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Review

Molecular pathways of Traditional Chinese medicine–derived compounds in cognitive decline and depressive disorders: Neuroinflammation, synaptic plasticity and stress axis regulation

Yandong Li[1], Linlin Du[2], Xingyu He[2] and Zongsuo Liang[1,3]*
[1]School of Pharmacy, Shaanxi University of Chinese Medicine
[2]College of Life Sciences, Northwest A and F University
[3]School of Life Science and Medicine, Zhejiang Sci-Tech University

Abstract: **Background**: Central pathophysiological mechanisms underlying cognitive impairment and mood disorders are complex. Traditional Chinese Medicine (TCM)–derived bioactive compounds have significant research value in this field. **Objective**: This study aimed to synthesize current preclinical and emerging clinical evidence on the neuroprotective and psychotropic effects of key TCM constituents, with a particular focus on their roles in modulating neuroinflammatory signalling, synaptic plasticity, oxidative balance and stress-related neuroendocrine pathways. **Methods**: A narrative synthesis of experimental and early clinical studies was conducted, emphasizing mechanistic investigations in rodent models and exploratory human trials. Outcomes of interest included inflammatory cytokine expression, inflammasome activation, redox homeostasis, synaptic signalling pathways, neuroendocrine regulation, behavioural performance and translational pharmaceutical considerations. **Results**: Multiple TCM constituents attenuate microglial activation and inflammasome signalling, suppressing interleukin-1β, interleukin-6 and tumor necrosis factor-alpha through inhibition of nuclear factor κB and NOD-like receptor pyrin domain-containing 3 pathways. These effects restore redox homeostasis, reduce synaptic loss and improve cognitive and behavioural outcomes in animal models. Concurrently, several compounds enhance synaptic resilience by upregulating brain-derived neurotrophic factor and tropomyosin receptor kinase B signalling, activating downstream mechanistic target of rapamycin complex 1 and cyclic adenosine monophosphate response element-binding protein pathways and preserving synaptic proteins. Key agents, including ginsenosides, baicalin and curcumin, have shown translational promise, with small human trials reporting improvements in depressive symptoms, cognitive function and biomarker profiles. Additionally, TCM compounds modulate HPA axis dynamics by attenuating stress-induced corticosterone elevation, restoring glucocorticoid receptor sensitivity and rebalancing monoaminergic and glutamatergic neurotransmission. However, pharmaceutical translation remains limited by challenges related to formulation, dosage standardization and poor oral bioavailability, particularly for flavonoids and saponins. **Conclusion**: TCM-derived compounds exert multifaceted neuroprotective and psychotropic effects, while successful clinical translation requires strengthened pharmaceutical characterization, standardized dosing strategies and advanced delivery systems such as nanoformulations, phytosomes and standardized granules to enhance bioavailability, reliability and regulatory acceptance.

Keywords: Cognitive decline; Molecular pathway; Neurodegenerative disorder; Neuroinflammation; Traditional Chinese medicine

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INTRODUCTION

Cognitive decline and depressive disorders are pervasive and often comorbid public health challenges. Across the world, aging populations are seeing a rising prevalence of mild cognitive impairment and dementia (particularly Alzheimer's disease (AD), while depression remains a leading cause of disability and poor quality of life (Ransohoff, 2016). Importantly, cognitive dysfunction is not only a hallmark of neurodegenerative diseases but is also frequently present in depressive disorders (e.g., impaired memory, attention, processing speed) and persistent depression increases the risk of later neurocognitive decline (Scheltens *et al.,* 2021). At the mechanistic level, both conditions share overlapping molecular pathways that drive disease progression (Tan *et al.,* 2010). Chronic neuroinflammation is a central feature, characterized by sustained activation of microglia and astrocytes, excessive release of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and activation of NF-κB and NLRP3 inflammasome pathways, which contribute to neuronal injury and synaptic loss (Leng *et al.,* 2021). Simultaneously, synaptic plasticity impairment mediated through reduced brain-derived neurotrophic factor (BDNF) expression, diminished TrkB and CREB signaling and destabilization of synaptic proteins such as PSD-95

**Corresponding author:* e-mail: liangzs@ms.iswc.ac.cn

disrupts learning, memory and mood regulation (Thakur *et al.,* 2023). Moreover, hypothalamic–pituitary–adrenal (HPA) axis dysregulation and chronic hypercortisolemia exacerbate these processes by impairing neurogenesis, altering glutamatergic and GABAergic neurotransmission and further amplifying inflammatory responses (Bitto *et al.,* 2017). Together, these interconnected pathways create a vicious cycle of neurodegeneration, cognitive dysfunction and mood disturbance. These disorders share three interconnected processes neuroinflammation, synaptic dysfunction and HPA axis dysregulation which drive neurodegeneration and mood disturbance (Milner *et al.,* 2021; Mert *et al.,* 2012). Conventional pharmacotherapies (antidepressants, cholinesterase inhibitors, NMDA antagonists, etc.) predominantly target one or two of these mechanisms, often with partial efficacy and with side effects. Prevention or treatment of cognitive decline in depression remains challenging (Shaito *et al.,* 2022). Thus, there is growing interest in complementary and alternative strategies, especially from Traditional Chinese Medicine (TCM), which historically emphasizes holistic, systemic regulation and often comprises multi-component herbal formulas and natural compounds (Li *et al.,* 2022; Armstrong, 2020).

Recent research (2023–2025) has provided stronger evidence for TCM-derived compounds in modulating these critical molecular pathways. Astragalus polysaccharides or its astragaloside IV form, which mitigate microglial activation, reduce NF-κB and NLRP3 inflammasome signaling and attenuate depressive-like behavior in animal models (He *et al.,* 2022; Huang *et al.,* 2024). Ganoderma lucidum polysaccharides (GLPs) and triterpenoids, which suppress IL-1β, TNF-α, reduce astrocyte/microglial overactivation and protect against cognitive impairment associated with chronic hypoperfusion or stress. Iridoid glycosides such as catalpol and geniposide, which have shown dual functions of reducing neuroinflammation and improving synaptic protein expression (BDNF/TrkB etc.) and ameliorating HPA axis dysfunction in preclinical models of depression (Manogaran *et al.,* 2018; Xie *et al.,* 2025). Given this emerging evidence, a synthesis is timely, mapping which TCM compounds or formulas target which molecular mechanisms and how strongly preclinical or clinical data support their use.

MATERIALS AND METHODS

This review aims to systematically describe TCM-derived natural products and formulas studied in relation to cognitive decline and depressive disorders, focusing on molecular pathways of neuroinflammation, synaptic plasticity and HPA axis regulation (Hashimoto *et al.,* 2017; Isola *et al.,* 2021). Another Clinical evidence is emerging but mixed: a multicenter RCT of Jia-wei Xiao Yao San (JWXYS, N=210) demonstrated non-inferiority to sertraline for mild–moderate depression (8 weeks), small RCTs of curcumin (e.g., 500 mg twice daily, N≈56, 8 weeks) report symptomatic and biomarker improvements and the delayed-start MLC901/NeuroAiD (ATHENE) add-on study in mild–moderate Alzheimer's disease (N≈125) showed acceptable safety with exploratory signals for slowed decline; meta-analyses for standardized Ginkgo biloba (EGb761) report modest cognitive benefits in dementia (120–240 mg/day). However, most trials used whole-extracts or proprietary preparations and lack pharmacokinetic, dose-finding and standardized chemical-marker data, limiting regulatory translation. Summarize the strength and gaps of evidence (animal vs. human; dose; pharmacokinetics; safety). Discuss translational challenges and strengths and suggest future directions for research and clinical application.

