



Exploring the mechanisms of action of *Cordyceps sinensis* for the treatment of depression using network pharmacology and molecular docking

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Background: Depression is the most common type of psychological disorder, with continuous, prolonged, and persistent bad moods as the main clinical feature. *Cordyceps sinensis* is a complex consisting of the ascospores and bodies of insect larvae from the Hepialidae family that have been parasitized by *Cordyceps sinensis militaris*. Previous studies have reported that this herb has antidepressant activity. The present study used network pharmacology and molecular docking techniques to investigate the potential antidepressant mechanisms of *Cordyceps sinensis*.

Methods: The active ingredients of *Cordyceps sinensis* were identified using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) and the potential targets were predicted using the PharmMapper platform. The GeneCards database was then used to obtain sub-targets for depression. Common targets were screened and enrichment analyses were performed using the Metascape platform. Finally, the relationship between the active ingredients and the core targets were verified by molecular docking.

Results: Through network pharmacological analysis, 7 active ingredients in *Cordyceps sinensis* and 41 common targets of drugs and diseases were identified. The active ingredients of *Cordyceps sinensis* may exert antidepressant effects by acting on important targets such as catalase (CAT), CREB binding protein (CREBBP), epidermal growth factor (EGF), and E1A binding protein P300 (EP300), and by modulating the signaling pathways in which these targets are involved. Subsequently, the core targets were docked to the active ingredients and good binding was observed.

Conclusions: The active ingredients of *Cordyceps sinensis* may exert antidepressant effects by regulating the CREB binding protein and anti-oxidative stress effects. The *foxo* signaling pathway (hsa04068), hypoxia-inducible factor 1 (HIF-1) signaling pathway (hsa04066), and Huntington's disease (hsa05016) may be involved in the underlying mechanisms of *Cordyceps sinensis*. The joint application of network pharmacology

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and molecular docking provides a new approach to study the mechanisms of action of traditional Chinese medicine. *Cordyceps sinensis* may play an important role in the future treatment of patients with depression.

Keywords: *Cordyceps sinensis*; depression; network pharmacology; molecular docking

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Introduction

Depression is a chronic mood disorder with a very high prevalence. It can be disabling for patients, who often experience a high incidence of suicide and relapse. Unfortunately, the curative rates for patients with depression are relatively low (1). The clinical manifestations of depression include apathy, loss of interest or pleasure in activities, and slowness in mental and physical activities (2). The etiology of depression is complex, and is often an interplay between genetic and environmental factors, as well as biological, social, and psychological factors (3). Sociologically, it is believed that the prevalence of depression also varies considerably between different ethnic groups and races (4). Psychologically, it is thought that adverse life events may increase the risk of depressive episodes (5). Furthermore, depression is associated with a variety of diseases, such as gastrointestinal disorders, sleep disorders, and neurological disorders (6-8). However, the antidepressants currently available are ineffective and have significant side effects (9). For example, tricyclic antidepressants (TCAs) regulate the concentration of monoamine neurotransmitters in the synaptic gap mainly by inhibiting the reuptake of synaptic gap 5-HT and NE. Common adverse effects are blurred vision, dry mouth, constipation, and in severe cases, urinary retention and intestinal paralysis. Monoamine oxidase inhibitors (MAOIs) are the first class of drugs used to treat depression. They produce antidepressant effects by inhibiting monoamine oxidase (MAO), reducing the metabolic inactivation of catecholamines, and increasing catecholamine content at synaptic sites, however, they have low potency, high side effects, and hepatotoxicity. Therefore, further research and development of antidepressant drugs is crucial.

Traditional Chinese medicine (TCM) and herbal medicines have been widely used for thousands of years to treat a wide variety of diseases (10). TCM is mainly derived from natural plants, which has the advantages of good

efficacy, low toxic side effects, and low costs (11). However, the complexity of the components involved in TCM and the unclear mechanisms of action have hampered its clinical application (12). *Cordyceps sinensis* (BerK.) Sacc. is a complex of the ascospores of the *Cordyceps sinensis* (BerK.) parasite that is found on the larvae of insects from the Hepialidae family and the bodies of the larvae and is primarily used to treat fatigue, night sweats and other symptoms related to aging (13). It is mainly found in high altitude areas around 4,000 meters above sea level in Qinghai, Tibet, Sichuan, Yunnan, Guizhou, and Gansu in China. It is believed to be a good tonic for the kidneys, beneficial for the lung, and can stop bleeding and resolve phlegm buildup (14). In recent years, most of the research on *Cordyceps sinensis* has focused on the chemical composition and pharmacological activities such as the treatment of diabetic nephropathy. However, less research has been conducted on its antidepressant effects and mechanisms (15) and warrant further investigation.

