Identification of the significant pathways of Banxia Houpu decoction in the treatment of depression based on network pharmacology

Zi-ying Chen1, Dan-feng Xie1, Zhi-yuan Liu1, Yong-qi Zhong1, Jing-yan Zeng1, Zheng Chen2*, Xin-lin Chen3*

1 Shenzhen Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, China, 2 Department of Stomatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, 3 School of Basic Medical Science, Guangzhou University of Chinese Medicine, Guangzhou, China

* chenxls@126.com (XLC); chenzh68@mail.sysu.edu.cn (ZC)

Abstract

Banxia Houpu decoction (BXHPD) has been used to treat depression in clinical practice for centuries. However, the pharmacological mechanisms of BXHPD still remain unclear. Network Pharmacology (NP) approach was used to explore the potential molecular mechanisms of BXHPD in treating depression. Potential active compounds of BXHPD were obtained from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform Database. STRING database was used to build an interaction network between the active compounds and target genes associated with depression. The topological features of nodes were visualized and calculated. Significant pathways and biological functions were identified using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses. A total of 44 active compounds were obtained from BXHPD, and 121 potential target genes were considered to be therapeutically relevant. Pathway analysis indicated that MAPK signaling pathway, ErbB signaling pathway, HIF-1 signaling pathway and PI3K-Akt pathway were significant pathways in depression. They were mainly involved in promoting nerve growth and nutrition and alleviating neuroinflammatory conditions. The result provided some potential ways for modern medicine in the treatment of depression.

Background

Depression is a widespread chronic mental illness characterized by low mood, sadness, and insomnia. Depression affects physical health [1]. The world health organization predicts that depression will be the leading cause of death of burden among all health diseases by 2030 [2].

Current therapies, including selective 5-serotonin reuptake inhibitors, serotonin-noradrenergic reuptake inhibitors and tricyclic antidepressants [3], can alleviate some major symptoms of depression. But these medications trigger a series of serious side effects like anxiety, gastrointestinal discomfort, drug resistance, withdrawal response and so on [4]. Therefore, it is necessary to develop safe, effective new drugs and therapies with lower side effects. Studies have shown that the use of complementary and alternative medicine (CAM) for the treatment of
Depression is common [5, 6]. As the important part of the CAM, traditional Chinese medicine (TCM) reported positive results for managing depression: less adverse reactions than other antidepressants and no significant differences from medication [7, 8].

Banxia Houpu decoction (BXHPD) is a famous Chinese medicine prescription, which firstly recorded in Jingui Yaolue (Synopsis of Prescriptions of the Golden Chamber) in Eastern Han Dynasty of Chinese history (25AD–220AD). BXHPD was 5 herbs, which included Pinellia rhizome (PR, Banxia), Magnolia officinalis cortex (MOC, Houpu), Poria (PO, Fuling), ginger rhizome (GR, Shengjiang), and Perilla folium (PF, Zisu). In the theory of TCM, BXHPD could promote chi, eliminate stagnation, calm the adverse chi and dissolve phlegm. BXHPD was widely used in the treatment of depression and achieved effective results [9, 10]. Zheng Q et al reported that the effective rate of BXHPD combined with western medicine was 94.5%, and the cure rate was 55.2%, compared to 81.1% and 22.9% treated with western medicine alone in the treatment of depression [10].

Some previous studies predicted the molecular mechanism on depression of BXHPD, which mainly included activation of the inflammatory response system [11], monoamine hypothesis [12], Hypothalamic Pituitary Adrenal (HPA) axis dysfunction [13], low expression of brain-derived neurotrophic factor (BDNF) [14] and so on. The biological mechanism in holistic manner are still unknown. The main problems are as follows: (1) On account of the complex composition, the biological effects on depression of BXHPD were not unified. BXHPD included many active compounds, most of which were different in therapeutic mechanism. For instance, Baicalein [15] and Luteolin [16] were related to the suppression of inflammation about nerve through the regulation of pathways or the expression level of inflammatory related factors. Beta-sitosterol might affect the content of neurotransmitter [17]. (2) The previous studies mainly focused on the gene targets or biological functions rather than multiple pathways: Anti-depression on BXHPD proved to elevate brain 5-hydroxytryptamine (5-HT) levels, attenuate abnormalities in dopaminergic system functions [18], ameliorate the damages of lipid peroxidation [19], and adjust the amino acid metabolism and energy metabolism [20].

In order to explore details of the mechanism and relevant pathways, it is essential to elucidate the molecular and biological basis of TCM preparations and NP approaches have been proven to be a powerful approach [21, 22]. The holistic philosophy of TCM shares similar characteristic of NP. TCM network pharmacology approach was established by “network target, multi-components” mode, which predicted the target profiles, revealed drug-gene-disease co-module associations, and interpreted the combinatorial rules and network regulation effects of herbal formulae [23]. Herein we focused on the following issues: (1) Which active ingredients were involved in the regulation of depression? (2) Which active ingredients and proteins regulated the target to achieve the biological activity? (3) What pathways or biological processes did the active ingredients regulate? The main contribution of our work was to clarify the potential mechanism of BXHPD in the treatment of depression using NP. The workflow of the experimental procedures was showed in Fig 1.

**Methods**

Identification of active compounds

The main chemical constituents of BXHPD were collected from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform Database (TCMSP) (http://tcmspw.com/tcmsp.php/) [24]. TCMSP database was a network pharmacological database of Chinese herbal medicines and it provided pharmacokinetic information for each compound [25], such as drug similarity (DL) and oral bioavailability (OB). Compounds with good drug-
Fig 1. The workflow of the experimental procedures.

https://doi.org/10.1371/journal.pone.0239843.g001
like were selected according to their characteristics (including absorption, distribution, metabolism and excretion [ADME]) [25].

