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Research Article

Network Pharmacology-Based Pharmacological Mechanisms of Ginseng for Depression in Post-COVID 19

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- Network Pharmacology
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Abstract

Introduction: The novel coronavirus disease 2019 (COVID-19) is in the midst of worldwide panic and global health concern since December 2019. In order to provide theoretical guidance for further clinical application in post-pandemic, we investigated active compounds and pharmacological mechanisms of ginseng to exert anti-depressant activity using network pharmacology, and discussed the active ingredients with immune-regulation and anti-depression.

Materials and Methods: Information on compounds in ginseng was obtained from public databases, and genes related to depression were gathered using the Gene Cards database. Networks of ginseng-associated targets and depression-related genes were constructed through STRING database. Potential targets and pathway enrichment analysis related to the therapeutic efficacy of ginseng for depression were identified using Cytoscape and Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: Network pharmacological analysis of ginseng in treatment of depression identified 16 active ingredients, 47 potential targets, 32 GO terms, and 8 target gene-regulated major pathways. Among them, kaempferol, beta-sitosterol, stigmasterol, fumarine and frutinone A are bioactive compounds and key chemicals. Core genes in PPI network were AKT1, CASP3, NOS3, TNF, and PPARG. Ginseng relieves depression by affecting biological processes associated with neurotransmitters, neurotrophic factors, neurogenesis, HPA axis and inflammatory response, which are reciprocally connected with each other. More importantly, we found that frutinone A and kaempferol are key ingredients in ginseng with dual activities of immune-regulation and anti-depression.

Conclusion: Ginseng can regulate whole-body systems through a complex genes-interaction network, resulting in a certain effect on depression. This research demonstrates that ginseng is a preferable herb clinically in post-pandemic and network pharmacology approach can be an effective tool to reveal the mechanisms of traditional Chinese medicine from a holistic perspective.

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2, is in the midst of worldwide panic and global health concern since December 2019 [1]. The most common symptoms of COVID-19 illness are fever, cough, and dyspnea [2]. In the most severe cases, people with poor immunity may develop pneumonia and multiple organ failure, eventually leading to death. However, no specific drug or vaccine has yet been developed and the epidemic will not be brought under positive control in the short term. To our knowledge, the onset of a sudden and immediately life-threatening illness could lead to posttraumatic stress disorder [3]. Quarantine is necessary to manage the outbreak, and the experience of being quarantined can, in some cases, lead to long-term adverse mental health consequences [4]. Furthermore, many other economic problems caused by epidemic, such as financial difficulties and loss of employment, undoubtedly increased public anxiety and depression. Based on these, it is of great significance to prevent the outbreak of depression after a global epidemic while improving the public immunity.

Panax ginseng Meyer, as a precious tonic traditional Chinese medicine (TCM), usually grows in cooler areas like Northeast China, Korea peninsula and Russia. The Greek term "Panax", which means "cure of all diseases", implied its important position in the medical field. Ginseng can regulates each type of immune cells, therefore maintaining homeostasis of the immune system and enhancing resistance to illness or microbial attacks [5]. Quan et al., also found ginseng and salviae herbs play a role as immune activators during influenza virus infection [6]. As recorded in the traditional Chinese work, Jingyue Quanshu (Jing-yue's Complete Works), ginseng has been used in the classic prescription Qifu Yin to treat neurasthenia and other nervous system diseases. Ginsenoside, as the main pharmacologically active components of ginseng, have been found to exhibit as novel antidepressant

agents [7]. It can be seen that ginseng has a good effect on both immune-regulation and anti-depression. Hao et al., integrated metabolomics and network pharmacology to study the immune-regulation mechanism of ginseng [8]. However, its anti-depression therapeutic mechanisms have not yet been clearly elucidated. In order to provide guidance for clinical application in post-pandemic, it is necessary to make clear the active ingredients and mechanism of ginseng's antidepressant effect.

Network pharmacology has been introduced in recent years for exploring the molecular mechanisms of TCM. The key ideas of emerging network pharmacology and network biology shares much with the holistic philosophy of TCM, updating the research paradigm from the current "one target, one drug" mode to a new "network target, multi-components" mode [9]. Through bridging the emerging network science and ancient TCM, we obtain novel methodologies and opportunities for discovering bioactive ingredients and biomarkers, potentially revealing mechanisms of action. Even though the anti-depression effects of ginseng have been reported, network pharmacology-based prediction of the bioactive components and target pathways has not been performed.

In this study, we investigated pharmacological mechanisms of ginseng to exert anti-depressant activity using network pharmacology. The flowchart of the experimental procedures of our study is shown in Figure 1. We also discussed the active ingredients with immune-regulation and anti-depression, in order to provide theoretical guidance for further clinical application in post-pandemic (Figure 1).

MATERIALS AND METHODS

Database construction and ADME screening of ginseng ingredients

All of the known ingredients of ginseng were manually collected from related literature and phytochemical databases [10]: Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, http://tcmspw.com/tcmsp.php). An in silico integrative model~ADME (absorption, distribution, metabolism, and excretion) was used to select the ingredients with favorable pharmacokinetics properties. The parameter used in this study included oral bioavailability (OB) and drug-likeness (DL). OB refers to the rate and degree of drug absorption into human circulation after oral administration and DL refers to the similarity of a compound to a known drug. They are two of the most commonly used pharmacokinetic properties in drug screening. Ingredients conforming to the requirements of both OB ≥30% and DL ≥0.18 were regarded as active ingredients in ginseng for further analysis.

