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Opinion

Rethinking Post-Traumatic Stress Disorder: A Systems-Level Disorder of Stress Dysregulation and the Role of Complementary and Alternative Medicine

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Abstract

Post-traumatic stress disorder (PTSD) is traditionally viewed as a brain-centered disorder characterized by impaired fear extinction and dysregulated emotional processing. Despite advances in pharmacologic and psychotherapeutic interventions, treatment resistance remains a major challenge for a substantial proportion of patients, highlighting the complexity of PTSD pathophysiology beyond central neural mechanisms. In addition, PTSD is associated with persistent dysregulation of systemic stress-regulatory networks, including the autonomic nervous system, immune-inflammatory pathways, and the gut-brain axis. This Opinion proposes that complementary and alternative medicine (CAM) interventions may exert therapeutic effects in PTSD by restoring disrupted homeostatic regulation across these interconnected systems. CAM modalities, such as acupuncture, herbal medicine, yoga, and breathing-based practices, may converge on common regulatory targets, including enhancement of vagal tone, modulation of inflammation, and stabilization of gut-brain communication. We propose that inconsistent clinical outcomes of CAM interventions in patients with PTSD may reflect, in part, inadequate patient stratification and outcome measures rather than an absence of therapeutic effects. Reconceptualizing PTSD as a disorder of systemic stress dysregulation provides a framework for investigating how CAM interventions might contribute mechanistically to an integrated, precision-oriented treatment paradigm.

Keywords: stress disorders; post-traumatic; gut-brain axis; complementary therapies

1. Why Post-Traumatic Stress Disorder (PTSD) Remains Refractory to Standard Treatments

Despite advances in psychopharmacology and psychotherapy, PTSD remains refractory in a substantial proportion of patients. The effects of first-line treatments, including trauma-focused psychotherapies and selective serotonin reuptake inhibitors (SSRIs), are modest, with many patients failing to achieve full remission [1,2,3,4]. A major limitation of current therapies is their narrow mechanistic focus. Most drugs target monoaminergic neurotransmission, although PTSD involves multisystem dysregulation, including autonomic imbalance, immune activation, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, impaired neuroplasticity, and gut-brain axis alterations [5]. Therefore, pharmacological interventions may alleviate mood and anxiety symptoms without adequately addressing the broader biological processes underlying chronic stress and symptom persistence. Real-world effectiveness is further limited by delayed therapeutic onset, adverse effects, and high discontinuation rates [6,7]. This challenge is compounded by the inherent heterogeneity of PTSD. Treating PTSD as a single disorder rather than as biologically distinct subtypes may obscure meaningful treatment responses and contribute to persistent treatment resistance [8,9]. These findings suggest that PTSD remains refractory because current therapies inadequately address its systemic biology. A shift toward mechanism-based phenotyping and integrative, system-oriented interventions may improve outcomes.

PTSD as a Disorder of Systemic Stress Dysregulation

PTSD is increasingly recognized as a systemic stress disorder involving whole-body dysregulation rather than a purely brain-centered condition. Chronic trauma leaves lasting changes across interconnected physiological systems, preventing restoration of homeostatic equilibrium [10]. A central feature of this process is HPA axis dysregulation, characterized by altered cortisol dynamics, heightened sensitivity to negative feedback, and impaired stress recovery [11]. These abnormalities impair stress recovery and appropriate termination of stress responses. In parallel, autonomic dysfunction, characterized by diminished vagal tone, locks patients into a cycle of physiological hyperarousal and restricted autonomic responsiveness [12]. PTSD is also associated with chronic low-grade systemic inflammation and immune activation, disrupting neural plasticity and stress signaling pathways [13,14]. Additional features include increased intestinal permeability and gut microbiota dysbiosis, suggesting disruption of the gut-brain

axis. Intestinal barrier dysfunction, partly linked to depletion of butyrate-producing bacteria, may promote chronic systemic inflammation [15,16,17]. Gut microbiome alterations may also contribute to PTSD through gut–brain–immune interactions, including reduced short-chain fatty acid production and increased pro-inflammatory signaling; however, evidence remains limited and requires further validation. Collectively, these findings suggest that PTSD is a disorder of systemic stress dysregulation rather than an isolated fear-based disorder. Therefore, PTSD treatment should adopt integrative, systems-level approaches that restore stress-regulatory balance across neuroendocrine, autonomic, immune, and gut-related pathways.