OB and DL were important indicators to evaluate ADME [26] characteristics. OB represented the correlation of effective compounds. OB ≥30% meant that the effective compounds had a strong correlation. DL of new molecules was assessed using the following formula [27]:

\[ f(A, B) = \frac{A \cdot B}{|A|^2 + |B|^2 - A \cdot B} \]

"A" is the molecular descriptor of BXHPD based on Dragon software (http://www.talete.mi.it/products/dragon_description.htm). "B" represents the average descriptor of all drugs based on The Drug Bank database [28]. The Dragon software calculates the average of all descriptors and the active molecules with DL ≥ 0.18 were selected. Therefore, compounds with OB ≥ 30% and DL ≥ 0.18 were selected for further study. Pinellia ternata, Magnolia officinalis, Poria cocos, Ginger and Perilla frutescens were used separately as search terms to gain the pharmacokinetic information of active compounds.

Screening of potential targets

An important step after screening active compounds was to identify their molecular targets for triggering biological effects [29]. UniProt (https://www.uniprot.org/) is a protein database with abundant information and extensive resources [30]. The protein targets retrieved from TCMSP database were put into Uniprot, and the corresponding gene names were extracted from UniProt KB. We restricted species to human beings and converted them into official gene names. Gene Cards (https://www.genecards.org/) is a searchable and comprehensive database which automatically integrates data from about 125 web-based sources of genes, including genomes, transcriptomes and proteomics [31]. Gene Cards database is applied to search disease targets for depression. Potential antidepressant targets of BXHPD were obtained by intersecting the targets of active ingredients and potential disease-related targets.

Construction and topological analysis of PPI network

STRING (https://string-db.org/cgi/input.pl) was used for expanding protein-protein interaction (PPI) network data [32]. The gene names of potential targets converted from UniProt were put into STRING to download interactive information table of PPI. Cytoscape V3.7.1 was used to visualize PPI and complete topological analysis [33]. Core genes of BXHPD for anti-depression were obtained meeting degree ≥ 38 (two times of median of all nodes).

"Degree", "Betweenness" and "Closeness" were used to assess the topological importance of the selected core genes [34]. "Degrees" is defined as the number of links to a node that reflects the node’s interaction with another node. Nodes with an extremely high level of degree tend to be critical in interaction networks. "Betweenness" is defined as the number of closest associations. "Closeness" indicates the sum of the nodes distance from all other nodes.

Biological function enrichment and metabolic pathway acquisition

The Gene Ontology (GO) is a database that functionally marks genes and proteins as three main terms: biological process (BP), cellular component (CC) and molecular function (MF) [35]. The function of genes can be defined and described in many ways through CC, BP and MF [36]. Kyoto Encyclopedia of Genes and Genomes (KEGG) database is used to determine advanced functions and biological correlation of a large number of genes [37]. KEGG pathways infer the relationships between proteins and the biological functional annotation of proteins. David 6.8 is used for GO and KEGG pathway analysis of the core antidepressant targets of BXHPD [38]. The corresponding data were obtained by using human genes as the range
and $P \leq 0.05$ as the screening value. The relevant biological processes or related pathways with the largest number of corresponding target points were selected to draw bar charts.

**Construction of a compound-target-pathway network**

The active compounds, core targets and signal pathways were utilized to construct a compound-target-pathway (C-T-P) network. In this C-T-P network, "nodes" of different colors represented the protein targets, compounds, signal pathways or diseases. "Edge" indicated the interaction of compound targets, compound pathways, or diseases. The networks were constructed by using Cytoscape v3.7.1.

**Results**

**Active compounds of BXHPD**

In the TCMSP database, 13 kinds of compounds from PR, 15 from PO, 5 from GR and 14 from MOC were included. After removed 5 duplicates from 49 compounds, 44 compounds were further studied (Table 1).

In the 44 compounds, 12 compounds had no protein targets. A total of 159 protein targets for 32 compounds were obtained from TCMSP. After inputting the 159 protein targets into the Uniprot, we found that 11 protein targets could not found the corresponding genes. The 11 protein targets above were removed. Adding up to 148 gene targets and 32 compounds were preserved for further researches.

**The construction of compounds-target network**

In order to identify the relationship between TCM and the corresponding targets [39], a compounds-target network was built to show the correspondence of active BXHPD compounds.

### Table 1. Basic information of active compounds of BXHPD.

| MOL ID  | MOL NAME                  | OB%  | DL | TARGETS NUMBER |
|---------|---------------------------|------|----|----------------|
| MOL00006 | luteolin                  | 36.16 | 0.25 | 55             |
| MOL002714 | baicalein                | 33.52 | 0.21 | 34             |
| MOL00358 | beta-sitosterol           | 36.91 | 0.75 | 34             |
| MOL00449 | Stigmasteryl              | 43.83 | 0.76 | 29             |
| MOL002670 | Cavidine                  | 35.64 | 0.81 | 26             |
| MOL005970 | Eucalyptol               | 60.62 | 0.32 | 24             |
| MOL002773 | beta-carotene            | 37.18 | 0.58 | 23             |
| MOL000296 | hederagenin              | 36.91 | 0.75 | 22             |
| MOL00519 | coniferin                 | 31.11 | 0.32 | 21             |
| MOL00492 | (+)-catechin              | 54.83 | 0.24 | 7              |
| MOL001749 | ZINC03860434             | 43.59 | 0.35 | 4              |
| MOL005980 | Neohesperidin            | 57.44 | 0.27 | 4              |
| MOL006957 | (3S,6S)-3-(benzy1)-6-(4-hydroxybenzyl)piperazine-2,5-quinone | 46.89 | 0.27 | 3              |
| MOL006129 | 6-methy1gingediacetate2  | 48.73 | 0.32 | 3              |
| MOL00953 | CLR                       | 37.87 | 0.68 | 3              |
| MOL001755 | 24-Ethylcholest-4-en-3-one | 36.08 | 0.76 | 2              |
| MOL005030 | gondoic acid             | 30.7  | 0.2  | 2              |
| MOL006936 | 10,13-eicosadienoic      | 39.99 | 0.2  | 2              |
| MOL003578 | Cycloartenol            | 38.69 | 0.78 | 2              |
| MOL006967 | beta-D-Ribofuranoside, xanthine-9 | 44.72 | 0.21 | 2              |

