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Active components, quality control, and molecular mechanisms of *Zanthoxyli pericarpium* in brain health

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ABSTRACT: Chinese herbal medicine *Zanthoxyli pericarpium* (ZP), derived from the dried pericarp of *Zanthoxylum schinifolium* Sieb. et Zucc. or *Zanthoxylum bungeanum* Maxim., contains diverse bioactive constituents including volatile oils, alkaloids, amides, flavonoids and their glycosides, coumarins, and lignans. With a long history of clinical application in traditional Chinese medicine (TCM), ZP is renowned for its warming middle energizer, analgesic, insecticidal, and anti-pruritic properties. Recent studies have highlighted its remarkable therapeutic potential in brain health management, particularly the pharmacological effects of ZP and its active components on cognitive enhancement, neuroprotection, anti-depressant activity, Alzheimer's disease intervention, and pain relief, which have garnered significant scientific attention. This review comprehensively summarizes the neuroactive components, quality control methodologies, analytical techniques, brain health-improving pharmacological mechanisms, and associated therapeutic targets of ZP, aiming to provide a scientific foundation for its clinical application in preventing and treating brain health-related disorders.

Keywords: *Zanthoxyli pericarpium*; brain health; memory enhancement; neuropsychiatric disorders; herapeutic targets

1. Introduction

Zanthoxyli pericarpium (ZP), the dried mature pericarp of either *Zanthoxylum schinifolium* Sieb. et Zucc. or *Zanthoxylum bungeanum* Maxim. [1], has served as both a culinary spice and medicinal agent for over two millennia. With a global distribution spanning temperate to tropical regions of Asia, Africa, and Americas, China represents a primary cultivation center, particularly in Sichuan, Shaanxi, Gansu, Yunnan, and Guizhou provinces. The *Zanthoxylum* genus encompasses approximately 250 species worldwide, including 45 species and 13 varieties native to China[2], among which three economically taxa predominate: the intensely tingling

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and spicy flavor of *Z. bungeanum* Maxim. from Hanyuan in Sichuan and Hancheng in Shaanxi [3]. The subtly aromatic green prickleyash (*Z. schinifolium* Sieb. et Zucc.) concentrated in Chongqing's Jiangjin and Yunnan's Zhaotong, and the humid-adapted *Zanthoxylum armatum* (*Z. armatum*) of Guizhou and Hubei[4]. These varietals exhibit distinct morphological, phytochemical, and sensory profiles shaped by their unique growing conditions, soil types, and climatic environments.

The concept of quality markers has emerged as a critical framework for assessing *Zanthoxylum* quality, with notable compositional variations observed across cultivars and geographical origins. Comparative analyses reveal that Hancheng's specimens contain elevated levels of quercetin and kaempferol relative to Yunnan's green prickleyash and Sichuan pepper, while northern cultivars generally demonstrate higher flavonoid content than their southern counterparts[5]. As established by leading researchers, effective quality markers must satisfy three fundamental criteria: traceability to botanical origin, demonstrable correlation with bioactivity, and reliable quantifiability through analytical methods[6]. Modern technological platforms have enabled the practical implementation of these parameters, with gas chromatography-mass spectrometry (GC-MS) providing precise volatile compound profiling[7], high performance liquid chromatography with diode array detector (HPLC-DAD) facilitating amide and alkaloid quantification[8], and fourier transform infrared (FTIR) allowing rapid geographical discrimination[9]. Advanced techniques such as electronic nose-based odor fingerprinting and convolutional neural network-driven species identification further enhance the classification accuracy[10,11], collectively establishing a robust, multidimensional system for quality control and efficacy evaluation.

Pharmacological investigations have elucidated ZP's considerable potential in brain health applications, with its bioactive constituents supporting multitarget neuromodulatory effects. Beyond their established anti-microbial and anti-inflammatory properties[12-13], ZP's components exert specific neuroactive capabilities. Particularly, alkaloids have shown anti-depressant activity through neurotransmitter modulation[14], and specialized extracts display blood-brain barrier permeability to disaggregate Aβ oligomer in Alzheimer's disease (AD)[15]. The compound hydroxy-α-sanshool (HSA) has been validated for cognitive improvement in preclinical models[16], and isolated ferulic acid derivatives possess notable neuroanti-inflammatory effects[17]. Neuroactive potency varies dramatically by chemotype, with Guangxi *Z. armatum*'s high nitidine chloride content conferring superior neuroprotection and Yunnan cultivars' abundant hesperidin enhancing anti-oxidant capacity[18]. Environmental factors further influence bioactivity, as evidenced by the higher total amide content observed in high-elevation specimens compared to lowland counterparts[19], potentially amplifying neuroprotective effects. These findings collectively provide both theoretical justification and material foundation for developing innovative brain-health-functional foods derived from ZP's unique phytochemical profiles.

In summary, this review aims to systematically summarize the bioactive components related to cerebral health in *Zanthoxylum* species, their quality control standards, and underlying molecular mechanisms. It provides a theoretical foundation for research on ZP-derived neurohealth products while identifying future

research directions for developing innovative targeted therapeutics and functional foods against neurological disorders. This work holds prominent implications for enhancing the scientific utilization value of characteristic Chinese spices and advancing the modernization process of TCM.

2. Historical background of the dual values of ZP as food and medicine

As a culturally botanical resource in China, ZP has long been recognized for its dual applications in culinary and medicinal contexts[20] (Fig.1). Its historical trajectory—from aromatic applications in ritual ceremonies to systemic integration in gastronomy and pharmacopeia—epitomizes the practical embodiment of the traditional "food and medicine homology" principle.

Archaeological evidence from the pre-Qin era reveals ZP's early incorporation into ceremonial practices. The *Shijing* of Zhou Dynasty documents ritual offerings of "pepper-infused wine to comfort elders and invoke ancestral blessings"[21], establishing ZP's dual roles as sacramental substance and longevity symbol. Historical records from the Han period, notably Fan Ye's *Houhan Shu*, further chronicle ZP's transition from ritual altars to aristocratic banquets through its distinctive sensory profile—combining pungent aroma with tingling and spicy flavor[22]. The Han Dynasty marked a pivotal transition through the *Shennong Bencao Jing*, which systematically classified ZP as a medium-grade medicinal herb. This foundational text delineated its therapeutic actions: "Expelling pathogenic qi, alleviating dyspneic cough, warming middle energizer , resolving necrotic tissues, dispelling cold-damp impediment pain, and directing qi downward. Prolonged use prevents hair greying, reduces corporeal heaviness, and extends lifespan"[23]. Such pharmacological codification formalized ZP's status in food-medicine integration. From the Wei-Jin to Tang-Song periods (3rd–13th century), ZP's dual applications underwent systematic refinement. As an agricultural compendium in Northern Wei period, *Qimin Yaoshu* detailed ZP's culinary protocols: "Harvested in verdant state for pickling, sun-dried and powdered for seasoning"[24] while Tang scholar Sun Simiao's *Beiji Qianjin Yaofang* prescribed "ZP decoctions" for postpartum cardialgia[25]. These developments crystallized the "food-as-medicine" therapeutic paradigm. The Song Dynasty pharmacopeia Zhenglei Bencao further advanced botanical understanding by elucidating ZP's triple energizer regulation and cold-damp dissipation mechanisms[26]. Ming-Qing scholars synthesized theoretical frameworks for ZP's synergistic applications. *Bencao Gangmu* pharmacognostic analysis established: "ZP manifests pure yang nature—pungent flavor with warming qi—effective in cold-damp expulsion, stagnation resolution, and digestive enhancement"[27]. *Suixi Ju yin Shipu* systematically cataloged dietary formulations while cautioning against gestational consumption risks[28], demonstrating matured understanding of ZP's benefit-risk profile.

This historical progression—from ritual aromatic to culinary staple and finally systematized medicinal agent—reveals a coherent developmental trajectory aligning with food and medicine homology principles. Contemporary pharmacological studies corroborate classical records, affirming ZP's enduring cultural-pharmacological values.

