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The potential of Chinese herbal medicines in treating anxiety disorders

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Author contributions

Jiaqi Xie conceived the review and wrote the initial manuscript. Jianmei Huang and Can Wang proofread and edited the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

DISS, 3, 6'-disinapoylsucrose; TCM, traditional Chinese medicine; CUMS, chronic unpredictable mild stress; 5-HT, 5-hydroxytryptamine; SA, sinapic acid; TFSA, tenuifoliside A; TMCA, 3,4,5-trimethoxycinnamic acid.

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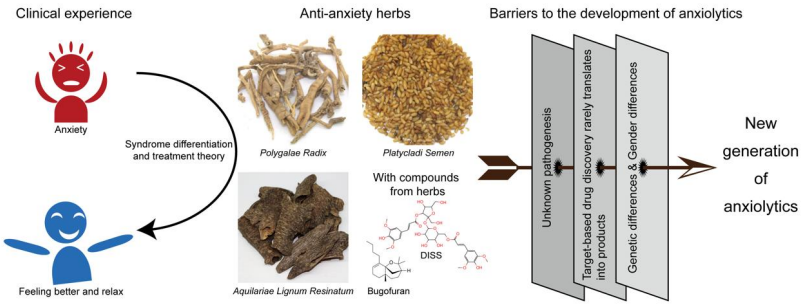
Abstract

In recent years, there has not been much progress in developing anxiolytic drugs. Amongst the barriers are the lack of clarity on the pathogenesis of anxiety disorders, low product conversion rates for developing drugs targeting the receptors, and species variability. Some scientists have focused on natural medicines, especially herbal medicines in traditional Chinese medicine. New drugs with excellent anxiolytic activity are hoped to be found in herbal medicines with anxiolytic effects. This mini-review summarised three Chinese herbal medicines with anxiolytic effects and anxiolytic herbal formulas used in the traditional Chinese medicine clinic. Several key issues that block the development of new anxiolytic drugs are also discussed. We hope to provide some ideas for researching and developing new anxiolytic drugs and studying anxiolytic components in traditional Chinese medicine.

Keywords: traditional Chinese medicine; anxiolytic drugs; Chinese herbal medicines



Background

The main symptom of the anxiety disorder is uncontrollable worry, which is felt by the sufferer most of the time for at least six months. Epidemiological studies have shown that the lifetime prevalence of generalized anxiety disorder was 5.7% and the anxiety disorder is persistent and can cause physical symptoms in addition to mental distress [1, 2]. Unfortunately, medications for anxiety disorder have made little progress for a long time [3]. The commonly used anxiolytics, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are less effective in the early stages of administration [4, 5], and benzodiazepines often have withdrawal syndromes [6], which are unwelcome in the treatment process. Taking anxiolytics will also increase the financial burden on patients, especially in middle/low-income countries [7]. There are numerous unknown active compounds in natural medicines. In this review, we focus on three Chinese herbal medicines with evidence of anxiolytic effects, which have been focused on their cognitive impairment-relieving or sedative-hypnotic effects in previous studies. Our previous studies have shown that *Polygalae Radix* and *Platycladi Semen* have anxiolytic effects, with the main anxiolytic active substance in *Polygalae Radix* being 3, 6'-disinapoylsucrose (DISS), and the main active substance in *Platycladi Semen* possibly being a constituent of the fatty oils, but further studies are needed. A component of *Aquilariae Lignum Resinatum* has been structurally modified for clinical trials as a new anxiolytic drug. Some Chinese herbal medicines were used as adjunctive treatments for anxiety disorders in traditional Chinese medicine (TCM) clinics, but there has been little research on their anxiolytic mechanisms. Yet, there are still many Chinese herbal medicines with anxiolytic activity which have not been deeply developed in its active ingredients and mechanisms. The strategy for new drugs development in TCM is usually based on their clinical efficacy (phenotype-based strategy), which is less efficient but has a higher success rate. We therefore believe that certain components of Chinese herbal medicines could be the source of a new generation of anxiolytics.

