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Exploring the mechanism of methyl parathion and its degradation product on depression through network toxicology and molecular docking

Min Cao, Bin-bin Fan, Lun-shan Xu, Jiao Xu✉ & Yi-hua Zhang✉

Methyl parathion and its degradation product p-nitrophenol have become important environmental problems due to their high toxicity and persistence. In this study, the toxicological mechanism of methyl parathion and p-nitrophenol exposure increasing the risk of depression was studied through network toxicology and molecular docking methods. Based on the comprehensive analysis of PharmMapper, STITCH, SwissTargetPrediction, Similarity ensemble approach (SEA) and GeneCards databases, 35 potential targets related to methyl parathion and p-nitrophenol exposure were identified. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed the key pathways of methyl parathion and p-nitrophenol affecting depression, included insulin-like growth factor receptor signaling pathway, serotonergic synapse. Combined with protein-protein interaction (PPI) network analysis and KEGG analysis, 14 core targets of depression related to methyl parathion and p-nitrophenol were screened out. Further, the targets MAP2K1 and APP with the highest binding scores with methyl parathion and p-nitrophenol, respectively, were screened by DeepPurpose, and the common target HRAS for molecular docking was determined. The molecular docking analysis further verified that methyl parathion and p-nitrophenol may have good binding activity with HRAS. This study provides valuable insights for understanding the molecular mechanism of environmental pollutants methyl parathion and p-nitrophenol affecting depression, and provides a theoretical basis for understanding the health risks of methyl parathion and p-nitrophenol.

Keywords Methyl parathion, p-nitrophenol, Depression, Network toxicology, Molecular docking

Methyl parathion is a highly toxic and persistent organophosphorus pesticide, which is widely used in agricultural and household pest control[1]. However, its high-intensity use and environmental durability have become an important threat to ecosystem and human health. The use of methyl parathion will lead to serious environmental pollution incidents and a large number of human poisoning and death cases[2]. And it also poses a potential threat to human health when released into environmental water[3]. Methyl parathion has toxic effects on the nervous system of humans and animals, and long-term exposure may lead to cognitive dysfunction and nervous system damage[4]. Research showed that methyl parathion exposure led to a significant decrease in the levels of norepinephrine, dopamine and serotonin in the central nervous system of rat pups, which may be related to changes in neuronal activity and inefficiency, leading to depression and impaired behavioral activities[5].

Depression is a common neuropsychiatric disease and a major mental health challenge worldwide[6,7], which is characterized by long-term, repeated low mood, pain and despair, pessimism and even suicidal tendency[8]. Depression affects 4.4% of the world's population[9]. From 1990 to 2021, the incidence of depression of individuals under the age of 30 increased by more than 50%. Individuals born after 2000 showed a higher prevalence of depression[10]. The pathogenesis of depression is complex, involving monoamines, neurotrophins and neurogenesis, excitatory and inhibitory neurotransmission, mitochondrial dysfunction, inflammation and many other interrelated pathways. These mechanisms ultimately affect synaptic activity through different pathways, and then affect mood, consciousness and behavior[11]. Monoamine neurotransmitters including serotonin,

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noradrenaline, and dopamine[12]. Research showed that depression is closely related to serotonergic synapse signaling pathway[13] and the dysregulation of the serotonin axis[14]. Antidepressants such as selective serotonin reuptake inhibitors have significantly improved the quality of life of patients with depression[15].

A study showed that more than half of the victims in the methyl parathion disaster in southern Mississippi had Center for Epidemiological Studies-Depression Scale (0–60) scores above the clinical threshold of 16, and the depression-symptom score rose with longer exposure to methyl parathion-contaminated homes[16]. In addition, methyl parathion treatment can elicit excitation of rat locus coeruleus neurons. The induced neuronal excitation may be the neurobiological basis for behavioral changes in humans caused by organophosphate insecticides, such as anxiety, depression, cognitive impairment, and sleep disorders[17].

Study indicated that organophosphorus pesticide exposure may affect the nervous system in various ways, thus increasing the risk of depression[18]. p-nitrophenol is a key metabolite in the degradation process of methyl parathion. The abiotic and biotic degradation of methyl parathion in soil can generate highly toxic transformation products such as nitroaromatic compounds that may lead to secondary pollution[4]. Another study showed that p-nitrophenol is a highly toxic, bioaccumulative, and persistent pollutant that can harm ecosystems and environmental sustainability[19]. Methyl parathion can enter the body through contact and ingestion, its degradation product p-nitrophenol can enter the body through inhalation, ingestion and contact[20].

Network toxicology explores the mechanisms and patterns of toxicity by studying the interaction between chemical substances and biological networks to better understand the toxic effects and predict potential risks[21,22]. By integrating compound targets with disease-related genes and mapping their network relationships, network toxicology can systematically reveal the potential molecular mechanisms through which environmental chemicals affect depression via multi-target actions[23].

The study was designed to investigate the effect of methyl parathion and its degradation product p-nitrophenol on the development of depression. The key proteins between methyl parathion and its degradation product and depression were screened through network toxicology to predict potential toxic targets and pathways. And the binding ability of the compound to the target is evaluated by predicting the binding energy via molecular docking. These can precisely pinpoint key toxic targets, elucidate underlying mechanisms, and offer essential insights into the toxicological impact of methyl parathion and its degradation product on depression.

Materials and methods

Collection of methyl parathion and p-nitrophenol targets

The SDF format of methyl parathion and p-nitrophenol were obtained using the PubChem database[24](https://pubchem.ncbi.nlm.nih.gov/). And then potential targets of methyl parathion and p-nitrophenol were predicted using the PharmMapper database[25] (http://www.lilab-ecust.cn/pharmmapper/). In addition, potential targets of methyl parathion and p-nitrophenol were also predicted using STITCH database[26] (http://stitch.embl.de/), SwissTargetPrediction database[27] (http://www.swisstargetprediction.ch/), Similarity ensemble approach (SEA) database[28] (http://sea.bkslab.org). We use multiple databases for prediction, which significantly improves the biological credibility and robustness of subsequent network toxicology inference in a complementary and multidimensional way.