https://doi.org/10.1371/journal.pone.0239843.t001
and targets (Fig 2). The compounds with the most amount of targets contained luteolin (55), baicalein (34), beta-sitosterol (34) and stigmasterol (29).

**Acquisition of core targets**

From Gene Cards database, 8,959 genes were related to depression. After intersecting 148 potential active targets with 8,959 depression related genes, 121 potential drug target genes were obtained. The PPI network was built by STRING (Fig 3). The PPI network consisted of 120 nodes and 1476 edges. After the visual topological analysis by CytoNCA (an application in Cytoscape), 24 core targets were obtained (Table 2). Among the 24 core targets, ALB has the greatest degree (71), followed by FOS (65), IL6 (63) and EGFR (60).

**GO and KEGG pathways analysis for core genes**

GO enrichment analysis and KEGG pathways analysis were performed on the 23 target genes by David (Fig 4). Pathways with P-value<0.05 were considered as significant pathways.

GO enrichment analysis contains three broad categories: BP, CC and MF. BP terms mainly contained response to estradiol, response to drug, positive regulation of transcription, DNA-templated, positive regulation of smooth muscle cell proliferation and positive regulation of transcription from RNA polymerase II promoter. CC terms mainly contained cytosol,
membrane raft, protein complex, and extracellular space and nucleus. MF terms mainly contained identical protein binding, enzyme binding, transcription factor binding and protein binding. KEGG pathways mainly contained MAPK signaling pathway, PI3K-Akt signaling pathway, Oxytocin signaling pathway, ErbB signaling pathway and HIF-1 signaling pathway.

Table 2. Core targets of BXHPD.

| Gene symbol | Degree | Gene symbol | Degree |
|-------------|--------|-------------|--------|
| ALB         | 71     | CCND1       | 49     |
| FOS         | 65     | ERBB2       | 47     |
| IL6         | 63     | ESR1        | 47     |
| EGFR        | 60     | APP         | 45     |
| VEGFA       | 60     | CAT         | 44     |
| TNF         | 59     | BCL2L1      | 44     |
| MAPK1       | 57     | MMP2        | 43     |
| JUN         | 57     | CYCS        | 43     |
| CASP3       | 57     | CASP8       | 43     |
| MYC         | 55     | PPARG       | 42     |
| MMP9        | 54     | CTNNB1      | 41     |
| PTGS2       | 52     | AR          | 41     |

https://doi.org/10.1371/journal.pone.0239843.t002
KEGG enrichment analysis

KEGG Enrichment Analysis reveals the possible biological processes of pathway by analyzing biological processes, which unlocks the molecular roles of targets in the treatment of depression. There were more than 20 pathways associated with depression. In these pathways, MAPK signaling pathway (Fig 5A) and PI3K-Akt signaling pathway (Fig 5B) were most closely related to depression.

One of the MAPK signaling pathway: ERK, part of the MAPK pathway in the prefrontal cortex and hippocampal played an important role in antidepressant processing [40]. ERK activates Elk-1, Sapla and c-Myc through phosphorylation. Elk-1, Sapla and c-Myc combine to form SRF, SRF activates c-fos through DNA, c-fos produces proliferation differentiation function, via DNA activation. The PI3K-Akt signaling pathway was one of the important pathways of depression. GF activates RTK on cell membrane, RTK activates IRS1, IRS1 activates PI3K (Class IA), PI3K activates AKT through PIP3, AKT inhibits BAD by phosphorylation, BAD ultimately affects Cell survival by inhibiting Bcl-xL and Bcl-2.

Component-target-pathway network

Compound-Target-Pathway networks of BXHPD were shown in Fig 6. There were 9 compounds, 24 targets and 17 pathways. The nodes represent drug compounds, active components and targets. The edges represent their relationship. Through the network, we could find that some pathways had high enrichment in the network such as PI3k-Akt pathway, which suggested that these pathways may play a key role in therapeutic effects of BXHPD.
Identification of the significant pathways of BXHPD in the treatment of depression

**Fig 5. KEGG enrichment diagram.** (A) MAPK signaling pathway. (B) PI3K-AKT signaling pathway. Red asterisks represent core targets.

https://doi.org/10.1371/journal.pone.0239843.g005

**Fig 6. Compound-target-pathway networks.** Green nodes stand for chemical compounds in BXHPD; Red nodes stand for known target genes from chemical compounds and depression; Blue nodes stand for the main biological pathway; Red lines stand for the relationship between compounds and target genes; Brown lines stand for the relationship between target genes and biological pathway.