Herbal medicines with anxiolytic activity: an example of three herbal medicines

Polygalae Radix

Polygalae Radix is frequently used in TCM for the treatment of mood and cognitive disorders and has a long history of application. Substances with psychopharmacological activity in *Polygalae Radix* are mainly saponins, oligosaccharides, and small-molecule phenolic acids. In previous studies, DISS, the main constituent of *Polygalae Radix*, was shown to have antidepressant and neuroprotective pharmacological activities, and its mechanism of action was related to the regulation of neurotransmitter levels and the endocrine system. DISS significantly reduced the serum levels of corticosterone, corticotropin-releasing hormone, and adrenocorticotropic hormone in chronic unpredictable mild stress (CUMS) rats, while increasing the mRNA expression levels of glucocorticoid and salocorticoid receptors [8], suggesting that DISS may be psychoactive by modulating the hypothalamic-pituitary-adrenal axis in animals. Another study showed that DISS enhanced 5-hydroxytryptophan (5-HT)-induced head tossing behavior and antagonized apomorphine-induced decrease in body temperature in mice [9], the former suggesting that DISS may increase 5-HT levels, and the latter suggesting that DISS may affect central norepinephrine reuptake and/or on norepinephrine transmission, which indicates that DISS may have anxiolytic-like behavioral activity. Besides, DISS can increase the expression of neural cell adhesion molecule-L1, cyclic-adenosine monophosphate response binding protein, and brain-derived neurotrophic factor at both mRNA and protein levels in the hippocampus of CUMS rats [10]. These three norepinephrines regulate the plasticity genes and neurotrophic factors involved in synaptic plasticity and neurite growth, and the increased expression may be one of the molecular and cellular mechanisms of DISS. We also demonstrated in earlier studies that DISS alleviates anxiety-like behavior in mice caused by the elevated plus maze [11]. However, none of these studies indicated the anti-anxiety mechanism of DISS. The metabolite sinapic acid (SA) of DISS has various biological activities such as anti-inflammatory [12, 13], antioxidant [14, 15], improvement of cognitive function [16, 17], and neuroprotection [18, 19]. Yoon found that 4 mg/kg of SA acted as an agonist at specific receptors and mediated anxiolytic effects through activation of gamma-aminobutyric acid receptors and potentiator chloride currents [20]. In addition to DISS and SA, polygalae total saponins [21], sibiricose A5, tenuifoliside A (TFSA), and 3,4,5-trimethoxycinnamic acid (TMCA, a metabolite of TFSA) also have anxiolytic activity. Polygalae total saponins could inhibit the reuptake of three monoamine neurotransmitters in vitro and could increase 5-HT, dopamine and norepinephrine contents in the rat prefrontal cortex [22]. TFSA could increase 5-HT levels and brain-derived neurotrophic factor content [23], and sibiricose A5 could inhibit Ca^{2+} release and regulate neurotransmitter release [24]. The mechanisms of TMCA are similar to SA, activating gamma-aminobutyric acid receptors and enhancing chloride currents [25]. However, polygalae total saponins is considered to have gastrointestinal toxicity [26], the levels of TFSA and sibiricose A5 are low, and there are fewer studies on TMCA.

Platycladi Semen

Platycladi Semen was recorded as 'Bai Zi Ren (in Chinese)' in *Shennong's Classic of Materia Medica* (Shen Nong, 200–250 C.E.) (Chinese Medicine Formulae Images Database, Hong Kong Baptist University, 2012) and was used for more than 2000 years in China to treat insomnia and mood disorders. TCM practitioner believes the Bai Zi Ren can treat palpitations, calm the five organs, benefit the Qi (Qi refers to the basic substance that constitutes the human body and maintains life activities, and is the unity of substance and function), and remove dampness and paralysis. Baizi Yangxin pills has been used clinically with some efficacy in the treatment of generalized anxiety. The anti-depression-like effect of *Platycladi Semen* in CUMS mice may be achieved by inhibiting monoamine oxidase and increasing the norepinephrines [27, 28]. *Platycladi Semen* extract has also been shown to enhance cognitive performance, modulate amyloid β aggregation [29, 30], and reduce glutamate-induced neurotoxicity and neuroinflammation [31, 32]. Our study demonstrated that the aqueous extract of *Platycladi Semen* and *Platycladi Semen* oil have anxiolytic activity [33], but their specific active components and mechanisms of action need further investigation.

