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REVIEW

Depression and Gastrointestinal Health Abnormalities: Treatment Approaches from the Perspective of Traditional Chinese Medicine

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Abstract: Depression is often associated with gastrointestinal issues, forming a self-sustaining cycle known as the emotion-gastrointestinal axis. Traditional Chinese Medicine (TCM) provides multi-component and multi-target therapies, though its mechanisms are not fully understood. This article reviews key studies on how TCM, including herbal formulas, single herbs, active ingredients, and acupuncture, influences the brain-gut axis in treating depression and gastrointestinal problems. This article reviews recent research on the pharmacological mechanisms of Chinese medicine, providing a basis for its targeted molecular therapy and future development. Additionally, it provides insights into enhanced treatment strategies for clinical patients and investigates the potential role of TCM in addressing depression and gastrointestinal-related health disorders.

Keywords: depression, gut-brain crosstalk, traditional chinese medicine, gastrointestinal-related health abnormalities

Introduction

Depression, characterized by its high prevalence among mental disorders globally, has emerged as a significant public health concern with profound implications for human health.[1] According to data from the World Health Organization (WHO), over one billion individuals worldwide are affected by mental health disorders, including anxiety and depression. Annually, depression accounts for more than 700,000 suicide deaths,[2] positioning it as the second leading cause of death following cancer and the foremost cause of disability. By 2030, depression is anticipated to constitute the largest global disease burden, with its detrimental effects on individual health, family dynamics, and societal productivity warranting significant attention.[3] The clinical manifestations of depression are notably complex, encompassing not only the central symptoms of low mood or irritability, loss of interest, and anhedonia but also decreased energy, fatigue, sleep disturbances, abnormal appetite and weight fluctuations, self-worth denial, and even suicidal ideation and behaviors. Furthermore, depression is frequently associated with gastrointestinal dysfunction. Through the bidirectional regulatory mechanism of the brain–gut axis, emotional disturbances in patients with depression can directly influence gastrointestinal motility, sensory function, and mucosal barrier integrity. Concurrently, gastrointestinal symptoms such as abdominal distension, constipation, diarrhea, functional abdominal pain, heartburn, and acid regurgitation can exacerbate depressive symptoms,[4] creating a detrimental cycle of emotional and gastrointestinal interactions. This cycle further complicates the patient's condition and increases the challenges associated with diagnosis and treatment.[5]

From a pathogenesis perspective, the pathological processes underlying depression involve disruptions in multiple pathways. Currently, the academic community recognizes that these processes are closely associated with an imbalance

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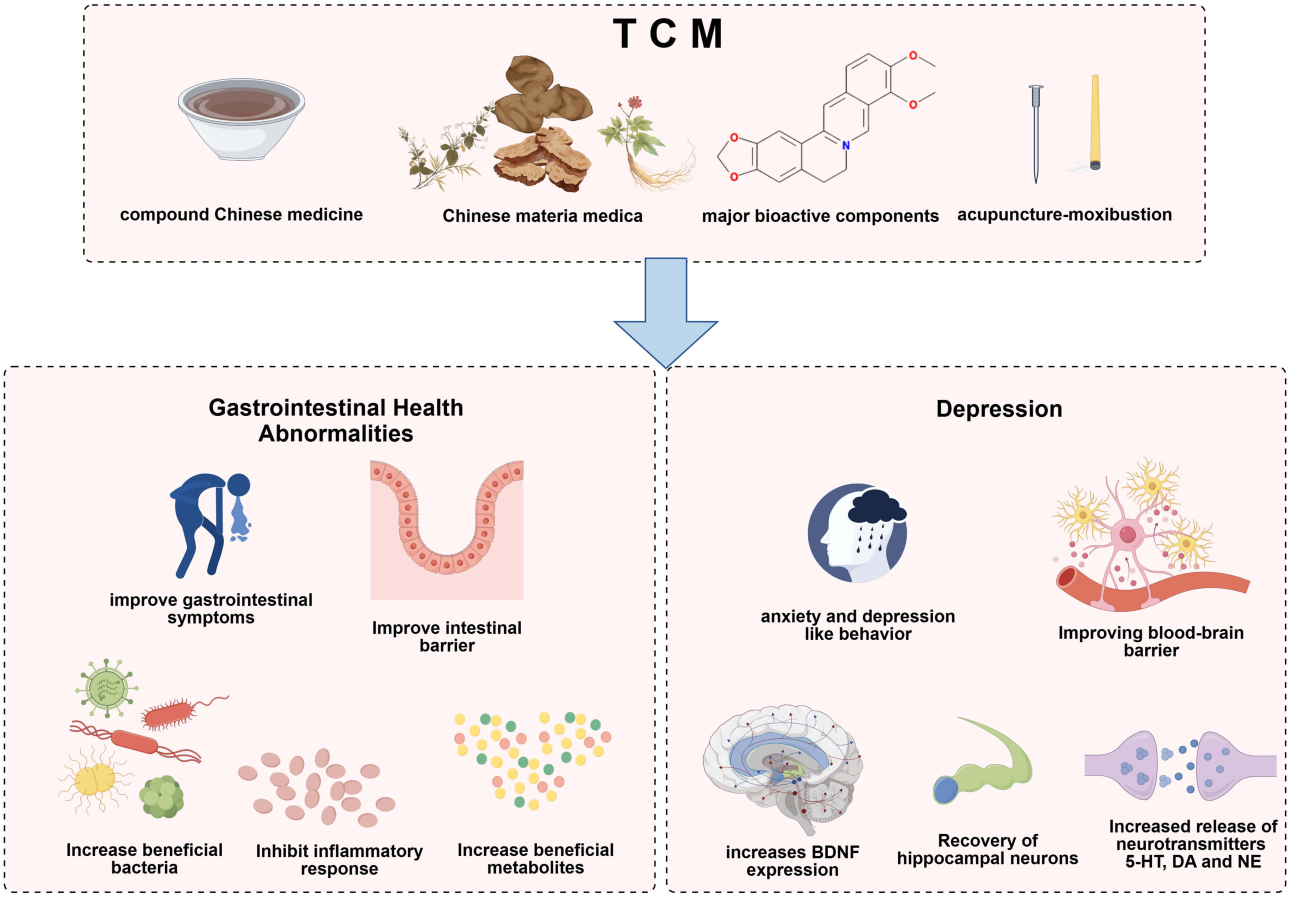
Graphical Abstract



of monoamine neurotransmitters,[6] excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis,[7] heightened immune-inflammatory responses,[8] impairments in neuroplasticity and neurogenesis,[9] and abnormalities in the structure of the gut microbiota[10.] (Figure 1). It is particularly noteworthy that the prevalence of psychosocial comorbidities, such as anxiety and depression, is significantly higher in patients with functional gastrointestinal disorders.[11] Moreover, these patients exhibit significantly elevated scores for anxiety and depression symptoms compared to individuals without gastrointestinal symptoms. The compositional characteristics of the intestinal microbiota are intricately linked to the host's physiological functions and neuropsychiatric health. The *Firmicutes*/*Bacteroidetes* ratio serves as a critical indicator of intestinal physiological status. Research indicates that a reduction in *Firmicutes* abundance typically signifies intestinal dysfunction,[12] while an imbalance with *Bacteroidetes* may influence the development of mental disorders via the gut-brain axis. Specifically, a decrease in *Firmicutes* coupled with an increase in *Bacteroidetes* can enhance IgA secretion in the intestinal mucosa, inhibit pathogenic bacterial colonization, and protect the intestinal mucosal barrier through symbiosis with the host. However, Mendelian randomization analysis suggests that this alteration in bacterial proportions may constitute a potential risk factor for depression. Concurrently, a decline in *Bacteroides* colonization levels may elevate the host's susceptibility to Alzheimer's disease.[13] Inflammation serves as a central mediator in the relationship between gut microbiota and depression, with its regulatory mechanisms being intricately linked to specific functional bacterial taxa. Butyric acid-producing bacteria, including *Romboutsia, Intestinimonas*, and *Ruminococcaceae_UCG011*, have been identified as protective factors against depression and exhibit a negative

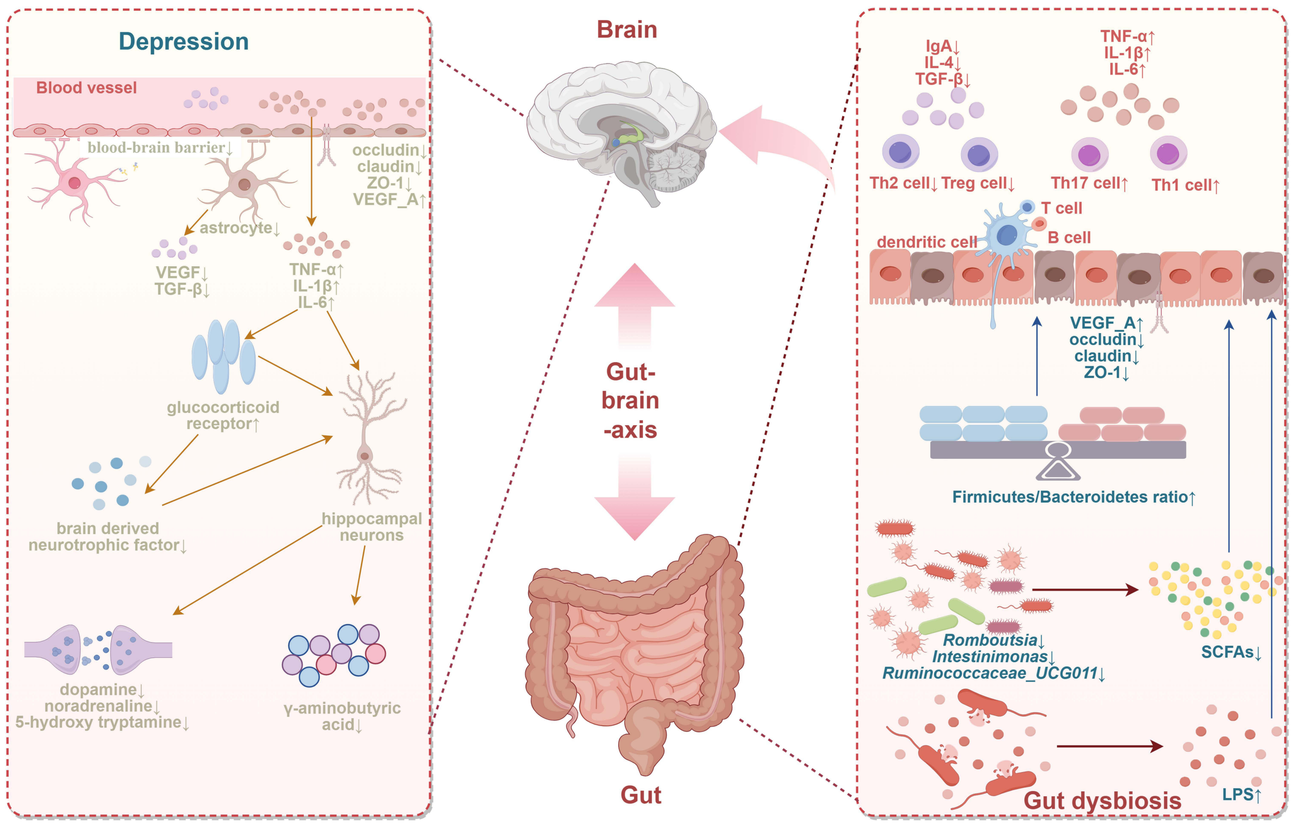


Figure 1 The effect of intestinal microbial imbalance on depression. (Note: The arrow↑ indicates upregulation, and the arrow↓ indicates downregulation).

correlation with pro-inflammatory cytokines. Notably, a decrease in *Romboutsia* is associated with compromised intestinal barrier integrity, upregulation of pro-inflammatory cytokines within the TNF family, exacerbation of neuroinflammation, and a reduction in neurotransmitter levels, collectively contributing to the onset of depression.[14] Conversely, an increased abundance of *Intestinimonas* can safeguard the intestinal mucosa by downregulating TNF-α, IL-1β, and IL-6 levels while upregulating IgA.[15] Additionally, *Ruminococcaceae* can enhance the intestinal mucosal barrier, downregulate VEGF-A expression, and inhibit the secretion of TNF-α and IL-6 by immune cells, thereby mitigating inflammation and exerting antidepressant effects.[16] In contrast, infections caused by pathogenic bacteria, including *Streptococcus pneumoniae*,[17] *Escherichia coli*[18] and *Mycobacterium tuberculosis*,[19] can lead to a pathological elevation in VEGF-A levels, compromise the integrity of the blood–brain barrier, and exacerbate meningitis. Conversely, symbiotic bacteria can directly detect microbial metabolites or products, such as short-chain fatty acids (SCFAs), through T cells or dendritic cells, thereby initiating the activation of regulatory T cells and facilitating an immune response. Furthermore, symbiotic bacteria promote the induction of Th17 cells, which in turn regulate the function and homeostasis of epithelial cells.[20]

Currently, the clinical management of depression is predominantly reliant on pharmacological interventions, which can be categorized into two treatment phases: the initial or acute phase (lasting 6–12 weeks) and the maintenance phase (spanning 4–9 months). The pharmacological options include Selective Serotonin Reuptake Inhibitors (SSRIs, such as fluoxetine), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs, such as venlafaxine), Norepinephrine and Specific Serotonin Antidepressants (NaSSAs, such as mirtazapine), Tricyclic Antidepressants (TCAs, such as amitriptyline), Serotonin Antagonists and Reuptake Inhibitors (SARIs, such as trazodone), and Monoamine Oxidase Inhibitors (MAOIs, such as phenelzine).[21] Nonetheless, existing pharmacotherapies exhibit significant limitations. Initially, the administration of these medications is frequently associated with a range of adverse effects. For instance, SSRIs may induce symptoms such as restlessness, anxiety, gastrointestinal disturbances, sleep disorders, as well as dizziness and headaches. Similarly, TCAs can result in side effects including dry mouth, constipation, sedation, and weight gain.[22]

Conversely, there are notable interindividual variations in patients' responses to pharmacological treatments, with the duration of efficacy often being prolonged. This is particularly pertinent for patients experiencing depression concomitant with gastrointestinal symptoms, as the gastrointestinal side effects of chemical medications may not only fail to ameliorate the condition but may also exacerbate the detrimental cycle of "emotion-gastrointestinal" interactions.[23] Furthermore, empirical evidence indicates that the prolonged administration of first-line antidepressants can alter the composition and metabolic profiles of gut microbiota in both patients with depression and rodent models. This alteration may further compromise intestinal barrier function, underscoring the critical need to identify safe and efficacious alternative therapeutic strategies.[24–26]

Methods

Search Strategy

A comprehensive literature review was conducted utilizing peer-reviewed and clinical databases such as PubMed, Web of Science, ClinicalTrials.gov, MEDLINE, EMBASE, and Springer LINK. The search employed keywords including Traditional Chinese Medicine (TCM) and depression and gastrointestinal health abnormalities (including irritable bowel syndrome, functional dyspepsia, gastrointestinal autonomic nerve dysfunction, non-erosive reflux disease, colorectal cancer, constipation, ulcerative colitis, gastric ulcer, and intestinal microbiota dysbiosis). The articles selected for review were published within the period from October 2010 to October 2025.

Inclusion Types

Consider including original studies, randomized controlled trials (RCTs), cohort studies, and experimental protocols.

Inclusion Criteria

Published in SCI journals (Q1-Q4).

Exclusion Criteria

Research involving conference abstracts, case reports, meta-analyses, and non-standardized outcome measures was excluded from consideration.

Traditional Chinese Medicine and Depression Combined with Gastrointestinal Health Abnormalities

Traditional Chinese medicine (TCM) presents distinct advantages in the treatment of depression.[27] TCM compounds, which are centered around natural products, along with physical therapies such as acupuncture and massage, exhibit multi-component and multi-target characteristics with minimal side effects.[28] In clinical trials, these methods target depression by addressing the link between mood disorders and gastrointestinal issues. This comprehensive approach eases gastrointestinal discomfort and improves depressive symptoms, providing a new treatment perspective for depression with gastrointestinal symptoms (Table 1). Given the crucial role of intestinal flora and its metabolites in managing intestinal barrier function and depression, numerous animal studies suggest that traditional Chinese medicine might offer dual treatment and regulation by influencing the intestinal flora-brain-gut axis pathway[29] (Table 2).

TCM is distinguished from modern medicine by two primary characteristics: the holistic concept and syndrome differentiation and treatment. The holistic concept in TCM posits that the five physiological systems—liver, heart, spleen, lung, and kidney—are interconnected and unified with the external environment and society. Consequently, alterations in one zang-fu organ can lead to changes in related organs, and both the natural and social environments can contribute to the onset of diseases. This perspective bears some resemblance to the contemporary understanding of depression in modern medicine. While the complete etiology of depression remains not fully elucidated, it is recognized that depression is associated with an imbalance of brain neurotransmitters.[111] Specifically, insufficient secretion or abnormal transmission of serotonin, dopamine, and norepinephrine can disrupt emotional regulation. Additionally, structural and functional abnormalities in the hippocampus and prefrontal cortex are implicated in the pathophysiology of

Table 1 The Clinical Efficacy of Traditional Chinese Medicine in the Treatment of Depression and Gastrointestinal Health Abnormalities