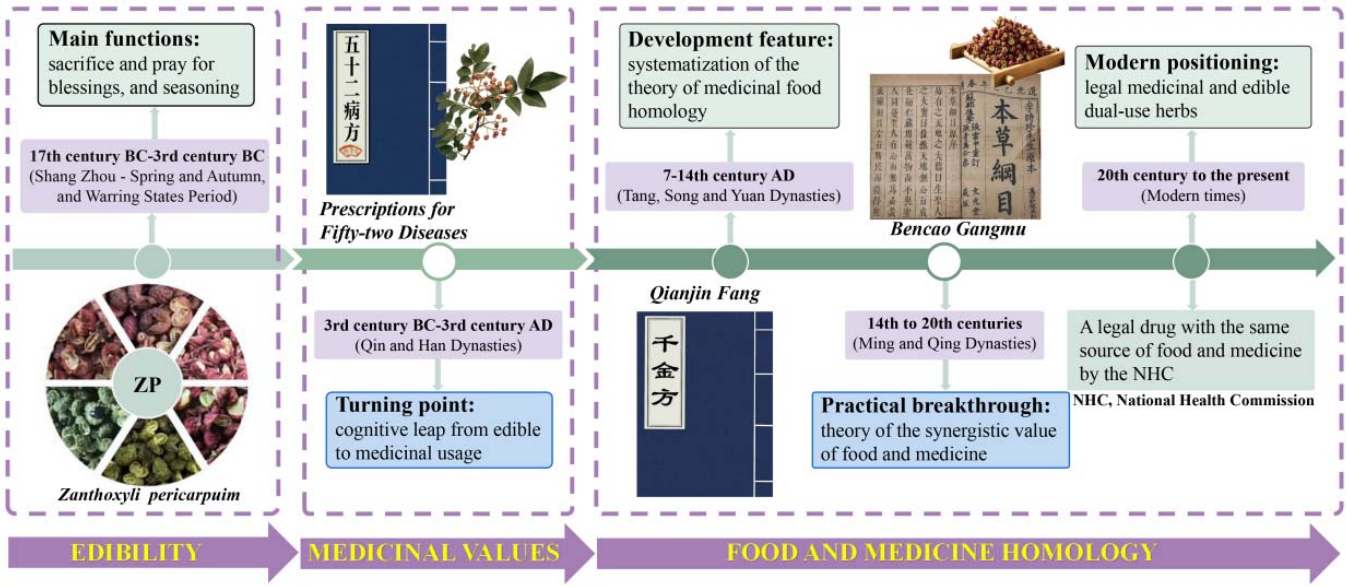

Fig. 1 Historical evolution of ZP.

3. Chemical components of ZP related to brain health, quality control methods, and detection technologies

3.1 Chemical components of ZP

The 2025 Edition of Chinese Pharmacopoeia specifies dried pericarps as the official medicinal material. Phytochemical studies have primarily examined *Z. schinifolium* and *Z. bungeanum*, revealing six major bioactive compound classes in ZP: volatile oils, alkaloids, flavonoids, amides, coumarins, and lignans (Fig. 2). These components demonstrate species-specific distribution patterns and processing-dependent compositional variations.

3.1.1 Volatile components

Volatile oils in ZP are concentrated in oil glands with dynamic chemical changes during processing. Zhang et al.[31] demonstrated the thermal stability of key terpenoids (linalool, *D*-limonene, and eucalyptol) in ZP's oil glands, confirming their role as structural backbone components. GC-MS analyses by Luo et al. [29] identified 33 volatile compounds, predominantly alkanes, oxygenated monoterpenes, and sesquiterpenes. Although stir-frying reduces volatile content, critical components like ethyl linalool and limonene retain structural integrity[30]. Comprehensive profiling identifies linalool and limonene as primary constituents, with caryophyllene oxide serving as a thermal degradation marker[31].

3.1.2 Alkaloids

ZP's alkaloids comprise four structural classes: quinoline-type, isoquinoline-type, phenanthridine-type, and quinolone-type compounds. Rahman et al. [32] isolated N-methylflindersine, zanthobungeanine and rutaecarpine from ZP. Nguyen et al.[33] isolated and identified a novel benzophenanthridine alkaloid (6-butanoyldihydrochelerythrine) from the stem bark of *Zanthoxylum* for the first time.. Processing methods significantly affect alkaloid content: stir-frying and vinegar processing increase total alkaloids by causing thermal-induced cell wall rupture, while salting reduces the content compared to raw materials[34].

3.1.3 Flavonoids and flavonoid glycosides

ZP's flavonoids primarily exist as glycosides in the pericarp, with glycosylation enhancing solubility and bioavailability. Recent studies have successfully identified over 30 flavonoid active components in *Z. bungeanum* through modern separation and analysis techniques, including quercetin, quercitrin, hyperoside, rutin, isorhamnetin, arbutin, and guaijaverin [35-36]. Quercetin and icariin F2 have been isolated from ZP. Separately, phenylethanol glycosides exhibiting unique antioxidant properties were identified in ZP acetone-water extracts[37].

3.1.4 Amides compounds

ZP's bioactive amides consist primarily of linear unsaturated fatty acid amides containing ≥2 conjugated double bonds. Major compounds include hydroxy-*α*-sanshool (HAS), hydroxy-*β*-sanshool, hydroxy-γ-sanshool, hydroxy-ε-sanshool, and hydroxy-γ-isosanshool[38]. Subsequent studies identified additional amides: qinbunamides A-C and amides A-D[39], zanthoamides A-D[40], and(2E,7E,9E)-N-(2-hydroxy-2-methylpropyl)-6,11-dioxo-2,7,9-dodecatrienamide[41].

3.1.5 Coumarins

ZP's coumarins include simple coumarins (e.g., umbelliferone), furanocoumarins (e.g., bergapten), and pyranocoumarins (e.g., xanthyletin). Specifically identified compounds are bergapten, 7-methoxycoumarin, umbelliferone, and xanthoxyletin [42,43].

3.1.6 Lignans

ZP's lignans derive from phenylpropanoid (C_6-C_3) monomer polymerization, predominantly existing as free dimers that isomerize under acidic conditions. Major types include dioxolane lignans (e.g., eudesmin) and dihydrofuran lignans (e.g., sesamin) [44], whose stereochemistry governs bioactivity.

3.1.7 Other components

ZP's fruit pericarp contains secondary metabolites including aromatic acid derivatives, triterpenes, sterols, hydrocarbons, trace elements, and fatty acids. Unsaturated fatty acids constitute 83.53% of total fatty acids, with oleic > linoleic > *α*-linolenic acid[45], contributing observably to anti-oxidant activity.

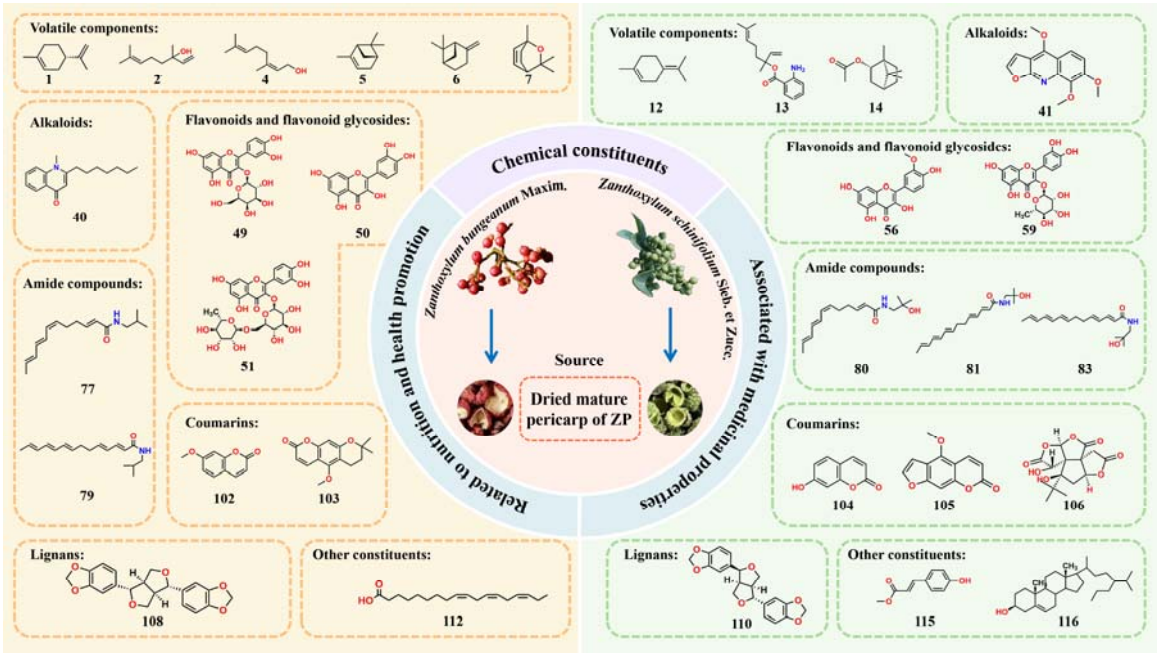

Fig. 2 Health-promoting components in ZP for brain references.