With the development of computer bioinformatics, network pharmacology has gradually become an emerging field. Network pharmacology is based on the principle of systems biology to construct biological networks for elucidating the potential mechanisms of drug therapy for complex diseases, while molecular docking is one of the common methods to study the interaction pattern between small molecules and large molecules, and the recognition between biomolecules. Since Chinese medicine is characterized by multi-components and multi-targets, network pharmacology allows us to effectively connect Chinese medicine to its components, targets, pathways, and diseases. This study examined the potential mechanisms of the antidepressant effects of *Cordyceps sinensis* by using network pharmacology and molecular docking techniques (Figure 1). We present the following article in accordance with the TRIPOD reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-762/rc>).

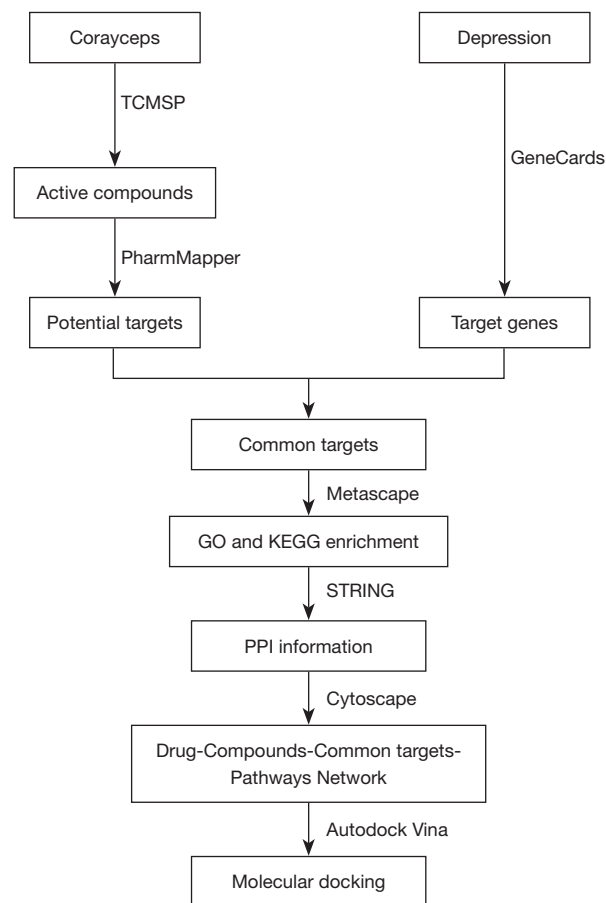


Figure 1 A schematic diagram showing the study framework, based on network pharmacology and molecular docking, used to study the antidepressant mechanisms of the active ingredients of *Cordyceps sinensis*. TCMSP, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction.

Methods

Identifying the active ingredients of *Cordyceps sinensis*

The active ingredients of *Cordyceps sinensis* were assessed using the Traditional Chinese Medicine Systematic Pharmacology Database and Analysis Platform (TCMSP, <http://tcmssp.com/tcmssp.php>) and 499 herbs with a total of 12,144 chemical substances were identified (16). The search was performed using “*Corayceps*” as the keyword, and oral bioavailability (OB) $\geq 30\%$ and drug-likeness (DL) ≥ 0.18 were applied as the screening conditions to obtain the eligible active ingredients.

Predicting the targets of the active ingredients

Target prediction of all active ingredients was performed through the PharmMapper ([http://www.lilab-ecust.](http://www.lilab-ecust.cn/pharmmapper)

[cn/pharmmapper](http://www.lilab-ecust.cn/pharmmapper)) platform, which is supported by the TargetBank, DrugBank, Binding DB, and PDTD databases with over 7,000 receptor-based pharmacological models (17-19). By submitting the active ingredient in mol2 or sdf format on this platform and selecting its default option in the parameter settings, the target information of the active ingredient was generated.