Acquisition of disease targets

The potential targets of depression were searched by GeneCards database (https://www.genecards.org/), and the key word was " depression ". After the retrieval is completed, the prediction results are derived, and according to the criteria of relevance score greater than 5, the targets obtained from GeneCards database are screened for subsequent analysis.

The intersection of compound targets and disease targets

Venny website (https://bioinfogp.cnb.csic.es/tools/venny/) was used to extract the intersection of compound targets and disease targets. The targets of methyl parathion and p-nitrophenol, as well as their combined target set, together with depression-related targets, were uploaded to the website for analysis.

Building compounds-targets-disease network

To clarify how methyl parathion and p-nitrophenol affect depression, a compounds–targets–disease network linking both chemicals to their targets and depression-related genes was constructed and visualized in Cytoscape (version 3.10.1).

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis

GO[29] (biological process, cellular component, molecular function) and KEGG[30–32] pathway of the common targets were analyzed by using DAVID database[33,34] (https://david.ncifcrf.gov/) to reveal their related signaling pathways in depression. Analysis results were visualized using https://www.bioinformatics.com.cn/, an online platform for data analysis and visualization.

Pathways-targets visualization analysis

To further explore the related pathways and targets relationship among methyl parathion, p-nitrophenol and depression, we selected top 10 enrichment pathways of 35 common targets for pathways-targets visualization analysis, and Cytoscape (version 3.10.1) was used for visualization.

Construction of protein–protein interaction (PPI) network

The 35 overlapping targets of methyl parathion and p-nitrophenol combined targets and disease targets were analyzed by STRING database (https://cn.string-db.org/), and the interaction score threshold was set to ≥ 0.4. The obtained PPI network is imported into Cytoscape (version 3.10.1) for visualization and analysis. CytoHubba can accurately screen out the important nodes in the network, and the Maximal Clique Centrality (MCC) algorithm has been proved to be a more accurate method to predict the important targets. CytoHubba plug-in is used to predict the top 9 important targets using the MCC method.

Binding score prediction with DeepPurpose

DeepPurpose, a comprehensive and easy-to-use deep learning library. BindingDB is a publicly knowledge base for protein-ligand binding data[35].The pre-trained model from DeepPurpose based on BindingDB dataset[36] was used to calculate the binding scores between targets and ligands. The amino acid sequences of the targets were obtained from UniProt database[37] (https://www.uniprot.org/), and the SMILES structures of the ligands were obtained from PubChem database. These sequences and SMILES structures were input into the pre-trained model to compute the binding scores.

Molecular docking

Molecular docking is a theoretical simulation method for predicting the binding mode and binding strength between molecules. The SDF format of methyl parathion and p-nitrophenol was obtained from PubChem database, the protein structure of the core target was collected from PDB database (https://www.rcsb.org/). After the target and ligand were processed, Vina in PyRx software (https://pyrx.sourceforge.io/) was used for molecular docking, and PyMOL software was used for visualization.

Results

Identification of potential targets of two compounds and depression

After integrating and de-duplicating the data obtained from PharmMapper database, STITCH database, SwissTargetPrediction database, SEA database, 260 methyl parathion targets, 214 p-nitrophenol targets, 328 combined targets of methyl parathion and p-nitrophenol were identified, and 392 depression-related targets were screened from GeneCards database. Among them, methyl parathion has 30 common targets with depression (Fig. 1A), p-nitrophenol has 21 common targets with depression (Fig. 1B), and 328 combined targets have 35 common targets with depression (Fig. 1C).

Construction compounds-targets-disease network for seek the potential targets of Methyl parathion and p-nitrophenol in depression

The compounds-targets-disease network was constructed, revealing that methyl parathion has 100 unique targets (dark green), p-nitrophenol has 63 unique targets (light purple), depression has 357 unique targets (light green),

