Network pharmacological investigation into the mechanism of Kaixinsan powder for the treatment of depression

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Abstract
Kaixinsan powder (KXS), a classic prescription of traditional Chinese Medicine (TCM), is widely used in the treatment of depression, but its mechanism remains unclear. The network pharmacology method was used to construct the “herb-component-target” network, and elucidated KXS potential mechanisms of action in the treatment of depression. Moreover, molecular docking was applied to validate the important interactions between the ingredients and the target protein. The “herb-component-target” network indicated that the ingredients of Girinimbin, Gomisin B and Asarone, and the protein targets of ESR, AR and NR3C1 mostly contribute to the antidepressant effect of KXS. KEGG pathway analysis highlighted the most significant pathways associated with depression treatment, including neuroactive ligand-receptor interaction pathway, serotonergic synapse pathway, PI3K-Akt signaling pathway and MAPK signaling pathway. Go enrichment analysis indicated that the mechanism of KXS in treating depression was involved in the biological process of GPCR signal transduction, hormone metabolism and nerve cell apoptosis. Moreover, molecular docking results showed that Polygalaxanthone III, Girinimbine and Pachymic acid performed greater binding ability with key antidepressant target 5-HTR. In conclusion, this study preliminarily revealed key active components in KXS, including Gomisin B, Asarone, Ginsenoside Rg1, Polygalaxanthone III and Pachymic acid, could interact with multiple targets (5-HTR, DR, ADRA, AR, ESR, NR3C1) and modulate the activation of multiple pathways (Neuroactive ligand-receptor interaction pathway, serotonergic synapse pathway, PI3K-Akt signaling pathway and MAPK signaling pathway).

Keywords Network pharmacology · Molecular docking · Kaixinsan powder · Depression · TCM

Abbreviations
KXS Kaixinsan powder
TCM Traditional Chinese Medicine
SSRIs Selective serotonin reuptake inhibitors
TCMSP Traditional Chinese Medicine System Pharmacology Database
OB Oral bioavailability

DL Drug-like
PPI Protein-protein interaction
GPCR G protein coupled receptor

Introduction
Depression is a widespread chronic psychiatric complaint, and approximately 3% of the world population suffer from this disease (Kiraly et al. 2017; Nestler et al. 2002). Depressive is often accompanied by negative affective states, painful physical symptoms, cognitive dysfunction, and impaired social function, causing an enormous social and economic burden. In addition, depression is comorbid with other medical conditions and making treatment more difficult (Singh et al. 2017a, b; Singh and Goel 2016, 2021; Pahwa et al. 2022). The etiology and pathophysiology of depression are generally believed to be associated with environmental and genetic factors, neurotransmitter abnormality (5-hydroxytryptamine, norepinephrine, and dopamine), receptor function alterations, inflammation,
neuroendocrine dysfunction (Dean and Keshavan 2017; Ménard et al. 2016). Clinically, selective serotonin reuptake inhibitors (SSRIs), such as Fluoxetine, Paroxetine and Citalopram, are often used to relieve depressive symptoms (Perez-Caballero et al. 2014), but people are gradually aware of its limitations due to the potential side effects and multidrug resistance (David and Gourion 2016b). Therefore, it is of great significance to develop novel effective and safe antidepressant medicine.

In recent years, traditional Chinese medicine (TCM) increasingly draws worldwide attention and is expected to provide an alternative treatment for depression. Kaixinsan powder (KXS), an ancient prescription in Beiji Qianjin Yao Fang, has been used for the treatment of depression for thousands of years (Yan et al. 2016). In 2018, KXS was officially included into the catalogue of Ancient Classic Prescriptions by the State Administration of Traditional Chinese Medicine. KXS is made by mixing the powders of four herbs in a ratio of 1:1:2:1(w/w), including Panax ginseng C. A. Mey (Gingseng), Polygala tenuifolia Willd (milkwort root), Poria cocos (Schw.) Wolf (Poria) and Acorus tatarinowii (Acorus gramineus soland). The significant antidepressant effect of KXS has been confirmed both in the vitro and vivo experiments (Dong et al. 2017; Zhu et al. 2016). The corresponding herbs in KXS are also extensively studied for its multiple activities in the nervous system. For example, Wang et al. indicated that ginsenoside Rg1 (the most important active ingredient of ginseng) could ameliorate neuroinflammation via suppression of Cx43 ubiquitination to attenuate depression. β-asarone is the main active ingredient of Acorus gramineus soland. It exerted an antidepressive effect on a rat model induced by the chronic unpredictable mild stress, and that the underlying molecular mechanism may be related to the activation of the ERK signaling pathway (Dong et al. 2019). Above study could provide evidence for the material basis of KXS against depression. However, the molecular mechanisms of KXS remain unclear.

