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Research article

Exploring the possible therapeutic mechanism of Danzhixiaoyao pills in depression and MAFLD based on "Homotherapy for heteropathy": A network pharmacology and molecular docking

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ABSTRACT

Objective: Danzhixiaoyao pills (DXP) is a traditional Chinese medicine formula that has been effectively used in clinical practice to treat depression and metabolic associated fatty liver disease (MAFLD), but its therapeutic mechanism is not yet clear. The purpose of this study is to explore the possible mechanisms of DXP in treating depression and MAFLD using network pharmacology and molecular docking techniques based on existing literature reports.

Methods: By combining TCMSP, Swiss ADME, Swiss TargetPrediction, and UniProt databases, the active ingredients and potential targets of DXP were screened and obtained. By searching for relevant disease targets through Gene Cards, OMIM, and TTD databases, intersection targets between drugs and diseases were obtained. The network of "Disease - Potential targets - Active ingredients - Traditional Chinese medicine - Prescriptions" was constructed using Cytoscape 3.9.1 software, and the PPI network was constructed using STRING 12.0 database. The core targets were obtained through topology analysis. GO function enrichment and KEGG pathway enrichment analysis were conducted based on DAVID. The above results were validated by molecular docking using PyMol 2.5 and AutoDock Tool 1.5.7 software, and their possible therapeutic mechanisms were discussed.

Results: Network pharmacology analysis obtained 130 main active ingredients of drugs, 173 intersection targets between drugs and diseases, and 37 core targets. Enrichment analysis obtained 1390 GO functional enrichment results, of which 922 were related to biological process, 107 were related to cellular component, 174 were related to molecular function, and obtained 180 KEGG pathways. Molecular docking has confirmed the good binding ability between relevant components and targets, and the literature discussion has preliminarily verified the above results.

Conclusion: DXP can act on targets such as TNF, AKT1, ALB, IL1B, TP53 through active ingredients such as kaempferol, quercetin, naringenin, isorhamnetin, glyuranolide, etc, and by regulating signaling pathways such as pathways in cancer, MAPK signaling pathway, lipid and atherosclerosis, to exert its effect of "homotherapy for heteropathy" on depression and MAFLD. In addition, glyuranolide showed the strongest affinity with TNF (−7.88 kcal/mol), suggesting that it may play a key role in the treatment process. The research results provide a theoretical basis for

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elucidating the scientific connotation and mechanism of action of traditional Chinese medicine compound DXP, and provide new directions for its clinical application.

1. Introduction

The incidence rate of depression and MAFLD is increasing all over the world [1–3], and they have become important risk factors for the mortality of emotional disorders and metabolic diseases [4–6]. Although the incidence of comorbidity between depression and MAFLD in clinical practice is not yet clear, there is increasing evidence to suggest a significant correlation between depression and MAFLD [7–9]. The interaction between depression and MAFLD poses a higher risk of comorbidity [10,11]. The pathogenesis of depression and MAFLD is extremely complex and insidious, mainly manifested as low mood, thinking disorders, impaired willpower and cognitive function, as well as discomfort, fatigue, and loss of appetite in the upper right abdomen. However, in clinical practice, there is limited selectivity in the types of drugs used to treat depression, and drug resistance and adverse reactions are more common [12]. The pathological changes of MAFLD are complex, including simple hepatic steatosis, steatohepatitis, liver fibrosis, cirrhosis, and even hepatocellular carcinoma. Moreover, there is currently no specific symptomatic medication for treating of MAFLD. Anti-inflammatory, enzyme lowering, and liver protecting drugs are commonly used to auxiliary in improving symptoms [13]. Therefore, how to effectively treat depression comorbid with MAFLD is an important goal of current clinical research.

DXP was first recorded in the "*Summary of Internal Medicine*" written by Xue Ji in the Ming Dynasty of China. It was improved on the basis of the Xiaoyao Pills in the official medical book "*Taiping Huimin He Ju Fang*" in the Song Dynasty. It is composed of peony skin, gardenia, angelica sinensis, radix paeoniae alba, radix bupleuri, atractylodes macrocephala, poria cocos, licorice, ginger, and mint. Its main efficacy is to soothe the liver and invigorate the spleen, nourish blood and clear heat, and treat various symptoms such as swelling and pain in the ribs and abdomen, low mood, mental fatigue, loss of appetite, irregular menstruation, and weak pulse. Modern clinical and pharmacological studies have shown that DXP has sedative, anti-inflammatory, antioxidant, immune promoting, and neuroendocrine regulating effects [14], and it has obvious targeted treatment for liver and gastrointestinal diseases. It also has a certain therapeutic assistance on mental illness such as premenstrual syndrome and gastric neurosis. Multiple randomized controlled clinical trials have shown that the application of DXP in the treatment of depression and MAFLD can achieve significant therapeutic effects: improving patient sleep quality and physical symptoms [15], improving liver function and blood lipid levels [16,17], reducing side effects of medication, and improving patient quality of life [18–20]. However, due to the complexity of traditional Chinese medicine ingredients, the molecular mechanism of DXP in treating depression and MAFLD has not been elucidated yet.

"Homotherapy for heteropathy" refers to the use of the same method for treatment if the pathogenesis of different diseases is the same [21]. Modern molecular biology technology has important academic significance in revealing the scientific principle of "homotherapy for heteropathy" [22]. Although depression and MAFLD are two different diseases, groups with both characteristics often have the same underlying causes and pathogenesis. Depression is a common emotional disorder mental illness, closely related to neurotransmitter imbalance, abnormal brain structure and function, endocrine and immune dysfunction, etc [23,24]. MAFLD is considered to be the expression of metabolic syndrome in the liver, and is associated with genetic factors, insulin resistance, lipid metabolism, oxidative stress, and inflammatory cytokines [25,26]. Inflammatory mediators, insulin resistance, and gut microbiota are considered common pathophysiological mechanisms in depression and MAFLD [27], and there is a bidirectional correlation between these two diseases [28,29]. Therefore, this study predicts the active ingredients, targets, and signaling pathways of DXP in the treatment of depression and MAFLD through network pharmacology. And preliminary verification of the affinity between core components and targets was carried out using molecular docking techniques [30]. We explored the possible therapeutic mechanism of DXP in depression and MAFLD based on "homotherapy for heteropathy", in order to provide reference for the selection and innovation of clinical medication [31].

2. Materials and methods

2.1. Acquisition of active ingredients and potential targets of DXP

The main components of DXP are *Radix bupleuri[Chai Hu, Bupleurum scorzonerifolium Willd., Umbelliferae, root], Peony skin[Mu Dan Pi, Paeonia suffruticosa Andr., Ranunculaceae, Root bark], Radix paeoniae alba[Bai Shao, Paeonia lactiflora Pall., Ranunculaceae, root], Licorice[Gan Cao, Glycyrrhiza uralensis Fisch. ex DC., Fabaceae, root], Gardenia[Zhi Zi, Gardenia jasminoides Ellis, Rubiaceae, ripe fruits], Gardenia[Bai Zhu, Atractylodes macrocephala Koidz., the composite family, root], Poria cocos[Fu Ling, Poria cocos (Schw.) Wolf., Polyporaceae, sclerotium], Angelica sinensis[Dang Gui, Angelica sinensis (Oliv.) Diels., Umbelliferae, root], Mint[Bo He, Mentha haplocalyx Briq., Labiatidae, Above ground], Ginger[Sheng Jiang, Zingiber offcinale Rosc., Zingiberaceae, Fresh rhizome]*. We used the TCMSP database (https://tcmspw.com/tcmsp.php) to search for the active ingredients of 10 traditional Chinese medicines and used two pharmacokinetic parameters, oral bioavailability (OB) $\geq$ 30 % and druglike-ness (DL) $\geq$ 0.18, as a preliminary screening condition for the active ingredients entering the bloodstream in DXP. Further screening was conducted using the Swiss ADME platform (http://www.swissadme.ch/), with the score of "high" for gastrointestinal absorption and at least two "Yes" for druglikeness. The canonical SMILES of the screened drug active ingredients were input into the Swiss Target Prediction database (http://www.swisstargetprediction.ch/) to predict the target of action. The predicted targets were corrected using the UniProt database (https://www.uniprot.org/), removing non-human genes, and obtaining information on the active ingredients and potential targets of DXP.