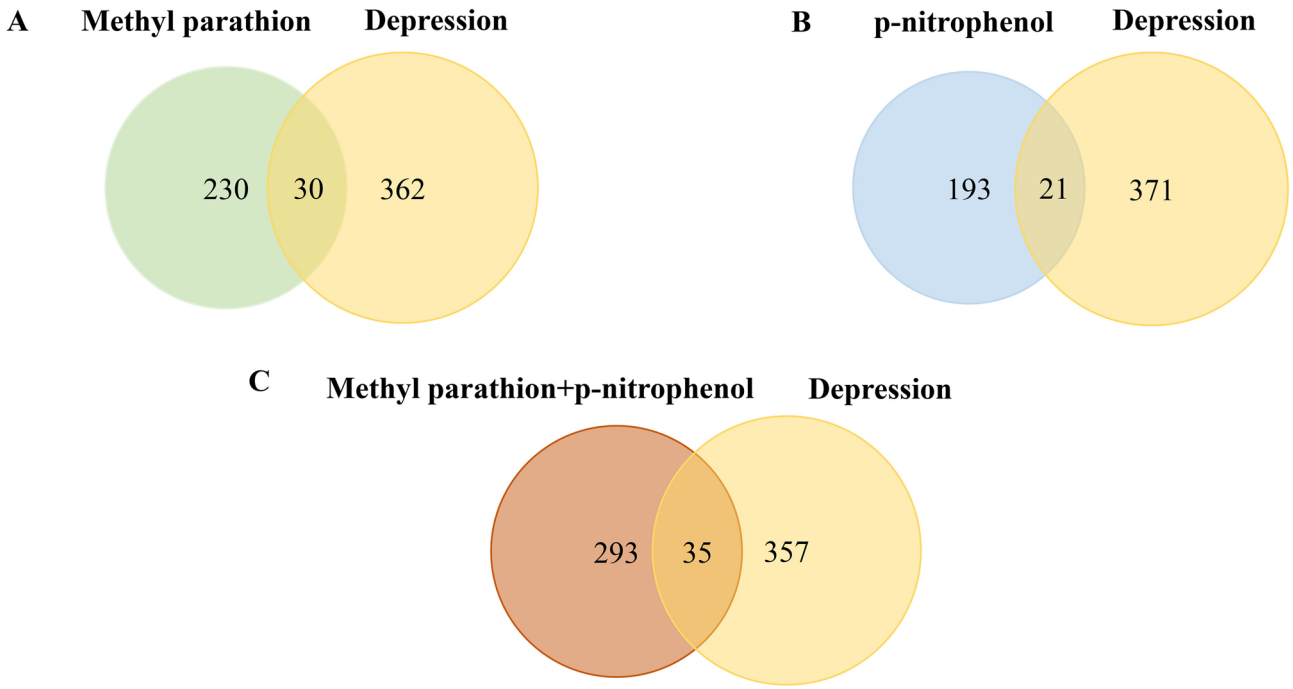

Fig. 1. Venn analysis of methyl parathion, p-nitrophenol and depression targets. (**A**) Venn analysis of methyl parathion and depression targets. (**B**) Venn analysis of p-nitrophenol and depression targets. (**C**) Venn analysis of 328 combined targets and depression targets.

and there are 16 common targets (red) among methyl parathion, p-nitrophenol, and depression. Additionally, there are 14 common targets (orange) between methyl parathion and depression, 5 common targets (light blue) between p-nitrophenol and depression, and 130 common targets (dark purple) between methyl parathion and p-nitrophenol, excluding the 16 common targets (Fig. 2). These common targets may be potential targets for depression and will be used for further analysis.

GO and KEGG pathway enrichment analysis

Depression is a complex disorder with many layers. Pinpointing the key signaling pathways is essential to connect molecular changes to behavior. DAVID database was used for GO and KEGG analysis of common targets, 35 common targets of methyl parathion, p-nitrophenol combined targets and depression targets were used for GO analysis, 30 common targets of methyl parathion and depression, 21 common targets of p-nitrophenol and depression, and 35 common targets of combined targets and depression targets were used for KEGG analysis. The top 10 terms of biological process, cellular component and molecular function were selected for presentation (Fig. 3A). The results showed that, biological process involved positive regulation of cell population proliferation, positive regulation of protein phosphorylation, insulin-like growth factor receptor signaling pathway, etc., cellular component involved postsynapse, cytosol, extracellular region, etc., molecular function included enzyme binding, NADP binding, etc. The top 20 terms of KEGG enrichment pathway were displayed, and 30 common target enrichment pathways included serotonergic synapse, PI3K-Akt signaling pathway, etc. (Fig. 3B). The 21 common targets were enriched to 14 pathways, involving serotonergic synapse, thyroid hormone signaling pathway, etc. (Fig. 3C). The top 20 terms of KEGG enrichment pathway for 35 common targets were displayed, included serotonergic synapse, prolactin signaling pathway, HIF-1 signaling pathway, etc. (Fig. 3D). The results showed that methyl parathion and p-nitrophenol may increase the risk of depression by affecting serotonergic synapse and other pathways.

Pathways- targets network analysis

We dug into the 35 common targets, the top 10 pathways enriched by 35 common targets were regarded as the key pathways associated with depression, and these 10 pathways and corresponding targets were used for pathways-targets visualization analysis (Fig. 4). This network consisted of 30 nodes and 69 edges, involving a total of 20 targets. Combined with Figs. 3 and 4, we noticed the serotonergic synapse pathway, it showed up in the KEGG analysis of three types of common targets. The optimal serotonin level in serotonergic synapses of

