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Computational biological analysis reveals that HIF-1 and FoxO signaling pathways influence cognitive impairment in patients with depression

Chuanjun Zhuo[1,2,5]✉, Ying Zhang[1,2,5], Qiuyu Zhang[1,2], Lei Yang[1,2], Ximing Chen[1,2], Xiaoyan Ma[1,2], Ranli Li[1,2], Lina Wang[1,2], Hongjun Tian[1,2,4] and Fuqiang Mao[1,2,3]

Cognitive impairment, a common symptom in patients with depression, significantly affects social functioning. Currently, no recognized treatment exists for depression-related cognitive dysfunction. The study aimed to use computational biology methods to investigate the potential molecular mechanisms underlying cognitive impairment in depression and identify potential antidepressants that may mitigate this impairment. Targets associated with depression and cognitive impairment were obtained from GeneCards and OMIM. Overlapping disease targets were integrated to generate a PPI network, and hub targets were identified using network topology metrics. KEGG pathway enrichment analyses were conducted using the DAVID database. Finally, core targets enriched in key signaling pathways were virtually screened for interactions with antidepressants. Of the 1621 overlapping targets identified, 46 key targets were selected based on topological parameters in Cytoscape software of a KEGG enrichment analysis. The analysis revealed that the HIF-1 and FoxO signaling pathways may contribute to depression-induced cognitive impairment via 13 target genes. Virtual screening of these 13 core targets against various antidepressants identified mosapramine as having strong binding affinity to the core targets, including AKT3, EGFR, IL6, INS, MAPK1, MAPK3, and PIK3R1, with docking scores of −7.6 to −12.9 kcal/mol. Based on our results, the HIF-1 and FoxO signaling pathways may influence cognitive impairment through multiple targets, and mosapramine may alleviate cognitive impairment in patients with depression via these targets and pathways. These findings provide a foundation for the modification and optimization of antidepressant drugs to improve the treatment of cognitive impairment in patients with depression.

Translational Psychiatry (2025)15:518; https://doi.org/10.1038/s41398-025-03775-9

INTRODUCTION

Approximately 300 million people worldwide suffer from depression, and depression may emerge as the biggest public health concern by 2030 [1]. Cognitive impairment is a common clinical symptom of depression. Major depression is associated with cognitive impairment in up to 73–94% of cases [2, 3]. Cognitive impairment associated with depression has garnered increasing attention recently [4–7]. Cognitive functioning, encompassing executive function, psychomotor speed, declarative memory, working memory, and attention, is severely impaired in both older and younger individuals with depression [4, 7, 8]. During acute depressive episodes, adults experience varying degrees of executive function (abnormalities in executive function are associated with an increased risk of suicide [9]), attention, processing speed, and memory decline [4, 5, 7]. Cognitive decline often reduces social and professional functioning [4, 10, 11]. Cognitive performance is affected in some patients even after remission [4, 10, 12]. and most individuals in the acute or remission phase experience significant difficulties concentrating [4, 13]. Additionally, cognitive impairment may increase the risk of relapse [4] and is linked to indicators of treatment response [6, 14, 15]. In a word, cognitive impairment contributes to both poor prognosis and disability in patients with depression [3, 4], resulting in increased healthcare costs and disease burden [16].

The pathogenesis of depression-related cognitive impairment involves multiple complex mechanisms. Early stress [17], childhood physical neglect [18], decreased plasma brain-derived neurotrophic factor (BDNF) levels [18], elevated cortisol levels [19], and oxidative stress [20] caused by depression contribute to cognitive impairment. Furthermore, changes in the prefrontal cortex, parietal cortex, basal ganglia, hippocampus, and amygdala are associated with depression and cognitive impairment [4, 21, 22]. Studies have reported that depressed patients exhibit negative cognitions (e.g., negativity and increased self-focus) [21, 23], and that depression-related cognitive impairment is linked to changes in the white matter of the brain [24].

[1]Laboratory of Computational Biology and Computational Psychiatry (CBCP-Lab), Tianjin Anding Hospital, Nankai University Affiliated Tianjin Anding Hospital, Tianjin Mental Health Center of Tianjin Medical University, Tianjin 300222, China. [2]Laboratory of Psychiatric-Neuroimaging-Genetic and Co-morbidity (PGNP-Lab), Tianjin Anding Hospital, Nankai University Affiliated Tianjin Anding Hospital, Tianjin Mental Health Center of Tianjin Medical University, Tianjin 300222, China. [3]Department of Psychiatry and Psychology, College of Basic Medical Sciences, Tianjin Medical University, Tianjin 300074, China. [4]Department of psychiatry, Tianjin Fourth Center Hospital, Tianjin 300040, China. [5]These authors contributed equally: Chuanjun Zhuo, Ying Zhang. ✉email: zhuochuanjun@tmu.edu.cn

Received: 14 March 2025 Revised: 30 October 2025 Accepted: 14 November 2025
Published online: 01 December 2025

Antidepressants induce neurotransmitter release in particular brain areas to elevate mood, and monoamine neurotransmitters [25, 26], including serotonin, dopamine, and norepinephrine, are linked to cognitive function [27]. Prefrontal catecholamines regulate executive functions, working memory, and attention [28, 29].

Studies have found that certain antidepressants, such as vortioxetine, escitalopram, sertraline, and ketamine [10, 21, 30–32], enhance cognitive function when included in an antidepressant regimen. Ketamine activates the mTORC1 signaling pathway and promotes the production of BDNF, thus increasing the levels of synaptic proteins and enhancing the number and function of synapses in the prefrontal cortex [21]. Vortioxetine improves monoaminergic transmission and glutamatergic function in the prefrontal cortex [33], while selective serotonin reuptake inhibitors influence hippocampal neurogenesis and function [31]. These changes collectively enhance neuroplasticity and ultimately contribute to improvements in cognitive function. However, a randomized longitudinal study by Shilyansky et al. found that antidepressants such as sertraline, venlafaxine, and escitalopram did not lead to significant improvements in cognitive impairment associated with depression [5]. At the same time, Keefe R.S. has pointed out that there are currently no recognized treatments for depression-related cognitive impairment and that the cognitive deficits in patients with depression should receive greater attention from relevant sectors [2, 10]. In summary, the inconsistency of existing research findings and the unclear underlying mechanisms have hindered the development of effective treatment strategies for cognitive impairment in patients with depression [10, 19]. The molecular mechanisms that influence cognitive function have not been adequately elucidated for most currently available drugs, and new methods to investigate the effects of antidepressants on cognitive function are urgently needed.

In recent years, the rise of computational biology has facilitated the exploration of complex pathological mechanisms underlying drug–disease interactions. Network pharmacology, which combines systems biology and pharmacology approaches, has been successfully used to identify key nodes in biological networks and multi-target interactions between drugs and diseases [34]. Understanding the interactions between multiple targets can enhance our understanding of the molecular mechanisms underlying complex diseases [35]. Virtual screening of large libraries of compounds can be performed as the starting point for streamlined drug discovery [36, 37] and to explore potential interactions with specific targets. [38] Molecular docking techniques are used to assess the binding modes and affinities of these compounds to the targets [39]. In this study, we employed network pharmacology, virtual screening, and molecular docking approaches to investigate the underlying molecular mechanisms for cognitive deficits associated with depression and explore the potential of existing antidepressant drugs to alleviate or prevent cognitive deficits. Figure 1 shows the workflow of this study.