2.2. Screening of common targets of diseases and potential targets of DXP acting on depression and MAFLD

"Depression" and "Metabolic associated fatty liver disease [32]" were used as keywords for disease retrieval, the common targets of two diseases were screened through the disease target databases Gene Cards (https://www.genecards.org/), OMIM (https://omim.org/), and TTD (http://db.idrblab.net/ttd/). When there are too many predicted target results, targets with a correlation score greater than the median are set as potential targets for the target disease. We summarized the results of the above database, removed duplicate targets, and standardized the names of disease targets through UniProt. The active ingredient targets of DXP, the disease targets of depression and MAFLD were imported into the jvenn online mapping software platform (https://www.bioinformatics.com.cn/static/others/jvenn/example.html) for intersection processing, to obtain the potential therapeutic targets of DXP for depression and MAFLD, and the Venn diagram was drawn to visualize the above data. The targets obtained from the intersection were submitted to STRING 12.0 (https://cn.stringdb.org/), and "Homo Sapiens" was selected as the organism for analysis, obtaining high confidence protein interaction data with a score >0.9. The data was downloaded and imported into Cytoscape 3.9.1 software, and the network diagram of "Diseases - Potential targets - Active ingredients - Traditional Chinese medicine - Prescriptions" was drawn. The core targets of DXP treatment for depression and MAFLD were identified through degree values, and the PPI network diagram was constructed.

2.3. GO functional enrichment analysis and KEGG pathway enrichment analysis

Enrichment analysis is a statistical method used to determine the presence of specific biological processes, functions, or metabolic pathways in a group of genes or proteins. Gene ontology (GO) analysis can be used to determine the degree of enrichment of a group of genes or proteins in biological processes, cellular components, and molecular functions. Kyoto encyclopedia of genes and genomes (KEGG) analysis can determine which pathways are enriched in these genes or proteins by comparing the input gene or protein list with the metabolic and signal transduction pathways in the KEGG database. Both are important tools used to explain the biological significance of gene or proteomic data, in order to help understand the function and regulation of genes or proteins within cells.

The DAVID database (https://david.ncifcrf.gov/) was used to conduct enrichment analysis of GO function and KEGG pathway for the intersection targets of drugs and diseases. Selected "official gene symble" and "gene list", with the species being "homo sapiens", and saved the analysis data results. The top 20 related items with pvalue<0.01 were selected for KEGG enrichment analysis, and the top 10 related items with pvalue<0.01 were selected for GO functional enrichment analysis. The data was imported into Omicshare (https://www.omicshare.com/) and the enrichment analysis results were visualized.

2.4. Molecular docking

The top 5 core active ingredients and core targets obtained above were validated through molecular docking. The 3D structure of the main active ingredients of the drug was downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and saved in mol2 format. The crystal structure of the core target protein used for docking was downloaded from the RCSB PDB database (https://www.rcsb.org/), and all proteins were processed using PyMol 2.5 software, including removing water molecules and small molecules, and optimizing the protein structure to obtain a file in pdbqt format. Molecular docking was performed using AutoDock Tool 1.5.7 software, and the docking results were visualized using PyMol 2.5 to analyze the affinity between ligands and receptors.

3. Results

3.1. Acquisition of active ingredients and potential targets of DXP

Retrieve keywords such as "Peony skin", "Gardenia", "Angelica sinensis", "Radix paeoniae alba", "Radix bupleuri", "Atractylodes

Table 1
Basic information on the main active ingredients of DXP (ranking in the top 15 OB values).

Mol ID	Molecule Name	OB (%)	DL
MOL002311	Glycyrol	90.78	0.67
MOL001918	paeoniflorigenone	87.59	0.37
MOL004990	7,2′,4′-trihydroxy - 5-methoxy-3 - arylcoumarin	83.71	0.27
MOL000471	aloe-emodin	83.38	0.24
MOL004904	licopyranocoumarin	80.36	0.65
MOL004891	shinpterocarpin	80.3	0.73
MOL004644	Sainfuran	79.91	0.23
MOL005017	Phaseol	78.77	0.58
MOL004841	Licochalcone B	76.76	0.19
MOL004810	glyasperin F	75.84	0.54
MOL001484	Inermine	75.18	0.54
MOL000500	Vestitol	74.66	0.21
MOL005007	Glyasperins M	72.67	0.59
MOL005190	eriodictyol	71.79	0.24
MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	71.12	0.18

macrocephala", "Poria cocos", "Licorice", "Ginger", and "Mint" from the TCMSP database. After screening and deduplication, 130 main active ingredients were obtained (Table 1), as well as 994 corresponding ingredient targets.

3.2. Screening of common targets of diseases and potential targets of DXP acting on depression and MAFLD

Based on the Gene cards database and keyword search, a total of 9363 MAFLD targets were obtained (the maximum and minimum values of correlation scores are 268.1813354 and 0.512426496) and 1874 depression targets. The higher the Relevance score in the Genecards database, the closer the target is associated with the disease. For too many MAFLD targets, 1172 MAFLD targets were screened by setting the relevance score greater than the median for three consecutive times (13.64116955, 23.57194614, 35.6125164). 440 MAFLD targets and 3 depression targets were retrieved from the OMIM database. 93 depression targets were retrieved from the TTD database.After removing duplicates, a total of 1570 disease targets of MAFLD were obtained. There were 1933 disease targets for depression. The targets of the active ingredients of DXP were intersected with the disease targets of depression and MAFLD, resulting in data on potential therapeutic targets. The data was imported into the jvenn online mapping software platform, and a Venn diagram (Fig. 1) was drawn and visualized for analysis, resulting in 614 common disease targets and 173 intersection targets between drugs and diseases. It can be observed that the disease targets of depression and MAFLD have a high degree of overlap, indicating that depression and MAFLD are highly likely to have similar pathogenesis, and DXP plays an important role in the treatment of these two diseases.

3.3. Construction of "diseases - potential targets - active ingredients - Traditional Chinese medicine - prescriptions" and PPI network, as well as screening of core targets

After matching the active ingredients of the drug with the intersection target, a total of 113 active ingredients were involved. Select the relevant data and import it into Cytoscape 3.9.1 software to construct the network of "Diseases - Potential targets - Active ingredients - Traditional Chinese medicine - Prescriptions" (Fig. 2). The deep red diamond in the picture represents diseases, the blue oval represents potential targets, the yellow rectangle represents active ingredients, the light green hexagon represents traditional Chinese medicine, and the deep green hexagon represents prescriptions. From the network relationship in the figure, it can be seen that the same active ingredient can act on multiple targets, and multiple ingredients can also correspond to the same target, indicating that traditional Chinese medicine can exert synergistic effects through multiple components and targets. Submit 173 intersecting targets of DXP therapy for depression and MAFLD to STRING 12.0 to obtain data on protein-protein interaction. Subsequently, settings were made (Betweenness unDir >141.8612717, Closeness unDir >0.003244423, Degree unDir >42.27745665) to obtain 37 core targets. Construct a PPI network graph in the form of concentric circles sorted by degree values (Fig. 3), which consists of 37 nodes and 576 edges. The larger the degree value of a node, the darker the color and larger the area in the graph, indicating that there are more proteins interacting with it, and the role of this node protein in the network is more important. Through analysis, it was found that TNF,

