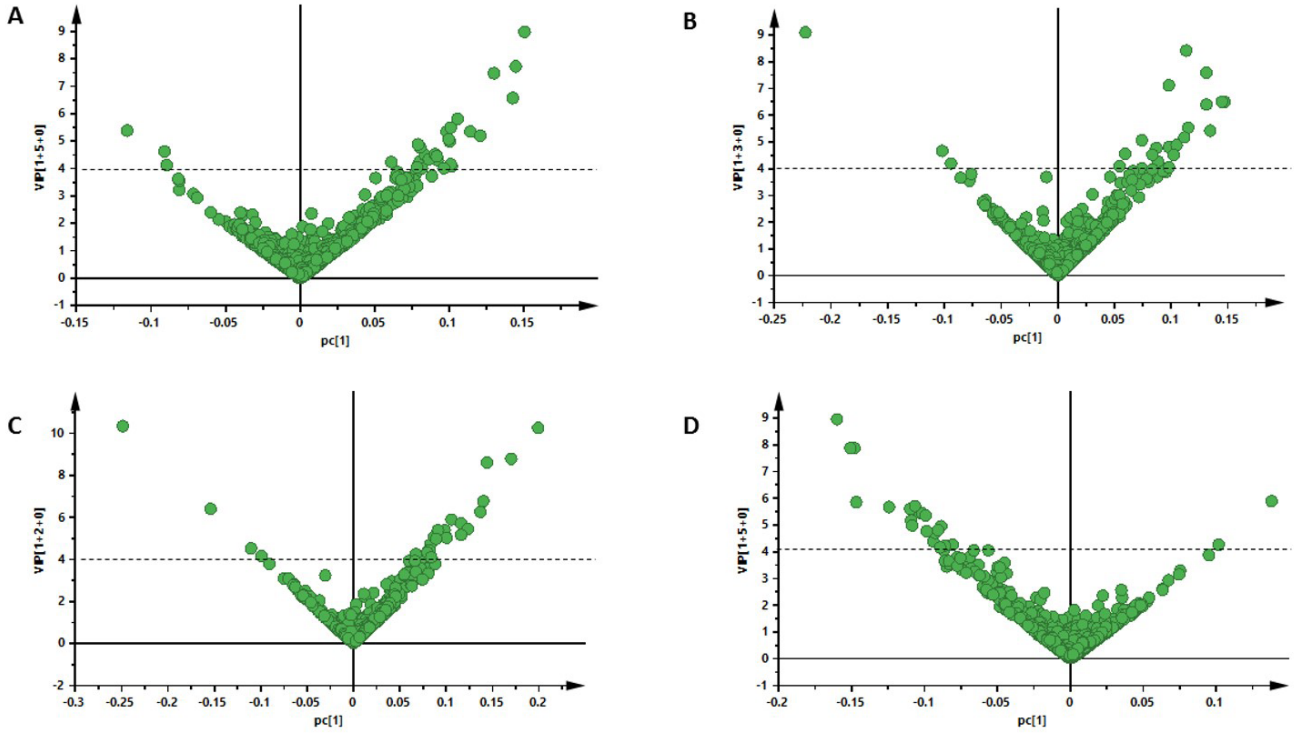

Figure 3. VIP plot of OPLS-DA model for screening different metabolites of *D. officinale*; (A) Xingyi *vs* Dushan; (B) Xingyi *vs* Danzhai; (C) Xingyi *vs* Taizhou; (D) Xingyi *vs* Yueqing.

and except for Methyl N-acetyl-sibirosaminide (**64**), which had no relevant targets, a total of 354 action targets were screened for the other 11 components. Further, Cytoscape software was used to construct a chemical composition-target network diagram (Figure 6), which included 465 nodes and 657 edges in total. The green squares represent the compounds, the red circles represent the action targets, and the black edges represent the interaction relationship between the compounds and the targets. The value of node degree indicates the number of routes connected to the node in the network, and the larger the value of node degree, the more important the point is in the network, indicating that it plays an important role in the network. Among the 11 components studied, the two components with the highest node degree values were N-tert-Butoxycarbonyl -L-glutamic acid dimethyl ester (**69**) and Pinellic acid (**88**), indicating that these two components have a key role in the pharmacological network.