Network Pharmacology is widely used in the research of TCM, especially in the fields of bioactive compound discovery, target prediction and mechanism exploration (Yu et al. 2018; Xiao et al. 2022). This study aims to explore the molecular mechanism of KXS in the treatment of depression through network pharmacology and molecular docking, which is expected to provide scientific support for further studies of antidepressants.

**Materials and methods**

**Screening of chemical components in KXS**

Chemical components of each herb in KXS were collected in the Traditional Chinese Medicine System Pharmacology Database (TCMSP, [http://lsp.nwu.edu.cn/](http://lsp.nwu.edu.cn/)). TCMSP is a system pharmacology platform that includes the relationship between chemicals, targets and diseases (Ru et al. 2014). The natural compounds with oral bioavailability (OB) value greater than 0.3 and drug-like (DL) value greater than 0.18 were considered to have good oral absorption and drug-like properties (Xu et al. 2012), but there was also the possibility of losing key ingredients. Chu et al. (Chu et al. 2016) conducted systematic research on the ingredients migrating to blood of KXS and found that the key ingredients of various herbs in KXS, such as Ginsenoside Rg1, Polygalaxanthone III, Pachymic acid, and Asarone. In this study, these reported ingredients of KXS migrating to blood were included into the ingredients database.

**Collection of compound-related targets and depression-related targets**

Firstly, the SMILES structures of compounds were obtained from the PubChem database ([https://pubchem.ncbi.nlm.nih.gov/](https://pubchem.ncbi.nlm.nih.gov/)). Then they were imported into SwissTargetPrediction ([http://www.swisstargetprediction.ch/](http://www.swisstargetprediction.ch/)) to predict the potential targets of these active components in KXS. SwissTargetPrediction ([http://www.swisstargetprediction.ch/](http://www.swisstargetprediction.ch/)) is one of the most commonly used databases for herbal ingredients targets collection. It allows its users to accurately predict the targets of bioactive molecular by the combination of 2D and 3D similarity measures, with high levels of prediction performance. (Daina et al. 2019). The targets with a probability value greater than 0.01 were all collected in this study.

Depression Targets were collected from four sources including GeneCards database (GC, [https://www.genecards.org/](https://www.genecards.org/)) (Rebhan et al. 1997), Online Mendelian Inheritance in Man database (OMIM, [https://omim.org/](https://omim.org/)) (Amberger et al. 2015), Comparative Toxicogenomics Database (CTD, [http://ctdbase.org/](http://ctdbase.org/)) (Mattingly et al. 2003) and Therapeutic Target Database (TTD, [http://db.idrblab.net/TTD/](http://db.idrblab.net/TTD/)) (Chen et al. 2002). The overlaps of the ingredient targets and the depression targets were the potential targets of KXS in the treatment of depression.

**Network construction**

The herbs, the chemical ingredients and the potential targets of KXS in the treatment of depression were introduced into Cytoscape3.7.1 software ([https://cytoscape.org/](https://cytoscape.org/)) (Lopes et al. 2010) to construct a “herb-component-target” network for visual analysis. In the network, different types of nodes were distinguished by different colors, and the edge between two nodes represents interaction relationship.
GO and KEGG pathway analysis

The potential target genes of KXS in treating depression were introduced into Metascape (https://metascape.org/) (Zhou et al. 2019) for KEGG pathway enrichment analysis. In order to further research the interaction between KEGG pathways, we selected the top ten related KEGG pathways to construct pathway network, which performed on the Omicshare platform (https://www.omicshare.com/).

Then, Metascape was used to establish protein–protein interaction (PPI) network consisted of potential targets above. We adopt the MCODE algorithm to decompose the network and identify the closely connected sub-modules. It is believed that the protein interactions within these sub-modules can undertake specific molecular functions. Therefore, GO enrichment analysis was conducted on each module to determine the GO Biological process that each sub-module participates in.