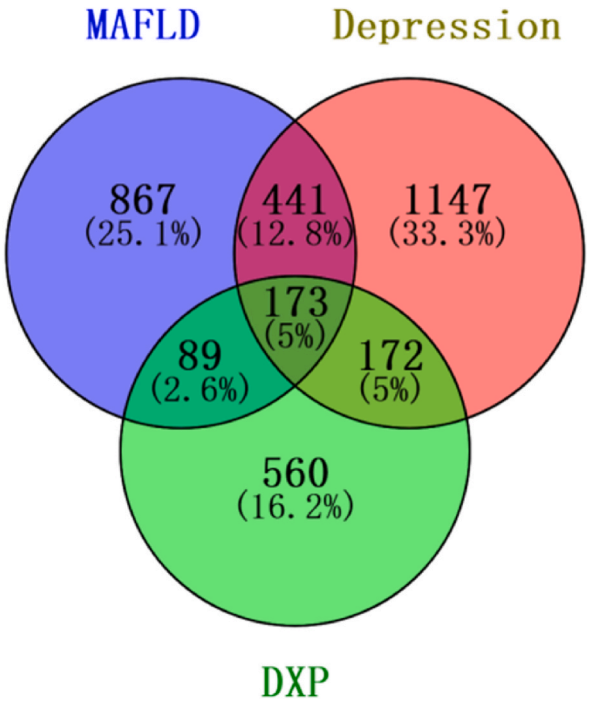

Fig. 1. Venn plot of intersection targets of DXP, Depression, and MAFLD.

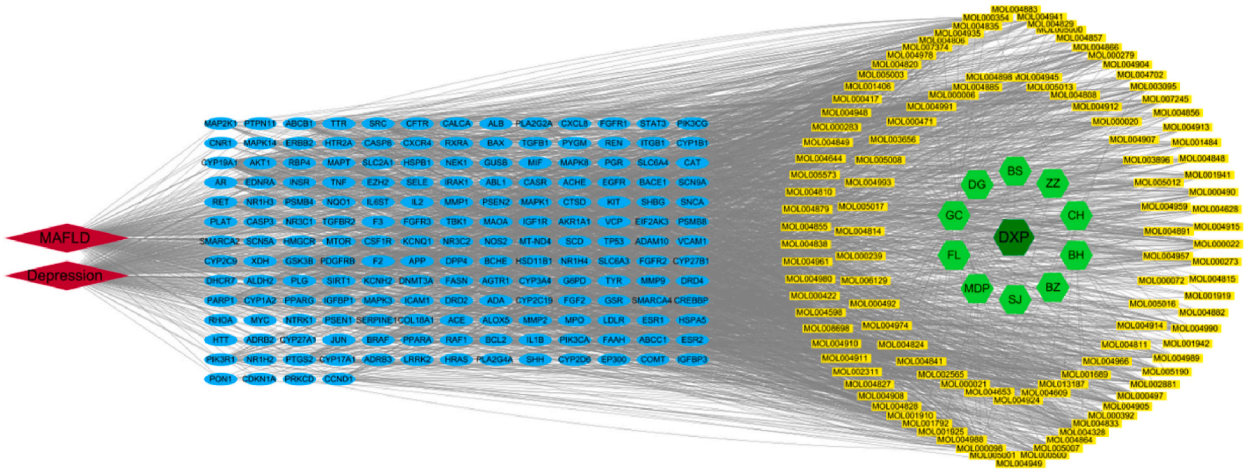

Fig. 2. Network diagram of "Diseases - Potential targets - Active ingredients - Traditional Chinese medicine - Prescriptions" (MDP: Peony skin; ZZ: Gardenia; DG: Angelica sinensis; BS: Radix paeoniae alba; CH: Radix bupleuri; BZ: Atractylodes macrocephala; FL: Poria cocos; GC: Licorice; SJ: Ginger; BH: Mint).

AKT1, ALB, IL1B and TP53 ranked relatively high in terms of degree values, closeness values, and betweenness values among numerous targets, and were the main core targets of action. It can be preliminarily believed that DXP mainly produces effects by regulating these core targets. In addition, the active ingredients of DXP, such as kaempferol, quercetin, naringenin, isorhamnetin and glyuranolide have high degree values, closeness values, and betweenness values (Fig. 4). These components are highly likely to be the core components of DXP in treating depression and MAFLD. The above results also reflect that DXP exerts pharmacological effects in treating depression and MAFLD through multiple components and targets.

3.4. GO functional enrichment analysis and KEGG pathway enrichment analysis

Perform GO functional enrichment analysis and KEGG pathway enrichment analysis on 173 key targets based on the DAVID database. 1390 GO enriched entries were obtained, including 922 biological process (BP), such as negative regulation of apoptotic process, positive regulation of cell proliferation, response to xenobiotic stimulus, protein phosphorylation and negative regulation of gene expression, etc, including 107 Cellular component (CC), such as plasma membrane, extracellular space, integral component of plasma membrane, mitochondrion and cell surface, etc, including 174 Molecular function (MF), such as identical protein binding, enzyme binding, protein serine/threonine/tyrosine kinase activity, protein homodimerization activity and protein kinase activity, etc. Sort all items according to their P-values and draw a three in 1 bar chart of enriched GO terms BP, CC, and MF for the top 10 items with higher significance (Fig. 5). According to the DAVID database, enrichment analysis was conducted on the KEGG pathway, resulting in a total of 180 pathway entries. Includes pathways in cancer, MAPK signaling pathway, lipid and atherosclerosis, proteoglycans in cancer, kaposi sarcoma-associated herpesvirus infection, hepatitis B, chemical carcinogenesis-receptor activation, endocrine resistance, AGE-RAGE signaling pathway in diabetic complications, proteoglycans in cancer, etc. This indicated that DXP may achieve therapeutic effects on depression and MAFLD through multiple pathways, and the top 20 pathways were selected and displayed in a bubble chart (Fig. 6).

3.5. Molecular docking

The top 5 core active ingredients(kaempferol, quercetin, naringenin, isorhamnetin, glyuranolide) and core targets TNF (1TNF),

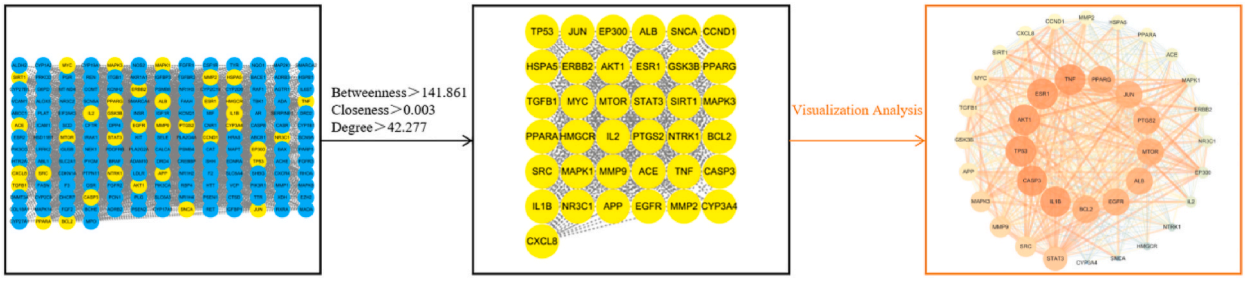

Fig. 3. PPI network diagram for DXP treatment of depression and MAFLD.