Reference	Disease	Design	Treatment	Outcome	Basic Characteristic of Study Participants (Treatment/Placebo)	Main Results
[30]	Depression combined with irritable bowel syndrome	Treatment (n=20) vs Placebo (n=22), 4 weeks	*Boswellia carterii Birdw., Zingiber officinale Roscoe, Achillea millefolium L.*	Severity and frequency of abdominal pain↓, Bloating and defecation frequency↓, Average depression score↓	Age 36.2±10.88/41.13±12.61, Female 55.4%/72.8%, Education Under diploma 50%/54.3%.	Abdominal pain severity mean score from 54.5 ±21.18 to 32.29±17.56, Bloating severity mean score from 61.43±28.7 to 40.20±24.20, Anxiety mean score from 19.36±2.48 to 16.5±3.40, Depression mean score from 17.46±2.62 to 14.41±4.16.
[31]	Depression combined with irritable bowel syndrome	Treatment (n=44) vs Placebo (n=43), 8 weeks	Tongxie Yaofang: *Saposhnikovia divaricata (Turcz.) Schischk., Paeonia lactiflora Pall., Atractylodes macrocephala Koidz., Pericarpium Citri Reticulatae*	Response rate↑, Fecal frequency↓, IBS-SSS score↓, Stool consistency↓, IBS-QOL↓, Anxiety and depression symptom score↓	Age 41.5±19.0 years/41.13±12.61 years, Female 33.3%/45.8%, Weight 70.0±15.0 kg/67.5±24.3 kg, Height 168.5±9.6 cm/167.5±8.4 cm, Disease duration 2.3±4.8 years/2.0±4.4 years, Married 93.8%/85.4%, Current smokers 37.5%/27.1%, Current drinkers 12.5%/16.7%, IBS-SSS score at baseline 232.5±120.0/227.5±102.5, Stool frequency at baseline 2.2±1.2/2.1±1.4, Stool consistency at baseline 5.6±0.6/5.6±0.7, IBS-QOL score at baseline 62.4±105.8/53.9±90.2, Anxiety score at baseline 36.0±17.3/38.0±13.8, Depression score at baseline 33.0±10.5/33.0±6.0.	Response rate from 39.6% to 79.5%, Proportion of patients who met the threshold for minimal clinically important difference from 54.2% to 84.1%, IBS-SSS score from 174.1±73.1 to 120.2±57.6, Stool frequency risk ratio (95% CI) 1.9, IBS-QOL risk ratio (95% CI) 29.6, Anxiety risk ratio (95% CI) 32.5, Depression risk ratio (95% CI) 30.0.
[32]	Depression combined with irritable bowel syndrome	Moxibustion (n=30) vs Electroacupuncture (n=30), 4 weeks	Moxibustion/Electroacupuncture: Tianshu (ST25), Shangjuxu (ST37)	Fecal frequency↓, HAMA and HAMD scores↓, 5-HT↓, 5-HT3R↓, 5-HT4R↓, Maximum pain perception threshold↑, VAS score↓	Moxibustion/Electroacupuncture: Age 39.53 ±8.91 years/42.75±10.22 years, Disease duration 6.29±6.49 years/5.79±5.97 years	Moxibustion/Electroacupuncture: Abdominal pain score from 5.89±1.57 to 1.89±1.69/from 5.95±1.77 to 2.47±1.71, Abdominal distension score from 6.57±1.79 to 1.90±1.58/from 6.68 ±1.61 to 2.51±1.81, Defecation emergency score from 5.83±1.51 to 1.98±1.50/from 5.58 ±1.40 to 4.99±1.57, Defecation frequency per week (time) from 4.97±1.81 to 1.70±1.02/from 5.06±1.73 to 4.52±1.33, Stool feature score from 6.40±0.62 to 4.57±0.82/from 6.24±0.61 to 6.03±0.73,
[33]	Depression complicated with functional dyspepsia	Treatment (n=45) vs Placebo (n=42), 4 weeks	Chaihu Shugan San: *Bupleuri Radix, Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Paeoniae Radix Alba, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Ligusticum sinense* "Chuanxiong", *Cyperi Rhizoma*	Self-rating Depression Score scores↓, Postprandial satiety↓, Upper abdominal pain score↓, Gastric emptying rate↑, HAMA scores↓, HAMD scores↓, FDDQL scores↓, *Blautia*↓, *Bifidobacterium*↓, *Streptococcus*↓, *Bacteroides*↑, *Faecalibacterium*↑, *Agathobacter*↑, *Roseburia*↑, *Lachnospiraceae_NK4A136*↑, *norank_f_Eubacterium*↑.	Mean age±SD 36.29±9.12 years/39.12±10.22 years, Female 68.89%/54.76%, Mean disease duration±SD (min) 40.67±16.68/38.71±15.69, Total symptoms score±SD 4.52±1.85/5.18 ±1.91, Gastric emptying rate±SD 31.09% ±15.07%/30.17%±16.53%, HAMA global score ±SD 19.84±7.99/19.21±8.43, HAMD global score±SD 13.60±4.67/12.74±4.92, FDDQL global score±SD 48.86±9.72/49.98±8.77.	SDS scores 2.49±1.50/3.79±1.77, Postprandial fullness and bloating (IQR) 1(1.00,2.00)/1.5 (0.00,1.00), Early satiety (IQR) 1(0.00,1.25)/1.00(0.75,1.00), Epigastric burning (IQR) 0.00 (0.00,1.00)/0.00 (0.00,1.00), Epigastric pain (IQR) 0.5(0.00,2.00)/1(0.00,1.00), Gastric emptying rate (SD) 54.53(16.33)/36.03(12.39), HAMA global score (SD) 13.64(6.76)/17.17 (8.17), Mental anxiety 8.31(4.52)/11.14(6.93), HAMD global score (SD) 8.16(3.35)/10.57 (4.60), FDDQL global score (SD) 68.93(7.61)/55.89(8.35).
[34]	Depression complicated with functional dyspepsia	Treatment (n=70) vs Placebo (n=71), 8 weeks	*Jiawei Xiaoyao San: Poria cocos (Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe, Paeonia suffruticosa Andr., Gardenia jasminoides J. Ellis*	Severity of indigestion symptoms↓, Depressive state↓	Age (years) 45.9±13.6 /43.0±12.1, Female 53/54, BMI (kg/m2) 22.8±3.1 22.7±3.1, Smoking present 5/7, Alcohol intake present 4/6, *Helicobacter pylori* infection positive 24/25, Baseline Gastrointestinal Symptom score 9.3±3.1/9.5±3.4, Baseline HAMD score 11.1±2.5/10.9±2.4, Baseline HAMA score 9.7±3.5/9.5±3.8.	Gastrointestinal Symptom Score mean change from baseline (95% CI) −6.7(−5.9,-7.4)/-5.3 (−4.6,-6.1), HAMD mean change from baseline (95% CI) −6.0(−5.2,-6.7)/-5.2(−4.5,-5.9), HAMA mean change from baseline (95% CI) −4.8 (−4.0,-5.6)/-4.2(−3.4,-4.9), Adverse events related to study drugs 4.3%/1.4%.

(*Continued*)

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Table 1 (Continued).

Reference	Disease	Design	Treatment	Outcome	Basic Characteristic of Study Participants (Treatment/Placebo)	Main Results
[35]	Depression complicated with functional dyspepsia	Treatment (n=135) vs Placebo (n=67), 4 weeks	*Xiangsha Liujunzi granules: Panax ginseng C. A. Mey., Atractylodes macrocephala Koidz., Poria cocos (Schw.) Wolf, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Pinellia ternata (Thunb.) Ten. ex Breitenb., Aucklandiae Radix, Amomum aurantiacum H. T. Tsai & S. W. Zhao*	PDSS scores↑, CGI scores↑, HADS scores↓, TCM symptom score↓, SF-36 scores↑, Gastric emptying rates↑, Postprandial satiety scores↓, Early satiety score↓, Upper abdominal pain score↓.	Age (years) 44.33±12.41/43.89±13.32, Female 64.2%/63.7%, Level of education degree or above 60%/61.2%.	Gastric emptying rate of proximal stomach (120min) from 75.39±13.91 to 82.31±7.35/ from 76.54±13.97 to 71.47±16.94, Gastric emptying rate of distal stomach (120min) from 57.52±27.02 to 67.66±13.41/from 61.61±21.85 to 61.89±15.26.
[36]	Depression complicated with functional dyspepsia	Treatment (n=64) vs Placebo (n=61), 8 weeks	Rikkunshito (Liujunzi Decoction): *Panax ginseng C. A. Mey., Atractylodes macrocephala Koidz., Poria cocos (Schw.) Wolf, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Pinellia ternata (Thunb.) Ten. ex Breitenb.*	Total satiety and postprandial/early satiety scores↑, Nausea/vomiting↓, Upper abdominal pain score↓, Total score of GOS scale↓, Total score of mFSSG scale↓, Anxiety scores↓, SF-8 scores↑, Overall efficacy scores↑, HADS scores↓, Anxiety scores↓.	Age (years) 50.4±14.9/50.4±13.7, Female 65.6%/77.0%, BMI (kg/m^2)(mean±SD) 20.9±3.8/ 21.4±2.8, Duration of functional dyspepsia ≤12 month 62.5%/68.9%.	Patient Assessment of Upper Gastrointestinal Symptom Severity Index (mean±SD): Total score from 1.3±0.6 to 0.7±0.6/from 1.1±0.6 to 0.8±0.7, Heartburn/Regurgitation from 0.7±0.8 to 0.4±0.7/from 0.6±0.6 to 0.3±0.4, Nausea/ Vomiting from 0.8±0.9 to 0.4±0.7/from 0.6±0.7 to 0.5±0.7, Postprandial fullness/Early satiety from 1.9±1.1 to 1.0±0.8/from 1.4±1.0 to 1.0 ±0.8, Bloating from 1.7±1.3 to 1.1±1.1/from 1.2 ±1.2 to 0.9±1.2, Upper abdominal pain from 1.9 ±1.2 to 1.1±1.2/from 2.0±1.2 to 1.4±1.2, Global Overall Symptom (mean±SD): Total score from 20.5±5.0 to 13.7±4.7/from 19.1±4.1 to 14.7±4.7, Dyspepsia from 12.5 ± 3.5 to 7.6 ± 3.1/from 11.7 ± 2.7 to 8.3 ± 3.5, Modified Frequency Scale for the Symptom of GERD (mean±SD): Total score from 17.8±8.1 to 10.1 ±8.1/from 14.9±6.7 to 9.7±7.0,HAD (mean ±SD): Total score from 9.7±6.6 to 7.8±6.4/from 7.3±5.5 to 7.0±5.3, Depression from 4.2±3.6 to 3.3±3.3/from 3.1±3.0 to 3.0±2.9, Anxiety from 5.5±3.6 to 4.2±3.6/from 4.3±3.2 to 4.0±3.2,
[37]	Depression with non-erosive reflux disease	Treatment (n=33) vs Placebo (n=37), 4 weeks	Jianpi Qinghua granules: *Codonopsis pilosula (Franch.) Nannf., Atractylodes Lancea (Thunb.) DC., Perilla frutescens (L.) Britt., Eupatorium fortunei Turcz., Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Scutellaria baicalensis Georgi, Coptis chinensis Franch., Sepiae Endoconcha, Massa Medicata Fermentata, Amomum aurantiacum H. T. Tsai & S. W. Zhao*	Gastroesophageal reflux disease visual analogue scale↓, Pyrosis visual analogue scale↓, TCM syndrome scores↑, GERD-HRQL scale↓, Gastroesophageal Reflux Disease-Health-Related Quality of Life score↓, Dyspepsia score↓, Intestinal Irregularity Score↓, Psycho-emotional score↓, Anxiety and depression score↓.	Female 53.85%/58.97%, Married or living together 66.67%/69.23%, Mental work 68.42%/ 66.67%, College and above 64.1%/50%.	Efficacy 79.49%/58.97, Reflux efficacy 69.23%/ 46.15%, Heartburn efficacy 58.97%/53.85%, Reflux VAS scores 4 weeks of treatment vs baseline (mean±SD) −1.97±1.7/−1.5±1.78, Heartburn VAS scores 4 weeks of treatment vs baseline (mean±SD) −1.75±1.71/−1.79±1.64, Total TCM syndrome scores 4 weeks of treatment vs baseline median (Q1,Q3) −4(−8, −2)/−3(−6,0), Improvement in TCM syndromes 69.23%/46.15%, SDS scores 25.76±7.47/29.18 ±9.2, SAS scores 27.16±7.11/27.55±7.12, Adverse events 2.56%/0%.
[38]	Depression combined with colorectal cancer	Treatment (n=38), 6 weeks	(1) Online conference platform online communication (2) TCM health promotion education, mindfulness practice (3) self-acupoint pressing	Self-rating Anxiety Score↓, Self-rating Depression Score↓, Fear of Cancer Recurrence Inventory↓, Standard Deviation↓, Cognitive and social functions↑, Symptom burden of insomnia and fatigue↓, *Intestinibacter*↑, *Terrisporobacter*↑, *Coprobacter*↑, *Gordonibacter*↑.	Age (years) 58±13, Female 36.8%, Rectum tumor 52.6%,Time since surgery >12 months 42.1%,	QLQ-C30 (mean±SD): Emotional function from 71.88±25.20 to 81.25±18.92,Cognitive function from 67.19±24.50 to 74.67±23.13, Social function from 59.90±28.35 to 68.00 ±24.02, Insomnia from 59.38±33.58 to 34.67 ±33.99, Fatigue from 44.79±24.84 to 30.67 ±23.41,

[39]	Depression combined with irritable bowel syndrome	Treatment (n=48) vs Placebo (n=48), 8 weeks	Tongxie Yaofang: *Saposhnikovia divaricata (Turcz.) Schischk., Paeonia lactiflora Pall., Atractylodes macrocephala Koidz., Pericarpium Citri Reticulatae*	-	-	-
[40]	Depression combined with irritable bowel syndrome	Treatment (n=85) vs False acupuncture (n=85), 4 weeks	Acupuncture: Tianshu (ST25), Shangjuxu (ST37), Zusanli (ST36), Neiguan (PC6)	–	–	–
[41]	Depression combined with senile functional constipation	Treatment (n=49) vs False acupuncture (n=49), 8 weeks	Acupuncture: Zhao Hai (KI 6), Da Zhong (KI 4), Tai Xi (KI 3), Tian Shu (ST 25), Shang Ju Xu (ST 37)	–	–	–
[42]	Depression combined with gastroesophageal reflux disease	Treatment (n=33) vs sham acupuncture (n=33), 10 weeks	Acupoint catgut embedding: Geshu (BL17), Ganshu (BL18), Danshu (BL19), Pishu (BL20), Weishu (BL21), Zusanli (ST36), Yanglingquan (GB34), Fenglong (ST40)	–	–	–
[43]	Depression combined with colorectal cancer	Treatment (n=140) vs vs (1) Psychological consultation, anti-anxiety antidepressant, meditation and relax training (n=70), 6 weeks	(1)The TCM syndrome differentiations (2) Acupuncture (3) The TCM Five-element Music Therapy	–	–	–
[44]	Depression complicated with functional dyspepsia	Yukguanja-tang (n=56) vs Pyeongwi-san (n=56) vs Usual care (n=56), 6 weeks	Liujunzi Decoction: *Panax ginseng C. A. Mey., Atractylodes macrocephala Koidz., Poria cocos (Schw.) Wolf, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Pinellia ternata (Thunb.) Ten. ex Breitenb.*	–	–	–

Note: The arrow↑ indicates upregulation, and the arrow↓ indicates downregulation.

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Table 2 The Mechanism of Traditional Chinese Medicine in the Treatment of Depression and Gastrointestinal Health Abnormalities in Animal Models

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[45]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (200±20 g); CUMS: 24 h Cage tilt, 24 h damp bedding, 1 h noise, 5 min 4 °C swimming in cold water, 5 min 50 °C exposure in laboratory, 24 h food deprivation, 24 h water deprivation, 1 min tail clamping, 15 electric shocks at unpredictable times.	Xiaoyao San: *Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	Ferulic acid; Liquiritin; isoliquiritin; albiflorin; paeoniflorin; catechins; gallic acid	23.1 g/kg, 46.2 g/kg, 92.4 g/kg; 3 week	Xiaoyao San improves depression by regulating metabolism. Body weight↑, sucrose preference↑; OFT: immobility time↓; L-tyrosine↓, kynurenic acid↓, TRP↑, a-ketoglutarate↑, citrate↑, creatinine↑; 5-HT↑, norepinephrine NE↑.
[46]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (200±20 g); CUMS: Food and water deprivation, heat stress, ice water swimming, noise stimulation, physical restraint, pinch tail foreign body stimulation.	Xiaoyao San: *Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	Paeoniflorin, liquiriti, isoliquiritin, glycyrrhizic acid, saikosaponin a, curcumin, ferulic acid	2.224 g/kg; 6 week	Xiaoyao San reatment can alleviate CUMS-induced depression-like behavior and improve intestinal permeability abnormalities, which may be related to the expression of tight-junction proteins (TJs). Body weight↑, food intake↑; OFT: total movement distance↑, the number of times into the central area↑, time in the central area↑; sucrose preference↑; Colon: lamina propria mucosa and muscle layer inflammatory cell infiltration and gland damage↓, the number of goblet cells↑, the size and number of microvilli↑; ZO-1↑, occludin↑, crodin-1↑, 5-HT↑.
[47]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (180–200 g); Chronic restraint stress	Xiaoyao San: *Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv). Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	–	1.12 g/kg, 2.224 g/kg; 3 week	Xiaoyao San negatively regulates PI3K/Akt/mTOR signaling, restores Th17/Treg balance, reduces the release of pro-inflammatory factors (such as IL-1β, TNF-α, IL-17, IL-21 and IL-22), and increases the release of anti-inflammatory factors (such as IL-10 and TGF-β) to treat depression. Body weight↑, sucrose preference↑, FST: immobility time↓; OFT: Total distance of motion↑, time spent in the central area↑; p-PI3K↓, p-Akt↓, andp-mTOR↓, andthep-PI3K/PI3K↓, p-Akt/Akt↓, p-mTOR/mTOR ratios↓, Foxp3↓, RORγt↓, percentage ofCD4+/CD25 +/Foxp3+ Tcells↓, percentage ofCD4+/CD25 +/Foxp3+ Tcells↑; TNF-α↓, IL-21↓, IL-22↓, TGF-β↑.

[48]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (200±20 g); CUMS	Xiaoyao San: *Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	-	23.1 g/kg	Xiaoyao San reshapes the gut microbiota, inhibits excessive activation of the TLR4/NLRP3 signaling pathway, maintains the integrity of the gut and the blood-brain barrier, thereby inhibiting gastrointestinal diseases and colonic neuroinflammation and exerting antidepressant effects. sucrose preference↑; OFT: number of times into the central area↑; LDB test: time spent in the lighting room↑, EPM test: time spent on the open arm↑; MWM test: number of times to enter the target platform↑, gastric emptying rate↑, intestinal transit rate↑, GAS↑, LPS↓; Intestinal flora: Bacteroidetes/Firmicutes↓, Lactobacillus↑, Adlercreutzia↑; TLR4↓, NLRP3↓, NF-κB↓, IL-1β↓, claudin-1↑, ZO-1↑.
[49]	Depression combined with intestinal microbiota dysbiosis	6-week-old male Sprague-Dawley rats (200±20 g); CUMS: 24-hour fasting, 24-hour water deprivation, 45°C thermal stimulation 10 minutes, swimming in 4°C water 5 minutes, tail clamp 2 minutes, foot shock 2 minutes, plastic tube restraint for 3 hours, circadian rhythm disorder and ultrasonic electromagnetic radiation 3 hours.	Xiaoyao San: *Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv,) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	Albiflorin, paeoniflorin, liquiritin, ferulic acid, atractylenolide III, atractylenolide I, and atractylenolide II	46.3 g/kg	Xiaoyao San regulates intestinal microbial composition and improves depression and gastrointestinal dysfunction. Body weight↑, sucrose preference↑, FST: immobility time↓; gastric residual rate↓, small intestine propulsion↑; Intestinal flora: Firmicutes↑, Actinobacteria↓, Corynebacteriaceae↓, Staphylococcaceae↓, Brevibacteriaceae↓, Dermabacteraceae↓, Yaniellaceae↓.
[50]	Depression combined with intestinal microbiota dysbiosis	8-week-old male C57Bl6/J mice; HFD (Research Diets, #D12492, 20% kcal from protein, 60% kcal from fat, and 20% kcal from carbohydrates)	Xiaoyao San: *Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	–	3.9 g/kg, 4 week	Xiaoyao Santreatment led to a significant remodeling of the gut microbiota, increased fecal SCFA, increased DRD2 expression to inhibit microglial activation and neuroinflammation, and reversed behavioral abnormalities in HFD-fed depressed mice. OFT: the time of movement of the central region↑, the frequency of entering the central region↑; EPM test: the number of times time into the arms↑, the frequency of entering both arms↑; sucrose preference↑; FST: immobility time↓; Intestinal flora: Faecalibaculumrodentium↑, Lactobacillusmurinus↑; SCFAs: acetate↑, butyrate↑, propionate↑, valerate↑;dopamine D2 receptor↓; Iba1↓, TNFα↓, IL-1β↓, IL-6↓.