3.2 Quality control methods and detection technologies

Quality control of ZP relies on the identification and quantification of its key molecular markers, encompassing both small and macromolecular constituents. These components critically determine ZP's sensory characteristics, pharmacological efficacies, and safety profiles. This section systematically reviews analytical methodologies for small-molecule and macromolecular markers in ZP's quality assessment.

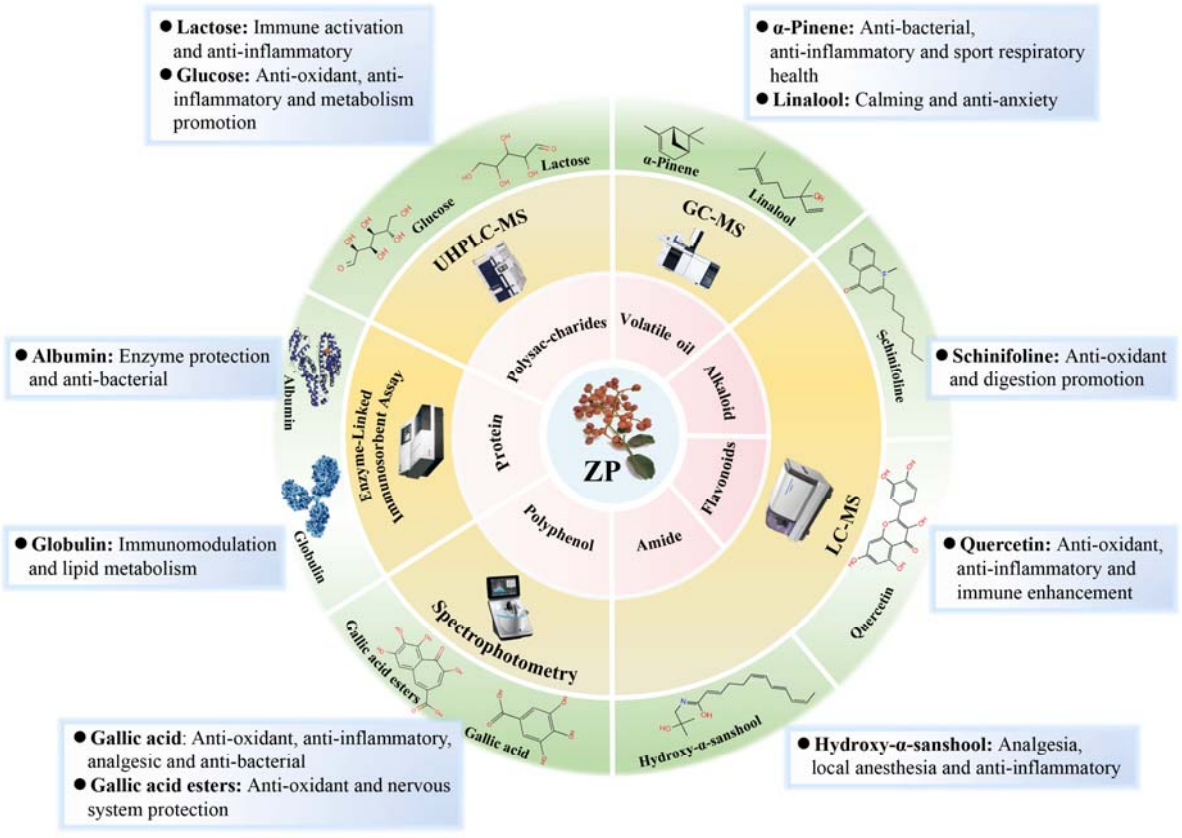

Fig. 3 Methods for detecting components in ZP.

3.2.1 Detection of small molecular indicative components

Small-molecule constituents including volatile oils, alkaloids, flavonoids, and amides constitute the primary determinants of ZP's aroma, numbing sensation, and therapeutic activity[46-47]. Effective detection requires methodologies with high sensitivity, specificity, and throughput to ensure accurate characterization of these bioactive markers, thereby supporting quality standardization, pharmacological investigation, and product development (Fig. 3).

3.2.1.1 Detection of volatile components

Volatile oils represent ZP's principal flavor compounds and bioactive agents. Conventional analytical approaches employ GC-MS, HPLC, and liquid chromatography-mass spectrometry (LC-MS), with GC-MS being the predominant technique[30,48,49]. This hyphenated method integrates GC's superior separation capacity with MS's structural elucidation capabilities, enabling sensitive and specific analysis of volatile constituents in complex matrices. Zhao et al.[50] demonstrated spectacular geographical and varietal influences on ZP volatile profiles through GC-MS analysis of Yueyang-sourced specimens. Steam-distilled extracts elevated polar compound concentrations compared to non-polar hydrocarbons, while chromatographic stationary phases substantially impacted peak resolution and retention time consistency. Complementary research by Wu et al.[51] identified limonene and eucalyptol as dominant aromatic markers, establishing their utility as quality indicators in ZP's products.

Emerging metabolomics platforms including liquid chromatography-quadrupole time-of-flight MS (LC-QTOF-MS) and gas chromatography-Orbitrap high-resolution mass spectrometry (GC-Orbitrap HRMS) now enable enhanced compound characterization. GC-Orbitrap HRMS provides exceptional mass accuracy and resolution, effectively discriminating structural isomers in complex mixtures. Database integration facilitates rapid annotation of known bioactives and mechanistic pathway elucidation. Vera et al.[52] successfully applied these techniques to identify anti-microbial terpenes in cherry extracts, suggesting analogous applications for ZP's volatile analysis. As noted by Stettin et al.[53], Orbitrap-based platforms offer unprecedented analytical depth for natural product metabolomics, particularly in resolving complex phytochemical matrices.

3.2.1.2 Detection of alkaloids

LC-MS[54,55] has become a mainstream analytical technique for identifying alkaloids. This hyphenated method integrates the superior separation efficiency of LC with the high sensitivity, mass resolution, and selectivity of MS, enabling precise characterization of trace alkaloids in complex matrices. During analysis, the HPLC component resolves chemical constituents through differential partitioning between stationary and mobile phases, while the MS unit ionizes separated analytes for mass-to-charge ratio (m/z)-based detection and quantification. This dual approach minimizes matrix interference and facilitates simultaneous qualitative-quantitative analysis of multiple alkaloids, including structural analogs like HAS and hydroxy-β-sanshool. Compared to conventional HPLC or GC-MS methods that struggle with ZP's complex chemical background, LC-MS achieves enhanced sensitivity through optimized chromatographic conditions

(e.g., column selection, and gradient elution) and mass parameter tuning (e.g., ionization mode, and collision energy). When coupled with tandem MS/MS, the system enables structural elucidation through characteristic fragmentation patterns, thereby improving analytical reliability.

Emerging detection strategies include molecularly imprinted polymers (MIPs), and synthetic materials engineered with molecular recognition cavities[56]. These affinity matrices improve sensitivity and selectivity through template-specific binding, enabling targeted alkaloid extraction. Li et al.[57] prepared surface MIPs with high selectivity for alkylamides in *Zanthoxylum*, and established a rapid method for detecting alkylamides in *Zanthoxylum* by combining with HPLC. Chen et al.[58] used triol structural analogs as dummy templates to prepare MIPs and developed molecularly imprinted solid-phase extraction columns, successfully isolating target amide components from *Z. bungeanum* oleoresin.