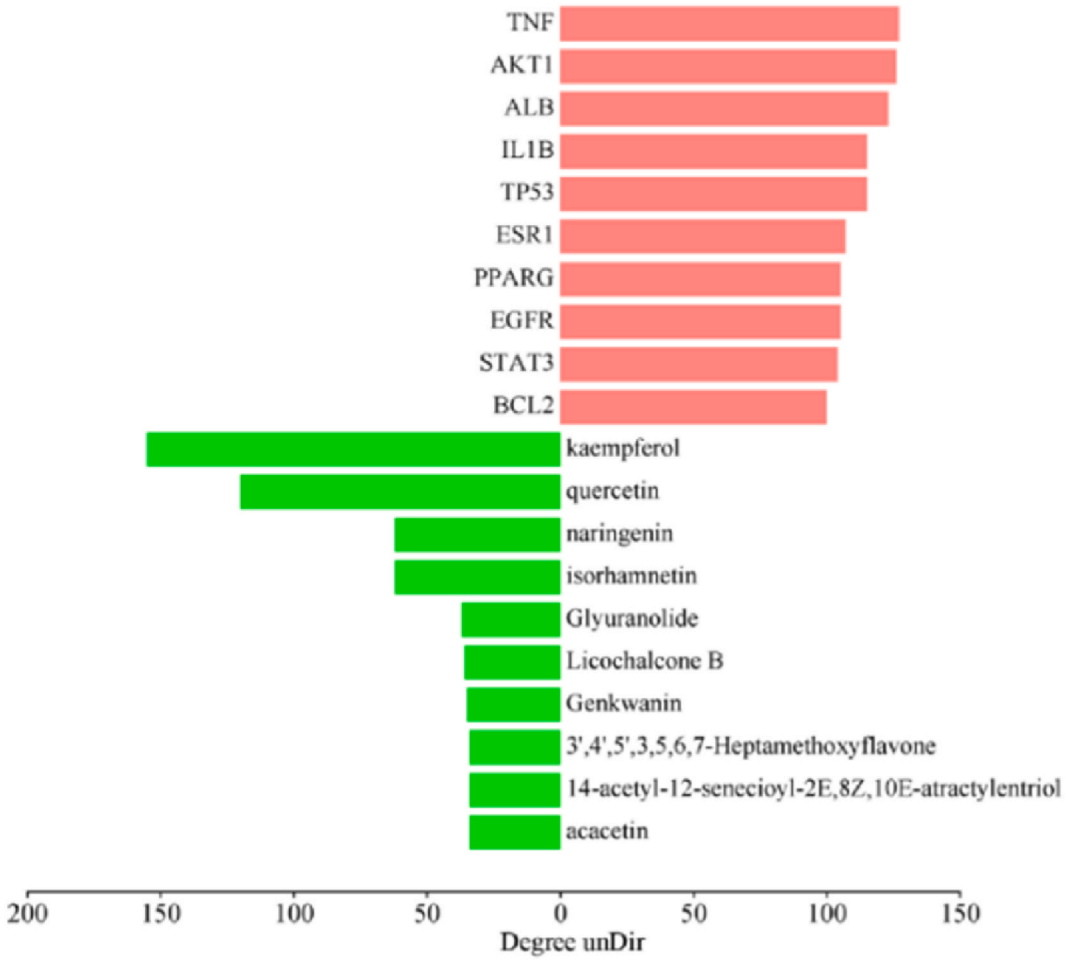

Fig. 4. The top 10 core target information and active ingredient information of Degree unDir.

AKT1 (1H10), ALB (6YG9), IL1B (1HIB), TP53 (3D06) selected based on topology analysis were validated through molecular docking using AutoDock-Tool 1.5.7 software. The binding energy between each core active ingredient and the target is displayed through the heatmap(Fig. 7). Molecular docking technology can calculate the interaction mode between receptors and ligands through matching principles and semi free energy calculation methods, predict the binding ability and stability of receptors and ligands, and thus predict the binding sites of receptors and ligands.

It is generally believed that when the binding energy is less than 0, it is indicated that the ligand and receptor can spontaneously bind. The lower the binding energy, the stronger the affinity, and the greater the possibility of interaction. The results of this molecular docking showed that these 5 core active ingredients had strong affinity with TNF, AKT1, ALB, IL1B, and TP53. The docking result between glyuranolide and TNF was the optimal binding energy. The molecular docking results of the top 5 groups in binding energy were visualized and analyzed using PyMol 2.5 (Fig. 8).

4. Discussion

The theory of "homeopathy for heteropathy" is a reflection of the principle that "treating diseases must be based on the root" in the "*Huangdi Neijing*", fully demonstrating the holistic concept and dialectical treatment thinking in the process of diagnosing and treating diseases in traditional Chinese medicine. DXP is a classic formula in traditional Chinese medicine for regulating abnormal emotional activity, it is composed of peony skin, gardenia, angelica sinensis, radix paeoniae alba, radix bupleuri, atractylodes macrocephala, poria cocos, licorice, ginger, and mint. DXP has the characteristics of flexibility in traditional Chinese medicine and safety in efficacy [33], and its advantages in regulating immune, endocrine, and metabolic diseases have gradually been discovered [34–36].

4.1. The therapeutic effects of the active ingredients of DXP in depression and MAFLD

This article uses network pharmacology methods to analyze and explore the mechanism of action of DXP in the treatment of

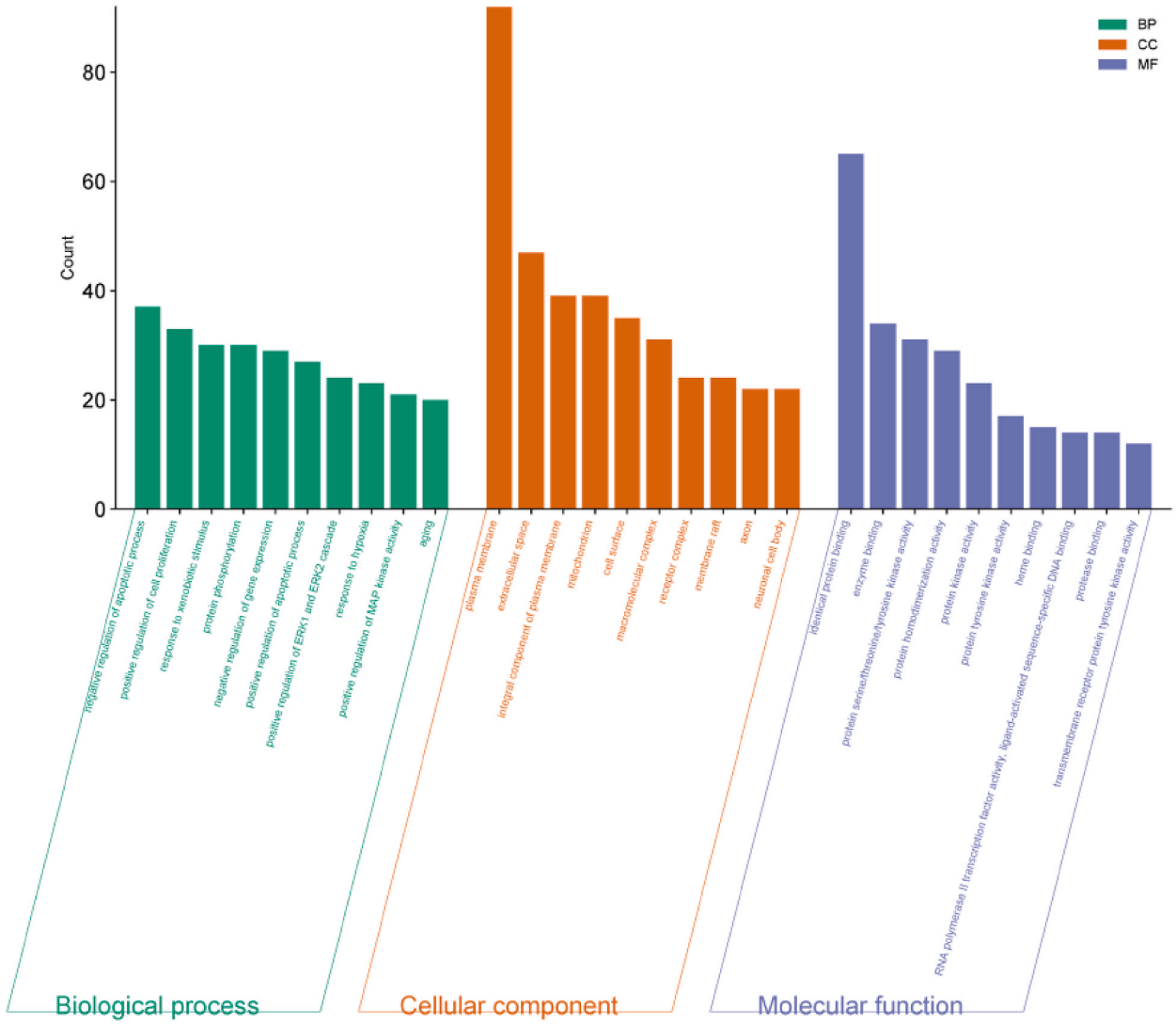

Fig. 5. GO functional enrichment analysis of key targets in DXP treatment of depression and MAFLD.