MATERIALS AND METHODS

Ethics approval and consent to participate

The current analysis does not require ethical approval, because our analysis only collects uploaded data information from the public database search. There are no human participants in this article and informed consent is not required.

Identifying possible targets for depression and cognitive impairment

The Online Mendelian Inheritance in Man (OMIM) database [40] (https://www.omim.org/) and the GeneCards database [41] (https://www.genecards.org/) were searched using the keywords "depressive disorder" to identify targets related to depression. The same databases were searched using the keywords "cognition disorders" to identify genes associated with cognitive impairment. Duplicates and non-protein-coding genes were eliminated from both target lists. The resulting target proteins were converted into their respective gene symbols for "*Homo sapiens*" using the UniProt (https://www.uniprot.org/) database [42]. The targets for depression and cognitive impairment were analyzed using the bioinformatics online tool [43] (http://www.bioinformatics.com.cn/) to generate a list of intersecting targets.

Constructing protein-protein interaction (PPI) networks and identifying hub targets

The common targets were imported into the STRING database [44] (https://cn.string-db.org/) to investigate the interactions among targets associated with depression and cognitive impairment. "*Homo sapiens*" was specified as the organism, the interaction confidence threshold was set at 0.9, and unconnected proteins were excluded. Cytoscape 3.10.1 [45] (https://cytoscape.org/) was used to import the filtered targets and generate the PPI network. The topological characteristics of each network node were assessed using the CytoNCA plug-in. The degree centrality, betweenness centrality, and closeness centrality were evaluated to examine the interactions between nodes and identify hub targets. Hub genes were identified after three rounds of continuous screening, using median values as cut-off thresholds. These three parameters collectively and comprehensively characterize the properties of each node within the interaction network [46]. A higher ranking indicates that the node has a more important role in the network. The targets identified through three rounds of screening were considered potential core targets for subsequent analysis [47].

Kyoto Encyclopedia of genes and genomes (KEGG) enrichment analyses

The hub targets were imported into the DAVID online platform [48] (https://david.ncifcrf.gov/) for the KEGG enrichment analysis (https://www.genome.jp/kegg/) [49]. The species was set to "*Homo sapiens*," and the p-value threshold was set at < 0.05. After sorting the pathways by p-value from smallest to largest, the top 20 pathways with the highest significant enrichment were selected. This approach ensured that the highlighted pathways had the strongest statistical support and potential biological importance. Bubble plots were created to visualize the outcomes for the top 20 significant signaling pathways using the Bioinformatics online tool. Important signaling pathways were visualized using the KEGG Mapper online tool (https://www.genome.jp/kegg/mapper/).

Virtual screening and molecular docking

Based on the results of the KEGG enrichment analysis, the hub targets enriched in significant signaling pathways were analyzed to identify core targets for virtual screening and molecular docking. The crystal structures of the core targets were downloaded from the RCSB Protein Data Bank database [50] (https://www.rcsb.org/). Only protein structures from *Homo sapiens* were chosen to ensure biological relevance. Furthermore, high-resolution protein structures were given priority to increase the precision and reliability of the docking analysis. Water molecules and small molecules were removed, and hydrogen atoms were added to the proteins. The proteins' active sites were identified using an online tool (https://proteins.plus/), and the docking box's center coordinates (X, Y, Z) were saved. The antidepressant compounds were identified in the PubChem database [51] (https://pubchem.ncbi.nlm.nih.gov/), and the 3D structures were downloaded. The ligands and receptors were converted into a software-readable format using the SailVina platform (https://vina.scripps.edu/) [52] of AutoDock Vina [53] before importing the docking site data. Finally, molecular docking and virtual screening were used to determine the binding of the antidepressant compounds with the target proteins. The optimal binding conformations of the small molecules were predicted with the docking algorithm utilizing a scoring system. For each target, the top five small molecules with the highest docking scores were selected for visual analysis. The molecular docking results for candidate small molecules and the relevant targets were visualized using PyMOL (https://pymol.org/2/) and AutoDockTools 1.5.6 (https://autodocksuite.scripps.edu/adt/) software.

