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Editorial

Traditional Herbal Medicines in Mood Disorders: A Promising Development Target

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The ancient Greek physician Hippocrates postulated a central wellbeing tenet, "healthy mind, healthy body," suggesting the match between physical and psychological health. Freud further developed the theory on how the mind is structured as well as how intervention should be implemented. A positive state of mind is capable of regulating negative feelings and promoting positive mental health, meaning that mind impairment may result in serious mental disorders requiring treatment.

Depression is one of the most common mental disorders, affecting more than 350 million people, and is a leading cause of public health burden globally, according to the World Health Organization. In particular, the emergence of the COVID-19 pandemic has posed huge challenges to the effective interventions against depression across the world since 2020. According to a recent systematic review, the prevalence of depression climbed by 27.6%, accounting for an additional 53.2 million cases worldwide during the COVID-19 pandemic.[1]

Patients with depressive disorder show multiple symptoms such as a long-lasting low mood, prolonged anhedonia (loss of interest and pleasure in events enjoyed previously), a persistent poor metabolic profile, and repeated suicidal attempts. The currently used first-line antidepressants for the treatment of depression in primary care mostly act on the brain's serotonergic or noradrenergic systems. According to the major role of these neurotransmitters in mood control and the action of antidepressants, selective serotonin (5-HT) reuptake inhibitors (SSRIs) and 5-HT and norepinephrine (NE) reuptake inhibitors (SNRIs) were developed to treat depression.[2] It has been well demonstrated by clinical and preclinical studies that antidepressants such as citalopram, fluoxetine, venlafaxine, and mirtazapine improve depressive disorders by targeting the 5-HT and NE systems.

However, at least one-third of depressed patients are resistant to antidepressant medications, leading to a higher rate of relapse among patients who will probably develop treatment-resistant depression.[3] Moreover, the prolonged response time (usually a lag of weeks to months) to achieve treatment outcomes as well as undesired adverse events result in some depressed patients being reluctant to maintain their current therapy. Therefore, the risk of committing suicide in vulnerable individuals will be increased. Thus, further optimizing antidepressants with a rapid-onset therapeutic action and reduced unwanted side events is urgently needed.

Since evidence has supported the contemporary usage of St. John's wort (*Hypericum perforatum* L.) as an antidepressant,[4] increasing research has been directed toward searching traditional herbal medicines for the development of antidepressant candidates. Among these herbal remedies, Chinese herbal medicines have been used in China for thousands of years as the main therapeutics, and such treatments for psychiatric disorders have been used for hundreds of years. Notably, the rising number of clinical trials and animal studies have reported that Chinese herbal medicines show comparative advantages in terms of regulating mood disorders, including depression. Many depressed patients prefer herbs for symptom relief due to their comparative efficacy and limited side effects. Despite a large body of evidence supporting the positive effects of herbal medicines on depression, the molecular mechanisms underlying their effects remain elusive.

In a recent research article published in the *Journal of Exploratory Research in Pharmacology*, Zou and colleagues explored the role of the compound Gaoziban tablet (CGZBT) in depression and the potential pharmacological mechanisms involved in its antidepressant activity.[5] CGZBT is a Chinese medicine showing multiple benefits such as the relief of insomnia, headache, and neurasthenia as well as the reversal of depression, with fewer side effects. The major active compounds identified in the CGZBT extracts were flavonoids, including sinapic acid, rutin, rosmarinic acid, myricetin, quercetin, luteolin, kaempferol, and apigenin. Highlighting the role of flavonoids in depression intervention, studies in both cell lines and animals have indeed shown that the antidepressant effects of CGZBT are related to its action on the amine mechanisms protecting from stress and the neuroendocrine and immune systems.[6] In addition, flavonoids have been found to be safe and free from side effects, implying that they are an important target for the development of antidepressants. Further studies on the molecular mechanisms and pharmacological effects of flavonoids may contribute to a better understanding of the pathogenesis of depression and to the discovery or identification of new biomarker targets for

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; CGZBT, compound Gaoziban tablet; CUMS, chronic unpredictable mild stress; IL-1β, interleukin-1beta; IL-6, interleukin-6; NE, norepinephrine; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TNF-α, tumor necrosis factor-alpha.

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the onset of depression, thus contributing to the development of better treatment strategies for depression.