depression and MAFLD. The main active ingredients of DXP obtained through screening reached 130, indicating a wide variety of DXP components and a complex pharmacological substance basis. The top 5 active ingredients ranked by topology analysis are kaempferol, quercetin, naringenin, isorhamnetin, and glyuranolide. Kaempferol has a wide range of therapeutic properties, which can protect nerves, liver, and myocardium through antioxidant, metabolic homeostasis regulation, inhibition of inflammatory response, and inhibition of protein kinase activity [37]. Currently, research has found that oxidative stress may be involved in the pathological process of depression. Patients with depression episodes have elevated MDA and decreased SOD, CAT, and GPX [38]. Kaempferol can significantly increase the activity of antioxidant enzymes in the serum of depression model rats, and reduce the apoptosis rate of hippocampal neurons by inhibiting cell autophagy in the hippocampus, slowing down the development of neurodegenerative diseases [39]. In addition, kaempferol can also inhibit lipid peroxidation induced by NADPH or Fe2+ in lipid particle systems, and the expression of antioxidant enzymes such as CAT, GPX, GST, etc. It can also clear superoxide anions and reduce oxidative stress response in mouse liver tissue caused by alcohol and polyunsaturated fatty acids [40]. By activating Sirt1/AMPK signaling to regulate liver lipid accumulation, kaempferol becomes a potential therapeutic agent for MAFLD [41]. Quercetin not only has multiple redox centers in its chemical structure [42], but also plays a regulatory role in the neurotransmitter system through various pathways such as the HPA axis, synaptic plasticity, and promotion of hippocampal neuronal regeneration [43]. Research has found that inflammatory factors are closely related to the occurrence of depression. The body releases inflammatory cytokines, leading to peripheral immune activation and causing dysfunction of the neuroendocrine and immune systems. Quercetin can increase the levels of 5-HT, SOD, GSH in depression like model mice, reduce the levels of inflammatory factors such as TNF-α and IL-6, and thereby alleviate the inflammatory state in vivo [44]. The mechanisms of lipid metabolism include regulating lipid digestion, reversing cholesterol transport, and low-density lipoprotein receptor expression [45]. Quercetin can reduce the levels of TRIG, TCHO, LDL-C, C-VLDL, and FFAs in the

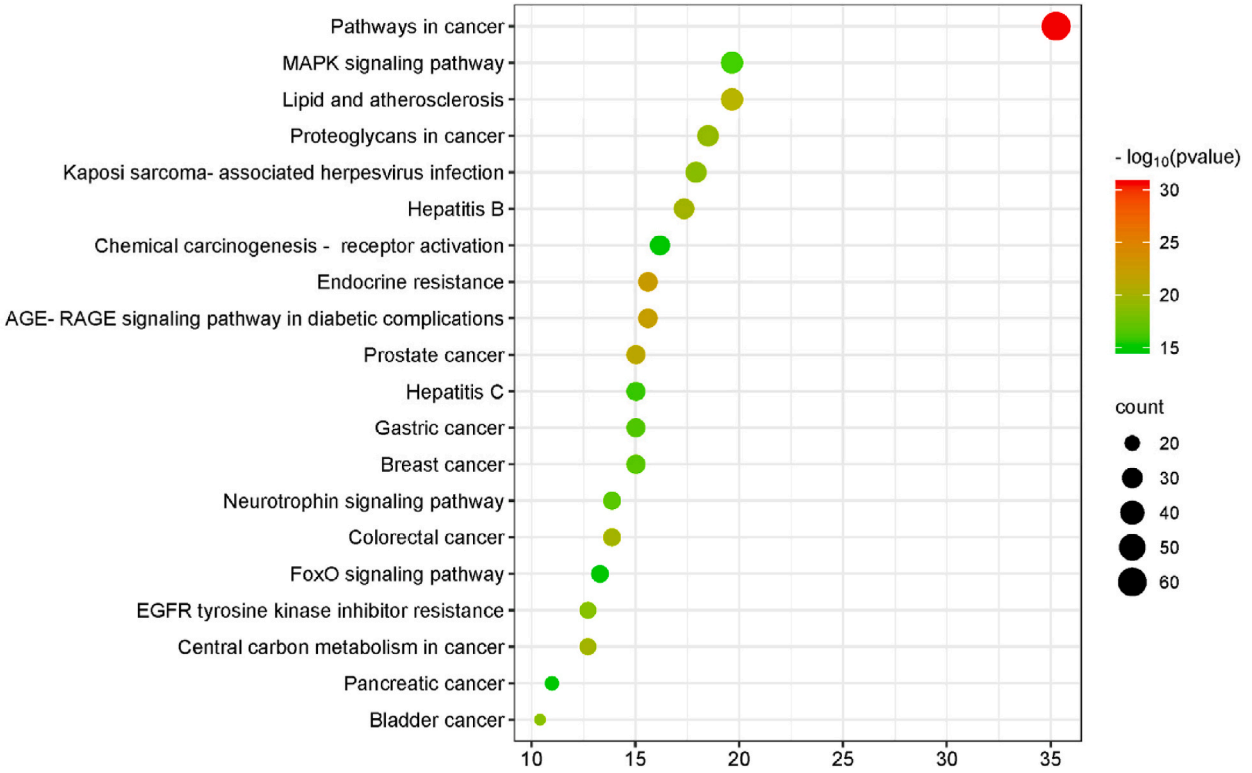

Fig. 6. KEGG pathway enrichment analysis of key targets in DXP treatment of depression and MAFLD.