Target genes related to the identified compounds

In the TCMSP database, the potantial targets of each active ingredient were found. The Uniprot data library (https://www.uniprot.org/) was used to convert the selected target into a gene name of Homo sapiens (Human) to prepare the target genes related to the identified compounds. Component-target data of ginseng were obtained after deleting the duplicates.

Collection of therapeutic targets of ginseng for depression

Information on depression-associated target genes was collected from the human gene database (Gene Cards, http://www.genecards.org/) using "depression" as the keywords, and only "Homo sapiens" proteins linked to depression were selected. With relevance score > 7.32 as the threshold, the obtained targets were screened. In order to obtain the potential anti-depressant targets of ginseng, the targets of each active ingredient were intersected with depression-related targets through an online mapping platform (http: //bioinfo. Genotoul.fr/jvenn/example.html).

Protein-protein interaction data

The potential anti-depressant targets of ginseng were

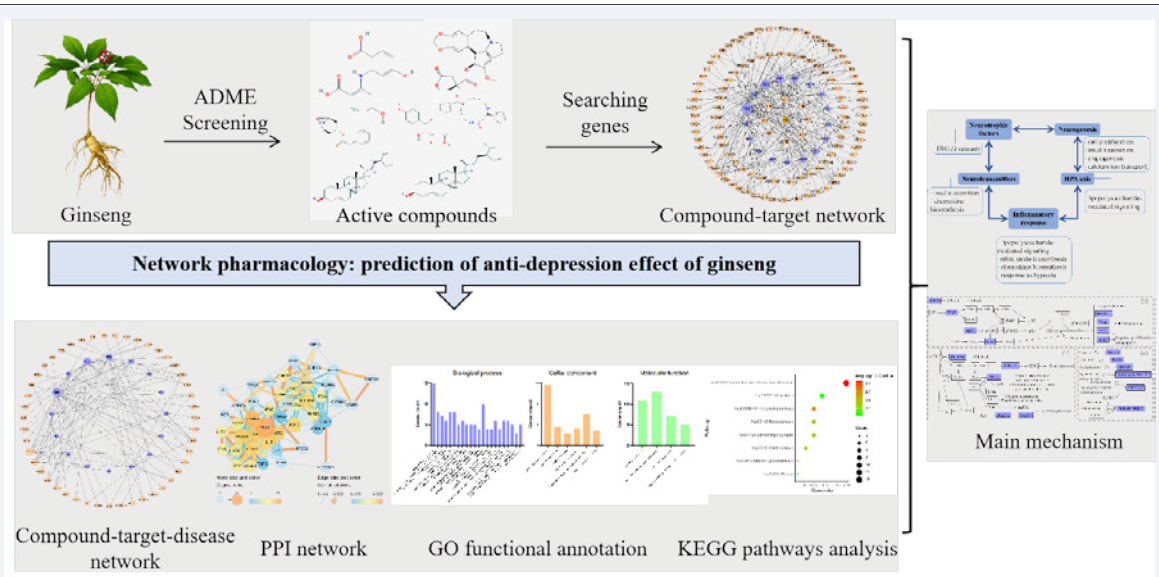

Figure 1 The flowchart of the network pharmacology-based strategy for deciphering the mechanisms of ginseng on depression.

imported into the String database (http://stringdb.org/) for the analysis of protein-protein interaction (PPI). A confidence score above 0.4 indicates an interaction relationship. Therefore, the confidence was set as confidence > 0.4, while other parameters remained defaults.

Construction of the pharmacological networks

All visualized network models were established via Cytoscape 3.8.0 (http://www.cytoscape.org/), an open software package project for visualizing, integrating, modeling and analyzing the interaction networks [11]. In the network, nodes represent compounds or target genes, while edges represent the interactions between them. The "Network Analyze" in Cytoscape 3.8.0 is used to analyze the topology properties of the Network. Three networks were constructed: (1) Compound-compound target network. The potential targets of each active ingredient in ginseng were used to generate it; (2) Compound-target-disease network. The potential anti-depressant targets of ginseng were used to generate it; (3) PPI network of depression-related targets in ginseng.

Gene ontology and pathway enrichment analysis

The potential anti-depressant targets of ginseng was input into the Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/tools.jsp) for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Gene species and background were limited to human. The false discovery rate (FDR) < 0. 05 was used as the filter to obtain the top GO terms of biological process (BP), cell component (CC) and molecular function (MF). The enrichment analysis of KEGG metabolic pathway was screened under the conditions of $P < 0.01$ and FDR < 0.05. The results were visualized using Graphpad Prism 8.0.2 (https://www.graphpad.com/).

RESULTS

Candidate compound screening for ginseng

Retrieved from TCMSP, there were 190 components related to ginseng in total. Under the screening thresholds of OB ≥30% and DL ≥0.18, 22 active ingredients were selected for further analysis (Table 1). Among them, there are five active ingredients with higher OB: Celabenzine (101.88%), Aposiopolamine (66.65%), Frutinone A (65.9%), Inermin (65.83%) and Girinimbin (61.22%). These components play important roles in the pharmacological activities of ginseng. (Table 1)

Potential target prediction for ginseng

Among the 22 active components, 5 of them did not find corresponding targets, while the remaining 17 components obtained 109 potential targets after removing duplicates. All active compounds, their targets and the interactions between them are presented in the compound-compound target network (Figure 2), which is composed of 126 nodes (17 components and 109 targets) and 246 edges. The pink nodes represent drug targets while the blue nodes represent compounds, and the edges represent the interactions between them. Degree, a topological parameter describing the importance of a node, stands for the number of edges connecting to the node. We used it to further determine the importance of each active component. Through analysis, we found that RS5 exhibited the largest number of potential targets connections (Kaempferol, degree = 59), followed by RS3 (Beta-sitosterol, degree = 36), RS2 (Stigmasterol, degree = 31), RS17 (Fumarine, degree = 24) and RS4 (Inermin, degree = 16). The same active ingredient can act on different targets,

Table 1: Active compounds and ADME parameters of ginseng (OB ≥30%, DL ≥0.18).