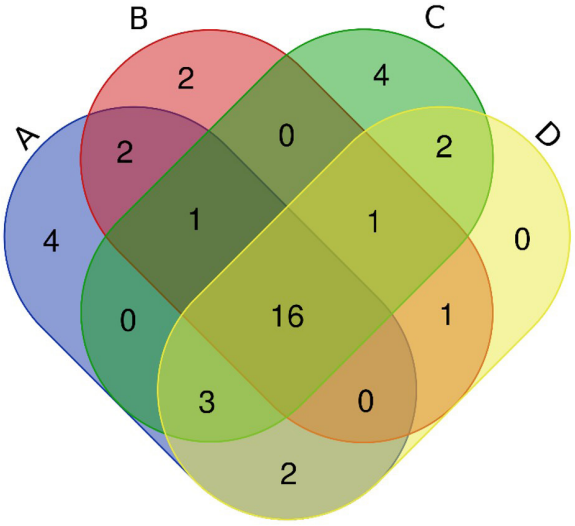

Figure 4. Venn diagram of OPLS-DA model for screening different metabolites at the breeding elevation of the near-wild *D. officinale*; (A) Xingyi *vs* Dushan; (B) Xingyi *vs* Danzhai; (C) Xingyi *vs* Taizhou; (D) Xingyi *vs* Yueqing.

Furtherly, the 354 potential targets screened were imported into the STRING database to produce protein interaction networks, and protein-protein interaction (PPI) data with a confidence score ≥ 0.9 were selected to create a visual network map using Cytoscape software (Figure 7). In the PPI network graph of potential targets of interaction consisting of 356 nodes and 2097 edges, the node size and color shades were proportional to the node Degree and BetweennessCentrality values, respectively. The PPI clusters are analyzed and can be divided into 21 clusters, of which there are 7 major clusters. The degree value of a node indicates the number of routes connected to that node in the network, and the larger the degree, the more important the point is in the network. There are four Degree > 50 in this network graph, which are lysophosphatidic acid receptor 1 (LPAR1), lysophosphatidic acid receptor 2 (LPAR2), lysophosphatidic acid receptor lysophosphatidic acid receptor 3 (LPAR3) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) with nodal values of 60, 59, 59 and 57, respectively.

3.5 KEGG analysis of differential secondary metabolites of D. officinale from different origins

The 354 potentially acting targets were enriched in KEGG pathways by STRING database, with FDR<0.05, P<0.05 as the screening condition, and sorted by FDR value from smallest to largest. KEGG enrichment analysis is to analyze multiple genes and expression information as a network for overall analysis, and KEGG pathway enrichment analysis was performed by STRING database to 354 potential action targets of *D. officinale* were enriched in 204 KEGG signaling pathways, and the top 20 pathways were selected for enrichment rate and gene number to present the location of the dots and the size of the dots. The pathways were mainly enriched in neuroactive ligand-receptor interactions (hsa04080), cancer pathway (hsa05200), calcium signaling pathway

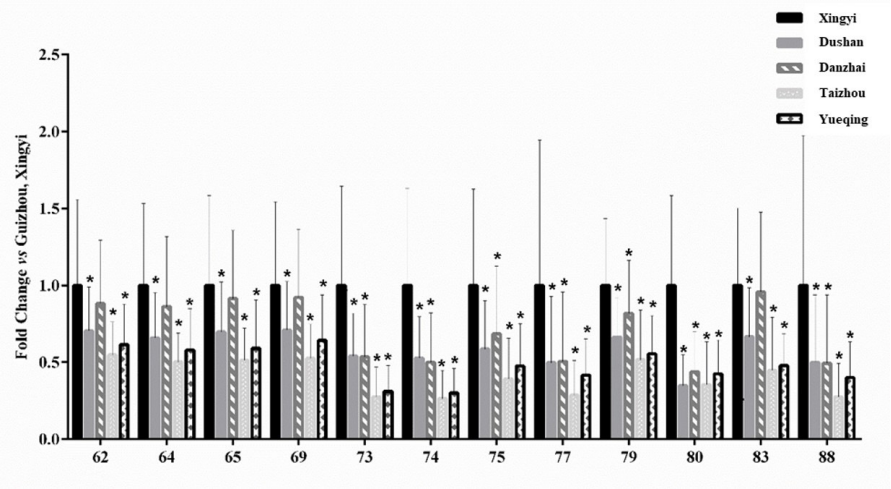

Figure 5. The bar chart of 12 screening different metabolites of *D. officinale* from different origins (¯x ±SD, *n*=19~81, **P* < 0.05).