Molecular docking

The 3D structures of candidate components were downloaded in the TCMSP database, and the crystal structures of candidate protein targets were downloaded from the RCSB PDB database (http://www.rcsb.org/) (Burley et al. 2017). Then the structure files of both the candidate components and protein targets were imported into Discovery studio 2016 software (San Diego, CA, USA) for modifying. It included ligand and water removal, hydrogen addition for protein targets and small molecular conformation optimization. Finally, molecular docking was executed by the LibDock module in Discovery Studio 2016. LibDock is a high-throughput compound virtual screening algorithm, which can accurate dock the ligand into the protein active sites based on the protein site features (polar and nonpolar hot spots). Other docking parameters were set by default. LibDockScore was used to evaluate affinity of the target proteins and its corresponding prototype ligand, and best-scored pose was chosen for each compound.

Results

KXS ingredients and potential targets in depression treatment

After OB and DL screening in the TCMSP database, 16 components in Ginseng, 3 components in milkwort root, 13 components in Poria and 3 components in Acorus gramineus soland were collected (Table S1). It is reported that the main components in KXS, including saponins, xanthones polysaccharides and volatile oils (Zhang et al. 2015). However, some components of high content in KXS could not be included because of lower value of OB and DL recorded in the TCMSP database. Chu et al. (Chu et al. 2016) have conducted systematic research on the ingredients migrating to blood of KXS and found that the key ingredients of various herbs in KXS, such as Ginsenoside Rg1, Polygalaxanthone III, Pachymic acid, and Asarone. In order to fully characterize the pharmacodynamics material basis of KXS, we included the reported ingredients migrating to blood of KXS into the ingredients database of our research (Table S2). At last, 83 ingredients in KXS were collected.

As shown in Fig. 1, the target genes of ingredients in KXS were intersected with depression-related targets collected from the four disease databases. Finally, 142 targets were found to be common targets, which were potential targets of KXS for the treatment of depression.

Network analysis

The corresponding relationships between “herb-component” and “component-target” were imported into Cytoscape software to establish the “herb-component-target” network, as shown in Fig. 2. The red nodes represented medicinal materials (4 in total), the yellow nodes represented active ingredients (83 in total), and the blue nodes represented targets (142 in total). It was found that the network degree values of Asarone (degree = 35) in Acorus tatarus and Girinimbin (degree = 29) and Gomssin B (degree = 29) in Ginseng were higher than other ingredients, which indicated that these three components can interact with most of the targets in the network. Similarly, the degree values of ESR (estrogen receptor, degree = 31), AR (androgen receptor, degree = 29), and NR3C1 (glucocorticoid receptor, degree = 26) were the top three among the protein targets, indicating that these three proteins had interaction relationship with most of the components in the network.

KEGG pathway analysis

In the analysis of KEGG pathways, a total of 158 KEGG pathways were obtained. Then, these entries were sorted in descending order according to the number of enriched genes, and the top 10 pathways were selected as shown in Table 1. In organisms, different genes coordinate with each other to conduct special biological functions. As a result, a KEGG pathway interaction network was established based on the KEGG database (Fig. 3) in order to further explore the core pathways in network. In this network, the nodes represent the KEGG pathway, the size of the node represents the number of genes enriched in the pathway, and the gradient color of the node represents the P value of the KEGG enrichment analysis. The results showed that most genes were enriched in the neuroactive ligand-receptor
interaction pathway, serotonergic synapse pathway and PI3K-Akt signaling pathway. MAPK signaling pathway had the highest network connectivity in the network. It interacted with seven pathways in the network. In general, these four pathways play a vital role in the antidepressant effect of KXS.

**Go enrichment analysis**

The MCODE algorithm was applied for decomposing the PPI network, and five closely connected sub-modules were identified. The PPI network was shown in Fig. 4. Then, the sub-modules were scored according to their
contribution degree in the network, as shown in Table 2. It is obvious that cluster 1 with the highest score of 7.8 is most important for the PPI network. Besides, Go biological process analysis was conducted on each sub-module to further understand the molecular functions undertaken by them. The results showed that Cluster1, Cluster3 and Cluster5 were all related to the G-protein coupled signaling pathway, while Cluster2 was related to hormone level regulation and metabolic process, and Cluster4 was related to nerve cell apoptosis. In conclusion, the regulation of G-protein-coupled signaling pathway may be closely related to the mechanism of treating depression with KXS, and the active components of KXS may have certain effects on the regulation of hormone levels and nerve cell apoptosis.