3.2.1.3 Detection of flavonoids

LC-MS[59] has emerged as the gold standard for analyzing low-molecular-weight flavonoids in ZP, combining chromatographic separation with mass spectral identification. Three key advantages distinguish this approach: (1) Ultrahigh sensitivity (ng-pg level detection) for quantifying trace bioactive compounds; (2) Structural differentiation of isomers and glycosides through MS/MS fragmentation coupled with molecular networking; (3) Dual ionization mode compatibility (positive/negative ion switching) that accommodates diverse structures including aglycones, monoglycosides, and diglycosides. Wang et al.[60] systematically investigated altitudinal effects on flavonoids in ZP's leaf using ethanol/water extraction with ultrasonic-assisted resin purification followed by LC-MS characterization, revealing conspicuous elevation-dependent concentration variations.

3.2.1.4 Detection of amides

ZP's bioactive amides are typically analyzed via HPLC, LC-MS, GC-MS, or nuclear magnetic resonance spectroscopy (NMR)[61]. While HPLC previously dominated due to its capacity for polar/thermolabile amide separation with high efficiency and rapid analysis, its limited sensitivity and demanding sample preparation prompted LC-MS adoption. Modern LC-MS systems synergize chromatographic resolution with mass spectral selectivity, enabling sensitive detection and structural confirmation of amides in complex samples through accurate mass measurement and isotopic pattern matching[62].

3.2.2 Detection of large molecular indicative components

ZP contain abundant polysaccharides, proteins, and polyphenolic polymers, which confer obvious nutritional value and bioactivities, including immune enhancement, anti-oxidant, and anti-bacterial properties. To optimize ZP's utilization, advanced detection methods for its macromolecular components are essential. Precise quantification enables deeper understanding of ZP's bioactive compounds, providing a scientific basis for developing high-value health products and expanding its applications.

3.2.2.1 Detection of polysaccharides

ZP's polysaccharides with notable immunomodulatory and anti-oxidant effects, drives interest in food and pharmaceutical research. While extraction and purification techniques are well-established, current detection methods face limitations. This section evaluates common ZP's polysaccharide detection approaches and their efficacy.

Colorimetric assays, including the phenol-sulfuric acid and anthrone-sulfuric acid methods, quantify polysaccharides through chromogenic reactions. Qi et al.[63] applied the phenol-sulfuric acid method to polysaccharides detection in ZP's leaf, leveraging its simplicity for rapid screening[64]. However, this method suffers from low sensitivity and interference by monosaccharides/oligosaccharides.

HPLC and ultra-high-performance liquid chromatography-mass spectrometry (UHPLC-MS) exploit differential compound partitioning between mobile and stationary phases. HPLC enables efficient polysaccharide separation in complex matrices but demands costly instrumentation and complex sample preparation[65,66]. Zhong et al.[67] demonstrated UHPLC-MS's utility for polysaccharide analysis in traditional medicines, highlighting its superior sensitivity, resolution, and capacity for structural elucidation. UHPLC-MS's ultra-high-pressure columns enhance analytical throughput, enabling multicomponent analysis.

ZP's polysaccharide structures are categorized as primary or higher-order, with the monosaccharide sequence, glycosidic bonds, and branching analyzed using HPLC (for monosaccharide composition), NMR (for glycosidic configurations), and FTIR (for glycosidic bond identification). The polysaccharides from *Z. bungeanum* pericarp were characterized by Hu et al.[68-69] using high-performance thin-layer chromatography enzymatic sugar mapping coupled with carbohydrate gel electrophoresis, and by Chen et al.[70] through structural characterization. These studies confirmed that their molecular structure contains various glycosidic linkages including 1,4-α-D-galacturonan, 1,4-α-D-galactan, and (1→4)-β-D-glucan, with an average molecular weight of 1.72×10^5 Da. The monosaccharide composition consists of mannose, rhamnose, galacturonic acid, glucose, galactose, and arabinose in a molar ratio of 4.93:5.03:71.01:16.01:24.87:18.79.

Meanwhile, Liu et al. [71-72] comprehensively applied sepharose CL-6B gel filtration chromatography, HPLC, fourier transform infrared spectroscopy, and NMR to study *Zanthoxylum* polysaccharides. Their research revealed that among the four components (WZBP-N, WZBP-A-I, WZBP-A-II, and WZBP-A-III), WZBP-A-III possesses a backbone composed of homogalacturonan and rhamnogalacturonan-I structural domains, with side chains rich in neutral polysaccharide structural units such as galactan and arabinan.

3.2.2.2 Detection of proteins

Anti-oxidant, anti-bacterial, and anti-inflammatory effects of ZP's proteins have been confirmed, which have garnered swingeing scientific interest. This section reviews predominant analytical methods for ZP's protein detection. Ruan et al.[73] employed the Lowry method for ZP's protein quantification, relying on tyrosine and tryptophan residues reacting with Folin-Ciocalteu reagent to generate a colorimetric blue chromophore. Compared to the Biuret method[74], this approach demonstrates superior sensitivity; however, the need for stringent experimental controls and suboptimal chromogenic responses for certain proteins limit its versatility.

MS serves as the gold standard for proteolytic peptide analysis[75]. Following enzymatic digestion, peptides undergo ionization through electrospray ionization or matrix-assisted laser desorption/ionization, which is coupled with LC-MS/MS or high-resolution MS to enhance detection specificity.Critical protocol parameters include optimization of enzymatic conditions (e.g., trypsin activity, and incubation time/temperature) to maximize peptide coverage, followed by solid-phase extraction desalting and vacuum concentration to stabilize MS signals. Database alignment tools enable comparison of MS data against theoretical peptide libraries, complemented by post-translational modification analysis using quantitative strategies like iTRAQ/TMT or label-free quantification. This high-resolution, and high-throughput platform has become indispensable in proteomics, biomarker discovery, and drug target identification. Notably, Hou et al.[76] characterized novel anti-microbial peptides from seeds of ZP through advanced peptide sequencing and bioinformatics.

Infrared spectroscopy[77,78] enables non-destructive protein analysis by detecting molecular vibration signatures (e.g., amide I band, and carboxyl absorption). This technique indirectly assesses secondary structures (α-helices, and β-sheets) and intermolecular interactions through chemical bond vibrations (C=O, N-H, and O-H). Unlike destructive traditional methods (e.g., Kjeldahl nitrogen determination), it preserves thermally labile ZP's components while requiring minimal sample preparation. However, quantitative accuracy is compromised by spectral interference from amino acids/peptides, necessitating chemometric modeling for matrix effect correction. Particle heterogeneity and impurities may also induce scattering artifacts, and reducing spectral resolution. Despite these limitations, infrared spectroscopy remains a valuable qualitative/semi-quantitative tool for ZP's protein quality control and functional assessment.

Enzyme-linked immunosorbent assay[79] leverages antigen-antibody specificity with enzymatic signal amplification for ultrasensitive protein quantification (detection limit: 0.1-1.0 ng/mL). Qian et al.[80] demonstrated its superiority over immunofluorescence in specificity for ZP's protein aggregation analysis. This high-throughput platform combines operational simplicity with exceptional reproducibility, making it ideal for rapid screening and expression profiling of plant-derived proteins in complex matrices like ZP's tissues.

3.2.2.3 Detection of polyphenolic polymers

ZP's polyphenolic polymers are structurally complex macromolecules comprising phenolic monomers linked by diverse chemical bonds. These compounds display broad-spectrum bioactivities including anti-oxidant, anti-inflammatory, anti-viral, and anti-cancer properties with spectacular therapeutic potential.

Spectrophotometry provides rapid polyphenol quantification through characteristic wavelength absorption. Established protocols include Folin-Ciocalteu assays, UV spectroscopy, and infrared methods. Xiong et al.[81] quantified total ZP's polyphenols via Folin-Ciocalteu, while Guo et al.[82] employed UV-vis spectroscopy. Xia et al.[83] extended UV-vis spectroscopy to volatile terpenoid derivatives despite inherent method limitations. The technique's simplicity, low cost, and reproducibility under controlled conditions make spectrophotometry a cornerstone for preliminary polyphenol analysis.With the rapid development of

high-resolution MS, the new generation of mass spectrometers has significantly improved the detection capability and identification accuracy of polyphenolic compounds in complex matrices, owing to their ultra-high sensitivity, precise molecular weight determination, and multiple fragmentation scanning.. Yang et al.[84] was the first to systematically identify and quantitatively analyze polyphenols in *Zanthoxylum* leaves using HPLC-ESI-MS/MS technology. In this study, Liu et al.[85] employed UPLC-Triple TOF MS/MS to analyze polyphenols in *Zanthoxylum* from eight regions across six provinces. A total of 35 polyphenols were identified, with chlorogenic acid, quercitrin, and hyperoside being the most abundant.

