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ORIGINAL RESEARCH

Cistanche deserticola Stem Extract Attenuates Depression Through NF-κB Pathway Modulation: Insights from Network Pharmacology and Experimental Validation

Shijie Jiang[1,*], Zhiguo An[1,*], Qiang Hu[2,*], Yong Song[3], Xiaofeng Zhao[4], Shuaishuai Gao[1], Qiyu Jia[5], Bin Xu[1]

[1]Department of Medical Psychology, The first Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, People's Republic of China; [2]Department of Psychiatry, Wuhu Hospital of Anding Hospital, Wuhu, Anhui, People's Republic of China; [3]Science and Technology Digital Resources and Literature Intelligence Center, Xinjiang Institute of Science and Technology Development Strategy, Urumqi, Xinjiang, People's Republic of China; [4]Xinjiang Science and Technology Project Service Center, Science and Technology Administration of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang, People's Republic of China; [5]School of Medicine, Nankai University, Tianjin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Qiyu Jia, School of Medicine, Nankai University, Tianjin, 300071, People's Republic of China, Email snjiaqiyu@163.com; Bin Xu, Department of Medical Psychology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, 830011, People's Republic of China, Email xubin681108007@163.com

Purpose: This study aims to elucidate the effects of *Cistanche deserticola* Y. C. Ma on depression and its mechanisms through a comprehensive approach involving network pharmacology evaluation, molecular docking, and animal experiments.

Methods: By integrating network pharmacology, molecular docking, and animal testing, we systematically revealed the molecular mechanisms of the antidepressant effects of *Cistanche deserticola*. The main active components of *Cistanche deserticola* were selected from the TCMSP database, and depression-related targets were cross-verified using the OMIM/DisGeNET databases. Subsequently, a protein-protein interaction network was constructed using STRING, and the relationships between drug, target, and pathway were visualized using Cytoscape. GO function and KEGG pathway enrichment analyses were performed using DAVID and Metascape, molecular docking of core components with target proteins was completed using AutoDock Vina. The antidepressant effects and neuroprotective effects of *Cistanche deserticola* were further evaluated in a chronic unpredictable mild stress (CUMS) mouse model through behavioral tests and immunofluorescence, Nissl, and HE staining in the hippocampus.

Results: Network pharmacology identified 6 key active components and 74 potential targets, focusing on 25 core targets. Molecular docking demonstrated that key components exhibited high affinity with core targets, with binding energies less than −5 kcal·mol^{-1}. KEGG enrichment analysis indicated that the NF-κB signaling pathway serves as a core regulatory axis ($FDR < 0.001$). Animal experiments confirmed that *Cistanche deserticola* significantly inhibited the activation of M1 microglia in the hippocampus of CUMS mice, reducing the expression of IL-1β, VCAM1, and NF-κB ($P < 0.0001$), while alleviating neuronal morphological damage and significantly improving depressive-like behaviors and cognitive impairments.

Conclusion: *Cistanche deserticola* exerts antidepressant effects by regulating the NF-κB signaling pathway and inhibiting neuroinflammation. This study provides preliminary theoretical and experimental evidence supporting the potential of *Cistanche deserticola* stem as a safe and tolerable plant-derived antidepressant.

Keywords: depression, *Cistanche deserticola*, network pharmacology, molecular docking, molecular mechanisms, targets

Introduction

As a leading cause of disability, depression poses a significant mental health challenge across the world, severely undermining individual physical and mental health while exacerbating social and economic pressures.[1–3] The initial

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therapeutic approach commonly utilizes antidepressants, with a focus on the SSRI class (selective serotonin reuptake inhibitors), for instance, fluoxetine (FLX). However, the side effects of these medications, including changes in appetite, weight gain, and cardiovascular adverse reactions, significantly diminish patient adherence to prescribed treatments.[4–6] Therefore, developing alternative strategies that can quickly alleviate symptoms while ensuring good safety profiles has become an urgent priority in psychiatric drug research.

In recent years, increasing evidence has collectively pointed to chronic neuroinflammation, particularly the aberrant signaling of nuclear factor-κB (NF-κB) and resulting neuroinflammation are now widely recognized as fundamental mechanisms driving the onset of depressive disorders. For example, Zheng et al demonstrated[7] that celecoxib, by inhibiting the NF-κB signaling pathway, can maintain the gap junctions of astrocytes, thereby significantly reducing neuroinflammation and improving depressive-like behaviors. Similarly, vilazodone, a novel antidepressant, has been shown to markedly alleviate depressive symptoms in patients with major depressive disorder, which is associated with reduced NF-κB activity.[8] Furthermore, Zhao et al[9] indicated that panaxynol exerts significant antidepressant properties by suppressing the hyperactivation of BV-2 microglia via modulation of the IκB-α/NF-κB axis. Concurrently, repetitive transcranial magnetic stimulation therapy effectively alleviated neuroinflammation and improved depressive symptoms by attenuating the hyperactivation of the hippocampal TLR4/NF-κB/NLRP3 axis and prefrontal cortex of mice subjected to chronic unpredictable mild stress (CUMS).[10] Recent studies have also shown that the natural compound notopterol can inhibit glioma growth and improve cognitive impairment and depressive-like behaviors in mice, largely via the potent suppression of neuroinflammation driven by the STAT3/NF-κB axis.[11] These findings suggest that multi-pathway interventions targeting NF-κB may present a novel breakthrough in the treatment of depression.

Meanwhile, the comorbidity between depression and cognitive impairment as well as neurodegenerative diseases has garnered increasing attention. Neurodegenerative pathologies, such as Alzheimer's disease (AD), are also accompanied by NF-κB-mediated brain inflammation.[12,13] Moreover, patients with depression often exhibit heightened inflammatory responses in the brain,[14–16] which further exacerbates cognitive decline. This "inflammation-cognition" dual dilemma necessitates new medications that not only alleviate depressive symptoms but also focus on neuroprotection and cognitive enhancement.

Natural medicines, due to their "multi-ingredient and multi-target" characteristics, demonstrate unique potential in the integrated regulation of neuroinflammation.[17] *Cistanche deserticola* Y. C. Ma is a representative example. Commonly known as "desert ginseng," *Cistanche deserticola* is a holoparasitic perennial herb belonging to the family Orobanchaceae. It survives by forming specialized haustoria to obtain water and nutrients from host plants, primarily species of *Haloxylon*, and is widely distributed in the desert regions of northwestern China, including Inner Mongolia, Gansu, and Xinjiang. *Cistanche deserticola* has a long history of medicinal use. It was first recorded in *Shennong Bencao Jing* (*Shennong's Classic of Materia Medica*), where it was classified as a superior-grade medicinal herb and described as having the functions of "nourishing the five zang-organs, regulating yin, and replenishing essence and vital energy".[18] In addition, classical Chinese materia medica texts, particularly *Bencao Gangmu* (*Compendium of Materia Medica*) and *Zhonghua Bencao* (*Chinese Materia Medica*), document its traditional functions of tonifying the liver and kidneys, nourishing essence and blood, strengthening muscles and bones, and moistening the intestines to relieve constipation.[19] Clinically, it has been widely used as an adjuvant therapy for kidney-yang deficiency, insufficiency of essence and blood, intestinal dryness with constipation, and consumptive weakness.[20–23] Since its inclusion in the list of substances with dual use as both food and medicine by the National Health Commission of China in 2020, research on *Cistanche deserticola* has increasingly shifted from the verification of traditional functions to the systematic investigation of its functional constituents.[20] Its broad therapeutic potential is thought to be attributable to a rich variety of bioactive constituents, including phenylethanoid glycosides, polysaccharides, iridoids, and lignans, which provide an important scientific basis for its pharmacological activities.[24–27] Previous studies have shown that *Cistanche deserticola* possesses multiple pharmacological properties, including immunomodulatory, antioxidant, anti-inflammatory, anti-fatigue, and anti-aging effects. Modern pharmacological studies have further demonstrated its diverse roles in neuroregulation and endocrine modulation, attracting increasing attention in recent years.[28–31] the extract of a closely related species, *Cistanche tubulosa*, significantly improves depressive-like behaviors and alleviates sexual dysfunction.[6] Furthermore, a study by Yang et al[32] and Fan et al[33] confirmed the pronounced antidepressant and anti-inflammatory potential of

Cistanche species in CUMS models. Given their highly similar phytochemical profiles, these findings provide compelling rationale to hypothesize that *Cistanche deserticola* may exert comparable or distinct neuroprotective and antidepressant effects. In the study of neurodegenerative diseases,[34] *Cistanche deserticola* significantly improved learning and memory impairments via the modulation of glial cell reactivity and the suppression of the TLR4/NF-κB cascade. Additionally, it reduced the expression of pro-inflammatory M1 microglial markers while enhancing the levels of M2 phenotype-associated markers, thereby improving the expression of synaptic proteins and demonstrating notable neuroprotective effects. In summary, in addition to its neuroregulatory and endocrine modulating effects mentioned above, *Cistanche deserticola* also demonstrates potential therapeutic effects in anti-inflammation, prevention and treatment of neurodegenerative diseases, and regulation of intestinal barrier function. This provides important evidence for exploring its application value in the treatment of depression, particularly in cases accompanied by cognitive impairment.