Exemplary TCM compounds / formulas: Sources and key molecular actions

Below is a table 1 summarizing selected TCM compounds and formulas recently studied (past few years), their herbal sources and their known molecular mechanisms relevant to neuroinflammation, synaptic plasticity, or HPA axis regulation. Human data are limited but growing. A multicenter, randomized, double-blind trial (JWXYS capsules vs sertraline, N=210, 8 weeks) found JWXYS non-inferior to sertraline on HAMD scores with similar adverse-event rates. Small RCTs of single compounds (for example, curcumin, 500 mg twice daily for 8 weeks, N≈56) have reported modest symptom and biomarker improvements, while the MLC901/NeuroAiD ATHENE delayed-start trial in mild–moderate Alzheimer's (≈125 subjects) found no safety signal and exploratory efficacy trends that require confirmation. Meta-analytic evidence for standardized Ginkgo biloba extract (EGb761, 120–240 mg/day) indicates modest cognitive benefits in dementia (Tian *et al.,* 2022; Isola *et al.,* 2021). Crucially, most of these human studies evaluate multi-component extracts or proprietary formulations and do not report systematic pharmacokinetic (PK) profiling, dose-ranging, or standardized chemical markers, which constrains interpretation and regulatory extrapolation (He *et al.,* 2017).

Gaps and considerations

Far fewer trials; many studies are in animals. Translation to humans (in terms of dose, safety, efficacy) remains under-explored. Herbal extracts or formulas vary in composition; purity, active compound concentration, or preparation method can differ, complicating comparison across studies (Ren *et al.,* 2024). Many natural compounds have low oral bioavailability, limited brain penetration, or rapid metabolism; delivery methods are often not optimized. Many compounds influence several pathways simultaneously; teasing out causality (which pathway is primary or downstream) is complex (Zhang, *et al.,* 2019; Sohn *et al.,* 2019). A major barrier to integrating TCM into evidence-based neuropsychiatric therapeutics is the lack of pharmaceutical standardization. Most herbal extracts exhibit considerable variability in their chemical composition depending on plant origin, extraction solvent and processing conditions, which complicates reproducibility across studies (Liu *et al.*, 2014; Shang *et al.,* 2010). Dosage inconsistencies between traditional decoctions, granules, capsules and concentrated extracts further limit dose–response interpretation. Unlike single-molecule pharmaceuticals, multi-component herbal preparations often lack defined active markers, standardized potency, or validated quality control profiles issues fundamental to pharmaceutical sciences and drug development (Aktary *et al.,* 2025).

Pharmacokinetics, bioavailability and safety challenges

Another critical limitation is the poor pharmacokinetic profile of many TCM-derived compounds. Flavonoids, terpenoids and saponins often demonstrate low oral bioavailability due to poor solubility, limited permeability, rapid metabolism and low blood–brain barrier (BBB) penetration (Chen *et al.,* 2020; Dinda *et al.,* 2017). These PK challenges restrict therapeutic translation and highlight the need for optimized dosage forms such as nanoparticles, liposomes, solid dispersions and phytosome-based systems that can enhance absorption and target delivery. Additionally, systematic toxicological assessments and herb–drug interaction data remain insufficient, underscoring the necessity for safety-focused pharmaceutical evaluation before widespread clinical adoption (Chen *et al.,* 2024; Jin *et al.,* 2019). Herb–drug interactions also represent a major developmental and regulatory challenge for TCM-derived therapies. Several commonly used constituents influence cytochrome P450 enzymes, drug transporters and coagulation pathways. For example, ginkgolides may potentiate bleeding risk when combined with anticoagulants or antiplatelet agents; berberine inhibits CYP3A4, CYP2D6 and P-glycoprotein, affecting the metabolism of antidepressants, statins and antidiabetic drugs; and compounds in licorice (present in Xiaoyaosan) can alter corticosteroid metabolism. Because multi-herb formulas contain dozens of pharmacologically active components, predicting interaction profiles is substantially more complex than with single-molecule drugs. Systematic herb–drug interaction screening and well-designed clinical pharmacology studies are therefore essential for safe clinical translation (Chen *et al.,* 2020; Dai *et al.,* 2013). A systematic limitation across published human trials is the near-absence of pharmacokinetic profiling, plasma biomarker/active-marker quantification and formal dose-finding: most RCTs report clinical outcomes for whole extracts or proprietary formulations without accompanying PK or standardized chemical-marker data a major barrier to regulatory and mechanistic translation (Gu *et al.,* 2010). Given these pharmaceutical gaps, this review not only synthesizes the mechanistic actions of TCM compounds but also highlights the essential pharmaceutical considerations formulation, standardization, pharmacokinetics, dosage and safety that influence their translational potential (Ndayisaba *et al.,* 2025; Mayne *et al.,* 2020).

Formulation and delivery innovations to enhance brain targeting of TCM-derived compounds

Traditional Chinese medicine–derived compounds face major pharmaceutical barriers to clinical translation, including poor aqueous solubility, rapid metabolism, limited permeability and low blood–brain barrier (BBB) penetration (Lai *et al.,* 2003; Sivandzade *et al.,* 2019). Recent advances in formulation science have enabled the development of delivery systems capable of improving bioavailability, stability and CNS targeting of flavonoids, terpenoids, saponins and other TCM-derived phytochemicals. Several classes of formulation and nanotechnology-based approaches show particular promise:

Nanoparticles (NPs)

Polymeric nanoparticles (PLGA, chitosan), lipid nanoparticles and solid–lipid nanoparticles have been used to encapsulate compounds such as curcumin, luteolin, baicalin and quercetin. These systems improve solubility, prolong circulation and enhance BBB transport via endocytosis and receptor-mediated uptake. For example, PLGA-curcumin nanoparticles exhibit markedly higher brain concentrations and improved cognitive outcomes in AD models compared to free curcumin (Wang *et al.,* 2022).

Liposomes

Liposomes facilitate protection from enzymatic degradation and offer tunable surface modification for brain targeting (e.g., transferrin-, lactoferrin-, ApoE-functionalized liposomes). Liposomal ginsenoside Rg1 has shown enhanced stability, improved pharmacokinetics and superior neuroprotective effects in preclinical ischemia and AD models (Mandal, *et al.,* 2022).

Phytosomes (phospholipid complexes)

Phytosome technology improves membrane permeability and systemic absorption by forming lipid-compatible complexes. Curcumin- and quercetin-phytosomes demonstrate 4–8-fold higher bioavailability clinically. Baicalin phytosomes have shown improved BBB penetration and greater antidepressant-like effects in rodent models (Ma, *et al.,* 2022).

Nanoemulsions and self-emulsifying drug delivery systems (SEDDS)

SEDDS formulations of compounds such as resveratrol, berberine and andrographolide enhance lymphatic uptake, avoid first-pass metabolism and improve oral absorption. Resveratrol nanoemulsions significantly increase plasma exposure and brain delivery in comparative PK studies (Wu, *et al.,* 2019).

Solid dispersions and cyclodextrin inclusion complexes

Cyclodextrin complexes increase the solubility and stability of poorly water-soluble flavonoids and terpenoids. Baicalin–cyclodextrin complexes show superior dissolution rates and anti-inflammatory activity. Curcumin-solid dispersions enhance oral bioavailability and provide more sustained pharmacodynamic responses.