4. Pharmacological effects of ZP and its chemical components on brain health

4.1 Improvement of cognitive function

ZP exerts multimodal therapeutic potential against cognitive decline through coordinated mechanisms involving amyloid-β (Aβ) clearance, neurotrophic modulation, oxidative stress reduction, and anti-inflammatory pathways. The mechanisms of action of ZP on brain health was shown in Fig. 4. Contemporary research reveals that multiple bioactive constituents in ZP synergistically improve cognitive deficits via these interconnected pathways.

The pathological aggregation of Aβ peptides into senile plaques constitutes a hallmark of AD pathogenesis[86]. Wei et al.[87] identified Gx-50 (N-[2-(3,4-dimethoxyphenyl) ethyl]-3-phenylpropenamide), a blood-brain barrier (BBB)-permeable amide from ZP's extracts, disassembles Aβ oligomers and prevents cortical plaque formation[15]. This neuroprotective activity reduces neuronal apoptosis and calcium-mediated toxicity, ultimately improving spatial memory in AD murine models.

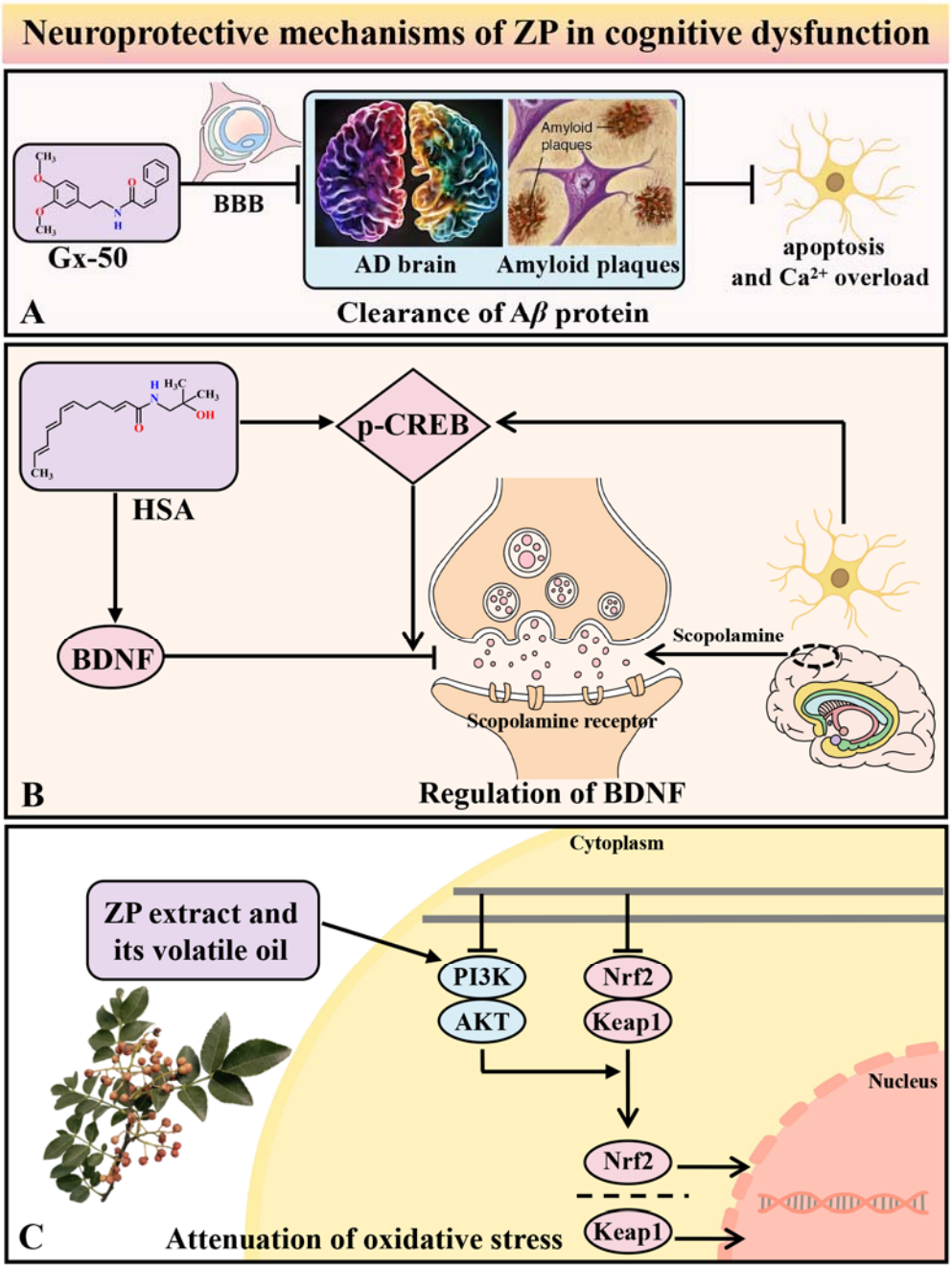

Fig. 4 Mechanisms of action of ZP on brain health.

ZP's components exhibit notable neurotrophic regulatory properties. Brain-derived neurotrophic factor critically regulates synaptic plasticity, while phosphorylated cAMP response element-binding protein mediates memory consolidation[88]. Zhang et al.[89] demonstrated that HAS upregulates BDNF/p-CREB expression, enhances cholinergic transmission, and reverses scopolamine-induced cognitive impairment.

The Nrf2/ Keap1 axis maintains redox homeostasis through PI3K AKT-mediated signaling[90,91]. ZP's dichloromethane extracts and volatile oils activate this pathway, inducing nuclear translocation of Nrf2 to counteract oxidative damage and improve memory deficits[92]. Furthermore, the metabolic conversion of α-linolenic acid to docosahexaenoic and eicosapentaenoic acids complements the activation of the Nrf2/Keap1 axis by enhancing synaptic neurotransmission, thereby further supporting cognitive function and alleviating memory deficits[93].

Age-related cognitive decline correlates with oxidative stress accumulation[94]. Zhang et al.[95] observed that ZP's polyphenolic compounds reduce escape latency in D-galactose-aged mice during Morris water maze testing. Meanwhile, ZP's polyphenolic compounds treatment elevated hippocampal superoxide dismutase activity while decreasing malondialdehyde levels, indicating enhanced anti-oxidant capacity and reduced lipid peroxidation. These findings position ZP's polyphenolic compounds as a promising therapeutic agent against oxidative aging mechanisms.

4.2 Anti-depressant and anxiolytic effects

Emerging evidence highlights ZP as potent neuromodulators with anti-depressant and anxiolytic properties. ZP's polyphenolic compounds possesses serotonergic activity by increasing cerebral 5-hydroxytryptamine levels in ovariectomy-induced depression models by inhibition of monoamine oxidase A[96-98]. Chronic stress models show ZP's polyphenolic compounds normalizes adrenal corticosterone/interleukin-1 beta (IL-1β) levels while preserving adrenal histoarchitecture, via modulating hypothalamic-pituitary-adrenal (HPA) axis[99,100]. Structural analysis indicates that isobutyl hydroxamic acids with unsaturated aliphatic chains exhibit superior anti-depressant efficacy in corticosterone-treated PC12 cells[101]. ZP's essential oils mitigate anxiety behaviors through HPA axis regulation and gut microbiota restoration[101]. The lipophilic nature of these terpenoids facilitates BBB penetration, making them particularly effective against neuropsychiatric disorders[100]. Li et al.[100] further argued that volatile oils reduced chronic unpredictable mild stress induced neuronal apoptosis via PI3K/Akt activation, providing molecular insights into their anti-depressant action.