2. Complementary and Alternative Medicine (CAM) as a Homeostatic Regulator Rather Than a Symptom-Targeting Therapy

Although CAM has traditionally been viewed as an adjunctive treatment for PTSD, emerging mechanistic evidence suggests it may represent a systems-oriented therapeutic approach capable of restoring stress-regulatory homeostasis [18,19]. As PTSD is increasingly viewed as a systemic disorder characterized by disrupted physiological equilibrium rather than isolated psychiatric symptoms, CAM modalities such as acupuncture, herbal medicine, and mind-body therapies may help restore mind-body homeostasis. We selected studies based on their relevance to PTSD, use of CAM interventions such as herbal medicine or acupuncture, and mechanistic significance (Table 1, Ref. [20,21,22,23,24] and Table 2, Ref. [25,26,27,28,29,30]). Priority was given to representative clinical and preclinical studies investigating key PTSD-related pathways, including HPA axis dysregulation, neuroinflammation, neurotransmitter systems, synaptic plasticity, and gut-brain axis modulation.

Clinical evidence for herbal medicine in PTSD remains limited, with only a small number of controlled or preliminary studies. In contrast, preclinical studies suggest that herbal medicines may improve PTSD-like symptoms through multitarget mechanisms involving the HPA axis, serotonergic signaling, GABAergic neurotransmission, neuroinflammation, hippocampal plasticity, and stress-related intracellular pathways (Table 3, Ref. [31,32,33] and Table 4, Ref. [34,35,36,37,38]).

CAM promotes physiological resilience by restoring homeostatic balance across multiple biological systems [39,40]. This systems-level approach positions CAM as a key component of integrative medicine targeting core stress-response dysregulation. Acupuncture may ameliorate PTSD by targeting core trauma-related symptoms and associated affective disorders. By modulating mind-body stress circuits, it addresses the multisystem nature of PTSD within an integrative framework [23,24]. In our view, autonomic nervous system (ANS) modulation may represent a key mechanistic intersection among diverse CAM modalities, providing a cohesive framework for their clinical effects in PTSD. Rather than focusing solely on symptom suppression, CAM integration may help restore the disrupted physiological homeostasis underlying trauma-related disorders.

2.1 Mechanistic Convergence: ANS Modulation

A key mechanism underlying diverse CAM modalities is their ability to modulate the ANS. Because PTSD is characterized by persistent sympathetic hyperarousal and impaired parasympathetic regulation, restoring autonomic balance represents a rational therapeutic target [12]. Clinical studies of acupuncture, herbal medicine, and mindfulness-based interventions consistently suggest a common mechanism: enhanced vagal activity and reduced sympathetic dominance [41,42,43]. These changes are reflected by improved heart rate variability (HRV) and normalized resting heart rate, supporting the role of CAM in regulating stress reactivity [44,45]. At the neurobiological level, CAM-induced autonomic modulation involves networks linking the amygdala, insula, and brainstem nuclei. Acupuncture and mind-body therapies may reduce amygdala hyperreactivity while strengthening prefrontal "top-down" inhibitory control [46]. This central recalibration manifests peripherally as enhanced autonomic flexibility, providing the physiological basis for efficient termination of acute stress responses. Yoga, Tai Chi, and meditative practices may also counteract PTSD-related structural changes by upregulating brain-derived neurotrophic factor (BDNF) [47,48]. By incorporating physical movement, these CAM modalities may create a "systemic-to-brain" feedback loop, promoting exercise-induced metabolites such as irisin that cross the blood–brain barrier and support neuroplasticity [48]. Enhanced vagal tone may also stabilize HPA axis dynamics and improve gut barrier integrity [49]. In PTSD, this regulation may help normalize impaired stress feedback, modulate FKBP5-related pathways [49,50,51], and suppress NF-κB-mediated neuroinflammation associated with chronic stress [52].

2.2 Mechanistic Convergence: Immune–Inflammatory Regulation

Beyond its psychological manifestations, PTSD is increasingly recognized as a disorder of chronic immune–inflammatory dysregulation, making neuroimmune modulation an important mechanistic target for CAM. Herbal medicine and acupuncture may exert convergent anti-inflammatory effects beyond symptom relief. Evidence from experimental and clinical studies suggests that certain herbal formulations and bioactive compounds may reduce interleukin-6, tumor necrosis factor-α, and C-reactive protein levels by modulating NF-κB signaling and oxidative stress pathways [53,54]. Acupuncture may exert similar anti-inflammatory effects through vagal–immune activation and stabilization of HPA axis function [55]. In

Table 1. Representative clinical studies on acupuncture for PTSD.