Intranasal delivery systems

Intranasal nanoformulations bypass the BBB via olfactory and trigeminal neural pathways and enable rapid CNS delivery. Intranasal baicalin nanoparticles and ginsenoside-loaded nanoemulsions have demonstrated improved antidepressant and cognitive effects with significantly lower dose requirements (Ma *et al.,* 2025).

Hybrid and multifunctional nanocarriers

Emerging systems combine targeting ligands, stimuli-responsive release and co-delivery of synergistic phytochemicals. Examples include ROS-responsive nanoparticles delivering both curcumin and resveratrol to inflamed microglia, showing superior anti-inflammatory and neuroprotective effects. Collectively, these formulation innovations provide a pathway to overcome fundamental pharmacokinetic limitations of TCM-derived compounds and significantly enhance their translational potential. Incorporating these technologies into future clinical development alongside standardized extraction, chemical-marker quantification and controlled human pharmacokinetic studies will be essential for advancing TCM-based neurotherapeutics toward regulatory approval and precision CNS delivery (Song *et al.,* 2012).

RESULTS

Traditional Chinese medicine in neuropsychiatric disorders

Traditional Chinese medicine (TCM) has been practiced for over 2,000 years, providing a holistic framework for understanding and treating neuropsychiatric disorders. TCM does not view mental health conditions merely as localized dysfunctions but as manifestations of systemic imbalances (Yang, *et al.,* 2024)**.** Core principles such as Yin-Yang equilibrium, Qi (vital energy) flow and the interactions among Zang-Fu organs (e.g., Heart–Shen, Liver–Qi, Kidney–Essence) form the foundation of diagnosis and therapy. Emotional disturbances, including depression and anxiety, are often linked to liver Qi stagnation or Heart Shen deficiency, whereas cognitive decline is associated with depletion of Kidney essence (Jiang *et al.,* 2022). This integrated perspective emphasizes the interconnection between mind, body and environment, guiding the development of multitarget therapeutic interventions (Luo *et al.,* 2014). The pharmacological diversity of TCM is discussed mechanistically in later sections; here we focus only on foundational theory and compound classes (Sun *et al.,* 2013; Calio, *et al.,* 2020). Their pharmacological effects are often multitargeted, influencing neurotransmission, neuroinflammation, oxidative stress and synaptic plasticity are mentioned below in table 2 (Araujo, *et al.,* 2022).

Neuropsychiatric disorders involve a complex interplay of neurotransmitter dysregulation, neuroinflammation, oxidative stress and hypothalamic-pituitary-adrenal (HPA) axis dysfunction. TCM compounds, particularly when administered in combination as part of polyherbal formulations, exhibit multisystem modulation, simultaneously targeting several pathological pathways. For example, a single TCM preparation may reduce proinflammatory cytokines, enhance neurotrophic factors, restore neurotransmitter balance and improve mitochondrial function. This systems-based approach aligns with the multifactorial etiology of disorders such as depression, anxiety and cognitive decline and shown in fig. 1.

Pathophysiological mechanisms underlying cognitive decline and depressive disorders

Cognitive decline and depressive disorders are increasingly recognized as interconnected conditions that share overlapping neurobiological substrates (Pajares *et al.,* 2020; Purushothaman and Sumathi, 2022). Mounting evidence indicates that their progression is not isolated but driven by convergent molecular pathways involving neuroinflammation, impaired synaptic plasticity and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. These mechanisms operate in parallel, interact synergistically and create self-reinforcing cycles of neuronal dysfunction (Song *et al.,* 2012).

Neuroinflammation and immune dysregulation

Persistent neuroinflammation is a hallmark of both dementia and depression. Activated microglia and astrocytes release excessive levels of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (Marogianni *et al.,* 2020; Su *et al.,* 2017). These cytokines activate the NF-κB and NLRP3 inflammasome pathways, driving oxidative stress and mitochondrial dysfunction. Chronic inflammation also compromises blood–brain barrier integrity, facilitating peripheral immune cell infiltration and amplifying neuroimmune signaling.

Sustained neuroinflammation contributes to synaptic pruning, neuronal apoptosis and impaired neurogenesis, thereby linking immune dysregulation to both cognitive decline and depressive symptomatology (Gao *et al.,* 2024; Sun *et al.,* 2022; Chen *et al.,* 2021).

Impaired synaptic plasticity and neurotrophic signaling

Synaptic plasticity the brain's ability to strengthen or weaken synaptic connections is crucial for learning, memory and mood regulation. In Alzheimer's disease, mild cognitive impairment and depression, reduced levels of brain-derived neurotrophic factor (BDNF) and its receptor TrkB are consistently reported](Ma *et al.,* 2021). This leads to attenuated activation of downstream signaling pathways such as CREB, mTOR and CaMKII. Loss of synaptic proteins including PSD-95 and synaptophysin further destabilizes synaptic architecture, impairing long-term potentiation (LTP). The net effect is diminished cognitive flexibility, memory deficits and heightened vulnerability to mood dysregulation (Benabid *et al.,* 2009; Jie *et al.,* 2022).

Table 1: Representative TCM-derived compounds and classical formulas with their molecular mechanisms, system-level effects and observed behavioral outcomes in neuropsychiatric disorder models.

S. No.	Compound	Herbal source(s)	Key molecular actions	System and behavioral effects
1.	Astragaloside IV (AS-IV)	Astragalus membranaceus (polysaccharides / astragaloside)	↓ Microglial activation; ↓ IL-1β, TNF-α; ↓ NF-κB phosphorylation; ↑ Nrf2/HO-1 pathway; modulates PPAR-γ; ameliorates NLRP3 inflammasome activation.	In mice: Reduced depressive-like behavior from LPS or restraint stress; improved cognition in Alzheimer-type or inflammation models.
2.	Ganoderma lucidum polysaccharides / triterpenoids	Ganoderma lucidum	↓ IL-1β, IL-6, TNF-α; inhibit microglial and astrocyte activation; regulate microglial polarization (M1→M2) via ERK/CREB etc.; protect synaptic integrity.	In rodent models of chronic stress, social defeat, hypoperfusion: Improved learning, memory, reduced depressive-like behavior.
3.	Catalpol	Iridoid glycoside (Rehmannia)	↓ NLRP3 inflammasome proteins; ↓ COX-2/PGE2; ↑ BDNF/TrkB; modulate HPA axis dysfunction.	In chronic mild stress (CMS) models: Improved behavioral metrics (sucrose preference, forced swim) and molecular markers.
4.	Geniposide	Gardenia jasminoides (Iridoid glycoside)	Downregulates BTK/TLR4/NF-κB; upregulates BDNF/TrkB; reduces IL-6, TNF-α; promotes anti-inflammatory microglia.	LPS or CMS induced depression in rodents: Improvement in mood-like behavior and synaptic markers.
5.	Curcumin, Kaempferol, Resveratrol, etc.	Phenolic compounds from turmeric, tea and various herbs	Multi-target: inhibit neuroinflammation (NF-κB, COX, etc.), reduce oxidative stress; inhibit Aβ aggregation or tau hyperphosphorylation; improve synaptic plasticity.	Models of Alzheimer's disease in animals; some *in vitro*; limited human pilot studies.
6.	TCM formulas (e.g. Zhi-Zi-Chi-Tang, Xiaoyaosan, Danggui-Buxue decoction, ZSQGY, etc.)	Multiple herbs in classical formulas	Activation of BDNF/CREB/TrkB, modulation of GSK-3β, improvement in synaptic protein expression (PSD-95, MAP2), suppression of pro-inflammatory cytokines; regulation of HPA axis components in some cases.	Animal models of depression (CUMS, MSG, etc.): Restored synaptic plasticity, improved behavioral outcomes. Some decoctions shown to affect neurogenesis and mitochondrial function.