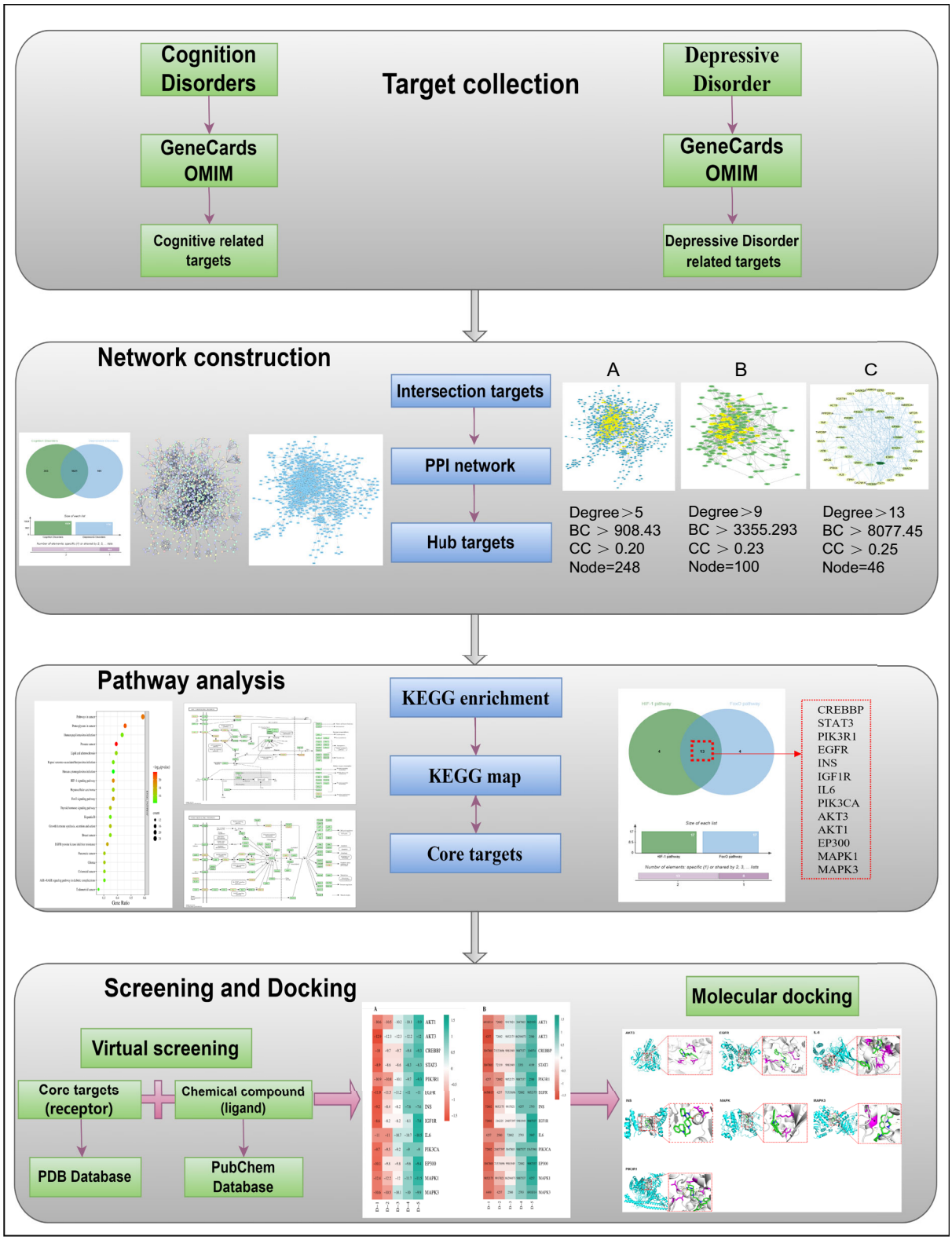

Fig. 1 Study flow diagram. OMIM, Online Mendelian Inheritance in Man; PPI, Protein-Protein Interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes; PDB, Protein Data Bank. BC, betweenness centrality; CC, closeness centrality; DC, degree centrality; AKT1, AKT serine/threonine kinase 1; AKT3, AKT serine/threonine kinase 3; CREBBP, CREB-binding protein; EGFR, epidermal growth factor receptor; EP300, histone acetyltransferase p300; INS, insulin A chain; IL-6, interleukin-6; IGF1R, insulin-like growth factor 1 receptor alpha chain; MAPK1, mitogen-activated protein kinase 1; MAPK3, mitogen-activated protein kinase 3; PIK3CA, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; PIK3R1, phosphatidylinositol 3-kinase regulatory subunit alpha; STAT3, signal transducer and activator of transcription 3.

RESULTS

Potential targets of depression, cognitive impairment, and common targets

After excluding non-protein-coding and median threshold truncation genes, 1386 targets associated with cognitive impairment and 1321 depression-related targets were retrieved from the GeneCards database. Following the removal of duplicate targets and entries without gene names, 613 targets associated with cognitive impairment and 571 targets related to depression were retrieved from the OMIM database. The targets from the two datasets were combined, and duplicates were eliminated, resulting in 1782 targets linked to depression and 1924 targets associated with cognitive impairment. The bioinformatics online tool was utilized to make a Venn diagram, and 1621 overlapping targets were ultimately identified (Fig. 2A).

Network of overlapping targets for depression and cognitive impairment and screening the hub targets

Figure 2B shows the established PPI network with 1243 nodes and 3006 edges. The information from the PPI network was imported into Cytoscape 3.10.1. Proteins without structures or links to other proteins were removed, resulting in 925 nodes and 2919 edges in the PPI network (Fig. 2C). The CytoNCA plugin was used to identify 46 hub targets based on topological parameters (degree centrality, betweenness centrality, and closeness centrality) with medians as cutoffs for three consecutive rounds (Fig. 2D–F, Supplementary Table 1).

KEGG Enrichment analyses and identification of core targets

The signaling pathways involved in impaired cognitive function with depression were identified using KEGG enrichment analysis. The top 20 enriched pathways from the 168 enriched pathways based on p-values are shown in Fig. 3A and Table 1. The hypoxia-inducible factor-1 (HIF-1) and forkhead box O (FoxO) signaling pathways were associated with cognitive impairment in depression. To identify the primary targets related to cognitive impairment induced by depression, the intersecting enriched targets of the two key signaling pathways were identified (Fig. 3B). Thirteen core targets were obtained, including cAMP response element-binding protein (CREB) binding protein (CREBBP), signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1), epidermal growth factor receptor (EGFR), insulin A chain (INS), insulin-like growth factor 1 receptor alpha chain (IGF1R), interleukin-6 (IL-6), phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA), RAC-gamma serine/threonine-protein kinase (AKT3), RAC-alpha serine/threonine-protein kinase (AKT1), histone acetyltransferase p300 (EP300), mitogen-activated protein kinase 1 (MAPK1), and mitogen-activated protein kinase 3 (MAPK3). Detailed information about the 13 targets is shown in Table 2. Figure 3C and D show the two signaling pathways, highlighting the positions of the core targets within these pathways.

Target-based in silico screening and molecular docking

223 antidepressant compounds were selected and downloaded in 3D format. Based on binding affinity rankings, the top five docking results were selected for visualization. The docking scores and PubChem compound CIDs are shown in Fig. 4A–B. The three compounds with the best docking results exhibited significant binding affinities to multiple targets: panuramine for INS, IGF1R, and PIK3CA; mosapramine for AKT3, PIK3R1, and IL6; and compound CID 3047803 for CREBBP, STAT3, and EP300. The first five docking scores of the 13 targets for antidepressants ranged from −7.6 to −12.9 kcal/mol. Panuramine, mosapramine, compound CID 3047803, adoprazine, and orvepitant exhibited strong binding to multiple targets (Supplementary Table 2). Notably, mosapramine showed the strongest binding in the first five dockings, interacting with seven targets, including three with the highest docking scores. The docking of mosapramine with seven targets is shown using PyMOL and Discovery Studio Visualizer software (https://www.3ds.com/) (Fig. 5, Table 3).

DISCUSSION

We identified 46 core targets using a network pharmacology approach. Based on a KEGG analysis of these targets, the FoxO and HIF-1 signaling pathways may play important roles in cognitive

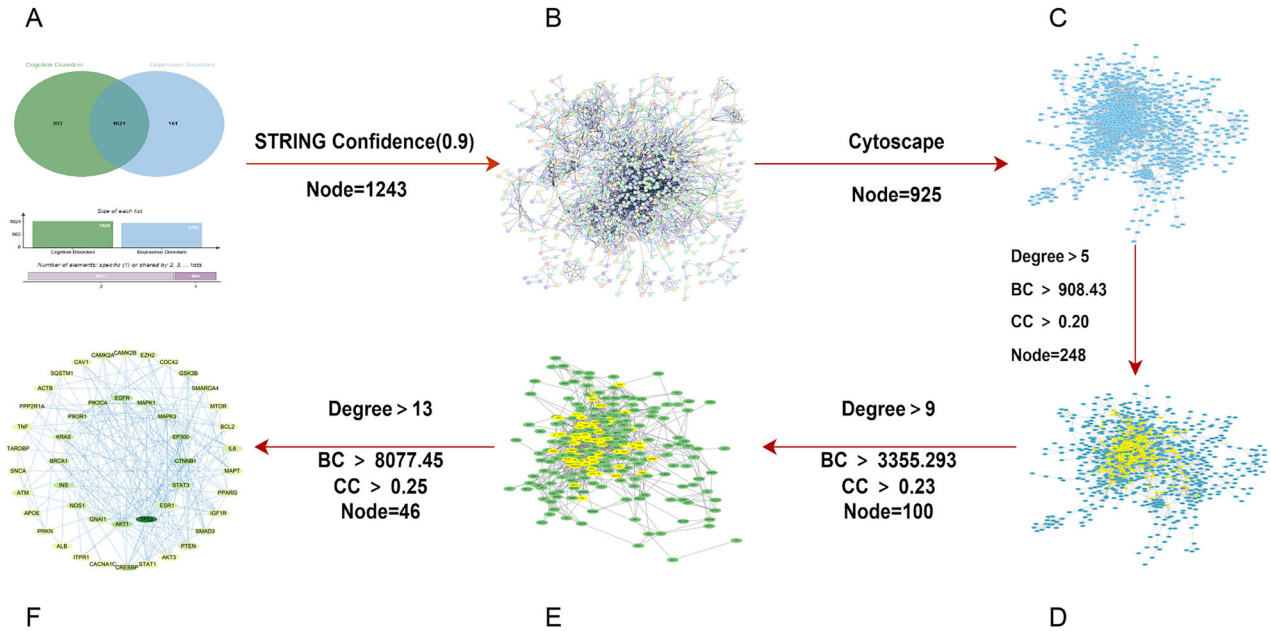

Fig. 2 Identification of hub targets via protein-protein interaction network analysis. (**A**) A Venn diagram illustrating the overlapping targets of depression and cognitive impairment. (**B–C**) Construction of PPI networks of intersecting targets using the Cytoscape program and the STRING database. The interaction confidence threshold was set to 0.9 in the STRING database. (**D-F**) Screening of hub targets based on topological parameters. BC, CC, DC.