Table 1 The top 10 KEGG pathways of KXS in the treatment of depression

| KEGG pathways                                | Enriched genes | Log(p-value) |
|----------------------------------------------|----------------|--------------|
| Neuroactive ligand-receptor interaction      | 30             | -26          |
| Serotonergic synapse                         | 22             | -24          |
| PI3K-Akt signaling pathway                   | 22             | -14          |
| MAPK signaling pathway                       | 21             | -15          |
| Calcium signaling pathway                    | 19             | -16          |
| TNF signaling pathway                        | 17             | -17          |
| Apoptosis                                    | 16             | -14          |
| Th17 cell differentiation                    | 15             | -14          |
| Neurotrophic signaling pathway               | 15             | -13          |
| IL-17 signaling pathway                      | 14             | -14          |

Fig. 3 KEGG pathway network of top 10

Molecular docking

The network analysis indicated that Girinimbin, Gomssin B and Asarone were the key chemical ingredients in KXS. Furthermore, representative ingredients of each herb in KXS, such as Ginsenoside Rg1 (Li et al. 2022; Wang et al. 2022), Polygalaxanthone III (Tu et al. 2008), Pachymic acid (Zhai et al. 2022), and Asarone (Chellian et al. 2018; Dong et al. 2019), have been reported to have an antidepressant effect. Thus, we included these 6 chemical ingredients into our research for molecular docking. In addition, in the result of KEGG pathway and GO enrichment analysis, we found that the protein target of 5-HTR was the common target of neuroactive ligand-receptor interaction pathway, serotonergic synapse pathway and GPCR signaling pathway. 5-HTR is also an important target of depression drugs. Therefore, we selected 5-HTR as the candidate target for molecular docking. Nefazodone, a positive medicine targeting 5-HTR, was selected as another candidate ingredient for reference. Then, these candidate ingredients and 5-HTR were led into DiscoveryStudio software for molecular docking calculation. Their docking ability was evaluated based on libdock score, hydrogen bond number and Pi-Pi bond, as shown in Table 3. The result showed that Ginsenoside Rg1 and Gomssin B failed to dock with 5-HTR, however, Polygalaxanthone III, Girinimbine and Pachymic acid performed greater binding ability with 5-HTR. For example, Polygalaxanthone III’s libdock score is 150, which was close to the positive drug of Nefazodone. It could interact with protein 5-HTR with 2 hydrogen bonds at the amino acid residues of LEU229, ASP155 and 2 Pi-Pi bonds at PHE340, PHE339. The Molecular docking diagram for 2D and 3D was shown in Fig. 5.
In this study, the key active ingredients including Girinimbine, Gomisin B and Asarone were screened out according to the degree value in the network. These three ingredients have an interaction relationship with 36 targets in total. It is reported that Girinimbine (Mohan et al. 2020) has anti-inflammatory and antioxidant effect. It can effectively reduce the level of NO, IL-6, TNF α in plasma of rats with gastric ulcer symptom to play a gastrointestinal protection role. Inflammation and oxidative stress are related to the pathogenesis of depression closely. Chronic unpredictable stress model rats were found to accompany intestinal inflammation and the injury of intestinal barrier function (Yan et al. 2020). The pharmacological effects of Gomisin B are seldom studied at present. However, Gomisin N, which has a similar structure with Gomisin B, has been proven to relieve depressive symptoms by reducing the inflammation of hypothalamus and amygdala (Araki et al. 2016). As for Asarone, it is the main ingredient in Acorus gramineus soland, which predicted as the key ingredient in KXS during network analysis. Asarone has been found to significantly shorten the fixed time of depression rats in tail suspension test and believed to have obvious antidepressant effect (Chellian et al. 2016).

It is important to note that the representative components migrating to the blood of KXS, including Ginsenoside Rg1, Polygalaxanthone III, Pachymic acid and Asarone (Chu et al. 2016). Cao et al. further ensured the antidepressant activity of these four representative components in vitro cell experiments (Cao et al. 2018). However, they were all excluded when screening chemical ingredient in KXS. This suggests that network pharmacology needs further improvement in component selection. In order to make up for this, we included Ginsenoside Rg1, Polygalaxanthone III, Pachymic acid and Asarone as effective ingredients in KXS when conducting molecular docking study. The molecular docking result showed that Polygalaxanthone III, Girinimbine and Pachymic acid were all have great combining ability with depression target 5-HTR.

