



Review Article

Polygonati Rhizoma at the medicine-food interface: mechanistic insights, quality innovations, and global applications

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Abstract: Huangjing (Polygonati Rhizoma), a cornerstone medicinal-edible resource in China, derives its therapeutic value from polysaccharides, saponins, and flavonoids through the mediation of metabolic and immune regulation. These bioactivities underpin 353 registered Chinese health foods, which are primarily developed through technologies such as total extract standardization and modernized polyherbal formulation. Among these products, 45.9% claim fatigue reduction and 44.5% claim immunity enhancement. The advancement of the industry faces three critical challenges: germplasm heterogeneity leading to bioactivity variation, deficient quality standards that rely on empirical processing methods like the traditional Nine-Steam-Three-Sun technique, and technological limitations that hinder the development of high-value products. This review integrates recent advances in understanding its health mechanisms, quality control methodologies, and industrial progress. We advocate for a three-dimensional quality marker (Q-marker) system to replace reliance on single-chemical markers. This system would encompass foundational specifications (e.g., polysaccharide molecular weight distribution), biofunctional indicators (e.g., macrophage phagocytosis rate), and authenticity verification measures. Strategies for cultural globalization, including obtaining ISO intangible heritage certification and promoting cultural-tourism integration, can support its expansion into global markets. Collectively, these approaches establish a scientific framework for sustainable resource utilization and high-value product development, ensuring global regulatory compliance.

Keywords: Huangjing; medicinal food homology; health benefits; quality marker (Q-marker); industrial standardization

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1 Introduction

Huangjing (Polygonati Rhizoma) originates from the dried rhizomes of *Polygonatum kingianum* Coll. et Hemsl., *Polygonatum sibiricum* Red., or *Polygonatum cyrtoneura* Hua (Liliaceae)^[1,2]. The genus *Polygonatum* encompasses over sixty species distributed across temperate and subtropical regions of the Northern Hemisphere. China represents a biodiversity hotspot for this genus, containing approximately 40 species—accounting for about seventy percent of global diversity. Three species are designated as pharmacopeial botanical origins in the *Chinese Pharmacopoeia* (2020 edition, ChP)^[3]. This genetic diversity facilitates resource utilization, as exemplified by the high-yield, autumn-sprouting variant *P. kingianum*, a valuable germplasm for cultivation enhancement^[4-6]. The three official *Polygonatum* species exhibit distinct morphological characteristics (Fig. 1), with *P. sibiricum*, *P. kingianum* and *P. cyrtoneura* showing differential leaf

arrangement and rhizome morphology.

Huangjing's documented medicinal and culinary applications span two millennia, with initial therapeutic descriptions appearing in the *Shennong Bencao Jing* (Divine Farmer's Classic of Materia Medica) circa 25–220 CE^[2,7]. Classical texts attribute specific bioactivities: the *Mingyi Bie Lu* (Records of Famous Physicians) documents its capacity to tonify the middle jiao, boost qi, and harmonize the five zang organs, whereas the *Bencao Gangmu* (Compendium of Materia Medica) emphasizes replenishing deficiencies and nourishing marrow^[8]. Traditional processing involving the Nine-Steam-Three-Sun method mitigates the irritant and allergenic properties of raw Huangjing rhizomes while potentiating tonic efficacy^[9]. Traditional Chinese medicine (TCM) characterizes Huangjing's pharmacodynamics as qi-nourishing, yin-tonifying, spleen-fortifying, lung-moistening, and kidney-invigorating^[10,11]. Its inclusion among China's inaugural 86 medicinal-food homologous substances, designated by the

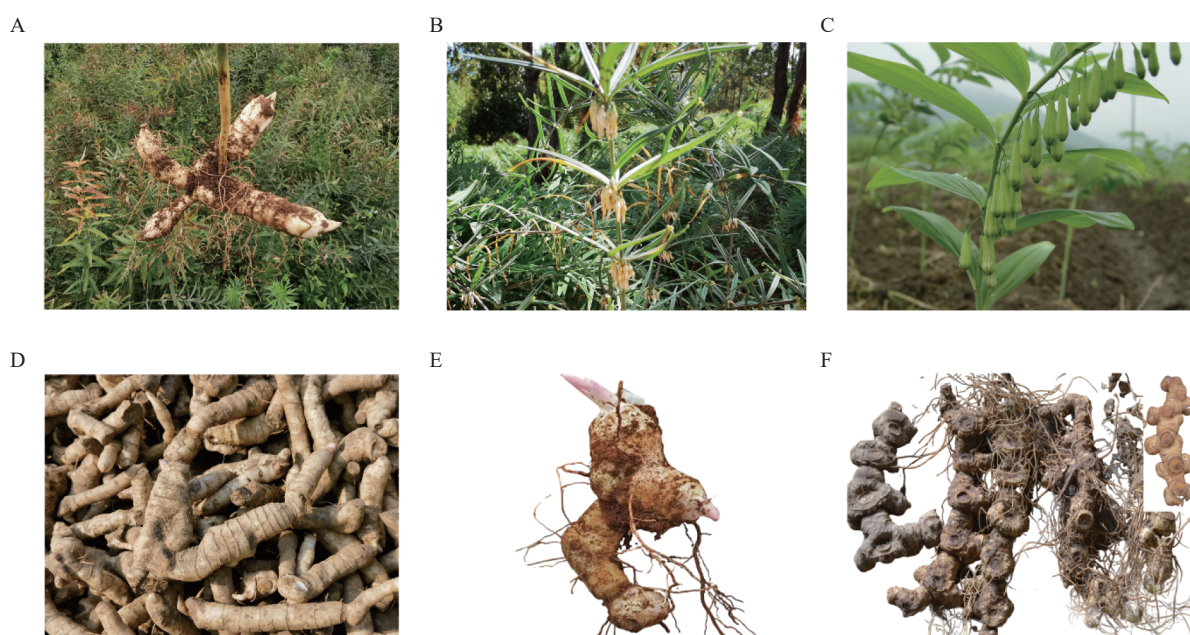


Figure 1 *P. sibiricum* (A, D), *P. kingianum* (B, E) and *P. cyrtoneura* (C, F).

Ministry of Health, reflects recognized therapeutic value^[12,13].

Contemporary research has expanded Huangjing applications beyond traditional domains^[14]. Its unique organoleptic properties and bioactive constituents—including heteropolysaccharides, steroidal saponins, and flavonol glycosides—enable functional food development, such as low-glycemic-index baked goods and starch-modulating products^[13,15]. Cosmetic formulations exploit its antioxidative and dermal-nourishing activities^[16]. Pharmacological studies have elucidated Huangjing's pleiotropic bioactivities, which include immunomodulation, antitumor effects, neuroprotection, antiviral activity, glycemic control, gut microbiota regulation, and antioxidant defense. These multifaceted actions provide mechanistic rationales for developing Huangjing-based therapeutics against diabetes, and immune-related disorders^[17–20]. Simultaneously, growing demand fueled by the Healthy China 2030 initiative is driving the Huangjing industry transformation from raw material supply to value-added manufacturing. Yet this transition faces formidable challenges: interspecific phytochemical diversity among *Polygonatum* species introduces compositional variability that hampers standardization, whereas disease pressures and biotic stresses undermine cultivation stability and yield predictability^[21,22]. Moreover, the lack of standardized quality metrics limits the availability of premium products^[23–25], while experience-based processing practices necessitate rigorous parameter optimization^[9,26]. Technological constraints further impede the development of Huangjing value-added formulations. Therefore, elucidating structure-activity relationships (SARs) that connect germplasm characteristics to health outcomes has emerged as a critical scientific priority for enabling precision resource management^[10,27]. To address these multifaceted challenges and advance the field, this review synthesizes global research progress on Huangjing pharmacological activities, quality control methodologies, and industrial applications, critically evaluating existing challenges and emerging opportunities to foster sustainable Huangjing resource utilization, innovative product development, and sectoral upgrading.

In this review, first, we examine the global patent landscape to delineate the core dynamics, challenges, and opportunities

associated with the Huangjing industry's transition from resource dependency to innovation-driven development. Building upon this analysis, we then synthesize the scientific mechanisms underpinning Huangjing's health effects and the resultant diversification of its product applications. This section not only defines the targets of industrial innovation but also underscores the critical importance of quality consistency. Subsequently, the review delves into the key bottlenecks within the current quality control paradigm and explores innovative, technology-based solutions. Finally, integrating the insights from the preceding analyses, we propose a forward-looking framework that synergizes scientific standardization with cultural globalization strategies to guide the sustainable advancement and global integration of the Huangjing industry.