Despite the encouraging existing evidence, the systematic mechanisms of *Cistanche deserticola* in "emotion-cognition dual phenotype" depression remain to be elucidated, particularly with a lack of direct comparisons to the first-line drug fluoxetine. Based on this, the present study employs a three-tiered closed-loop framework of "network pharmacology prediction—molecular docking validation—empirical verification in a CUMS model mouse" to first analyze the core active components, potential targets, and signaling pathway enrichment characteristics of *Cistanche deserticola* from a holistic perspective. Subsequently, it quantitatively assesses the affinity advantages of key molecules to the NF-κB axis target proteins and compares the intervention effects of *Cistanche deserticola* and fluoxetine on the dual phenotype of emotion and cognition in animal models. Finally, the study combines immunofluorescence and histological staining of hippocampal tissue to verify the ability to regulate microglial polarization and inhibit neuroinflammatory responses. This aims to establish a rigorous mechanistic foundation for the use of *Cistanche deserticola* in the treatment of depression accompanied by cognitive impairment and to provide a feasible pathway for developing "multi-target, low-side-effect" natural antidepressants. Integrated study design for investigating the antidepressant effects of *Cistanche deserticola* is shown in Figure 1.

Materials and Methods

Network Pharmacology and Bioinformatics Target Analysis

We initiated our study by integrating data from the OMIM and DisGeNET databases, using "Depressive disorder" and "Homo sapiens" as keywords. The sources of the databases are shown in Table 1. This process was conducted to compile a comprehensive list of genes associated with depression. Subsequently, we performed a crossover analysis to refine and identify the potential targets specifically related to "Depressive disorder".

To evaluate the biological properties of *Cistanche deserticola*, essential information such as chemical name, molecular weight, oral bioavailability (OB), and drug similarity (DL) were obtained from the TCMSP database. Notably, an OB of $\geq 30\%$ was considered indicative of good bioavailability, and a DL ≥ 0.18 was deemed characteristic of a drug-like compound based on prior research.[35] Following this, details regarding the target pairs of the active ingredient within *Cistanche deserticola* were obtained from the TCMSP database. To standardize gene symbols, a conversion operation was performed using the UniProt database.

The potential targets associated with *Cistanche deserticola* were cross-referenced with depression-related genes to identify the central targets. A Venn diagram, generated using Venny 2.1.0, visually represented the overlapping targets. Subsequently, Afterwards, String database analysis was conducted, specifying the target gene type as "Homo sapiens" with a confidence level of 0.7000. The resulting protein-protein interaction (PPI) network was visualized using Cytoscape 3.9.1 software.

Leveraging data from the analysis, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed through the DAVID and Metascape databases. Core targets, identified with a significance threshold $P < 0.05$, underwent GO functional enrichment analysis and KEGG pathway analysis. The top 10 pathways, based on gene number values (Count), were visualized in bubble/bar graphs using bioinformatics online tools. The Metascape database analysis results were employed to create the *Cistanche deserticola* targeting pathway network. Cytoscape 3.9.1 software facilitated the analysis of network connectivity using Degree metrics.

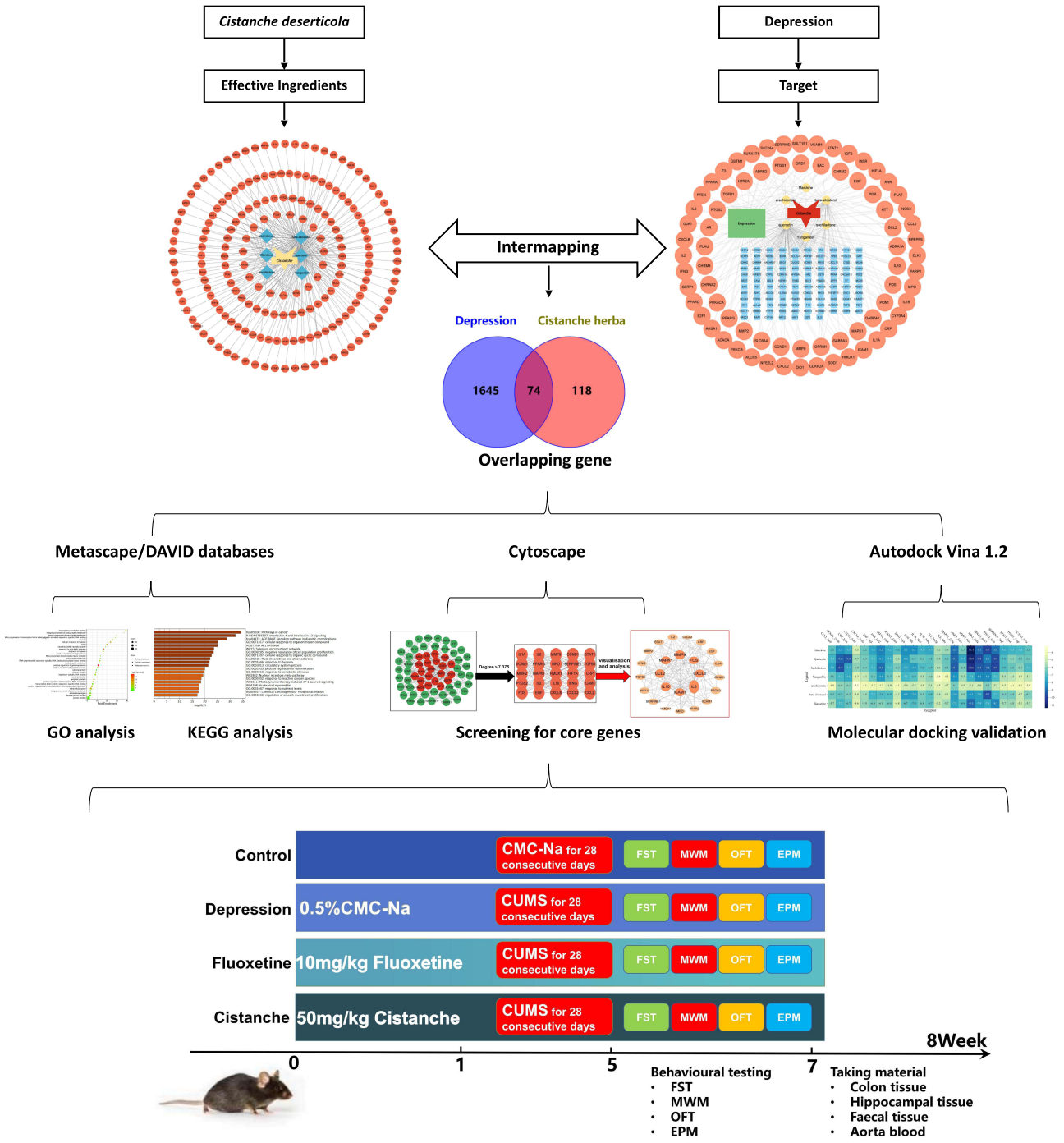

Figure 1 Integrated study design for investigating the antidepressant effects of Cistanche using network pharmacology, molecular docking, and in vivo validation. The study design comprised active-compound screening and target prediction for Cistanche, collection of depression-related targets, identification of overlapping targets, construction of a protein-protein interaction network, GO and KEGG enrichment analyses, and molecular docking of hub targets with key compounds. The predicted antidepressant-related mechanisms were subsequently validated in a chronic unpredictable mild stress (CUMS) mouse model. The lower panel illustrates the schematic timeline of the animal experiment, including CUMS exposure, drug treatment, behavioral testing, and tissue collection.

Validation of Molecular Docking

Molecular docking studies were conducted using Autodock Vina1.1.2 software, examining the interaction between proteins corresponding to the screened core targets and the effective active ingredients of *Cistanche deserticola*. Docking results, indicative of the binding strength of each small molecule ligand and receptor protein, were analyzed.