Aquilariae Lignum Resinatum

Aquilariae Lignum Resinatum is a resinous wood of the family agarwood or Aquilaria. Traditional Chinese medicine believes that Agarwood has the effect of relieving Qi and can be used to treat gastrointestinal diseases and cardiovascular diseases. Chinese medicine believes that the abnormal functioning of Qi can lead to mood disorders, so regulating the functioning of Qi can alleviate mood-related illnesses. Clinical studies have found that the volatile oils in *Aquilariae Lignum Resinatum* have anxiolytic and hypnotic effects, and some proprietary Chinese herbal preparations containing *Aquilariae Lignum Resinatum* have been proven to have the same effects [34]. The α-Agarofuran in *Aquilariae Lignum Resinatum* has been structurally modified to exhibit favorable anxiolytic effects and is now in clinical trials as an innovative anti-anxiety drug. The TCM formula containing *Aquilariae Lignum Resinatum* was able to reduce anxiety-like behaviors in CUMS mice, and this effect may be produced by modulating the hypothalamic-pituitary-adrenal axis, increasing the content of brain-derived neurotrophic factor and related proteins, as well as inhibiting apoptosis (Figure 1) [35].

Ingredients in anti-anxiety herbs show potential for development

DISS and SA in *Polygalae Radix* and α-Agarofuran in *Aquilariae Lignum Resinatum* have shown good anxiolytic efficacy, while no serious

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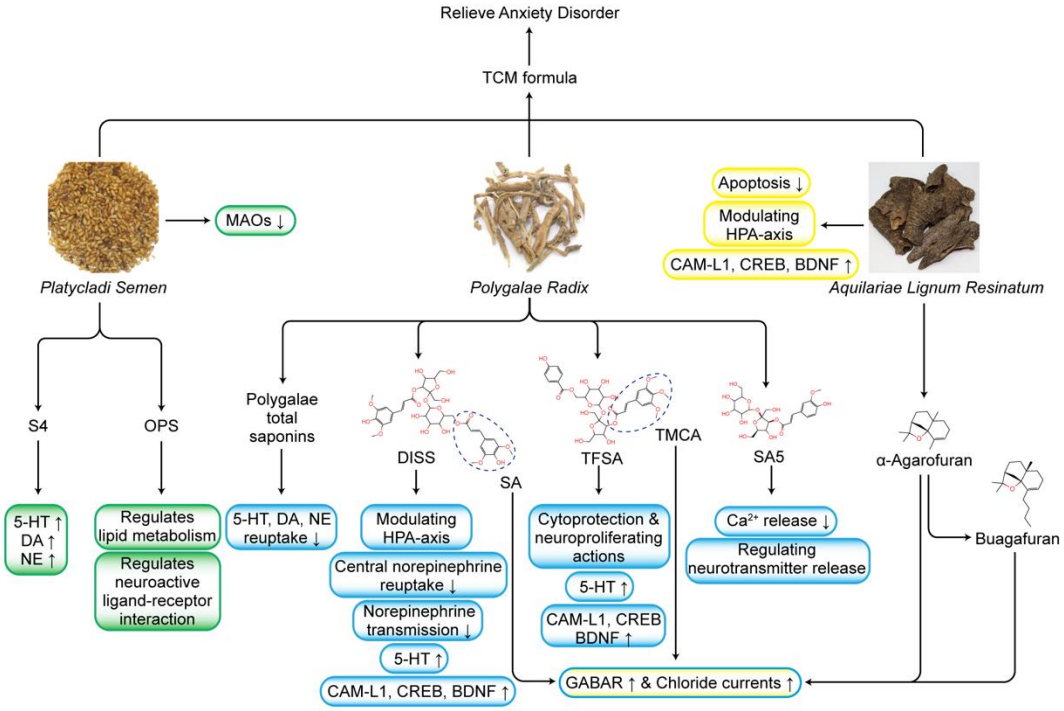