Fig. 3 KEGG pathway enrichment analysis results and the distribution of hub targets within key signaling pathways. (**A**) KEGG pathway enrichment analysis of the top 20 pathways ($P < 0.05$). (**B**) The significant KEGG signaling pathway-enriched targets were merged to identify common targets. (**C**, **D**) Maps illustrating the distribution and mechanisms of the common targets in important signaling pathways, including (**C**) the HIF-1 signaling pathway and (**D**) the FoxO signaling pathway. The common targets for both pathways are indicated in red.

impairment in depression. The HIF-1 and FoxO signaling pathways regulate a variety of biological processes, including neuroimmune [54, 55], inflammatory [56–58], synaptic plasticit [54, 59]y, neuronal signaling [59], and oxidative stress [58, 60, 61] processes, that can be targeted to treat depression. In the brain, FoxO functions as a central regulatory factor integrating serotonergic signaling and neurotrophic pathways, exerting antidepressant and anxiolytic effects [62]. Moreover, the BDNF–FoxO1 signaling pathway in the medial prefrontal cortex was shown to regulate depression-like behaviors in postpartum mice [63]. In recent years, several studies have demonstrated that FoxO plays a critical role in improving dementia and cognitive impairment, suggesting that FoxO may represent a novel therapeutic target for ameliorating cognitive deficits [64, 65]. The mechanistic role of FoxO in cognitive impairment associated with depression warrants further investigation. Elevated HIF-1 levels enhance the mTOR signaling pathway and upregulate vascular endothelial growth factor (VEGF) expression, which is implicated in the treatment of depression [58]. One study found that HIF-1α regulated cognitive deficits in post-stroke depression model rats and may serve as a potential therapeutic target [66]. In addition, elevated HIF-1α levels have been associated with cognitive impairment in patients undergoing hemodialysis [67]. Li et al. demonstrated that FG-4592, a prolyl hydroxylase inhibitor, activates the HIF-1 and BDNF signaling pathways to promote dendritic growth and improve depression and cognitive functioning, providing strong evidence to support

our findings [68]. In summary, it is hypothesized that HIF-1 and FoxO may affect cognition by influencing BDNF. It has been found that HIF-1 may play a crucial role in the BDNF and pro-BDNF activation pathway [69]. Changes in this pathway are strongly associated with both depression and cognitive impairment [69]. Furthermore, BDNF regulation of FoxO-related genes regulates neuronal survival, differentiation, and synaptic plasticity [70]. Activation of CREB/BDNF signaling induces antioxidant and antidepressant activities [1]. Recent studies have shown that quercetin promotes hippocampal neurogenesis via the CREB/BDNF signaling pathway and the forkhead box transcription factor G1, thereby enhancing both depressive symptoms and cognitive function [60]. In summary, previous studies provide indirect and direct evidence supporting the role of HIF-1 and FoxO signaling in depression and cognitive function. We utilized computational biology to validate previous experimental results, highlighting the reliability of computational biology methods.

Table 1. Basic information about the KEGG enrichment results.

ID	Term	Count	P-value
hsa05215	Prostate cancer	18	1.14401E-22
hsa05205	Proteoglycans in cancer	21	1.33874E-21
hsa05200	Pathways in cancer	27	8.54526E-21
hsa04066	HIF-1 signaling pathway	17	4.3245E-20
hsa01521	EGFR tyrosine kinase inhibitor resistance	15	9.86619E-19
hsa04068	FoxO signaling pathway	17	1.05761E-18
hsa04935	Growth hormone synthesis, secretion, and action	16	1.23793E-17
hsa04919	Thyroid hormone signaling pathway	16	1.23793E-17
hsa05214	Glioma	14	2.76556E-17
hsa05212	Pancreatic cancer	14	3.31516E-17
hsa05225	Hepatocellular carcinoma	17	6.63851E-17
hsa05417	Lipid and atherosclerosis	18	1.2212E-16
hsa05210	Colorectal cancer	14	1.77983E-16
hsa05224	Breast cancer	16	2.41589E-16
hsa05165	Human papillomavirus infection	20	5.03756E-16
hsa05167	Kaposi sarcoma-associated herpesvirus infection	17	6.54983E-16
hsa05161	Hepatitis B	16	1.04635E-15
hsa04933	AGE-RAGE signaling pathway in diabetic complications	14	1.34848E-15
hsa05213	Endometrial cancer	12	3.78966E-15
hsa05163	Human cytomegalovirus infection	17	6.51922E-15

KEGG kyoto encyclopedia of genes and genomes.

Analysis of the enriched targets in the HIF-1 and FoxO signaling pathways revealed 13 common targets, including AKT1, AKT3, PIK3R1, PIK3CA, MAPK1, MAPK3, INS, IGF1R, STAT3, CREBBP, IL-6, EP300, and EGFR. These targets play critical roles in cell signaling, neuronal development, synaptic plasticity, learning, memory, and neuroinflammatory processes [1, 57, 71, 72]. AKT is a serine/threonine protein kinase that regulates neuronal survival, development, and signaling. Three isoforms of AKT, including AKT1, AKT2, and AKT3, are widely expressed [1]. PIK3R1 and PIK3CA are involved in phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling, which plays a significant role in stress responses, neural plasticity, and cell survival [60, 71]. The expression of PI3K and AKT is markedly decreased in the brains of mice with depression, suggesting that the PI3K/AKT signaling pathway plays a significant role in depression and cognitive function [1]. The PI3K/AKT signaling pathway also regulates downstream molecular targets, including FoxO and HIF-1, processes that are associated with oxidative stress and neuroinflammatory responses [1, 54, 56, 57]. Oxidative stress and neuroinflammation are considered central mechanisms underlying both depression and neuroplasticity [55, 72].

IL-6 and MAPK-related targets may contribute to depression and cognitive impairment through the FoxO signaling pathway. IL-6 levels are elevated in the blood and cerebrospinal fluid of patients with depression [57]. Additionally, IL-6 activates the HIF-1α, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), MAPK/CREB, Ras-MAPK, and PI3K signaling pathways [72]. These pathways promote neuronal development and glial cell differentiation, which influence depression and memory [72]. Other studies have shown that phosphorylated FoxO1 regulates the transcription of toll-like receptor 4 and enhances IL-6 expression [1, 57]. Baicalin alleviated neuroinflammation-induced depression-like behavior by significantly reducing IL-6 levels and promoting the phosphorylation of FoxO1 [57]. MAPK is an upstream kinase of FoxO, and its phosphorylation regulates various transcriptional functions [54]. IL-6 also activates the MAPK/CREB and Ras-MAPK signaling

Table 2. Topological information about the core targets.