https://doi.org/10.1371/journal.pone.0239843.g006
Discussion

Through the screening of active compounds, Luteolin (53 targets), Baicalein (34 targets), Beta-sitosterol (34 targets), Stigmasterol (29 targets) and Cavidine (26 targets) might have primary effects for antidepressant in BXHPD. (1) As an active flavonoid derived from astragalus root, baicalein could alleviate the development of depressive symptoms by up-regulating the level of dopamine in the hippocampus and the level of BDNF [41]. Additionally, it stimulated the activity of Erks, a member of MAPK family [42], and inhibited the down-regulation of nuclear factor-kappa B (NF-κB) pathway [43, 44], such as IL-6 and TNF-α, to inhibit neuroinflammation and to protect nerves. (2) Luteolin was also a flavonoid from a variety of plants that prevented nerve cell death [45] and suppressed the levels of inflammatory factors such as IL-6 and TNF-α to reduce nerve damage [46]. Not only the activity of Acetylcholinesterase and antioxidant enzymes could be improved, but the formation of nitric oxide could be done by luteolin to achieve antioxidant and anti-inflammatory effects [16]. (3) Cavidine was an isoquinoline alkaloid from Corydalis impatiens, which was an anti-inflammatory substance that inhibited NF-κB pathway related pro-inflammatory substances such as IL-6 and TNF-α [47, 48]. Cavidine might be related to the suppression of inflammation about nerve. (4) Zhao et al. found that beta-sitosterol affected the content of dopamine and 5-HT, which might be a potential drug ingredient target [49]. (5) Stigmasterol was famous for the treatment of depression in TCM, which might regulate the level of nerve steroids to control depressive symptoms [50].

Our results showed that the important pathways of BXHPD mainly contained PI3k-Akt signaling pathway, MAPK signaling pathway, Oxytocin signaling pathway, ErbB signaling pathway and HIF-1 signaling pathway. These pathways are linked to the core genes chiefly including FOS, IL6, TNF-α, Bcl-2, c-Jun, ERK, and EGF gene in our research in the treatment of depression. Those results were supported by lots of studies. (1) PI3k-Akt pathway phosphorylates the downstream factor Forkhead box O3a and inhibits neurotoxic apoptosis conducted by Corticosterone (CORT), which is the effective antidepressant process [51, 52]. In addition, PI3k-Akt pathway controlled BDNF (such as IL-6, TNF-α) to reverse depression-like behavior in a neurotrophic and neuroprotective way [53, 54]. PI3k-Akt pathway was related to neuroplasticity and could achieve anti-depression effect by enhancing the formation of synapses and the extension of axon dendrites [55, 56]. PI3k-Akt pathway also adjusted downstream molecular to achieve antidepressant effects, such as Bcl-2 [57] and c-Jun [58], both of which appeared in core targets of our research (Table 2). (2) MAPK pathway was a well-known pathway related to neuronal proliferation and differentiation among depression [59]. ERK, an important gene of MAPK pathway in the prefrontal cortex and hippocampal played an important role in antidepressant processing, such as increasing the expression of BDNF [40] and promoting growth-related microtubulin in the hippocampus [60]. Patel et al. showed that MAPK pathway could promote the formation of nitric oxide (NO), thus improving neuroplasticity and inhibiting apoptosis (Fig 4A) [61]. (3) Oxytocin signaling pathway affected nerve excitation transmission [62] through the modulation of 5-HT [63] and interaction with gamma-aminobutyric acid [64]. Wang et al. found that Oxytocin signaling pathway could reverse depression by down-regulating CORT and by affecting the HPA axis [65]. Oxytocin improved depression symptom by down-regulating c-fos protein and by inhibiting the ERK pathway as well [66]. (4) The ErbB pathway was also associated with depression by adjusting neuregulin and affecting downstream Akt and ERK signaling pathways [67, 68]. EGF and VEGF were parts of the ErbB family and were associated with nerve growth and nutrition [69]. (5) HIF-1 signaling pathway was also relevant to depression in our study. In the pathway, Hypoxia-inducible factor (HIF-1) was a main regulator in hypoxia response and played a role in energy supply in depression through neurotransmitter transmission [50]. (6) Other pathways in our result (Fig
were indirectly linked to depression, in terms of nerve growth and inflammation, such as FoxO signaling pathway [70, 71], Jak-STAT signaling pathway [72, 73], prolactin signaling pathway [74, 75] and TGF-beta signaling pathway [76, 77].

Our research had some limitations. First, it was uncertain whether Chinese medicine was absorbed in the intestinal tract as the active compounds in our research. Second, core genes of specific pathways related to downstream products were not objectively presented in our results. Third, whether the role of pathways in our study was up-regulated or down-regulated was unclear. Fourth, our study used the network construction method to speculate the potential anti-depression targets of BXHPD, which still needs to be further verified by biological experiments.

Conclusions

BXHPD can effectively alleviate the symptoms of depression through the molecular mechanisms predicted by NP. NP analysis demonstrates that there were multi-scale curative activity in regulating depression related biological processes. Pathway enrichment analysis indicated that MAPK signaling pathway, ErbB pathway, HIF-1 pathway and PI3K-Akt pathway were significant pathways in depression. They mainly were involved in promoting nerve growth and nutrition and alleviating neuroinflammatory conditions. This study provided some potential ways for modern medicine in the treatment of depression.

Supporting information

S1 File.

(RAR)

Acknowledgments

All the authors of the manuscript are immensely grateful to their respective universities and institutes for their technical assistance and valuable support in the completion of this research project.

Author Contributions

Data curation: Zi-ying Chen, Dan-feng Xie, Zhi-yuan Liu, Yong-qi Zhong, Jing-yan Zeng.

Writing – original draft: Zi-ying Chen, Dan-feng Xie, Zhi-yuan Liu, Yong-qi Zhong, Jing-yan Zeng.

Writing – review & editing: Zheng Chen, Xin-lin Chen.