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[51]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (150–170 g); CUMS: 12 h fasting, 12 h water deprivation, 12h cage tilting, 24 h wetting the bedding, 5 min clamping the tail with clips, 20 min 4°C cold stimulation, 10s electric shock, 5 min swimming in ice water, 1 h behavioral restraint.	Xiaoyao San: *Poria cocos(Schw;) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe*	Albiflorin, paeoniflorin, liquiritin, glycyrrhizic acid, and saikosaponin B2	0.75 g/kg, 1.5 g/kg, 3 g/kg; 4 week	Xiaoyao Sancan be transformed into antidepressant components that can enter the brain under the action of gut microbiota, and the metabolites derived from gut microbiota may also promote antidepressant effects by directly inhibiting the level and activity of FAAH in the brain. sucrose preference↑, total intake↑; FST: immobility time↓; Brain: stearic acid↓, sodium oleate↓, arachidonic acid↓; fatty acid amide hydrolase↓, fumarate, proline↓, uracil↓, lysine↓ serine↓, hypoxanthine↓, aspartate↓; NE↑, DA↑, GABA↑; Intestinal flora: Firmicutes↑, Lachnospiraceae_NK4A136↑, Colidextribacter↑, Streptococcus↑, Oscillibacter↑, Bacteroidetes↓, Blautia↓, Allobaculum↓, Lachnoclostridium↓.
[52]	Depression combined with intestinal microbiota dysbiosis	6-week-old male C57BL/6 mice(19–21 g); Restraint stress exposure	Chaihu Shugan San: *Bupleuri Radix, Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Paeoniae Radix Alba, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Ligusticum sinense* 'Chuanxiong', *Cyperi Rhizoma*	–	0.5 g/kg, 1 g/kg, 4 g/kg; 5 days	Chaihu Shugan San alleviate anxiety and depression by regulating the expression of BDNF involved in intestinal microflora and NF-κB. EPM: time spent in the open arm↑; TST: immobility time↓; LDT task: time spent in the light box↑; TST: immobility time↓; FST: immobility time↓; Hippocampus: IL-6↓, p-p65/p65↓, Cort↓; Colon: p-p65/p65↓, TNF-α↓, IL-6↓; Lactobacillaceae↑, Prevotellaceae↑, γ-Proteobacteria↓.
[53]	Depression combined with intestinal microbiota dysbiosis	Male Wistar rat (200±20 g); Chronic variable stress	Chaihu Shugan San: *Bupleuri Radix, Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Paeoniae Radix Alba, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Ligusticum sinense* 'Chuanxiong', *Cyperi Rhizoma*	–	7.0 g/kg-1, 4 week	Chaihu Shugan San treats depression by improving metabolic disorders associated with depression through gut microbiota. sucrose preference↑, 5-HT↑, Glu↑, DA↑, NE↑, GABA↑; IL-1β↓, IL-6↓; Intestinal flora: Bacteroidetes↑, Lactobacillus↑, Oscillibacter↓; 3-Hydroxypicolinic acid↑, Inosine↑.

[54]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (160–200 g); Chronic unpredictable stress	Shugan Hewei Decoction: *Bupleuri Radix, Paeonia lactiflora Pall., Citrus aurantium L., Curcuma longa L., Amomum aurantiacum H. T. Tsai & S. W. Zhao, Amomum verum Blackw., Atractylodes Lancea (Thunb.) DC., Aucklandiae Radix, Coptis chinensis Franch., Tetradium ruticarpum (A. Juss.) T. G. Hartley, Glycyrrhiza uralensis Fisch.*	Paeoniflorin, liquiritin, naringin, hesperidin, neohesperidin, palmatine chloride, and Saikosaponin A	1.34 g/kg, 2.68 g/kg; 1 week	Shugan Hewei Decoction alleviates cecal mucosal damage and improves depression and anxiety like behavior by regulating the cecal microbiota and inhibiting excessive activation of NLRP3 inflammasome in the cecum and serum. Body weight↑, sucrose preference↑; OFT: total movement distance↑, immobility time↓, number of times through the central area↑; FST: immobility time↓; Feces: Bristol Stool Form Scale↑, water content↑; Blind intestine: inflammatory cell infiltration↓, mucosal injury degree↓, crypt depth↓; Intestinal flora: Bacteroidetes↑, Prevotellae_9↑, Roseburia↑, Blautia↑, Prevotella_1↑, Firmicutes↓, Lactobacillus↓, Lachnospiraceae_NK4A136↓; NLRP3↓, caspase-1↓, IL-1β↓, IL-18↑, TLR4↑, p-NF-κB/NF-κB↑, MyD88↑.
[55]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (190–200 g); CUMS	Shugan Hewei Decoction: *Bupleuri Radix, Paeonia lactiflora Pall., Citrus aurantium L., Curcuma longa L., Amomum aurantiacum H. T. Tsai & S. W. Zhao, Amomum verum Blackw., Atractylodes Lancea (Thunb.) DC., Aucklandiae Radix, Coptis chinensis Franch., Tetradium ruticarpum (A. Juss.) T. G. Hartley, Glycyrrhiza uralensis Fisch.*	Paeoniflorin, liquiritin, naringin, hesperidin, neohesperidin, palmatine chloride, saikosaponin A	7.34 g/kg, 14.68 g/kg; 2 week	Shugan Hewei Decoction regulates microbial-derived tryptophan metabolism and AMPK/mTOR pathway, enhances intestinal barrier function, and improves depression-like behavior. Body weight↑, sucrose preference↑; FST: immobility time↓; OFT: total movement distance↑, number of times through the central area↑, immobility time↓; Intestinal flora: Prevotella↑, Parabacteroides↑, Prevotella↑, Escherichia↑, Parasutterella↑, Ruminococcus↓, Eubacterium↓, Lactobacillus↓, Blautia↓, Dorea↓; tryptophan↑, tyrosine↑, histidine↑, bile acid↓, prenol lipids↓, fatty acids↓; LPS↓, D-LA↓, DAO↓; ZO-1↑, Occludin↑; AMPK↑, mTOR↓, LC3↑, ATG5↑, Beclin1↑, p-AMPK↑, p-mTOR↓, p62↓.
[56]	Depression combined with intestinal microbiota dysbiosis	8-week-old Kunming male mice (18±2g); CUMS	Changpu San: *Acori Tatarinowii Rhizoma, Panax ginseng C. A. Mey., Polygala tenuifolia Willd., Rehmanniaglutinosa (Gaertn). Libosch. ex Fisch. and C. A. Mey., Poria cocos (Schw.) Wolf, Dioscorea polystachya Turcz., Cinnamomum cassia (L.) D. Don*	–	6.76 g/kg, 13.52 g/kg, 27.04 g/kg; 3 week	Changpu Sanaffect the gut-brain axis and tryptophan metabolism by regulating the abundance of beneficial bacteria Prevotella and Bacillus, while alleviating Helicobacter related pro-inflammatory bacteria, thereby alleviating depression-like symptoms. Sucrose preference↑; OFT: distance of activity in the central region↑, activity time in the central area↑; TST: immobility time↓; tryptophan↑, kynurenine↓, Hippocampal serotonin↑, TNF-α↓, IL-1β↓; Intestinal flora: Lactobacillaceae↓, Helicobacteraceae↓, Lactobacillus↓, Ruminococcus↑, Ruminococacae↑, Bacteroidaceae↑.

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[57]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (180–220 g); CUMS: 12 h light/dark cycle reversal, 2 h behavioral limitation, 5 min 40 °C forced swimming, 10s electric shock, 10 min 0°Cexposure, 24 h water shortage, 5 min 40°C exposure, 24 h fasting, 1 min squeeze tail.	Shugan Jieyu Capsule: *Hypericum perforatum L., Acanthopanax senticosus (Rupr.etMaxim.) Harms*	Hypericin, Hyperoside. Pseudohypericin, Quercetin, Eleutheroside E, Isofraxidin	150 mg/kg−1, 8 week	Shugan Jieyu Capsulesignificantly change the intestinal flora and intestinal microbiome function of depression model rats and alleviate depression. Sucrose preference↑, CMO↓, adrenal index↓, 5-HT↑; Intestinal flora: Actinobacteria↓, Tenericutes↑, Ruminococcaceae↑.
[58]	Depression combined with intestinal microbiota dysbiosis	6-week-old male Balb/c mice (20±2 g); CUMS: 16 h wet cage, 24 h water shortage, 24 h fasting, 24 h 45° cage tilt, 40 min 200 r/min shake, 6 h bondage, night lighting.	Jianpi Jieyu Decoction: *Astragalus membranaceus (Fisch.) Bunge, Pseudostellaria heterophylla, Acanthopanax senticosus (Rupr.etMaxim.) Harms, Atractylodes macrocephala Koidz., Paeonia lactiflora Pall., Hyriopsis cumingii (Lea), Polygala tenuifolia Willd., Glycyrrhiza uralensis Fisch.*	–	9.2 g/kg, 2 week	Jianpi Jieyu Decoction regulates the production of GABA by Lactobacillus to exert antidepressant effects. TST: immobility time↓; food intake↑; FST: immobility time↓; Intestinal flora: Epsilonbacteraeota↑, Bacteroidetes↑, Lactobacillus↑, Helicobacter↑, Epsilonbacteraeota↑, Firmicutes↓, Proteobacteria↓, Actinobacteria↓, Odoribacter↓, Desulfovibrio↓; GABA↑, GluR1↑, p-Tau↑.
[59]	Depression combined with intestinal microbiota dysbiosis	6-week-old male Sprague-Dawley rats; CUMS: 3 h bound, 24 h water deficiency, 24 h fasted, 15 min 200 r/min shaking, 5 min tail-clamping, 24 h wet bedding, 5 min swimming in 10°C cold water, light and dark reversed, 36 h lightening.	YangXin JieYu Decoction:*Panax ginseng C. A. Mey., Ophiopogon japonicus (L.f.) Ker-Gawl., Schisandrae Chinensis Fructus, Epimedium brevicornu Maxim., Allium macrostemon Bunge, Rosae Rugosae Flos, Albizia julibrissin Durazz., Curcuma aromatica Salisb., Acori Tatarinowii Rhizoma, Citrus reticulata Blanco*	、Ginsenoside Rg3、、Ginsenoside Rf、、Magnoflorine	0.525 g/kg, 1.05 g/kg, 2.1 g/kg; 6 week	Yangxin Jieyu Decoction increased the abundance of monoglobulin and up-regulated the enzymes involved in propionic acid metabolism and TCA cycle, and the regulation of intestinal microbiota and metabolites was antidepressant. Sucrose preference↑; OFT: total activity distance↑, FST: immobility time↓; COR↓, L-isoleucine↑, succinic acid↓; taurine↓, dihydroxyacetone↓, L-malic acid↓, 1-methylhistidine↓, 2-furoylglycine↓;hippuric acid↑, melatonin↑; Intestinal flora: Actinobacteria↓, Bifidobacterium↓, Bacteroides↓, Parabacteroides↓, Proteobacteria↓, Desulfobacterota↑, Cyanobacteria↑, Patescibacteria↑, Lachnospiraceae_NK4A136↑.
[60]	Depression combined with intestinal microbiota dysbiosis	Male Institute of Cancer Research mice (20–25 g); CUMS: food deprivation, electric shocks, water shortages, overnight lighting, forced swimming, wet cages and restraints.	Kaixin San: *Panax ginseng C. A. Mey., Polygala tenuifolia Willd., Acori Tatarinowii Rhizoma, Poria cocos (Schw.) Wolf*	–	3 g/kg, 10 g/kg; 1 week	Kaixin San increases the supply of neurotransmitters and neurotrophic factors, inhibits the over-stimulated HPA axis, and exerts antidepressant effects by regulating the gut-brain axis. Sucrose preference↑; FST: immobility time↓; LPS↓, IL-1β↓、IL-6↓, TNF-α↓, ZO-1↑, occludin↑; CRF↓, ACTH↓, 皮质酮↓; Intestinal flora: Allobaculum↑, Bifidobacterium↑, Turicibacter↑, Coprococcus↓, Helicobacter↓, Mucispirillum↓, Odoribacter↓, Oscillospira↓.

[61]	Depression combined with intestinal microbiota dysbiosis	2-3-week-old male Institute of Cancer Research mice (20–25 g); CUMS: 24 h water shortage, 24 h fasting, placed in an inclined cage, electric shock, 4 h restraint, exposure to moist cushions, day/night upside down.	Kaixin San: Panax ginseng C. A. Mey., Polygala tenuifolia Willd., Acori Tatarinowii Rhizoma, Poria cocos(Schw.) Wolf	–	1.5 g/kg, 4.5 g/kg; 4 week	Kaixin San relieves intestinal damage, improves intestinal ecological disorders, antibiotic resistance, intestinal barrier damage and dysfunction in the treatment of depression. Body weight↑, TST: immobility time↓; FST: immobility time↓; Colon: intestinal epithelial cell apoptosis↓, villus length↑, gastrointestinal propulsion rate↑; Intestinal flora: Parasutterella↑, unclassified_f_Muribaculaceae↑; caspase-3↓, TNF-α↓, IL-6↓; ZO-1↑.
[62]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (200±20 g); CUMS: 3 h restraint, 10 min vibration cage, 24 h food deprivation, 24 h water deprivation, 24 h wet padding, 10 min 50 °C high temperature stimulation, 10 min swimming in ice water, 3 min tail clamping, 6 h 100 Hz ultrasound stimulation.	Yueju Wan: *Cyperi Rhizoma, Ligusticum sinense* 'Chuanxiong', *Gardenia jasminoides J. Ellis, Atractylodes Lancea (Thunb.) DC., Massa Medicata Fermentata*	–	1.9 g/kg, 3.8 g/kg, 7.6 g/kg; 6 week	Yueju Wan exerts antidepressant effects by improving the structure of the intestinal microflora and affecting tryptophan metabolism, purine metabolism, glutamate metabolism, and primary bile acid biosynthesis. Body weight↑; OFT: activity distance of central area↑; TST: immobility time↓; FST: immobility time↓; ZO-1↑, IL-1β↓, NLRP3↓, ASC↓, caspase-1↓; Intestinal flora: Prevotella↓, Bacteroides↓, Eubacterium↑, Roseburia↑, Oscillibacter↑; kynurenic acid↓, tryptophan↑, xanthine↓, hypoxanthine↓; glutamate↓, cholic acid↑, taurine deoxycholic acid↑.
[63]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (200±20 g); CUMS: 20 h wet cage, 24 hours 45°cage tilt, 2 h behavioral limitation, 5 min Swimming in 4 °C water, 15 minutes cage shaking, 1 min tail pinching, 24 h food deprivation, 24 h water deprivation.	Zhizi Chi Decoction: *Gardenia jasminoides J. Ellis, Sojae Semen Praeparatum*	–	10 g/kg; 4 week	Zhizi Chi Decoction improves depression by regulating the disorders of microbiota related to inflammation and 5-HT Metabolism, increasing the levels of other beneficial bacteria and regulating the production of butyrate to improve the disorders of proinflammatory cytokines, BDNF, Neurotransmitters and Amino acids. Sucrose preference↑, TST: immobility time↓;FST: immobility time↓; Number of Nissl bodies↑; Intestinal flora: Firmicutes↑, Candidatus_Saccharibacteria↑, Saccharibacteria_genera_incertae_sedis↑, Barnesiella↑, Lachnospiracea_incertae_sedis↑, Streptococcus↓; butyric acid↑; TNF-α↓, IL-1β↓, IL-6↓, BDNF↑;5-HT↑, DA↑;5HIAA↓, Kyn↓, 5-HIAA/5-HT↓, Kyn/Trp↓.

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[64]	Depression combined with intestinal microbiota dysbiosis	5-week-old male C57BL/6 mice; Chronic restraint stress + subcutaneous injection of CORT suspension in the neck and back	Zhizi Chi Decoction: Gardenia jasminoides J. Ellis, Sojae Semen Praeparatum	–	12 g/kg; 3 week	Zhizi Chi Decoction exerts a pleiotropic antidepressant effect by regulating HPA axis and intestinal microflora, participating in the process of neuroactive ligand/receptor interaction, regulating the secretion of prolactin and estrogen, and interfering with MAPK and TNF signaling pathways to reduce inflammation levels. Sucrose preference↑, FST: immobility time↓; OFT: activity distance of central area↑, activity time of central area↑; EPM: total activity distance↑, activity distance of the open arm in the area↑; CRH↓, ACTH↓, CORT↓, IL-1β↓, TNF-α↓, 5-HT↑, DA↑, GABA↑, IL-10↑; Fos↑, Junb↑, Egr2↑, Dusp1↑, Nr4a1↑, Btg2↑, Gast↓, Cyp2a5↓, Stx11↓, Trim5↓; Intestinal flora: Candidatus↑, Arthromitus↑, Corynebacterium↑, Allobaculum↑, Lactobacillus↑, Acinetobacter↑, Peptostreptococcus↑, Prevotella↑, Parabacteroides↓, Bilophila↓, Fusobacterium↓, Desulfovibrio↓.
[65]	Depression combined with intestinal microbiota dysbiosis	8-week-old Sprague-DawLey rats; CUMS: 24 h food deprivation, 24 h water deprivation, 24 h continuous lighting, 24 h wet padding, 250 mL of water per cage, 24 h 45°tilt cage, 90s tail clip, 6 min forced swimming 4°C water, 60 min forced swimming 42°C water.	Gegen Qinlian Decoction: *Pueraria montana (Lour.) Merr., Scutellaria baicalensis Georgi, Coptis chinensis Franch., Glycyrrhiza uralensis Fisch.*	–	18 g/kg; 5 week	Gegen Qinlian Decoction improves depression by significantly enhancing the composition of the intestinal microbiota, correcting metabolism, and improving depression. Sucrose preference↑; Colon: mucosal lamina propria density ↑, intestinal gland spacing↓, goblet cell abundance↑; Intestinal flora: Bacteroides↑, Prevotella↑, Helicobacter↑, Phascolarctobacterium↑, Pseudomonas↑, Eubacterium_ruminantium↓, Lachnoclostridium↓, Marvinbryantia↓, Ruminococcaceae UCG-009↓, Ruminococcaceae NK4A214↓, Fournierella↓, Pygmaiobacter↓, Ruminococcus↓, Family_XIII_AD3011↓, Christensenellaceae↓, Clostridia_vadinBB60↓; Fasciculic acid B↓, Spermine↓, Fludrocortisone acetate↓, Alpha-Ketoglutaric acid↓, 2-Oxoglutaric acid↓, N'-(benzoyloxy)-2-(2, 2-dichlorocyclopropyl) ethanimidamide↓, N6-Succinyl Adenosine↓, Oleanolic acid↑, KQH↑, Ergosta-5, 7, 9(11), 22Tetraen-3-beta-Ol↑, Gentisic acid↑, 4-Hydroxyretinoic Acid↑, Leucine-enkephalin↑, N-lactoylphenylalanine↑.