Determining the targets of *Cordyceps sinensis* in depression

The GeneCards (<https://www.genecards.org>) database was searched and the target genes for depression were determined by taking the median value of triplicate readings (20). Subsequently, the potential targets of the drug active ingredients were converted into Gene Symbol through the Uniprot (<https://www.uniprot.org>) platform (21). Finally, the overlapping targets of the *Cordyceps sinensis* active

ingredients and depression were screened and identified. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Enrichment analysis

To determine the biological functions and signaling pathways involved in the common targets of the drug active ingredients and depression, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the Metascape (<https://metascape.org>) platform (22). A P value ≤ 0.05 for GO and $P \leq 0.05$ for KEGG pathway were considered significantly enriched. The results of the enrichment analyses were plotted using <http://www.bioinformatics.com.cn>, a free online platform for data analysis and visualization.

Construction of a drug, components, targets (including protein-protein interaction), pathway network

The STRING (<https://string-db.org>) database is a platform used to predict protein-protein interaction (PPI) networks (23). This platform was used to submit the common targets of the active ingredients of *Cordyceps sinensis* and depression to obtain PPI network maps and information. Based on the active ingredients, common targets, and signaling pathways, a network model of drug, components, targets, signaling pathways, and diseases was constructed with the Cytoscape 3.9.0 software (24). Drug, components, targets, pathways, and diseases are represented as nodes, and their interactions are represented as edge connections.

Molecular docking

The top 10% of targets from the above network were selected as receptors and their structures were obtained from the Uniprot platform. The active ingredients that can bind to these targets were used as ligands. Molecular docking of the ligand to the receptor was performed using Autodock Vina software (25), and the conformation and minimum binding energy of the ligand to the receptor were obtained after the docking was completed. Subsequently, their binding images were plotted in the pymol software (26).

Statistical analysis

Data processing was performed using GraphPad Prism8.0,

protein-protein interaction analysis was performed using Cytoscape 3.9.0, and pathway enrichment analysis was performed by Metascape version 3.5. Molecular docking analysis of proteins and active ingredients was performed using Autodock Vina version 1.2.2. The results of all relevant data analysis are presented in the Result section below.

Results

The active ingredients in *Cordyceps sinensis*

A total of 7 active ingredients in *Cordyceps sinensis* were identified using the TCMSP database, namely, arachidonic acid, linoleyl acetate, beta-sitosterol, peroxyergosterol, cerevisterol, cholesteryl palmitate, and cholesterol (CLR). The specific characteristics of these active ingredients are shown in *Table 1*.

Common targets of the active ingredients and depression

The top 300 targets for each active ingredient were identified using the PharmMapper platform. The GeneCards database was used to obtain 12,902 target genes associated with depression, and 1,525 target genes were obtained by taking the median number three times. By taking the intersection of the active ingredient targets and the disease-related targets, a total of 41 common targets were obtained (*Figure 2*), and the specific information of these targets is shown in *Table 2*.

Enrichment analysis of KEGG pathways and GO

The common targets were uploaded to the Metascape platform and the P value was set to < 0.05 . Enrichment analyses of KEGG pathways, GO biological processes, GO cellular components, and GO molecular functions were performed. A total of 388 GO biological processes (GO BP), 36 GO cellular components (GO CC), 36 GO molecular functions (GO MF), and 23 KEGG pathways were identified.

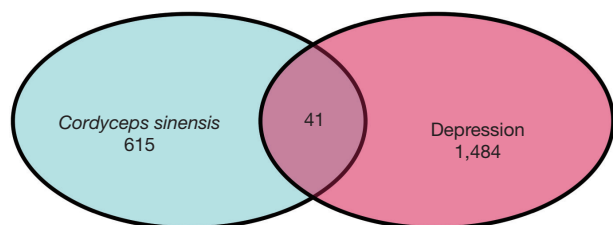
KEGG pathway analysis

All KEGG pathways were selected for analysis and mapping (*Figure 3*). The potential targets of *Cordyceps sinensis* activity for the treatment of depression were mainly enriched in foxo signaling pathway (hsa04068), HIF-1 signaling pathway (hsa04066), and Huntington's disease (hsa05016). These