Study design/Participants	Main findings	Limitations	Reference
RCT; 84 patients with PTSD	Acupuncture significantly reduced PTSD symptoms and showed efficacy comparable to CBT	Small sample size and short follow-up period	[20]
Clinical trial in military-related PTSD patients	Acupuncture combined with standard care improved PTSD-related symptoms, including anxiety and sleep disturbances	Limited mechanistic evaluation	[21]
Systematic review and meta-analysis of 8 studies involving 656 adults with PTSD	Acupuncture was associated with significant improvements in PTSD symptom severity, depression, anxiety, and functional outcomes	Limited number of high-quality RCTs and heterogeneity in acupuncture protocols and outcome measures	[22]
Randomized clinical trial; 93 combat veterans with PTSD	Verum acupuncture significantly improved PTSD symptoms and fear extinction responses compared with sham acupuncture	Conducted primarily in combat veterans; generalizability to civilian PTSD populations remains uncertain	[23]
RCT in veterans with combat-related PTSD	Acupuncture significantly improved anxiety, depression, and sleep quality over time. However, differences between verum and sham acupuncture were generally not significant, suggesting substantial nonspecific treatment effects	Secondary outcome analysis; sham acupuncture also produced improvements, making it difficult to distinguish specific acupuncture effects	[24]

RCT, randomized controlled trial; CBT, cognitive behavioral therapy; PTSD, post-traumatic stress disorder.

PTSD, inflammatory signaling engages in bidirectional "cross-talk" with neuroendocrine and neural systems, creating a self-sustaining cycle of stress sensitivity. Pro-inflammatory cytokines may impair fear extinction and disrupt monoaminergic signaling, whereas glucocorticoid resistance weakens the body's anti-inflammatory regulation [52]. Persistent peripheral inflammation may drive microglial activation and neuroinflammatory cascades underlying emotional dysregulation in PTSD [56]. Emerging preclinical data suggest that herbal medicine and acupuncture may inhibit microglial activation and promote a more neuroprotective phenotype [57,58], supporting CAM as a biologically grounded intervention targeting the systemic pathology of PTSD.

2.3 The Gut-Brain Axis as an Integrative Regulatory Node

The gut-brain axis has emerged as an important yet frequently overlooked component of PTSD pathophysiology. Beyond psychological trauma, patients with PTSD commonly experience gastrointestinal comorbidities, including irritable bowel symptoms, chronic abdominal pain, and functional dyspepsia, at higher rates than the general population [59]. These observations suggest that PTSD is not merely a brain-centered disorder but also involves gastrointestinal dysregulation, with the gut serving as an underexplored site of trauma-induced pathology [60]. Altered gut microbiota composition has been implicated in heightened anxiety, hyperarousal, and stress sensitivity in PTSD [17]. Trauma exposure and chronic stress disrupt microbial diversity and metabolic capacity, reducing beneficial taxa involved in short-chain fatty acid production and immune regulation while increasing pro-inflammatory microbial profiles [15,60]. These changes increase intestinal permeability, allowing microbial products to enter the circulation and activate immune and neuroinflammatory pathways that influence brain function. Microbiota-derived signals modulate neural circuits through vagal afferent signaling, cytokine-mediated immune communication, and HPA axis regulation [61]. Dysregulation of these pathways may lower the threshold for threat perception and reinforce autonomic hyperarousal, contributing to persistent anxiety and exaggerated stress responses.

Within this framework, CAM may exert therapeutic effects by targeting multiple regulatory components of the gut–brain–immune network. Herbal medicines and dietary interventions may reshape gut microbial diversity, increase short-chain fatty acid-producing taxa, and reduce pro-inflammatory microbial profiles [62,63]. Probiotic and prebiotic supplementation may improve intestinal barrier integrity, downregulate lipopolysaccharide-driven immune activation, and attenuate HPA axis hyperreactivity [63,64]. Acupuncture and vagus nerve-engaging mind–body therapies may further modulate autonomic tone, enhance parasympathetic activity, and suppress systemic inflammation through vagal–immune pathways, producing coordinated effects across neural, immune, and gastrointestinal systems [65,66,67]. In contrast, conventional pharmacotherapies primarily target central monoaminergic neurotransmission and have limited direct effects on gut microbial ecology or intestinal barrier function. Evidence

Table 2. Representative preclinical studies on acupuncture for PTSD.