Table 2: Representative classes of bioactive compounds in traditional Chinese medicine and their neuropsychiatric effects, including key mechanisms of action.

S. No.	Compound class	Representative examples	Neuropsychiatric effects	Mechanisms of action
1.	Flavonoids	Baicalin, Hesperidin	Cognitive enhancement, anxiolysis	Antioxidant, anti-inflammatory, modulation of GABAergic and serotonergic systems
2.	Alkaloids	Berberine, Huperzine A	Neuroprotection, antidepressant	Cholinesterase inhibition, neurotransmitter modulation
3.	Saponins	Ginsenosides, Astragalosides	Neurotrophic support, stress resilience	Promote synaptic plasticity, anti-inflammatory signaling
4.	Terpenoids	Ginkgolides, Andrographolide	Cognitive support, neuroprotection	Antioxidant activity, inhibition of neuroinflammation
5.	Polysaccharides	Lycium barbarum polysaccharides	Neuroimmune modulation, anti-stress	Anti-inflammatory, neurotrophic, immune-regulatory effects

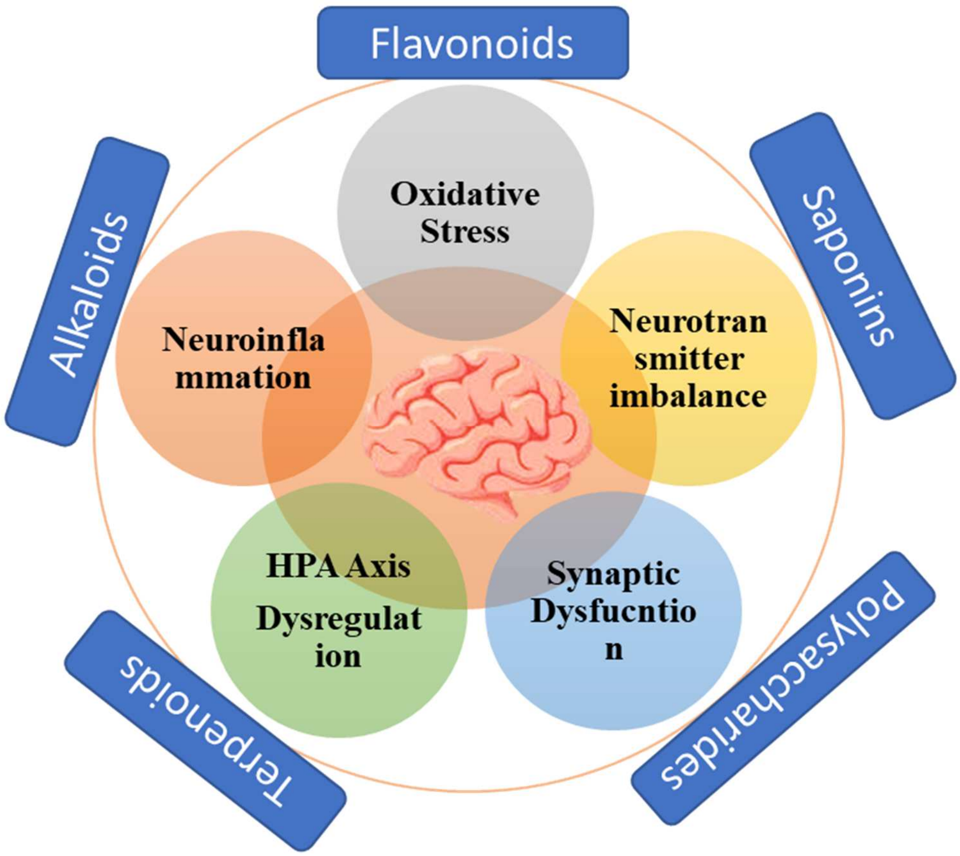

Fig. 1: Multitarget mechanisms of TCM compounds in neuropsychiatric disorders

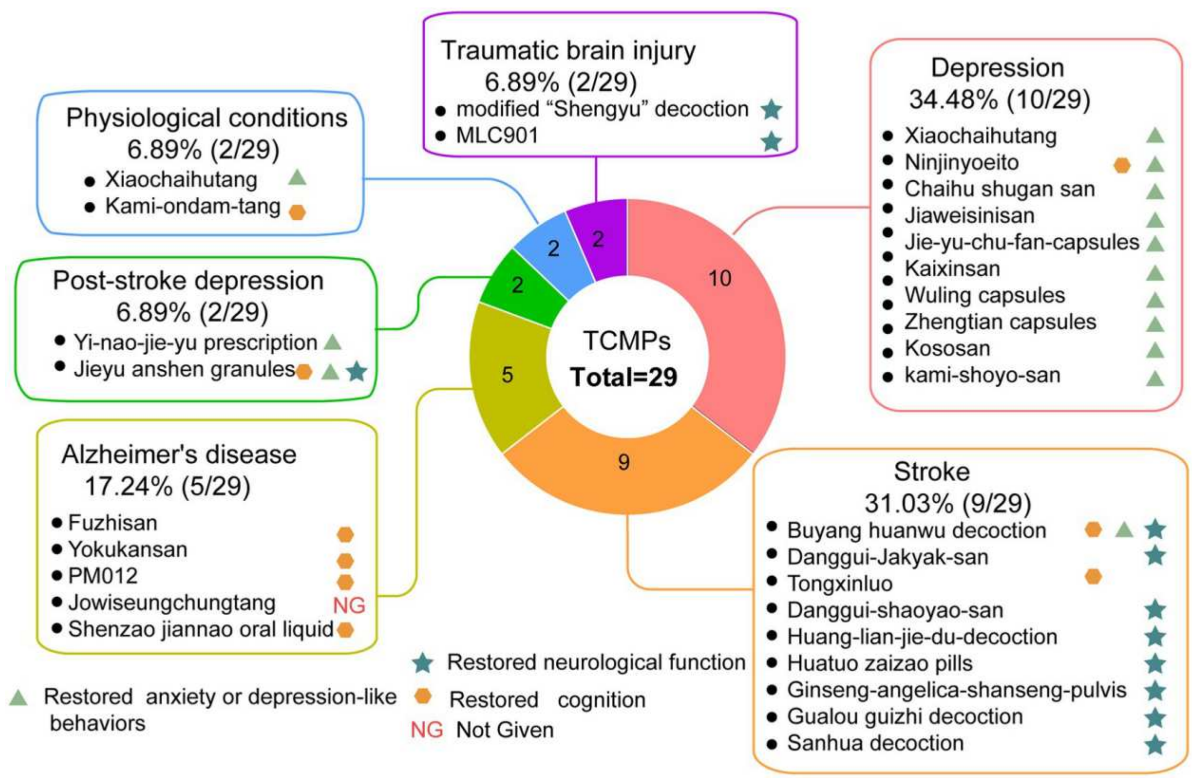

Fig. 2: Summary of traditional Chinese medicine prescriptions (TCMPs) used for neurological and psychiatric disorders.