Table 1 Characteristics of the active ingredients found in *Cordyceps sinensis*

Molecule ID	Molecule name	MW	OB (%)	Caco-2	BBB	DL
MOL001439	Arachidonic acid	304.52	45.57	1.2	0.58	0.2
MOL001645	Linoleyl acetate	308.56	42.1	1.36	1.08	0.2
MOL000358	Beta-sitosterol	414.79	36.91	1.32	0.99	0.75
MOL011169	Peroxyergosterol	428.72	44.39	0.86	0.43	0.82
MOL008998	Cerevisterol	432.76	39.52	0.35	-0.29	0.77
MOL008999	Cholesteryl palmitate	625.19	31.05	1.45	0.68	0.45
MOL000953	CLR	386.73	37.87	1.43	1.13	0.68

MW, molecular weight; OB, oral bioavailability; Caco-2, ingredients' transport rates (nm/s) in Caco-2 monolayers; BBB, blood-brain barrier; DL, drug-likeness; CLR, cholesterol.

**Figure 2** A Venn diagram showing the common targets between depression and *Cordyceps sinensis*.

results suggested that the active ingredients of *Cordyceps sinensis* may exert antidepressant effects by regulating the CREB binding protein and catalase (CAT).

GO analysis

The top 20 items of the GO biological processes, GO cellular components, and GO molecular functions enrichment analyses were further examined (Figure 4A-4C). The potential targets of the active ingredients of *Cordyceps sinensis* for the treatment of depression are mainly involved in steroid hormone response and anti-oxidative stress response.

Network analysis of drug-component-target (including PPI)-pathway

By submitting the targets in the STRING database, the PPI interactions network information was obtained, and the network diagram of drug-component-target (including

Table 2 The common targets of the active ingredients of *Cordyceps sinensis* and depression

Disease	Compound	Common targets
Depression	MOL008998	MAOB, DLG1, CREBBP, AR, HSD11B1, DDC, ESR2, CAT, SOD2, USH1C, F2, HSD17B4, CD8A, BCL2A1, GDI1, NPC2, MMP2, ALAD, SMS, RBP4
	MOL000953	CREBBP, AR, HSD11B1, ACHE, CAT, EGF, SOD2, F2, HSD17B4, CD8A, GDI1, MOG, NPC2, RBP4, ACTA1, HEXA
	MOL000358	MAOB, CREBBP, AR, ACHE, USP8, EGF, SOD2, F2, GDI1, NPC2, RBP4, HEXA
	MOL001645	GAD1, DLG1, S100B, CREBBP, EP300, AR, ACHE, DDC, ZEB2, ESR2, CAT, SOD2, USH1C, F2, HSD17B4, INSR, CD8A, BCL2A1, CDH11, GDI1, MOG, SIN3A, NPC2, ALAD, RBP4, ACTA1
	MOL011169	DLG1, CREBBP, AR, ACHE, ESR2, CAT, SPD2, HSD17B4, MANB1, CDH11, GDI1, MOG, NPC2, RBP4
	MOL001439	GAD1, MAOB, DLG1, S100B, CREBBP, AR, DDC, ZEB2, ESR2, CAT, SOD2, USH1C, F2, HSD17B4, CD8A, GDI1, MOG, SIN3A, NPC2, HBB, MMP2, ALAD, RBP4, ACTA1, ANXA5
	MOL008999	ESR1, GAD1, S100B, CREBBP, EP300, AR, ACHE, DDC, ESR2, SYNGAP1, CAT, SOD2, F2, HSD17B4, VDR, CD8A, HMOX1, GDI1, MOG, NPC2, HBB, CNP, RBP4, ACTA1