References

1. Cui RJCN. Editorial (Thematic Selection: A Systematic Review of Depression). Curr Neuropharmacol. 2015; 13(4): 480. https://doi.org/10.2174/1570159x1304150831123535 PMID: 26412067
2. Yang L, Zhao Y, Wang Y, Liu L, Zhang X, Li B, et al. The Effects of Psychological Stress on Depression. Curr Neuropharmacol. 2015; 13(4):494–504. https://doi.org/10.2174/1570159x1304150831150507 PMID: 26412069
3. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. Journal of psychiatric research. 2007; 41(3–4):189–206. https://doi.org/10.1016/j.jpsychires.2006.05.008 PMID: 16870212
4. Wang SM, Han C, Bahk WM, Lee SJ, Patkar AA, Masand PS, et al. Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review. Chonnam Med J. 2018; 54(2):101–12. https://doi.org/10.4068/cmj.2018.54.2.101 PMID: 29854675
Identification of the significant pathways of BXHPD in the treatment of depression

5. Knautd PR, Connor KM, Weisler RH, Churchill LE, Davidson JR. Alternative therapy use by psychiatric outpatients. The Journal of nervous and mental disease. 1999; 187(11):692–5. https://doi.org/10.1097/00005053-199911000-00007 PMID: 10579598

6. Kessler RC, Soukup J, Davis RB, Foster DF, Wilkey SA, Van Rompay MI, et al. The use of complementary and alternative therapies to treat anxiety and depression in the United States. The American journal of psychiatry. 2001; 158(2):289–94. https://doi.org/10.1176/appi.ajp.158.2.289 PMID: 11156813

7. Butler L, Pilkinson K. Chinese herbal medicine and depression: the research evidence. Evid Based Complement Alternat Med. 2013; 739716. https://doi.org/10.1155/2013/739716 PMID: 23476701

8. Yeung WF, Chung KF, Ng KY, Yu YM, Ziea ET, Ng BF. A systematic review on the efficacy, safety and types of Chinese herbal medicine for depression. Journal of psychiatric research. 2014; 57:165–75. https://doi.org/10.1016/j.jpsychores.2014.05.016 PMID: 24974002

9. Feng DD, Tang T, Lin XP, Yang ZY, Yang S, Xia ZA, et al. Nine traditional Chinese herbal formulas for the treatment of depression: an ethnopharmacological, phytochemistry, and pharmacology review. Neuropsychiatr Dis Treat. 2016; 12:2387–402. https://doi.org/10.2147/NDT.S114560 PMID: 27703556

10. Zheng Q, Tian CL, Liu Xs. Meta Analysis of the Clinical Efficacy of Banxia Houpu Decoction in the Treatment of Depression. world latest medicine information. 2018;43.

11. van West D, Maes M. Activation of the inflammatory response system: A new look at the etiopathogenesis of major depression. Neuro endocrinology letters. 1999; 20(1–2):11–7 PMID: 11473226

12. Delgado PL. Depression: the case for a monoamine deficiency. The Journal of clinical psychiatry. 2000; 61 Suppl 6:7–11 PMID: 10775018

13. Catalan R, Gallart JM, Castellanos JM, Galard R. Plasma corticotro pin-releasin g factor in depressive disorders. Biological psychiatry. 1998; 44(1):15–20. https://doi.org/10.1016/s0006-3223(97)00539-8 PMID: 9646879

14. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biological psychiatry. 2006; 59(12):1116–27. https://doi.org/10.1016/j.biopsych.2006.02.013 PMID: 16631126

15. Zhang R, Guo L, Ji Z, Li X, Zhang C, Ma Z, et al. Radix Scutellariae Attenuat es CUMS-I nduced Depres- sion. Neuroendocrinology. 2013; 61 Suppl 6:7–11 PMID: 10775018

16. Kalariya M, Parmar S, Sheth NJPB. Neuropharmacological activity of hydroalcoholic extract of leaves of Colocasia esculenta. 2010; 48(11):1207–12

17. Yi LT, Zhang L, Cheng CH, Zhang WY, Tan WZ. Behavioral and biochemical studies on chronic mild stress models in rats treated with a Chinese traditional prescription Banxia-houpu decoction. Life sciences. 2003; 74(1):55–73. https://doi.org/10.1016/j.lfs.2003.06.030 PMID: 14575813

18. Li JM, Kong LD, Wang YM, Cheng CH, Zhang WY, Tan WZ. Behavioral and biochemical studies on chronic mild stress models in rats treated with a Chinese traditional prescription Banxia-houpu decoction. Life sciences. 2003; 74(1):55–73. https://doi.org/10.1016/j.lfs.2003.06.030 PMID: 14575813

19. Ma Z, Ji W, Qu R, Wang M, Yang W, Zhan Z, et al. Metabonomic study on the antidepressant-like effects of banxia hooupu decoction and its action mechanism. Evidence-based complementary and alternative medicine: eCAM. 2013; 2013:213793. https://doi.org/10.1155/2013/213793 PMID: 24250712

20. Zhao F, Guochun L, Yang Y, Shi L, Xu L, Yin L. A network pharmacology approach to determine active ingredients and rationality of herb combinations of Modified-Simiaowan for treatment of gout. Journal of ethnopharmacology. 2015; 168:1–16. https://doi.org/10.1016/j.jep.2015.03.035 PMID: 25824593

21. Fang J, Wang L, Wu T, Yang C, Gao L, Cai H, et al. Network pharmacology-based study on the mechanism of action for herbal medicines in Alzheimer treatment. Journal of ethnopharmacology. 2017; 196:281–92. https://doi.org/10.1016/j.jep.2016.11.034 PMID: 27888133

22. Li S, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. Chinese journal of natural medicines. 2013; 11(2):110–20. https://doi.org/10.1016/S1875-5364(13)60037-0 PMID: 23787177