Acupuncture	Experimental model	Main findings	Proposed mechanisms	Reference
EA	SPSS-induced PTSD mouse model	EA improved anxiety-like behaviors and reduced exaggerated fear responses	Modulation of glutamate neurotransmission through normalization of NMDAR1 expression and glutamate-related signaling	[25]
Acupuncture	SPS-induced PTSD rat model	Acupuncture significantly reduced anxiety-like behavior, contextual fear memory, and cognitive impairment	Activation of the mTOR signaling pathway, restoration of synaptic plasticity-related proteins (PSD95, Syn1, GluR1), and enhancement of hippocampal neuroplasticity	[26]
Acupuncture	SPS-induced PTSD rat model	Acupuncture reduced hippocampal inflammatory responses and improved behavioral abnormalities	Suppression of microglial activation and reduction of IL-1β expression	[27]
EA	TBI rat model	EA improved neurological function and reduced neuroinflammatory responses following TBI	Inhibition of NF-κB/COX2 signaling, suppression of pro-inflammatory cytokines, and regulation of microglial polarization	[28]
EA	CRS-induced anxiety mouse model	EA significantly alleviated anxiety-like behaviors and partially restored chronic stress-induced gut microbiota dysbiosis. It increased beneficial bacterial taxa and improved stress-related behavioral abnormalities	Modulation of the gut-brain axis through restoration of gut microbial diversity and composition and regulation of microbiota-associated metabolic pathways	[29]
Acupuncture/EA	Narrative review	Acupuncture consistently improved PTSD-related symptoms, including fear memory, anxiety, depression, sleep disturbances, and cognitive dysfunction	Regulation of the HPA axis, autonomic nervous system, neurotransmitter systems (5-HT, DA, NE, GABA, glutamate), neuroinflammation, synaptic plasticity, hippocampal neurogenesis, and fear-related neural circuits	[30]

PTSD, post-traumatic stress disorder; EA, electroacupuncture; SPSS, single prolonged stress and shock; TBI, traumatic brain injury; CRS, chronic restraint stress.

Table 3. Representative clinical studies on herbal medicine for PTSD.

Herbal medicine	Design/Participants	Main findings	Limitations	Reference
XTJYF	Randomized placebo-controlled trial; 245 Sichuan earthquake survivors with PTSD	XTJYF significantly improved overall psychological status, including PTSD symptoms, compared with placebo	Mechanisms were not directly investigated; authors suggested modulation of emotional regulation, stress responses, and psychological resilience through the multicomponent actions of the herbal formulations.	[31]
SKK	Randomized, observer-blinded, controlled trial; 43 survivors of the Great East Japan Earthquake and Tsunami with PTSD	SKK significantly reduced PTSD symptom severity and improved psychological distress compared with control treatment	Mechanisms were not directly examined; the authors suggested that SKK may regulate stress responses, emotional dysregulation, autonomic function, and sleep disturbances associated with PTSD	[32]
Kava (*Piper methysticum*)	Culturally based pilot/clinical-development approach	Suggested potential benefit for trauma-related symptoms, especially in Pacific populations	Preliminary findings; clinical efficacy remains under investigation.	[33]

XTJYF, Xiao-Tan-Jie-Yu-Fang; PTSD, post-traumatic stress disorder; SKK, Saikokeishikankyoto.

Table 4. Representative preclinical studies on herbal medicine for PTSD.

Herbal medicine/ compound	Model	Main findings	Proposed mechanisms	Reference
BJIGT	SPSS-induced PTSD mouse model	BJIGT significantly alleviated PTSD-like behaviors, including anxiety-like behavior, social avoidance, and cognitive impairment	Regulation of HPA axis, GABAergic neurotransmission, and enhancement of neuroplasticity-related signaling	[34]
HFE	SPSS-induced PTSD mouse model	Reduced anxiety-like behavior and fear responses; improved short-term memory and hippocampal function	Activation of the Reelin/Dab-1 pathway; restoration of synaptic plasticity; regulation of Kv4.2/ERK/CREB signaling; enhancement of hippocampal neurogenesis and neuronal maturation	[35]
KRG	SPS-induced PTSD rat model	KRG significantly attenuated PTSD-triggered depression-like behaviors and improved emotional abnormalities	Activation of the serotonergic system through increased 5-HT synthesis and signaling; upregulation of TPH; restoration of hippocampal neurotransmission and neuroendocrine stress responses	[36]
Albiflorin	SPS-induced PTSD rat model	Albiflorin significantly reduced PTSD-like behaviors, including anxiety-like behavior, exaggerated fear responses, and depression-like symptoms	Regulation of the HPA axis; normalization of corticosterone levels; modulation of monoaminergic neurotransmission	[37]
Flavonoids	ESPS and conditioned fear stress models	Flavonoid treatment significantly reduced anxiety-like behaviors and alleviated PTSD-associated emotional abnormalities	Modulation of GABAergic neurotransmission; enhancement of inhibitory signaling; regulation of stress-related monoaminergic pathways	[38]