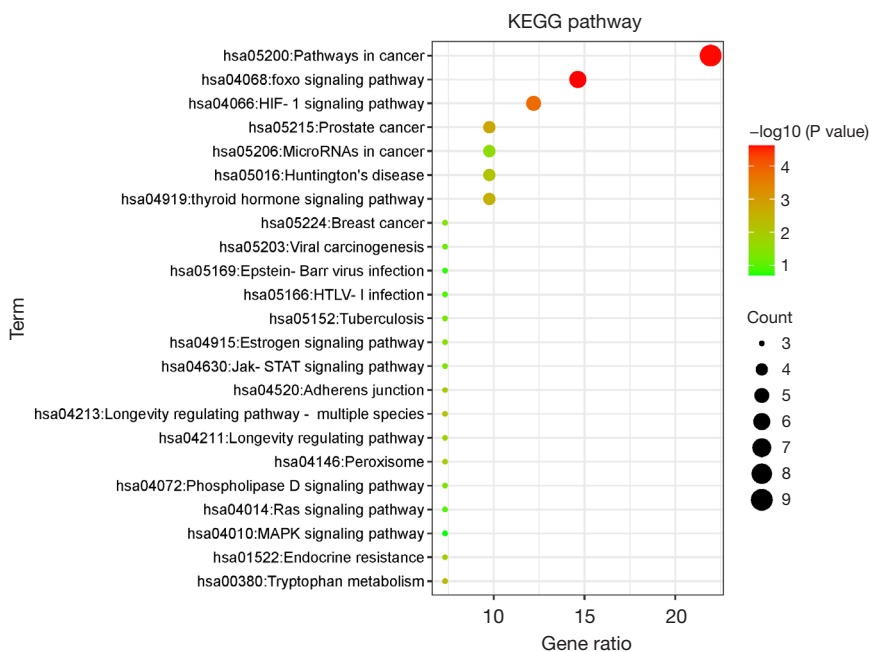


Figure 3 The results of the KEGG enrichment analysis. KEGG, Kyoto Encyclopedia of Genes and Genomes.

PPI-pathway was obtained in Cytoscape 3.9.0 by collating the data, as shown in *Figure 5*. There were 73 nodes (disease: 1 node; drug: 1 node; active ingredients: 7 nodes; targets: 41 nodes; and pathways: 23 nodes) and 353 edges in the network (137 for ingredient-target connections, 84 for PPI, 84 for pathway-target connections, 41 for disease-target connections, and 7 for drug-active ingredient connections).

Molecular docking

The top 10% of targets in the network (including CREBBP, EP300, EGF, and CAT) were docked to the relevant active ingredients using Autodock Vina. The results showed a total of 17 binding interactions, with all molecules showing a binding energy less than 0 with the targets (*Table 3*), suggesting that the ligand can spontaneously bind to the receptor. *Figure 6A* shows the docking results of cerevisterol with CREBBP, and *Figure 6B* shows the docking results of cerevisterol with CAT.

Discussion

Depression is a common mood disorder, usually caused by mental stress. It is characterized by low mood and weight loss (27). Unfortunately, the current antidepressant drugs available on the market are not effective and thus, continued

research into antidepressant therapy is crucial. However, it is difficult to study the antidepressant effects of *Cordyceps sinensis* based on traditional Chinese medicine pharmacology and instead, network pharmacology may be used to study the pharmacological mechanisms of action based on big data and computer technology (28). Network pharmacology provides a new approach to the development of traditional Chinese medicine by analyzing network properties through nodes and relationships in biological networks to elucidate drug mechanisms of action. Currently, network pharmacology is widely used in the study of TCM. For example, it can be applied to screen the active ingredients and potential targets; elucidate the complex mechanisms of drugs and prescriptions for treating diseases; and reveal the medicinal properties of herbs. However, there are still some difficulties to overcome for the further development of this discipline, such as the comprehensiveness of target information in the database needs to be improved, the protein interaction network needs to be further enhanced, and the relevant prediction results need to be experimentally verified. By combining Chinese medicine database and computer software, we not only improve the research level of traditional Chinese medicine, but also greatly promote its internationalization. The results of this present study suggested that the active ingredients in *Cordyceps sinensis* may exert its antidepressant effects by regulating CREB