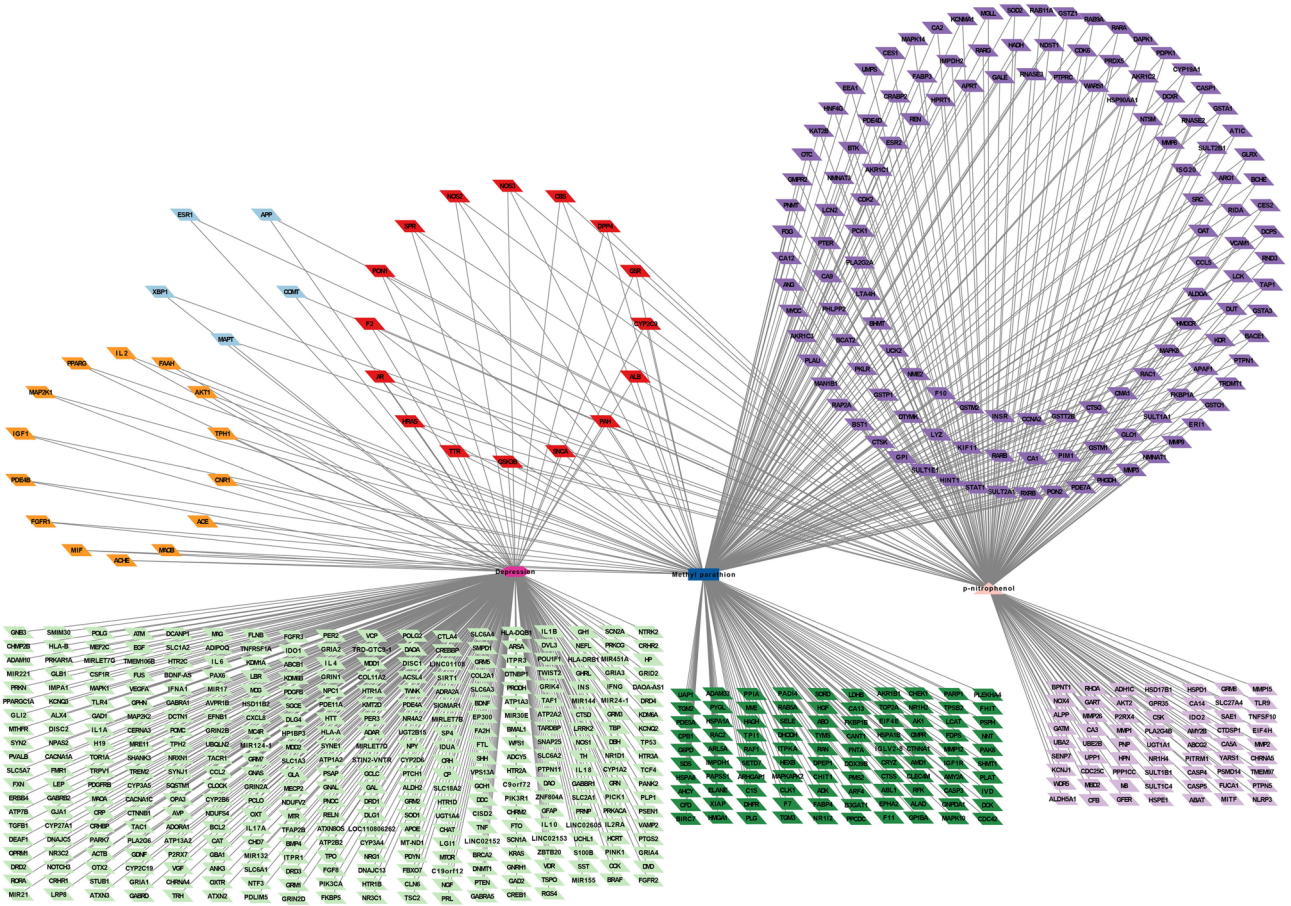

Fig. 2. Compounds-targets-disease network.

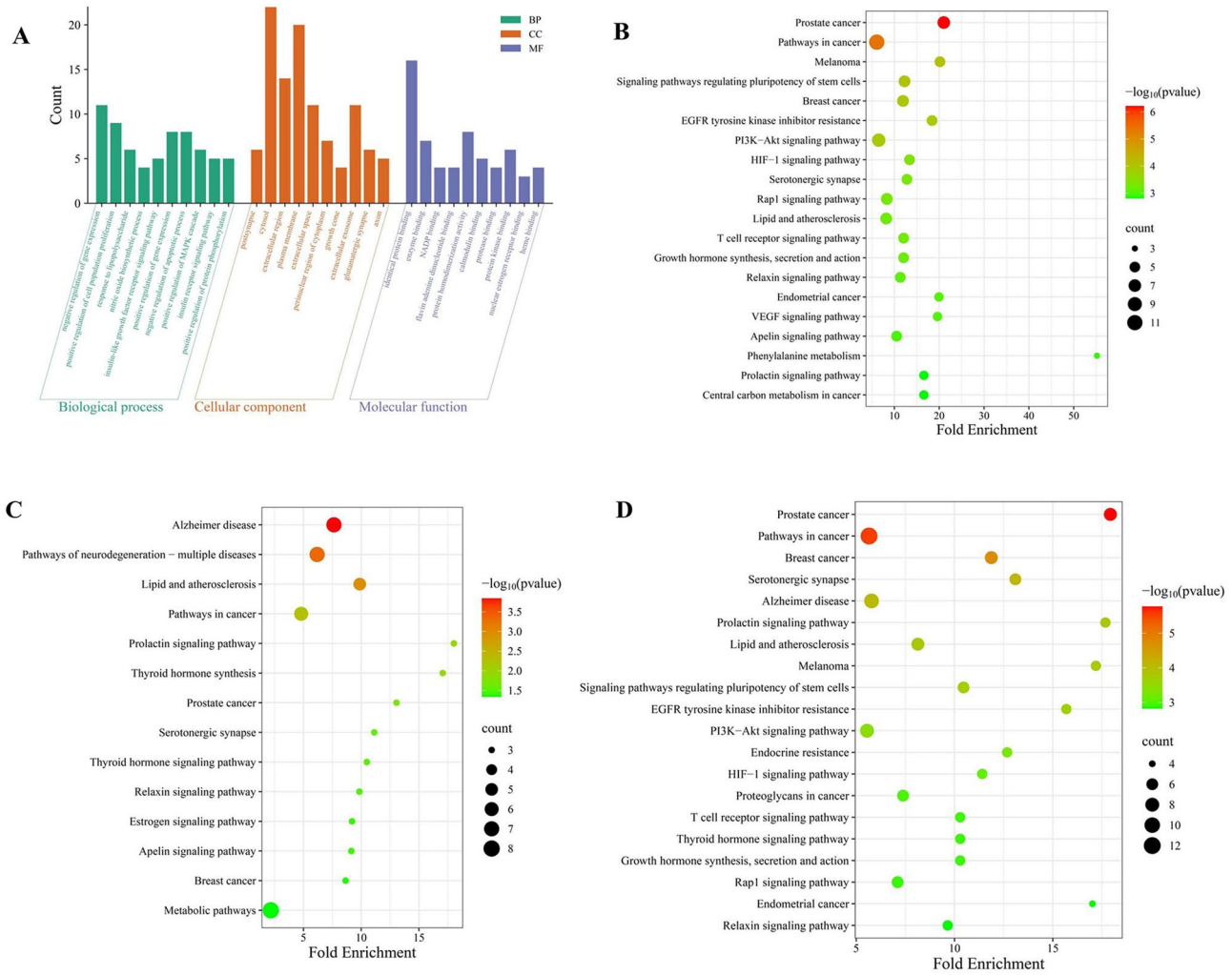

Fig. 3. Enrichment analysis results of common targets. (**A**) GO enrichment results of 35 common targets. (**B**) KEGG enrichment results of 30 common targets. (**C**) KEGG enrichment results of 21 common targets. (**D**) KEGG enrichment results of 35 common targets.

the central nervous system is related to mood, behavior and sleep, and patients with depression usually show a decrease in serotonin level. We speculated that this pathway may be the core pathway for methyl parathion and p-nitrophenol to increase the risk of depression. In pathways-targets network, the pathway of serotonergic synapse involved six targets, including CYP2C9, APP, MAP2K1, TPH1, MAOB and HRAS. This indicated that these six targets may be the core ones involving methyl parathion and p-nitrophenol to increase the risk of depression.