Figure 1 Mechanisms of the main anxiolytic active substances in *Polygalae Radix*, *Platycladi Semen* and *Aquilariae Lignum Resinatum*. TCM, traditional Chinese medicine; MAOs, monoamine oxidase; OPS, oil of Platycladi Semen; 5-HT, 5-hydroxytryptamine; DA, dopamine; NE, norepinephrine; DISS, 3, 6'-disinapoylsucrose; HPA-axis, hypothalamic-pituitary-adrenal axis; CAM-L1, neural cell adhesion molecule L1; CREB, cyclic-AMP response binding protein; BDNF, brain-derived neurotrophic factor; SA, sinapic acid; GABAR, gamma-aminobutyric acid receptors; TFSA, tenuifoliside A; TMCA, 3,4,5-trimethoxycinnamic acid; SA5, sibiricose A5.

adverse effects have been detected yet, suggesting that these components are promising for development. Through structural modification, α-Agarofuran-based bugofuran has completed phase II clinical trials. Bugofuran significantly alleviated anxiety-like behaviors, reduced adrenocorticotrophic hormone levels and increased brain 5-HT levels in rats and mice after oral administration [36]. It has entered phase III clinical trials and is expected to become an anxiolytic chemical drug of traditional Chinese medicine origin.

However, we also found that there are still many anxiolytic Chinese herbal medicines for which the pharmacological substances are not yet known. Researchers used liquid chromatography-mass spectrometry to identify components in these herbal medicines and related herbal formulas, but it is difficult to characterize the anxiolytic activity of all the compounds in them. At the same time, these active components with anxiolytic effects may have extremely low content and complex structures, and the preparation cost may be very expensive.

The use of Chinese herbal medicine in the treatment of anxiety disorders in TCM clinics

TCM clinics use prescription preparations and herbal decoction to treat mood disorders. Some of the more classic prescription preparations include Zaoren Anshen capsule, Baizi Yangxin pills, Tianwang Buxin pills, and Jiawei Xiaoyao powder. Based on the syndrome differentiation and treatment theory [37], different patients need different treatment plans, so decoctions are a better choice. The herbal decoction is formulated by a TCM practitioner for the patient's condition. Since there is no diagnosis of anxiety disorders in TCM, the patient's diagnosis usually consists of the diagnoses of "dazed", "panic", "disturbed" and "insomnia". Different herbal medicines are considered to have different focuses, so TCM practitioners will mix different herbal medicines in certain proportions to achieve the best application to the patient's symptoms. However, limited by factors such as most people's misunderstanding of patients with anxiety disorders, the consultation rate of Chinese patients with anxiety disorders is relatively low [38]. Hence, the sample size of studies on the treatment of anxiety disorders with traditional Chinese medicine is relatively small and unrepresentative.

The advantages of herbal medicine in the treatment of anxiety disorders are fewer adverse effects and the absence of withdrawal symptoms and exacerbation of symptoms during the initial period of medication. When used in combination with commonly used anxiolytic chemicals, they can reduce the adverse effects of the chemicals and synergize their effects [39]. However, herbal tonics are more complicated to use and patients may prefer to use simple-to-use herbal formulas with chemical drugs.

Barriers to the development of anxiolytics

The pathogenesis of anxiety disorders is unknown. The possible pathogenesis of anxiety disorders includes, in addition to genetic factors, the endocrine dysregulation hypothesis, the monoamine neurotransmitter hypothesis, and the immune impairment hypothesis, as well as social factors that influence the onset of the disease in patients. Anti-anxiety drugs are usually symptomatic, and the absence of an identified pathogenesis makes it difficult to find a suitable target for new anti-anxiety drugs.