23. Ru J, Li P, Wang J, Zhou W, Li B, Huang C, et al. TC MSP: a database of systems pharmacology for drug discovery from herbal medicines. J Cheminform. 2014; 6:13. https://doi.org/10.1186/1758-2946-6-13 PMID: 24735618

24. Tibbitts J, Canter D, Graff R, Smith A, Khawli LA. Key factors influencing ADME properties of therapeutic proteins: A need for ADME characterization in drug discovery and development. Mabs. 2016; 8 (2):229–45. https://doi.org/10.1080/19420862.2015.115937 PMID: 26636901
26. Xu X, Zhang W, Huang C, Li Y, Yu H, Wang X, et al. A novel chemometric method for the prediction of human oral bioavailability. International journal of molecular sciences. 2012; 13(6):6964–82. https://doi.org/10.3390/ijms13066964 PMID: 22837674

27. Yamanishi Y, Kotera M, Kanehisa M, Goto S. Drug-target interaction prediction from chemical, genomic and pharmacological data in an integrated framework. Bioinformatics (Oxford, England). 2010; 26(12):i246–54. https://doi.org/10.1093/bioinformatics/btq176 PMID: 20529913

28. Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic acids research. 2006; 34(Database issue):D668–72. https://doi.org/10.1093/nar/gkj067 PMID: 16381995

29. Schenone M, Dančič V, Wagner BK, Clemons PA. Target identification and mechanism of action in chemical biology and drug discovery. Nat Chem Biol. 2013; 9(4):232–40. https://doi.org/10.1038/nchembio.1199 PMID: 23508189

30. Marunaka Y, Marunaka R, Sun H, Yamamoto T, Kanamura N, Inui T, et al. Actions of Quercetin, a Polyphenol, on Blood Pressure. Molecules. 2017; 22(2). https://doi.org/10.3390/molecules22020209 PMID: 28146071

31. 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 Bioinformatics. 2016; 54:1.30.1–1.3. https://doi.org/10.1002/cpbi.5 PMID: 27322403

32. von Mering C, Jensen LJ, Snel B, Hooper SD, Krupp M, Fogliermi M, et al. STRING: known and predicted protein-protein associations, integrated and transferred across organisms. Nucleic Acids Res. 2005; 33(Database issue):D433–7. https://doi.org/10.1093/nar/gki005 PMID: 15608232

33. 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(11):2498–504. https://doi.org/10.1101/gr.1239303 PMID: 14597658

34. Guo Q, Zhong M, Xu H, Mao X, Zhang Y, Lin N. A Systems Biology Perspective on the Molecular Mechanisms Underlying the Therapeutic Effects of Buyang Huanwu Decoction on Ischemic Stroke. Rejuvenation research. 2015; 18(4):313–25. https://doi.org/10.1089/rej.2014.1635 PMID: 25687901

35. The Gene Ontology C. The Gene Ontology Resource: 20 years and still GOing strong. Nucleic acids research. 2019; 47(D1):D330–D8. https://doi.org/10.1093/nar/gkx1055 PMID: 30953331

36. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nature genetics. 2000; 25(1):25–9. https://doi.org/10.1038/75556 PMID: 10802651

37. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. Nucleic acids research. 2000; 28(1):27–30. https://doi.org/10.1093/nar/28.1.27 PMID: 10592173

38. Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nature protocols. 2009; 4(1):44–57. https://doi.org/10.1038/nprot.2008.211 PMID: 19131956

39. Li S, Zhang ZQ, Wu LJ, Zhang XG, Li YD, Wang YY. Understanding ZHENG in traditional Chinese medicine in the context of neuro-endocrine-immune network. IET systems biology. 2007; 1(1):51–60 https://doi.org/10.1049/iet-syb:20060032 PMID: 1730429

40. Wang JQ, Mao L. The ERK Pathway: Molecular Mechanisms and Treatment of Depression. Mol Neurobiol. 2019; 56(9):6197–205. https://doi.org/10.1007/s12035-019-1524-3 PMID: 30737641

41. Lee B, Sur B, Park J, Kim SH, Kwon S, Yeom M, et al. Chronic administration of baicalein decreases depression-like behavior induced by repeated restraint stress in rats. The Korean journal of physiology & pharmacology: official journal of the Korean Physiological Society and the Korean Society of Pharmacology. 2013; 17(5):393–403. https://doi.org/10.4196/kjpp.2013.17.5.393 PMID: 24227939

42. Xiong Z, Jiang B, Wu PF, Tian J, Shi LL, Gu J, et al. Antidepressant effects of a plant-derived flavonoid baicalein involving extracellular signal-regulated kinases cascade. Biological & pharmaceutical bulletin. 2011; 34(2):253–9. https://doi.org/10.1248/bpb.34.253 PMID: 21415537

43. Du HX, Chen XG, Zhang L, Liu Y, Zhan CS, Chen J, et al. Microglial activation and neurobiological alterations in experimental autoimmune encephalitis-induced depressive-like behavior in mice. Neuropsychiatry. 2019; 15:2231–45. https://doi.org/10.2147/NDT.S211288 PMID: 31496706

44. Chen B, Luo M, Liang J, Zhang C, Gao C, Wang J, et al. Surface modification of PGP for a neuropeptide nanocarrier co-vehicle to enhance the antidepressant effect of baicalein. Acta pharmacologica Sinica B. 2018; 8(1):64–73. https://doi.org/10.1016/j.apsb.2017.11.012 PMID: 29872623