Building a PPI network to identify core targets

The 35 common targets of methyl parathion, p-nitrophenol combined targets and depression targets were used to construct PPI network, which has 35 nodes and 194 edges (Fig. 5A). The top 12 targets based on degree values were ALB (29), AKT1 (26), PPARG (21), ESR1 (18), APP (17), IGF1 (17), ACE (17), GSK3B (16), NOS3 (16), IL2 (15), MAOB (14) and SNCA (14). Further, based on MCC method, we found that ALB, AKT1, PPARG, NOS3, APP, IGF1, ESR1, IL2, ACE were the top 9 targets according to MCC, and they are the central targets of depression induced by methyl parathion, p-nitrophenol. There are 9 nodes and 36 edges in the PPI network of the hub target (Fig. 5B).

Binding score analysis

The 6 targets involved in serotonergic synapse pathway and the top 9 targets according to MCC were considered as important targets for binding score analysis. High-throughput analysis was used to predict the potential ligand-target interactions between two compounds and 14 targets (removing duplicate parts). Here, according to the previously screened compound-target relationship, we perform binding score analysis on the compound and the corresponding target. Methyl parathion corresponds to CYP2C9, HRAS, TPH1, IL2, NOS3, MAP2K1, ACE, IGF1, PPARG, ALB, MAOB, AKT1, and p-nitrophenol corresponds to CYP2C9, APP, HRAS, NOS3, ESR1, ALB.

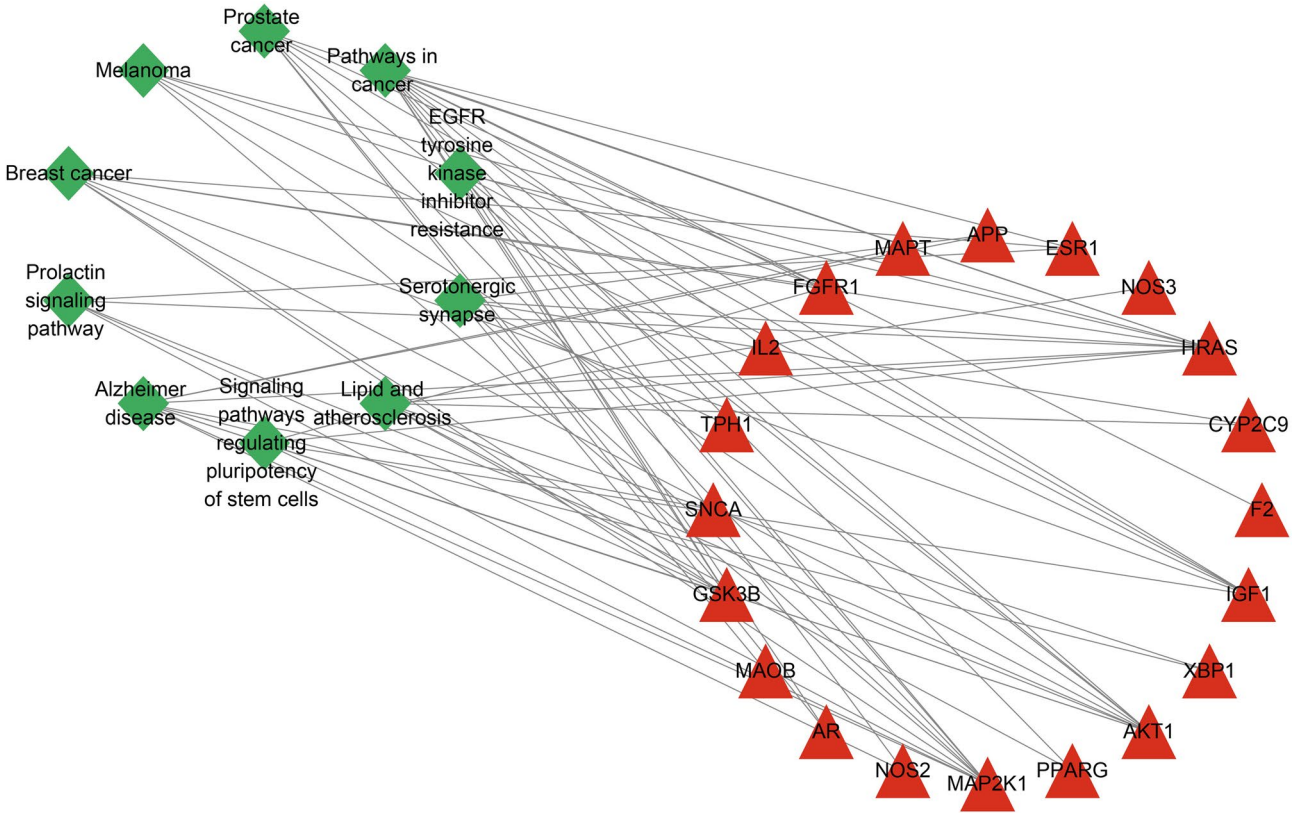

Fig. 4. Pathways-targets network of the top 10 enrichment pathways with 35 common targets. The green nodes represent the pathway and the red nodes represent the target.