Gene	Target name	Degree	Betweenness	Closeness
AKT1	AKT Serine/Threonine Kinase 1	40	57352.09	0.31
EP300	Histone acetyltransferase p300	37	49399.96	0.29
EGFR	Epidermal Growth Factor Receptor	36	31560.54	0.29
STAT3	Signal Transducer and Activator of Transcription 3	34	21156.33	0.28
INS	Insulin A chain	34	79505.92	0.28
MAPK3	Mitogen-Activated Protein Kinase 3	32	18474.8	0.29
MAPK1	Mitogen-Activated Protein Kinase 1	31	14619.249	0.29
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	30	9443.74	0.27
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	30	11462.88	0.28
CREBBP	CREB binding protein	26	17603.55	0.28
IL6	Interleukin 6	24	13892.6	0.27
IGF1R	Insulin-like growth factor 1 receptor	21	13749.2	0.28
AKT3	AKT Serine/Threonine Kinase 3	17	8461	0.28

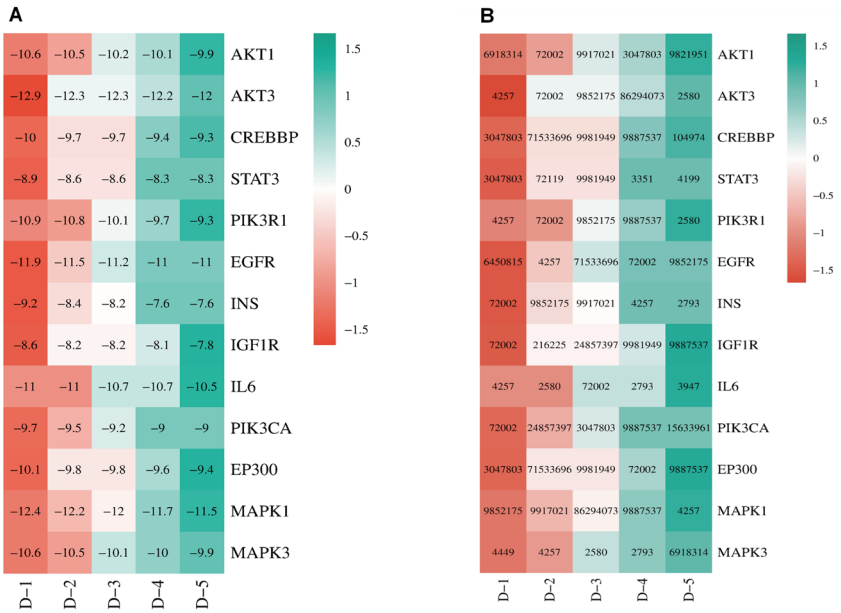

Fig. 4 Docking scores and PubChem Compound CIDs. (**A**) The top 5 docking scores for binding of the 13 core targets to the antidepressants. (**B**) The PubChem CID numbers for antidepressants that align with the docking results presented in (**A**). D-1 to D-5 indicate the first- to fifth-place docking scores for each target.

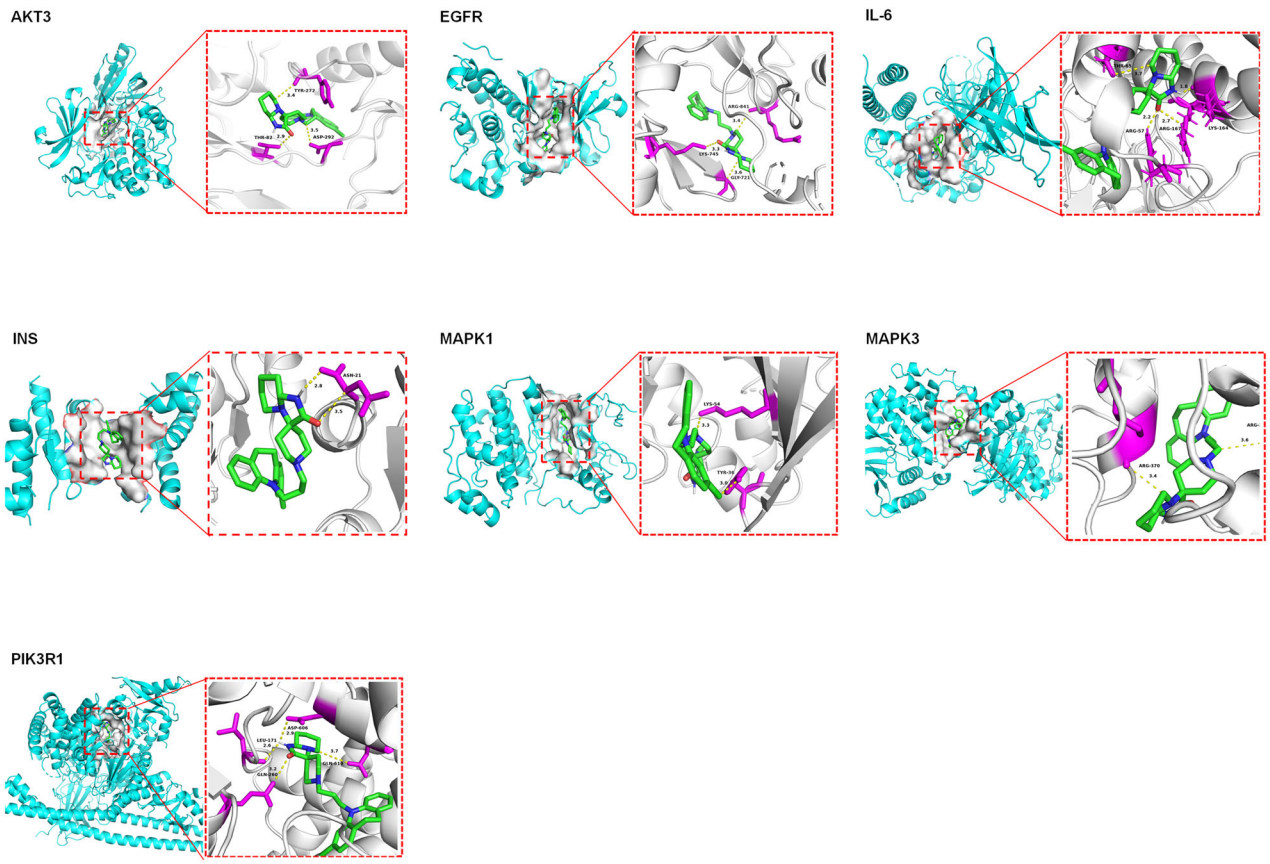

Fig. 5 Molecular docking results. Molecular docking results for mosapramine and seven targets, including AKT3 (AKT Serine/Threonine Kinase 3), EGFR (epidermal Growth Factor Receptor), IL6 (interleukin 6), INS (insulin A chain), MAPK1(mitogen-activated protein kinase 1), MAPK3 (mitogen-activated protein kinase 3), PIK3R1 (phosphoinositide-3-kinase regulatory subunit 1).

Table 3. Molecular docking of mosapramine with the core target proteins.