ID	MOL ID	Molecule Name	OB(%)	DL
RS1	MOL002879	Diop	43.59	0.39
RS2	MOL000449	Stigmasterol	43.83	0.76
RS3	MOL000358	Beta-sitosterol	36.91	0.75
RS4	MOL003648	Inermin	65.83	0.54
RS5	MOL000422	Kaempferol	41.88	0.24
RS6	MOL005308	Aposiopolamine	66.65	0.22
RS7	MOL005317	Deoxyharringtonine	39.27	0.81
RS8	MOL005318	Dianthramine	40.45	0.20
RS9	MOL005320	Arachidonate	45.57	0.20
RS10	MOL005321	Frutinone A	65.9	0.34
RS11	MOL005344	Ginsenoside Rh2	36.32	0.56
RS12	MOL005348	Ginsenoside Rh4	31.11	0.78
RS13	MOL005356	Girinimbin	61.22	0.31
RS14	MOL005376	Panaxadiol	33.09	0.79
RS15	MOL005384	Suchilactone	57.52	0.56
RS16	MOL005399	Alexandrin	36.91	0.75
RS17	MOL000787	Fumarine	59.26	0.83
RS18	MOL004492	Chrysanthemaxanthin	38.72	0.58
RS19	MOL005314	Celabenzine	101.88	0.49
RS20	MOL005357	Gomisin B	31.99	0.83
RS21	MOL005360	Malkangunin	57.71	0.63
RS22	MOL005401	Ginsenoside Rg5	39.56	0.79

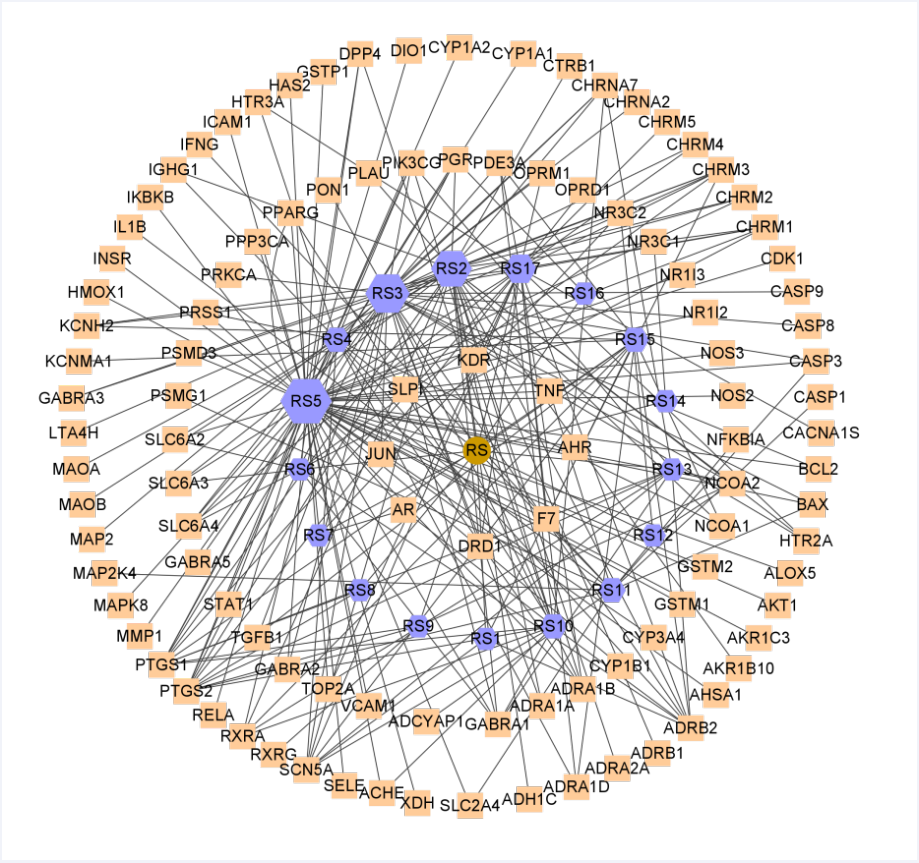

Figure 2 Compound-compound target network. The size of the node is proportional to the value of the degree.

and different active ingredients can also act on the same target, which fully reflects the multi-component, multi-target action characteristics of ginseng. (Figure 2)

Collection of therapeutic targets of ginseng for depression

A total of 11478 disease targets were obtained from GeneCards with "depression" as the keyword. Among them, 975 depression-related genes meet the requirement of relevance score > 7.32 and ginseng have 47 potential targets for depression (Figure 3a). Compound-target-disease network (Figure 3b) with 63 nodes and 102 edges linked 16 compounds and 47 target genes related to depression. Among the 16 candidate compounds, RS5 exhibited the largest number of potential anti-depression targets connections (Kaempferol, degree = 24), followed by RS3 (Beta-sitosterol, degree = 18), RS2 (Stigmasterol, degree = 14), RS17 (Fumarine, degree = 9) and RS10 (Frutinone A, degree = 8). For the 47 potential anti-depression targets, the network showed PTGS2 had the largest number of compound-target interactions, followed by SCN5A, GABRA1, CHRNA7 and SLC6A4, while the remaining 42 targets showed interactions with up to three compounds. (Figure 3)