Table 3: Selected recent studies/reviews relevant to neuroinflammation, synaptic plasticity and HPA-axis dysregulation (2023–2025)

S. No.	Research study	Model / Population	Key mechanistic findings (brief)	Primary pathway(s)
1.	Microglial NLRP3 inflammasome-mediated neuroinflammation in depression (review).	Human data + animal models (review)	Consolidates evidence that NLRP3 inflammasome activation is elevated in major depressive disorder and mediates IL-1β/IL-18 release; discusses upstream triggers (TLR4, ROS) and therapeutic targeting strategies.	NLRP3 inflammasome → neuroinf lammation
2	Updated insights into the NLRP3 inflammasome in POCD and CNS disease (review)	Animal and translational studies (review)	Summarizes recent mechanistic data linking NLRP3 activation to postoperative cognitive dysfunction and neurodegeneration; highlights microglial pyroptosis and cross-talk with Aβ/tau pathology.	NLRP3 / microglial-mediated neuroinflammation
3	NLRP3 inflammasome in Alzheimer's disease (review)	Review of human and experimental AD literature	Details how Aβ/tau species, mitochondrial ROS and lysosomal damage activate NLRP3; NLRP3 drives IL-1β and contributes to synaptic loss and cognitive impairment.	NLRP3 ↔ Aβ/tau → neuroinflammation and synaptic damage
4	From synaptic plasticity to neurodegeneration: BDNF as a convergent node (review)	Review (molecular / translational)	Argues BDNF/TrkB signaling is central to LTP, dendritic spine maintenance and resistance to neurodegeneration; reviews strategies to enhance BDNF signaling in AD and depression.	↓ BDNF/TrkB → impaired synaptic plasticity
5	Association of plasma BDNF and MMP-9 with mild cognitive impairment (clinical study)	Human cohort (MCI vs controls)	Lower plasma BDNF associated with MCI; suggests peripheral BDNF as a biomarker for cognitive decline; links to synaptic health and cognitive performance.	BDNF disruption — clinical correlation with cognition
6	Hypothalamic-Pituitary-Adrenal (HPA) Axis: Unveiling the links to AD and depression (review)	Review (human and animal evidence)	Summarizes how chronic HPA activation, hypercortisolemia and GR resistance impair hippocampal neurogenesis, exacerbate glutamate excitotoxicity and potentiate inflammation.	HPA axis dysregulation → impaired neurogenesis and inflammation
7	HPA and gut-brain axes in depression (review)	Review (integrative)	Emphasizes HPA–gut interactions (microbiome/serotonin) that modulate systemic inflammation and central neurotransmitters relevant to mood and cognition.	HPA ↔ gut-brain → systemic inflammation and neurotransmitter imbalance
8	Inflammasome-mediated neuroinflammation in AD (review)	Review (AD molecular focus)	Details inflammasome-driven IL-1β/IL-18 release, pyroptosis and downstream synaptic dysfunction, and discusses inflammasome inhibitors as potential therapies.	Inflammasome → neuroinflammation → synaptic loss

Stress axis dysregulation and neurotransmitter imbalance

Dysregulation of the HPA axis represents another shared pathogenic pathway. Chronic stress leads to hypercortisolemia and glucocorticoid receptor resistance, which suppresses hippocampal neurogenesis and exacerbates glutamatergic excitotoxicity (Ma *et al.,* 2017). Alterations in monoamine neurotransmission, including reduced serotonergic, dopaminergic and noradrenergic activity, compound the problem, reinforcing depressive symptoms and accelerating cognitive decline (Subhramanyam *et al.,* 2019; Saba *et al.,* 2021). Furthermore, elevated glucocorticoids amplify neuroinflammation, creating a feedback loop that further disrupts synaptic and neuronal integrity.

Integration of mechanisms

Rather than acting independently, these pathological processes converge in a vicious cycle: neuroinflammation impairs synaptic plasticity, stress hormones exacerbate immune responses and neurotransmitter imbalances further reduce synaptic resilience (Tan *et al.,* 2025; Yang *et al.,* 2024). Understanding this interplay provides a mechanistic framework to explore how Traditional Chinese Medicine–derived compounds, with their multi-targeted actions, may offer therapeutic advantages by simultaneously modulating multiple pathways in table 3 (Rui *et al.,* 2020).

Mechanistic overview of TCM compounds in neuropsychiatric disorders

Traditional Chinese medicine (TCM) has shown significant potential in the management of neuropsychiatric disorders through its diverse bioactive compounds, including flavonoids, saponins, terpenoids, curcumin, icariin, paeoniflorin, baicalin, magnolol and schisandrin (Juliana *et al.,* 2019; Reimer *et al.,* 2018). In addition, they regulate the stress axis by restoring HPA homeostasis, increasing glucocorticoid receptor sensitivity and rebalancing key neurotransmitters including serotonin, dopamine, norepinephrine, glutamate and GABA (Zou *et al.,* 2018). In this review, we identified 29 Traditional Chinese Medicine prescriptions (TCMPs) evaluated across different neurological and psychiatric conditions. As illustrated in fig. 2, the majority of studies focused on depression (34.48%) and stroke (31.03%), followed by Alzheimer's disease (17.24%), while fewer TCMPs were reported for post-stroke depression, traumatic brain injury and other physiological conditions (each 6.89%). The therapeutic benefits varied, with most prescriptions demonstrating improvements in anxiety/depression-like behaviors, cognition and neurological recovery, highlighting the diverse potential of TCMPs in addressing neuropsychiatric disorders.

TCM-derived compounds targeting neuroinflammation

Neuroinflammation underlies the pathophysiology of numerous neuropsychiatric disorders, including depression, Alzheimer's disease and anxiety. Traditional Chinese medicine (TCM) offers bioactive compounds capable of modulating inflammatory signaling, oxidative stress and microglial activation. Key classes include flavonoids, saponins and terpenoids. Flavonoids (e.g., baicalin, baicalein, luteolin, quercetin) suppress pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), inhibit NF-κB signaling and attenuate NLRP3 inflammasome activation (Li *et al.,* 2018; Lee *et al.,* 2014). Saponins, particularly ginsenosides (Rg1, Rb1, Rd), promote microglial polarization toward an anti-inflammatory phenotype and upregulate neurotrophic factors such as BDNF. Terpenoids (e.g., ginkgolides, tanshinones) inhibit NF-κB, reduce cytokine release and activate antioxidant pathways, including Nrf2/HO-1 (Mittal *et al.,* 2014). These compounds exert multitarget effects that converge on reducing neuroinflammation, restoring synaptic plasticity and improving behavioral outcomes. Preclinical studies consistently demonstrate amelioration of cognitive deficits and depressive-like behaviors in rodent models, while limited clinical evidence suggests potential translational benefits as shown below in table 4 (Dressman *et al.,* 2022; Li *et al.,*2022).

Mitochondrial dysfunction is a central hallmark in the pathogenesis of neurodegenerative diseases. Traditional Chinese Medicine (TCM) has been shown to modulate non-coding RNAs, thereby influencing mitochondrial biogenesis, dynamics, autophagy, oxidative stress responses, calcium homeostasis and apoptotic pathways (Sosna *et al.,* 2018; Liang *et al.,* 2017). As depicted in fig. 3, these mechanisms are closely linked with the onset and progression of Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis, underscoring the therapeutic potential of TCM in targeting mitochondrial-related pathways in neurodegeneration.