KEGG enrichment analysis indicated that neuroactive ligand-receptor interaction pathway, serotonergic synapse pathway, PI3K-Akt signaling pathway...
Table 2  GO enrichment analysis of KXS in treating depression

| Score | Enriched genes | Cluster network | GO biological process | Log(p-value) |
|-------|----------------|----------------|-----------------------|--------------|
| 7.8   | ADRA2A, AP, HTR1A, CX, CL8, DRD2, ADR2C, DRD4, HTR1B, DRD3, OPRD1, PK1, BDKR1, MTRN1A, NPY5R, HCA2, P2RY12, CNR1 | ![Cluster network image] | Adenylate cyclase-modulating G protein-coupled receptor signaling pathway (GO:0007188) | -21 |
|       |                |                | Adenylate cyclase-inhibiting G protein-coupled receptor signaling pathway (GO:0007193) | -21 |
|       |                |                | G protein-coupled receptor signaling pathway (GO:0007187) | -21 |
| 4.3   | PRKCA, MAPK1, STAT3, PT, PN11, BCL2, CASP8, MAPK8, AKT1, FKBP5, FGFR1, JUN, FGFR2, HRAS, PDGFRA, EGFR, PPAR, CYR61, CYP17A1, CYP19A1, PARP1, CYP1A1, CYP1A2, CYP2D6, CYP2C9, CYP2C19 | ![Cluster network image] | Estrogen metabolic process (GO:0008210) | -13 |
|       |                |                | Hormone metabolic process (GO:0042445) | -12 |
|       |                |                | Regulation of hormone levels (GO:0010817) | -12 |
| 3.4   | GRM1, HCRT2, TACR1, HTR2A, HTR2C, TACR3, HTR2B, F2, GSK3B, ADRA1A, AR, NFE2L2, RELA, RARA, ESR1, MAPK14, NR3C1 | ![Cluster network image] | Phospholipase C-activating G protein-coupled receptor signaling pathway (GO:0007200) | -18 |
|       |                |                | Regulation of cytosolic calcium ion concentration (GO:0051480) | -13 |
|       |                |                | Cellular calcium ion homeostasis (GO:0006874) | -12 |
| 2.0   | DRD1, DRD5, HTR7, CRHR1, TAAR1 | ![Cluster network image] | Regulation of neuron death (GO:1901214) | -10 |
|       |                |                | Positive regulation of cell death (GO:0010942) | -10 |
|       |                |                | Neuron death (GO:0070097) | -10 |
| 1.6   | MAP2K1, VCP, JAK2, MAPK3, BCL2L1, NF, MAPT, CASP3, MTP | ![Cluster network image] | Activation of adenylyl cyclase activity (GO:0007190) | -8 |
|       |                |                | G protein-coupled receptor signaling pathway (GO:0007187) | -7 |
|       |                |                | Regulation of blood vessel size (GO:0050880) | -6 |
and MAPK signaling pathway were the core pathways of KXS in the treatment of depression. The specific mechanism is shown in the Fig. 6. The target of norepinephrine receptor (ADR), dopamine receptor (DRD) and 5-hydroxytryptophan receptor (5-HTR) were all enriched in the neuroactive ligand-receptor interaction pathway. These three are monoamine neurotransmitter receptors. The disorder of metabolism of monoamine neurotransmitters NE, DA and 5-HT is one of the pathogenesis of depression (Rühé et al. 2007). Monoamine receptor regulating drugs have been applied in the treatment of depression. They can increase the concentration of monoamine neurotransmitters in the brain by antagonizing the monoamine receptor to play an anti-depressive effect (David and Gardier 2016a). Serotonin synaptic pathway enriched the protein target including serotonin transporter (SERT) and monoamine oxidase A (MAOA). They are involved in the transport and metabolism of 5-HT, which are closely related to the maintenance of 5-HT homeostasis. There is evidence to show that increase in MAOA expression is one of important pathogenic factors in depressive disorders (Naoi et al. 2018). The high activity of MAOA increases activities such as decomposition and metabolic inactivation of 5-HT, leading to a decrease in the content of 5-HT in the brain. SERT is mainly responsible for transporting 5-HT in the synaptic cleft, and the expression of SERT in the brain of depressed subjects was found to significantly down-regulated (Newberg et al. 2012), which results in a decrease in the content of 5-HT. Therefore, inhibiting 5-HT metabolism and transport-related target proteins to improve the content of 5-HT in brain is an important mechanism of the antidepressant effect of KXS. In addition, multiple genes were enriched in PI3K-Akt and MAPK signaling pathways. Cao et al. (Cao et al. 2019) found that the expression levels of PI3K and Akt were both decreased in rats with perimenopausal depression. The downstream of the PI3-Akt signaling pathway includes multiple pathways such as mTOR, NF-kB, FOXO and MAPK, which are closely related to the pathogenesis of depression (Guo et al. 2019; Caviedes et al. 2017). Therefore, KXS may play an antidepressant role by regulating the PI3-Akt signaling pathway to affect the expression of mTOR, NF-kB, FOXO and MAPK. Si et al. (Si et al. 2018) have constructed mRNA and miRNA molecular map for the brain of CUMS depression rat, and found that in the ligand-receptor interaction pathway, serotonergic synaptic pathway and MAPK pathway, some genes expression level with significant changes. These results are all consistent with our study.