2 Innovation landscape: a patent-driven analysis of industrial transformation

2.1 Global patent profile

As a paradigmatic medicinal and edible resource, Huangjing embodies the intersection of traditional therapeutics and modern biotechnology. Huangjing's industrial modernization is fundamentally tied to intellectual property development, wherein global patent landscapes function not merely as archives of innovation but as diagnostic instruments for identifying technical bottlenecks, assessing market competition, and predicting future technology trajectories^[28]. This systematic patent analysis quantifies critical Huangjing industrial challenges—including standardization deficits and low value-chain positioning—while delineating the current frontiers of technological innovation. By doing so, it provides empirical evidence to elucidate Huangjing's transformation of Huangjing from a traditional resource into a modern health commodity^[29].

An analysis of major global patent databases, including IncoPat (a commercial patent database), EPO (European Patent Office), JPO (Japan Patent Office), KIPO (Korean Intellectual Property Office), and WIPO (World Intellectual Property Organization), identified 8,115 valid granted and published patents. The search

strategy combined the international patent classification (IPC) code A61K36/8969 with relevant keywords such as “Huangjing”, “*Polygonati Rhizoma*”, and “*Polygonatum*”. As illustrated in Figs. 2A and B, our analysis reveals three defining characteristics of the global patent landscape. First, a marked geographical concentration is evident: China accounts for over 80% of total filings, consolidating its position as the global epicenter for both Huangjing resource endowment and innovation activity. However, this volumetric dominance stands in stark contrast to China’s share of the international high-value-added product market, which remains below 30%. This disparity illuminates a structural dissonance between patent quantity and the efficiency of patent-to-commercial-value conversion^[30,31]. Second, the application domains exhibit a high degree of concentration. Analysis of IPC codes reveals that pharmaceutical applications account for nearly half (48.2%) of total filings, with substantial proportions additionally categorized under food and beverage sectors. This distribution pattern directly corroborates Huangjing’s dual medicinal-edible identity of Huangjing and delineates the principal arenas for industrial innovation^[29,32]. Third, innovation content is stratified across the entire Huangjing value chain. It spans upstream cultivation and breeding, exemplified by a patent for drought-resistant hybrids, midstream processing and extraction, such as the use of supercritical fluid extraction, and downstream product applications, including microbial co-fermented health foods^[33]. While this breadth indicates comprehensive industrial engagement, it simultaneously suggests a potential dispersion of innovative effort, wherein absolute dominance in any high-barrier technological segment remains elusive. This panoramic observation raises a pivotal question concerning how the industry has evolved within this expansive patent ecosystem and what constitutes its key driving forces. Such inquiry logically necessitates an examination of the technology lifecycle^[34].

2.2 Technology lifecycle evolution: phased development and core drivers

The technology lifecycle curve (Fig. 2C) delineates the dynamic trajectory of Huangjing innovation, with each phase closely correlated with macro-policies, market demand, and scientific breakthroughs^[35,36]. The exploratory germination phase (2006–2011) witnessed modest growth in annual Huangjing patent applications, from 41 to 146, representing a compound annual growth rate (CAGR) of 23.1%. Innovation during this period was dispersed among 148 applicants, with over 80% of patents concentrated on primary processing methodologies—namely Huangjing drying and slicing. The overarching technological objective centered on securing a stable and scalable supply of Huangjing raw materials, reflecting the initial modernization of Huangjing traditional production chains characterized by relatively low innovation intensity^[5,37].

The scale-growth phase (2012–2020) commenced with a notable surge to 210 Huangjing-related applications in 2012, followed by sustained incremental growth. The onset of this phase aligns precisely with the launch of China’s Healthy China 2030 initiative and the concurrent emergence of the wellness-oriented consumer market. The innovation focus visibly expanded toward Huangjing functional foods and health products, with patents increasingly encompassing specific Huangjing compound formulations, efficacy claims, and dosage form designs^[29,38,39]. This period signifies a strategic pivot from the production of raw medicinal materials to the development of consumer-oriented

products, wherein market pull emerged as a predominant driving force.

The rapid-growth phase (2021–present) is characterized by an exponential surge in Huangjing patenting activity, with applications escalating from approximately 700 to 1,348 by 2024. This explosive growth is propelled by multiple convergent factors: an unprecedented global post-pandemic emphasis on immune health that substantially amplified Huangjing market demand; the progressive elucidation of molecular mechanisms underlying the immunomodulatory, metabolic, and neuroprotective effects of Huangjing’s core bioactive constituents—notably polysaccharides and saponins—thereby furnishing robust scientific rationale for product innovation and the expanding global acceptance of the medicinal-food homology concept within the natural health products sector^[40–42]. Within this dynamic landscape, major industry players have cultivated differentiated patent strategies contingent upon their respective industrial foundations and strategic objectives, thereby vying for advantageous positioning within the global value chain^[43,44].

2.3 Divergent national strategies and global value chain competition

In response to this shared innovation imperative, principal stakeholders in the global Huangjing industry—most notably China, Japan, and South Korea—have adopted divergent patent strategies, engaging in strategic competition to secure dominant positions within the global value chain^[45,46]. Japan exemplifies a strategy of Process Refinement and Cultural Valorization. Its patent portfolio excels in marrying traditional techniques with modern technology, such as optimizing parameters for the Huangjing Nine-Steamming-Nine-Sunning process or utilizing supercritical extraction for enhanced purity. Crucially, Japan integrates Huangjing deeply into its institutional framework, notably the food for specified health uses (FOSHU) system, and into high-end culinary culture^[47]. Specific patents safeguard formulations and preparation methodologies for medicinal cuisine, thereby generating high-margin cultural consumables and securing dominance over the branded service and experiential segments of the value chain. In contradistinction, South Korea pursues a paradigm of Technology Integration and Brand Engineering. Its patent prowess resides in the sophisticated compounding of Huangjing active constituents and the development of novel dosage forms, with particular emphasis on Huangjing-based cosmeceuticals and complex dietary supplements^[48,49]. Korean patents strategically integrate Huangjing polysaccharides with other premium constituents—notably red ginseng extract—utilizing advanced delivery systems to formulate products with substantiated efficacy claims under the umbrella K-Health brand. This strategy of leveraging convergent technologies to underpin brand premiumization has demonstrably propelled substantial annual export growth, thereby securing dominance over the high-value-added research, development, and marketing segment of the value chain^[15].

In contradistinction, China’s patent landscape is currently undergoing a strategic reorientation from Resource Dominance toward Innovation Catch-up. Early-stage patents were predominantly resource-centric, encompassing *Polygonatum* cultivation, harvesting, and primary processing modalities—reflecting the nation’s inherent advantage as the primary Huangjing resource origin. More recently, leading enterprises have successfully penetrated high-end market segments, notably Huangjing cosmetic ingredients, securing patents covering