TCM-derived compounds enhancing synaptic plasticity

Synaptic plasticity, particularly long-term potentiation (LTP), is fundamental to learning and memory processes and is often impaired in neurodegenerative and neuropsychiatric disorders (Huang *et al.,* 2008; Ross and Poirier, 2004). Traditional Chinese medicine (TCM)-derived compounds have shown promising potential in restoring synaptic plasticity through modulation of neurotrophic signaling pathways, synaptic proteins and neurogenesis. Several bioactive compounds such as ginsenosides, curcumin, icariin and paeoniflor have demonstrated the ability to enhance brain-derived neurotrophic factor (BDNF)/TrkB signaling, activate CREB phosphorylation and upregulate key synaptic proteins including PSD-95 and synapsin I. Preclinical studies in rodent models of Alzheimer's disease, depression and learning impairments confirm that these compounds significantly improve cognitive performance and hippocampal synaptic plasticity. A summary of these compounds, their molecular targets and preclinical evidence is provided in table 5.

Table 4: TCM-derived compounds targeting neuroinflammation: Molecular mechanisms and preclinical evidence

S. No.	Compound class	Representative compounds	Molecular targets and Mechanisms	Preclinical/Clinical evidence
1.	Flavonoids	Baicalin, Baicalein, Luteolin, Quercetin	↓ IL-1β, IL-6, TNF-α; inhibit NF-κB; suppress NLRP3 inflammasome; antioxidant	Rodent models of depression, neuroinflammation, cognitive impairment: Improved behavior and synaptic markers
2.	Saponins	Ginsenosides Rg1, Rb1, Rd	Modulate microglial polarization (M1→M2); ↑ BDNF; anti-inflammatory	Chronic stress and Alzheimer's models: Enhanced cognition and mood
3.	Terpenoids	Ginkgolides, Tanshinones	Inhibit NF-κB; ↓ pro-inflammatory cytokines; activate Nrf2/HO-1	Rodent ischemia and AD models: Reduced neuroinflammation and oxidative stress

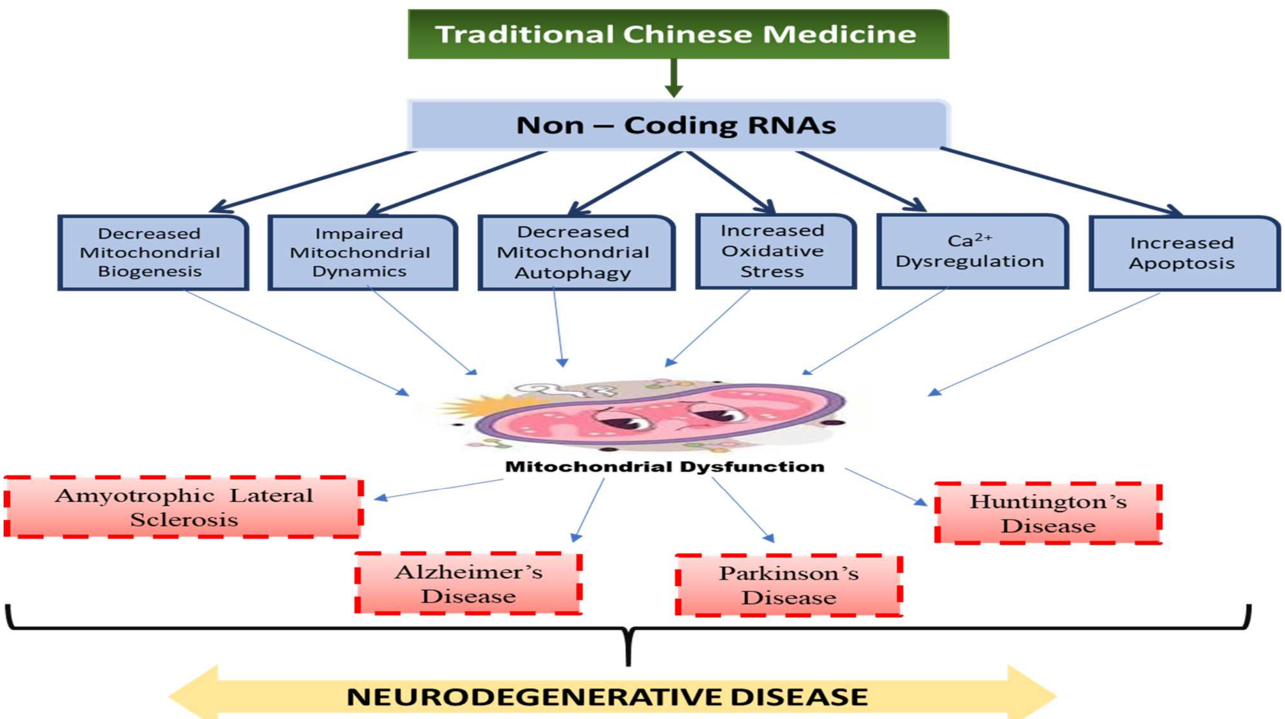

Fig. 3: Role of TCM in regulating non-coding RNAs and mitochondrial dysfunction in neurodegenerative diseases.

Table 5: TCM-derived compounds enhancing synaptic plasticity

S. No.	Compound	Herbal source	Molecular targets	Preclinical evidence
1	Ginsenosides (Rg1, Rb1)	Panax ginseng	↑ BDNF/TrkB, ↑ p-CREB, ↑ synaptic proteins (PSD-95, synapsin I), LTP enhancement	Rodent models of chronic stress and Alzheimer's disease: Improved learning, memory, and hippocampal synaptic plasticity
2	Curcumin	Curcuma longa	↑ BDNF, ↑ p-CREB, ↑ PSD-95, synapsin I; modulates HPA axis; antioxidant	Rodent AD and depression models: Restored synaptic function and cognitive performance
3	Icariin	Epimedium spp.	Activates BDNF-TrkB signaling; promotes synaptic protein expression; neurogenesis	Rodent models of learning and memory impairment: Improved cognition and synaptic plasticity
4	Paeoniflor	Paeonia lactiflora	↑ BDNF/TrkB, promotes neurogenesis, enhances LTP	Rodent models of cognitive impairment: Enhanced synaptic plasticity and memory performance

Table 6: TCM compounds targeting HPA axis and stress response

S. No.	Compound	Herbal source	Mechanism of action	Preclinical evidence
1.	Ginsenosides (Rg1, Rb1)	Panax ginseng	Normalize CRH/ACTH/ corticosterone; ↑ GR sensitivity; rebalance 5-HT, DA, NE	Rodent chronic stress models: Reduced depressive- and anxiety-like behaviors
2.	Baicalin	Scutellaria baicalensis	↓ CRH/corticosterone; ↑ GR expression; modulates GABA and 5-HT	Rodent CUS and LPS-induced depression models: Improved mood and stress resilience
3.	Magnolol	Magnolia officinalis	↓ corticosterone; ↑ GR sensitivity; modulates 5-HT, NE	Chronic stress rodent models: Anxiolytic and antidepressant-like effects
4.	Schisandrin	Schisandra chinensis	Enhances GR-mediated feedback; modulates 5-HT/GABA	Rodent chronic stress models: Restored HPA function and behavioral improvement

Table 7: Classical and modified TCM formulations targeting neuroinflammation, synaptic plasticity and HPA axis in neuropsychiatric disorders