Drug discovery targeting specific receptors rarely translates into products. Target-based drug discovery is the dominant approach to drug discovery, and much of the recent development of new anxiolytic drugs has been based on this model [3]. However, the efficiency of new drug discovery is still very low [40, 41]. In contrast to the inefficiency of phenotype-based drug discovery, nearly 90% of small molecule drugs approved by the United States Food and Drug Administration are based on phenotype discovery. In the case of TCM development, phenotype-based research accounts for the vast majority of studies, in which we first know exactly what a TCM does, and only then study the active substances in it. Therefore, to a certain extent, we can think that new anti-anxiety drugs developed with Chinese

medicines with anti-anxiety effects have great development prospects.

Differences between experimental animals and humans result in the inability of drugs with anxiolytic effects in animal experiments to act in humans. The first major concern is that the paradigm of anxiety triggering implemented in experimental animals may not be the same as the pathogenesis in humans with anxiety disorders. The methods used to test whether animals produce anxiety-like behaviors also tend to favor responses in the face of fear over anxiety-like behaviors [42]. At the same time, the genetic differences between humans and experimental animals cannot be ignored, and interspecies differences may result in drugs that work in one species but are ineffective in another. Differences in hormone levels between females and males can also affect the development of anxiolytics, with females being more inclined to suffer from anxiety and depression [43–46]. Still, most anxiolytics studies use male animals [47, 48].

Anxiolytic efficacy data of TCM are summarised from clinical experience, and the research process is “efficacy-to-mechanism”, while the clinical data take into account different genders. TCM theory has a different understanding of emotional disorders, such as anxiety disorders, than modern medicine and TCM practitioners can treat patients according to the cause of their illness. For example, patients with liver Qi stagnation can be treated with herbs that can ease the liver and regulate Qi, which can achieve better results. Therefore, a new generation of anti-anxiety drugs may be better discovered from Chinese medicine.

Conclusion

Natural products in herbs may serve as a source of next-generation anxiolytics. However, more research on the anxiolytic activity of herbal monomers is needed as it is not yet clear what the active substances are in most anxiolytic herbs. It is also necessary to find representative methods for rapid screening of anxiolytic compounds to increase the rate of potential actives into drugs.