Targets	PDB ID	Residue involved in H bonding	Binding energy (kcal/mol)
AKT3	7NH5	THR-82, ASP-292, TYR-272	−12.9
EGFR	8A2D	LYS-745, GLY-721, ARG-841	−11.5
IL6	5MJ3	ARG-57, ARG-167, LYS-164, SER-162, THR-65	−11
INS	8IPZ	ASN-21	−7.6
MAPK1	4QTA	TYR-36, LYS-54	−11.5
MAPK3	6GES	ARG-318, ARG-370	−10.5
PIK3R1	6PYR	GLN-260, LEU-171, ASP-606, GLN-610	−10.9

PDB protein data bank.

pathways, influencing hippocampal neurons and contributing to both depression and cognitive impairments [72]. IL-6 and MAPK-related targets synergize within the FoxO pathway, contributing to the development of both depression and cognitive impairment.

CREBBP is a direct binding protein of CREB. CREB signaling pathways play a crucial role in the nervous system and are closely associated with biological processes such as learning, memory, and neuroplasticity [54, 61, 71]. CREB regulates the transcription of genes, including BDNF and tropomyosin receptor kinase B [61]. Research demonstrates that natural products enhance memory and spatial learning via both pathways [71]. Previous animal studies have reported reduced levels of CREB phosphorylation associated with depressive behavior [1, 73]. Cordyceps sinensis was found to exert antidepressant effects through CREBBP [61]. Previous studies indicate a role of CREBBP in the pathophysiology of depression and cognitive impairment. STAT proteins are primarily activated through the JAK/STAT pathway but can also be activated via the MAPK and PI3K pathways to mediate their biological functions. The STAT pathway influences neuroplasticity and suppresses hippocampal neurogenesis [72]. This process may be synergistically involved in cognitive impairment in depression with other targets and pathways (IL-6, HIF-1α, JAK/STAT, MAPK/CREB, Ras-MAPK) [72].

During stress, 5-hydroxytryptamine regulates the FoxO and the insulin/insulin-like growth factor 1 (IGF-1)/AKT signaling pathways [54, 62]. This may contribute to neuronal atrophy and depression [54]. An additional study has shown that natural products modulate the insulin/IGF-1/AKT signaling pathway to exert neuroprotective effects [71]. Other studies have identified FoxO as a critical mediator of insulin/IGF-1 signaling, and IGF-1 plays a pivotal role in the reduction of cerebral white matter volume in individuals with depression [54]. In addition, EGFR and EP300 are important targets in treating depression [61, 74]. EGFR is expressed in the neurons of the hippocampus, cerebellum, and cerebral cortex [75]. EP300 binding to CREB proteins may play a role in the inflammatory response that contributes to depression [76]. Although there is no direct evidence to support that all of the above targets are involved in cognitive impairment in depression, the results of the present study deepen our understanding of the pathological mechanisms of cognitive impairment in depression.

To identify drugs that effectively alleviate cognitive function in individuals with depression, we conducted a virtual screening of antidepressants against the 13 targets. This screening aimed to identify antidepressants with strong binding affinity to these targets for subsequent drug optimization. Our results show that mosapramine exhibited the highest binding affinity to multiple target proteins. Mosapramine, which was developed in Japan, is an iminodibenzyl antipsychotic classified as an atypical antipsychotic, acting on dopamine 2 receptors and serotonin 2 receptors in the frontal cortex [77]. Optimal docking was observed between mosapramine and three targets: AKT3, PIK3R1, and IL-6. The corresponding docking scores were −12.9, −10.9, and −11 kcal/mol, respectively. AKT3 and PIK3R1 are involved in the PI3K/AKT signaling pathway, which plays a significant role in depression and cognitive function [1] and may regulate HIF-1 [56] and FoxO signaling pathways [54, 57] to induce neuroinflammation that affects both depression and cognition. Additionally, numerous studies have highlighted the significant role of IL-6 in cognitive impairment associated with depression [57, 72]. IL-6 may modulate the HIF-1 and FoxO signaling pathways through PI3K/AKT signaling, leading to neuroinflammation and alterations in synaptic plasticity [1, 57, 72]. In addition, another study found that mosapramine enhances FoxO protein expression in the prefrontal lobes of the brain, similar to clozapine, and may help improve the negative symptoms of schizophrenia [78], which share some commonalities with cognitive impairment [79]. Mosapramine may affect FoxO expression, thereby alleviating cognitive impairment in depression. Patients with schizophrenia and depression frequently exhibit impaired cognitive functioning. Mosapramine is structurally similar to tricyclic antidepressants and butyrophenones [77]. Previous studies have found that the antidepressants venlafaxine [80] and agomelatine [81] affect HIF-1 and FoxO signaling, ameliorate neuronal apoptosis, and exhibit antioxidant effects. Future research should focus on elucidating the intrinsic relationship between mosapramine, HIF-1, the FoxO signaling pathway, and multiple targets.

There are several limitations to this study. First, the database of disease targets has not been recently updated and does not comprehensively include all disease-related targets. Second, the database of small-molecule compounds is limited, and some newly discovered or synthesized compounds were not included. Third, construction of the PPI networks mainly depends on known and annotated interactions, which may not accurately represent dynamics taking place in the central nervous system. Fourth, this study's network pharmacology and molecular docking methods are computational predictions that do not take into consideration pharmacokinetic characteristics (such as absorption, distribution, metabolism, and excretion). Finally, the results of this study are based on a computational approach and still need experimental validation.

CONCLUSIONS

In this study, biological and computational approaches were employed to investigate the potential molecular mechanisms underlying cognitive impairment in depression and identify candidate therapeutic drugs that may mitigate this impairment. Our findings suggest that the HIF-1 and FoxO signaling pathways are regulated by multiple targets and may represent key mechanisms contributing to cognitive dysfunction in depression. Mosapramine may impact the HIF-1 and FoxO signaling pathways through AKT3, EGFR, IL6, INS, MAPK1, MAPK3, and PIK3R1 to alleviate cognitive impairment in depression. This study provides a foundation for future research on drug repurposing and optimization. However, it is important to note that these findings require further experimental validation.

DATA AVAILABILITY

Data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Guo N, Wang X, Xu M, Bai J, Yu H, Le Zhang. PI3K/AKT signaling pathway: molecular mechanisms and therapeutic potential in depression. Pharmacol Res. 2024;206:107300.