Table 1 The Database Sources

Database Name	Website
TCM Systematic Pharmacology Database and Analysis Platform (TCMSP)	http://tcmspw.com/tcmsp.php
UniProt Knowledgebase	https://www.uniprot.org/
OMIM Data Base	https://www.omim.org/
The DisGeNET database	https://www.disgenet.org
VENNY2.1	https://bioinfogp.cnb.csic.es/tools/venny/index.html
STRING Data Base	https://string-db.org
The DAVID database	https://david.ncifcrf.gov/
Bioinformatics	http://www.bioinformatics.com.cn/
Cytosape3.9.1	https://cytoscape.org/
Metascape Data Base	https://metascape.org/

Generally, a higher absolute value of the binding energy signifies increased binding affinity. A favorable interaction between the ligand and the target protein is generally suggested by a binding energy lower than –5 kcal/mol.[36] Additionally, the widely used antidepressant fluoxetine served as a reference drug for comparison with the *Cistanche deserticola* in this molecular docking analysis.

Validation of Animal Experiments

Animal Experiments

Animal procedures followed the recommendations outlined in the ARRIVE guidelines and the National Research Council's *Guide for the Care and Use of Laboratory Animals* (8th Edition). The Experimental Animal Ethics Committee of Xinjiang Medical University reviewed and approved the study protocols (Approval No. A240522-111). Throughout the study, animals were monitored daily for any signs of distress.

This study utilized 40 specific pathogen-free (SPF) male C57BL/6N mice (age: 6 weeks; weight: 15–18 g) sourced from the Animal Experiment Center of Xinjiang Medical University. The mice were kept in a climate-controlled facility (25 ± 2°C; 55 ± 10% humidity) under a 12-hour light/dark schedule with unrestricted access to standard diet and water. Subsequent to one week of adaptation, the animals were assigned randomly to four experimental cohorts (n=10 each) via a random number generator.[37] To induce a depressive-like state, mice in all experimental groups, except for the control group, were subjected to a CUMS paradigm for 4 weeks.[38] This paradigm is designed to induce depressive-like behaviors and associated neurobiological alterations, serving as an established animal model to evaluate the efficacy of potential antidepressant agents; the specific stressors, detailed in Table S1, were applied randomly throughout the 4-week period. The reference medicinal material of *Cistanche deserticola* Y. C. Ma (Orobanchaceae), consisting of the powdered dried fleshy stem with scale leaves, was purchased from Yuanye Bio-Technology Co., Ltd. (Shanghai, China, Cat. No. B27090). Quality control was performed by the manufacturer in accordance with the Chinese Pharmacopoeia using thin-layer chromatography (TLC) with echinacoside as the reference standard. For the experiment, the powder was suspended in normal saline (0.85% NS) and administered to mice by oral gavage as detailed in the Experimental Drug Administration Design section and Table 2. The doses of fluoxetine[33,39–41] and *Cistanche deserticola* extract[42–44] were determined based on previous studies.

Table 2 Subjects and the Dosage for Mice in Each Group

Class	Mice		
	Group	Subjects	Dosage
Control	Control	Saline Solution	Equal volume of saline
Model	CUMS	CUMS+ Saline Solution	Equal volume of saline
Treatment	Fluoxetine	CUMS+ FLX	10 mg/kg/day
	Cistanche	CUMS+ Cistanche	50 mg/kg/day

Experimental Drug Administration Design

The entire experimental period lasted for 8 weeks. Mice in the model and treatment groups were initially subjected to the CUMS paradigm for 4 weeks to induce depressive-like behaviors. From week 5 to the end of week 8, the stress protocol was terminated, and drugs or vehicles were administered by oral gavage once daily. This post-stress treatment design was employed to evaluate the therapeutic and reparative effects of *Cistanche deserticola* on established depressive phenotypes. Samples were collected on the last day of week 8.

Control Group: Normal saline (0.85% NS) was administered by oral gavage at an equivalent volume.

CUMS Group: The CUMS model was established. Normal saline (0.85% NS) was administered by oral gavage at an equivalent volume.

Fluoxetine Group: The CUMS model was established. Fluoxetine (10 mg/kg/d) was dissolved in normal saline and administered by oral gavage.

Cistanche Group: The CUMS model was established. *Cistanche deserticola* powder (50 mg/kg/d) was suspended in normal saline and administered by oral gavage.

Following the 4-week drug interventions, all mice underwent a battery of behavioral tests at the end of weeks 4 and 8. The behavioral assessments included the Forced Swim Test (FST),[45] Open Field Test (OFT),[46] Elevated Plus Maze (EPM),[47] and Morris Water Maze (MWM).[48] Prior to each test session, mice were transported to the testing room and allowed to acclimate for at least 60 minutes to minimize non-specific stress. For the MWM, a 1-day habituation session was first conducted, during which each mouse was allowed to swim freely for 60 seconds in the pool without the platform to familiarize them with the water environment. This was followed by a 4-day spatial acquisition training phase, in which escape latency was recorded to assess spatial learning ability. On the final day, a probe trial was performed with the platform removed to evaluate spatial memory retention.

The experimental schedule[49,50] for these behavioral evaluations is depicted in Figure 2, and detailed methodologies for all tests are provided in Table S2. All behavioral scoring was performed by an experimenter blinded to the experimental group assignments.

Sample Collection and Biochemical Analysis

Following the behavioral tests, fasting mice were euthanized by an intraperitoneal overdose of pentobarbital sodium (150 mg/kg[51]). Upon confirmation of deep anesthesia and the absence of reflexes, whole blood collection was performed using the cardiac puncture technique to prepare serum. Subsequently, the mice were transcardially perfused with physiological saline. The brains were then immediately dissected, fixed in 4% paraformaldehyde (PFA) solution (containing 4% PFA and 2.5% glutaraldehyde in 0.1 M phosphate-buffered saline, PBS), and processed for paraffin embedding and sectioning according to the stereotaxic atlas of the mouse brain. H&E staining was performed on the tissue slices to visualize cellular integrity and the influx of inflammatory cells. Furthermore, immunohistochemical staining was performed to evaluate the hippocampal levels of inflammatory mediators, specifically NF-κB, interleukin-1 beta (IL-1β), and inducible nitric oxide synthase (iNOS). Concurrently, the expression of vascular cell adhesion molecule 1 (VCAM-1), ionized calcium-binding adapter molecule 1 (Iba-1), and cluster of differentiation 206 (CD206) was also assessed. Detailed methodologies for immunohistochemistry and data processing are provided in Table S3.

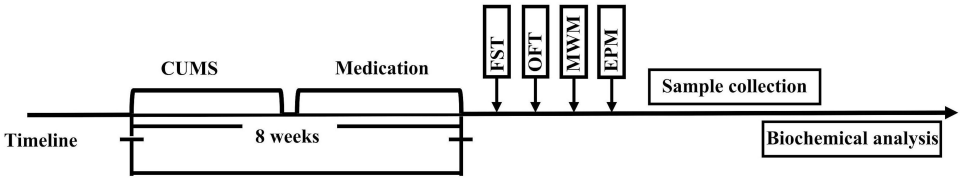

Figure 2 Experimental timeline for the chronic unpredictable mild stress mouse model and subsequent pharmacological intervention. Mice were subjected to a 4-week CUMS regimen, followed by 4 weeks of drug administration. A comprehensive battery of behavioral assessments was then conducted, after which tissues and serum were harvested for biochemical analyses.

Statistical Analysis

In this study, all data were analyzed using SPSS software (version 20.0) and presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using one-way ANOVA. When the assumption of homogeneity of variance was met, post hoc multiple comparisons were conducted using the Least Significant Difference (LSD) test. If the data were normally distributed but variances were unequal, Dunnett's T3 test was used. A *p*-value of less than 0.05 was considered statistically significant.

Results

Results of Network Pharmacology and in silico Target Analysis

Using OB ≥ 30% DL ≥ 0.18 as screening criteria, a total of 75 active compounds and 658 putative targets associated with *Cistanche deserticola* were retrieved from the TCMSP database. Among them, the major bioactive constituents included quercetin, beta-sitosterol, yangambin, suchilactone, arachidonate, and marckine. Subsequently, 192 potential targets corresponding to the key bioactive compounds (Table S4) were intersected with 1719 depression-related genes (Table S5), resulting in 74 common targets (Figure 3A).

A protein–protein interaction (PPI) network was constructed based on the STRING database and visualized and analyzed using Cytoscape software (v3.9.1). The resulting network consisted of 64 nodes and 236 edges, suggesting that the antidepressant effects of *Cistanche deserticola* may involve a complex multi-target regulatory mechanism.