45. Ishisaka M, Kakefu K, Yamauchi M, Tsuruma K, Shimazawa M, Tsutara A, et al. Luteolin shows an antidepressant-like effect via suppressing endoplasmic reticulum stress. Biological & pharmaceutical bulletin. 2011; 34(9):1481–6. https://doi.org/10.1248/bpb.34.1481 PMID: 21881237
Identification of the significant pathways of BXHPD in the treatment of depression

46. Gadotti VM, Andonegui G, Zhang Z, M’Dahoma S, Baggio CH, Chen L, et al. Neuroimmune Responses Mediate Depression-Related Behaviors following Acute Colitis. iScience. 2019; 16:12–21. https://doi.org/10.1016/j.isci.2019.05.012 PMID: 31146128

47. Niu X, Liu F, Li W, Zhi W, Zhang H, Wang X, et al. Cavidine Ameliorates Lipopolysaccharide-Induced Acute Lung Injury via NF-kappaB Signaling Pathway in vivo and in vitro. Inflammation. 2017; 40 (4):1111–22. https://doi.org/10.1007/s10753-017-0553-1 PMID: 28365871

48. Niu X, Zhang H, Li W, Wang Y, Mu Q, Wang X, et al. Protective effect of cavidine on acetic acid-induced murine colitis via regulating antioxidant, cytokine profile and NF-kappaB signal transduction pathways. Chemico-biological interactions. 2015; 239:34–45. https://doi.org/10.1016/j.cbi.2015.06.026 PMID: 26102009

49. Zhao D, Zheng L, Qi L, Wang S, Guan L, Xia Y, et al. Structural Features and Potent Antidepressant Effects of Total Sterols and beta-sitosterol Extracted from Sargassum horneri. Marine drugs. 2016; 14 (7). https://doi.org/10.3390/md14070123 PMID: 27367705

50. Li J, Zhang SX, Wang W, Cheng K, Guo H, Rao CL, et al. Potential antidepressant and resilience mechanism revealed by metabolomic study on peripheral blood mononuclear cells of stress resilient rats. Behavioural brain research. 2017; 320:12–20. https://doi.org/10.1016/j.bbr.2016.11.035 PMID: 27880890

51. Zeng B, Li Y, Niu B, Wang X, Cheng Y, Zhou Z, et al. Involvement of PI3K/Akt/FoxO3a and PKA/CREB Signaling Pathways in the Protective Effect of Fluoxetine Against Corticosterone-Induced Cytotoxicity in PC12 Cells. Journal of molecular neuroscience: MN. 2016; 59(4):567–78. https://doi.org/10.1007/s12031-016-0779-y PMID: 27412469

52. Kuang WH, Dong QZ, Tian LT, Li J. IGF-1 defends against chronic-stress induced depression in rat models of chronic unpredictable mild stress through the PI3K/Akt/FoxO3a pathway. The Kaohsiung journal of medical sciences. 2018; 34(7):370–6. https://doi.org/10.1016/j.kjms.2018.02.004 PMID: 30063009

53. Caviedes A, Lafourcade C, Soto C, Wyneken U. BDNF/NF-kappaB Signaling in the Neurobiology of Depression. Current pharmaceutical design. 2017; 23(21):3154–63. https://doi.org/10.2174/1381612823666170111141915 PMID: 28078988

54. Ye Y, Yao S, Wang R, Fang Z, Zhong K, Nie L, et al. PI3K/Akt/NF-kappaB signaling pathway regulates behaviors in adolescent female rats following with neonatal maternal deprivation and chronic mild stress. Behavioural brain research. 2019; 362:199–207. https://doi.org/10.1016/j.bbr.2019.01.008 PMID: 30630016

55. Wu Z, Wang G, Wei Y, Xiao L, Wang H. PI3K/AKT/GSK3beta/CRMP-2-mediated neuroplasticity in depression induced by stress. Neuroreport. 2018; 29(15):1256–63. https://doi.org/10.1097/WNR.0000000000001096 PMID: 30113922

56. Dalmagro AP, Camargo A, Severo Rodrigues AL, Zeni ALB. Involvement of PI3K/Akt/GSK-3beta signaling pathway in the antidepressant-like and neuroprotective effects of Morus nigra and its major phenolic, syringic acid. Chemico-biological interactions. 2019; 314:108843. https://doi.org/10.1016/j.cbi.2019.03.012 PMID: 31586550

57. Luo L, Liu XL, Li J, Mu RH, Liu Q, Yi LT, et al. Macranthol promotes hippocampal neuronal proliferation in mice via BDNF-TrkB-PI3K/Akt signaling pathway. European journal of pharmacology. 2015; 762:357–63. https://doi.org/10.1016/j.ejphar.2015.05.036 PMID: 26004527

58. Radin DP, Patel P. A current perspective on the oncopreventive and oncolytic properties of selective serotonin reuptake inhibitors. Biomedicine & pharmacotherapy = Biomedicine & pharmacotherapie. 2017; 87:636–9. https://doi.org/10.1016/j.biopha.2017.01.024 PMID: 28088112

59. Duric V, Banasr M, Licznerski P, Schmidt HD, Stockmeier CA, Simen AA, et al. A negative regulator of MAP kinase causes depressive behavior. Nature medicine. 2010; 16(11):1328–32. https://doi.org/10.1038/nm.2219 PMID: 20953200

60. Yang X, Guo Z, Lu J, Zhao B, Fei Y, Li J, et al. The Role of MAPK and Dopaminergic Synapse Signaling Pathways in Antidepressant Effect of Electroacupuncture Pretreatment in Chronic Restraint Stress Rats. Evidence-based complementary and alternative medicine: eCAM. 2017; 2017:2357653. https://doi.org/10.1155/2017/2357653 PMID: 29234374