2. Colwell MJ, Tagomori H, Chapman S, Gillespie AL, Cowen PJ, Harmer CJ, et al. Pharmacological targeting of cognitive impairment in depression: recent developments and challenges in human clinical research. Transl Psychiatry. 2022;12:484.
3. Flinkenflügel K, Meinert S, Hirtsiefer C, Grotegerd D, Gruber M, Goltermann J, et al. Associations between white matter microstructure and cognitive decline in major depressive disorder versus controls in Germany: a prospective case-control cohort study. Lancet Psychiatry. 2024;11:899–909.
4. Chakrabarty T, Hadjipavlou G, Lam RW. Cognitive dysfunction in major depressive disorder: assessment, impact, and management. Focus (Am Psychiatr Publ). 2016;14:194–206.
5. Shilyansky C, Williams LM, Gyurak A, Harris A, Usherwood T, Etkin A. Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. Lancet Psychiatry. 2016;3:425–35.
6. Simons CJ, Jacobs N, Derom C, Thiery E, Jolles J, van Os J, et al. Cognition as predictor of current and follow-up depressive symptoms in the general population. Acta Psychiatr Scand. 2009;120:45–52.
7. Baune BT, Fuhr M, Air T, Hering C. Neuropsychological functioning in adolescents and young adults with major depressive disorder-a review. Psychiatry Res. 2014;218:261–71.
8. Yin J, John A, Cadar D. Bidirectional associations of depressive symptoms and cognitive function over time. JAMA Netw Open. 2024;7:e2416305.
9. Keilp JG, Gorlyn M, Russell M, Oquendo MA, Burke AK, Harkavy-Friedman J, et al. Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. Psychol Med. 2013;43:539–51.
10. Keefe RS. Treating cognitive impairment in depression: an unmet need. Lancet Psychiatry. 2016;3:392–3.
11. Buist-Bouwman MA, Ormel J, de Graaf R, de Jonge P, van Sonderen E, Alonso J, et al. Mediators of the association between depression and role functioning. Acta Psychiatr Scand. 2008;118:451–8.
12. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. J Affect Disord. 2011;134:20–31.
13. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol Med. 2011;41:1165–74.
14. Trivedi MH, Greer TL. Cognitive dysfunction in unipolar depression: implications for treatment. J Affect Disord. 2014;152-4:19–27.
15. Tozzi L, Goldstein-Piekarski AN, Korgaonkar MS, Williams LM. Connectivity of the cognitive control network during response inhibition as a predictive and response biomarker in major depression: evidence from a randomized clinical trial. Biol Psychiatry. 2020;87:462–72.
16. Xiang X, An R. The impact of cognitive impairment and comorbid depression on disability, health care utilization, and costs. Psychiatr Serv. 2015;66:1245–8.
17. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10:434–45.
18. Grassi-Oliveira R, Stein LM, Lopes RP, Teixeira AL, Bauer ME. Low plasma brain-derived neurotrophic factor and childhood physical neglect are associated with verbal memory impairment in major depression–a preliminary report. Biol Psychiatry. 2008;64:281–5.
19. Grant MM, Thase ME, Sweeney JA. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. Biol Psychiatry. 2001;50:35–43.
20. Bailey DM, Brugniaux JV, Filipponi T, Marley CJ, Stacey B, Soria R, et al. Exaggerated systemic oxidative-inflammatory-nitrosative stress in chronic mountain sickness is associated with cognitive decline and depression. J Physiol. 2019;597:611–29.
21. Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry. 2020;25:530–43.
22. Millan MJ, Agid Y, Brüne M, Bullmore ET, Carter CS, Clayton NS, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov. 2012;11:141–68.
23. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. Proc Natl Acad Sci USA. 2009;106:1942–7.
24. Meinert S, Nowack N, Grotegerd D, Repple J, Winter NR, Abheiden I, et al. Association of brain white matter microstructure with cognitive performance in major depressive disorder and healthy controls: a diffusion-tensor imaging study. Mol Psychiatry. 2022;27:1103–10.
25. Delgado PL. Depression: the case for a monoamine deficiency. J Clin Psychiatry. 2000;61 Suppl 6:7–11.
26. Moghaddam B, Abbas AI. Depression and prefrontal cortex: all roads lead to dopamine. Biol Psychiatry. 2022;91:773–4.
27. Cools R, Arnsten AFT. Neuromodulation of prefrontal cortex cognitive function in primates: the powerful roles of monoamines and acetylcholine. Neuropsychopharmacology. 2022;47:309–28.
28. Ramos BP, Arnsten AF. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacol Ther. 2007;113:523–36.
29. Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry. 2005;57:1377–84.
30. McIntyre RS, Xiao HX, Syeda K, Vinberg M, Carvalho AF, Mansur RB, et al. The prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. CNS Drugs. 2015;29:577–89.
31. Ainsworth NJ, Marawi T, Maslej MM, Blumberger DM, McAndrews MP, Perivolaris A, et al. Cognitive outcomes after antidepressant pharmacotherapy for late-life depression: a systematic review and meta-analysis. Am J Psychiatry. 2024;181:234–45.
32. Etkin A, Patenaude B, Song YJ, Usherwood T, Rekshan W, Schatzberg AF, et al. A cognitive-emotional biomarker for predicting remission with antidepressant medications: a report from the iSPOT-D trial. Neuropsychopharmacology. 2015;40:1332–42.
33. Smith J, Browning M, Conen S, Smallman R, Buchbjerg J, Larsen KG, et al. Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. Mol Psychiatry. 2018;23:1127–33.
34. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol. 2008;4:682–90.
35. Morphy R, Rankovic Z. Fragments, network biology and designing multiple ligands. Drug Discov Today. 2007;12:156–60.
36. Carlsson J, Luttens A. Structure-based virtual screening of vast chemical space as a starting point for drug discovery. Curr Opin Struct Biol. 2024;87:102829.
37. Sadybekov AV, Katritch V. Computational approaches streamlining drug discovery. Nature. 2023;616:673–85.
38. Bedart C, Simoben CV, Schapira M. Emerging structure-based computational methods to screen the exploding accessible chemical space. Curr Opin Struct Biol. 2024;86:102812.
39. Muhammed MT, Aki-Yalcin E. Molecular docking: principles, advances, and its applications in drug discovery. Lett Drug Des Discov. 2024;21:480–95.
40. Amberger JS, Hamosh A. Searching online mendelian inheritance in man (OMIM): a knowledgebase of human genes and genetic phenotypes. Curr Protoc Bioinforma. 2017;58:1.2.1–1.2.12.
41. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards suite: from gene data mining to disease genome sequence analyses. Curr Protoc Bioinforma. 2016;54:1.30.31–31.30.33.
42. UniProt Consortium. UniProt: a worldwide hub of protein knowledge. Nucleic Acids Res. 2019;47:D506–d515.
43. Bardou P, Mariette J, Escudié F, Djemiel C, Klopp C. jvenn: an interactive Venn diagram viewer. BMC Bioinforma. 2014;15:293.
44. Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M, et al. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. Nucleic Acids Res. 2017;45:D362–d368.
45. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003;13:2498–504.
46. Li X, Wei S, Niu S, Ma X, Li H, Jing M, et al. Network pharmacology prediction and molecular docking-based strategy to explore the potential mechanism of huanglian jiedu decoction against sepsis. Comput Biol Med. 2022;144:105389.
47. Li C, Zhuo C, Ma X, Li R, Chen X, Li Y, et al. Exploring the molecular targets of fingolimod and siponimod for treating the impaired cognition of schizophrenia using network pharmacology and molecular docking. Schizophrenia (Heidelb). 2024;10:80.
48. Dennis G Jr., Sherman BT, Hosack DA, Yang J, Gao W, Lane HC, et al. DAVID: database for annotation, visualization, and integrated discovery. Genome Biol. 2003;4:P3.
49. Kanehisa M, Sato Y, Kawashima M. KEGG mapping tools for uncovering hidden features in biological data. Protein Sci. 2022;31:47–53.
50. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The protein data bank. Nucleic Acids Res. 2000;28:235–42.
51. Kim S, Chen J, Cheng TJ, Gindulyte A, He J, He SQ, et al. PubChem 2023 update. Nucleic Acids Res. 2023;51:D1373–D1380.
52. Feng X, Song Z, Tao A, Gong P, Pei W, Zong R. Prediction of active marker of seabuckthorn polysaccharides for prevention and treatment of cervical cancer and mechanism study. Front Nutr. 2023;10:1136590.
53. Eberhardt J, Santos-Martins D, Tillack AF, Forli S. AutoDock vina 1.2.0: new docking methods, expanded force field, and python bindings. J Chem Inf Model. 2021;61:3891–8.
54. Rana T, Behl T, Sehgal A, Mehta V, Singh S, Sharma N, et al. Elucidating the possible role of FoxO in depression. Neurochem Res. 2021;46:2761–75.
55. Hu XN, Pang HX, Liu J, Wang Y, Lou YF, Zhao YF. A network medicine-based approach to explore the relationship between depression and inflammation. Front Psychiatry. 2023;14:1184188.