[66]	Depression combined with intestinal microbiota dysbiosis	6-8-week-old Male Sprague-Dawley rats (180–200 g); Chronic restraint stress	Shugan granule: *Angelica sinensis (Oliv.) Diels, Bupleuri Radix, Cyperi Rhizoma, Paeonia lactiflora Pall., Atractylodes macrocephala Koidz., Mentha canadensis L., Poria cocos(Schw.) Wolf, Gardenia jasminoides J. Ellis, Paeonia suffruticosa Andr., Glycyrrhiza uralensis Fisch.*	–	0.63 g/kg; 4 week	Shugan granule target the PI3K/Akt/mTOR pathway by altering gut microbiota and metabolites, thereby improving altered behavior and inflammation in the hippocampus. Body weight↑, sucrose preference↑; FST: immobility time↓; OFT: immobility time↓; TNF-α↓, IL-1β↓, IL-6↓;PI3K↑, Akt↑, mTOR↑; Intestinal flora: Bacteroides↓, Butyricimonas↑, Candidatus↑.
[67]	Depression combined with intestinal microbiota dysbiosis	4-week-old male C57BL/6J mice (16–18 g); CUMS: fasting and water deprivation, empty bottle stimulation, dirty cages, spatial constraints, tilted cages, wet cages, white noise	*Lilium lancifolium Ker Gawl., Rehmanniaglutinosa (Gaertn.) Libosch. ex Fisch. and C. A. Mey.*	Verbascoside	Lilii Bulbus-Rehmannia Root: 6.25 g/kg; Verbascoside: 60 mg/kg; 3 week	Lilii Bulbus-Rehmannia Root and Verbascoside regulate the two-way communication between the intestine and the brain through GMBA to achieve the balance of multi-system function in patients with depression. Sucrose preference↑, FST: immobility time↓: MWM test: platform crossing duration↓; IL-1β↓, IL-6↓, IL-17↓, TNF-α↓; Intestinal flora: Mucispirillum↑, Candidatus_Arthromitus↑, Parabacteroides↑, Adlercreutzia↑, Desulfovibrio↓, Prevotella↓, Alistipes↓, Bacteroides↓, Prevotella↓.
[68]	Depression combined with intestinal microbiota dysbiosis	8-week-old male Kunming mice (18±2 g); CUMS: 24 h water shortage, 24 h fasting, 24 h cage tilt, 24 h wet bedding, 1 min tail pinching, 5 min forced swimming in ice water.	*Valeriana officinalis* L.	–	5.7 mg/kg, 11.4 mg/kg, 22.9 mg/kg; 3 week	*Valeriana officinalis L. affects microbial production of vitamin B12 and regulates the expression of CUBN and AMN, affects ileal homeostasis, and reduces homocysteine penetration into the central nervous system, thereby reducing depressive symptoms. FST: immobility time↓; NSFT: eating latency↓; Hippocampus: methionine synthase↑, homocysteine↓; ileum: epithelial cell shedding↓, crypt structure damage↓; vitamin B12↑; Intestinal flora: Brevundimonas↑, Gemmobacter↑, Luteimonas↑, Romboutsia↑, Turicibacter↑, Parasutterella↑.*
[69]	Depression combined with intestinal microbiota dysbiosis	6-week-old male C57BL/6 mice (23–27 g); CUMS: 24 h day/night cycle reversal, 24 h food deprivation, 24 h water deprivation, 5 min Swimming in 4°C water, 5 min tail pinching, 2 h restraint, 12 h exposed to wet padding, 12 h 45°tilt cage, 10 min horizontal oscillation.	*Linderae Radix*	–	1.2 g/kg, 3.6 g/kg; 6 week	*Linderae Radix protects hippocampal neurons by regulating BDNF/TrkB/CREB signaling pathway. Sucrose preference↑; FST: immobility time↓; TST: immobility time↓; OFT: total activity distance↑, number of times through the central area↑, activity distance in the central area↑; ACTH↓, ghrelin↑, Small intestinal transport rate↑; Number of neurons↑, Number of Nissl bodies↑; CREB↑, TrkB↑, BDNF↑.*
[70]	Depression combined with intestinal microbiota dysbiosis	6-8-week-old male C57BL/6 mice; Chronic restraint stress	*Hypericum perforatum* L.	–	100 mg/kg, 250 mg/kg, 500 mg/kg; 3 week	*Hypericum perforatum L. plays antidepressant effect by regulating intestinal microbial composition and tryptophan metabolism. Sucrose preference↑, FST: immobility time↓; TST: immobility time↓; 5-HT↑; LPS↓, IL-1β, TNF-α↓, IL-6↓, IL-10↑, Nlrp2↓, Caspase1↓, IL-22↑, Zo-1↑, Occludin; Intestinal flora: Akkermansia↑, Bifidobacterium↑, Parabacteroides↑, Bacteroides↑; KYN↓, tryptophan↓, 5-HTP↓.*

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[71]	Depression combined with intestinal microbiota dysbiosis	8-week-old male C57BL/6J mice (20–23 g); CUMS: 24 h food deprivation, 24 h water deprivation, 12 h 45°tilt cage, 5 min shake cage, 2 h bound, l5 min pinch tai, swimming in 4°C cold water, swimming in 45°C hot water, 24 h exposed to wet padding, 24 h remove padding, 3 h noise lasted, 3 h odor stimulation, 2 s 3-times of electric shock stimulation.	–	*Polygonatum sibiricum* polysaccharide	400 mg/kg, 2 week	Polygonatum sibiricum polysaccharide improve depression-like behavior by regulating the gut microbiota-lipopolysaccharide-paraventricular nucleus signal axis. OFT: immobility time↓, time of activity in central area↑, distance of total activity↑; colon: number of goblet cells↑, number of glands↑, gland size↑, mucus secretion↑; occludin↑, claudin 1↑, ZO-1↑; LPS↓, 5-HT↑, CORT↓; Measurement of local field potential: number of c-fos+ neurons in the PVN↓; energy of LFPs in the PVN↑; δ, θ, αbands in the PVN↓; Intestinal flora: Muribaculaceae↓, Lactobacillaceae↓, Ruminococcaceae↓, Erysipelotrichaceae↓, Akkermansiaceae↑, Helicobacter↑.
[72]	Depression combined with intestinal microbiota dysbiosis	7-8-week-old male BALB/c mice; CUMS: 5 min swimming in 4°C water, 5 min swimming in 40°C water, 24 h congestion pressur; 12 h food deprivation, 12 h water deprivation, 12 h exposure to damp bedding, 12 h overnight lighting, 3 min tail pinch, 1 h empty bottle, 24 h light/dark cycle reversal, 30 min noise stress, 4 h constraint stress.	–	*Polygonatum sibiricum* polysaccharide	400 mg/kg, 65 day	Polygonatum sibiricum polysaccharide exerts antidepressant like effects through the MGB axis and interacts with the PI3K/AKT/TLR4/NF-κB and ERK/CREB/BDNF signaling pathways. Body weight↑, sucrose preference↑; OFT: total movement distance↑, total movement time↑; eating latency↓; ACTH↓, CORT↓; 5-HT↑, NE↑; TNF-α↓, IL-1β↓, IL-6↓; TLR4↓, p65↓, PI3K↑, p-AKT/AKT↑; BDNF↑, pCREB/CREB↑; ZO-1↑, Occludin↑.
[73]	Depression combined with intestinal microbiota dysbiosis	Male Institute of Cancer Research mice (20.0±2.0 g); CUMS: 24 h food deprivation, 24 h water deprivation, 24 h exposed to wet padding, 12 h paired feeding, overnight lighting, 24 h light/dark cycle reversal, 30 min noise exposure, 1 min tail pinching.	–	Puerarin	30 mg/kg, 100 mg/kg; 4 week	Puerarin improves anti-inflammatory bacteria to reduce harmful or inflammatory bacteria antidepressants. Sucrose preference↑, FST: immobility time↓; Intestinal flora: Firmicutes↑, Actinobacteria↑, Lachnospiraceae↑, Prevotella_1↑, Oscillopira↑, Bacteroidetes↓, Proteobacteria↓, Bacteroidales↓, Campylobacterzles↓, Desulfovibrionales↓.

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[74]	Depression combined with intestinal microbiota dysbiosis	Male Sprague-Dawley rats (230±20 g); CUMS: 5 min swimming in 4°C cold water, 24 h food deprivation, 24 h water deprivation, 1 min tail pinching, 24 h 150 flashes per minute, 24 h white noise exposure, 2 h behavioral limitation, overnight lighting, 24 h exposed to wet padding.	–	*Polygalae radix* oligosaccharide esters	42 mg/kg, 84 g/kg, 126 mg/kg; 8 week	Polygalae radix oligosaccharide esters increase the level of monoamine neurotransmitters in the brain, reduce the hyperfunction of HPA axis, regulate the imbalance of intestinal microflora in rats, and regulate the levels of SCFA in feces and LPS and IL-6 in serum to exert antidepressant effects. Body weight↑, sucrose preference↑; FST: immobility time↓; OFT: total activity distance↑, time spent in central area↑; 5-HT↑, NE↑, DOPAC↑, 5-HIAA↑; CORT↓, ACTH↓; Intestinal flora: Bacteroides↓, Oscillibacter↓, Parasutterella↓, Intestinimonas↓, Romboutsia↑, Roseburia↑, Lachnospiraceae_NK4A136↑, Prevotella_9↑, Eubacterium_coprostanoligenes↑; Colon: TRP↑, crypt depth↓; occludin↑, IL-6↓, LPS↓;5-HT2A↓, 5-HT1A↑, IDO1↓, TNF-α↓; acetic acid↑, propionic acid↑, butyric acid↑.
[75]	Depression combined with intestinal microbiota dysbiosis	8-week-old male Sprague-Dawley rats (180–200 g); CUMS: 2 minutes 3 mA electric shock, 2 min tail pinching, 3 h 100 decibels noise, 5 min swimming in 4°C cold water, 5 min swimming in 45°C hot water, 24 h food deprivation, 24 h water deprivation.	–	*Pogostemon cablin* essential oil	0.8 mL/kg, 4 week	Pogostemon cablin essential oilalleviates antidepressant effects by affecting 5-HT levels in the brain by regulating gut microbiota and SCFA-mediated gut-brain axis. OFT: number of times into the central area↑, time to enter the central area↑; FST: immobility time↓; 5-HT↑; Intestinal flora: Bacteroides↑, Blautia↑, Ruminococcus_1↓, Ruminococcus _2↓, Oscillibacter↓; propionic acid↑, hexanoic acid↓.
[76]	Depression combined with intestinal microbiota dysbiosis	8-week-old male Sprague-Dawley rats (200–220 g); CUMS: 24 h food deprivation, 24 h water deprivation, 5 min tail pinching, 24 h light/dark cycle reversal, 5 min swimming in 4°C cold water, 5 min swimming in 45°C hot water, 24 h exposed to wet padding, 45°tilt cage, 4 h constraint stress, 45 min 60 Hz horizontal vibration.	–	Berberine	40 mg/kg, 200 mg/kg	Berberine has therapeutic effect on chronic stress and depression. Body weight↑, OFT: time to enter the central area↑, immobility time↓; sucrose preference↑, gastric mucosa and intestinal microvilli injury↓.
[77]	Depression combined with intestinal microbiota dysbiosis	6-week-old Male Institute of Cancer Research mice (20±5 g); CUMS: 80–90% humidity, 80 decibels noise, 2 h behavioral limitation, 24 h food deprivation, 24 h water deprivation, odor of alcohol and garlic, 5 min 80 rpm horizontal vibration、1 min tail pinching, a piece of plastic foreign matter, 24 h light/dark cycle reversal, 5 min swimming in cold water, 5 min swimming in 35 – 40°C hot water, 45°tilt cage.	–	Gastrodin	100 mg/kg; 3 week	Gastrodin inhibits activation of the gut-brain axis and regulates gut microbiota dysbiosis Antidepressant. Sucrose preference↑; TST: immobility time↓; FST: immobility time↓; EPM: activity distance↑, activity time↑, number of entries↑, escape latency↓; Intestinal flora: Lactobacillus↑, Bacteroides↑, Lactobacillus↑, Corynebacterium↑, Staphylococcus↑, Bacteroides↑, Psychrobacter↑, Alistipes↑.

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[78]	Depression combined with intestinal microbiota dysbiosis	6-week-old male Institute of Cancer Research mice (18–20 g); CUMS	–	*Cistanche tubulosa* total glycosides	4.55 g/kg, 1 week	Cistanche tubulosa total glycosides antidepressant by alleviating the bidirectional interaction of HPA axis overactivation and low-grade inflammation that reduces intestinal barrier damage, and reducing pro-inflammatory cytokine release and tryptophan-kynurenine metabolism. Sucrose preference↑, OFT: total activity distance↑, immobility time↓; Serum: CORT↓, CRF↓, ACTH↓, TNF-α↓, IL-1β↓, IFN-γ↓; Hippocampus: TNF-α↓, 5-HT↑, BDNF↑; GnRH↑, cAMP↑, cAMP/cGMP↑, cGMP↓; Colon: number of goblet cells↑, mucus layer thickness↑; ZO-1↑; Intestinal flora: Firmicutes↓, Bacteroidetes↓, Ruminococcaceae↓, Peptococcaceae↓, Erysipelotrichaceae↑, Muribaculaceae↑; tryptophan↑, kynurenine↓, Kyn/Trp↓, IDO1↓.
[79]	Depression combined with intestinal microbiota dysbiosis	6-8-week-old male Sprague-Dawley rats (200±20 g); CUMS: 20 h food deprivation, 24 h water deprivation, 24 h 45°tilt cage, 24 h light/dark cycle reversal, exposed to wet padding, 5 min swimming in 4°C cold water, 5 min horizontal shaking, 2 h behavioral limitation	–	Hesperidin	50 mg/kg, 3 week	Hesperidininhibits the expression of BDNF and 5-HT and protects the gut microbiota to reduce depressive behavior. Body weight↑, food intake↑, sucrose preference↑; FST: immobility time↓; OFT: activity distance of central area↑; BDNF↑, 5-HT↑; Intestinal flora: Bacteroidota↑, Proteobacteria↑, Ruminococcaceae↑, Prevotellaceae↑.
[80]	Depression combined with intestinal microbiota dysbiosis	4-week-old male Institute of Cancer Research mice (21–23 g); CUMS: food deprivation, water deprivation, 90 dB white noise, stroboscopic light source, odor stimulation, 45°tilt cage, exposed to wet padding, 6 h behavioral limitation, 5 min swimming in 4°C cold water, 10 min heat stress in 55°C oven, 2 h shake cage, 2 min tail pinching, 50s 0.6 mA electrical stimulation.	–	Gardeniae Fructus oil	122 mg/kg, 2 week	Gardeniae Fructus oil play an antidepressant role by regulating intestinal flora and mediating hippocampal TLR4/NF-κB/NLRP3 pathway. Body weight↑, sucrose preference↑; OFT: time spent in the central area activities↑, distance of the central area activities↑; FST: immobility time↓; NSFT: feeding latency↓; TST: immobility time↓; EPM: activity time↑; 5-HT↑, DA↑, BDNF↑; DAO↓, LPS↓, IL-1β↓, IL-6↓, TNF-α↓; ZO-1↑, occludin↑, claudin-1↑, TLR4↓, p-NF-κB↓, NLRP3↓, ASC↓, IL-1β↓.

[81]	Depression combined with irritable bowel syndrome	6-8-week-old male C57BL/6J mice (20–25 g); Sanna Leaf gastric irrigation+CUMS: 24 h food deprivation, 24 h water deprivation, 24 h light/dark cycle reversal, 3 h behavioral limitation, 1 min swimming in 0°C cold water, 0vernight noise exposure, 1 min tail pinching.	Xiaoyao San: Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe	–	1.9 g/kg, 3.8 g/kg, 7.6 g/kg, 1 week	Xiaoyao San improved the intestinal symptoms of IBS by regulating intestinal CCL2 and alleviating inflammatory response through IL-17-related ACT1/TRAF6/p38MAPK/AP-1 signaling pathway, and improved depressive symptoms by regulating dopamine release in the brain through the DRD2/TH signaling pathway. Body weight↑, fecal water content↓, AWR score↓; OFT: total activity distance↑, time spent in the central area↑; EPM: time spent in the open arm↑; TST: immobility time↓; FST: immobility time↓; sucrose preference↑; ZO-1↑, Obcludin↑, Claudin 4↑, Claudin 2↓, IL-17A↓, IL-17F↓, AP-1↓, TNF-α↓, CCL2↑, ACT1↓, TRAF6↓, P38MAPK↓, DRD2↑; 5-HT↑, BDNF↑, DA↑, CORT↓.
[82]	Depression combined with irritable bowel syndrome	6-week-old male Sprague-Dawley rats (220–240 g); Sanna Leaf gastric irrigation	Baizhu shaoyao Decoction: *Saposhnikovia divaricata (Turcz.) Schischk., Paeonia lactiflora Pall., Atractylodes macrocephala Koidz., Pericarpium Citri Reticulatae*	–	3.8 g/kg, 7.65 g/kg, 15.3 g/kg; 1 week	Baizhu Shaoyao Decoction mediates the treatment of diarrhea, abdominal pain, and depression through intestinal barrier repair, regulation of brain gut peptide expression, and reduction of sIgA levels through the Foxo signaling pathway. Body weight↑; OFT: total activity distance↑, time to enter the central area↑; food intake↑, stool water content↓, sucrose preference↑, AWR index↑; intestinal permeability↓, 5-HT↓, DAO↓, D-LA↓, FITC↓; Colon: villus length↑; ZO-1↑, claudin-1↑, occludin↑, MCT↓, VIP↓, SP↓, PAF↓, CCK↓, GMFBs↓, NPY↑, sIgA↓, Foxo1↑, Gsk3b↑, Foxo3↑.
[83]	Depression combined with irritable bowel syndrome	6-week-old male Sprague-Dawley rats (180–200 g); CUMS	Changkang Fang Formula: *Salvia miltiorrhiza Bunge, Paeonia lactiflora Pall., Fagopyrum dibotrys (D. Don) Hara, Saposhnikovia divaricata (Turcz.) Schischk., Cuscutachinensis Lam., Rehmanniaglutinosa (Gaertn.) Libosch. ex Fisch. and C. A. Mey., Coptis chinensis Franch., Cicadae Periostracum*	–	5.0 g/kg	Changkang Fang Formula induced structural changes in the gut microbiota and improved IBS and depression-like behavior through the microbiota-gut brain axis. Body weight↑, fecal water content↓, GI transit↓, AWR index↓, sucrose preference↑; FST: immobility time↓; Colon: 5-HT↓, BDNF↓, PKA↓, CREB↓; Hippocampus: 5-HT↑, BDNF↑, PKA↑, CREB↑; Intestinal flora: Bacteroidetes↑, Clostridiales↓, Corynebacteriales↓, Christensenellaceae_R-7↓, Ruminococcaceae↓, Lachnospiraceae↓, Dubosiella↑, Lactobacillus↑.
[84]	Depression combined with irritable bowel syndrome	Newborn male Sprague-Dawley rats; Chronic restraint stress	Chang'an II decoction:*Atractylodes macrocephala Koidz., Paeonia lactiflora Pall., Saposhnikovia divaricata (Turcz.) Schischk., Astragalus membranaceus (Fisch.) Bunge*	–	2.85 g/kg, 5.71 g/kg, 11.42 g/kg; 2 week	Chang'an II Decoction alleviates intestinal stress syndrome and depressive symptoms through anti-inflammatory, immune regulation, and protection of intestinal mucosa. AWR score↑; OFT: number of times into the central area↑; sucrose preference↑, Colon: Mucosal barrier integrity↑; CD8+ cell count↓, CD4+/CD8+ cell ratio↑, IL-1β↓, IL-4↑.

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Table 2 (Continued).

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[85]	Depression combined with irritable bowel syndrome	6-8-week-old male C57BL/6 mice; CUMS: 24 h food deprivation, 24 h water deprivation, 1 min swimming in 0°C cold water, 1 min tail pinching, overnight lighting, 0vernight noise exposure, 6 h exposed to wet padding	–	Costunolide	1.25 mg/kg-1, 5 mg kg-1, 20 mg kg-1; 3 week	Costunolide improved gastrointestinal dysfunction and depression-like behavior in stress-induced IBS mice by inhibiting the activation of mast cells in the intestinal mucosa and the inhibition of 5-HT reuptake by SERT in the hippocampus. Body weight↑, fecal water content↓, tryptase↓; IL-6↓, TNF-α↓; Colon permeability↓; sucrose preference↑, OFT: time of activity in the central area↑; BDNF↑, GluN2A↑, p-ERK↑, p-CREB↑, 5-HT↑, 5-HIAA↓.
[86]	Depression combined with irritable bowel syndrome	Male Sprague-Dawley rats (200–220 g); Chronic acute combined stress	–	Curcumin	10 mg/kg, 20 mg/kg, 40 mg/kg; 3 week	Curcumin affects IBS with depression by regulating neurotransmitters, BDNF and CREB signaling in the brain and peripheral intestinal system. FST: immobility time↓; stool quantity↓, visceral pain↓; Hippocampus: 5-HT↑, BDNF↑; Colon: 5-HT↓, BDNF↓; pCREB↓.
[87]	Depression combined with irritable bowel syndrome	1-week-old lactating male Sprague-Dawley rats; Chronic acute combined stress	–	Gallic Acid	20 mg/kg, 4 week	Gallic Acid alleviates visceral pain and depressive behavior by inhibiting the expression of P2X7 receptors in the hippocampus, spinal cord and DRG and inhibiting ERK1/2 phosphorylation and inflammatory cytokines. AWR index↓; OFT: distance of the central area activity↑, time of the central area activity↑; sucrose preference↑; FST: immobility time↓; P2X7↓, GFAP↓, p-ERK1/2↓, IL-β↓, TNF-α↓, BDNF↓, IL-10↑.
[88]	Depression combined with irritable bowel syndrome	6-8-week-old male C57BL/6J mice (22±2 g); Chronic acute combined stress+Injection of 3% glacial acetic acid into the colon	Electroacupuncture: Tianshu (ST25), Dachangshu (BL25), Baihui (GV20)	–	1 week	Electroacupuncture alleviates IBS-D through the PVNCRF-MC/TRPV1 pathway. OFT: distance of the central area activity↑, time of the central area activity↑; visceral sensitivity↓, CRF↓, MCT↓, PAR2↓, TRPV1↓.
[89]	Major depression with endothelial dysfunction and gastrointestinal disorders	Male Sprague-Dawley rats (240±10 g); Acute forced swimming: 15 min forced swimming in 20–22°C water	Chaihu Shugan San: Bupleuri Radix, Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Paeoniae Radix Alba, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Ligusticum sinense 'Chuanxiong', Cyperi Rhizoma	Ferulic acid	30 g/kg	Chaihu Shugan San improved the levels of depression, ED, GD, inflammation and OS-related biomarkers, as well as HE staining in gastric antrum and aortic sections, and improved behavioral abnormalities. OFT: immobility time↓; 5-HT↑, BDNF↑, DA↑, NA↑;IL-6↓, IL1β↓, TNF-α↓, MDA↓.
[90]	Depression combined with gastrointestinal motility disorders	Male Sprague-Dawley rats (150–180 g); Acute forced swimming: 15 min forced swimming in water	Chaihu Shugan San: Bupleuri Radix, Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Paeoniae Radix Alba, Glycyrrhiza uralensis Fisch., Pericarpium Citri Reticulatae, Ligusticum sinense 'Chuanxiong', Cyperi Rhizoma	Ferulic acid	30 g/kg	Chaihu Shugan San has antidepressant effect and promotes jejunum contraction and intestinal motility through central and peripheral mechanisms. FST: immobility time↓; 5-HT↑, ACTH↓, CRH↓, GE↑.