4.3 Analgesic effects

ZP exhibits overtly analgesic and anti-inflammatory properties, with well-documented clinical applications in treating pain and inflammation-associated conditions. Mechanistic investigations reveal that both aqueous extracts and volatile oils from ZP modulate nociceptive signaling through distinct pathways. Notably, *Z. schinifolium* displays superior analgesic efficacy[102]. Experimental models show that volatile oils from raw and stir-fried ZP markedly reduce acetic acid-induced writhing responses in mice[103]. Synergistic effects emerge when ZP's volatile oil is combined with verapamil, enhancing analgesia while inhibiting action potential conduction in amphibian sciatic nerves[104]. Clinically, ZP's volatile oil asserts the therapeutic value of pain for ulcerative colitis, lumbar sprains, and rheumatoid arthritis[105-107]. Dose-dependent analgesic effects are observed in thermal pain models, where ZP's alkaloids prolong murine paw-licking latency[108].

The anti-inflammatory potency of ZP's volatile oil intensifies miraculously after stir-frying processing[103]. Mechanistic investigations implicate cyclooxygenase-2 inhibition in ZP's ability to mitigate nocifensive behaviors induced by thermal, chemical, and inflammatory stimuli[109]. Linalool in *Z. schinifolium*'s volatile oil alleviates migraine in rodent models through vascular modulation, NF-κB pathway suppression, and neurogenic inflammation reduction [110]. In ulcerative colitis models, ZP's volatile oil downregulates pro-inflammatory mediators while enhancing anti-inflammatory factors[111]. Notably,

α-sanshool exerts analgesia through inhibition of Aδ mechanoreceptors and blockade of voltage-gated sodium channels in sensory neurons [112].

4.4 Anesthetic effects

ZP and its bioactive constituents announce marked local anesthetic properties through reversible inhibition of neural impulse transmission and modulation of neuronal excitability. Experimental evidences reveal that ZP's aqueous extract reduces excitability in isolated toad sciatic nerves and blocks nerve impulse conduction, establishing a mechanistic basis for its anesthetic activity[113]. Clinically, ZP's volatile oil has been utilized for oral mucosal anesthesia during dental extractions[114]. Bryant et al.[115] identified HAS in traditional ZP preparations, which induces a sensation of numbness in the tongue lasting for 10 to 20 min, confirming the anesthetic potency of amides in ZP. The study by Bian et al. showed that the ether extracts of different processed products of *Z. bungeanum* all exhibited splendid infiltration anesthesia effects, with the vinegar-processed product demonstrating particularly outstanding effects[116]. Li et al. methodically investigated the conduction anesthesia effects of aqueous extracts from different processed products of *Z. bungeanum* and found that all exhibited prodigious local anesthetic activity, with the salt-processed product showing the most pronounced effect[117]. Further studies have revealed that sanshools , as the primary active constituents of *Zanthoxylum*, exhibit markedly different anesthetic properties depending on the structural variations of their amide compounds. Specifically, α-sanshool predominantly induces intense and long-lasting tingling and burning sensations, whereas HAS mainly produces distinct stinging and numbing effects[118].

Electrophysiological data confirm ZP's extracts reversibly inhibit sciatic nerve conduction in amphibians, with aqueous fractions showing greater potency than volatile oils[119]. While 20% ZP's water extracts demonstrate impulse-blocking kinetics similar to procaine, interspecies comparisons among various anesthetic agents, including lidocaine and bupivacaine, indicate that the superior amide content of Z. schinifolium significantly enhances its anesthetic efficacy in conduction models[120]. Due to its remarkable anesthetic effects, sanshool has been widely used as a soothing agent in clinical dentistry [121].

4.5 Neuroprotection and other effects

ZP exhibits multi-faceted neuroprotective mechanisms through nerve growth factor (NGF) potentiation and ferroptosis inhibition. Tian et al.[39] demonstrated that amide compounds in ZP enhance NGF-mediated neurite outgrowth in PC12 cells, while isobutyl amides mitigate ferroptosis by reversing erastin-induced HT22 cell death and attenuating lipid peroxidation in a dose-dependent manner[122]. Carbazole alkaloids derived from ZP display broad neuroprotective activity, including oxidative stress reduction , AChE/BACE-1 enzymatic inhibition, and prevention of Aβ aggregation[123,124]. Further explorations by Chen et al.[101] identified isobutyl hydroxamic acid as a protective agent against corticosterone-induced PC12 cell damage. It has been proved that ZP's volatile oil manifests therapeutic potential for central nervous system disorders through HPA axis modulation in chronic stress models, PI3K/Akt/Nrf2 pathway activation in aging-related cognitive decline, and gut microbiota-mediated restoration of stress-induced gut-brain axis dysfunction[92,125,126].

5. Relevant action targets of ZP in promoting brain health

The key targets of this study are summarized in Fig. 5. HAS, a bioactive long-chain unsaturated amide isolated from ZP, exerts high affinity for neurological targets including cannabinoid receptors and transient receptor potential vanilloid 1 (TRPV1). Structural analogs (hydroxy-*β*-sanshool, and hydroxy-γ-sanshool) exhibit multimodal ion channel modulation, with substantiated efficacy in cognitive enhancement, analgesia, and anesthetic potentiation[127].

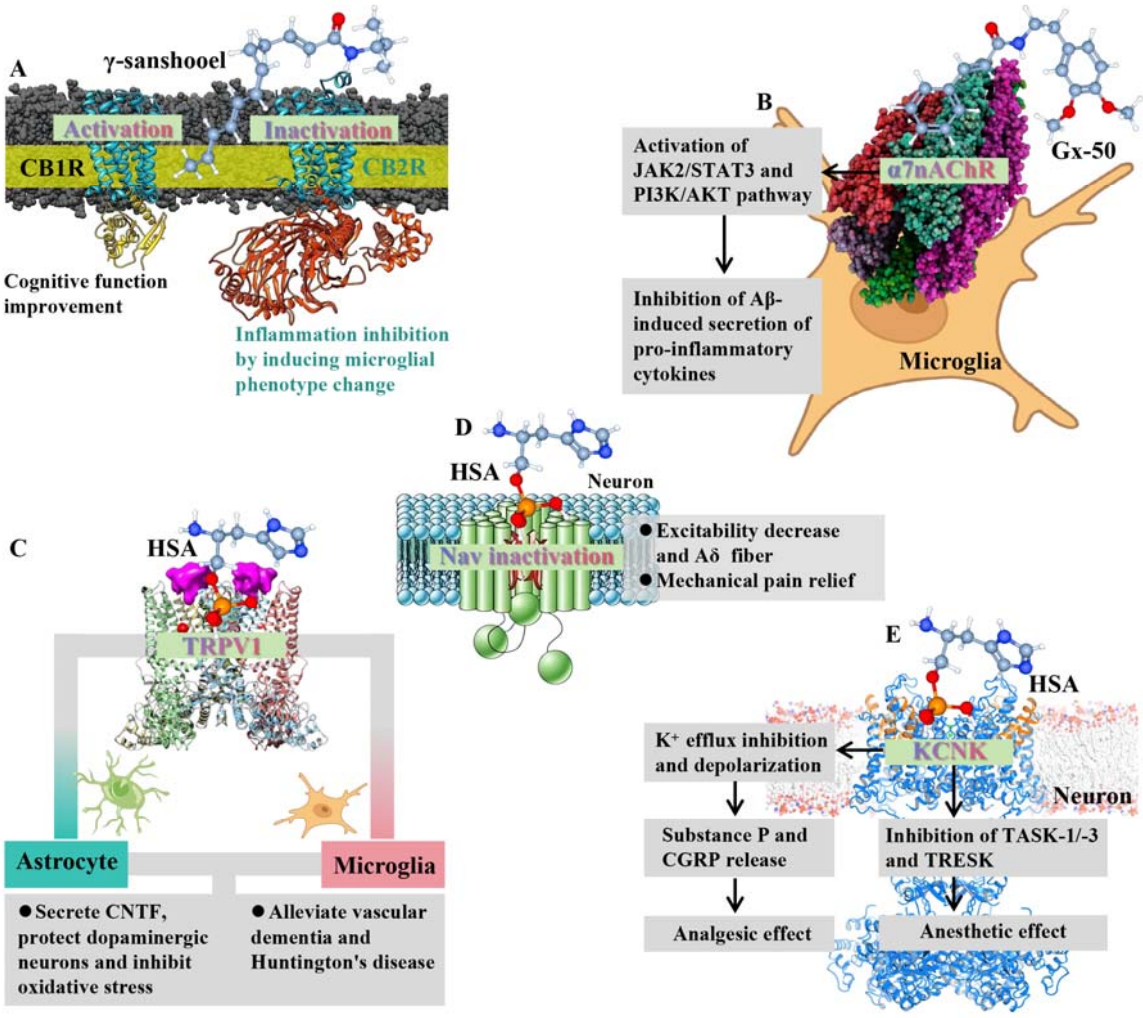

Fig. 5 Key targets through which ZP exerts its effects on brain health.