S. No.	Formulation	Key herbal components	Mechanisms of action	Evidence / Model
1.	Jia Wei Xiao Yao San (JWXYS)	Bupleurum, Angelica, Paeonia, Poria, Additional herbs	↓ Neuroinflammation (cytokine suppression); ↑ BDNF/TrkB-CREB signaling; HPA axis normalization	Clinical: 192 patients with mild-to-moderate depression/anxiety; improved HAMD and CGI scores; better sleep quality
2.	Modified Huang-Lian-Jie-Du-Tang (HLJDT)	Coptis, Scutellaria, Phellodendron, Gardenia	↓ Neuroinflammation (microglial activation, amyloid-β load); ↑ Synaptic integrity and neurogenesis; modulates GR signaling	Preclinical: AD animal models; reduced amyloid-β, improved synaptic plasticity
3.	Modified Shen-Qi-Wan	Rehmannia, Cornus, Dioscorea, Poria, Alisma	↓ Pro-inflammatory cytokines; ↑ Synaptic protein expression and neurogenesis; HPA axis regulation	Clinical and Preclinical: Improved cognitive function, reduced fatigue, modulated neuroinflammation
4.	Xiaoyaosan (XYS)	Bupleurum, Angelica, Paeonia, Poria, Licorice, Ginger	↓ Cytokine-mediated neuroinflammation; ↑ BDNF-mediated synaptic plasticity; HPA axis regulation	Preclinical: Rodent models of depression and chronic stress; restored hippocampal plasticity and behavior
5.	Danggui-Shaoyao-San (DSS)	Angelica, Paeonia, Ligusticum, Alisma, Poria	↓ Microglial activation; ↑ Hippocampal neurogenesis; modulates TLR4/NF-κB, JAK2/STAT3, AKT-GSK3β; HPA axis effects	Preclinical: Depressive-like behavior in mice; improved neurogenesis and synaptic markers

TCM-derived compounds regulating stress axis

HPA axis dysregulation is a central feature of stress-related neuropsychiatric disorders. TCM-derived compounds, including ginsenosides, baicalin, magnolol and schisandrin, restore HPA homeostasis by normalizing CRH, ACTH and corticosterone levels and enhancing glucocorticoid receptor (GR) sensitivity (Li *et al.,* 2018; Ran *et al.,* 2021). These compounds also modulate key neurotransmitter systems 5-HT, DA, NE, glutamate and GABA leading to improved stress resilience, antidepressant-like effects and cognitive stabilization in preclinical models as compounds shown in table 6.

Integrated multi-pathway effects

TCM exerts therapeutic effects in neuropsychiatric disorders through complex, interconnected mechanisms that simultaneously target neuroinflammation, synaptic plasticity and the HPA axis (Mittal *et al.,* 2014). These pathways are highly interdependent: chronic neuroinflammation can impair synaptic plasticity, while HPA axis dysregulation exacerbates both inflammatory responses and synaptic dysfunction. TCM-derived compounds, by acting on multiple molecular and cellular targets, are uniquely positioned to modulate these intersecting systems in a coordinated manner (Dressman *et al.,* 2022). Neuroinflammation is attenuated through suppression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), inhibition of NF-κB and NLRP3 inflammasome signaling and enhancement of antioxidant defenses via Nrf2/HO-1 activation (Sengupta *et al.,* 2023). Concurrently, HPA axis regulation is achieved through normalization of CRH, ACTH and corticosterone levels, restoration of glucocorticoid receptor sensitivity and rebalancing of neurotransmitters including serotonin, dopamine, norepinephrine, glutamate and GABA, resulting in improved stress resilience and mood stabilization (Ross & Poirier, 2004; Jin *et al.,* 2024).

Preclinical studies have shown that these formulas can simultaneously reduce neuroinflammatory markers, enhance BDNF-mediated synaptic signaling and normalize HPA axis function in rodent models of depression, chronic stress and cognitive impairment (Yuan *et al.,* 2025; Liu *et al.,* 2022). Limited clinical evidence also suggests beneficial effects on mood regulation, cognitive performance and stress adaptation in patients, supporting their translational potential (Pan *et al.,* 2021). This section synthesizes the interactions between pathways, rather than repeating individual mechanisms described earlier (Liu *et al.,* 2024). A summary of these formulations, their key components, mechanisms of action and evidence is provided in table 7, highlighting their integrative, multi-targeted effects.

DISCUSSION

While preclinical studies have established the mechanistic basis of TCM-derived compounds and formulations in modulating neuroinflammation, synaptic plasticity and the HPA axis, their translation into clinical practice is still emerging. Several classical formulas, including XYS, JWXYS, DSS, HLJDT and Modified Shen-Qi-Wan, have demonstrated promising effects in humans (Pattanashetti *et al.,* 2025; 61. Li and browy., 2009). Clinical trials have reported improvements in depressive symptoms, anxiety, cognitive performance and stress resilience. For instance, JWXYS has shown efficacy in patients with mild-to-moderate depression, improving mood and sleep quality, while DSS has been associated with enhanced cognitive function and neurogenesis (Ding *et al.,* 2015; Day *et al.,* 2003). Some of these formulations are available in the market as standardized herbal products, such as XYS marketed as “Free and Easy Wanderer,” and are commonly used as adjunctive therapies for depression, anxiety and related neuropsychiatric conditions. (He *et al.,* 2009; Gogna *et al.,* 2024). A translational framework integrating safety, standardization, clinical trials and computational approaches is illustrated in fig. 4. Complex herbal mixtures are characterized for active compounds and tested in preclinical and clinical studies (Li *et al.,* 2023). Data from these studies feed into databases**,** enabling high-throughput screening and network pharmacology approaches to systematically explore multi-target mechanisms and optimize translational application as shown below in fig. 4.

Ongoing clinical trials aim to strengthen the evidence base. For example, studies on Jiu-Wei-Xi-Feng granules and acupuncture-based interventions are investigating efficacy in pediatric tic disorders and long COVID-related neuropsychiatric symptoms, respectively (Isola *et al.,* 2019). Advances in nanoformulations, bioavailability enhancers and network pharmacology further facilitate mechanistic understanding and translational application of TCM. Collectively, the major translational barriers including standardization, PK limitations, interaction risks and extract variability are summarized in Section 1.3 and require coordinated pharmaceutical development strategies., TCM formulations could serve as effective complementary or adjunctive strategies for neuropsychiatric disorders, offering multi-targeted modulation of key biological pathways (Kang *et al.,* 2019) . Several Traditional Chinese medicine (TCM) formulations have been developed and marketed for the management of neuropsychiatric disorders such as depression and anxiety (Li *et al.,* 2017). These products are available in various forms, including capsules, granules, teapills and tinctures and are often sold under different brand names. It's important to note that while these products are widely used, the regulatory standards and quality control measures may vary by region (Table 8).

These formulations are commonly used in clinical practice to address various neuropsychiatric symptoms. For instance, Xiaoyaosan is frequently prescribed for conditions related to liver Qi stagnation and blood deficiency, which are often associated with depression and anxiety. Jia Wei Xiaoyaosan, a modified version of Xiaoyaosan, is used to clear heat and resolve toxicity, making it suitable for conditions with irritability and restlessness (Kragh *et al.,* 2009). Danggui Shaoyao San is utilized for blood deficiency leading to symptoms like muscle cramps and spasms. It's essential for healthcare providers to consider individual patient conditions and consult relevant clinical guidelines when recommending these formulations (Liu *et al.,* 2013). Additionally, patients should be informed about the potential benefits and limitations of TCM products and be encouraged to discuss their use with their primary healthcare providers to ensure safe and coordinated care.