[91]	Depression combined with gastrointestinal motility disorders	Male Sprague-Dawley rats (200±20 g); CUMS: electric shock stimulation, horizontal shakin, food deprivation, water deprivation, behavioral limitation, swimming in water	Xiaoyao San: Poria cocos(Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis (Oliv.) Diels, Atractylodes macrocephala Koidz., Glycyrrhiza uralensis Fisch., Mentha canadensis L., Zingiber officinale Roscoe	–	7.65 g/kg, 15.3 g/kg, 30.6 g/kg; 3 week	Xiaoyao San down-regulated the rectal CNP/NPR-B pathway and improved depression and gastrointestinal motility disorders. Body weight↑, OFT: number of times into the central area↑; CNP↓, NPR-B↓.
[92]	Depression combined with gastrointestinal motility disorders	Male Sprague-Dawley rats (220–240 g); CUMS: 24 h 45° tilt cage, 2 min electric shock stimulation, 5 min tail pinching, 5 min swimming in 4°C cold water, (5) 24 h exposed to wet padding, overnight lighting, 10 min swimming in 45–50°C hot water, 4 h behavioral limitation.	Zhiqiao Chuanxiong Decoction: *Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Ligusticum sinense* 'Chuanxiong'	Meranzin hydrate, senkyunolide I	6 g/kg, 12 mg/kg	Zhiqiao Chuanxiong Decoction reversed depression-like behavior and gastrointestinal motility disorders by regulating glutamatergic system, AMPAR/BDNF/mTOR/synaptic protein I pathway, ghrelin signaling and gastrointestinal nitric oxide synthase. food intakes↑, sucrose preference↑; FST: immobility time↓; iNOS↓, nNOS↓, NR-1↓, GluA2↓, mTOR↓, p-mTOR↓, GFAP↓, synapsin I↓; GE↓, IT↓, PGE2↓, COX-2↓, IL-1β↓, IDO↓, caspase-3↓, C-fos↓.
[93]	Depression combined with gastrointestinal motility disorders	7-week-old male C57BL/6J mice; Chronic social defeat model: A C57BL/6J mouse was placed in a cage of CD-1 mice for 10 minutes of direct interaction each day, and a CD-1 mouse with an aggressive tendency was selected as an attacker.	Zuojin Wan: *Tetradium ruticarpum (A. Juss.) T. G. Hartley, Coptis chinensis Franch.*	Jatrorrhizine, coptisine, palmatine, berberine, rutaecarpine, and evodiamine	225 mg/kg, 450 mg/kg, 910 mg/kg; 3 week	Zuojin Wan enhanced FXR expression, thereby regulating the interaction of BAgut microbiota and treating depression-like behavior and gastrointestinal dysfunction in mice. Social interaction time↑, sucrose preference↑; TST: immobility time↓; FST: immobility time↓; neuronal structural damage↓; total gastrointestinal transit time↓; colon movement ↑, gastric residual rate↓, small intestinal propulsion rate↑; MTL↑, GAS↑, VIP↓, FXR↑;bile acid↑; Intestinal flora: Oscillospirales↑, Christensenellales↑, Ruminococacae↑, Christensenellae↑, Bifidobacteriales↓, Bifidobacteriaceae↓.
[94]	Depression combined with gastrointestinal motility disorders	7-week-old male C57BL/6J mice; CUMS: food deprivation, water deprivation, 45° tilt cage, exposed to wet padding, light/dark cycle reversal, tail pinching, cage shaking, swimming in cold water, behavioral limitation.	Zuojin Wan: Tetradium ruticarpum (A. Juss.) T. G. Hartley, Coptis chinensis Franch.	–	225 mg/kg, 450 mg/kg, 910 mg/kg; 3 week	Zuojin Wan plays an antidepressant and restores gastrointestinal motility by increasing the expression of TPH2 in the hippocampus and intestinal nerves, thereby increasing 5-HT levels and protecting nerve cells. BDNF↑, 5-HT↑, TPH2↑, gastric residues↓, small intestine propulsion↑.
[95]	Depression combined with gastrointestinal motility disorders	6-8-week-old male C57BL/6J mice; CUMS: 4 h behavioral limitation, 24 h 45° tilt cage, 24 h exposed to wet padding, 5–10 mintail pinching, 5–10 min swimming in 4°C cold water, 3 h noise exposure	Electroacupuncture: Zusanli (ST36), Zhongwan (CV12)	–	1 week	Electroacupuncture alleviates depression and gastric dysfunction by activating BNSTGABA neurons to inhibit excessive autophagy in gastric cells. Body weight↑, structural damage of gastric mucosa↓, gastric motility amplitude↑, Co-labeling rate of GABA and c-Fos↑.

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[96]	Depression combined with constipation	7-week-old C57BL/6J mice; CUMS: 24 h food deprivation, 24 h water deprivation, 12 h 45° tilt cage, 5 min swimming in 4°C cold water, 5 min swimming in 40°C hot water, 12 h placed in an inclined cage, light/dark cycle reversal, 5 min tail pinching, 12 h exposed to wet padding, 10 min cage shaking, 2 h behavioral limitation.	Electroacupuncture+Tongbian decoction: Yintang (EX-HN3), Neiguan (PC6); *Toosendan Fructus, Ophiopogon japonicus (L.f) Ker-Gawl., Scrophularia ningpoensis Hemsl., Rehmanniaglutinosa (Gaertn.) Libosch. ex Fisch. and C. A. Mey., Semen Armeniacae Amarum., Atractylodes macrocephala Koidz., Citrus × aurantium f. deliciosa (Ten.) M.Hiroe, Magnolia officinalis Rehd. et Wils., Trichosanthes kirilowii Maxim., Cannabis Sativa L., Pruni Semen, Aucklandiae Radix*	–	2 week	Electroacupuncture+Tongbian decoction decoction reduced intestinal inflammation, restored neuronal morphology, increased tryptophan hydroxylase 2 expression in the prefrontal cortex and colon, promoted the synthesis and production of 5-HT in the gastrointestinal tract and brain, restored cognitive function, and enhanced gastrointestinal motility. Body weight↑, sucrose preference↑, OFT: distance of the central area activity ↑, time of the central area activity↑, water maze test: number of times through the platform↑; defecation time↓, fecal water content↑, intestinal propulsion rate↑; structural damage of prefrontal neurons↓; Colon: inflammatory cell infiltration↓, goblet cells↑; TPH1↑, TPH2↑, 5-HT↑, 5-HTP↑.
[97]	Depression combined with constipation	Male Institute of Cancer Research mice; Oral loperamide	–	Nobiletin	100 mg/kg, 300 mg/kg; 10 week	Nobiletin treats constipation and depression by activating MAPT and inhibiting MAPK signaling pathways. Number of fecal particles↑, fecal water content↑, intestinal propulsion rate↑; Colon: inflammatory cell infiltration↓, mucosal injury↓; MAPT↓, TNF-α↓, IL-1β↓, IL-6↓, IFN-γ↓; P38↓, JNK↓, ERK↓, NF-κB p65↓; OFT: total activity distance↑; FST: immobility time↓; TST: immobility time↓.
[98]	Depression combined with constipation	5-week-old male Institute of Cancer Research mice (22–25 g); Oral loperamide+CUMS: light/dark cycle reversal; 6 min swimming in 4°C cold water, 24 h food deprivation, 24 h water deprivation, 24 h exposed to wet padding, 24 h 45° tilt cage, 1.5 min tail pinching, overnight lighting.	–	Norisoboldine	2.5 mg/kg, 5 mg/kg, 10 mg/kg; 2 week	Norisoboldine inhibits abnormal activation of intestinal innate immunity, rebalances Th1/Treg cell populations, promotes anti-inflammatory polarization of microglia, and protects hippocampal neurons. Incubation period of the initial black stool↓, number of fecal particles↓, fecal weight↓, fecal water content↓; sucrose preference↑, OFT: immobility time↓, total activity distance↑; EPM: Open arm entry rate↑, open arm time spent on the open arm↑; ILC3↓, Th1↓, Treg↑, IL-17A↓, IFN-γ↓, IL-22↑, IL-10↑, IL-1β↓, TNF-α↓, IL-6↓, p-p65/p65↓, p-IκBα/IκBα↓, p-IKKα/IKKα↓, BDNF↑, PSD-95↑.
[99]	Depression complicated with ulcerative colitis	Male C57BL/6J mice; 3% dextran sodium sulfate	Sini San: *Bupleuri Radix, Citrus × aurantium f. deliciosa (Ten.) M. Hiroe, Paeonia lactiflora Pall., Glycyrrhiza uralensis Fisch.*	–	2.5 g/kg, 5.0 g/kg, 10.0 g/kg; 1 week	Sini San enhances intestinal and blood-brain barrier, reduces inflammation, improves depression-like behavior in mice, and treats UC and depression. Colon: structural damage↓, inflammatory cell infiltration↓; OFT: total activity distance↑, frequency of entering the central area↑, activity time↑; FST: immobility time↓; OFT: immobility time↓; TNF-α↓, IL-1β↓, IL-6↓, IL-10↑, ZO-1↑, Occludin↑.

[100]	Depression complicated with ulcerative colitis	6-week-old male C57BL/6 mice (20±2 g); 2% dextran sodium sulfate	Vinegar-*Schisandrae Chinensis Fructus*	–	1.95 g/kg-1, 3.90 g/kg-1; 5 day	Schisandra chinensis enhanced its intestinal microflora and tryptophan metabolism, up-regulated aromatic hydrocarbon receptors, inhibited NF-κB p-p65 activation, restored the integrity of colonic mucosa and blood-brain barrier, and reduced the damage of hippocampal neurons. DAI score↓, colon length↑, CMDI score↓, Occludin↑, Claudin-5↑, ZO-1↑, TNF-α↓, IL-1β↓, IL-10↑, AhR↑, NF-κB p-p65↓; Intestinal flora: Bacteroides↑, Parabacteroides↑, Candidatus_Amulumruptor↓; MWM: escape latencies↓; FST: immobility time↓; TST: immobility time↓; OFT: total activity distance of the central area↑, activity time of the central area↑; trp↑, kyn↓, kyn/trp ratio↓, XA↓.
[101]	Depression complicated with ulcerative colitis	4-week-old male C57BL/6J mice; 2.5% dextran sodium sulfate+chronic acute combined stress	–	Total flavone of Abelmoschus manihot	62.5 mg/kg, 125 mg/kg; 37天	Total flavone of Abelmoschus manihot improved intestinal inflammation aggravated by depression by regulating the intestinal barrier in a gut microbiota-dependent manner. DAI score↓; Colon: histological score↓,length↑; IL-6↓, IL-1β↓, TNF-α↓; OFT: total activity distance of central area↑; TST: immobility time↓; FST: immobility time↓; MUC2↑, KLF4↑, ZO-1↑; Intestinal flora: Bacteroides↑, Roseburia↑, Alistipes↑, Oscillibacter↑, Rikenellaceae_RC9↑, Ruminiclostridium_9↑, Alloprevotella↑, Lactobacillus↓, Helicobacter↓, Candidatus_Saccharimonas↓, Enterorhabdus↓, Lachnospiraceae_UCG-006↓.
[102]	Depression complicated with ulcerative colitis	6-8week-old C57BL/6J male mice (26–28 g); Dextran sodium sulfate+CUMS	Wuling Powder: *Poria cocos(Schw.) Wolf, Polyporus umbellatus (Pers.) Fr., Alisma plantago-aquatica L., Cinnamomum cassia Presl, Atractylodes macrocephala Koidz.*	–	0.5 g/kg, 1.0 g/kg, 2.0 g/kg; 1 week	Wuling Powder exerts its antidepressant effect by correcting abnormal proBDNF/BDNF signals, Wuling Powder combined with mesalazine has antidepressant effect and can alleviate intestinal inflammation. FST: immobility time↓; OFT: total activity distance↑; DAI score↓; TNF-α↓, IL-6↓; BDNF↑, TrkB↑, p75NTR↓, sortilin↓.
[103]	Depression complicated with ulcerative colitis	8-week-old female C57BL/6J mice(18–22 g); Dextran sodium sulfate	–	Corylin	10 mg/kg, 30 mg/kg, 90 mg/kg	Corylin alleviated the symptoms of colitis by reversing the changes of neurotransmitter levels in the colon and brain, and inhibited the inflammatory response in the colon and brain. Body weight↑, colon length↑, survival rate↑, DAI score↓, IL-6↓, TNF-α↓, ZO-1↑, occludin↑, Iba1↓, 5-HT↓, GABA↑, EP↑; Intestinal flora: Enterorhabdus↑, Candidatus_Stoquefichus↑, Turicibacter↓.

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Table 2 (Continued).

Reference	Disease	Model and Inducers	TCM	Main Active Ingredients	Dose and Period	Main Effects and Mechanisms
[104]	Depression combined with gastric ulcer	6-7-week-old male Sprague-Dawley rats (200–250 g), 7-week-old male NIH mice (18–22 g); SD rats: cytokinereleasestorm release induces ulceration, NIH mice: FST, TST, 5-HTP induced head twitching	–	Zinc(II)–curcumin complex	SD rats: 12 mg/kg, 24 mg/kg, 48 mg/kg; NIH mice: 17 mg/kg, 34 mg/kg, 68 mg/kg	Zinc(II)–curcumin complex plays a gastric protective and antidepressant role. ulcer index↓, MDA↓, H+-K+-ATP enzymatic activity↓, HSP70↓, iNOS↓; FST: immobility time↓; TST: immobility time↓; 头部抽搐时间↑.
[105]	Depression combined with colorectal cancer	6-8-week-old male BALB/c mice (22±2 g); Chronic acute combined stress+CT26-Luc colon cancer cells were subcutaneously injected into the right armpit	Tongxie Yaofang: Saposhnikovia divaricata (Turcz). Schischk., Paeonia lactiflora Pall., Atractylodes macrocephala Koidz., Pericarpium Citri Reticulatae	–	6.825 g/kg, 13.65 g/kg; 3 week	Tongxie Yaofang inhibits HPA axis and promotes DC maturation by stimulating immune response, thereby activating T cells and enhancing anti-tumor immune response. Body weight↑, tumor volume↓, tumor weight↓; TST: immobility time↓; FST: immobility time↓; CORT↓, ACTH↓, CRH↓, 5-HT↑; Th1 cell↑, Th2 cell↓, IL-2↑, IFN-γ↑, IL-4↓, IL-10↓.
[106]	Depression combined with colorectal cancer	Male C57BL/6J mice (16–18 g), Chronic acute combined stress+MC38 cells were injected into the right armpit	Xiao Chaihu Tang: *Bupleuri Radix, Pinellia ternata (Thunb.) Ten. ex Breitenb., Panax ginseng C. A. Mey., Scutellaria baicalensis Georgi, Zingiber officinale Roscoe, Glycyrrhiza uralensis Fisch., Ziziphus jujuba Mill.*	–	10.27 g/kg, 20.54 g/kg; 4 week	Xiao Chaihu Tang nhibits chronic stress-induced colorectal cancer progression by regulating glycolysis and inflammatory response through the IL-6/JAK2/STAT3 pathway. OFT: distance of the central area activity↑, time of the central area activity↑; tumor volume↓, tumor weight↓; IL-6↓, IL-12↓;CD4+ cell↓, CD8+ cell↓, F4/80+ macrophage↓, JAK2↓, STAT3↓; GLUT1↓, HK2↓, PFKP↓.
[107]	Depression combined with colorectal cancer	Male BALB/c mice (18–22 g); HT29 mixed HSC cells were injected into the body and the transplanted tumor was implanted into the liver+CUMS	–	Mangiferin	10 mg/kg, 50 mg/kg, 100 mg/kg; 4 week	Mangiferin improves chronic stress behavior and inhibits WAVE2 signaling pathway by reducing inflammatory cytokines, leading to TGF-β1-induced HSC inhibition, thereby reducing depressive behavior and tumor growth. Sucrose preference↑, TST: immobility time↓; FST: immobility time↓; tumor volume↓, tumor weight↓; IL-6↓, IL-18↓, TNF-α↓, β2AR↓, WAVE2↓, VEGF↓,α-SMA↓.
[108]	Depression complicated with inflammatory bowel disease	7-week-old male C57BL/6 mice; 2% dextran sodium sulfate	Electroacupuncture:Zusanli (ST36), Tianshu (ST25), Taichong (LR3)	–	1 week	Electroacupuncture regulates the IL-4-JAK1-STAT6 signaling pathway, inhibits the activation of abnormal microglia, promotes its polarization to the M2 phenotype, reduces neuroinflammation, and improves IBD and depression. Incidence of bloody stool↓, body weight↑, DAI score↓, IL-1β↓; OFT: total activity distance↑; sucrose preference↑; FST: immobility time↓; IL-4↑, IL-10↑, TGF-β1↑, JAK1↑, p-STAT6↑, STAT6↑, GATA3↑, CD206↑, Arg-1↑.

[109]	Depression complicated with inflammatory bowel disease	6-8-week-old male C57BL/6 mice; 2% dextran sodium sulfate	Electroacupuncture: Zusanli (ST36), Tianshu (ST26), Taichong (LR3)	–	1 week	Electroacupuncture reduced oxidative stress, inhibited the recruitment of NLRP3 inflammasome, alleviated central nervous system inflammation, inhibited oxidative stress and microglia activation in PFC region, and alleviated depressive symptoms in IBD mice. Colon: length↑, inflammatory infiltration↓, nuclear pyknosis↓, cell membrane swelling↓; IL-1β↓, IL-6↓, IL-18↓, TNF-α↓, NF-κB p65↓, p-NF-κBp65↓; FST: immobility time↓; OFT: total activity distance of central area↑; sucrose preference↑, Iba1 positive cells↓, NLRP3↓, ASC↓, Caspase-1↓, GSDMD↓, GSDMD-N↓.
[110]	Depression combined with Crohn 's disease	Male Sprague-Dawley rats (150±20 g); 5% 2,4,6-trinitrobenzenesulfonic acid sol.+50% ethanol mixture enema	Moxibustion: Tianshu (ST25), Qihai (CV6), Baihui (GV20)	–	1 week	Moxibustion inhibits the expression of intestinal pro-inflammatory cytokines and IDO1, suppresses excessive KP metabolism of tryptophan, weakens the role of KP metabolites in the gut brain axis, and inhibits hippocampal neuron activation and microglial cell activation. Body weight↑, DAI score↓, CMDI score↓, Colonic histopathological score↓, sucrose preference↑; FST: immobility time↓; OFT: distance of central area activities↑; IDO1↓, IL-1β↓, TNF-α↓, c-fos↓, Iba-1↓, KYNA/KYN ratio↑, KYN/mRP ratio↓, KYNA/QUIN ratio↑.