Protein-protein interaction analysis

After removing a free target, the PPI network (Figure 4) contains 46 nodes and 259 edges, with average node degree of 11 and average local clustering coefficient of 0.533. Target size and color are used to reflect the degree, while edge thickness and color are used to reflect the combine score. The important targets were painted red and located centrally in the network. AKT1 (degree = 25), CASP3 (degree = 20), NOS3 (degree = 19), TNF (degree = 19), PPARG (degree = 18), SLC6A4 (degree = 18), ACHE (degree = 18), IL1B (degree = 17), PTGS2 (degree = 17) and MAOA (degree = 16) were the top ten genes regarding their degree. AKT1 also has the highest closeness centrality (0.67), indicating the faster the signal is transferred to other nodes. Due to the highest betweenness centrality (0.14), AKT1 is considered a bottleneck node in monopolistic position between modules in the network and more suitable as a therapeutic target. (Figure 4)

GO biological process and KEGG pathway enrichment analysis

Through DAVID database, we obtained 305 GO terms (226 BP terms, 31 CC terms and 48 MF terms) and 68 pathways in total. With FDR < 0.05 as the screening condition, 32 GO terms (22 BP terms, 6 CC terms and 4 MF terms) were selected (Figure 5). The BP terms were mainly involved in neurotransmitters, neurotrophic factors, neurogenesis, HPA axis and inflammatory response. The processes were, in the aspect of neurotransmitters: insulin secretion (GO:0050796) and positive regulation of chemokine biosynthetic process (GO:0045080); in the aspect of neurotrophic factors: positive regulation of ERK1 and ERK2 cascade (GO:0070374); in the aspect of neurogenesis: positive regulation of cell proliferation (GO:0008284), insulin

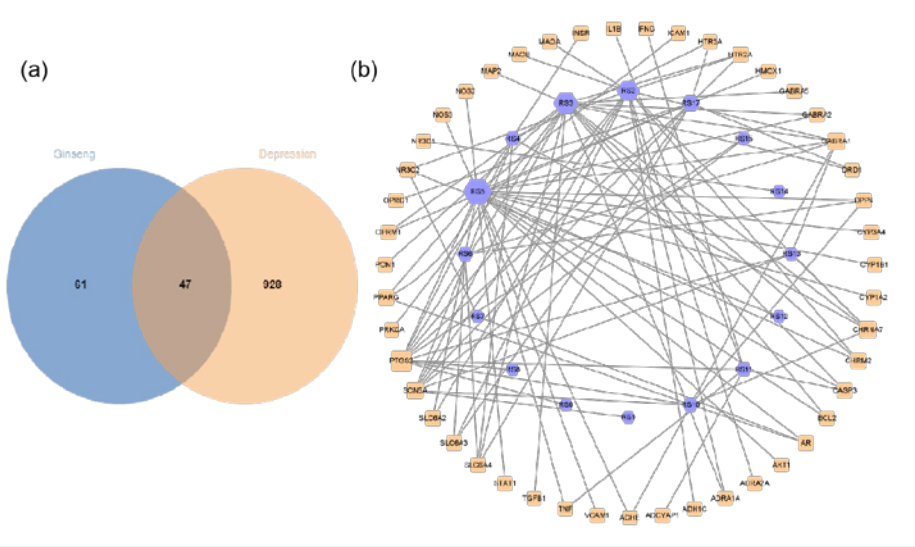

Figure 3 (a) Venn diagram. (b) Compound-target-disease network with 63 nodes and 102 edges.

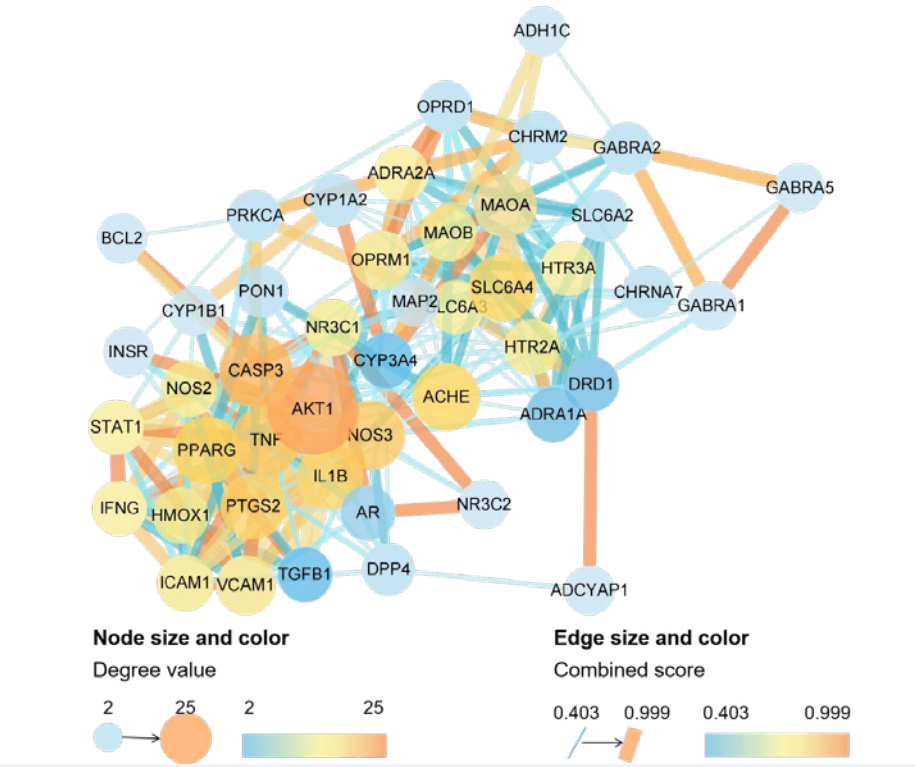

Figure 4 PPI network of depression-related targets in ginseng.