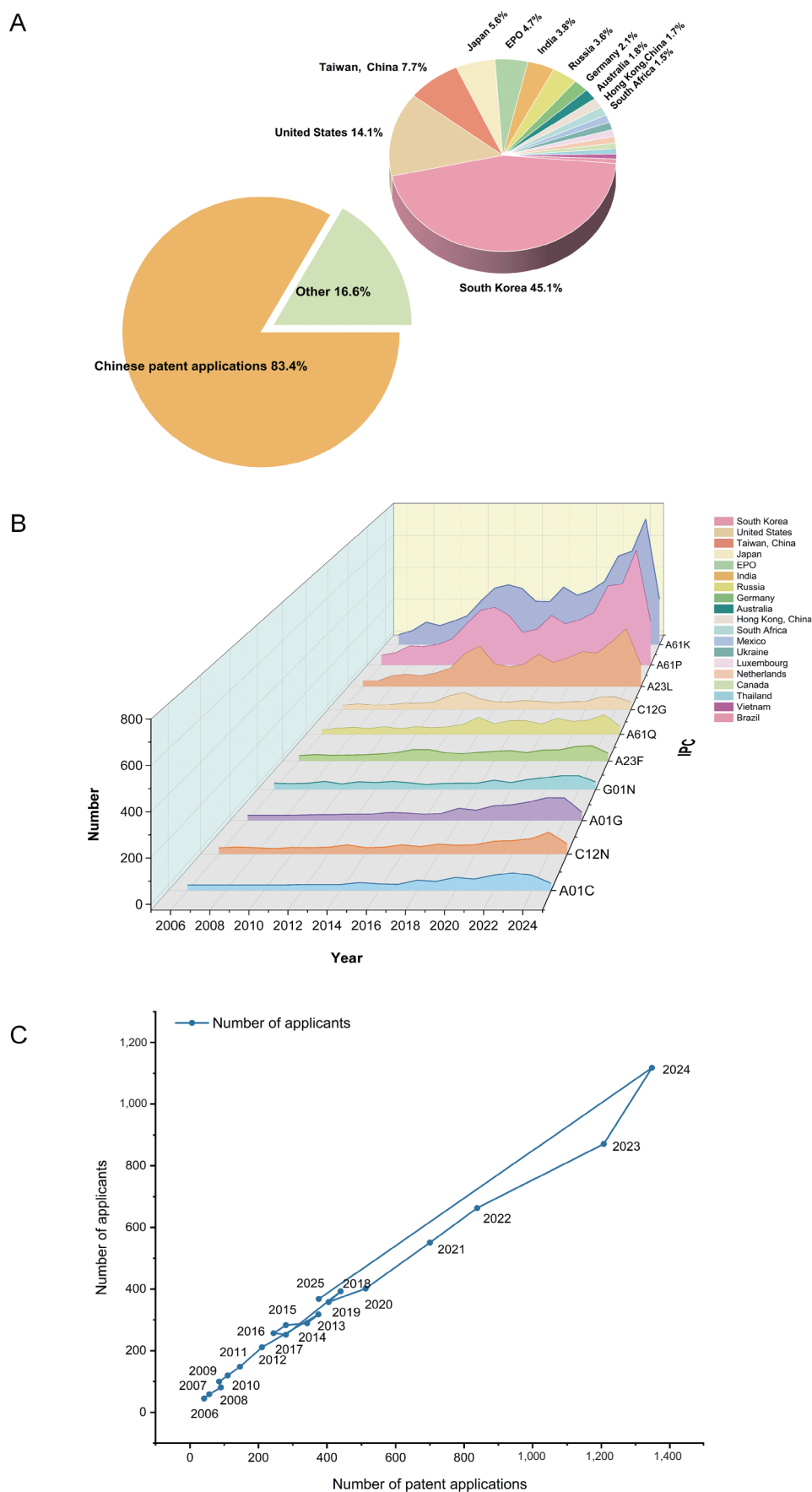


Figure 2 Patent analysis and technology lifecycle of Huangjing industry. (A) Patent filing trends in jurisdictions excluding China. (B) Evolutionary patterns of primary IPC subclasses. (C) Global technology lifecycle stages.

sophisticated technologies such as Huangjing saponin lipid encapsulation^[3,50]. This development challenges extant international monopolies and signals China's strategic ascent toward the core technology and premium ingredient supply segments of the global value chain^[51,52]. Nevertheless, substantial challenges persist. The pronounced disparity between China's dominant share of global patents and its comparatively modest share of the deep-processed international market underscores a critical conversion bottleneck—namely, the translation of patent advantage into tangible market leadership. A fundamental root cause resides in the absence of internationally recognized Huangjing quality standards—specifically those centered on bio-efficacy assessment—within many process patents, thereby impeding technology transfer and product certification. Concurrently, influence within international standard-setting bodies remains constrained, with no Huangjing-specific standard system yet established. This regulatory vacuum enables countries possessing mature product definitions and standards to exert indirect influence over international market configurations^[53]. This strategic interplay among nations is fundamentally rooted in their divergent adoption of innovation paradigms, which is systematically analyzed in the subsequent section.

2.4 Core innovation paradigms: the evolutionary path from empirical utilization to precision development

Systematic content analysis of global Huangjing patent portfolios reveals three distinct yet progressively evolutionary innovation paradigms. These paradigms represent ascending echelons of scientific sophistication and constitute a hierarchical framework of Huangjing industrial technological advancement^[4,54]. The first paradigm, designated Total Extract Utilization, encompasses patents protecting chemically complex mixtures derived through well-defined biotechnological processes—notably enzymatic hydrolysis or microbial fermentation—and typically classified under IPC category A61K36/8969. The underlying scientific premise explicitly acknowledges and strategically leverages Huangjing's holistic bioactivity arising from the synergistic interactions among multiple phytoconstituents^[55]. These patents constitute the foundational infrastructure underpinning contemporary health food and select proprietary Chinese medicine sectors, predominantly employing macroscopic quality metrics exemplified by polysaccharide content quantification. This paradigm exhibits comparatively modest entry barriers and serves as a critical enabler for accelerating technology diffusion and achieving initial market penetration^[56].

The second paradigm, designated Modernized Polyherbal Formulation, embodies the systematic modernization and strategic intellectual property protection of traditional herbal compatibility theory. Corresponding patents safeguard fixed-ratio combinations of Huangjing with complementary medicinal-food substances—notably ginseng and astragalus—together with their contemporary dosage formulations^[57,58]. The underlying scientific rationale entails systematic exploration of multi-component synergistic mechanisms. These patents effectively translate empirical heritage into commercialized products characterized by consistent quality and substantiated functional claims. They occupy a dominant position within the health supplement markets of China and other East Asia countries, capitalizing upon profound cultural acceptance and resultant market stability^[59].

The third and most prospective paradigm, designated Single Compound Development, encompasses patents predominantly classified under IPC categories C07D (heterocyclic compounds) or

C07K (peptides). These patents seek to protect structurally elucidated, isolated, or synthetically modified single active molecular entities derived from Huangjing—exemplified by specific Huangjing saponins, flavonoids, or bioactive peptides. The underlying scientific objective entails rigorous mechanistic elucidation and systematic assessment of pharmaceutical development feasibility^[60,61]. Although presently constituting a relatively modest share of core patents with limited direct commercial outputs, their strategic significance remains paramount. These patents serve as instrumental enablers for constructing enduring technological moats, penetrating the rigorously regulated international pharmaceutical market, and ultimately securing research and development sovereignty at the apex of the value chain^[34,62]. These paradigms do not constitute merely parallel alternatives but embody a systematic intellectual progression—from holistic experiential knowledge through component-level synergistic integration to ultimate molecular entity elucidation. In aggregate, they propel the industry from traditional empiricism toward modern precision-guided scientific development^[63].

2.5 Industrial transformation insights from the patent vantage point

In summary, global patent analysis functions as a multifaceted lens that illuminates a profound paradigm shift within the Huangjing industry. This transformation is characterized by Huangjing's strategic transition from resource-dependent extraction toward innovation-driven sustainable development^[64,65]. The data reveal that although China maintains a dominant quantitative position in Huangjing patent filings, it confronts urgent imperatives to enhance Huangjing patent quality, facilitate the commercialization of Huangjing intellectual property into market value, and amplify its voice in international Huangjing standard-setting frameworks. Conversely, Japan and South Korea have cultivated distinct competitive advantages in high-value segments of the global Huangjing value chain through strategic differentiation—Japan leveraging cultural valorization of Huangjing traditional knowledge (Kampo) and South Korea deploying technology-driven Huangjing branding (Korean Traditional Medicine)—thereby securing premium market positioning despite lower patent volumes^[66,67].

More fundamentally, patent content analysis elucidates Huangjing's intrinsic evolutionary trajectory of industrial innovation, characterized by a tripartite progression: an initial phase predicated upon the composite bioactivity of Huangjing crude botanical extracts; an intermediate stage exploring synergistic polypharmacology within modernized multi-herb formulations; and an ultimate trajectory toward the precision frontier exemplified by single-compound therapeutics and target-specific drug development^[68,69]. This trajectory of deepening scientific cognition imposes two critical imperatives upon the Huangjing industry's future development. First, it necessitates rigorous molecular deconstruction of Huangjing's bioactive constituents and their mechanistic modalities, thereby effecting the epistemological translation of Huangjing's empirical traditional claims into evidence-based, pathway-specific pharmacological frameworks^[70]. Second, it necessitates the establishment of contemporary Huangjing quality standard frameworks that transcend conventional dependence on univariate chemical markers through the systematic integration of bio-functional efficacy assessments. These comprehensive

frameworks would function as an international credentialing mechanism, ensuring product consistency, safety, and therapeutic efficacy across global markets^[71]. These dual imperatives—mechanistic elucidation and robust, efficacy-anchored standardization—constitute the foundational drivers for sustainable Huangjing industrial development. The subsequent exposition synthesizes contemporary advances in Huangjing bioactive mechanism understanding with the concomitant quality control exigencies, thereby establishing a coherent analytical framework for addressing these strategic necessities^[72].