To identify the key genes involved in the therapeutic effects of *Cistanche deserticola* against depression, hub proteins were screened using a degree centrality threshold greater than the average value (7.375), yielding 25 hub proteins (Figure 3B). These hub targets exhibited markedly higher connectivity with other nodes in the network, indicating their central roles in mediating the pharmacological effects of *Cistanche deserticola*. Notably, 23 of the 25 hub targets (92%) were functionally associated with inflammatory processes, including inflammation-initiating factors (IL1A, IL6, IL2, and IFNG), signaling mediators (STAT1, MAPK1, HIF1A, and FOS), inflammatory effector molecules (MMP9, MMP2, MPO, PTGS2, VCAM1, ICAM1, CXCL8, CXCL2, CCL2, CRP, and SERPINE1), and anti-inflammatory regulators (PPARG, IL10, TGFB1, and HMOX1).

GO enrichment analysis revealed that the core targets were significantly enriched in molecular functions such as enzyme binding, transcription coactivator binding, RNA polymerase II-specific DNA-binding transcription factor binding, and transcription factor binding. In terms of cellular components, these targets were mainly associated with the

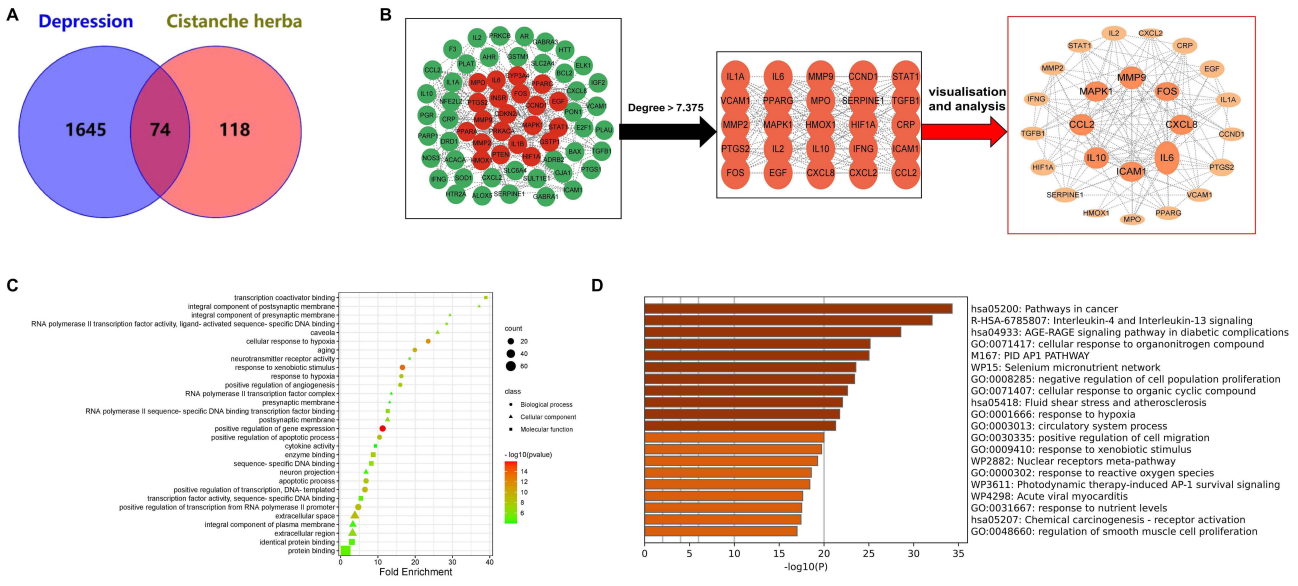

Figure 3 Network pharmacology and bioinformatics exploration of *Cistanche deserticola* against depression. (**A**) Venn diagram illustrating the overlap between depression-associated genes and the predicted targets of *Cistanche deserticola*. (**B**) Protein–protein interaction (PPI) network of the overlapping genes with hub genes highlighted. (**C**) Bubble plot ranking the ten most prominent hub genes. (**D**) KEGG enrichment analysis of the shared targets.

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Table 3 Key Signaling Pathways and Associated Targets

Term	Pathway	Key Targets in the Pathway
hsa04064	NF-kappa B signaling pathway	VCAM1, CXCL8, PARP1, PLAU, PRKCB, IL1β, BCL2, PTGS2, CXCL2, ICAM1

postsynaptic membrane, presynaptic membrane, and membrane microdomains. For biological processes, the identified targets were primarily involved in the positive regulation of gene expression, response to external stimuli, and cellular response to hypoxia (Figure 3C).

KEGG pathway analysis showed that, after excluding pathways associated with other diseases, the overlapping targets between *Cistanche deserticola* and depression were significantly enriched in the NF-κB signaling pathway (*FDR*<0.01, Table S6 and Figure 3D), indicating that this pathway may play a pivotal role in the antidepressant effects of *Cistanche deserticola* (Table 3).

Validation Results of Molecular Docking

To comprehensively evaluate the multi-target interactions of *Cistanche deserticola*, molecular docking was performed on all 25 hub targets identified from the PPI network. The results indicated that 87.3% of the core targets exhibited a binding energy of < –5.0 kcal/mol to the effective active ingredients, indicating stable computational binding capabilities. Among all compound-target pairs, marckine, quercetin, and suchilactone demonstrated the most potent binding affinities, with the strongest interactions observed at MMP9 (Marckine: –11.4 kcal/mol; Quercetin: –10.9 kcal/mol; Suchilactone: –10.6 kcal/mol), PTGS2 (Suchilactone: –9.9 kcal/mol; Quercetin: –9.8 kcal/mol), and PPARG (Beta-sitosterol: –9.7 kcal/mol) (in Table S7).

Furthermore, targeted analysis of the NF-κB neuroinflammatory axis—including VCAM1, IL1B, and IL6—revealed that Suchilactone, Marckine, and Quercetin exhibited superior binding affinities (–7.1, –7.7, and –6.6 kcal/mol, respectively) compared to the first-line antidepressant fluoxetine (–5.5, –6.7, and –5.7 kcal/mol, respectively), further corroborating the network pharmacology prediction that modulation of the NF-κB signaling pathway represents a core therapeutic mechanism of *Cistanche deserticola*.

Overall, 71% of the 25 core targets demonstrated stronger computational binding affinities compared to fluoxetine, suggesting that the multi-component synergy of *Cistanche deserticola*, particularly through Quercetin, Suchilactone, and Marckine, may provide broader multi-target modulation over single-target pharmacotherapy in the context of depression-associated neuroinflammation (Table 4 and Figure 4).

Table 4 Docking Energies and Target Analysis of Different Ingredients

Target	Ingredient/Docking Energy						
	Arachidonate	Beta-Sitosterol	Marckine	Quercetin	Suchilactone	Yangambin	Fluoxetine
CCL2	−4	−6.5	−6.8	−7.3	−7.8	−6.6	−5.7
CCND1	−6	−6.7	−8.1	−9.2	−9.7	−7.2	−7.2
CRP	−6.1	−6.3	−7.7	−9.4	−7.7	−7.6	−6.7
CXCL2	−3.1	−5	−5	−5.7	−6	−4.7	−4.6
CXCL8	−4.1	−5.8	−6.6	−6.4	−6.4	−5.3	−5.9
EGF	−4.2	−7.3	−7.8	−7.2	−7.3	−6.6	−6.4
FOS	−4.3	−7	−8.6	−8.3	−9	−8	−6.1
HIF1A	−4.9	−6.9	−7.6	−7.5	−7.2	−6.7	−6.4
ICAM1	−4.1	−5.2	−7	−5.6	−6.3	−5	−4.8
IFNG	−5	−8	−8.3	−8	−7.7	−7.2	−6.7

(*Continued*)

Table 4 (Continued).