BJIGT, Bojungikgi-tang; HFE, Herbal Formula Extract; KRG, Korean Red Ginseng; SPSS, single prolonged stress and shock; SPS, single prolonged stress; ESPS, enhanced single prolonged stress; HPA, hypothalamic–pituitary–adrenal.

suggests that antidepressants, including SSRIs, can alter microbial composition and reduce microbial diversity, potentially exacerbating dysbiosis and peripheral inflammation in susceptible individuals [68,69]. Collectively, these findings highlight the systems-level potential of CAM to restore stress-regulatory homeostasis through mechanisms not readily targeted by conventional pharmacotherapy. Conceptualizing the gut-brain axis as a key component of PTSD supports integrating gut-focused CAM strategies into mechanism-informed, systems-level treatment approaches.

3. Conclusion and Future Directions: Toward a Systems-Based Treatment Paradigm for PTSD

Recognizing PTSD as a disorder of systemic stress dysregulation calls for a re-evaluation of current therapeutic strategies. Trauma persistence likely reflects dysfunction across interconnected autonomic, immune, endocrine, and gut–brain regulatory networks rather than isolated monoaminergic abnormalities. Accordingly, PTSD treatment should prioritize restoration of physiological homeostasis rather than symptom suppression alone. Within this paradigm, CAM may offer therapeutic potential by targeting multiple stress-regulatory systems. Future studies should determine whether disruption of specific regulatory pathways defines distinct patient phenotypes and identify interventions that most effectively restore physiological balance. This will require biomarker-guided approaches incorporating HRV, inflammatory markers, neuroendocrine profiles, and gut microbiome characteristics to guide treatment selection. Such an approach could facilitate a transition toward precision psychiatry by enabling mechanism-based, individualized treatment of PTSD (Fig. 1). As illustrated in Fig. 1, autonomic imbalance, chronic immune activation, and gut–brain dysfunction interact bidirectionally to reinforce systemic stress dysregulation, whereas CAM interventions are proposed to restore physiological homeostasis by enhancing vagal activity, attenuating inflammatory signaling, and stabilizing gut–brain communication.