Note: The arrow↑ indicates upregulation, and the arrow↓ indicates downregulation.

depression.[112] Nevertheless, it is not solely the brain that is implicated; lesions in other organs can also precipitate or exacerbate depression. For instance, a decline in thyroid function within the endocrine system can result in symptoms such as depression and fatigue, thereby inducing depression-like behaviors.[113] Research has demonstrated that individuals with diabetes may exhibit depressive symptoms due to neuropathy caused by prolonged metabolic disturbances.[114] Furthermore, in the context of digestive system disorders, chronic hepatitis and cirrhosis can disrupt endotoxin metabolism and neurotransmitter synthesis, thereby influencing the onset of depression.[115] Studies have highlighted that gastrointestinal diseases may impact depression via the "brain-gut axis." For example, conditions such as colitis and irritable bowel syndrome can affect neurological and psychiatric disorders through alterations in the intestinal microbiota, their metabolites, or the intestinal environment.[116] The etiology of depression extends beyond the physiological domain to encompass social dimensions. Depression exhibits a pronounced familial aggregation, with relatives of affected individuals facing a 2–10 times higher risk compared to those in the general population.[117] Research indicates that within the social milieu, factors such as significant life changes, prolonged social stress, adverse interpersonal relationships, and certain personality traits can serve as precipitating factors for depression. Furthermore, depression is linked to environmental contexts. Studies have demonstrated an increase in depression and anxiety among adolescents and young adults aged 14–24 residing in urban areas, suggesting that enhanced exposure to green spaces and reduced urban noise may mitigate the risk of these mental health disorders.[118] Interaction with natural environments, even through simulated audio-visual experiences, has been shown to alleviate stress and improve emotional well-being.[119] Contemporary medical research suggests that the etiology of depression is multifactorial, involving genetic predispositions, neurobiological factors, depression related to physical illnesses, and psychosocial environments, and may also be influenced by urban or natural environmental conditions.[120] Consequently, altering a single condition may not suffice to achieve the desired therapeutic outcome and could potentially result in recurrent depressive episodes. TCM frequently employs a holistic approach in the management of diseases.[121] This approach not only addresses the diverse syndromes associated with depression, which are triggered by various symptoms, by rectifying the imbalance among different organs, but also enhances the overall equilibrium of patients.[122] This is achieved through a combination of TCM prescriptions, acupuncture, massage, physical exercises such as Taijiquan and Baduanjin, music therapy, dietary interventions, and other modalities, all aimed at regulating patients' emotional states and ameliorating depressive symptoms.

While a lot of studies have demonstrated that TCM positively impacts depression, digestive symptoms, and the intestinal environment, there remains a lack of comprehensive literature reviews specifically addressing the treatment of depression and gastrointestinal health abnormalities through TCM. This article aims to systematically review recent literature concerning the treatment of depression associated with gastrointestinal health abnormalities using TCM. The review focuses on TCM interventions for various gastrointestinal symptoms, including depression comorbid with irritable bowel syndrome, functional dyspepsia, intestinal microflora disorders, gastrointestinal motility disorders, and gastrointestinal ulcers. These interventions are evaluated from the perspectives of clinical efficacy and mechanisms of action. The objective is to provide a theoretical foundation and practical reference for the treatment of these conditions with TCM, thereby fostering the innovative application of TCM in the domain of mental-gastrointestinal comorbidities.

Clinical Study on TCM for Depression with Gastrointestinal Health Abnormalities

Clinical investigations into the efficacy of traditional Chinese medicine for the treatment of IBS accompanied by depression have demonstrated that *Boswellia carterii* Birdw., *Zingiber officinale Roscoe*, and *Achillea millefolium* L., when compared to a placebo, may significantly alleviate abdominal pain and enhance depression scores. However, it is important to note that the study's findings are limited by a small sample size, comprising only 42 participants.[30] A clinical trial involving 87 patients diagnosed with irritable bowel syndrome with diarrhea (IBS-D) demonstrated that an 8-week regimen of Tongxie Yaofang granules—comprising *Saposhnikovia divaricata* (Turcz.) Schischk., *Paeonia lactiflora* Pall., *Atractylodes macrocephala* Koidz., *Pericarpium Citri Reticulatae*— reduced the severity and frequency of diarrhea compared to the placebo group. Additionally, the treatment was associated with improvements in quality of life and a reduction in symptoms of anxiety and depression.[31] In this study, 60 IBS-D patients participated in a trial comparing electroacupuncture and moxibustion at Tianshu (ST25) and Shangjuxu (ST37). After 1 month, electroacupuncture improved urgency and defecation frequency, while moxibustion enhanced stool consistency. Both groups showed reduced anxiety and depression scores. After 3 months, only the moxibustion group maintained low emotional scores. Both treatments lowered 5-HT, 5-HT3R, and 5-HT4R levels, increased intestinal perception threshold, and decreased VAS scores, limitations include a small sample size and no placebo control.[32]

In the domain of clinical research concerning functional dyspepsia accompanied by depression, Japanese researchers have conducted a multi-center, randomized, placebo-controlled, double-blind clinical trial evaluating the efficacy of Rikkunshito—a Chinese herbal medicine comprising *Panax ginseng* C. A. Mey., *Atractylodes macrocephala* Koidz., *Poria cocos (Schw.) Wolf, Glycyrrhiza uralensis* Fisch., *Pericarpium Citri Reticulatae, Pinellia ternata* (Thunb.) Ten. ex Breitenb.—derived from the traditional Chinese Liujunzi Decoction. This study encompassed 125 patients across 56 hospitals. The findings indicated that the incidence of "significant improvement" and "improvement" in the overall therapeutic effect (OTE) questionnaire was markedly higher in patients within the Rikkunshito group compared to those in the placebo group at both the 4th and 8th weeks of treatment. Concurrently, this patient cohort exhibited a significant trend of improvement in the total score of the gastrointestinal symptom severity assessment index (PAGI-SYM), as well as in scores for dyspepsia, postprandial satiety/early satiety, and abdominal distension. Additionally, there was a notable enhancement in the total score of the hospital anxiety and depression scale (HADS) and its anxiety dimension score. Nonetheless, this study is limited by the absence of a post-treatment follow-up plan, which hinders the evaluation of the long-term sustainability of the treatment's efficacy.[36] A further randomized, double-blind, placebo-controlled trial investigating Liujunzi Decoction (specifically, Xiangsha Liujunzi Decoction, which includes the addition of *Aucklandiae Radix, Amomum aurantiacum* H. T. Tsai & S. W. Zhao to the original formulation) was conducted with 216 patients over a treatment period of four weeks. This study corroborated previous findings by demonstrating that, in comparison to the placebo group, patients receiving Xiangsha Liujunzi Decoction exhibited improvements in several measures: the Postprandial Distress Severity Scale (PDSS), the HADS, the TCM Symptom Score, the 36-Item Short Form Health Survey (SF-36), and the Clinical Global Impression (CGI) score. Additionally, the gastric emptying (GE) rate of both the proximal and distal stomach was enhanced.[35] Collectively, these studies indicate that both the original and modified prescriptions (Rikkunshito and Xiangsha Liujunzi Decoction), with Liujunzi Decoction as the foundational component, have a beneficial therapeutic effect on alleviating depression and anxiety, while concurrently ameliorating gastrointestinal symptoms in patients with functional dyspepsia. The above studies have limitations that do not mention the follow-up plan after the end of treatment.

A study involving 144 patients with functional dyspepsia across nine regions in China investigated the effects of the traditional Chinese medicine formulation, Jiawei Xiaoyao Pill. This prescription comprises *Poria cocos (Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis* (Oliv.) Diels, *Atractylodes macrocephala* Koidz., *Glycyrrhiza uralensis* Fisch., *Mentha canadensis* L., *Zingiber officinale* Roscoe, *Paeonia suffruticosa* Andr., *Gardenia jasminoides* J. Ellis. The intervention lasted for four weeks. The findings indicated improvement in dyspeptic symptoms and a reduction in scores on both the Hamilton Depression Scale and the Hamilton Anxiety Scale when compared to the placebo group. However, the differences between the treatment and placebo groups were not statistically significant.[34] A study involving 87 patients with functional dyspepsia (FD) was conducted using Chaihu Shugan Powder, which consists of *Bupleuri Radix, Citrus* × *aurantium* f. *deliciosa* (Ten.) M. Hiroe, *Paeoniae Radix Alba, Glycyrrhiza uralensis* Fisch., *Pericarpium Citri Reticulatae, Ligusticum sinense* "Chuanxiong", *Cyperi Rhizoma*, known for its properties in soothing the liver and invigorating the spleen. Following the intervention, the patient's self-rating depression scale score was lower compared to the placebo group. Additionally, there was reduction in postprandial satiety and upper abdominal pain, alongside increase in the gastric emptying rate. Additionally, improvements were observed in the Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), and the functional dyspepsia quality of life scale. Analysis of the intestinal microbiota revealed a decrease in the relative abundance of *Blautia, Bifidobacterium*, and *Streptococcus*, while there was an increase in *Bacteroides, Faecalibacterium, Agathobacter, Roseburia, Lachnospiraceae_NK4A13*, and *norank_f_Eubacterium*. These findings suggest that, compared to a placebo, Chaihu Shugan Powder may be more effective in alleviating clinical symptoms, enhancing gastric motility, and improving anxiety, depression, and overall quality of life in FD patients. Furthermore, it appears to exert a positive regulatory effect on the composition and relative abundance of intestinal microbial communities in these patients.[33]

In the clinical management of gastrointestinal-related disorders, a study on non-erosive reflux disease involving 39 patients with spleen deficiency and dampness-heat syndrome revealed that a 4-week treatment with Jianpi Qinghua granules [*Codonopsis pilosula* (Franch.) Nannf., *Atractylodes Lancea* (Thunb.) DC., *Perilla frutescens (L.) Britt., Eupatorium fortunei* Turcz., *Citrus* × *aurantium* f. *deliciosa* (Ten.) M.Hiroe, *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Sepiae Endoconcha, Massa Medicata Fermentata, Amomum aurantiacum* H. T. Tsai & S. W. Zhao] improved therapeutic outcomes, demonstrating long-term efficacy. The total score of TCM symptoms was substantially reduced, and improvements were observed in the self-rating depression and anxiety scales.[37] A single-arm clinical trial investigating the integration of TCM with group psychotherapy demonstrated the efficacy of interventions organized for colorectal cancer (CRC) patients via online meeting platforms. Participants engaged in 90-minute virtual sessions that included TCM health promotion education, mindfulness exercises, and self-acupoint pressing targeting CRC-related symptoms following their diagnosis. Post-intervention assessments revealed a significant reduction in symptoms of insomnia and fatigue, alongside notable improvements in scores on the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS). Additionally, analysis of the intestinal microflora indicated a significant increase in the abundance of probiotics such as *Enterobacteriaceae, Trichobacter, Faecalibacterium*, and *Gordonia*. These findings suggest that the combination of TCM and group psychotherapy may effectively mitigate psychological distress in patients with colorectal cancer.[38] Building upon the findings of this single-arm study, the research team subsequently developed a Phase II randomized controlled clinical trial. This trial is designed to employ a synergistic intervention approach, incorporating TCM syndrome differentiation treatment, acupuncture, and TCM five-element music therapy.[43] The primary focus is to evaluate the impact of this combined intervention program on the postoperative quality of life in colorectal cancer patients, thereby highlighting the diversity and potential efficacy of TCM treatment modalities for complex syndromes. However, this study only set up the treatment group and lacked the comparison with the placebo group, which could not clarify the clinical advantages of the intervention.

Mechanism Study on TCM for Depression with Gastrointestinal Health Abnormalities

TCM in Regulating Depression Combined with Intestinal Flora Disorder

There exists bidirectional communication between the gut microbiota and the central nervous system, primarily mediated by the microbiota-gut-brain axis. Clinical research has demonstrated that individuals with depression, particularly major depressive disorder (MDD), exhibit a gut microbiota composition that significantly differs from that of healthy individuals.[123] This is characterized by reduced diversity and abundance, an increased prevalence of Enterobacteriaceae, *Bacteroidetes*, and Aliteplase, and a decreased presence of *Faecalibacterium, Lactobacillus, Bifidobacterium*, and *Actinobacteria*.[124] Additionally, there is a noted reduction in short-chain fatty acids (SCFAs) in fecal matter.[125] Animal studies have further corroborated these findings, showing that the transplantation of fecal microbiota from patients with depression into germ-free mice can induce behaviors akin to depression. However, these behaviors can be mitigated through probiotic interventions or antidepressant treatments, which also tend to normalize the microbial composition.[126] From a regulatory pathway perspective, an imbalance in intestinal flora initially compromises the integrity of the intestinal mucosal barrier.[127] This imbalance leads to a reduction in the number of goblet cells in the colon and a decrease in the thickness of the mucus layer, as well as diminished expression of tight junction proteins such as ZO-1 and occludin.[128] Consequently, intestinal permeability is increased, allowing endotoxins like lipopolysaccharide (LPS) to enter the bloodstream,[129] thereby activating a systemic inflammatory response. Proinflammatory cytokines, including TNF-α, IL-6, and IFN-γ, subsequently breach the blood–brain barrier (BBB),[130] inducing neuroinflammation. Concurrently, the gut microbiota influences depression by modulating tryptophan metabolism,[131] which affects both tryptophan hydroxylase 1-mediated 5-hydroxytryptamine synthesis and the kynurenine pathway.[132] Additionally, it regulates hyperactivity of the HPA axis and alters SCFAs levels.[133] SCFAs play a role in regulating microglial activation, neurogenesis, and synaptic plasticity; their reduction exacerbates neuroinflammation, anxiety, and depression. Furthermore, this imbalance affects the expression of brain-derived neurotrophic factor (BDNF), where downregulation of BDNF impairs hippocampal neuroplasticity.[134] In addition, stressors such as chronic unpredictable mild stress (CUMS) can induce intestinal dysbacteriosis and intestinal barrier damage, forming a vicious cycle of “stress-dysbacteriosis-intestinal inflammation-depression”. Natural products or probiotics can alleviate intestinal inflammation and depression-like behavior by repairing intestinal barrier, regulating flora composition and metabolite levels, suggesting that intestinal microbiota may be a controllable target for the prevention and treatment of depression.[135]

Xiaoyao Powder, comprising *Poria cocos (Schw.) Wolf, Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis* (Oliv.) Diels, *Atractylodes macrocephala* Koidz., *Glycyrrhiza uralensis* Fisch., *Mentha canadensis* L., *Zingiber officinale* Roscoe, has been traditionally utilized in the clinical management of depression characterized by liver stagnation and spleen deficiency syndrome.[136] It has demonstrated notable efficacy and safety in mitigating depressive symptoms. Numerous in vivo studies have substantiated its effectiveness in ameliorating depression associated with intestinal barrier dysfunction and dysbiosis. A study conducted in 2012 revealed that CUMS in rats led to weight loss, decreased sucrose preference, and increased resting time in the open field test, indicative of depression, after three weeks of treatment. Biomarkers related to energy metabolism, amino acid metabolism, and alterations in intestinal microbiota were identified in the urine of these rats, suggesting that Xiaoyao Powder may exert its therapeutic effects through these metabolic pathways.[45] Ding et al discovered that Xiaoyao Powder, administered for six weeks in a CUMS-induced rat depression model, effectively alleviates depression-related physiological and behavioral issues. It reverses weight loss, boosts food intake and sucrose preference, and improves movement and exploration behaviors. Additionally, Xiaoyao Powder mitigates colonic damage, enhances intestinal barrier proteins (ZO-1, occludin, claudin-1), and increases 5-HT levels in the hypothalamus and colon. These findings suggest Xiaoyao Powder may regulate depression by influencing the brain-gut axis and enhancing intestinal barrier function.[46] Zhu et al demonstrated that in a rat model of depression induced by chronic immobilization stress (CIS), a three-week treatment with Xiaoyao Powder significantly reduced the release of pro-inflammatory cytokines, including IL-1β, TNF-α, IL-17, IL-21, and IL-22, by modulating the PI3K/Akt/mTOR signaling pathway in the colon. This treatment also enhanced the secretion of anti-inflammatory cytokines, such as IL-10 and TGF-β, and adjusted the Th17/Treg balance, thereby ameliorating depression-like behaviors.[47] In a study by Liu et al, it was observed that the components of Xiaoyao Powder, categorized into liver-soothing herbs [*Paeoniae Radix Alba, Bupleuri Radix, Angelica sinensis* (Oliv.) Diels, *Mentha canadensis* L.] and spleen-invigorating herbs (*Poria cocos (Schw.) Wolf, Atractylodes macrocephala* Koidz., *Glycyrrhiza uralensis* Fisch., *Zingiber officinale* Roscoe), effectively counteracted the intestinal dysbiosis in rats subjected to CUMS. Notably, the liver-soothing herbs exhibited superior efficacy compared to Xiaoyao Powder and spleen-invigorating herbs in modulating the cecal microbiota of the depressed rats.[49] Subsequent research has demonstrated that Xiaoyao Powder can decrease the *Bacteroides*/*Firmicutes* ratio and the abundance of *Bacteroides* and *Corynebacterium*, while enhancing the abundance of *Lactobacillus* and *Adlercreutzia*. Additionally, this formulation can attenuate the significant enrichment of LPS in depressed rats. It also reduces the expression of factors involved in the TLR4/NLRP3 signaling pathway in colon and brain tissues, thereby enhancing the integrity of the intestinal tract and the BBB, ultimately mitigating depression-like behaviors in rats via the brain-gut axis.[48] Furthermore, a study by Yang et al on a high-fat diet-induced obesity model revealed that Xiaoyao Powder treatment could ameliorate obesity-related anxiety and depression-like behaviors. The underlying mechanism may involve the upregulation of *Faecalibaculum_rodentium* and *Lactobacillus_murinus* abundance in the intestine, an increase in their metabolites, SCFAs, an improvement in the transcription level of the dopamine D2 receptor (DRD2) in the medial prefrontal cortex (mPFC), and the inhibition of central nervous system (CNS) inflammation.[50] Xiaoyao Powder undergoes metabolic transformation in the intestinal microflora to yield compounds such as benzoic acid, liquiritigenin, glycyrrhetinic acid, and saikosaponin D. These metabolites have been shown to inhibit the activity of fatty acid amide hydrolase (FAAH) in the brain, thereby preventing the hydrolysis of fatty acid amides.[51] Research indicates that Xiaoyao Powder enhances the integrity of the intestinal barrier, modulates gut microbiota, and ameliorates neuroinflammation and metabolic disorders via the brain-gut axis by altering metabolite profiles.