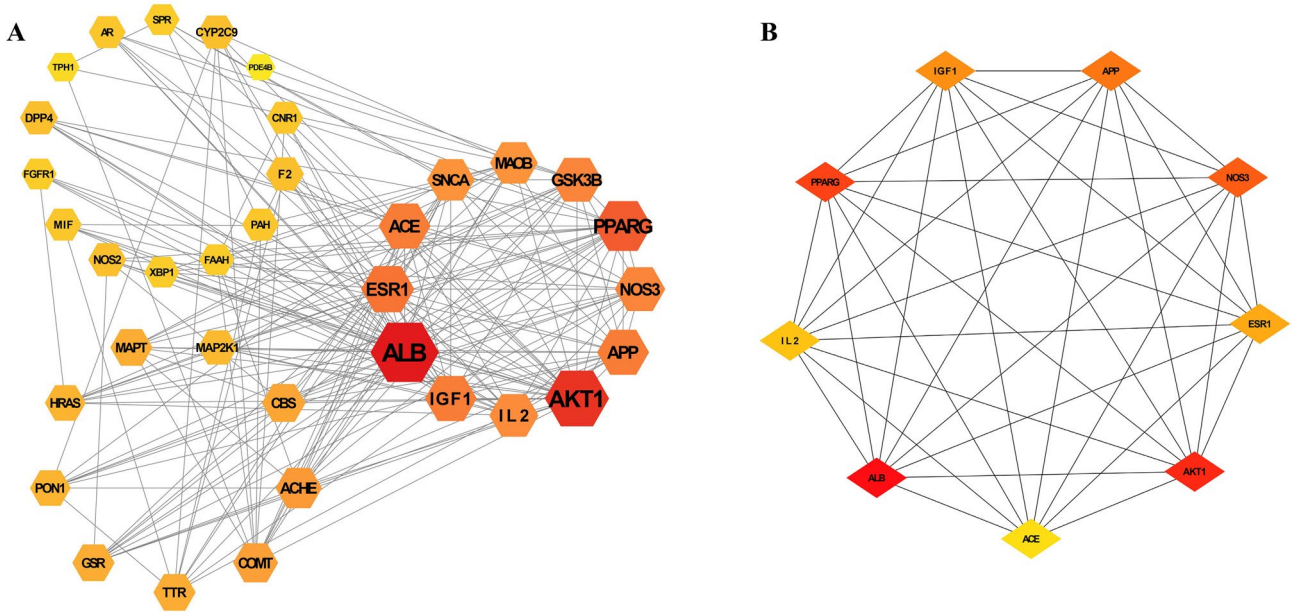

Fig. 5. Identification core targets of methyl parathion, p-nitrophenol induced depression. (**A**) Construction of PPI network by 35 common targets. (**B**) The MCC method was used to confirm the hub targets.

Their common targets are CYP2C9, HRAS, NOS3, ALB. The predicted binding score between MAP2K1 and methyl parathion is 5.8886 (Fig. 6A), which is the highest among all the predicted values, indicating that there may be a strong interaction between them. The binding score between APP and p-nitrophenol is the highest, which is 5.4603 (Fig. 6B), indicating that there may be a strong combination between them. MAP2K1 and APP are both involved in serotonergic synapse signaling pathway, indicating that MAP2K1 and APP are closely related to serotonergic synapse and may be related to the increased risk of depression. Combined with KEGG enrichment analysis and the binding score analysis of common targets, we found that HRAS participated in several signaling pathways, included serotonergic synapse, PI3K-Akt signaling pathway. Meanwhile, both methyl parathion and p-nitrophenol may act on the HRAS target, the binding score is 5.5538 and 5.3691, respectively. Therefore, we chose HRAS for molecular docking to determine the binding strength with methyl parathion, p-nitrophenol.

Molecular docking of HRAS

Molecular docking was carried out to confirm the binding ability between HRAS (PDB ID: 1P2U) and methyl parathion and p-nitrophenol. The value of docking energy is less than −5.0 kcal/mol, which indicates that they may have good binding activity. HRAS has good binding activity with methyl parathion and p-nitrophenol, and the binding energies are −6.0 kcal/mol (Fig. 7A) and −5.9 kcal/mol (Fig. 7B) respectively. The results of molecular docking further showed that there may be a potential strong interaction between the two compounds and HRAS, a potential target of depression.

Discussion

Depression is a common mental disorder in clinic, with 12% of the population suffering from major depressive disorder[38], which brings a serious burden to individuals and society[39]. Selective serotonin re-uptake inhibitors are the front-line drug therapy for major depressive disorder[40]. Methyl parathion is one of the most neurotoxic pesticides. Methyl parathion can be degraded to p-nitrophenol in the environment[41]. At high concentration, p-nitrophenol can significantly decrease the activities of the neuron-specific enzymes choline acetyltransferase and glutamic acid decarboxylase, suggesting that it may have toxic effects on neurons[42]. Methyl parathion has toxic effects on human and animal nervous system[4,17,43]. And other study showed that pesticide exposure increases the neurotoxicity of agricultural workers, and there is a significant correlation between this neurotoxicity and depression[44]. Previous study has showed that the longer the exposure to methyl parathion, the more serious the depressive symptoms[16]. Although previous studies have found that methyl parathion and its degradation product p-nitrophenol are neurotoxic, and there is a correlation between methyl parathion and depressive symptoms, the potential toxic mechanism of methyl parathion and its degradation product p-nitrophenol exposure on depression remains unclear.