5.1 Cannabinoid receptor

The endogenous cannabinoid system features two principal receptor subtypes: CB1R (predominantly modulating synaptic plasticity) and CB2R (primarily expressed on microglia). CB2R agonists ameliorate AD pathology and behavioral deficits in murine models[128]. Notably, CB2R exhibits pathology-dependent high expression dynamics during AD progression, Huntington's disease, and simian immunodeficiency virus encephalitis[129,130]. *In vitro* trials using A*β*-treated neuron-microglia co-cultures demonstrate that CB2R-selective agonists mitigate microglia-mediated neurotoxicity via suppression of reactive oxygen species generation and proinflammatory cytokine release[130]. Dossou et al.[131] identified γ-sanshool from ZP as a CB2R partial agonist (64% efficacy) with concomitant CB1R antagonism. This dual activity suggests

therapeutic potential for neuroinflammatory regulation while circumventing CB1R-associated neuropsychiatric adverse effects.

5.2 TRPV1 receptor

TRPV1, a nonselective cation channel activated by capsaicin, mediates neuroimmune crosstalk through the expression of glial cells. In rat PD models, astrocytic TRPV1 activation stimulates ciliary neurotrophic factor production, preserving dopaminergic neurons viaα receptor, a type of adrenergic receptor that plays a role in various physiological processes[132]. TRPV1highlights pleiotropic neuroprotection by mitigating oxidative stress in vascular dementia and Huntington's disease models[133]. Koo et al.[134] characterized HAS as a selective TRPV1 agonist in HEK293, and the calcium influx and neurotransmitter release induced by HAS suggest its modulatory roles in nociception.

5.3 Nicotinic acetylcholine receptor (nAChR)

Theα7nAChR, a pivotal member of the ligand-gated ion channel family, forms a homopentameric structure comprising five identical subunits and exhibits high calcium ion permeability. This receptor is predominantly localized in the central nervous system, with enriched expression in cognition-associated regions such as the hippocampus, prefrontal cortex, and thalamus, representing one of the most abundant nicotinic receptor subtypes in the brain. Beyond its neuronal expression, α7nAChR is also detected in glial cells and plays critical roles in neuroprotective mechanisms and cognitive enhancement. Emerging evidence highlights the regulatory functions of α7nAChR in glial cells. Specifically, astrocytic and microglial α7nAChR modulates neuroinflammatory progression via the cholinergic anti-inflammatory pathway. Activation by acetylcholine or selective agonists inhibits NF-κB nuclear translocation, suppresses synthesis of pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β), and enhances anti-inflammatory IL-10 expression, thereby attenuating neuroinflammation in AD[135]. Furthermore the ZP-derived amide compound Gx-50 demonstrates high α7nAChR affinity to upregulate α7nAChR expression, subsequently activating JAK2/STAT3 and PI3K/AKT signaling pathways to inhibit Aβ-induced pro-inflammatory cytokine secretion (e.g., IL-1β) in microglia[136].

5.4 Two-pore domain K^+ channels (KCNK)

KCNK constitutes a family of voltage-independent K^+ channels characterized by a unique topology. Each subunit contains P1 and P2 pore-forming domains and assembles into functional dimers via four transmembrane helices These channels regulate resting membrane potential, action potential frequency, and synaptic integration by maintaining neuronal background K^+ currents, making them key targets for neuronal excitability modulation. Whole-cell patch-clamp electrophysiology reveals that HAS inhibits pH- and anesthetic-sensitive KCNK3, KCNK9, and KCNK18 subtypes, with highest potency against KCNK3 and KCNK18[137]. This selectivity arises from interactions between HAS's α, β-unsaturated amide group and histidine residues in channel extracellular loops, stabilizing closed-channel conformations. Electrophysiological analyses indicate that HAS blocks outward K^+ currents in somatosensory neurons,

inducing membrane depolarization and tingling sensations [138]. In rat dorsal root ganglion neurons, HAS reduces outward K^+ current amplitude, lowers action potential thresholds, and triggers voltage-gated Ca^{2+} influx. Subsequent release of substance P and calcitonin gene-related peptide from C-fiber terminals underlies its sensory effects [138].

5.5 Voltage-gated Na^+ channels

HASserves as the principal bioactive agent underlying ZP's analgesic properties. HAS exerts its therapeutic effect by selectively targeting voltage-gated Na^+ channels (Nav) in Aδ mechanonociceptorsto inhibit neuronal excitability. These channels mediate the conversion of mechanical stimuli into action potentials for central nervous system transmission, establishing a mechanistic basis for pain relief. Experimental evidence demonstrates HAS-mediated inhibition of both acute mechanical pain and chronic inflammatory pain via Aδ fiber modulation in a dose-dependent attenuation of mechanical hypersensitivity while maintaining intact thermal sensitivity[139]. Electrophysiological studies reveal that HAS preferentially alters Nav1.7 channel dynamics to produce a hyperpolarizing shift in the steady-state inactivation curve and reduce current amplitudes in heterologously expressed systems. While Nav1.8 current amplitude decreases are also observed, the predominant inhibitory effect on Nav1.7 suggests subunit-specific modulation[112]. This selective blockade likely prevents action potential generation in somatosensory neurons expressing specific Nav channel combinations, providing a molecular mechanism for its modality-specific analgesic action.

6. Evaluation of the safety and toxic side effects of ZP and its existing prepared formulations in improving brain health

ZP demonstrates potential as a therapeutic agent for neurological disorders, though clinical evidence regarding its safety profile remains limited. Current preclinical studies indicate low toxicity across experimental models. Wei et al.[125] reported no mortality or neurobehavioral abnormalities in rats administered oral doses ranging from 55 to 2000 mg/kg over a period of 14 days. Functional magnetic resonance imaging analysis revealed no structural brain alterations in human subjects following consumption of 0.1 g ZP pericarp powder over a period of 60 days[89]. Zhao et al.[92] demonstrated that both aqueous extracts and volatile oil fractions of ZP ameliorated AD pathology in D-galactose-induced murine models through selective upregulation of nuclear Nrf2 expression, without affecting cytoplasmic Nrf2 levels. Histopathological examination showed no brain toxicity. Water-soluble ZP's components (Hydroxy-*α*-sanshool) exhibited neuroprotective effects against PD's pathology[16]. Dose-dependent anxiolytic effects were observed for volatile oil in chronic unpredictable stress models, with 100 mg/kg, 150 mg/kg, and 200 mg/kg doses suppressing corticotropin-releasing hormone mRNA elevation[140]. It was revealed that linalool lacked irritant effects on trigeminal responses, while hydroxy-*α*-sanshool and sesquiterpenes induced stinging/burning sensations[141-142]. Notably, 6-paradol functioned Ca^{2+} mobilization in HEK293 cells, suggesting potential neuroexcitatory risks. Conversely, Tang et al.[15] and Fan et al.[143] disclosed that Gx-50 penetrated BBB to preserve Ca^{2+} homeostasis with no cardiovascular and immune toxicity, as well with no acute and subchronic toxicity at therapeutic doses (2.5-5 mg/kg). Amusingly,

microglial viability remained unaffected by 100 μM Gx-50, though phosphorylation cascades were tremendously modulated[144] 5 mg/kg HAS administration mitigated oxidative stress and neuronal apoptosis in AD models[89,145].