3 Health effects and product application

The patent analysis presented in Section 2 reveals that the frontier of industrial innovation is shifting from empirical utilization toward precision development grounded in mechanistic discovery. The fundamental scientific basis for this transition resides in the elucidation of the principal bioactive constituents of Huangjing, notably polysaccharides, saponins, and flavonoids, and their synergistic mechanisms of action. This chapter systematically reviews the molecular mechanisms underlying these health effects and explicates their translation into specific product applications across diverse sectors, thereby furnishing the scientific substantiation for the industrial innovation pathways delineated previously.

3.1 Health effects and molecular mechanisms

The principal bioactive constituents of Huangjing comprise polysaccharides, saponins, and flavonoids, with the associated health benefits ascribed to their synergistic interactions. Pharmacopeial standards stipulate a minimum polysaccharide content of 7.0%. These structurally diverse heteropolysaccharides exhibit pronounced interspecific heterogeneity, which exerts direct influence upon their immunomodulatory and metabolic activities. Saponins constitute an additional principal constituent class, encompassing both steroidal and triterpenoid structural types^[73]. They mediate anti-inflammatory and antitumor effects through their inherent amphiphilicity, which facilitates interaction with cellular membranes. The flavonoid fraction is distinguished by Asparagaceae-specific homoisoflavonoids, which exhibit structural configurations conducive to enhanced blood-brain barrier permeability, thereby facilitating neuroprotective activity^[74]. These structurally diverse bioactive constituents, including steroidal saponins and homoisoflavonoids, constitute the molecular basis for Huangjing's therapeutic efficacy (Fig. 3). Collectively, these constituents elicit systemic biological effects through multi-target pathway modulation, manifesting pronounced polypharmacology and synergistic interactions^[75].

3.1.1 Immunomodulation

In the context of innate immunity, Huangjing polysaccharides predominantly modulate the toll-Like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/nuclear factor κ B (NF- κ B) signaling axis^[17,45]. Within lipopolysaccharide (LPS)-induced acute lung injury (ALI) models, these polysaccharides markedly attenuate TLR4/MyD88/NF- κ B pathway activation, concomitantly reducing pulmonary tissue myeloperoxidase (MPO) activity by 40% and malondialdehyde (MDA) concentrations by 53%^[76,77]. Notably, polysaccharides derived from plant-associated endophytic fungi manifest comparable immunomodulatory effects *via* macrophage activation and cytokine regulation, thereby substantiating the extensive potential

of bioactive polysaccharides in immune modulation^[78]. Concurrently, these polysaccharides markedly attenuate serum concentrations of pro-inflammatory cytokines tumor necrosis factor (TNF)- α and interleukin (IL)-1 β , with reductions approaching 60%, through the suppression of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation^[79]. Beyond these biochemical synergies, the immunomodulatory effects encompass critical biophysical interactions, including membrane receptor clustering, nanoscale ligand presentation, and supramolecular assembly dynamics^[80,81]. For instance, non-covalent interactions, notably hydrogen bonding, between polysaccharides and saponins stabilize these supramolecular assemblies and markedly potentiate the clustering and engagement of pattern recognition receptors, exemplified by TLR4, on immune cell membranes^[82].

Huangjing fructans are metabolized by gut microbiota to produce short-chain fatty acids (SCFAs), which promote regulatory T cell differentiation through the activation of SCFA receptors and enhanced Foxp3 expression^[83]. Huangjing saponins, particularly dioscin, markedly suppress the production of IL-6 and TNF- α through inhibition of the TLR4/mitogen-activated protein kinase (MAPK) signaling pathway, thereby exerting dual regulatory effects on TLR4 signaling in coordination with polysaccharides^[84]. During adaptive immune responses, Huangjing polysaccharides potentiate NK cell cytotoxicity through activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway and facilitate T lymphocyte proliferation and differentiation, thereby restoring the T helper 1/T helper 2 (Th1/Th2) immune balance, as demonstrated by a 2.8-fold elevation in the serum IL-2/IL-10 ratio^[85]. Clinical investigations provide additional mechanistic support, demonstrating that Huangjing polysaccharides augment IL-10 secretion from macrophages through activation of the TLR2/MyD88 signaling pathway and exhibit anti-influenza A virus subtype H₁N₁ (H₁N₁) activity with a half-maximal effective concentration (EC₅₀) of 8.7 μ g/mL^[46]. Furthermore, Huangjing polysaccharides promote the recovery of leukocytes in patients undergoing chemotherapy through activation of the JAK-STAT signaling pathway, with counts reaching 80% of baseline levels^[86]. Collectively, *P. sibiricum* polysaccharides (PSPs) orchestrate pleiotropic protective effects through coordinated modulation of multiple signaling cascades (Fig. 4), spanning immunomodulation, metabolic regulation, and cellular homeostasis.

3.1.2 Metabolic regulation

Huangjing modulates glucose and lipid metabolism through the synergistic interactions of its constituent saponins, polysaccharides, and flavonoids. Specifically, saponins such as dioscin enhance insulin sensitivity by regulating the miR-125a-5p-mediated phosphoinositide 3-kinase (PI3K)/Akt/forkhead box O1 (FoxO1) signaling pathway, whereas polysaccharides independently promote glucose transporter type 4 (GLUT4) translocation through the insulin receptor substrate 1 (IRS1)/PI3K/Akt signaling axis^[87]. Saponins, including dioscin and polygonatoside C, act cooperatively with polysaccharide-metal complexes to activate the peroxisome proliferator-activated receptor gamma (PPAR γ)/GLUT4 pathway, resulting in a 55% increase in adipocyte glucose uptake efficiency and a 180% elevation in GLUT4 translocation rates^[88]. This enhanced translocation is partially mediated by the physical modulation of membrane fluidity and microdomain organization, which is