secretion (GO:0050796), angiogenesis (GO:0045766) and negative regulation of calcium ion transport (GO:0051926); in the aspect of HPA axis: lipopolysaccharide-mediated signaling (GO:0031663); in the aspect of inflammatory response: positive regulation of nitric oxide biosynthetic process (GO:0045429), lipopolysaccharide-mediated signaling (GO:0031663), positive regulation of chemokine biosynthetic process (GO:0045080) and response to hypoxia (GO:0001666). The 6 CC terms were involved in plasma membrane (GO:0005886), integral component of plasma membrane (GO:0005887), membrane raft (GO:0045121), neuron projection (GO:0043005), postsynaptic membrane (GO:0045211) and Caveola (GO:0005901). Among them, plasma membrane and integral component of plasma membrane accounted for the largest proportion, with 29 and 15 targets respectively. Depending on the outcomes of GO enrichment, the enriched molecular function ontologies were

dominated by protein homodimerization activity (GO:0042803), enzyme binding (GO:0019899), heme binding (GO:0020037), extracellular ligand-gated ion channel activity (GO:0005230). Under the conditions of P < 0.01 and FDR < 0.05 (Table 2), we found that pathways in neuroactive ligand-receptor interaction (hsa04080), African trypanosomiasis (hsa05143), HIF-1 signaling pathway (hsa04066), Leishmaniasis (hsa05140), Toxoplasmosis (hsa05145), Serotonergic synapse (hsa04726), Tuberculosis (hsa05152) and Malaria (hsa05144) are the interaction pathways that ginseng exerts combined antidepressant effects (Figure 5 and 6) (Table 2).

DISCUSSION

Depression is a complex disorder with multiple etiologies including genetic, epigenetic, and environmental factors. All of the proposed pathophysiological mechanisms of depression are not separate but integrally related and interact bidirectionally [12]. First-line antidepressants, SSRIs (selective 5-HT reuptake inhibitors), were forced to stop taking due to its inhibition of gastrointestinal motility. Tricyclic antidepressants have a nonnegligible side effect on the heart and brain. Their therapeutic approaches are both single-target. TCM is characterized by multi-target, multi-pathway and low side effect. Multi-component therapy produces "synergies", in which the combined effects are greater than the sum of the individual effects. To our knowledge, the anti-depression mechanisms of active ingredients from TCM can be summed up as following: increasing synaptic availability of monoamines [13], alleviation of the HPA axis dysfunctions [14], regulation of the cAMP signaling pathway [15], and caspases [16], and amelioration of the dysregulation of immune and inflammation [17]. Ginseng has been shown to be a precious herbal medicine with dual activities of immune-regulation and anti-depression. In this study, we investigated pharmacological mechanisms of ginseng to exert anti-depressant activity using network pharmacology.

The screened active components can be classified as flavonoids, saponins, sterols, organic acids and etc. Some nodes are more concentrated in the network than others [18]. We found that several key compounds, including kaempferol, beta-sitosterol, stigmasterol, fumarine and frutinone A, play dominant roles in this network. As the most common flavonoid, kaempferol has attracted much attention due to its anti-cancer, anti-inflammatory, antioxidant, antibacterial and antiviral effects. Gao