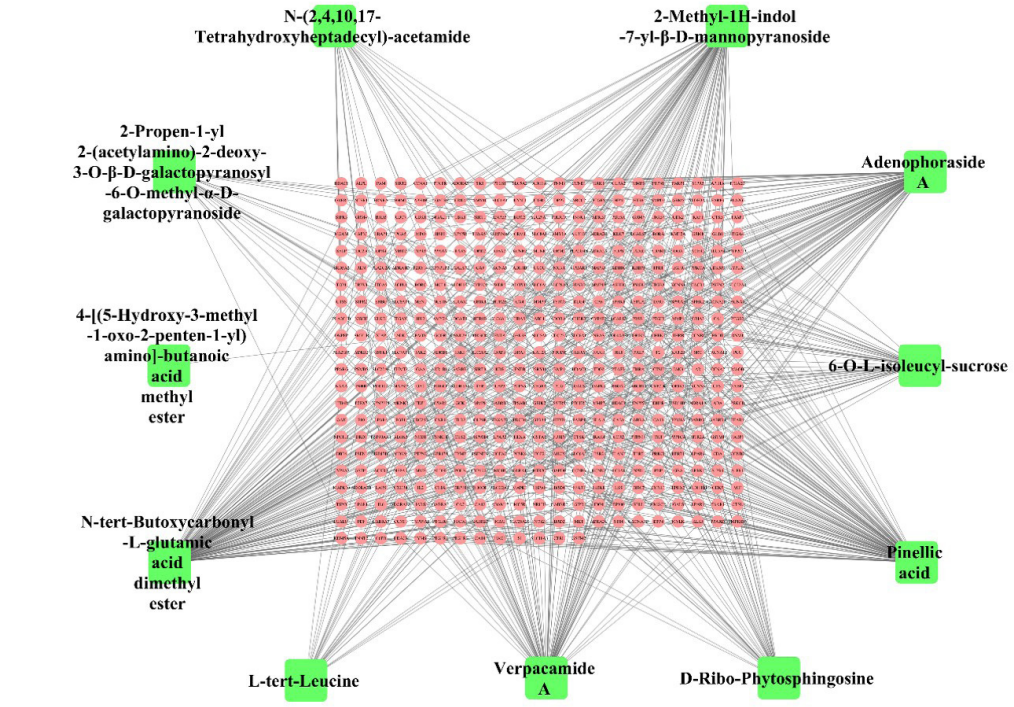

Figure 6. Characteristic chemical compositions - targets network of *D. officinale*.

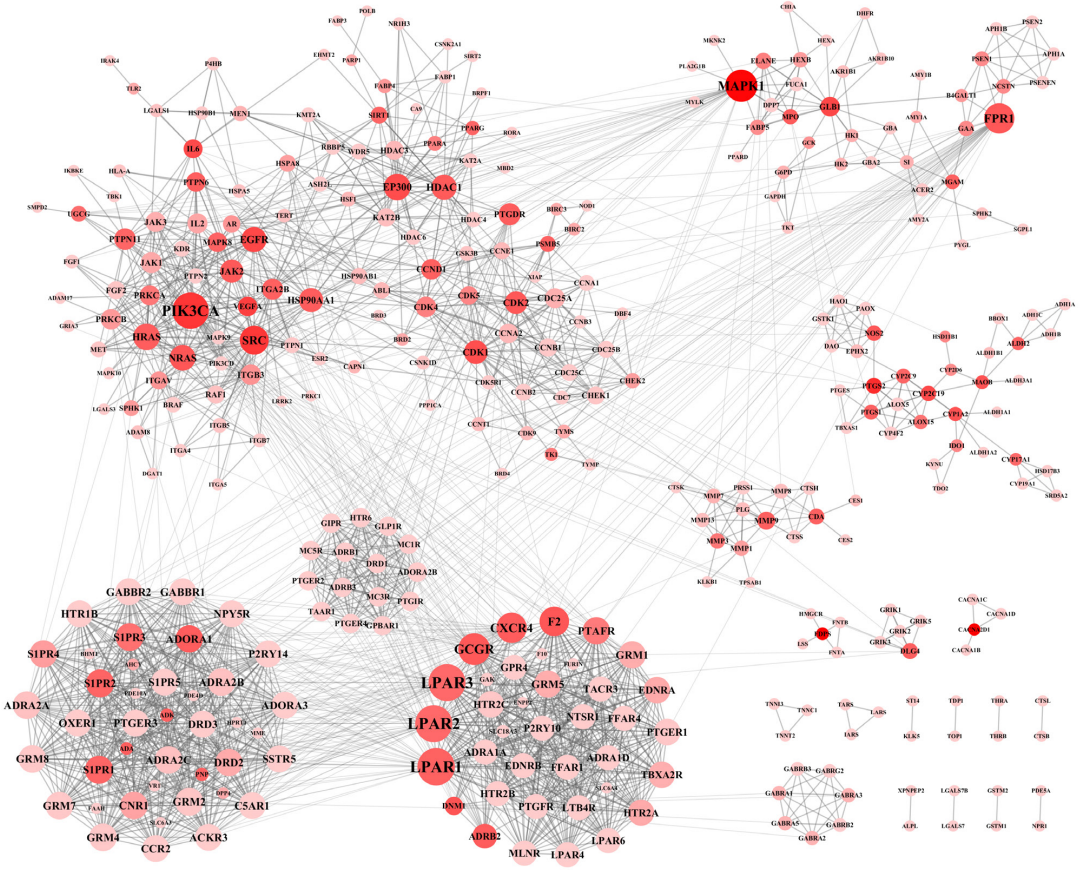

Figure 7. PPI network of targets of dominant chemical compositions of *D. officinale*.