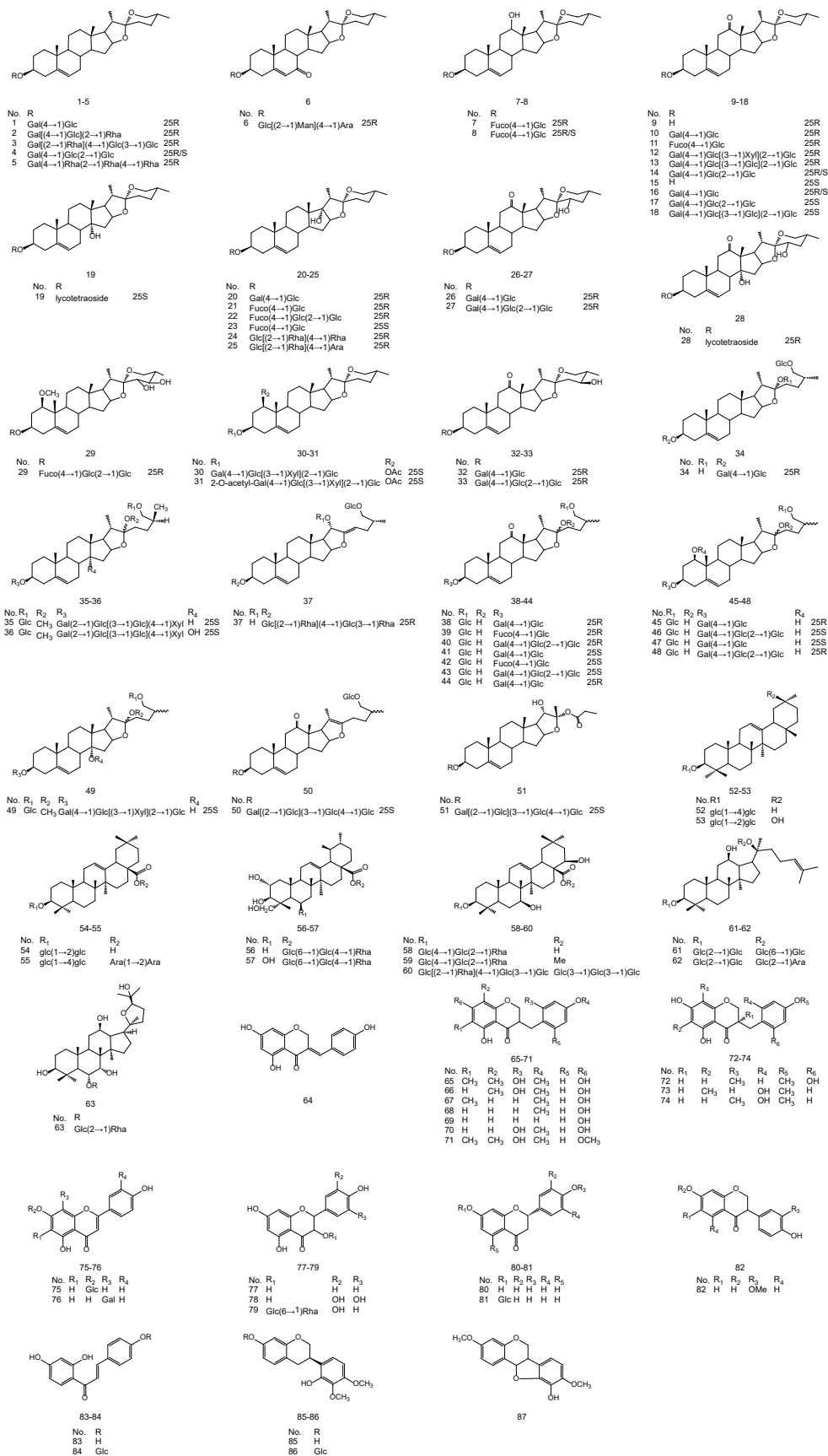


Figure 3 Structures of major saponins and homoisoflavonoids in Huangjing.

facilitated by the incorporation of amphiphilic saponins into the cellular lipid bilayer.

In the context of lipid metabolism, Huangjing activate the adenosine 5'-monophosphate (AMP)-activated protein kinase

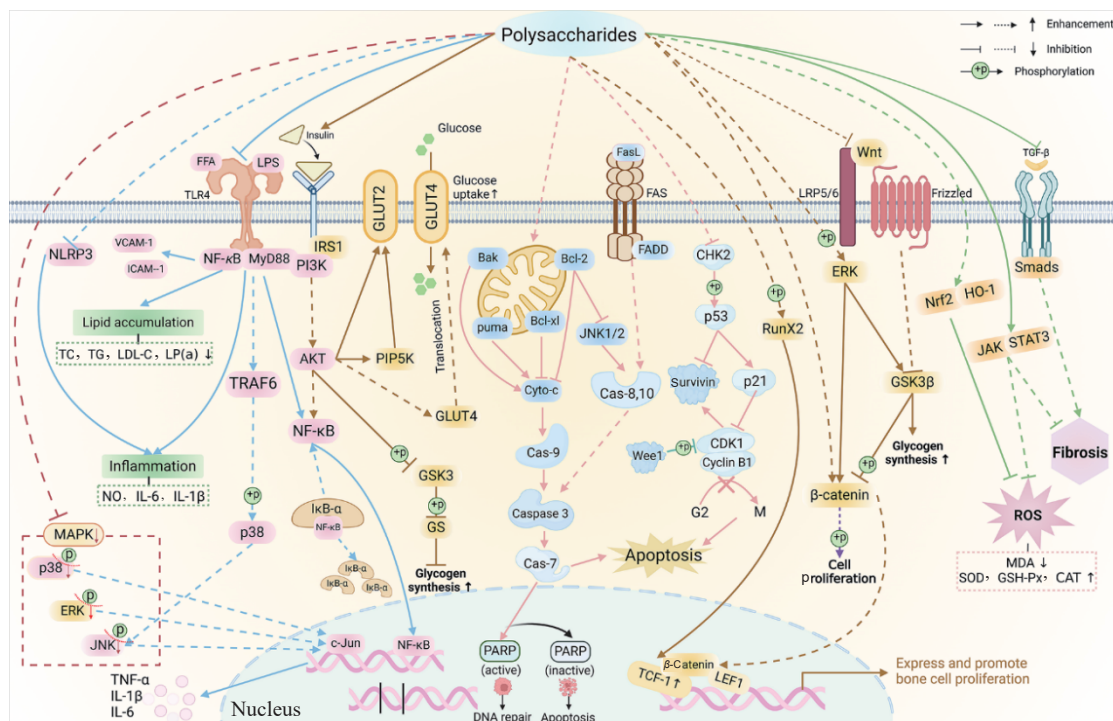


Figure 4 Molecular mechanisms of PSPs in cell cycle regulation, apoptosis, and multi-system therapeutic effects (anti-inflammatory, antidiabetic, anticancer, anti-osteoporotic, and neuroprotective).

(AMPK)/PPAR γ coactivator 1- α (PGC-1 α) signaling axis to enhance mitochondrial β -oxidation in skeletal muscle, thereby reducing circulating free fatty acids by 28%. Concurrently, these agents alleviate hepatic fibrosis through inhibition of the transforming growth factor (TGF)- β /small mothers against decapentaplegic (Smad) signaling pathway, resulting in significant reductions in serum triglycerides and low-density lipoprotein (LDL) cholesterol levels in hyperlipidemic models^[89]. Huangjing polysaccharides stimulate glucagon-like peptide-1 secretion from intestinal L-cells through the T1R2/T1R3-mediated cyclic adenosine monophosphate (cAMP) signaling pathway, thereby directly enhancing glycemic control. Concurrently, low-polymerization-degree fructans derived from Huangjing, with degrees of polymerization ranging from 3 to 10, exhibit unique energy-supplying functions through colonic microbiota fermentation, generating acetate and butyrate. These SCFAs activate the AMPK/PGC-1 α signaling axis to promote mitochondrial biogenesis, resulting in a 40% prolongation of endurance capacity^[90].

With respect to gluconeogenesis and inflammation, Huangjing saponins suppress hepatic protein tyrosine phosphatase 1B (PTP1B) activity, whereas Huangjing flavonoids modulate the farnesoid X receptor/small heterodimer partner signaling pathway, thereby reducing phosphoenolpyruvate carboxykinase expression by 62%^[91]. Furthermore, Huangjing flavonoids attenuate inflammatory cytokine secretion from adipocytes through the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway, while saponins inhibit NOD-like receptor family pyrin domain-containing 3 inflammasome activation to ameliorate vascular injury. Collectively, these mechanisms establish a tripartite regulatory axis encompassing enhanced glucose uptake, promoted lipid oxidation, and suppressed gluconeogenesis. Clinical evidence corroborates these effects, demonstrating that a Huangjing formulation enriched with 32% saponins reduced urinary protein

excretion by 42% in patients with diabetic nephropathy through activation of the PI3K/protein kinase B (Akt) signaling pathway^[92]. Huangjing polysaccharide intervention reduced hepatic triglyceride content by 39% in patients with non-alcoholic fatty liver disease (NAFLD) through AMPK-mediated acetyl-CoA carboxylase inhibition and suppression of lipogenesis, concurrently improving metabolic homeostasis via modulation of the gut microbiota and short-chain fatty acid production^[12]. At the systemic level, Huangjing coordinate spatiotemporal crosstalk between the AMPK/PI3K/Akt and TLR4/MyD88/NF- κ B signaling pathways. For instance, Huangjing polysaccharides prolong the half-life of saponins, thereby synergistically ameliorating metabolic syndrome and immuno-inflammatory cascades, as demonstrated by multinational clinical investigations^[93]. Huangjing saponins exert multimodal therapeutic actions via distinct molecular pathways (Fig. 5), converging on inflammation resolution, metabolic homeostasis, and neuroprotection.