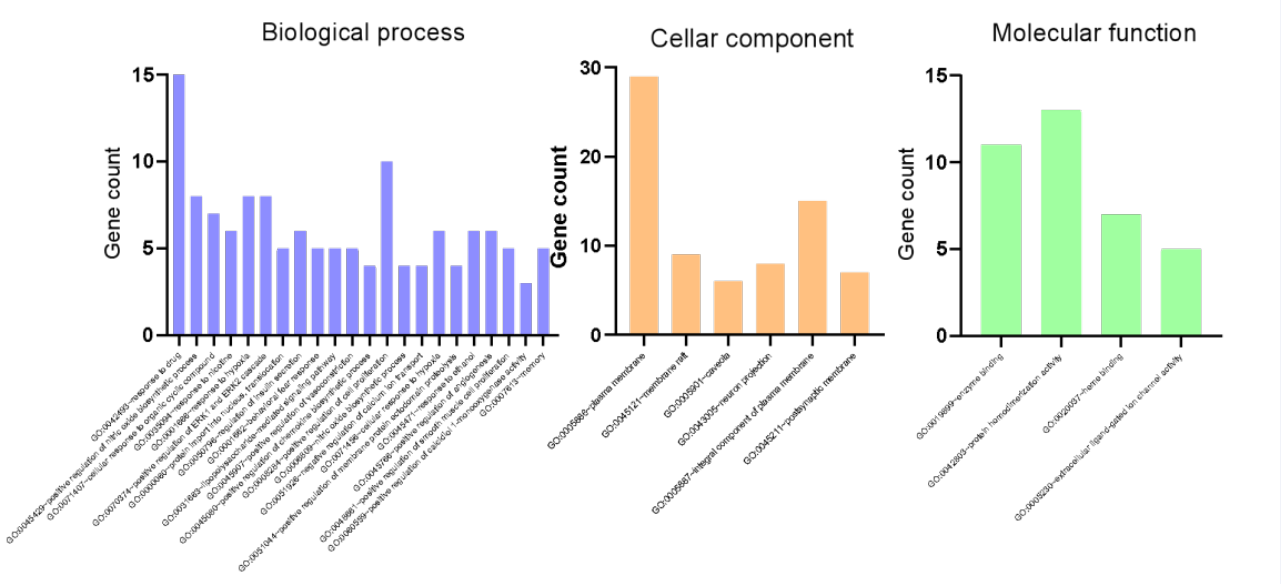

Figure 5 GO functional annotation analysis of 47 target genes were sorted according to FDR < 0. 05.

Table 2: Functions of potential target genes based on KEGG pathway analysis.

Pathway ID	Term	Target genes	Count
hsa04080	Neuroactive ligand-receptor interaction	OPRM1, DRD1, GABRA2, GABRA1, CHRM2,GABRA5,DRA2A,ADRA1A, CHRNA7, NR3C1, OPRD1, HTR2A	12
hsa05143	African trypanosomiasis	PRKCA,VCAM1,ICAM1, TNF, IFNG, IL1B	6
hsa04066	HIF-1 signaling pathway	PRKCA,AKT1,HMOX1, BCL2, IFNG, NOS3, NOS2, INSR	8
hsa05140	Leishmaniasis	TNF, PTGS2, IFNG, IL1B, NOS2, STAT1, TGFB1	7
hsa05145	Toxoplasmosis	AKT1, CASP3, TNF, BCL2, IFNG, NOS2, STAT1, TGFB1	8
hsa04726	Serotonergic synapse	PRKCA, CASP3, PTGS2, MAOA, SLC6A4, MAOB, HTR3A, HTR2A	8
hsa05152	Tuberculosis	AKT1, CASP3, TNF, BCL2, IFNG, IL1B, NOS2, STAT1, TGFB1	9
hsa05144	Malaria	VCAM1, ICAM1, TNF, IFNG, IL1B, TGFB1	6

et al. have comfirmed that antidepressive effects of kaempferol are mediated by reduction of oxidative stress, proinflammatory cytokines and up-regulation of AKT/β-catenin cascade [19]. Stigmasterol has been found to exert neuro-protective effect through reduction of oxidative stress and inactivation of autophagy via AMPK/mTOR and JNK pathways [20]. It has been reported that β-sitosterol has protective effects on various brain-related diseases independent of their lipid-lowering effects. Moreover, β-sitosterol can also suppress the development of cerebral aneurysm by inhibiting inflammatory reactions including TNF-α [21]. This indicated that our prediction of the active ingredient in ginseng that plays an antidepressant role is reasonable. However, frutinone A are mostly considered as an active ingredient of the broad spectrum antimicrobial herbal extract up to now and anti-depression may be its potential pharmacological activity that has not yet been discovered. As mentioned above, main compounds of ginseng on immune-regulation were selected by the network pharmacology analysis, including ginsenoside Re, ginsenoside Rg1, frutinone A, and kaempferol [8]. Through analysis, we found frutinone A and kaempferol are also the major ingredients in ginseng to exert anti-depressant activity. Therefore, these two ingredients are the key ingredients in ginseng with dual activities of immune-regulation and anti-depression.

In the PPI network, AKT1 has the highest degree, closeness centrality and betweenness centrality. It is in the monopolistic position between modules in the network and more suitable as a therapeutic target. AKT1, a downstream enzyme that has been implicated in the pathogenesis of serotonin-related disorders, facilitates growth factor-mediated cell survival and block apoptosis through the regulation of its downstream effector (GSK-3) in depressants [22-23]. Moreover, SLC6A4 is responsible for the serotonergic neurotransmission, which is an important substance that regulates neural activity. The serotonin-linked polymorphic region (5-HTTLPR) is a degenerate repetition of the gene encoding the 5-hydroxytryptamine transporter (SLC6A4). The S/S genotype in this region is associated with decreased serotonin expression and increased susceptibility to depression [12]. TNF and IL-1B may be involved in major depression not just by activating certain cascades of inflammation but also by many other mechanisms [24]. It is not difficult to see that ginseng's treatment of depression involves neurotransmitters (especially serotonin), inflammation, neurotrophic factors and many other aspects. Furthermore, inflammatory cytokines have been shown to reduce monoamine levels in depressed patients by increasing the metabolism of tryptophan, an important precursor to serotonin [12]. It also reconfirmed the factors that influence depression are not separate but integrally related and interact bidirectionally. These results were consistent with our enrichment analysis, and have been previously reported to be related to depression.