In the investigation of alternative prescriptions for depression in conjunction with intestinal microbiota disorders, a range of treatments demonstrated notable efficacy. Specifically, in the restraint stress-induced C57BL/6 mouse model, varying dosages (0.5 g/kg, 1 g/kg, 4 g/kg) were administered. Following a 5-day treatment period, a significant reduction in anxiety and depression-like behaviors was observed in the mice. Concurrently, the treatment effectively ameliorated the dysbiosis of intestinal flora induced by restraint stress. This was evidenced by a reversal in the declining abundance of probiotics such as *Lactobacillaceae* and *Prevotellaceae*, as well as a reduction in the increasing abundance of *γ*-

Proteobacteria. The underlying mechanism is likely associated with the modulation of NF-κB activation levels in colon tissue, leading to the downregulation of TNF-α and IL-6 expression, and subsequent upregulation of BDNF expression, ultimately alleviating depressive symptoms.[52] A separate investigation into Chaihu Shugan Powder demonstrated its efficacy in ameliorating intestinal flora imbalances in pseudo-sterile mice. This was evidenced by a marked increase in the abundance of *Bacteroidetes* and *Lactobacillus* within the intestine, alongside a notable reduction in *Oscillibacter* levels. Concurrently, there was a significant elevation in the concentrations of metabolites 3-hydroxy picolinic acid and inosine, coupled with a substantial decrease in the pro-inflammatory cytokines IL-1β and IL-6. These changes subsequently led to an upregulation of 5-HT and Glu levels in the hippocampus, ultimately ameliorating metabolic disorders associated with depression through the modulation of the intestinal microbial community structure.[53] Furthermore, the research conducted by Yue et al on Shugan Hewei Decoction, comprising *Bupleuri Radix, Paeonia lactiflora* Pall., *Citrus aurantium* L., *Curcuma longa* L., *Amomum aurantiacum* H. T. Tsai & S. W. Zhao, *Amomum verum* Blackw., *Atractylodes Lancea* (Thunb.) DC., *Aucklandiae Radix, Coptis chinensis* Franch., *Tetradium ruticarpum* (A. Juss.) T. G. Hartley, *Glycyrrhiza uralensis* Fisch., demonstrated that this formulation can modulate the cecal microflora in a rat model subjected to chronic unpredictable stress. Specifically, it was observed to increase the abundance of *Bacteroidetes, Prevotellae_9, Roseburia, Blautia*, and *Prevotella_1*, while reducing the abundance of *Firmicutes, Lactobacillus*, and *Lachnospiraceae_NK4A136*. Concurrently, the decoction inhibits the excessive activation of the NLRP3 inflammasome and the TLR4/NF-κB signaling pathway in both the cecum and serum, thereby mitigating cecal mucosal injury and alleviating depressive symptoms.[54] Subsequent investigations have corroborated that the prescription also exerts antidepressant effects by enhancing the tryptophan metabolism of intestinal microorganisms and modulating the AMPK/mTOR pathway.[55]

In the context of the HPA axis regulation pathway, the Shugan Jieyu Capsule—composed of *Hypericum perforatum* L., and *Acanthopanax senticosus* (Rupr.etMaxim.) Harms, and approved by the State Food and Drug Administration for the treatment of mild-to-moderate depression—has been shown to modulate gut microbiota composition. Specifically, it reduces the abundance of *Actinobacteria* while increasing the abundance of *Tenericutes* and *Ruminococcaceae*, thereby influencing HPA axis function and mitigating depression-like behaviors.[57] Furthermore, a separate investigation into *Hypericum perforatum* L. revealed that it may alleviate depressive symptoms by promoting the growth of *Akkermansia_muciniphila*, modulating tryptophan metabolism, decreasing kynurenine (KYN) levels, and regulating the NFκB/NLRP2/Caspase-1/IL-1β signaling pathway.[70]

Kaixin San, a traditional prescription comprising *Panax ginseng* C. A. Mey., *Polygala tenuifolia* Willd., *Acori Tatarinowii Rhizoma, Poria cocos* (Schw.) *Wolf*, modulates inflammatory pathways through multiple mechanisms. It achieves this by reducing the abundance of *Helicobacter*, increasing the prevalence of beneficial bacteria such as *Allobaculum*, decreasing levels of pro-inflammatory factors like LPS and IL-1β, enhancing the integrity of the intestinal tract and blood–brain barrier, and down-regulating the excessive activation of the HPA axis, thereby ameliorating symptoms of depression.[60] Conversely, another study indicated that fluoxetine intake exacerbated the imbalance of the intestinal microbiome and compromised the intestinal barrier in CUMS mice. However, the administration of Kaixin San effectively mitigated the intestinal damage induced by fluoxetine and influenced depression-like behaviors by restoring microbial homeostasis and providing direct cytoprotection to intestinal epithelial cells.[61] The administration of Yueju Wan, comprising *Cyperi Rhizoma, Ligusticum sinense* "Chuanxiong", *Gardenia jasminoides* J. Ellis, *Atractylodes Lancea* (Thunb.) DC., *Massa Medicata Fermentata*, was observed to decrease the abundance of *Prevotella* and *Bacteroides* while increasing the abundance of *Eubacterium*. This formulation also modulated purine and tryptophan metabolism, among other pathways, leading to a reduction in IL-1β levels within the hippocampus and inhibition of NLRP3 inflammasome activation, thereby ameliorating neuroinflammation.[62] The administration of Shugan granules, comprising *Angelica sinensis* (Oliv.) Diels, *Bupleuri Radix, Cyperi Rhizoma, Paeonia lactiflora* Pall., *Atractylodes macrocephala* Koidz., *Mentha canadensis* L., *Poria cocos* (Schw.) *Wolf, Gardenia jasminoides* J. Ellis, *Paeonia suffruticosa* Andr., *Glycyrrhiza uralensis* Fisch., resulted in a reduction in the abundance of *Bacteroides* and an increase in the abundance of *Butyricimonas*. This intervention also influenced alterations in intestinal metabolites, leading to the inactivation of the PI3K/Akt/mTOR pathway within the hippocampus. Consequently, this process inhibited the expression of inflammatory factors, including TNF-α, IL-1β, and IL-6, and suppressed the activation of microglia in the hippocampus.[66]

A recent study on Changpu San, a prescription comprising *Acori Tatarinowii Rhizoma, Panax ginseng* C. A. Mey., *Polygala tenuifolia* Willd., *Rehmanniaglutinosa* (Gaertn.) Libosch. ex Fisch. and C. A. Mey., *Poria cocos (Schw.) Wolf, Dioscorea polystachya* Turcz., *Cinnamomum cassia* (L.) D. Don, has demonstrated its potential in modulating neurotransmitter synthesis and metabolic regulation pathways. The study found that Changpu San up-regulates beneficial bacteria such as *Prevotella* and *Bacillus*, which enhances tryptophan metabolism, elevates tryptophan levels in the brain, reduces KYN levels and kynurenine pathway (KP) activity, decreases neurotoxic metabolites, and lowers pro-inflammatory factors. These effects collectively contribute to reducing systemic inflammation and restoring the balance between the serotonin pathway (SP) and KP, thereby alleviating depression-like symptoms.[56] Additionally, the Jianpi Jieyu Decoction, consisting of *Astragalus membranaceus* (Fisch). *Bunge, Pseudostellaria heterophylla, Acanthopanax senticosus* (Rupr.etMaxim). *Harms, Atractylodes macrocephala* Koidz., *Paeonia lactiflora* Pall., *Hyriopsis cumingii* (Lea), *Polygala tenuifolia* Willd., *Glycyrrhiza uralensis* Fisch., has been shown to mitigate depression-like behaviors in CUMS mice. It achieves this by reversing the reduction in Tau phosphorylation levels in the hippocampus, up-regulating GluR1 expression, and increasing GABA levels in both serum and hippocampus, ultimately enhancing cognitive function.[58] Zhizi Chi Decoction, composed of *Gardenia jasminoides* J. Ellis and *Sojae Semen Praeparatum*, has been shown to enhance the levels of beneficial gut bacteria, increase butyric acid production, and decrease pro-inflammatory markers such as TNF-α. It also reverses the elevated levels of 5-HIAA and kynurenine in the plasma, ileum, and hippocampus of rats subjected to CUMS. This intervention reduces the ratios of 5-HIAA to 5-HT and kynurenine to tryptophan (KYN/TRP), thereby exerting an antidepressant effect via the gut-brain axis.[63] Furthermore, another study indicates that Zhizi Chi Decoction mitigates inflammation through modulation of the HPA axis and intestinal microbiota. It is involved in the neuroactive ligand–receptor interaction process, regulates the secretion of prolactin and estrogen, and modulates MAPK and TNF signaling pathways, thereby demonstrating a multifaceted antidepressant effect.[64] Yangxin Jieyu Decoction, comprising *Panax ginseng* C. A. Mey., *Ophiopogon japonicus* (L.f.) Ker-Gawl., *Schisandrae Chinensis Fructus, Epimedium brevicornu* Maxim., *Allium macrostemon* Bunge, *Rosae Rugosae Flos, Albizia julibrissin* Durazz., *Curcuma aromatica* Salisb., *Acori Tatarinowii Rhizoma, Citrus reticulata* Blanco, has been shown to enhance the abundance of intestinal bacteria such as *Lactobacillus, Romboutsia*, and *Bilophila*. It also reverses alterations in depression-related metabolites, including succinic acid and taurine, increases the abundance of immunoglobulin, and upregulates enzymes associated with propionic acid metabolism and the TCAs cycle. These effects may contribute to its potential antidepressant properties through the modulation of the central inhibitory neurotransmitter GABA.[59] Similarly, Gegen Qinlian Decoction, which consists of *Pueraria montana* (Lour.) Merr., *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Glycyrrhiza uralensis* Fisch., can enhance the composition of bacterial genera such as *Ruminococcus* and influence depression by modulating metabolites like oleanolic acid.[65]

In the investigation of TCM and its active constituents for the treatment of depression, various components exert antidepressant effects by modulating the intestinal flora, influencing inflammatory responses, and interacting with the brain-gut axis pathway. A study examining the co-decoction of *Lilium lancifolium* Ker Gawl. and *Rehmanniaglutinosa* (Gaertn.) Libosch. ex Fisch. and C. A. Mey., along with its key active ingredient, verbascoside, demonstrated that improvements in intestinal microflora, specifically increasing *Mucispirillum, Candidatus_arthromitus, Parabacteroides*, and *Adlercreutzia*, while reducing *Desulfovibrio, Prevotella, Alistipes*, and *Bacteroides*, help maintain host homeostasis through the gut microbiome-brain axis. This modulation also results in decreased levels of inflammatory factors such as IL-1β, IL-6, IL-17, and TNF-α, thereby ameliorating depression.[67] Furthermore, *Valeriana jatamansi* has been shown to improve behavioral symptoms and intestinal tissue damage in depressed mice, as well as regulate the diversity of intestinal microorganisms. This is evidenced by an increase in the abundance of *Brevundimonas, Gemmobacter, Luteimonas, Romboutsia, Turicibacter*, and *Parasutterella*, accompanied by a reduction in serum vitamin B12 levels. Additionally, it reduces the penetration of homocysteine into the central nervous system, a mechanism associated with the upregulation of cubilin and amnionless levels in intestinal tissue and methionine synthase levels in the hippocampus.[68] *Lindera aggregata* (Sims) Kosterm. enhances gastrointestinal motility by elevating serum concentrations of D-xylose and ghrelin. Additionally, it confers neuroprotective effects in the hippocampus by upregulating the expression of BDNF and facilitating the activation of TrkB and cAMP response element-binding protein (CREB) in the hippocampi of mice subjected to CUMS or in HT22 cells damaged by corticosterone.[69]

A prior study demonstrated that Berberine has the potential to mitigate damage to the gastric mucosa and intestinal microvilli within the stomach, ileum, cecum, and colon, thereby ameliorating behaviors associated with depression.[76] Glycyrrhizin and Cistanche tubulosa total glycosides were shown to increase the abundance of *Lactobacillus* and *Bacteroides*, respectively.[77] Additionally, alterations in the microbial community, including a decrease in *Proteobacteria* and regulatory flora such as *Firmicutes, Bacteroidetes, Ruminococcaceae*, and *Peptococcaceae*, alongside an increase in *Erysipelotrichaceae* and *Muribaculaceae*, were observed.[78] These changes, along with modifications in metabolic pathways—such as the reduction of TNF-α, IL-1β, and IFN-γ levels, and improvements in tryptophan metabolism and the regulation of the HPA axis—contribute to antidepressant effects. Furthermore, both Puerarin and Pogostemon cablin essential oil were found to influence depressive symptoms through modulation of the gut microbiota.[73] Specifically, Puerarin decreased the abundance of *Proteobacteria, Flexispira*, and *Desulfovibrio*, while increasing *Firmicutes, Bacillales*, and *Lactobacillus*. In contrast, Pogostemon cablin essential oil reduced the abundance of *Ruminococcus_1* and *Ruminococcus_2*, while enhancing the abundance of *Bacteroides* and *Blautia*, and modulating short-chain fatty acids by increasing propionic acid and decreasing caproic acid levels.[75] Subsequent research has demonstrated that Gardeniae Fructus oil modulates the intestinal microbiota and influences the hippocampal TLR4/NF-κB/NLRP3 signaling pathway, thereby mitigating neuroinflammation and enhancing the concentrations of 5-HT, dopamine (DA), and BDNF in the hippocampus.[80] Additionally, Polygalae Radix Oligosaccharide Esters were found to increase the abundance of *Romboutsia, Roseburia, Lachnospiraceae_NK4A136, Prevotella_9*, and *Eubacterium_coprostanoligenes*, while decreasing the abundance of *Bacteroides, Oscillibacter, Parasutterella*, and *Intestinimonas*. This modulation resulted in elevated levels of acetic acid, propionic acid, and butyric acid in fecal matter, alongside reduced levels of serum LPS, IL-6, and TNF-α in the cerebral cortex and duodenum. Consequently, both neural and systemic inflammation were alleviated.[74] Polygonatum sibiricum polysaccharide has been shown to inhibit serum LPS levels by modulating the composition of intestinal microbiota. Specifically, it decreases the abundance of *Muribaculaceae, Lactobacillaceae, Ruminococcaceae*, and *Erysipelotrichaceae*, while increasing the abundance of *Akkermansiaceae* and *Helicobacter*. This modulation contributes to the amelioration of abnormal neuronal activation and alterations in local field potentials (LFP) within the paraventricular nucleus.[71] Additionally, the polysaccharide exerts its effects by reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and by regulating signaling pathways including PI3K/AKT/TLR4/NF-κB and ERK/CREB/BDNF, thereby enhancing HPA axis function and monoamine neurotransmitter levels.[71,72] Similarly, research on Hesperidin derived from *Pericarpium Citri Reticulatae* has demonstrated an increase in the abundance of *Pseudomonadota* and *Bacteroidota*, improvement of the intestinal barrier, elevation of BDNF and 5-HT expression, and a significant reduction in depressive symptoms.[79]

TCM in Regulating Depression Combined with Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder marked by abdominal pain, bowel habit changes, and altered fecal characteristics.[137] It often coexists with psychological issues like depression and anxiety, affecting 20% to 60% of IBS sufferers. This comorbidity worsens visceral pain and reduces quality of life, stemming from brain-gut axis dysfunction. An imbalance in this axis, which connects the central and enteric nervous systems, influences the disorder through various pathways.[138] Firstly, the hyperactivation of the HPA axis leads to increased release of corticotropin-releasing factor (CRF) by the hypothalamus during stress, which in turn causes the pituitary-adrenal axis to secrete glucocorticoids abnormally. This process not only alters gastrointestinal motility and enhances rectal sensitivity but also exacerbates central emotional disorders.[139] Secondly, there is an imbalance between neurotransmitters and brain-gut peptides, with 5-HT playing a crucial role in regulating intestinal motility and mood. Additionally, the abnormal expression of neuropeptide Y (NPY), which is associated with post-traumatic stress disorder and intestinal motility, is observed.[140] For instance, a pro-inflammatory state induced by early life stress can up-regulate the activity of indoleamine-2, 3-dioxygenase,[141] thereby disrupting 5-HT metabolism[142] and subsequently affecting intestinal peristalsis and emotional regulation. Thirdly, intestinal neuroimmune disorders are evident, wherein depression-related psychological factors can increase the number of intestinal mucosal mast cells in patients with IBS, induce low-grade inflammation of the cecal mucosa, compromise the integrity of the intestinal barrier, and potentially alter the composition of the intestinal microbiota. This further perpetuates the vicious cycle of "intestinal abnormalities-central mood disorders" through the brain-gut axis.[143,144] Moreover, abnormalities in the autonomic nervous system, the interaction between sex hormones (such as estrogen) and 5-hydroxytryptamine,[145] and alterations in brain activity in patients with IBS, as evidenced by functional magnetic resonance imaging, are mediated by depression and contribute to pathological processes.

Research on traditional Chinese medicine prescriptions and their active components for IBS and depression has demonstrated that various interventions operate synergistically through multi-dimensional mechanisms. At the level of intestinal barrier repair, a study conducted in 2015 revealed that the Chang 'an II Formula comprising *Saposhnikovia divaricata* (Turcz.) Schischk., *Paeonia lactiflora* Pall., *Atractylodes macrocephala* Koidz., *Astragalus membranaceus* (Fisch.) Bunge, mitigates intestinal mucosal inflammation, repairs the mucosal barrier, and reverses the effects in post-infectious IBS (PI-IBS) model rats, which included conditions such as early sibling deprivation, restraint, and rectal administration of TNBS. The study observed a significant decrease in the CD4+/CD8+ cell ratio in the lamina propria and submucosa, alongside an increase in IL-1β expression in the intestinal mucosa. Conversely, IL-4 expression was reduced. The treatment effectively reversed the alterations in CD4+/CD8+ cell ratio and the expression levels of IL-1β and IL-4 induced by PI-IBS. This intervention protects the intestinal mucosa from PI-IBS through its anti-inflammatory, immunomodulatory, and anti-anxiety properties.[84] Baizhu Shaoyao Decoction, composed of *Saposhnikovia divaricata* (Turcz.) Schischk., *Paeonia lactiflora* Pall., *Atractylodes macrocephala* Koidz., *Pericarpium Citri Reticulatae*, has been shown to enhance the expression of tight junction proteins (Claudin-1, ZO-1, Occludin), thereby reducing intestinal epithelial permeability and restoring the integrity of the intestinal barrier in IBS-D rats. Additionally, it may influence metabolism and stress response by modulating the expression of FoxO1 and FoxO3a in the small intestine of IBS-D rats, and it may alter neurotransmitter levels to alleviate depression.[82] Furthermore, Costunolide, an active constituent of *Aucklandiae Radix*, has demonstrated efficacy in ameliorating gastrointestinal dysfunction and depression-like behavior in stress-induced IBS mice. This is achieved by enhancing intestinal mucosal permeability, inhibiting mast cell activation, upregulating the expression of colonic atresia protein, downregulating Claudin 2 expression, and upregulating the expression of GluN2A, BDNF, p-ERK1/2, and p-CREB in hippocampal cells through the modulation of 5-HT metabolism, thereby maintaining the function of the intestinal mucosal barrier and mitigating depression-like behavior.[85]

Xiaoyao Powder modulates the ACT1/TRAF6/P38 MAPK/AP-1 signaling pathway to decrease IL-17A, IL-17F, and TNF-α, thereby improving neuroinflammation in an IBS mouse model induced by CUMS and senna leaf gavage. Additionally, it elevates brain dopamine levels by regulating DRD2 and TH, which alleviates depressive symptoms and affects brain-derived neurotrophic factors and the HPA axis in IBS and depression patients. This treatment improves gastrointestinal symptoms, fecal water content, AWR score, and reduces colonic permeability.[81] Gallic Acid mitigates visceral pain and depression by downregulating P2X7 receptor and p-ERK1/2 expression in the hippocampus, spinal cord, and DRG, lowering serum IL-1β and TNF-α levels, and increasing IL-10 levels.[87]

At the level of neurotransmitter-brain-gut axis regulation, prior research on Curcumin has demonstrated its impact on IBS through the modulation of neurotransmitters, as well as BDNF and CREB signaling within both the central nervous system and the peripheral intestinal system.[86] The Changkang Fang Formula, which comprises *Salvia miltiorrhiza Bunge, Paeonia lactiflora* Pall., *Fagopyrum dibotrys* (D. Don) *Hara, Saposhnikovia divaricata* (Turcz.) Schischk., *Cuscutachinensis* Lam., *Rehmanniaglutinosa* (Gaertn.) Libosch. ex Fisch. and C. A. Mey., *Coptis chinensis* Franch., *Cicadae Periostracum*, exerts its regulatory effects on the brain-gut axis by upregulating microbial taxa such as *Bacteroidetes, Dubosiella, Lactobacillus, Clostridiales, Corynebacteriales, Ruminococcaceae*, and *Lachnospiraceae*. This modulation enhances the production of brain-gut peptides (BGPs), thereby alleviating pain and reversing intestinal motility disorders. Furthermore, the Changkang Fang Formula influences the levels of BDNF and 5-HT in both the colon and hippocampus, alongside the expression of genes associated with BGP pathways. It is posited that these effects are mediated through the 5-HT-PKA-CREB-BDNF signaling pathway.[83]

A study on electroacupuncture demonstrated that stimulation at the acupoints Tianshu (ST25), Dachangshu (BL25), and Baihui (GV20) effectively inhibited the hyperactivation of CRF neurons in the paraventricular nucleus (PVN), as well as the overexpression of serum CRF, colonic CRF, CRF-R1, MCT, protease-activated receptor 2, and TRPV1 in a mouse model. Additionally, this intervention modulated the signaling pathways of the hypothalamic paraventricular nucleus and colonic adrenocorticotropic hormone-releasing factor, thereby ameliorating negative emotional states and visceral hypersensitivity in the mice.[88]

TCM Regulating Depression Combined with Gastrointestinal Motility Disorder

Gastrointestinal motility disorders are primarily characterized by irregularities in the rhythm, intensity, or coordination of gastrointestinal smooth muscle contractions,[146] leading to symptoms such as abdominal distension, abdominal pain, and altered bowel habits. Constipation, a prevalent manifestation of gastrointestinal motility disorders, has been found to have a significant association with depression. Epidemiological studies indicate that between 9% and 40% of individuals with depression report experiencing constipation, and those with constipation exhibit notably higher anxiety and depression scores compared to healthy individuals.[147] Furthermore, constipation preceding the onset of depression may serve as a potential early indicator, offering valuable insights for the early diagnosis of depression.[148] The relationship between the two phenomena is bidirectional: constipation may contribute to the pathogenesis of depression through mechanisms such as low-grade intestinal inflammation, including mast cell infiltration and activation, and the release of cytokines into the bloodstream, thereby serving as a risk factor for depression.[149] Conversely, depression can activate the HPA axis, leading to the release of stress-related factors that exacerbate gastrointestinal motility disorders, thus rendering constipation a somatic symptom of depression. Alterations in hippocampal synaptic plasticity associated with depression, disruptions in neurotransmitter systems such as 5-HT[150] and GABA,[151] and imbalances in the intestinal microbiota—whose metabolites, including short-chain fatty acids and lipopolysaccharides, can influence both gastrointestinal motility and central mood regulation—collectively mediate the pathological cycle of "gastrointestinal motility disorder-depression".