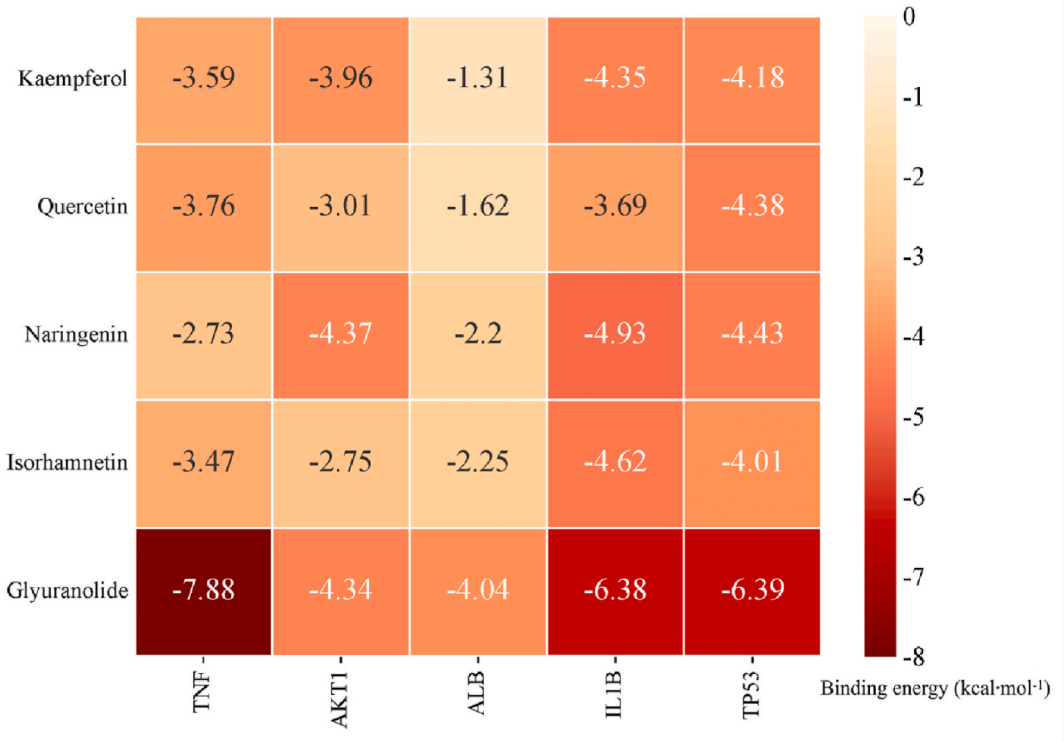

Fig. 7. Molecular docking binding energy between core components and targets.

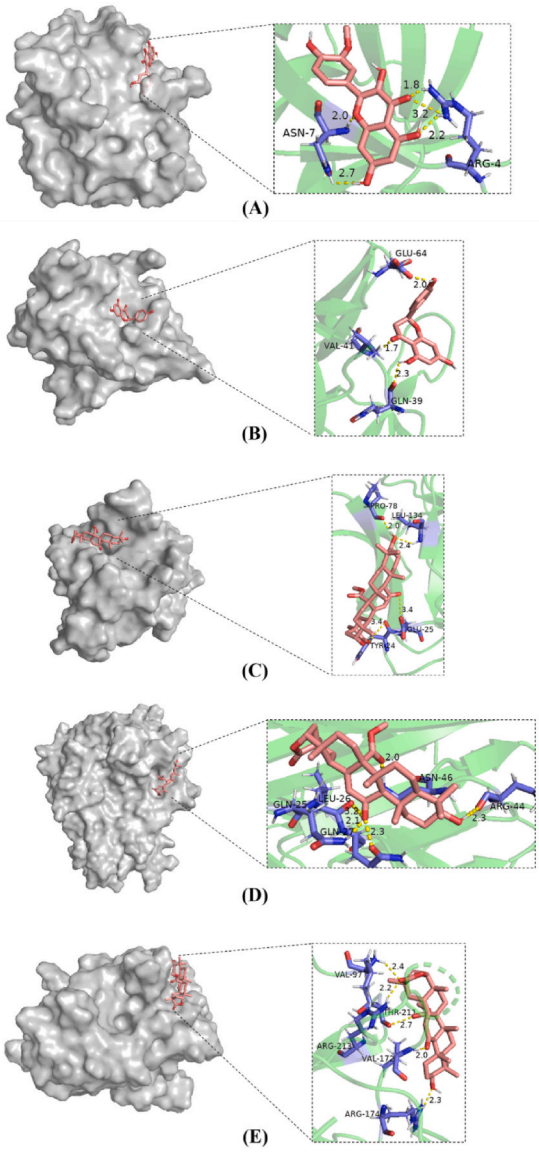

Fig. 8. Visualization analysis of docking results of top 5 molecules with binding energy ranking(A: Molecular docking diagram of isorhamnetin and IL1B; B: Molecular docking diagram of naringenin and IL1B; C: Molecular docking diagram of glyuranolide and IL1B; D: Molecular docking diagram of glyuranolide and TNF; E: Molecular docking diagram of glyuranolide and TP53).

plasma of experimental animals, increase the levels of HDL-C and ADPN [46], and reduce fat accumulation in liver cells [47]. This suggests the effectiveness of quercetin in lipid and carbohydrate metabolism [48], supporting its applicability as a treatment for depression and MAFLD [49].

The increase of 5-HT and NE receptors, activation of BDNF, and decrease of blood cortisol are considered to be the basis of antidepressant like effects. Naringenin can exert antidepressant effects by increasing neurotrophic factors, restoring 5-HT and NE in the brain, and restoring changes in the renin pathway through its antioxidant and anti-inflammatory potential [50]. Naringenin can reduce the increase in iNOS and NF-κB expression, as well as the loss of amygdala neurons, indicating that naringenin improves depressive like behavior in mice exposed to hypoxic stress by regulating oxidative inflammation damage and NF-κB/BDNF expression [51]. In addition, naringenin can activate Nrf2 nuclear transcription factor, promote the generation of SOD and CAT, and thus exert anti liver oxidative stress effects [52], and by downregulating the NLRP3/NF-κB signaling pathway in kupffer cells and liver cells, MAFLD can be prevented, thereby reducing inflammation in mouse liver [53]. It also inhibits the activity of HMGCoA reductase, reduces the blood lipid level in hyperlipidemia rat models, improves the abnormal lipid metabolism in hyperlipidemia rats, and inhibits the formation of atherosclerosis and MAFLD [54]. It is also possible to alleviate MAFLD and obesity by directly and indirectly activating AMPK to increase energy expenditure and regulate autophagy [55]. Neurofilaments are a key component in the process of neural process extension, and their expression levels can serve as markers of neuronal differentiation. Many neurological disorders are associated with

insufficient NGF, especially some neurodegenerative diseases such as depression and Alzheimer's disease. Given that the application of Isorhamnetin enhances NGF induced neurite growth. Therefore, isorhamnetin may be used to treat differentiation problems caused by insufficient NGF [56]. In addition, isorhamnetin also enhanced the antidepressant effect of escitalopram and effectively restored the levels of Nrf2, BDNF, and HO-1 in the cortex, indicating that Isorhamnetin has the potential to enhance the efficacy of traditional antidepressant therapy through antioxidant and anti-inflammatory effects [57]. PPAR-γ as a major regulatory factor in adipocyte differentiation, it has been identified as a key molecule in coordinating the accumulation, type, and function of regulatory T cells in visceral adipose tissue. Quercetin and isorhamnetin at the same concentration have similar inhibitory effects on liver mitochondrial lipid peroxidation in vitro [58]. In addition, research has shown that isorhamnetin is a novel PPAR-γ antagonist that can inhibit adipocyte differentiation induced by the PPAR-γ agonist rosiglitazone, which can help prevent obesity and treat hepatic steatosis [59]. Glyuranolide is a trace amount of triterpenoid saponin isolated from the total saponin in the root and stem of glycyrrhiza uralensis fisch [60], there are few reports on its research both domestically and internationally, and further exploration is needed. It is worth noting that, kaempferol, quercetin, naringenin, isorhamnetin, acacetin, and licochalcone are all flavonoids with broad-spectrum pharmacological effects, which are of great significance for human metabolism, immunity, cancer, inflammation, as well as the treatment and prevention of neurological and psychiatric disorders [61].