GO analysis revealed that ginseng relieves depression by affecting biological processes associated with neurotransmitters, neurotrophic factors, neurogenesis, HPA axis and inflammatory response, which are reciprocally connected with each other (Figure 7). For example, inflammation leads to HPA hyperactivity and HPA hyperactivity in turn plays an adverse role in the inflammatory process, forming a vicious circle. The target genes were majorly associated with the biological process of response to drug, indicated the key requirement of avoiding drug dependence in depression drug development and clinical treatment [25]. Extracellular signal-regulated kinase 1/2 (ERK1/2) signaling, which belongs to the large family of mitogen-activated protein kinase signaling cascases, showed low activity in the frontal cortex (Brodmann 8, 9, 10) and hippocampus in depressed patients [26]. It has been shown to have significant effects on the regulation of long-term enhancement, long-term depression, and neuronal survival through neurotrophic/growth factors [27-28]. In recent years, more and more studies have proved that astrocytes not only have a supporting effect, but also regulate physiological processes by secreting neurotrophic factors. This suggests that ginseng can play a direct and indirect therapeutic role by acting on astrocytes or nerve cells. Intracellular Ca2+ accumulation or overload can lead to a series of neuronal injuries (neuronal degeneration, necrosis, and apoptosis) by the activation of CaMK signal transduction pathways. Angiogenesis is also closely related to neuronal regeneration. A variety of angiogenic factors, especially the vascular endothelial growth factor (VEGF), not only has effect on promoting angiogenesis, but also on the nerve nutrition and neurogenesis. Through negative regulation of calcium ion transport, positive regulation of angiogenesis and cell proliferation, ginseng promote neurogenesis, which is thought to contribute to anti-stress recovery and underlie the clinical efficacy of antidepressants [29]. Moreover, ginseng can regulate insulin secretion, and insulin in the nervous system is related to the growth of nerve cells and the release of neurotransmitters. Chemokines not only regulate neurotransmitters but also affect inflammation. In recent years, studies have shown an increasing link between depression and chemokines. Glucocorticoid is the main cytokine released by macrophages, and ginseng's effect on lipopolysaccharide-mediated signaling is important to regulate inflammation and HPA axis dysfunction. Besides that, the positive regulation of ginseng in smooth muscle cell proliferation provides support for brain-smooth muscle axis hypothesis. The hypothesis holds that there is a bidirectional neuroendocrine pathway that regulates specific brain regions and smooth muscles through local CYP enzymes and endogenous active substances, thus alleviating depression. Furthermore, results showed the main cell component terms were involved in plasma membrane and integral component of plasma membrane, while protein homodimerization activity and enzyme binding dominated the enriched molecular function ontologies. (Figure 7)

In addition, KEGG pathway analysis were primarily pertaining to neuroactive ligand-receptor interaction, serotonergic synapse and HIF-1 signaling pathway, which followed the previous reports that these pathways participate in crucial functions in the progression and development of depression (Figure 8). It is worth mentioning that there were several pathways, which are concerned with diseases, such as African trypanosomiasis, Leishmaniasis, Toxoplasmosis, Tuberculosis, and Malaria, prompting that ginseng may have potential therapeutic efects on these diseases. Twelve targets enriched onto neuroactive ligand-receptor interaction pathway were mostly neurotransmitter receptors. Monoamine neurotransmitters (serotonin, norepinephrine and dopamine) have a potential role

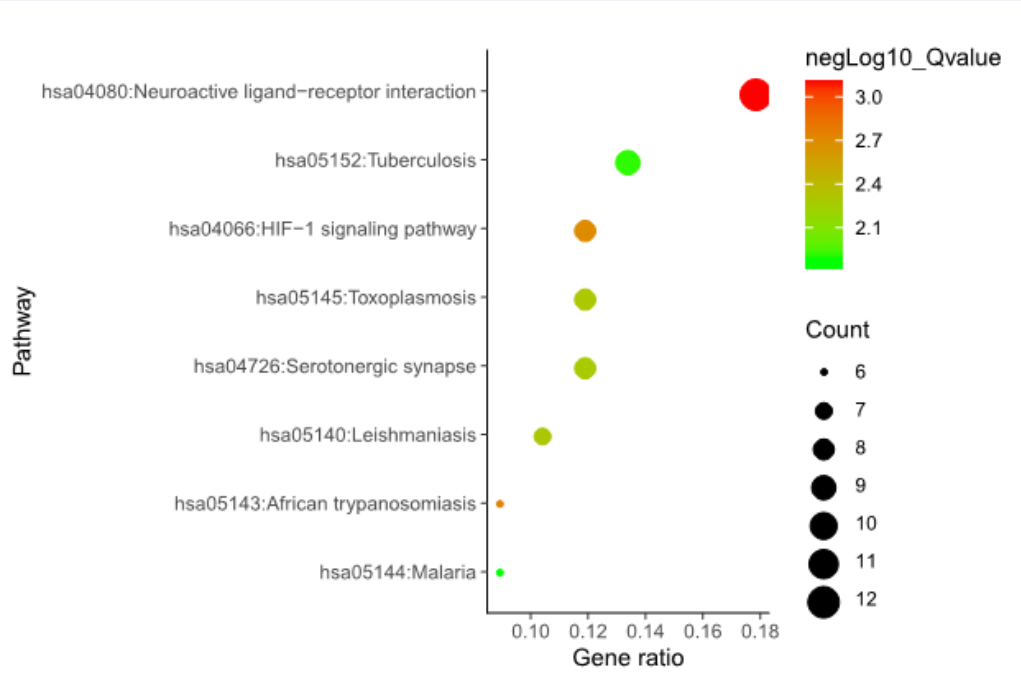

Figure 6 KEGG pathways analysis of 47 target genes were sorted according to P < 0.01 and FDR < 0.05.