Target	Ingredient/Docking Energy						
	Arachidonate	**Beta-Sitosterol**	**Marckine**	**Quercetin**	**Suchilactone**	**Yangambin**	**Fluoxetine**
IL10	−5.2	−7.9	−8.3	−6.7	−7.9	−6.9	−7
IL1A	−4.8	−6.3	−7.5	−6.6	−7	−5.5	−6.4
IL1B	−5.4	−6.9	−7.7	−6.8	−6.9	−6	−6.7
IL2	−4.5	−5.4	−5.6	−5.8	−5.6	−3.6	−5.2
IL6	−4.7	−5.1	−5.8	−6.6	−6.5	−4.2	−5.7
MAPK1	−6.4	−7.9	−8.9	−9.1	−9.3	−8.2	−7.8
MMP2	−4.9	−5.9	−6.4	−7.7	−6.4	−5.7	−6.9
MMP9	−5.1	−8.1	−11.4	−10.9	−10.6	−7.4	−9.1
MPO	−5	−7.9	−9.1	−9.8	−9.4	−8.4	−7.9
PPARG	−6.2	−9.7	−9.9	−8.6	−9.2	−8.4	−7.6
PTGS2	−5.2	−7.3	−8.9	−9.8	−9.9	−7.2	−8.5
SERPINE1	−4.5	−6.3	−7.6	−7	−7	−5.5	−5.7
STAT1	−4.1	−6.4	−7.3	−6.1	−6.6	−5.4	−5.8
TGFB1	−4.1	−5.2	−7.2	−6.5	−6.1	−4.7	−5.1
VCAM1	−3.8	−6.2	−6.8	−6.6	−7.1	−5.3	−5.5

Validation Results of Animal Experiments

Depressive-Like Behaviors of CUMS Mice

This study investigated the effects of *Cistanche deserticola* on depressive-like behavior using the FST after a 60-minute environmental acclimation. As shown in Figure 5A, Body weight did not differ significantly between the control group. CUMS group, fluoxetine group, and Cistanche group during the baseline phase of the experiment. However, after CUMS modeling, the body weight of the mice in the CUMS, fluoxetine, and Cistanche groups significantly decreased compared to the control group ($P < 0.0001$). After 4 weeks of continuous drug intervention, the body weight of the mice in the CUMS group remained significantly lower than that of the control group ($P < 0.0001$), whereas the body weights of the fluoxetine and Cistanche groups showed a significant recovery trend compared to the CUMS group. ($P > 0.05$). However, in the FST, CUMS-treated mice exhibited a markedly increased duration of immobility relative to controls ($P < 0.01$). Following 4 weeks of intervention, both fluoxetine and *Cistanche deserticola* significantly reduced the immobility time compared to the CUMS group (Figure 5B, $P < 0.0001$), suggesting that the administration of *Cistanche deserticola* has pronounced antidepressant-like effects.

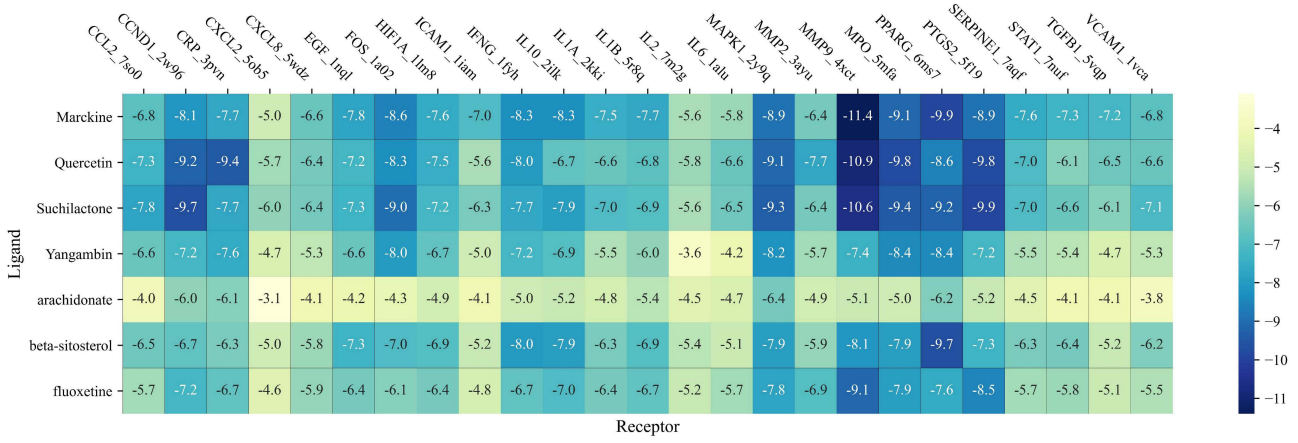

Figure 4 Heatmap of molecular-docking binding energies. Color shifts from yellow to black indicate progressively stronger binding affinities.

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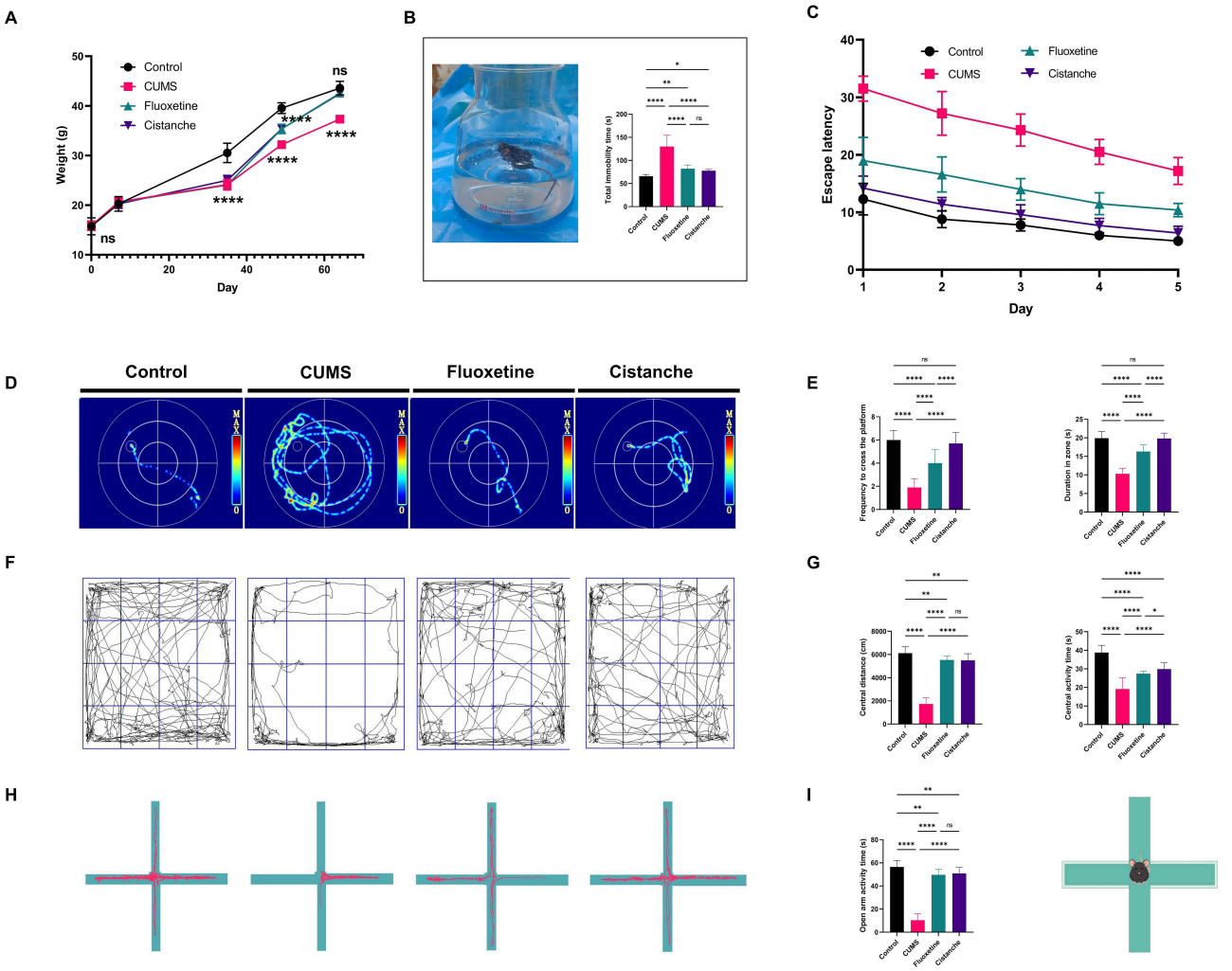

Figure 5 Behavioral impact of *Cistanche deserticola* in a mouse model of depression. (**A**) Changes in body weight of mice across the experimental period. (**B**) Representative image of the Forced Swim Test and the quantitative analysis of total immobility time. (**C**–**E**) Morris Water Maze test results evaluating spatial learning and memory: (**C**) Escape latency across the 5-day training phase; (**D**) Representative swimming trajectories/heatmaps during the probe trial; (**E**) Quantitative analysis of the probe trial, including frequency to cross the platform, duration in the target quadrant, and time of first arrival at the platform. (**F** and **G**) Open Field Test results evaluating locomotor activity and anxiety-like behaviors: (**F**) Representative movement tracking maps in the open field arena; (**G**) Quantification of total distance, central distance, and central activity time. (**H** and **I**) Elevated Plus Maze test results: (**H**) Representative tracking maps in the EPM; (**I**) Quantification of open arm time and close arm time. Statistical significance: ns, not significant, *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

To assess spatial learning and memory, mice were subjected to MWM test. After 1 day of habituation, mice underwent 4 days of spatial acquisition training. As shown in Figure 5C, escape latency decreased progressively in all groups, indicating a learning effect. However, the CUMS group showed longer escape latencies than the Control group, suggesting impaired spatial learning after CUMS exposure. Both fluoxetine and Cistanche treatment shortened the escape latency (Figure 5D). The probe trial was then performed to evaluate spatial memory retention (Figure 5E). Compared with the Control group, mice in the CUMS group spent less time in the target quadrant, crossed the former platform location fewer times, and exhibited a longer latency to first reach the platform location ($P < 0.0001$), indicating impaired spatial memory. Cistanche treatment significantly improved these deficits, restoring target quadrant time and platform crossings to levels comparable to those in the Control group ($P < 0.0001$). These results indicate that the learning and memory abilities of the CUMS model mice were impaired, while *Cistanche deserticola* was more effective in improving cognitive dysfunction, exhibiting better performance compared to the fluoxetine group.