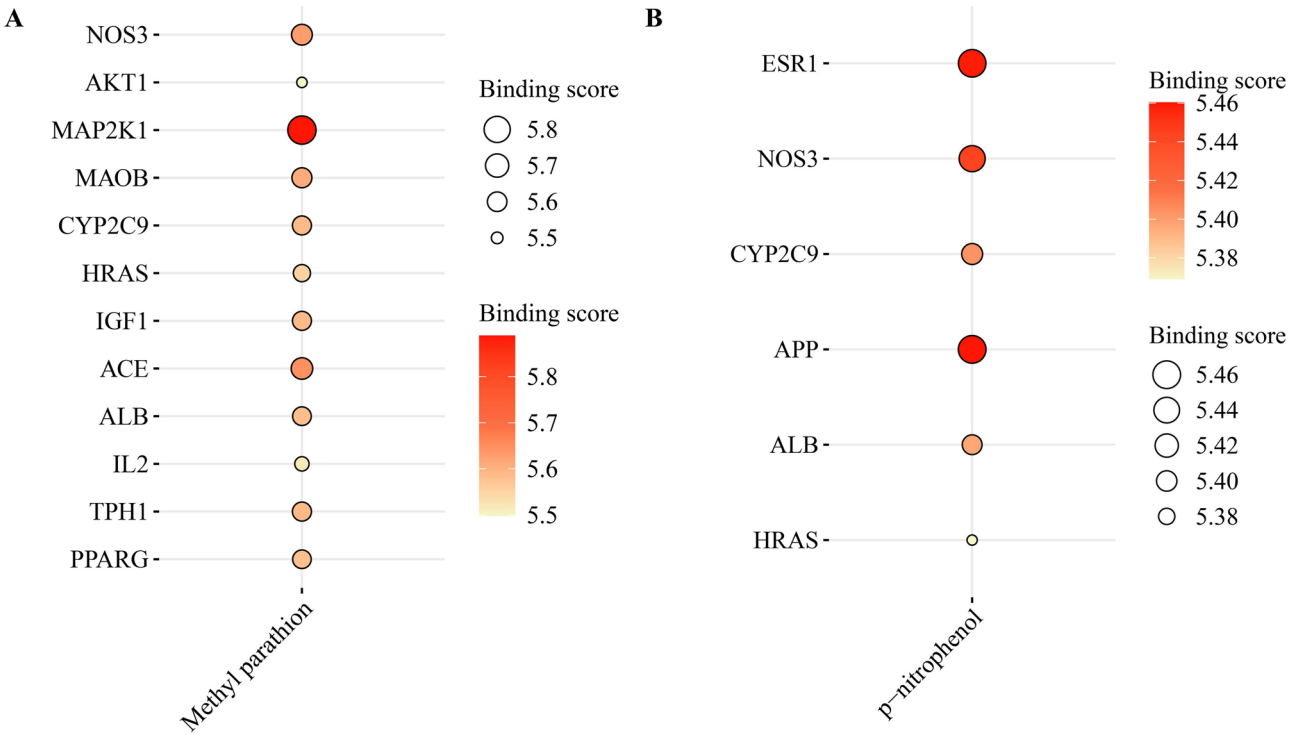

Fig. 6. Binding score prediction. (**A**) The bubble plot of prediction results of methyl parathion. (**B**) The bubble plot of prediction results of p-nitrophenol. The color and size of dots indicate the level of binding score. Larger dots and redder colors indicate higher binding scores.

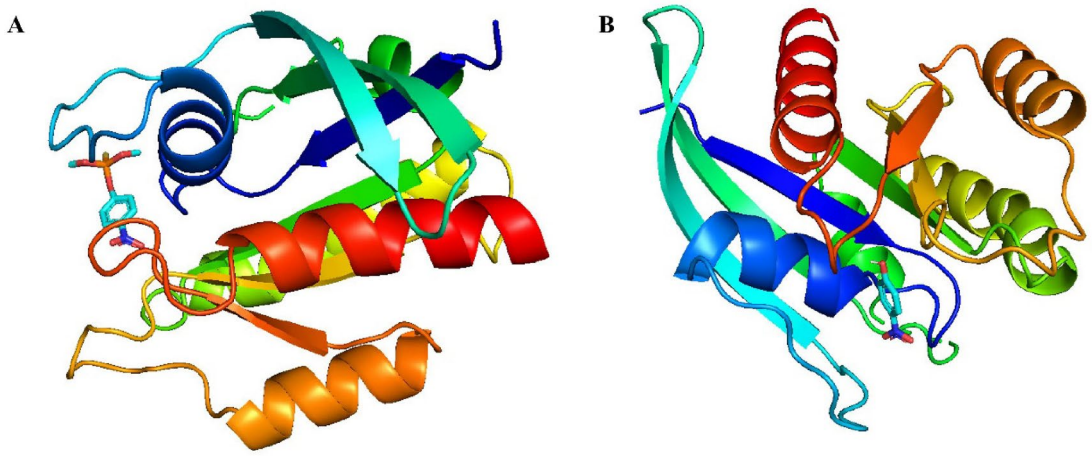

Fig. 7. Molecular docking assay analysis. (**A**) The molecular docking visualization result of methyl parathion and HRAS (– 6.0 kcal/mol). (**B**) The molecular docking visualization result of p-nitrophenol and HRAS (– 5.9 kcal/mol).

In this study, the potential toxic mechanism of methyl parathion and p-nitrophenol on depression was systematically evaluated via network toxicology and molecular docking. We identified 35 potential targets related to depression caused by exposure to methyl parathion and p-nitrophenol, including MAP2K1, HRAS, AKT1, APP, ALB, etc., and the key signaling pathways involved were revealed through GO and KEGG analysis. These findings provide a new perspective for understanding the effects of methyl parathion and p-nitrophenol on depression.