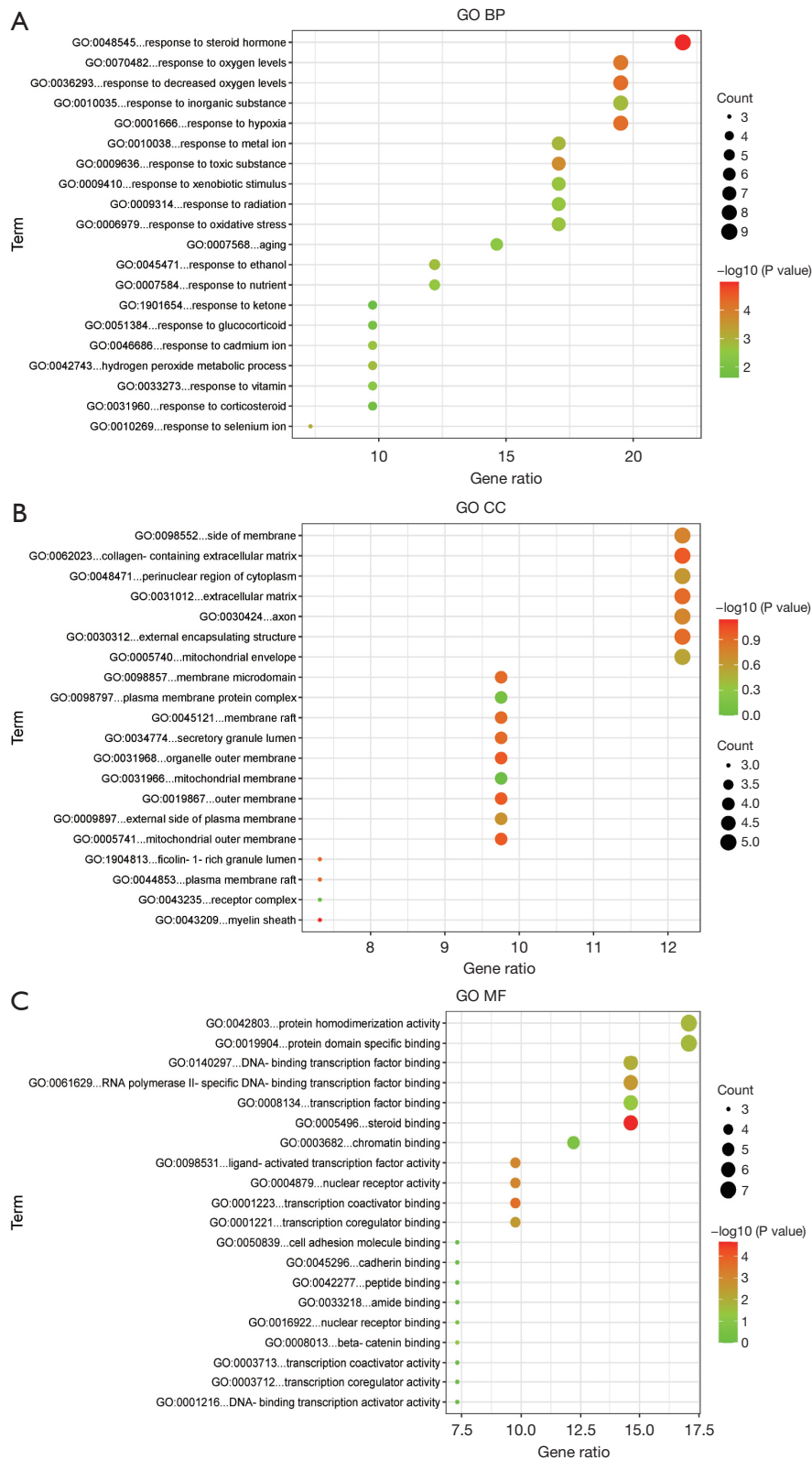


Figure 4 The results of the GO enrichment analysis. (A) GO biological processes; (B) GO cellular components; (C) GO molecular functions. GO, Gene Ontology; BP, biological processes; CC, cellular components; MF, molecular functions.