3.1.3 Neuroprotection and anti-aging effects

Huangjing exhibits neuroprotective and anti-aging properties through multicomponent spatiotemporal synergy. Huangjing flavonoids, exemplified by polygonatum flavone A, enhance synaptic plasticity through activation of the brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B signaling pathway^[11]. Huangjing homoisoflavonoids inhibit tau hyperphosphorylation through C-8 isopentenyl-mediated penetration of the blood-brain barrier. Huangjing alkaloids delay neuronal apoptosis by inhibiting glycogen synthase kinase-3 beta (GSK-3 β) signaling, whereas Huangjing cyclopeptides promote serotonin release in the prefrontal cortex through sigma-1 receptor activation, with a median effective dose of 5 mg/kg, and attenuate dopamine degradation through monoamine oxidase B (MAO-B) inhibition^[40].

Synergistic interactions amplify these effects. Specifically,

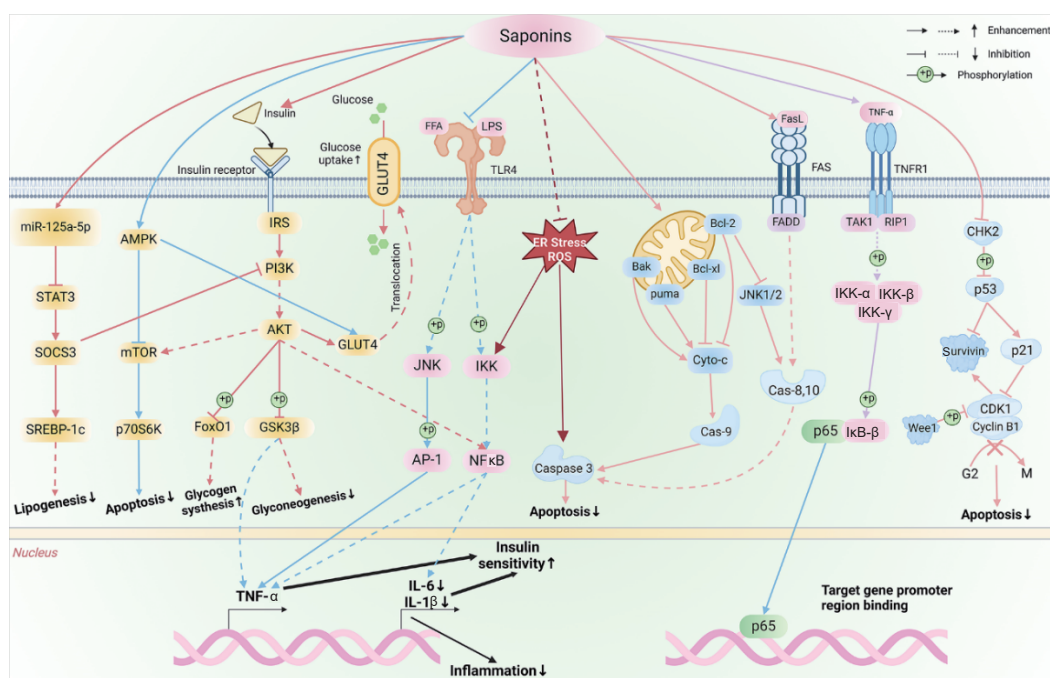


Figure 5 Molecular mechanisms of Huangjing saponins in metabolic, inflammatory, and neuroprotective activities.

Huanguing luteolin glycosides enhance the oscillation amplitude of Clock/Bmal1 genes by 40%, thereby optimizing circadian rhythms, while sirtuin 1 (SIRT1)/PGC-1 α signaling drives mitochondrial biogenesis and extends telomeres by 17%. Furthermore, PSPs and saponins cooperatively downregulate IL-6 and TNF- α through TLR4/MyD88/NF- κ B pathways, while concurrently elevating superoxide dismutase (SOD) activity 3.1-fold *via* Nrf2/HO-1 activation^[17,52]

Clinical studies confirm multidimensional efficacy, with PSPs reducing Morris water maze escape latency by 40% in Alzheimer's disease (AD) models through decreased BCL2-associated X protein (BAX)/B-cell lymphoma 2 (BCL-2) ratios, suppressed caspase-3 activity, and enhanced synaptic plasticity via ribosomal protein S6 kinase (p70S6K)/PI3K/Akt pathway activation. In post-traumatic stress disorder models, PSPs most effectively ameliorated fear behaviors at 400 mg/kg through Nrf2 modulation, while Huangjing cyclopeptides reduced immobility time by 91.8% in tail suspension tests using depressive models, demonstrating translational potential across neurodegenerative disorders^[8].

3.1.4 Anti-inflammatory and antioxidant activities

Huangjing flavonoids mediate anti-inflammatory and antidiabetic effects through specific molecular targets (Fig. 6). The anti-inflammatory and antioxidant activities of Huangjing are mediated by multiscale synergy among its primary bioactive constituents, namely polysaccharides, saponins, and flavonoids. Huangjing flavonoids directly scavenge reactive oxygen species (ROS) while inhibiting NLRP3 inflammasome assembly, thereby suppressing caspase-1 activation by 80%^[94]. Their antioxidant action extends to the biophysical level, where flavonoid aglycones incorporate into and stabilize lipid bilayers, thereby physically inhibiting the propagation of chain reactions in lipid peroxidation within cellular membranes. These compounds further mitigate oxidative stress through 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging. Concurrently, PSPs upregulate SOD and glutathione peroxidase (GSH-Px) activities *via* the Nrf2/HO-1 pathway^[52].

Huangjing homoisoflavonoids enhance binding affinity to the Keap1-Kelch domain through C-8 isopentenyl modification, thereby increasing Nrf2 nuclear translocation efficiency 3.1-fold and elevating SOD activity. This critical modification enhances molecular lipophilicity, a key biophysical property that promotes passive diffusion across the blood-brain barrier and integration into neuronal membranes, thereby exerting direct antioxidant effects. Huangjing phenolic acids suppress prostaglandin synthesis by inhibiting the cyclooxygenase-2 (COX-2)/prostaglandin E₂ (PGE₂) pathway. Synergistically, Huangjing polysaccharides are metabolized by gut microbiota into SCFAs, which activate the SCFA-Nrf2 axis to amplify antioxidant responses^[95]. Huangjing saponins, such as dioscin, downregulate pro-inflammatory cytokines (e.g., IL-6 and TNF-α) through the TLR4/MyD88/NF-κB pathway. Collectively, these mechanisms form a tripartite regulatory network encompassing ROS clearance, NLRP3/NF-κB/Nrf2 modulation, and SCFA-mediated microecological regulation^[96].

Organ-level evidence demonstrates that Huangjing phenolic acid-enriched extracts at 32% reduce collagen deposition by 55% in pulmonary fibrosis models through TGF- β 1/Smad3 pathway inhibition. Oligosaccharides from *P. cyrtonema* significantly decrease serum TNF- α and IL-1 β levels, while PSPs inhibit MPO activity and reduce MDA levels, thereby alleviating LPS-induced ALI^[9].

3.1.5 Antitumor activity

The antitumor properties of Huangjing primarily rely on saponin-polysaccharide synergy. Steroidal saponins, such as methyl protodioscin (MPD), activate caspase cascades, upregulate FAS and caspase-3/8 expression, induce mitochondrial apoptosis *via* cytochrome c (Cyto-c) release, and inhibit PI3K/Akt/mechanistic target of rapamycin (mTOR) signaling to impede cancer cell proliferation^[94]. The initial trigger for this apoptotic pathway often involves biophysical disruption of cancer cell membranes, wherein the amphiphilic structure of saponins integrates into lipid rafts, alters membrane permeability, and