References

1. Stein MB, Sareen J. CLINICAL PRACTICE. Generalized Anxiety Disorder. *N Engl J Med.* 2015;373(21):2059–2068. Available at: https://doi.org/10.1056/NEJMcp1502514
2. DeMartini J, Patel G, Fancher TL. Generalized Anxiety Disorder. *Ann Intern Med.* 2019;170(7):ITC49. Available at: http://doi.org/10.7326/aitc201904020
3. Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. *Nat Rev Drug Discov.* 2013;12(9):667–687. Available at: http://doi.org/10.1038/nrd4075
4. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression. *N Engl J Med.* 2006;354(12):1231–1242. Available at: http://doi.org/10.1056/NEJMoa052963
5. Suresh V, Mills JA, Croarkin PE, Strawn JR. What next? A Bayesian hierarchical modeling re-examination of treatments for adolescents with selective serotonin reuptake inhibitor-resistant depression. *Depress Anxiety.* 2020;37(9):926–934. Available at: http://doi.org/10.1002/da.23064
6. Cosci F, Chouinard G. Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications. *Psychother Psychosom.* 2020;89(5):283–306. Available at: http://doi.org/10.1159/000506868
7. Szuhany KL, Simon NM. Anxiety Disorders. *JAMA.* 2022;328(24):2431. Available at: http://doi.org/10.1001/jama.2022.22744
8. Ping Liu PL, Yuan Hu YH, Hong-Bo Liao H-BL, et al. A bioactive compound from Polygala tenuifolia regulates efficiency of chronic stress on hypothalamic-pituitary-adrenal axis. *Pharmazie.* 2009;64(9):605–608. Available at: http://doi.org/10.1691/ph.2009.9580
9. Liu P, Wang D, Guo D, et al. Antidepressant Effect of 3', 6-Disinapoyl Sucrose from Polygala tenuifolia Willd in Pharmacological Depression Model. *Chin Pharm J.* 2008;18:1391–1394. Available at: https://kns.cnki.net/kcms2/article/abstract?v=WVDzDAe5jxZQdrEhpxYPeuf4vFpFEYkvVgvWg4AcMxhlZOetiTDNglp9vVzNUPXPA30xaLog0_sjVZWPb9cDzbV50SWgJKBXAmgPwacmBSr-wVBGNP6Qmw==&uniplatform=NZKPT
10. Hu Y, Liao H-B, Dai-Hong G, Liu P, Wang Y-Y, Rahman K. Antidepressant-like effects of 3,6′-disinapoyl sucrose on hippocampal neuronal plasticity and neurotrophic signal pathway in chronically mild stressed rats. *Neurochem Int.* 2010;56(3):461–465. Available at: http://doi.org/10.1016/j.neuint.2009.12.004
11. Zhang J, Xie J, Liang Y, et al. Anxiolytic effects, metabolism and plasma pharmacokinetics of 3, 6′ -disinapoylsucrose. *Biomed Pharmacother.* 2022;149:112913. Available at: http://doi.org/10.1016/j.biopha.2022.112913
12. Lee J-Y. Anti-inflammatory effects of sinapic acid on 2,4,6-trinitrobenzenesulfonic acid-induced colitis in mice. *Arch Pharm Res.* 2018;41(2):243–250. Available at: http://doi.org/10.1007/s12272-018-1006-6
13. Yun K-J, Koh D-J, Kim S-H, et al. Anti-Inflammatory Effects of Sinapic Acid through the Suppression of Inducible Nitric Oxide Synthase, Cyclooxygase-2, and Proinflammatory Cytokines Expressions via Nuclear Factor-κB Inactivation. *J Agric Food Chem.* 2008;56(21):10265–10272. Available at: http://doi.org/10.1021/jf802095g
14. Gaspar A, Martins M, Silva P, et al. Dietary phenolic acids and derivatives. Evaluation of the antioxidant activity of sinapic acid and its alkyl esters. *J Agric Food Chem.* 2010;58(21):11273–11280. Available at: https://doi.org/10.1021/jf103075r
15. Chen C. Sinapic Acid and Its Derivatives as Medicine in Oxidative Stress-Induced Diseases and Aging. *Oxid Med Cell Longev.* 2016;2016:1–10. Available at: http://doi.org/10.1155/2016/3571614
16. Shahmohamady P, Eidi A, Mortazavi P, Panahi N, Minai-Tehrani D. Effect of sinapic acid on memory deficits and neuronal degeneration induced by intracerebroventricular administration of streptozotocin in rats. *Pol J Pathol.* 2018;69(3):266–277. Available at: http://doi.org/10.5114/pjp.2018.79546
17. Karakida F, Ikeya Y, Tsunakawa M, et al. Cerebral Protective and Cognition-Improving Effects of Sinapic Acid in Rodents. *Biol Pharm Bull.* 2007;30(3):514–519. Available at: http://doi.org/10.1248/bpb.30.514
18. Zare K, Eidi A, Roghani M, Rohani AH. The neuroprotective potential of sinapic acid in the 6-hydroxydopamine-induced hemi-parkinsonian rat. *Metab Brain Dis.* 2014;30(1):205–213. Available at: http://doi.org/10.1007/s11011-014-9604-6
19. Bais S, Kumari R, Prashar Y. Ameliorative Effect of Trans-Sinapic Acid and its Protective Role in Cerebral Hypoxia in Aluminium Chloride Induced Dementia of Alzheimer's Type. *CNS Neurol Disord Drug Targets.* 2018;17(2):144–154. Available at: https://doi.org/10.2174/1871527317666180309130912
20. Yoon BH, Jung JW, Lee J-J, et al. Anxiolytic-like effects of sinapic acid in mice. *Life Sci.* 2007;81(3):234–240. Available at: http://doi.org/10.1016/j.lfs.2007.05.007
21. Yao Y, Jia M, Wu J-G, et al. Anxiolytic and sedative-hypnotic activities of polygalasaponins fromPolygala tenuifoliain mice. *Pharm Biol.* 2010;48(7):801–807. Available at: http://doi.org/10.3109/13880200903280042
22. Jin Z, Gao N, Li X, et al. The antidepressant-like pharmacological profile of Yuanzhi-1, a novel serotonin,