61. Patel NJ, Chen MJ, Russo-Neustadt AA. Norepinephrine and nitric oxide promote cell survival signaling in hippocampal neurons. European journal of pharmacology. 2010; 633(1–3):1–9. https://doi.org/10.1016/j.ejphar.2010.01.012 PMID: 20149790

62. Xiao L, Priest MF, Kozorovitsky Y. Oxytocin functions as a spatiotemporal filter for excitatory synaptic inputs to VTA dopamine neurons. eLife. 2018;7. https://doi.org/10.7554/eLife.33892 PMID: 29676731

63. Mottolese R, Redoute J, Costes N, Le Bars D, Sirigu A. Switching brain serotonin with oxytocin. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111(23):8637–42. https://doi.org/10.1073/pnas.1319810111 PMID: 24912179
64. Lonstein JS, Maguire J, Meinlschmidt G, Neumann ID. Emotion and mood adaptations in the peripartum female: complementary contributions of GABA and oxytocin. Journal of neuroendocrinology. 2014; 26 (10):649–64. https://doi.org/10.1111/jne.12188 PMID: 25074620

65. Wang T, Shi C, Li X, Zhang P, Liu B, Wang H, et al. Injection of oxytocin into paraventricular nucleus reverses depressive-like behaviors in the postpartum depression rat model. Behavioural brain research. 2018; 336:236–43. https://doi.org/10.1016/j.bbr.2017.09.012 PMID: 28889022

66. Wang Y, Zhao S, Wu Z, Feng Y, Zhao C, Zhang C. Oxytocin in the regulation of social behaviors in medial amygdala-lesioned mice via the inhibition of the extracellular signal-regulated kinase signaling pathway. Clinical and experimental pharmacology & physiology. 2015; 42(5):465–74. https://doi.org/10.1111/j.1440-1681.2013.12378 PMID: 25707920

67. Wang Y, Zhao S, Wu Z, Feng Y, Zhao C, Zhang C. Oxytocin in the regulation of social behaviors in medial amygdala-lesioned mice via the inhibition of the extracellular signal-regulated kinase signaling pathway. Clinical and experimental pharmacology & physiology. 2015; 42(5):465–74. https://doi.org/10.1111/j.1440-1681.2013.12378 PMID: 25707920

68. Zhou L, Fisher ML, Cole RD, Gould TJ, Parikh V, Orbinski P, et al. Neuregulin 3 Signaling Mediates Nicotine-Dependent Synaptic Plasticity in the Orbitofrontal Cortex and Cognition. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2018; 43(6):1343–54. https://doi.org/10.1038/npp.2017.278 PMID: 29114105

69. Carboni L, Marchetti L, Lauria M, Gass P, Vollmayr B, Redfern A, et al. Cross-species evidence from human and rat brain transcriptome for growth factor signaling pathway dysregulation in major depression. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2018; 43(6):1343–54. https://doi.org/10.1038/npp.2017.278 PMID: 29114105

70. Qiao J, Sun Y, Wu J, Wang L. Investigation of the underlying mechanism of ketamine for antidepressant effects in treatment-refractory affective disorders via molecular profile analysis. Experimental and therapeutic medicine. 2019; 18(1):580–8. https://doi.org/10.3892/etm.2019.7633 PMID: 31281448

71. Poitier A, Yang S, Zmijewska AA, van Groen T, Paik JH, Depinho RA, et al. Forkhead box class O transcription factors in brain: regulation and behavioral manifestation. Biological psychiatry. 2009; 65 (2):150–9. https://doi.org/10.1016/j.biopsych.2008.08.005 PMID: 18923877

72. Shariq AS, Brietzke E, Rosenblat JD, Pan Z, Rong C, Raggauet RM, et al. Therapeutic potential of JAK/STAT pathway modulation in mood disorders. Reviews in the neurosciences. 2018; 30(1):1–7. https://doi.org/10.1515/revneuro-2018-0027 PMID: 29992157

73. Mcgregor G, Irving AJ, Harvey J. Canonical JAK-STAT signaling is pivotal for long-term depression at adult hippocampal temporoammonic-CA1 synapses. FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 2017; 31(8):3449–66. https://doi.org/10.1096/fj.201601293RR PMID: 28461339

74. Tian RH, Bai Y, Li JY, Guo KM. Reducing PRLR expression and JAK2 activity results in an increase in BDNF expression and inhibits the apoptosis of CA3 hippocampal neurons in a chronic mild stress model of depression. Brain research. 2019; 1725:146472. https://doi.org/10.1016/j.brainres.2019.146472 PMID: 31545956

75. Gratacos M, Costas J, de Cid R, Bayes M, Gonzalez JR, Baca-Garcia E, et al. Identification of new putative susceptibility genes for several psychiatric disorders by association analysis of regulatory and non-synonymous SNPs of 306 genes involved in neurotransmission and neurodevelopment. American journal of medical genetics Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics. 2009; 150b(6):808–16. https://doi.org/10.1002/ajmg.b.30902 PMID: 19086053

76. Caraci F, Spampinato SF, Morgese MG, Tascedda F, Salluzzo MG, Giambiritone MC, et al. Neurobiological links between depression and AD: The role of TGF-bet1 signaling as a new pharmacological target. Pharmacological research. 2018; 130:374–84. https://doi.org/10.1016/j.phrs.2018.02.007 PMID: 29438781

77. Pacher P, Sharma K, Csordas G, Zhu Y, Hajnoczky G. Uncoupling of ER-mitochondrial calcium communication by transforming growth factor-beta. American journal of physiology Renal physiology. 2008; 295(5):F1303–12. https://doi.org/10.1152/ajprenal.09343.2008 PMID: 18653477