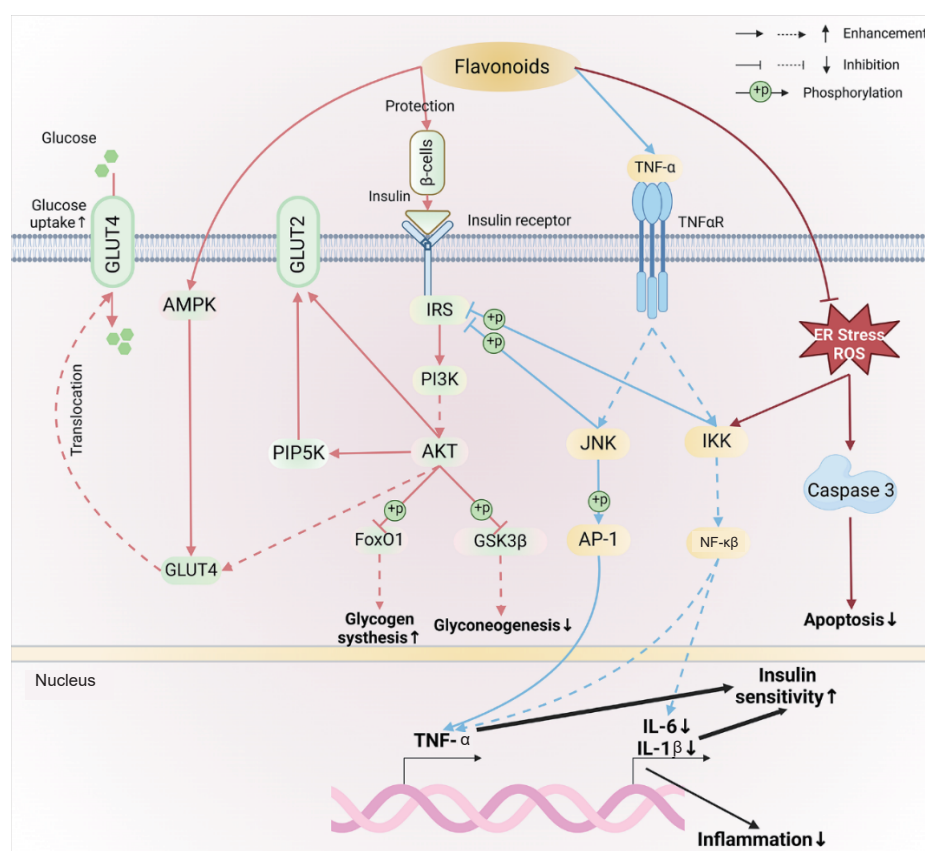


Figure 6 Potential molecular mechanisms for the anti-inflammatory and antidiabetic activities of Huangjing flavonoids. Image created with bioRender.com, with permission.

facilitates Cyto-c release^[97]. PSPs induce G₂/M phase arrest by modulating the GSK-3 β -cyclin/cyclin dependent kinase (CDK) axis, significantly increasing G₂/M-phase cell populations while suppressing tumor cell migration and invasion through TLR4-MAPK/NF- κ B pathway inhibition^[98]. Synergistic interactions broaden the anticancer spectrum by enabling Huangjing homoisoflavonoids to inhibit the growth of MCF-7 breast cancer and HepG2 hepatocellular carcinoma cells via the insulin receptor-IRS-PI3K axis, while saponins remodel the tumor microenvironment through TNF- α and IL-6 downregulation mediated by c-Jun N-terminal kinase (JNK)/IKK signaling. Concurrently, polysaccharides from PSPs attenuate chemotherapy-induced cardiac hypertrophy via JAK2/STAT3 inhibition^[39].

Experimental evidence supports these mechanisms, with polysaccharides from PSPs inhibiting invasion and metastasis in esophageal carcinoma Eca109 cells, reducing migration rates by over 60%, while enhancing G₂/M phase arrest by 40% in human cervical cancer cells (HeLa) cervical cancer cells. Lung adenocarcinoma models demonstrate that Huangjing saponin-polysaccharide co-administration reduces tumor volume by 52%^[98].

3.1.6 Bone metabolism regulation

PSPs exert anti-osteoporotic effects by targeting bidirectional bone metabolism pathways. Specifically, PSPs activate both extracellular signal-regulated kinase (ERK)/GSK-3 β /catenin beta 1 (β -catenin) and Wntless/integrated signaling pathway (Wnt)/LDL receptor-related protein 5 (LRP5)/ β -catenin cascades, thereby promoting β -catenin nuclear translocation and interaction with lymphoid enhancer-binding factor 1 (LEF1)/transcription factor 1 (TCF-1) transcription complexes. This signaling initiation relies on specific carbohydrate-protein recognition events, wherein

the three-dimensional conformation of PSPs directly engages the extracellular domain of the LRP5/6 co-receptor, thereby stabilizing the Wnt ligand-receptor complex. This interaction upregulates the key osteogenic factor runt-related transcription factor 2 (RUNX2) while stabilizing β -catenin protein through GSK-3 β inhibition, thereby driving bone marrow stromal cell differentiation into osteoblasts^[99]. These mechanisms restore bone homeostasis through a triple cascade: enhancing osteoblast mineralization via PI3K-Akt activation, suppressing osteoclastogenesis through Hippo pathway and miR-1224 regulation, and optimizing bone matrix synthesis via core target genes such as JUN, thereby establishing a coordinated pro-osteogenic/anti-osteoclastic network^[100]. In osteoporosis models, PSPs significantly increase bone mineral density by 28%, as quantified by micro-CT scanning, reverse bone loss, elevate trabecular bone number by 35%, and boost collagen deposition by 42%^[101].

3.1.7 Anti-COVID-19 and antiviral activities

Huangjing demonstrates potential efficacy against viral infections, including COVID-19, through two primary mechanisms: direct antiviral activity and modulation of host immune responses. Computational studies have identified key bioactive compounds, notably diosgenin and (+)-syringaresinol-O- β -D-glucoside, which exhibit high binding affinities to critical SARS-CoV-2 targets, including the spike protein and RNA-dependent RNA polymerase. These findings suggest that these compounds may inhibit both viral entry and replication^[102]. This high-affinity binding suggests a potential biophysical mechanism of action, wherein these compounds may sterically hinder the conformational changes of the viral spike protein required for host cell attachment and membrane fusion. Concurrently, the established immunoregulatory activities of Huangjing

polysaccharides, particularly through suppression of the TLR4/MyD88/NF- κ B pathway and NLRP3 inflammasome activation, may mitigate the excessive proinflammatory cytokine release (e.g., IL-6, TNF- α) associated with severe COVID-19 progression^[76, 103]. Extending the application of its bioactive polysaccharides, a novel surgical suture incorporating *Rhizoma Polygonati* polysaccharide (PRP) has been developed (Chinese Patent CN113509588A). This suture, fabricated from a composite of gelatin, silk fibroin, and PRP, represents a localized drug delivery system. It potentially offers adjunctive benefits in surgical contexts during the pandemic by providing sustained, localized immunomodulatory and antiviral activity at the wound site. These mechanisms align with its inclusion in TCM formulations recommended for COVID-19 management and recovery, underscoring its role within the medicinal-food homology framework in addressing viral threats and post-infection sequelae^[104].

3.2 Functional markers in health foods

These elucidated mechanisms provide the scientific basis for establishing functional markers in health products. Huangjing has emerged as a core functional ingredient in the global health food market due to its medicinal-food homology status. The association between its efficacy markers and health effects demonstrates significant scientific consensus alongside regional variations.

In metabolic regulation products, core functional markers include Huangjing polysaccharides (β -glucans with molecular weights of 50–200 kDa comprising mannose, galactose, and glucose, wherein PSPs feature branched mannans) and steroidal saponins such as dioscin^[32]. Huangjing polysaccharides enhance GLUT4-mediated glucose uptake through IRS1/PI3K/Akt pathway activation, whereas saponins regulate lipid metabolism by inhibiting fatty acid synthase (FASN)^[105]. Chinese products use polysaccharide content of $\geq 7\%$ (ChP 2020) as the basis for auxiliary blood glucose reduction claims. In contrast, international formulations such as Japanese *Polygonatum* extract granules incorporate low-degree polymerization fructans (DP 3–10) as supplementary markers, emphasizing their role in improving insulin resistance *via* gut microbiota-short-chain fatty acid modulation^[106]. For immunomodulation, acidic polysaccharides with galacturonic acid content exceeding 30% and specific glucuronic acid (GlcA)- β 1-3-Gal oligosaccharide sequences serve as primary markers. In vitro studies confirm their activation of macrophages through the TLR4/MyD88/NF- κ B signaling pathway, achieving 82% inhibition against H₁N₁ virus^[46]. These components constitute the functional core in 44.8% of commercial capsule formulations. Neuroprotective products focus on fucose-modified polysaccharides, such as Fuc- α 1-6-GlcNAc structures, and cycloartane saponins, such as cyrtomin. The European Food

Safety Authority requires saponin content of at least 5% to ensure clinical efficacy, evidenced by 2.7-point improvements in montreal cognitive assessment (MoCA) scores through mechanisms involving downregulation of the BAX/BCL-2 ratio and inhibition of caspase-3^[107]. Anti-aging product standardization employs polyphenols, such as caffeoylquinic acids, and SOD-mimetic polysaccharides with processing-derived 5-hydroxymethylfurfural at or above 0.1% as an essential marker. An 18.7% lifespan extension in *C. elegans* correlates with DPPH radical scavenging and antioxidant enzyme enhancement^[108]. However, marker standardization faces dual challenges, with processing methods significantly impacting component-efficacy relationships, as demonstrated by steamed Huangjing showing a negative correlation between adenosine content and immunomodulatory effects, necessitating quantitative processing-component transformation-efficacy models. Additionally, international standards require cross-species bioavailability evidence, such as Caco-2 cell absorption of at least 15%, which traditional marker studies often lack, highlighting the critical role of standardized efficacy markers in product development.