Future directions

Despite promising preclinical and emerging clinical evidence, the integration of TCM-derived compounds into mainstream neuropsychiatric therapeutics requires robust, high-quality randomized controlled trials (RCTs). Many existing studies are limited by small sample sizes, short intervention durations, or heterogeneous patient populations, which constrain generalizability. Future RCTs should focus on standardized formulations, well-defined patient cohorts and rigorous outcome measures, including both clinical endpoints and biomarker assessments (Li *et al.,* 2023)

Omics-driven approaches offer unprecedented opportunities to elucidate the molecular mechanisms of TCM. Genomic, transcriptomic, proteomic, metabolomic and microbiome analyses can identify biomarker

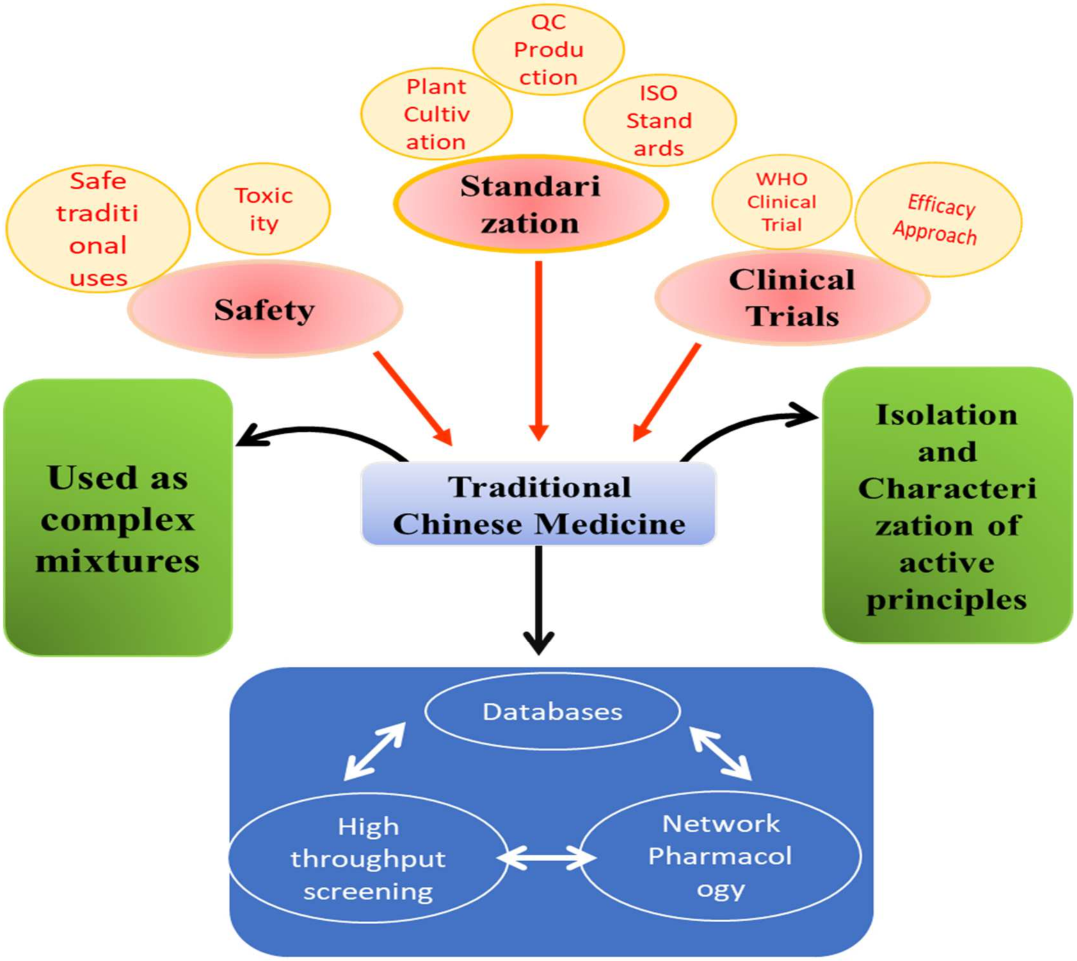

Fig. 4: Translational framework for Traditional Chinese Medicine (TCM) research

Table 8: Marketed TCM Formulations for Neuropsychiatric Disorders

S. No.	Formulation	Brand names	Common dosage forms	Primary indications
1.	Xiaoyaosan (XYS)	Free and Easy Wanderer, Relaxed Wanderer	Capsules, Granules, Teapills	Depression, Anxiety, Stress, Menstrual disorders
2.	Jia Wei Xiaoyaosan (JWXYS)	Jia Wei Xiao Yao San, Bupleurum and Peony Formula	Capsules, Granules, Teapills	Mood swings, Hormonal imbalances, Menstrual Issues
3.	Danggui Shaoyao San (DSS)	Dang Gui Shao Yao San	Capsules, Granules	Menstrual cramps, Blood deficiency
4.	Modified Shen-Qi-Wan	Shen Qi Wan	Capsules, Granules	Fatigue, Kidney Qi deficiency
5.	Modified Huang-Lian Jie Du Tang (HLJDT)	Huang Lian Jie Du San	Capsules, Granules	Inflammation, Detoxification

signatures, drug targets and patient-specific responses, enabling a mechanistic understanding of multi-compound formulations and their interactions with host biology. Such integrative analyses may also clarify inter-individual variability in response and inform personalized therapeutic strategies.

Precision medicine approaches combining TCM with conventional pharmacotherapy represent a promising direction. By tailoring treatment to the individual's molecular and clinical profile, these strategies can maximize efficacy while minimizing adverse effects. Network pharmacology and computational modeling can further optimize multi-target interventions, guiding the rational design of combination therapies that harness both conventional drugs and TCM formulations. In summary, advancing TCM in neuropsychiatric disorders requires a synergistic integration of rigorous clinical trials, omicsbased mechanistic studies and precision medicine frameworks, paving the way for evidence-based, multi-targeted and personalized interventions.

CONCLUSION

TCM derived compounds and classical formulations represent a promising multi-target approach for the management of neuropsychiatric disorders, including depression, anxiety and cognitive decline. Preclinical studies have consistently demonstrated that these compounds modulate key interconnected pathways, suppressing neuroinflammation, enhancing synaptic plasticity and regulating the HPA axis, thereby addressing the multifactorial nature of neuropsychiatric pathophysiology. Flavonoids, saponins, terpenoids and polysaccharides, as well as multi-herb formulations such as Xiaoyaosan, Jia Wei Xiaoyaosan, Danggui-Shaoyao-San, Modified Huang-Lian-Jie-Du-Tang and Modified Shen-Qi-Wan, have shown synergistic effects across these pathways, supporting the principle of systems-based modulation central to TCM. A key finding of this review is the integration of preclinical and clinical evidence, showing that these formulations not only exert neuroprotective and antidepressant-like effects in animal models but also improve depressive symptoms, cognitive performance and stress resilience in humans, with a generally favorable safety profile. Some formulations, such as Xiaoyaosan, are already marketed and used clinically, underscoring their translational relevance.

Despite these promising outcomes, the review also identifies critical gaps, including variability in herbal composition, limited high-quality randomized controlled trials and incomplete understanding of pharmacokinetics and herb–drug interactions. Addressing these gaps through standardized formulations, rigorous clinical studies and omics-driven mechanistic research is essential to advance TCM into mainstream neuropsychiatric therapeutics. In summary, the findings of this review underscore that TCM-derived compounds offer a mechanistically grounded, multi-pathway and patient-centric approach. With continued research, standardization and clinical validation, these compounds and formulations have the potential to become effective complementary or adjunctive strategies in the management of neuropsychiatric disorders, bridging traditional medicine with contemporary biomedical innovation.

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Authors' contributions
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