In addition, MAFLD is a group of highly heterogeneous diseases. Its diagnostic criteria are based on histological (liver biopsy), imaging and blood biomarker evidence of liver fat accumulation (hepatocyte steatosis), and one of the three conditions of overweight/obesity, type 2 diabetes, and metabolic dysfunction, which is closely related to metabolic syndrome. Metabolic syndrome is a group of syndromes with central obesity, dyslipidemia, hypertension, diabetes or abnormal glucose tolerance. Therefore, based on a common biological mechanism, obesity and metabolic syndrome are considered confounding factors for depression and MAFLD [61,62]. Multiple randomized clinical controlled trials and animal experiments have shown that DXP can significantly reduce body mass index, waist to hip ratio, and blood lipids in patients, improve insulin resistance while protecting the liver and lowering enzymes, and have advantages in controlling fasting blood glucose, 2-h postprandial blood glucose, and glycated hemoglobin. It can effectively alleviate physical symptoms such as depression and insomnia, increase patient compliance during the treatment process, and thus more effectively control the progression of related diseases [63,64]. In addition, DXP can also affect glucose and lipid metabolism in rats [65], inhibit oxidative stress and inflammatory reactions, reduce blood sugar, blood lipids, free fatty acids, and increase the expression of IRS-2, PI3–K, and Akt mRNA in liver tissue. Its therapeutic mechanism may be related to correcting the disrupted HPA axis and increasing the gene expression of IR and IRS-1 in liver tissue, thereby improving the peripheral tissue insulin signal transduction of insulin [66,67].

4.2. The mechanism of action of core proteins in DXP treatment of depression and MAFLD

173 common targets between drugs and diseases were obtained by intersecting potential targets, and 37 core targets were identified through PPI network and topology analysis. This confirms the correlation between DXP treatment for depression and MAFLD, indicating that DXP may exert therapeutic effects on depression and MAFLD through them. Among them, the top 5 core target proteins for DXP acting on depression and MAFLD are TNF, AKT1, ALB, TP53, and IL1B, respectively. As a classic pro-inflammatory cytokine, TNF has been revealed to affect the homeostasis of central tryptophan neurotransmitters by regulating the activity of glial 5-HT receptors, making the association between chronic inflammatory diseases and depression easier to understand [68,69]. The addition of DXP to traditional antidepressant drugs has a more significant therapeutic effect on PSD [70], and the combination of DXP and HUC-MSCs can also achieve good therapeutic effects in the treatment of PSD [71]. Its mechanism may be related to inhibiting the TLR4/NF-κB pathway in microglia, increasing the release of monoamine neurotransmitters, stimulating the secretion of neurotrophic factors in the brain, and inhibiting hippocampal neuroinflammation and reducing neuronal apoptosis. In addition, TNF may affect in vivo fat storage and liver lipid dynamics in the context of a healthy diet [72]. When the deposition of fat in the liver causes inflammation, the presence of endotoxin-induced liver injury activates kupffer cells in the liver, promoting the release of cytokines such as TNF-α [73]. Besides TNF, IL-1β also plays a broad and crucial role in neuroinflammation. Pathological level IL-1β can induce an inflammatory cascade reaction, promote the expression of inflammatory factors such as TNF-α, and inhibit brain-derived neurotrophic factors and hippocampal nerve regeneration. Research has shown that the negative effects of IL-1β on pharmacological responses and amygdala and ACC function involve the same genotype of two SNPs (rs16944, rs116343) [74]. There is a lack of association between the genetic polymorphism of IL-1β (especially its rs16944 variant, which leads to an increase in IL-1β expression) and SSRI responsiveness [75]. The changes in the 5-HT nerve and HPA axis caused by IL-1β may lead to the occurrence of depression [76]. The ethyl acetate site can counteract depression like behavior induced by neuroinflammation in mice, activate the NLRP3/Caspase-1/IL-1β pathway, thereby inhibiting microglial cell activation, reducing neuroinflammation and neuronal damage [77]. In addition, studies have confirmed that the IL-1 family genes are involved in the genetic background of obesity [78], and the high-fat microenvironment induces MAELD liver cell fibrosis through HIF-1α/YAP/IL-1β [79].

Inhibition of AKT in the central nervous system can also lead to signal transduction defects, resulting in mental symptoms including depression [80]. Among them, there is an association between rs3001371 polymorphism and cognitive impairment in severe depressive disorder [81], and here is a significant association between rs2494746 polymorphism and suicidal ideation and anxiety symptoms in patients with depression [82]. The anti depression effect of DXP is mediated by activating the PIK3CA-AKT1-NFE2L2/BDNF signaling pathway to alleviate oxidative stress and enhance neuroprotective effects [83]. In addition, AKT signaling is closely related to adipocyte differentiation, and the development and maintenance of brown adipose organs require AKT [84]. The activity of AKT is rapidly activated and continuously maintained during the adipogenic differentiation process of BM-MSCs. Activated AKT can regulate the glucose metabolism process and other biological functions of the body by regulating the

activity of downstream targets. Insulin promotes glycogen synthesis in muscles and liver through the PI3K/AKT pathway, and inhibits gluconeogenesis in liver and fat, allowing glucose to be stored in the form of glycogen and fat in muscles, liver, and fat, thereby maintaining a relatively constant blood sugar level in the body [85]. Research has found that the lack of glycolytic enzyme ppk1 promotes MAFLD through the activation of the PI3K/AKT/PDG1 axis [86]. Quercetin can improve the degree of hepatic steatosis and alleviate liver inflammation in NASH rats by regulating the PI3K/AKT/NF-κB signaling pathway. ALB is synthesized by liver parenchymal cells and is the main protein in human plasma, maintaining body nutrition and osmotic pressureLe [87]. Research has found that serum CRP and TNF-α are highly expressed in patients with depression, and are positively correlated with HAMD scores. Serum ALB and PA show low expression levels in patients with depression, and are negatively correlated with HAMD scores in patients with depression [88–90]. In addition, decreased ALB is an independent risk factor for MAFLD [91]. There is a significant correlation between serum ALT, AST, and ALB levels in MAFLD patients and liver fibrosis, and these three may serve as early predictive markers for MAFLD liver fibrosis [92]. TP53, as a tumor suppressor protein, checkpoint for cell cycle regulation, regulator of energy metabolism, and balancer of oxidative stress, is located at the core of multiple cellular signaling pathways [93]. The secondary allele 72C of TP53 gene has a protective effect on MDD [94]. The MAPK signaling pathway has been identified as a related pathway for the development of MDD, and the miRNAs-TFs-HRAS/TP53/MAPK8 axis may play a key role in MDD [95]. In addition, TP53 is associated with the occurrence, cell differentiation, and malignancy of adipose tissue derived tumors, and its inhibitory effect on adipocyte differentiation may be achieved through the AKT signaling pathway [96,97]. During the differentiation process of adipocytes, the expression of TP53 first increases and then decreases. By interacting with PXR, it regulates the transcription of SCD1 and participates in the occurrence and development of MAFLD [98].