GO and KEGG analysis revealed that exposure to methyl parathion and p-nitrophenol may affect the progression of depression through various pathways, including insulin-like growth factor receptor signaling pathway, serotonergic synapse, etc. These pathways are closely related to the pathological process of depression. The chronic restraint stress (CRS) induces depressive behavior, CRS can reduce the level of insulin-like growth factor 2 (IGF2) in hippocampus, while enhancing the expression of IGF2 in hippocampus can alleviate depressive symptoms[45]. In addition, compared with healthy individuals, IGF-1 level and its mRNA expression have different changes in major depressive disorder patients. Animal experiments showed that central and peripheral administration of IGF-1 to rodents can produce antidepressant-like effect[46]. IGF-1 showed antidepressant effect in animal models by promoting hippocampal neurogenesis and interacting with 5-hydroxytrptamine 3 receptor[47]. Serotonin system regulates neurotransmitter transmission in different brain regions through a variety of serotonin receptor subclasses, and its functional state is closely related to emotion, cognition and neuroplasticity[48]. Research indicated selective serotonin reuptake inhibitors are the first-line treatment for depression in children and adolescents[49]. Rose damascena essential oil reduced the depression-like behavior and significantly increased the level of serotonin in chronic unpredictable mild stress rats, and its mechanism may involve the regulation of serotonergic synapse signaling pathway[13].

Pathways-targets analysis and PPI analysis showed that serotonergic synapse may be the core pathway for methyl parathion and p-nitrophenol to increase the risk of depression, the 6 targets involved in this pathway and top 9 targets according to MCC are 14 core targets (removing duplicate parts) related to depression, including MAP2K1, HRAS, AKT1, APP, ALB, etc. Research indicated polymorphisms rs1549854 and rs1432441 in the MAP2K1 gene might be associated with major depressive disorder[50]. The downregulation of 2210408F21Rik increased the level of miR-1968-5p and decreased the expression of HRAS, thus affecting the neuronal excitability of chronic unpredictable mild stress mice[51]. AKT1 gene polymorphisms correlated with depression severity, anxiety symptoms, work and activity, and suicide attempts in individuals with depression[52]. APP can cause changes in synaptic plasticity and lead to memory deficits in Alzheimer's disease[53]. The decrease of ALB level may reflect the increase of systemic inflammation and oxidative stress[54]. And serum ALB could be a warning measure for depression[55]. Study found that low serum ALB level is related to depressive symptoms in various patient groups and suicide attempts[56], and serum ALB concentration is negatively correlated with depressive symptoms[57]. In addition, MAP2K1, HRAS, AKT1, APP and ALB play an important role in synaptic plasticity, cell signaling transduction and regulation of cell survival, proliferation and metabolism, neuroprotective effects, inflammatory response[55,58–61]. The abnormal function or variation of these genes may affect the clinical manifestations and disease progression of patients with depression by affecting these processes. Methyl parathion and p-nitrophenol exposure may increase the risk of depression through these targets.

The binding score analysis showed that MAP2K1 and APP had the highest scores with methyl parathion and p-nitrophenol, respectively. The anomaly of the MAP2K1 function leads to changes in synaptic plasticity[58] and neuroinflammation caused by abnormal metabolism of the APP[62], which are closely related to the serotonergic synapse signaling pathway[63,64], and serotonin receptor is closely related to depression[65]. Serotonin receptors (especially serotonin 1 A and 1B)[66] regulate serotonin release and downstream neural network activities through the dual mechanism of their own receptors and heteroreceptors, which is the key molecular hub connecting

abnormal serotonin signal with the occurrence, development and treatment outcome of depression. Serotonin receptors affect the behavior of depression and the efficacy of antidepressants by regulating serotonin signal transduction, affecting neuronal activity and neuroplasticity[67], and methyl parathion and p-nitrophenol may eventually interfere with serotonin signal transmission, leading to abnormal emotional regulation, thus increasing the risk of depression.

Molecular docking showed that methyl parathion and p-nitrophenol bind well to HRAS, a gene in the Ras oncogene family, protein encoded by HRAS gene plays a key role in cell signal transduction, cell proliferation and cell differentiation. HRAS gene was identified as one of the key genes of major depressive disorder, and the HRAS gene was significantly down-regulated in patients with depression[68]. Study found that the decrease of HRAS expression may be related to the occurrence of depression. HRAS affects the excitability of neurons via regulating the expression of synapse-related proteins, and then participates in the pathogenesis of depression[51]. Based on the potential role of HRAS in the physiological process related to depression, the good binding activities of methyl parathion and p-nitrophenol with HRAS may mean that they can increase the risk of depression by altering the function of HRAS or its related physiological process.

Based on the network toxicology method, this study uncovered how methyl parathion and p-nitrophenol affect depression, though it has limitations. The extremely strong toxicity of methyl parathion and p-nitrophenol means this research lacks direct experimental verification. Future research should combine data from many sources to deeply explore their mechanisms and interactions with other environmental factors, to better understand their overall health impact.

Conclusion

In conclusion, this study takes methyl parathion and p-nitrophenol as the breakthrough point, systematically integrates network toxicology and molecular docking technology, and expounds the potential molecular mechanism of these two environmental pollutants affecting depression. The enrichment analysis of GO and KEGG suggested that the insulin-like growth factor receptor signaling pathway and serotonergic synapse were the core processes affecting depression. PPI network and key pathway screening locked 14 core targets (MAP2K1, HRAS, AKT1, APP, ALB, etc.) related to depression. Among them, the binding score analysis showed that MAP2K1 and APP had the highest binding scores with methyl parathion and p-nitrophenol, respectively. Molecular docking verified that HRAS, a common target, may be stably bound to both compounds. The above findings not only expand the theoretical horizon of environmental toxicology, but also provide new clues for evaluating the health risks, and lay a foundation for the subsequent formulation of accurate intervention public health policies.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Received: 7 August 2025; Accepted: 30 September 2025
Published online: 05 November 2025

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Author contributions
The study was conceptualized and designed by M.C. and Y.-H.Z. M.C. drafted the manuscript. In-silico experiments and data analysis were carried out by M.C., B.-B.F., L.-S.X., J.X. and Y.-H.Z. Y.-H.Z. and J.X. provided overall supervision and contributed to revising and proofreading the manuscript. All authors reviewed the final version of the manuscript.

Funding
No funding was received for this study.

Declarations

Competing interests
The authors declare no competing interests.

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