56. Li AX, Liu ZZ, Ali T, Gao RY, Luo YH, Gong QC, et al. Roxadustat (FG-4592) abated lipopolysaccharides-induced depressive-like symptoms via PI3K signaling. Front Mol Neurosci. 2023;16:1048985.
57. Guo LT, Wang SQ, Su J, Xu LX, Ji ZY, Zhang RY, et al. Baicalin ameliorates neuroinflammation-induced depressive-like behavior through inhibition of toll-like receptor 4 expression via the PI3K/AKT/FoxO1 pathway. J Neuroinflammation. 2019;16:95.
58. Sharma D, Khan H, Kumar A, Grewal AK, Dua K, Singh TG. Pharmacological modulation of HIF-1 in the treatment of neuropsychiatric disorders. J Neural Transm (Vienna). 2023;130:1523–35.
59. Qiu XY, Yazdi MD, Wang CC, Kosheleva A, Wu HT, Vokonas PS, et al. Extracellular microRNAs associated with psychiatric symptoms in the normative aging study. J Psychiatr Res. 2024;178:270–7.
60. Cui ZF, Zhao XT, Amevor FK, Du XX, Wang Y, Li DY, et al. Therapeutic application of quercetin in aging-related diseases: SIRT1 as a potential mechanism. Front Immunol. 2022;13:943321.
61. Zhang XF, Wang MY, Qiao YJ, Shan ZS, Yang MM, Li GQ, et al. Exploring the mechanisms of action of cordycepssinensis for the treatment of depression using network pharmacology and molecular docking. Ann Transl Med. 2022;10:282.
62. Polter A, Yang SF, Zmijewska AA, van Groen T, Paik JH, DePinho RA, et al. Forkhead box, class o transcription factors in brain: regulation and behavioral manifestation. Biol Psychiatry. 2009;65:150–9.
63. Liu J, Meng F, Dai J, Wu M, Wang W, Liu C, et al. The BDNF-FoxO1 axis in the medial prefrontal cortex modulates depressive-like behaviors induced by chronic unpredictable stress in postpartum female mice. Mol Brain. 2020;13:91.
64. Maiese K. Forkhead transcription factors: formulating a FOXO target for cognitive loss. Curr Neurovasc Res. 2017;14:415–20.
65. Lin CL, Huang WN, Li HH, Huang CN, Hsieh S, Lai C, et al. Hydrogen-rich water attenuates amyloid β-induced cytotoxicity through upregulation of Sirt1-FoxO3a by stimulation of AMP-activated protein kinase in SK-N-MC cells. Chem Biol Interact. 2015;240:12–21.
66. Yu Y, Tan Y, Liao X, Yu L, Lai H, Li X, et al. HIF-1A regulates cognitive deficits of post-stroke depressive rats. Behav Brain Res. 2024;458:114685.
67. Guo L, Jia C, Luo K, Liang J, Wang L, Hui T. Elevated HIF-1α levels in maintenance hemodialysis patients: a potential link to increased cognitive impairment risk. Front Aging Neurosci. 2024;16:1455596.
68. Li GF, Zhao M, Cheng X, Zhao T, Feng ZL, Zhao YQ, et al. FG-4592 improves depressive-like behaviors through HIF-1-mediated neurogenesis and synapse plasticity in rats. Neurotherapeutics. 2020;17:664–75.
69. Gabryelska A, Sochal M. Evaluation of HIF-1 involvement in the BDNF and ProBDNF signaling pathways among obstructive sleep apnea patients. Int J Mol Sci. 2022;23:14876.
70. Zhu W, Bijur GN, Styles NA, Li X. Regulation of FOXO3a by brain-derived neurotrophic factor in differentiated human SH-SY5Y neuroblastoma cells. Brain Res Mol Brain Res. 2004;126:45–56.
71. Fakhri S, Iranpanah A, Gravandi MM, Moradi SZ, Ranjbari M, Majnooni MB, et al. Natural products attenuate PI3K/Akt/mTOR signaling pathway: A promising strategy in regulating neurodegeneration. Phytomedicine. 2021;91:153664.
72. Eyre H, Baune BT. Neuroplastic changes in depression: a role for the immune system. Psychoneuroendocrinology. 2012;37:1397–416.
73. Yang F, Wang H, Chen H, Ran D, Tang Q, Weng P, et al. RAGE Signaling pathway in hippocampus dentate gyrus involved in GLT-1 decrease induced by chronic unpredictable stress in rats. Brain Res Bull. 2020;163:49–56.
74. Teng F, Lu Z, Gao F, Liang J, Li J, Tian X, et al. Systems biology approaches to identify potential targets and inhibitors of the intestinal microbiota to treat depression. Sci Rep. 2023;13:11225.
75. Wong RW, Guillaud L. The role of epidermal growth factor and its receptors in mammalian CNS. Cytokine Growth Factor Rev. 2004;15:147–56.
76. Melas PA, Lennartsson A, Vakifahmetoglu-Norberg H, Wei Y, Åberg E, Werme M, et al. Allele-specific programming of Npy and epigenetic effects of physical activity in a genetic model of depression. Transl Psychiatry. 2013;3:e255.
77. Kishi T, Matsunaga S, Matsuda Y, Iwata N. Iminodibenzyl class antipsychotics for schizophrenia: a systematic review and meta-analysis of carpipramine, clocapramine, and mosapramine. Neuropsychiatr Dis Treat. 2014;10:2339–51.
78. Fujimura M, Hashimoto K, Yamagami K. The effect of the antipsychotic drug mosapramine on the expression of Fos protein in the rat brain: comparison with haloperidol, clozapine and risperidone. Life Sci. 2000;67:2865–72.
79. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship?. Schizophr Bull. 2006;32:250–8.
80. Geng RJ, Li HB, Wang H, Ye CY, Mao YM, Huang X. Venlafaxine inhibits the apoptosis of SHSY-5Y cells through active Wnt/β-catenin signaling pathway. Neuropsychiatr Dis Treat. 2021;17:1145–51.
81. Alruhaimi RS, Hassanein EHM, Bin-Jumah MN, Mahmoud AM. Cadmium-induced lung injury is associated with oxidative stress, apoptosis, and altered SIRT1 and Nrf2/HO-1 signaling; protective role of the melatonin agonist agomelatine. Naunyn Schmiedebergs Arch Pharm. 2024;397:2335–45.

ACKNOWLEDGEMENTS

We thank the developers of the databases that were used in this work.

AUTHOR CONTRIBUTIONS

Chuanjun Zhuo conceived, designed, and supervised the entire study, and drafted the manuscript. Ying Zhang, Qiuyu Zhang, Lei Yang, Ximing Chen, Xiaoyan Ma, Ranli Li, Lina Wang, Hongjun Tian, and Fuqiang Mao acquired and analyzed data, and reviewed and edited the manuscript. All authors read and approved the submitted version of the manuscript.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (Nos. 82171503 and 81871052) to Chuanjun Zhuo.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-025-03775-9.

Correspondence and requests for materials should be addressed to Chuanjun Zhuo.

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