Furthermore, after a 60-minute environmental habituation, the open field test results revealed that pharmacological interventions (particularly the fluoxetine and Cistanche groups) significantly increased the time mice spent in the central

area (Figure 5F and G), indicating that the treatments effectively alleviated anxiety-like behaviors. Consistent results were observed in the elevated plus maze test: compared to the control group, mice in the fluoxetine and Cistanche groups spent significantly more time in the open arms (Figure 5H and I). Collectively, these behavioral changes demonstrate that *Cistanche deserticola* also exerts anxiolytic-like effects.

Hippocampal Neuroinflammation of CUMS

Depression can induce significant pathological damage in the hippocampus of mice.[52] To evaluate the severity of these structural alterations, we performed both hematoxylin-eosin (H&E) and Nissl staining on the hippocampal tissues. As evidenced by H&E staining, hippocampal neurons in the control group maintained a well-organized architecture with clear morphology. In contrast, the CUMS cohort displayed neuronal disarray and indistinct cell margins. Conversely, such histological lesions were significantly ameliorated following treatment with *Cistanche deserticola* or fluoxetine (Figure 6A). Nissl staining further corroborated that, relative to controls, neurons in the CUMS group exhibited signs of somatic atrophy and degeneration. Importantly, these pathological changes were significantly reversed by fluoxetine or *Cistanche deserticola* treatment (Figure 6B). These results indicate that CUMS-induced depression can lead to significant pathological changes in the hippocampus of mice, whereas treatment with *Cistanche deserticola* effectively alleviates this damage and promotes neuronal repair.

Based on the results of previous network pharmacology analyses, *Cistanche deserticola* exerts its antidepressant effects primarily through the modulation of the NF-κB signaling axis to attenuate neuroinflammation. To verify this hypothesis, we initially utilized immunofluorescence staining to assess the protein abundance of critical components within the NF-κB signaling axis, specifically IL-1β, VCAM-1, and NF-κB, in murine hippocampal tissues. Considering that microglia act as the primary innate immune cells within the CNS and are pivotal drivers of neuroinflammation, we examined the hippocampal abundance of Iba-1 (general marker), alongside specific indicators for M1 (iNOS) and M2 (CD206) phenotypes. Treatment with *Cistanche deserticola* significantly downregulated hippocampal NF-κB expression relative to the CUMS group ($P < 0.0001$; Figure 7A). Additionally, the release levels of key downstream inflammatory factors IL-1β and VCAM-1 were also markedly decreased ($P < 0.001$) (Figure 7B and C). These findings suggest that *Cistanche deserticola* alleviates depressive behaviors and inflammation primarily through the blockade of NF-κB pathway activation, which consequently curtails the secretion and synthesis of pro-inflammatory mediators. The analysis of microglial polarization further confirmed these results (Figure 8A and B): the expression level of the microglial marker

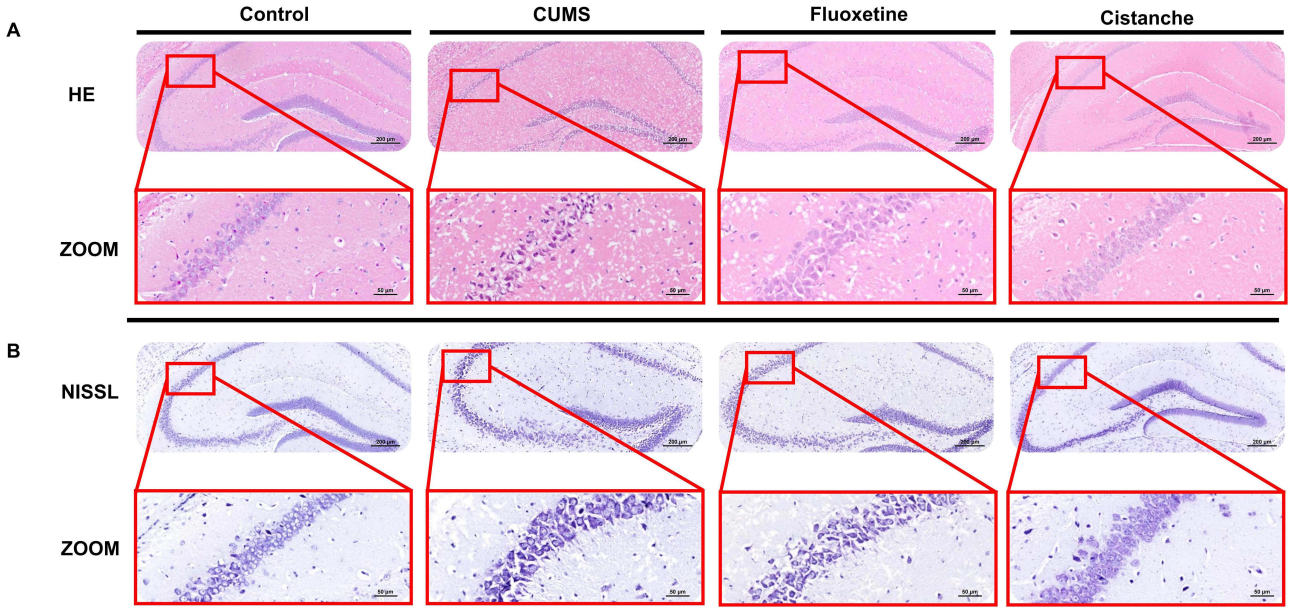

Figure 6 Pathological alterations in the hippocampus of CUMS-exposed mice. (**A**) H&E staining of mouse hippocampus (scale bars: 200 μm and 50 μm; n = 3). (**B**) Nissl staining of mouse hippocampus (scale bars: 200 μm and 50 μm; n = 3).