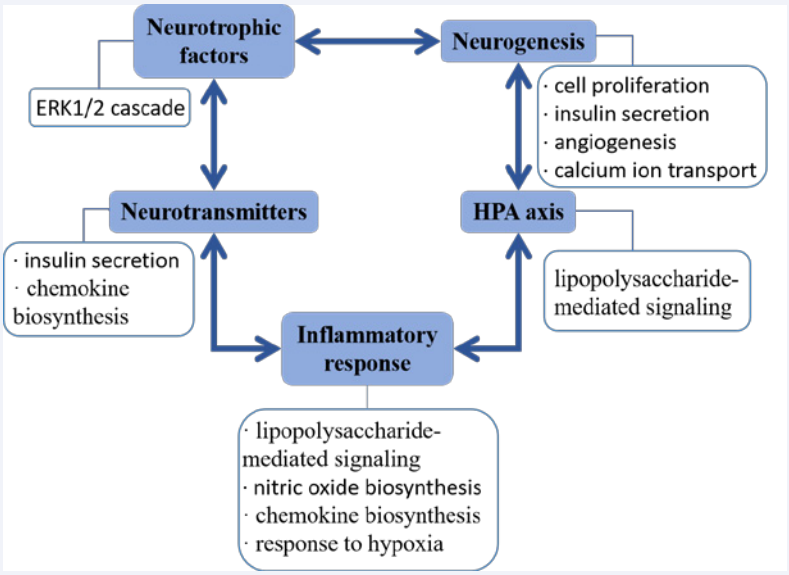

Figure 7 Illustration of the crucial biological processes caused by putative targets and known therapeutic targets for depression.

in the pathogenesis of depression and monoamine hypothesis explained how antidepressants work [30]. HIF-1 signaling pathway is associated with AKT, NF-κB signaling pathways and the transcription of VEGF, which interferes with inflammatory injury, oxidative stress, apoptosis and tumor growth. FG-4592 improves depressive-like behaviors through HIF-1-mediated neurogenesis and synapse plasticity in rats [31]. Taken together, these results indicate that ginseng can regulate whole-body systems through a complex genes-interaction network, resulting in a certain effect on depression (Figure 8).

LIMITATIONS

In this study, due to the traffic restrictions because of the Coronavirus disease COVID-19-related pandemic, we were unable to perform experiment to validate the theoretical predictions. Further work should address these issues to improve the reliability of the results.

CONCLUSIONS

Past experience shows that mental health problems often occur in the public following a major epidemic. This study

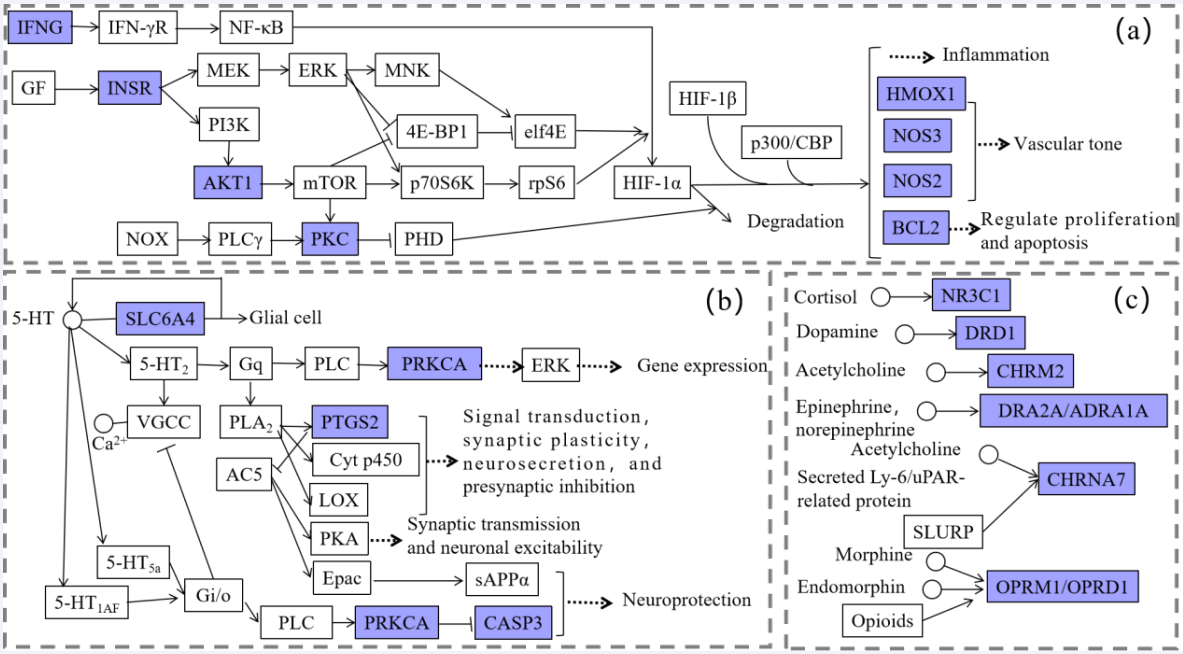

Figure 8 The anti-depression pathway of ginseng. The blue nodes represent the targets of ginseng acting on the pathway. (a) HIF-1 signaling pathway. (b) Serotonergic synapse. (c) Neuroactive ligand-receptor interaction.

used a scientifc approach, network pharmacology, to decipher the pharmacological mechanisms of ginseng in the treatment of depression. We discovered that the therapeutic activities of ginseng for depression mainly involve neurotransmitters, neurotrophic factors, neurogenesis, HPA axis and inflammatory response, which are reciprocally connected with each other and implied these were involved in the underlying mechanisms of ginseng on depression. These findings could provide theoretical guidance in the investigation of ginseng for further clinical application in post-COVID-19. And network pharmacology approach can be an effective tool to reveal the mechanisms of traditional Chinese medicine from a holistic perspective.

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