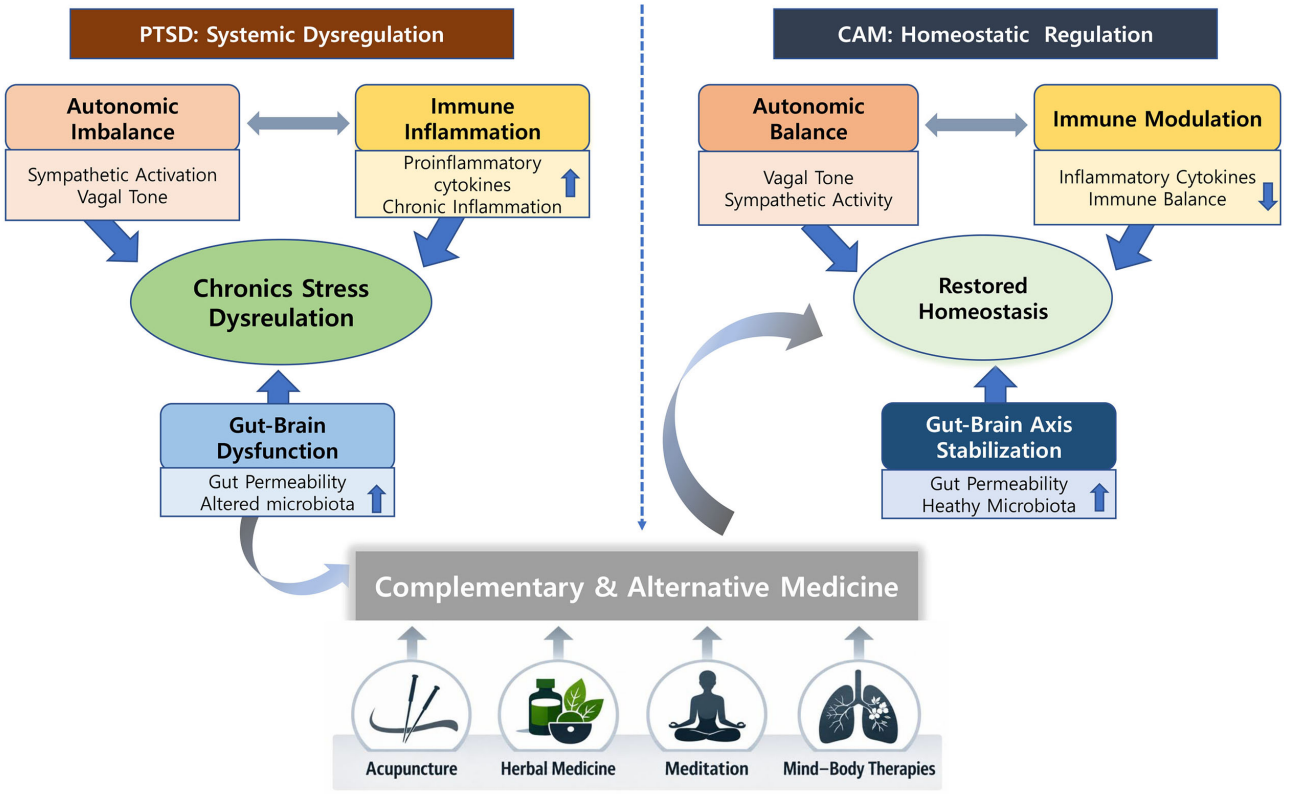

Fig. 1. Multisystemic view of PTSD pathophysiology and recalibration of stress homeostasis through CAM interventions. This schematic representation conceptualizes PTSD as a disorder of systemic stress dysregulation (left panel), encompassing a feedback loop of sympathetic overactivity, systemic inflammation, and compromised intestinal integrity. Collectively, these disturbances undermine physiological homeostasis. In contrast, the right panel highlights the therapeutic potential of CAM interventions, including acupuncture, herbal medicine, meditation, and mind–body therapies, to restore homeostasis. Through autonomic and immune–inflammatory modulation, modalities such as acupuncture and herbal medicine engage multiple regulatory nodes to stabilize the gut-brain axis. CAM functions as a systems-level intervention designed to restore the underlying stress-response circuitry in PTSD. Some pathways shown in the figure are proposed based on emerging evidence and have not yet been definitively established in the context of PTSD.

This systems-oriented framework is not intended to replace conventional pharmacological or psychotherapeutic approaches but to integrate them within a broader biological model. Pharmacotherapy remains essential for managing acute symptoms, whereas CAM may complement conventional treatment by restoring autonomic flexibility, attenuating chronic immune activation, and enhancing neuroendocrine resilience. Positioning these modalities as complementary rather than competing strategies may strengthen integrative PTSD care. Although integrated treatment may offer greater benefit than monotherapy, current evidence remains limited and heterogeneous, highlighting the need for comparative clinical studies.

While animal studies provide compelling mechanistic evidence supporting CAM effects on neuroimmune regulation, autonomic function, and the gut-brain axis, translation to clinical efficacy in PTSD remains limited. Clinical findings are more heterogeneous, likely reflecting differences in patient populations, intervention protocols, and outcome measures. Future biomarker-guided clinical trials are needed to identify patients most likely to benefit from CAM-based interventions. CAM also has important limitations. Herbal medicines present challenges related to standardization, potential hepatotoxicity, and drug–herb interactions, while acupuncture and mind–body therapies may be influenced by placebo effects. Patient heterogeneity and variability in treatment protocols further contribute to inconsistent clinical outcomes. Future studies should prioritize standardized interventions, rigorous clinical trials, and biomarker-guided patient stratification to strengthen the clinical evidence supporting CAM in PTSD.

Author Contributions

EJY designed the article and wrote the manuscript. HRP contributed to the literature search and participated in discussions regarding the manuscript content. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

ChatGPT was used solely to assist with language editing and grammatical improvement of the manuscript and to generate graphical icons representing acupuncture, herbal medicine, meditation, and mind-body therapies in Fig. 1. The authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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