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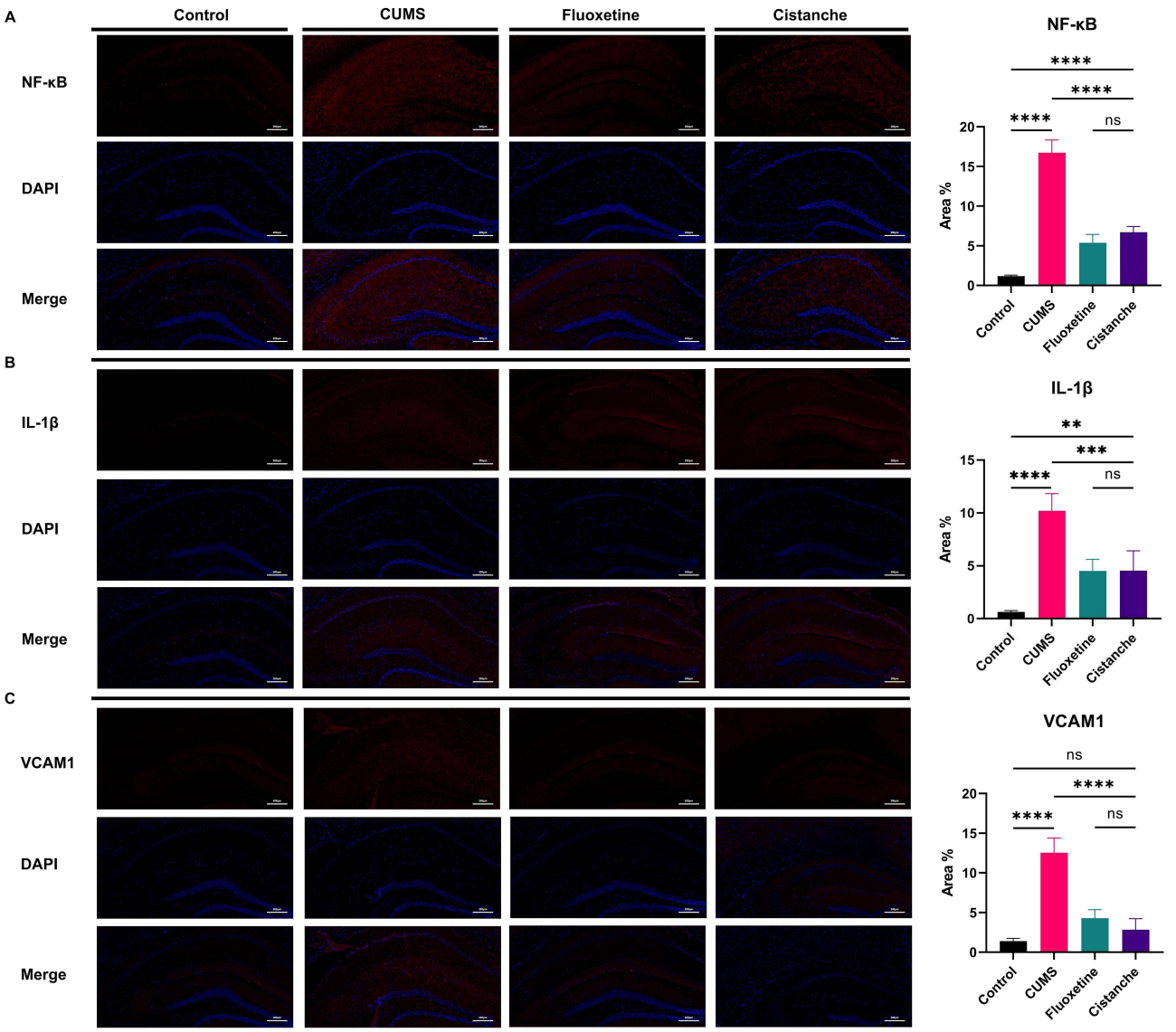

Figure 7 Effects of Cistanche and Fluoxetine on the Expression of NF-κB, IL-1β, and VCAM-1 in the Hippocampus of CUMS Mice. (**A**) Representative immunofluorescence images and quantitative analysis of hippocampal NF-κB (scale bar = 200 μm; n = 3). (**B**) Representative immunofluorescence images and quantitative analysis of hippocampal IL-1β (scale bar = 200 μm; n = 3). (**C**) Representative immunofluorescence images and quantitative analysis of hippocampal VCAM-1 (scale bar = 200 μm; n = 3). Statistical significance: ns, not significant, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

Iba-1 was significantly elevated in the CUMS group, while intervention with *Cistanche deserticola* reduced the abnormal expression of Iba-1 (Figure 8C). Quantitative analysis further showed that Cistanche significantly attenuated the CUMS-induced upregulation of the M1 marker iNOS (Figure 8D) while promoting the expression of the M2 marker CD206 (Figure 8E). These results suggest that, Cistanche promoted the transition of microglia to the immunoregulatory M2 phenotype and inhibited the expression of the pro-inflammatory M1 phenotype, thereby exerting neuroprotective effects.

Discussion

The inflammatory processes orchestrated by the NF-κB signaling axis have been identified as a pivotal factor in the pathology of neuropsychiatric disorders.[53–55] The mechanisms underlying the antidepressant effects of *Cistanche deserticola* remain only partially understood. Our study provides the first evidence that it may alleviate depressive symptoms by modulating the NF-κB signaling pathway. Specifically, *Cistanche deserticola* significantly inhibits the

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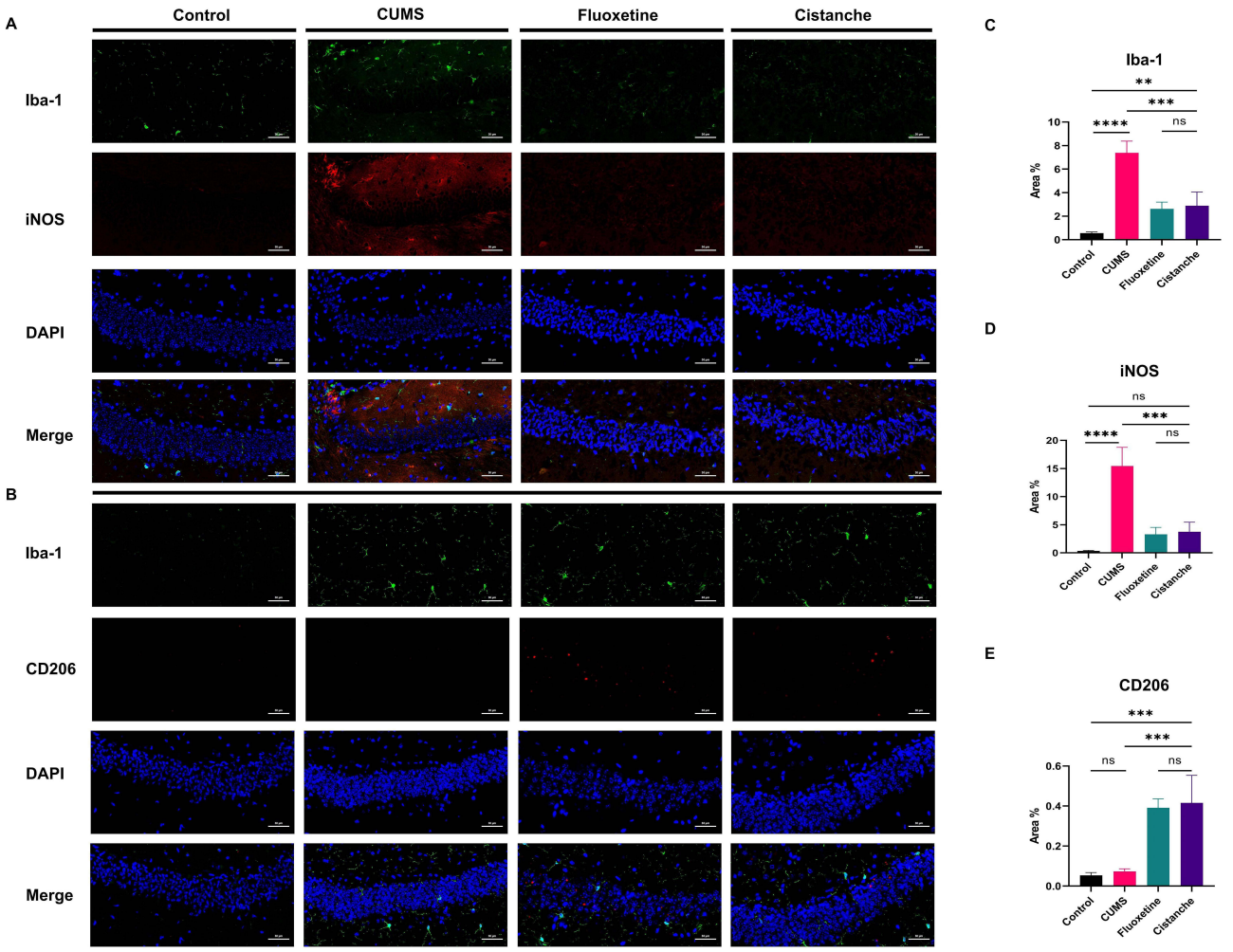

Figure 8 Effects of *Cistanche deserticola* and Fluoxetine on Hippocampal Iba-1, iNOS and CD206 Expression in CUMS Mice. (**A**) Representative immunofluorescence images of hippocampal Iba-1 (green), iNOS (red), and DAPI (blue) staining across experimental groups (Control, CUMS, Fluoxetine, and Cistanche). Scale bar = 30 μm. (**B**) Representative immunofluorescence images of hippocampal Iba-1 (green), CD206 (red), and DAPI (blue) staining across experimental groups. Scale bar = 30 μm. (**C**) Quantitative analysis of Iba-1 positive area percentage in the hippocampus (n = 3). (**D**) Quantitative analysis of iNOS positive area percentage in the hippocampus (n = 3). (**E**) Quantitative analysis of CD206 positive area percentage in the hippocampus (n = 3). Statistical significance: ns, not significant, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

activation of the NF-κB signaling pathway, thereby reducing the release and expression of downstream pro-inflammatory factors. This results in a dual effect of anti-inflammatory action and improvement of depressive symptoms.