norepinephrine and dopamine reuptake inhibitor. *Eur Neuropsychopharmacol.* 2015;25(4):544–556. Available at: http://doi.org/10.1016/j.euroneuro.2015.01.005
23. Yang WS, Shi Z, Dong X, Liu P, Chen M, Hu Y. Involvement of 5-HT-BDNF signaling axis in mediating synergistic antidepressant-like effects after combined administration of two oligosaccharide esters. *Food Sci Nutr.* 2021;9(2):1180–1191. Available at: http://doi.org/10.1002/fsn3.2098
24. Li S, Liu S, Liu Z, Liu C, Song F, Pi Z. Bioactivity screening, extraction, and separation of lactate dehydrogenase inhibitors from Polygala tenuifolia Willd. based on a hyphenated strategy. *J Sep Sci.* 2017;40(6):1385–1395. Available at: https://doi.org/10.1002/jssc.201601216
25. Leem Y-H, Oh S. 3,4,5-Trimethoxycinnamin acid ameliorates restraint stress-induced anxiety and depression. *Neurosci Lett.* 2015;585:54–59. Available at: http://doi.org/10.1016/j.neulet.2014.11.016
26. Wen L, Xia N, Tang P, et al. The Gastrointestinal Irritation of Polygala Saponins and Its Potential Mechanism In Vitro and In Vivo. *BioMed Res Int.* 2015;2015:1–8. Available at: http://doi.org/10.1155/2015/918048
27. Liu J, Qiao W, Yang Y, Ren L, Sun Y, Wang S. Antidepressant-like effect of the ethanolic extract from Suanzaorenhehuan Formula in mice models of depression. *J Ethnopharmacol.* 2012;141(1):257–264. Available at: http://doi.org/10.1016/j.jep.2012.02.026
28. Yan L, Wang J, He X, et al. Platycladus orientalis seed extract as a potential triple reuptake MAO inhibitor rescue depression phenotype through restoring monoamine neurotransmitters. *J Ethnopharmacol.* 2022;295:115302. Available at: http://doi.org/10.1016/j.jep.2022.115302
29. NISHIYAMA N, CHU P, SAITO H. Beneficial Effects of Biota, a Traditional Chinese Herbal Medicine, on Learning Impairment Induced by Basal Forebrain-Lesion in Mice. *Biol Pharm Bull.* 1995;18(11):1513–1517. Available at: http://doi.org/10.1248/bpb.18.1513
30. NISHIYAMA N, WANG Y, SAITO H. Beneficial Effects of S-113m, a Novel Herbal Prescription, on Learning Impairment Model in Mice. *Biol Pharm Bull.* 1995;18(11):1498–1503. Available at: http://doi.org/10.1248/bpb.18.1498
31. Choi Y, Moon A, Kim YC. A pinusolide derivative, 15-methoxypinusolidic acid from Biota orientalis inhibits inducible nitric oxide synthase in microglial cells: Implication for a potential anti-inflammatory effect. *Int Immunopharmacol.* 2008;8(4):548–555. Available at: http://doi.org/10.1016/j.intimp.2007.12.010
32. Koo KA, Kim SH, Lee MK, Kim YC. 15-Methoxypinusolidic acid from Biota orientalis attenuates glutamate-induced neurotoxicity in primary cultured rat cortical cells. *Toxicol In Vitro.* 2006;20(6):936–941. Available at: http://doi.org/10.1016/j.tiv.2006.02.001
33. Xie J, Li Y, Liang Y, Kui H, Wang C, Huang J. Integration of non-targeted metabolomics with network pharmacology deciphers the anxiolytic mechanisms of Platycladi Semen extracts in CUMS mice. *J Ethnopharmacol.* 2023;315:116571. Available at: http://doi.org/10.1016/j.jep.2023.116571
34. Gong B, Wang C, Wu Y, Liu Y, Wei J. The anti-anxiety/depression effect and mechanism of agarwood line incense burning on regulating multi-neurotransmitter pathways. *Chin J New Drugs.* 2023;32(13):1368–1376. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=-0THPtffOh1zcnU2ZVxXhUAOQlZAzcFv-86UYqP9b0paLbKwyFTFZRT-luEDvJHG_sUmt03cX5tzIXw_hNfAirY8ySZFKLnRM9PYpHDDSVgThw6SGgj9ce8tTeulNSGFY73KqcY0U4=&uniplatform=NZKPT