As early as 2011, research indicated that the antidepressant Chaihu Shugan Powder and its main component, Ferulic acid, have dual benefits: they act as antidepressants and enhance intestinal function. Behaviorally and gastrointestinally, they reduce mice's resting time, boost activity, and speed up gastric emptying and intestinal transit. Mechanistically, they regulate the monoamine system by inhibiting the reuptake of 5-HT, norepinephrine, and dopamine. They also lower CRH and ACTH levels in the HPA axis. Additionally, they increase ghrelin levels and induce intestinal contractions in vitro, achieving a combined antidepressant and intestinal motility effect.[90] The recent study revealed that Chaihu Shugan Powder and its primary active component, Ferulic acid, have significant effects on endothelial cell function, promoting vascular health, mitigating oxidative damage, alleviating depressive symptoms, and modulating multiple depression-related disorders. These effects are mediated through the Ghrl-Edn1/MECP2/P-mTOR/VEGFA-OS pathway in forced swimming rat models exhibiting MDD, endothelial dysfunction (ED), and gastrointestinal disorders (GD).[89] Furthermore, research indicates that the combination of *Citrus* × *aurantium* f. *deliciosa* (Ten.) M.Hiroe and *Ligusticum sinense* "Chuanxiong", both constituents of Chaihu Shugan Powder, can counteract the elevation of cysteine aspartic protease-3 and c-fos protein levels induced by CUMS, as well as the activation of the COX-2/PGE2 and IL-1β/IDO pathways. Additionally, these compounds can reverse the reduction in GFAP, BDNF, and mTOR expression levels. Improvements in depression-like behaviors and gastrointestinal motility disorders were observed, attributed to the modulation of the glutamatergic system, the AMPAR/BDNF/mTOR/synapsin I pathway, the immune system, and ghrelin signaling.[92] Zuojin Wan, composed of *Tetradium ruticarpum* (A. Juss.) T. G. Hartley and *Coptis chinensis* Franch., has been shown to increase Oscillospirales and decrease Parabacteroides, potentially modulating depression-like behavior and gastrointestinal dysfunction through the FXR-BA gut microbiota and the liver-brain-gut axis.[93] Additionally, research indicates that Zuojin Wan influences TPH2, facilitating the growth of GABAergic and dopaminergic neurons, which in turn elevates the 5-HT content in intestinal neurons. This process supports the development and survival of GABAergic and intestinal dopaminergic neurons, thereby ameliorating depression-induced gastrointestinal dysfunction.[94]

A study investigating the effects of electroacupuncture at specific acupoints, namely ST36 (Zusanli) and CV12 (Zhongwan), demonstrated that the inhibition of GABAergic neurons in the bed nucleus of the stria terminalis (BNST) was alleviated following intervention. This finding elucidates the neural mechanism by which chemical activation of BNST GABAergic neurons modulates autophagy in gastric cells, thereby mitigating gastric dysfunction associated with depression. Consequently, this research offers a theoretical foundation for the application of electroacupuncture in the

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treatment of emotional disorders that are accompanied by somatic symptoms.[95] A study investigating the combined effects of electroacupuncture at acupoints Yintang (EX-HN3) and Neiguan (PC6) with Tongbian Decoction—comprising *Toosendan Fructus, Ophiopogon japonicus* (L.f). Ker-Gawl., *Scrophularia ningpoensis* Hemsl., *Rehmanniaglutinosa* (Gaertn.) Libosch. ex Fisch. and C. A. Mey., *Semen Armeniacae* Amarum., *Atractylodes macrocephala* Koidz., *Citrus × aurantium* f. *deliciosa* (Ten.) M. Hiroe, *Magnolia officinalis* Rehd. et Wils., *Trichosanthes kirilowii* Maxim., *Cannabis Sativa* L., *Pruni Semen, Aucklandiae Radix*—on depression accompanied by constipation demonstrated that this combined treatment exhibited a more pronounced antidepressant effect compared to electroacupuncture alone. This synergistic approach was found to mitigate intestinal inflammation, restore neuronal morphology, and enhance the expression of TPH2 in both the PFC and colon. Additionally, serum levels of 5-HTP were elevated, and the TPH2/5-HT pathway was modulated via the gut-brain axis, indicating a coordinated regulatory effect on the nervous and gastrointestinal systems, with significant antidepressant and pro-motility outcomes.[96]

Nobiletin, the primary active compound extracted from the Wenyang Yiqi Formula, has been demonstrated to reduce the expression of MAPT in colon tissue and decrease serum levels of TNF-α, IL-1β, IL-6, IFN-γ, and the MAPK pathway. It also enhances fecal particle count, water content, intestinal propulsion rate, and ameliorates colon pathological damage and depression-like behaviors, potentially by modulating the function of interstitial cells of Cajal (ICCs) through targeting microtubule-associated protein tau (MAPT) in colon tissue.[97] A study on Norisoboldine, derived from *Lindera aggregata* (Sims) Kosterm., revealed that Norisoboldine suppresses the abnormal activation of intestinal innate immunity, inhibits M1 markers (CD86, iNOS), upregulates M2 markers (CD206, Arg-1), rebalances the Th1/Treg cell population, and inhibits the activation of the NF-κB signaling pathway. This results in reduced levels of IL-1β, TNF-α, and IL-6, decreased neuronal apoptosis, and increased expression of nerve repair proteins, including BDNF and PSD-95, thereby alleviating depression-like behaviors.[98]

TCM Regulating Depression Combined with Ulcerative Gastrointestinal Diseases

The primary clinical manifestations of ulcerative colitis (UC) include weight loss, recurrent diarrhea, abdominal pain, rectal bleeding, and hematochezia.[152] The precise pathogenesis of UC remains unclear;[153] however, contemporary medical understanding suggests a strong association with infections,[154] immune system abnormalities,[155] and psychological factors.[156,157] The fluctuating nature of the disease significantly elevates the prevalence of mental disorders, particularly depression and anxiety, among patients with UC.[158] There exists a bidirectional relationship wherein intestinal inflammation exacerbates mental health issues, and psychological factors, in turn, influence intestinal inflammation and disease recurrence.[159] Intestinal inflammation may induce neuroinflammation by increasing intestinal mucosal permeability, allowing inflammatory mediators to enter the central nervous system via systemic circulation and compromise the blood–brain barrier. Patients with UC often endure prolonged psychosocial stress and economic burdens due to the chronic recurrence of the disease, making them more susceptible to negative emotions such as anxiety and depression, which further exacerbate intestinal damage.[160] The fundamental mechanism underlying this association is intricately linked to the regulation of the gut-brain axis. This involves the bidirectional communication between gut microbiota and the host, with 5-HT, synthesized by intestinal chromaffin cells, serving as a crucial mediator.[161] Notably, its precursor, tryptophan, is capable of crossing the blood–brain barrier. The preservation of the integrity of both the intestinal mucosal barrier and the blood–brain barrier is vital for sustaining gut–brain homeostasis.[162]

In the investigation of depression in conjunction with ulcerative gastrointestinal disorders, prior research has demonstrated that a zinc (II)-curcumin complex enhances mucosal resistance through its involvement in free radical scavenging and the upregulation of HSP70 expression. This process subsequently mitigates the elevation of iNOS expression and indirectly facilitates the release of 5-HT, thereby exerting antidepressant effects through the activation of 5-HT receptors, as well as exhibiting anti-ulcer and anti-depressive properties.[104] Furthermore, the combination of Wuling Powder (comprising *Poria cocos(Schw.) Wolf, Polyporus umbellatus* (Pers.) Fr., *Alisma plantago-aquatica* L. *Cinnamomum cassia* Presl, *Atractylodes macrocephala* Koidz.) with mesalazine has been shown to balance antidepressant effects and alleviate colitis-associated intestinal inflammation by modulating the ProBDNF/p75NTR/sortilin and BDNF/TrkB signaling pathways.[102] A study identified that Corylin, a representative flavonoid compound isolated from *Cullen corylifolium* (L.) Medik., can bind to 5-HTPDC, thereby promoting its enzymatic degradation. This process results in the accumulation of 5-HTP in the colon, which can subsequently enter the circulatory system and cross the blood–brain barrier, serving as a novel source of 5-HT in the brain. Concurrently, Corylin modulates the intestinal microflora by increasing *Enterorhabdus, Candidatus_Stoquefichus* populations while decreasing *Turicibacter*. This modulation aids in ameliorating chronic UC by influencing the inflammatory interactions along the gut-brain axis. Additionally, Corylin's binding to 5-HTPDC leads to an elevated production of 5-HTP in the colon, contributing to improvements in both intestinal and central nervous system disorders.[103] Furthermore, the herbal formula Sini San, comprising *Bupleuri Radix, Citrus* × *aurantium* f. *deliciosa* (Ten.) M.Hiroe, *Paeoniae Radix Alba, Glycyrrhiza uralensis* Fisch., was shown to enhance the integrity of the intestinal and blood-brain barriers. It also reduced pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, while increasing the anti-inflammatory factor IL-10. These effects collectively restored the integrity of the intestinal mucosal and blood–brain barriers, alleviated depression-like behavior in mice, and provided therapeutic benefits for UC and depression.[99] Vinegar-processed *Schisandrae Chinensis Fructus* improved the abundance of *Bacteroides* and *Parabacteroides*, decreased the abundance of *Candidatus_Amulumruptor*, increased the level of tryptophan, decreased the levels of kynurenine and xanthate, up-regulated the aromatic hydrocarbon receptor (AhR), inhibited the activation of NF-κB p-p65, improved the level of inflammation, restored the integrity of colonic mucosa and blood-brain barrier, and reduced the damage of hippocampal neurons. Improvement of depression-like behavior in chronic UC mice.[100] The total flavone content of *Abelmoschus manihot* (L.) Medicus has been shown to enhance the abundance of bacterial genera such as *Bacteroides, Roseburia, Alistipes, Oscillibacter, Rikenellaceae_RC9*, and *Ruminiclostridium_9*, while down-regulating the presence of *Alloprevotella, Lactobacillus, Helicobacter, Candidatus_Saccharimonas, Enterorhabdus*, and *Lachnospiraceae_UCG-006*. This modulation of gut microbiota is associated with improvements in intestinal barrier integrity and the regulation of intestinal inflammation.[101]

Discussion

Depression is a multifaceted mental disorder characterized by high prevalence and a significant rate of recurrence, frequently accompanied by comorbidities affecting multiple systems. Its pathogenesis is understood to involve intricate interactions across several dimensions, including genetic susceptibility, neurobiological abnormalities, immune-inflammatory imbalances, disruptions in the gut-brain axis, and psychosocial stressors. Despite extensive research, a comprehensive and unified cognitive framework for understanding depression has yet to be established. TCM excels in treating depression linked to gastrointestinal issues through its core principle of "overall regulation." Its strengths lie in diverse treatment options (eg, TCM, acupuncture, moxibustion), a holistic approach to body regulation, and safety (non-addictive, well-tolerated, minimal side effects). It coincides with the pathological characteristics of depression combined with gastrointestinal symptoms "physical and mental comorbidity", providing a unique path different from chemical drugs for the treatment of such complex diseases.

Nevertheless, current research on this disease within the domain of TCM is subject to numerous limitations, which must be addressed objectively to advance the field. Foremost among these limitations is the inadequacy in the standardization and representativeness of clinical studies. There is a notable absence of large-scale, multi-center, and multi-sample longitudinal studies, particularly concerning the various clinical phenotypes of gastrointestinal-related health disorders associated with depression. This gap is especially evident in the context of depression subtypes corresponding to diarrhea-type and constipation-type gastrointestinal dysfunction. The disparity in efficacy remains uncertain. Second, existing clinical studies predominantly rely on questionnaires as the primary method for assessing efficacy, lacking comprehensive collection and analysis of objective laboratory indicators such as serum inflammatory factors, intestinal flora composition, neurotransmitter metabolites, and brain functional imaging. This deficiency results in a low level of research evidence. Third, there is a lack of transparency and content integrity in the research; some studies have not disclosed their experimental designs in a timely manner, and key results have not been fully reported. Additionally, some experimental studies have not identified the principal active ingredients of TCM compounds or preparations, making it challenging to trace the material basis of efficacy, thereby hindering the interpretation of mechanisms and the translation of findings into practice. Fourth, the inconsistency in animal experimental design poses significant challenges. Variations in the construction of animal models can result in differing phenotypes of depression and gastrointestinal comorbidity, as seen with the use of diverse experimental animals such as Sprague-

Dawley rats, C57BL/6J mice, and Kunming mice, alongside various depression modeling methods like chronic unpredictable mild stimulation and chronic social defeat models. Additionally, there is a lack of standardization in drug intervention dosages, with some studies failing to establish high, medium, and low multi-dose groups to adequately explore dose–effect relationships and potential toxicity. Furthermore, the non-uniformity in the duration of drug interventions further diminishes the comparability of research outcomes, potentially introducing bias. Notwithstanding the aforementioned limitations, the integration of clinical studies with animal experimental data collectively substantiates the efficacy of TCM, encompassing herbal treatments and acupuncture, in modulating multiple targets. These targets include neurotransmitter imbalances, emotional regulation, hyperactivity of the HPA axis, neuroimmune inflammation, and the homeostasis of the gut-brain axis (Tables 1 and 2).

Given the aforementioned limitations, future research should prioritize the "holistic concept" of TCM by developing a research framework and intervention model that embody greater disciplinary specificity. It is imperative to enhance the standardization and scientific rigor of research design. In clinical studies, multi-center, large-sample, and long-term follow-up cohort studies should be conducted to examine various gastrointestinal symptom phenotypes and depression subtypes. Concurrently, the integration of objective laboratory indicators with subjective symptom scores is essential to elevate the quality of evidence. In the realm of basic research, there is a need to standardize animal model criteria—such as explicit modeling methods and stress intensity—alongside the regulation of drug dosage gradients and intervention durations. Furthermore, identifying active ingredients is crucial to provide a robust foundation for clinical translation. Conversely, this approach underscores the distinctive features and benefits of TCM through its concept of "mind-body co-governance". It transcends the constraints of isolated pharmacological interventions by establishing a comprehensive intervention framework that integrates "body-spirit-environment" collaborative conditioning. This is achieved through the use of TCM compounds or acupuncture to regulate physiological aspects such as the nervous system, immunity, and gut microbiota. Concurrently, TCM psychological counseling, including emotional adjustment, is employed to enhance mental well-being. Additionally, environmental optimization, such as adjustments in living and rest conditions, and the construction of a social support system are incorporated. This results in a multi-dimensional, holistic intervention model that ultimately facilitates the synergistic improvement of both depression and gastrointestinal-related health issues.

Conclusion

In conclusion, TCM holds potential in addressing depression alongside gastrointestinal-related health abnormalities through its multi-target mechanisms. These mechanisms include the modulation of neurotransmitter systems such as monoamines, GABA, and glutamic acid; the restoration of function in emotional regulation brain regions like the prefrontal cortex and hippocampus; the inhibition of excessive activation of the HPA axis; the mitigation of neuroimmune inflammation imbalances; and the regulation of the intestinal flora-gut-brain axis homeostasis. Despite its promising potential, the clinical value of TCM remains constrained by the limitations of current research. To fully realize its benefits, it is imperative to overcome these limitations by standardizing research design, enhancing the quality of evidence, and emphasizing the holistic characteristics of TCM. Advancing TCM from an empirical treatment approach to one that is evidence-based and standardized will provide innovative and effective solutions for the treatment of global psycho-gastrointestinal comorbidities.

Abbreviations

5-HIAA, 5-Hydroxyindole-3-acetic acid; 5-HT, 5-hydroxytryptamine; 5-HT3R, 5-hydroxytryptamine type 3; 5-HT4R, 5-hydroxytryptamine type 4; AhR, aromatic hydrocarbon receptor; Akt, Protein Kinase B; BBB, blood–brain barrier; BGPs, brain-gut peptides; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; CIS, chronic immobilization stress; CRC, colorectal cancer; CRP, C-reactive protein; CRF, corticotropin-releasing factor; CUMS, chronic unpredictable mild stress; DA, dopamine; DRD2, dopamine D2 receptor; ED, endothelial dysfunction; ENS, enteric nervous system; FAAH, fatty acid amide hydrolase; FD, functional dyspepsia; FMT, fecal microbiota transplantation; GABA, γ-aminobutyric acid; GD, gastrointestinal disorders; GE, gastric emptying; GluR1, Glutamate Receptor 1; HADS, Hospital Anxiety and Depression Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HPA, hypothalamic-pituitary-adrenal; ICCs, interstitial cells of Cajal; IFN-γ, Interferon-γ; IL-6, Interleukin-6; IBS, Irritable bowel syndrome; KYN, kynurenine; KP, kynurenine pathway; LPS, lipopolysaccharide; LFP, local field potentials; MAPK, mitogen-activated protein kinase; MAPT, microtubule-associated protein tau; MAOIs, Monoamine Oxidase Inhibitors; mPFC, medial prefrontal cortex; mTOR, mammalian Target of Rapamycin; MCT, mast cell tryptase; MDD, major depressive disorder; NaSSAs, Norepinephrine and Specific Serotonin Antidepressants; NF-κB, nuclear factor kappa-B; NPY, neuropeptide Y; PDSS, Postprandial Distress Severity Scale; PAGI-SYM, Patient Assessment of Gastrointestinal Symptom Severity Index; PI3K, Phosphatidyqinositol-3 kinase; PI-IBS, post-infectious IBS; PVN, paraventricular nucleus; SAS, Self-Rating Anxiety Scale; SARIs, Serotonin Antagonists and Reuptake Inhibitors; SCFAs, short-chain fatty acids; SDS, Self-Rating Depression Scale; SNRIs, Serotonin and Norepinephrine Reuptake Inhibitors; SS, Symptom Score; SSRIs, Selective Serotonin Reuptake Inhibitors; SP, serotonin pathway; TCAs, Tricyclic Antidepressants; TGF-β, Transforming Growth Factor-β; Th17, T helper cell 17; TLR4, Toll Like Receptor 4; TCM, Traditional Chinese medicine; TPH2, tryptophan hydroxylase 2; Treg, Regulatory T cells; TRP, tryptophan; VAS, visual analogue scale; WHO, World Health Organization; ZO-1, Zonula occludens-1.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval for the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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