Prior research has established that TLR-mediated activation of the NF-κB pathway in microglia leads to the upregulation of pro-inflammatory mediators, thereby shaping immunological processes within the CNS.[56] Microglial activation can be classified into classical M1 activation and alternative M2 activation under optimal conditions.[57] During this activation process, persistent inflammatory stimulation transforms microglia from a neuroprotective phenotype to a neurotoxic one, recruiting peripheral immune cells to cross the blood-brain barrier (BBB), ultimately leading to cognitive and emotional dysfunction.[58,59] In light of this evidence, we propose that *Cistanche deserticola* may modulate the phenotypic polarization of microglia via the suppression of the NF-κB signaling axis. Specifically, by curtailing the generation of M1 microglia, it likely ameliorates the cognitive and emotional impairments induced by neuroinflammation.

To verify this hypothesis, we first conducted virtual screening through network pharmacology and identified six key antidepressant components in *Cistanche deserticola*, including β-sitosterol, quercetin, and suchilactone. Numerous studies have confirmed that quercetin and β-sitosterol possess antidepressant properties, further corroborating the reliability of our computational predictions.[60,61]

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Subsequently, molecular docking analysis preliminarily confirmed that these components could effectively bind to 25 core antidepressant targets, demonstrating a binding success rate of 87.3%. Notably, their target-binding efficacy surpassed that of the clinical antidepressant fluoxetine. This observation implies that the bioactive constituents of *Cistanche deserticola* likely achieve their antidepressant efficacy via a multi-targeted mode of action. Additionally, their superior target-binding capacity compared to fluoxetine implies that the components of *Cistanche deserticola* may possess more precise and effective antidepressant properties.

Building upon these molecular docking findings, the protein-protein interaction network analysis further revealed multi-target synergistic effects, with core target proteins forming a high-density interaction network (node degree > 7.375). Notably, these candidate targets showed predominant enrichment within the NF-κB signaling axis (*FDR* < 0.001, Table S6). In fact, the NF-κB signaling pathway is closely associated with cognitive impairment.[62,63] As one of the first drugs approved by the FDA for the treatment of AD, memantine acts effectively to alleviate AD-related neuroinflammation and neurodegenerative changes by inhibiting the activity of NF-κB and its dependent adhesion molecules in human brain microvascular endothelial cells.[64] Although the central role of NF-κB in neuroinflammation-induced depression has been extensively demonstrated in preclinical and clinical studies,[65,66] the potential role of the NF-κB signalling pathway in improving depression-related cognitive impairments remains to be fully elucidated.

To address this gap, we administered *Cistanche deserticola* continuously for 28 days in a CUMS induced depression mouse model, which significantly improved cognitive and depressive-like behavioral abnormalities in the model animals. This was specifically manifested as a reduction in immobility time during the forced swim test[67] and an increase in central activity time in the open field test.[68] Additional assessments using the Morris water maze[69] and elevated plus maze[70] further suggested a positive effect on cognitive function, with some indicators outperforming the positive control group treated with fluoxetine. This finding is consistent with research reports on its closely related species, Cistanche tubulosa: existing evidence demonstrates that total glycosides of Cistanche tubulosa can significantly ameliorate various classic CUMS-induced depressive-like behaviors, including those in the FST and TST.[6,33] In conjunction with our computer simulation experiments, this suggests that the improvement in depressive behaviour may be related to the action of its active compounds. Specifically, quercetin has been reported to significantly reduce immobility time in both the FST and TST and to restore sucrose preference.[71–73] β-Sitosterol has similarly been shown to ameliorate despair-like behaviors through modulation of central monoaminergic systems.[74] Furthermore, arachidonic acid has been reported to significantly ameliorate depression-related behavioral outcomes, including performance in the open field test, forced swim test.[75,76]

The hippocampus is the central brain region for emotional and spatial cognitive regulation, and its structural impairment constitutes the key pathological basis for the CUMS-induced behavioral deficits mentioned above. To determine the intrinsic structural basis for the behavioral benefits of *Cistanche deserticola*, we assessed hippocampal histological changes. Our staining results showed that *Cistanche deserticola* effectively ameliorated CUMS-induced pathological damage, prominently reversing neuronal atrophy, karyorrhexis, nucleolar transparency, and general neurodegeneration. This histomorphological protection is highly consistent with previous research on *Cistanche* extracts, where Nissl staining also revealed a significant increase in the number of intact pyramidal cells in a stress model.[76]

Our computational simulation studies indicate that neuroinflammation represents a critical mechanism through which *Cistanche deserticola* exerts its antidepressant effects. Some clinical antidepressants have been found to affect the activation state of microglia and the levels of neuroinflammation.[77,78] For example, non-steroidal anti-inflammatory drugs alleviate depressive symptoms by inhibiting microglial activation,[79] while minocycline significantly improves depressive-like behaviors by suppressing the activation of microglia in the prefrontal cortex and hippocampus.[80] Corroborating this view, our data demonstrate that *Cistanche deserticola* administration significantly suppressed the abundance of NF-κB alongside its associated pro-inflammatory mediators, VCAM1 and IL-1β, while facilitating a microglial shift toward the M2 phenotype.

As demonstrated in a study by the Harvard Medical group,[81] BBB can be either disrupted or repaired following microglial activation. Under inflammatory conditions, the permeability of the BBB is exacerbated by microglia and peripheral immune cells (eg., leukocytes) via the release of IL-1β or the upregulation of adhesion molecules including ICAM1, VCAM1, and E-selectin. Meixensberger et al[82] further pointed out that endothelial VCAM-1 is closely related to

age, inflammation-induced microglial activation, impaired neurogenesis, and cognitive deficits. Moreover, a post-mortem report on elderly individuals with depression showed[83] that microvascular disease and the presence of ICAM1 and VCAM1 after ischemia were significantly elevated in the dorsolateral prefrontal cortex of these individuals. Recent studies indicate that[84–86] IL-1β triggers a pro-inflammatory transformation within endothelial cells and vascular smooth muscle cells (VSMCs). This state is distinguished by the upregulation of adhesion proteins (ICAM-1, VCAM) and a surge in matrix metalloproteinases (MMPs) and cytokines/chemokines (eg., IL-6, MCP-1, IL-8), which collectively promote macrophage recruitment. These findings provide new evidence for the potential pathogenic mechanisms of depression, particularly highlighting the important role of inflammation in the development of depression. Additionally, they suggest that antidepressant drugs may exert their effects through complex neural and signaling pathways involving changes in adhesion molecules and inflammatory mediators. This may partly explain the delayed effects encountered with antidepressant medications in clinical use.

Limitations

This study has several limitations. First, although we have preliminarily elucidated the potential mechanisms underlying the antidepressant effects of *Cistanche deserticola*, as a compositionally complex botanical extract, it may exert therapeutic effects through multiple synergistic pathways, and the specific contribution of individual phytochemicals remains to be verified through bioactivity-guided fractionation. Second, this study did not address several critical issues, including dose-response relationships, the time course of symptom relapse following treatment cessation, and whether the observed mechanistic changes—such as microglial polarization modulation and NF-κB signaling inhibition—exhibit reversible or irreversible properties. Furthermore, the current findings are derived solely from a single CUMS model using young male mice, which does not adequately capture the sexual dimorphism and age-related heterogeneity of depression; thus, further validation across different sexes, age gradients, and multiple depression paradigms is warranted to establish the generalizability of these results.

Conclusion

Cistanche deserticola ameliorated CUMS-induced depressive-like behaviors and cognitive impairment, which may be associated with its anti-neuroinflammatory and neuroprotective effects. Our findings further demonstrated that *Cistanche deserticola* modulated NF-κB-related signaling, promoted the polarization of microglia from the M1 to the M2 phenotype, downregulated the expression of IL-1β and VCAM1, and alleviated hippocampal neuroinflammation and synaptic injury. These results highlight the potential of *Cistanche deserticola* as a candidate for antidepressant development. In addition, the bioactive phytochemicals identified in this study may provide a basis for investigating the pharmacodynamic material basis and for screening lead compounds, while the mechanisms implicated herein may offer valuable insights for future antidepressant drug development, optimization of therapeutic strategies, and preclinical investigation. Nevertheless, to comprehensively delineate its pharmacological profile, future investigations must prioritize single-compound validation, rigorous dose-response analyses, and the systematic evaluation of the duration and persistence of its antidepressant activity—particularly focusing on the reversible or irreversible nature of its mechanistic targets. Addressing these aspects will clarify its core active constituents and pharmacological characteristics, thereby facilitating its future translation from bench to bedside.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author Bin Xu upon reasonable request.

Ethics Statement

This study was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University (A240522-111) and carried out in accordance with the ethical standards set out in the Helsinki Declaration.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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