By splitting the PPI network with the MCODE algorithm, five sub-modules were determined to be mainly responsible for the biological process of the G protein coupled receptor (GPCR) signaling pathway, hormone level regulation and metabolism, and nerve cell apoptosis. Abnormal regulation of GPCR signals has been noted in a variety of early stress models, which considered to be an important participant in abnormal emotional programming (Tiwari et al. 2021). G protein signal can be accidentally duplicate amine neurotransmitter, neuropeptides and many kinds of hormone receptors to involve in regulating the function of the nervous system (Proulx et al. 2014). Various ingredients in KXS have an interaction relationship with multiple GPCRs, such as 5-HTR, DR, ADRA, NPY5R, AR and NR3C1 (Fig. 6). Comprehensive regulation of GPCR mediated signaling pathways may be the basis of antidepressant effect of KXS. In addition, in the “herb-ingredient-target” network, we found that many components in KXS can act on hormone receptors, including AR, ESR and NR3C1. This is consistent with the result of Go analysis that KXS involved in the hormone level regulation process. Depression may cause abnormal expression of hormone receptors or indirectly cause dysfunction of hormone receptors by affecting hormone secretion, resulting in disorders of the hypothalamic–pituitary–adrenal/gonadal (HPA/HPG) axis (Vermeersch et al. 2013; Du et al. 2015) and injury of

### Table 3 Molecular docking studies with the 5-HTR

| Ingredient      | Target | Libdock score | Hydrogen Bond | Hydrogen bonding residues | Pi-Pi Bond | Pi-Pi bonding residues |
|-----------------|--------|---------------|---------------|---------------------------|------------|------------------------|
| Girinimbine     | 5-HTR  | 103           | 0             | /                         | 7          | PHE243 (3), SER159 (2), TRP336 (2) |
| Asarone         | 5-HTR  | 59            | 1             | SER159                    | 1          | PHE340                 |
| Polygalaxanthone III | 5-HTR | 150           | 2             | LEU229, ASP155            | 2          | PHE340, PHE339         |
| Pachymic acid   | 5-HTR  | 125           | 2             | SER159, VAL156            | 0          | /                      |
| Nefazodone      | 5-HTR  | 159           | 0             | /                         | 4          | PHE340, PHE243, TRP336, PHE339 |
nerve cells. Ginsenoside Rg1, the main component of KXS, has been proved to improve the levels of NR3C1 and AR of depression rats, which contribute to regulating the disturbance of HPA and HPG axis, and thus significantly improve the depressive symptoms (Mou et al. 2017). Therefore, the regulation of the hormone level of KXS is also an important mechanism of its antidepressant effect.
Conclusion

Based on network pharmacology and molecular docking methods, this study analysed the key components, targets and pathways of KXS in the treatment of depression. The chemical ingredients in KXS, including Gomisin B, Asarone, Ginsenoside Rg1, Polygalaxanthone III and Pachymic acid, can act on 5-HTR, DR, ADRA, AR, ESR, NR3C1 targets to comprehensively regulate the process of GPCR signal transduction, hormone metabolism and nerve cell apoptosis. Neuroactive ligand receptor interaction pathway, serotonergic synapse pathway, PI3K-Akt signaling pathway and MAPK signaling pathway are the key pathways in this regulation process of antidepressant effect of KXS.

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Authors’ contributions  Y-SK and H-CG provided the concept and designed the study. D-LJ and Z-XN conducted the main experiments and wrote the paper. S-YF participated in data analysis. L-SS and J-HZ supported the research design, reviewed the proposal, and participated in the revision of the manuscript.

Data availability  Data will be made available on reasonable request.

Declarations

Consent to publish  All the authors listed have approved the manuscript that is enclosed.

Conflicts of interest  Declarations of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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