(hsa04020), serotonergic synapses (hsa04726), metabolic pathway (hsa01100), and cAMP signaling pathway (hsa04024) (Figure 8).

3.6 Disease enrichment analysis of differential secondary metabolites of D. officinale from different origins

The bioinformatics platform tool WebGestalt was used to perform disease enrichment analysis of 354 potential targets of differential chemical composition by Over-Representation Analysis (Ruiz-Cisneros et al., 2022) method, and 183 diseases were screened at a confidence interval of FDR<0.05. The top disease entries were screened according to the number of genes in descending order, namely Schizophrenia, Alcoholic Intoxication (Chronic), Mental Depression, Mood Disorders, Bipolar Disorder, Depressive disorder, Major Depressive Disorder, Unipolar Depression, etc. (Figure 9). These results indicated that the differential secondary metabolites of *D. officinale* from different origins are mainly involved in diseases such as neuropsychiatric related disorders, and the influence of the herb origin should be paid more attention to when applied to the treatment of this category of diseases in clinical practice.

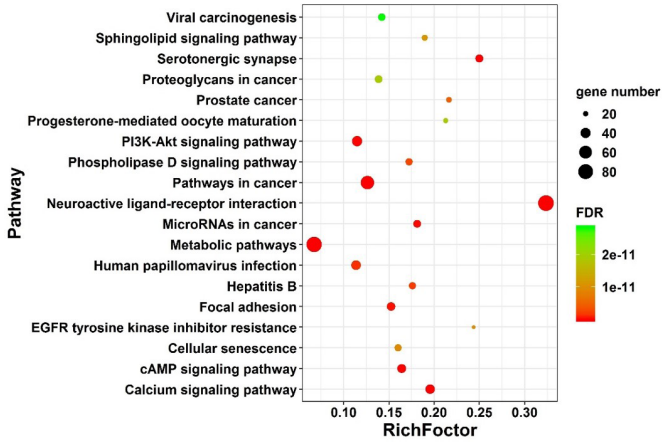

Figure 8. KEGG enrichment analysis of dominant chemical compositions of *D. officinale*.

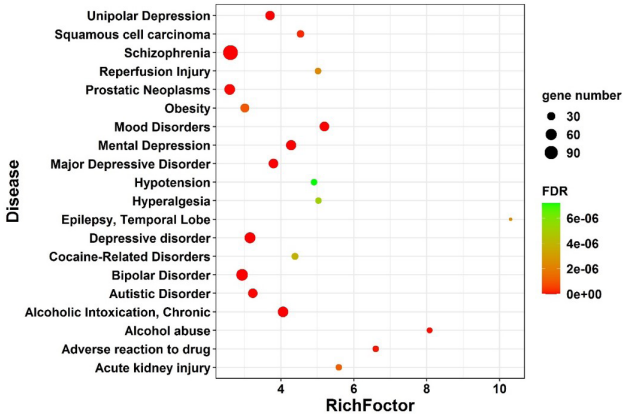

Figure 9. Disease enrichment bubble chart of dominant chemical compositions of *D. officinale*.

4 Conclusion

Polysaccharides were generally considered to be the main active components in *D. officinale*, and polysaccharide content was used as the main index for quality evaluation of *D. officinale* in Ch.P.. There has been a lot of literature confirming that the polysaccharide content in *D. officinale* was influenced by factors such as origin. However, besides polysaccharides, *D. officinale* contains many other types of secondary metabolites, and comparative analysis studies on secondary metabolites in *D. officinale* from different origins are relatively rare. In the present study, we compared and analyzed the secondary metabolites in *D. officinale* from four major production areas by UPLC-Q/TOF-MS method. The results revealed that the secondary metabolites in *D. officinale* from different production areas were significantly different, and 12 differential secondary metabolite components were identified. Further network pharmacological studies showed that these differential components were mainly associated with neurological disorders, which is consistent with the application of neuroprotective effects of Dendrobium. However, the present study also has some limitations, such as only the influence of origin was considered, and in fact factors including harvesting time and cultivation method may also contribute to certain effects, which need to be continuously and continuously studied in the future. In any case, the results of this study indicated that using polysaccharide content alone as an index for quality evaluation of *D. officinale* is not comprehensive, and the influence of *D. officinale* origins need to be paid more attention, in the clinical application of neurological diseases.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Material

Supplementary material accompanies this paper.

Figure S1. The total ion chromatogram of secondary metabolites in D. officinale (A) Positive ion mode (B) Negtive ion mode.

Table S1. Sample information of D. officinale.

Table S2. Chemical composition identification of D. officinale by UPLC-QTOF / MS.

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