The study by Zou and colleagues revealed that CGZBT ameliorated depression-like behaviors; restored the levels of NE, 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA); increased GSK-3β phosphorylation, which subsequently enhanced Wnt/β-catenin activation in the hippocampus; and decreased the concentrations of serum tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6) in rats. In addition, CGZBT treatment also significantly improved the number of neurons in the rat CA1 region. Preclinical and clinical studies have shown that adult hippocampal neurogenesis, during which newborn granule neurons produced from progenitors are located in the subgranular zone of the dentate gyrus, is one of the central mechanisms of depression and the target of some antidepressants.[7,8] Both the decreased neurogenesis in the brains of depressed humans and the enhanced hippocampal neurogenesis by antidepressants in laboratory animals highlight the importance of hippocampal neurogenesis in mood regulation and antidepressant efficacy.[9] Consistent with this hypothesis, a reduction in the number of neurons in the hippocampal CA1 region was also observed in a chronic unpredictable mild stress (CUMS) rat depression model. CUMS is a widely used animal model in laboratory studies to reproduce anhedonia (measured by a decreased sucrose preference in rodents), which is a core symptom demonstrated in patients suffering from depression. Here, CGZBT treatment significantly improved the number of neurons in this brain region, suggesting that CGZBT treatment may enhance the proliferation and maturation of CA1 neurons and thus reduce the risk of developing depression.

To further clarify the molecular mechanism, the therapeutic relevance of CGZBT on regulating inflammatory processes was also considered. The possible causal relationship between inflammation and depression has been widely demonstrated previously. For example, increasing levels of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, have been found both at the periphery and in the brain of patients with depression.[10] Furthermore, Zou and colleagues showed that treatment with CGZBT significantly decreased the concentrations of serum TNF-α, IL-1β, and IL-6 induced by CUMS. It is well known that the attenuation of 5-HT and NE neurotransmission within the brain is also linked to depression. Moreover, activated cytokine levels also affect 5-HT, NE, dopamine, and NE function, resulting in impaired neurogenesis, which are critical biological processes that contribute to the pathogenesis and treatment of depression. In this study, treatment with CGZBT restored the levels of NE, 5-HT, and 5-HIAA in the hippocampal tissues of CUMS rats, supporting the concept that enhancing the monoamine neuronal system may contribute to the antidepressant effect of CGZBT.

The emerging evidence that traditional herbal medicines can be new targets for the development of antidepressants raises hopes that traditional Chinese medicine aiming at multiple links or systems can become a major option to treat complicated mood disorders such as depression. However, the challenges in the translation from bench to bedside mainly lie in the high-quality studies with confirmed pharmacological parameters like active components, dose-dependent relationships, and biological mechanisms.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Concept and design (WLZ and ZHZ), manuscript writing (ZHZ and WLZ), critical revision of the manuscript for important intellectual content (ZBD, XW, KW and SXL). All authors approved the contents of the manuscript and this submission.

References

[1] COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 2021;398(10312):1700–1712. doi:10.1016/S0140-6736(21)02143-7, PMID:34634250.

[2] Blier P, de Montigny C. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. Neuropsychopharmacology 1999;21(2 Suppl):91S–98S. doi:10.1016/S0893-133X(99)00036-6, PMID:10432494.

[3] Dowlati Y, Herrmann N, Swardfager WL, Reim EK, Lanctôt KL. Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: a meta-analysis. Can J Psychiatry 2010;55(2):91–99. doi:10.1177/070674371005500205, PMID:20181304.

[4] Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression—an overview and meta-analysis of randomised clinical trials. Br Med J 1996;313(7052):253–258. doi:10.1136/bmj.313.7052.253, PMID:8704532.

[5] Zou XS, Yin HL, Shi L, Li HP, Wang MH, Song WC, *et al*. Treatment with Gaoziban tablet ameliorates depression by promoting GSK-3β phosphorylation to enhance the Wnt/β-catenin activation in the hippocampus of rats. J Explor Res Pharmacol 2021. doi:10.14218/JERP.2021.00016.

[6] Khan H, Perviz S, Sureda A, Nabavi SM, Tejada S. Current standing of plant derived flavonoids as an antidepressant. Food Chem Toxicol 2018;119:176–188. doi:10.1016/j.fct.2018.04.052, PMID:29704578.

[7] Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci 2007;10(9):1110–1115. doi:10.1038/nn1969, PMID:17726477.

[8] Sahay A, Drew MR, Hen R. Dentate gyrus neurogenesis and depression. Prog Brain Res 2007;163:697–722. doi:10.1016/S0079-6123(07)63038-6, PMID:17765746.

[9] Mahar I, Bambico FR, Mechawar N, Nobrega JN. Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. Neurosci Biobehav Rev 2014;38:173–192. doi:10.1016/j.neubiorev.2013.11.009.

[10] Wohleb ES, Franklin T, Iwata M, Duman RS. Integrating neuroimmune systems in the neurobiology of depression. Nat Rev Neurosci 2016;17(8):497–511. doi:10.1038/nrn.2016.69, PMID:27277867.