4.3. Enrichment analysis of DXP treatment for depression and MAFLD

Go functional enrichment analysis includes biological processes such asnegative regulation of apoptotic process, positive regulation of cell proliferation and response to xenobiotic stimulus. Plasma membrane, extracellar space, and integral component of plasma membrane constitute cellular components. And molecular functions such as identical protein binding, enzyme binding, protein serine/threonine/tyrosine kinase activity, protein homodimerization activity and protein kinase activity. The KEGG pathway enrichment analysis mainly involves pathways in cancer, MAPK signaling pathway, lipid and atherosclerosis, proteoglycans in cancer, kaposi sarcoma-associated herpesvirus infection, hepatitis B, chemical carcinogenesis-receptor activation, endocrine resistance, AGE-RAGE signaling pathway in diabetic complications and proteoglycans in cancer. Depression and MAFLD have become risk factors for various diseases [99], increasing the risk of adverse outcomes such as cardiovascular disease, stroke, cancer-related mortality, and all-cause mortality in patients [100]. As a manifestation of chronic psychological stress, long-term depression can activate HPA [101], promote the synthesis and secretion of adrenal cortex hormones, especially glucocorticoids, leading to accumulation of fat in liver cells and increased blood sugar concentration, and inducing insulin resistance. The absorption and output of fatty acids, the recurrence of fat generation, and the utilization of fat regulate liver lipid metabolism through a comprehensive process. The persistent presence of IR can lead to disturbances in liver lipid metabolism, leading to low-grade systemic inflammatory reactions and an increase in inflammatory mediators such as TNF-α and IL-6 in the plasma [102]. In the context of MAFLD, inflammatory mediators can stimulate kupffer cells and hepatic stellate cells to activate the fibrotic pathway [103–105]. Chronic inflammation and malignant transformation are common processes in the occurrence and development of the vast majority of cancers [106]. Neuroinflammation is also involved in the pathogenesis of various central system diseases related to cognitive impairment, including depression [107], which increases the possibility of MAFLD developing into liver cancer. And in the process of metabolic disorders in cancer, a large amount of fat and protein are consumed, with protein consumption being the most severe, causing damage to the body's function [108]. MAPK can be activated by various inflammatory stimuli, mainly consisting of three pathways: ERK, p38, and JNK. ERK1/2 and p38 rapidly phosphorylate and activate in the area of nerve injury, reducing the impact of nerve injury on the body. Phosphorylated JNK aggregates at the site of nerve injury, promoting neuronal apoptosis and exacerbating the occurrence of nerve injury. ERK5 is an essential signaling protein in cell proliferation and differentiation, organogenesis, and embryonic development. Phosphorylated ERK5 promotes neuronal survival by promoting insulin expression in neurons. It is now believed that the ERK1/2/MAPK signaling pathway is the target of antidepressants and an important pathway involved in cell plasticity [109,110]. The MAPK signaling pathway also plays a very important role in adipocyte differentiation, and the regulation of ERK and p38MAPK signaling pathways on adipocyte differentiation is manifested in two different forms: positive regulation and negative regulation in different experimental models. And another member, JNK, can phosphorylate serine, thereby interfering with insulin signaling and inhibiting the adipogenic differentiation of BMSCs, thereby exerting a negative regulatory effect on adipocyte differentiation [111,112]. Inhibiting the expression of NF-κBp65 and p38MAPK proteins, as well as phosphorylated p38MAPK proteins, may be one of the mechanisms underlying the anti MAFLD effects of the different treatment methods mentioned above [113,114]. These network analysis and literature research results fully demonstrate that DXP plays a synergistic role in preventing and treating depression and MAFLD through multiple components, targets, and pathways.

4.4. Molecular docking

Perform molecular docking on the main active ingredients and key target proteins in the screened DXP. The results showed that these small molecule components can spontaneously bind well to multiple amino acid residues of key target proteins, reflecting the stable binding force between drug key components and core target genes, confirming the reliability of network pharmacology prediction results, and emphasizing the multi-component, multi pathway, and multi target treatment mode of DXP for depression and

MAFLD. The core compounds of DXP for treating depression with MAFLD are "kaempferol, quercetin, naringenin, isorhamnolide, and glyuranolide". Kaempferol comes from white radix paeoniae alba, gardenia, peony skin, radix bupleuri and licorice, quercetin comes from gardenia, peony skin, radix bupleuri and licorice, naringenin comes from licorice and mint, isorhamnolide comes from radix bupleuri and licorice, and glyuranolide comes from licorice. It can be seen that the active ingredients of liquorice play an important role in the network, which is consistent with the role of liquorice in "harmonizing various drugs" in DXP. Meanwhile, it was found that glyuranolide has strong affinity with various target proteins. This suggests that it may make a significant contribution in the treatment of depression and MAFLD, but due to the lack of relevant reports, further in-depth research is needed.

5. Conclusion

This study is based on the integration of network pharmacology and biological information, combined with molecular docking technology to verify the predicted binding ability between key active ingredients and core target proteins. And based on current relevant literature research, the results were confirmed, and the main bioactive components and potential mechanisms of action of DXP in the treatment of depression and MAFLD were systematically analyzed and predicted. To provide scientific basis for promoting the clinical application and mechanism research of the classic formula DXP, and to provide reference and guidance for the prevention and treatment of emotional disorders and metabolic diseases such as depression and MAFLD, which have complex pathogenesis and similar triggers.

However, due to the limitations of network pharmacology in treating diseases from a single drug/monomer perspective, the possible therapeutic mechanism of DXP for depression combined with MAFLD identified in this study is only reflected in the relationship between components and targets. Traditional Chinese medicine formulas have strict prescription principles and compatibility ratios, which are different from the "only component theory" thinking and focus more on the overall and synergistic nature of drugs. During the process of decocting traditional Chinese medicine formulas, complex physical and chemical reactions (neutralization, oxidation, substitution, polymerization, condensation, precipitation, etc.) can also cause interactions between active ingredients. This makes DXP unable to demonstrate the actual dose-response relationship in different drug ratios. It is urgent to design corresponding network algorithms to quantitatively evaluate how drugs act, providing better predictive guidance for the safety and effectiveness of traditional Chinese medicine formulas. In addition, it is also necessary to carry out corresponding cross-sectional surveys and experimental research on comorbidities. On the one hand, it is necessary to clarify the incidence rate of depression with MAFLD and its related risk factors. On the other hand, it is necessary to organically combine DXP related "network pharmacology", "serum drug chemistry", and "metabolomics" to verify the accuracy of information and provide reliable basis for DXP to treat depression with MAFLD.The follow-up research on the treatment of depression combined with MAFLD with traditional Chinese medicine DXP, which has the characteristics of "multiple components, multiple targets, and multiple pathways", still has a long way to go.

Data availability statement

The data related to the study has been added to the attachment.

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Consent for publication

All authors agree that this study will be published in this journal.

CRediT authorship contribution statement

YunHang Chu: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **BingYao Pang:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Ming Yang:** Writing – review & editing, Formal analysis, Conceptualization. **Song Wang:** Writing – review & editing, Writing – original draft. **Qi Meng:** Formal analysis, Data curation. **HongChi Gong:** Formal analysis, Data curation. **YuDong Kong:** Data curation. **Yan Leng:** Writing – review & editing, Formal analysis, Conceptualization.

Declaration of competing 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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Abbreviations

MAFLD	Metabolic associated fatty liver disease
DXP	Danzhixiaoyao pills
TCMSP	Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform
OMIM	Online Mendelian Inheritancein Man Database
TTD	Therapeutic Target Database
PPI	protein-protein interaction
DAVID	The Database for Annotation, Visualization and Integrated Discovery
GO	Gene ontology
KEGG	Kyoto encyclopedia of genes and genomes
XP	Xiaoyao pill
TNF	Tumornecrosisfactor
AKT1	RAC-alpha serine/threonine-protein kinase
ALB	Albumin
IL1B	Interleukin 1, beta
TP53	Tumor Protein P53
BP	Biological process
CC	Cellular component
MF	Molecular function
MDA	Malonic dialdehyde
SOD	Superoxide dismutase
CAT	Catalase
GPX	Glutathione Peroxidase
GST	Glutathione S-transferase
HPA	Hypothalamic-pituitary-adrenal
5-HT	5-Hydroxytryptamin
GSH	Glutathione
TRIG	Triglyceride
TCHO	Total cholesterol
LDL-C	Low density lipoprotein cholesterol
C-VLDL	Cholesterol Vehicled by Very Low Density Lipoproteins
FFAs	Free fatty acids
HDL-C	High-density lipoprotein cholesterol
ADPN	Adiponectin
NE	Norepinephrine
BDNF	Brain-derived neurotrophic factor
NGF	Nerve Growth Factor
PPAR-γ	Peroxisome proliferator-activated receptor-γ
TNF-α	Tumor Necrosis Factor-α
IL-6	Interleukin-6
PSD	Post-stroke depression
HUC-MSCs	Umbilical cord mesenchymal stem cells
SSRI	Selective serotonin reuptake inhibitor
CRP	Capacity Requirements Planning
PA	Prealbumin
ALT	alanine aminotransfease
AST	Aspartate Transaminase
MDD	Major Depressive Disorder
MAPK	Mitogen-activated protein kinase
IR	Insulin resistance
BMSCs	Bonemesenchymalstemcells

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35309.

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