35. Choi JE, Park D-M, Chun E, et al. Control of stress-induced depressive disorders by So-ochim-tang-gamibang, a Korean herbal medicine. *J Ethnopharmacol.* 2017;196:141–150. Available at: http://doi.org/10.1016/j.jep.2016.12.025
36. Wang H, Hu J, Hu J, et al. Antidepressant effect of 4-Butyl-alpha-agarofuran via HPA axis and serotonin system. *Brain Res Bull.* 2023;198:3–14. Available at: http://doi.org/10.1016/j.brainresbull.2023.04.003
37. Mei MF. A systematic analysis of the theory and practice of syndrome differentiation. *Chin J Integr Med.* 2011;17(11):803–810. Available at: http://doi.org/10.1007/s11655-011-0890-0
38. Lu J, Xu X, Huang Y, et al. Prevalence of depressive disorders and treatment in China: a cross-sectional epidemiological study. *Lancet Psychiatry.* 2021;8(11):981–990. Available at: http://doi.org/10.1016/s2215-0366(21)00251-0
39. Xiong F, Song PR. Observation on Clinical Effect of Addition and Subtraction Therapy with Danzhi Xiaoyao Powder on the Treatment of Anxiety. *Chin J Ration Drug Use.* 2019;16(01):16–19. (Chinese) Available at: https://doi.org/10.3969/j.issn.2096-3327.2019.01.005
40. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov.* 2012;11(3):191–200. Available at: http://doi.org/10.1038/nrd3681
41. Sadri A. Is Target-Based Drug Discovery Efficient? Discovery and "Off-Target" Mechanisms of All Drugs. *J Med Chem.* 2023;66(18):12651–12677. Available at: http://doi.org/10.1021/acs.jmedchem.2c01737
42. Harrison DJ, Creeth HDJ, Tyson HR, et al. Unified Behavioral Scoring for Preclinical Models. *Front Neurosci.* 2020;14:313. Available at: http://doi.org/10.3389/fnins.2020.00313
43. Schuch JJJ, Roest AM, Nolen WA, Penninx BWJH, de Jonge P. Gender differences in major depressive disorder: Results from the Netherlands study of depression and anxiety. *J Affect Disord.* 2014;156:156–163. Available at: http://doi.org/10.1016/j.jad.2013.12.011
44. Farhane-Medina NZ, Luque B, Tabernero C, Castillo-Mayén R. Factors associated with gender and sex differences in anxiety prevalence and comorbidity: A systematic review. *Sci Prog.* 2022;105(4):003685042211354. Available at: http://doi.org/10.1177/00368504221135469
45. Gao W, Ping S, Liu X. Gender differences in depression, anxiety, and stress among college students: A longitudinal study from China. *J Affect Disord.* 2020;263:292–300. Available at: http://doi.org/10.1016/j.jad.2019.11.121
46. Lam YH, Leung MT, Ching CK, Mak TWL. Simultaneous detection of 24 oral antidiabetic drugs and their metabolites in urine by liquid chromatography–tandem mass spectrometry. *J Chromatogr B.* 2020;1141:122020. Available at: http://doi.org/10.1016/j.jchromb.2020.122020
47. Mamlouk GM, Dorris DM, Barrett LR, Meitzen J. Sex bias and omission in neuroscience research is influenced by research model and journal, but not reported NIH funding. *Front Neuroendocrinol.* 2020;57:100835. Available at: http://doi.org/10.1016/j.yfrne.2020.100835
48. Will TR, Proaño SB, Thomas AM, et al. Problems and Progress regarding Sex Bias and Omission in Neuroscience Research. *eNeuro.* 2017;4(6):ENEURO.0278-17.2017. Available at: https://doi.org/10.1523/ENEURO.0278-17.2017