ZP, while classified as a dual-purpose food and medicinal agent, has historical documentation noting respiratory distress with excessive consumption[146-147]. Should be avoided for use in infants and young children when employed as traditional medicine[148]. The plant's toxicological profile exhibits distinguishing geographical variation[149]. Pharmacotoxicological investigations reveal a median lethal dose (LD_{50}) of 51.14 g/kg for water extracts in murine models via oral administration[149,150]. Subacute exposure studies by Zhao et al.[151] demonstrated dose-independent mild hepatotoxicity (500-4000 mg/kg) and occasional renal hemorrhage at supratherapeutic doses. Comparatively, essential oil showed greater toxicity with an LD_{50} of 2.27 g/kg [152-153], though demonstrating favorable safety parameters in dermal models with IC_{50} values of 2.435 mg/mL (HaCaT) and 3.649 mg/mL(CCC-ESF-1) respectively[154]. However, essential oil of ZP had stronger contact toxicity than other plant essential oils[155]. Current therapeutic formulations primarily employ ZP in traditional Chinese patent medicines for analgesic and anti-pruritic purposes, with limited use in sedation and insufficiently characterized adverse effects.Yuan et al.[156] developed a transdermal patch containing ZP water extract demonstrating acute dermal safety in murine models, though transient irritation was observed in rabbit models. The toxicity of ZP is affected by its origin, medicinal properties, processing methods, dosage and administration, and patient constitution[148]. Notably, water-soluble components and amide derivatives (Gx-50) show superior clinical potential due to favorable BBB permeability and low toxicity. While volatile oils exhibit neuroprotective properties through TRPV channel modulation, process optimization remains crucial to mitigate genotoxic risks associated with α-sanshool derivatives[155].

7. Challenges and prospects

As a traditional Chinese herbal medicine with dual food-medicinal properties, ZP exhibits infinite potential in brain health research. Its diverse bioactive constituents, multifunctional biological activities, and therapeutic applications have garnered substantial scientific interest. Contemporary studies have advanced the identification of active compounds, quality standardization, and mechanistic investigations, establishing a foundation for modern pharmaceutical development and industrial utilization. Nevertheless, critical challenges persist, including incomplete elucidation of bioactive mechanisms, non-standardized quality control frameworks, suboptimal BBB penetration efficiency, and ambiguous pathways for clinical translation. Addressing these limitations necessitates interdisciplinary collaboration and technological innovation to unlock ZP's full therapeutic potential in brain health. The challenges and prospects of ZP in treating brain health are summarized in Fig. 6.

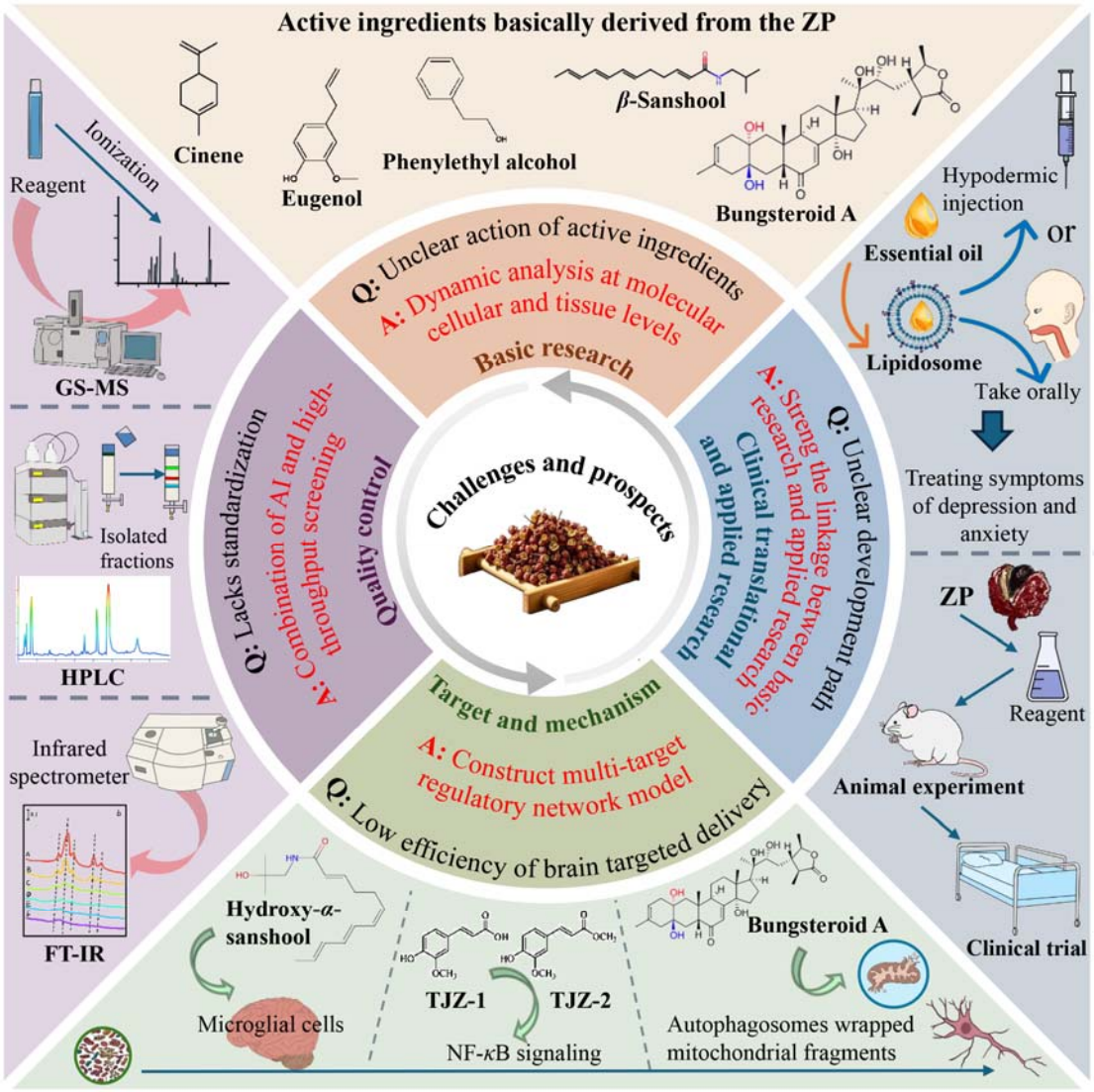

Fig. 6 Challenges and prospects of ZP in treating brain health.

7.1 Mechanistic elucidation of bioactive components

The complex polypharmacology of ZP's bioactive compounds remains insufficiently characterized. While neuroprotective constituents—including volatile oils, alkaloids, and flavonoids—have been identified, their molecular targets and signaling pathways require systematic investigation. Emerging methodologies such as single-cell transcriptomics, spatial metabolomics, and patient-derived organoid models could enable multiscale analysis (molecular, cellular, and tissue-level) of neuron-glia interactions and disease-modifying mechanisms.

7.2 Quality control standardization

Current quality assessment protocols—reliant on HPLC, GC-MS, and bioactivity assays—fail to address variability induced by cultivation environments, harvesting practices, and processing techniques. A transformative approach integrating artificial intelligence-driven predictive modeling with blockchain-enabled supply chain traceability could enhance standardization across cultivation, processing, and analytical workflows. Concurrently, genomic editing and synthetic biology platforms offer opportunities

for metabolic pathway optimization and high-yield strain development, thereby improving compound consistency and yield.

7.3 Enhanced bioavailability and targeted delivery

Structural limitations of key constituents impede BBB permeability, reducing therapeutic bioavailability. Nanocarrier-based delivery systems and molecular glue technologies represent promising strategies for brain-targeted drug delivery. Rational molecular engineering and stimuli-responsive carrier designs could improve cerebral biodistribution while preserving compound stability and activity.

7.4 Multi-target regulatory networks

The neuroprotective efficacy of ZP's derivatives stems from synergistic anti-inflammatory, anti-oxidant, and microbiota-modulating effects. Systems biology approaches incorporating multi-omics integration could delineate dose-responsive polypharmacological networks, enabling precision modulation of neurodegenerative pathways and optimization of combination therapies.

7.5 Clinical translation and industrial integration

Bridging TCM principles (e.g., warming the middle and unblocking orifices) with modern neuropharmacology may reveal novel therapeutic synergies for brain cognitive impairment. Accelerated clinical translation demands strengthened academia-industry partnerships to streamline preclinical-to-clinical development pipelines and establish evidence-based therapeutic protocols.

While ZP holds substantial promise in brain health innovation, realizing its full potential requires mechanistic clarification, quality standardization, delivery system optimization, and validated clinical pathways. These advancements will not only elucidate its neuroprotective mechanisms but also propel TCM modernization, offering globally relevant solutions for brain health management.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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