Table 3 The docking of the core targets with active compounds

Molecule ID	Target	PDB ID	Binding energy (kcal/mol)
MOL008998	CREBBP	7JFM	-8.6
MOL000953	CREBBP		-7.3
MOL000358	CREBBP		-7.8
MOL001645	CREBBP		-4.3
MOL011169	CREBBP		-7.7
MOL001439	CREBBP		-4.7
MOL008999	CREBBP		-5.9
MOL001645	EP300	6V90	-3.8
MOL008999	EP300		-5.6
MOL000953	EGF	3NJP	-4.4
MOL000358	EGF		-6.7
MOL008998	CAT	1QQW	-9.2
MOL000953	CAT		-6.2
MOL001645	CAT		-2.6
MOL011169	CAT		-4.1
MOL001439	CAT		-2.8
MOL008999	CAT		-6.3

PDB, Protein Data Bank; CREBBP, CREB binding protein; EP300, E1A binding protein P300; EGF, epidermal growth factor; CAT, catalase.

interactions with other proteins of the transcriptional complex. This gene is involved in the transcriptional co-activation of many different transcription factors such as CREB, which plays a key role in embryonic development, growth control and homeostasis by linking chromatin remodeling to transcription factor recognition. Many target genes regulated by the cAMP signaling pathway are mediated by CREB and its phosphorylation, and ultimately regulate the transcription of genes such as brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) (37). Studies have shown that depressed patients have reduced levels of CREB phosphorylation (38), while those who are responsive to antidepressant treatment have significantly higher levels of CREB phosphorylation (39). There is evidence to suggest that oxidative stress is present in depression and that CAT protease has the ability to scavenge peroxides produced by cellular metabolism, thereby protecting cells from the toxic effects of peroxides (40). Studies have shown that very small amounts of EGF can strongly stimulate cell growth and inhibit senescence gene expression (41,42). Depression is associated with a variety of neurological disorders, such as autism (43). *EP300* is a gene that expresses the p300 protein (44) which is a histone acetyltransferase that works by grafting acetyl groups on top of histones so that the gene can be expressed. Mutations in the *EP300* gene may cause autism disorders (45). The active ingredients of *Cordyceps sinensis* may act on targets such as CREBBP, CAT, EGF, and *EP300*, as well as their associated

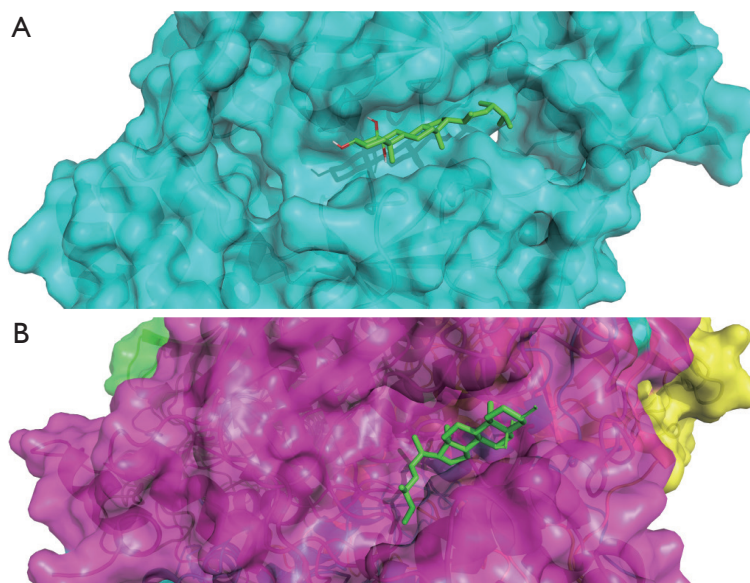


Figure 6 Molecular docking results with the lowest binding energy. (A) Molecular docking of MOL008998 and CREBBP; (B) molecular docking of MOL008998 and CAT. CAT, catalase.

pathways to achieve antidepressant effects.

Conclusions

The present study explored the antidepressant mechanisms of *Cordyceps sinensis* by jointly applying network pharmacology and molecular docking techniques. The results suggested that the active components of *Cordyceps sinensis* may exert antidepressant effects through anti-oxidative stress and modulation of the CREB binding protein (29,46). In addition, the *foxo* signaling pathway (hsa04068), HIF-1 signaling pathway (hsa04066), and Huntington's disease (hsa05016) may be involved in the mechanisms of action (47-49). This study lends support to the use of computer biology to facilitate further research on *Cordyceps sinensis* for the treatment of patients with depression and contributes to the development of traditional Chinese medicine for future clinical applications worldwide.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-762/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-762/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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