3.3 Product applications

As a core resource of medicinal-food homology, Huangjing exhibits diversified applications in global markets, with health effects primarily targeting antioxidant activity, metabolic regulation, immune enhancement, and neuroprotection, aligning with all functional categories in China's Health Food Function Catalog (2023 Edition)^[32]. As of July 2025, market data from registered health food products in China reveal a dual-core functional claim dominance among 353 Huangjing-containing formulations, which predominantly rely on total extract and modernized ancient formulation technologies, with diversified extensions across the sector. Fatigue alleviation claims constituted 162 products (45.9%), while immunity enhancement featured in 157 products (44.5%), collectively accounting for 90.4% market share (Fig. 7A). This distribution reflects the well-established scientific basis of Huangjing-derived polysaccharides and saponins, which modulate metabolic homeostasis through mechanisms such as GLUT4 translocation *via* IRS1/PI3K/Akt activation, supporting fatigue alleviation claims. Concurrently, these bioactive compounds regulate immune responses, including macrophage activation through TLR4/MyD88/NF- κ B signaling, underpinning immunity enhancement functionalities^[109]. Auxiliary blood glucose control involving 49 products and lipid regulation covering 13 products constitute emerging growth areas highlighting Huangjing's value in metabolic syndrome intervention while specialty functions including antioxidant effects melasma improvement and sleep enhancement leverage multi-target activities such as SOD/GSH-Px antioxidant enzyme

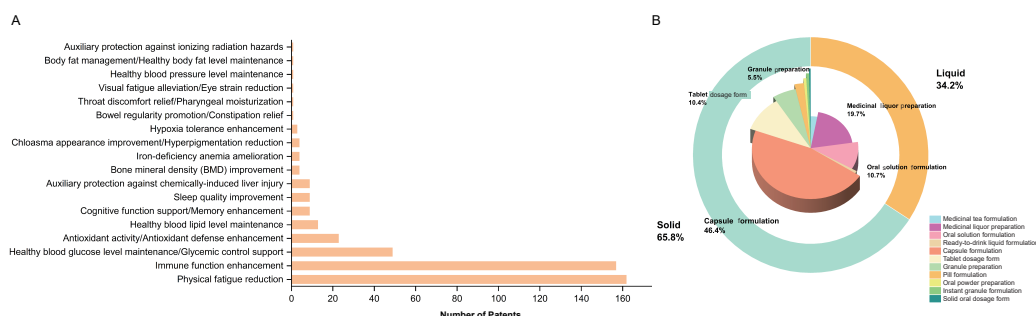


Figure 7 Health function claim analysis (A) and formulation distribution (B) of Huangjing-containing health products in China.

activation. Product formulations are predominantly solid at 65.6% alongside liquid forms at 34.2% primarily as capsules tablets and oral solutions providing versatile carriers for pharmaceutical nutraceutical and cosmeceutical development. These distinct functional claims and versatile dosage forms underpin Huangjing's applications across three major sectors including pharmaceuticals functional foods and cosmetics as detailed below (Fig. 7).

3.3.1 Pharmaceutical products

Huangjing holds a fundamental position in pharmaceutical development, seamlessly integrating its identity as a medicinal-food homologous resource into evidence-based therapeutic strategies. Its pharmaceutical applications are strategically developed across three primary functional domains, each leveraging distinct bioactive constituents and validated mechanisms within commercial products^[32].

The management of metabolic disorders represents a core application. This function is primarily driven by steroidal saponins, such as dioscin, which enhance glucose uptake in skeletal muscle through activation of the IRS1/PI3K/Akt pathway^[110]. Formulations such as Huangjing saponin capsules and traditional preparations, including Jiuzhuan Huangjing Pills, embody this application. Clinical evidence supports their utility, with studies indicating that co-administration of Huangjing saponins can reduce urinary protein by 42% in patients with diabetic nephropathy, an effect mediated through modulation of the AMPK/PI3K-Akt pathway^[111].

In the domain of neuroprotection, Huangjing polysaccharides serve as the principal active components. Standardized polysaccharide extracts have demonstrated efficacy in improving cognitive function in models of AD. Their mechanism involves downregulation of the BAX/BCL-2 ratio and inhibition of caspase-3 activity. Complementary bioactivity is provided by Huangjing cyclopeptides, which promote serotonin release *via* σ -1 receptors, contributing to measurable cognitive improvements in clinical observations^[112]. For immunomodulation, specific acidic polysaccharide fractions are utilized. These components, particularly those containing over 30% galacturonic acid, function by enhancing natural killer cell cytotoxicity through the TLR4/NF- κ B signaling pathway. This scientific foundation supports both complex traditional prescriptions and modern, single-function extracts, the latter often standardized to contain a minimum of 7% polysaccharides in accordance with pharmacopeial standards to ensure consistency and compliance^[113].

Collectively, the pharmaceutical application of Huangjing operationalizes the medicinal-food homology concept through a dual trajectory. It preserves the holistic, multi-target approach inherent in traditional formulations while simultaneously advancing standardized, quality-controlled products for targeted therapeutic interventions. This synthesis of traditional wisdom and modern scientific rigor facilitates its integration into diverse global pharmaceutical markets and regulatory frameworks.

3.3.2 Functional foods and beverages

As a certified medicinal-food homologous substance, Huangjing possesses a recognized safety profile and a robust scientific foundation for use in functional foods and beverages. Its application capitalizes on the intrinsic bioactivities of its polysaccharides and saponins, enabling the development of products that seamlessly integrate nutritional value with targeted

health benefits, thereby realizing the concept of food as medicine^[14]. A prominent application lies in energy and fatigue-alleviation products. This functionality is largely attributed to Huangjing fructans with a low degree of polymerization (DP). These compounds resist digestion in the upper gastrointestinal tract and are fermented by colonic microbiota into SCFAs. Subsequent activation of the AMPK/PGC-1 α pathway enhances mitochondrial biogenesis, which underlies a documented 40% extension in endurance capacity^[114]. This mechanism has been translated into commercial formulations, including ready-to-drink functional beverages and granulated extracts designed as beverage additives. Commercial data indicate that such products have gained significant traction, particularly within the sports nutrition and consumer health sectors targeting physical fatigue management^[115].

Another significant domain involves metabolic and gut health modulation. The synergy between Huangjing polysaccharides and gut microbiota is central to this process. Huangjing polysaccharides derived from *Polygonatum* are metabolized by intestinal bacteria to produce SCFAs, including acetate and butyrate, which subsequently enhance glucose and lipid homeostasis. Clinical evidence indicates that Huangjing polysaccharide interventions can reduce hepatic triglyceride levels by 39% in patients with NAFLD^[106]. These scientific findings drive product innovation in diverse sectors, including prebiotic supplements, functional baked goods with low glycemic indices, and synbiotic beverages. The increasing consumer emphasis on gut health further amplifies the market potential for such Huangjing-enriched products^[116].

Traditional culinary applications continue to flourish through modernized formats, thereby reinforcing cultural acceptance. Classic preparations such as Huangjing-stewed chicken and herbal cakes are being reimagined as convenient, standardized health food products. Furthermore, innovative products such as Malaysian Huangjing coffee, which incorporates a 34.7% liquid extract, demonstrate successful localization and appeal to younger demographics by addressing contemporary wellness trends within familiar consumption contexts^[117].

In essence, the evolution of Huangjing in functional foods and beverages transcends mere ingredient incorporation. It represents a systematic translation of mechanistic research into diverse product formats that bridge traditional dietary culture with modern nutritional science. This approach consolidates its position within the functional food industry, where demand for ingredients possessing dual heritage and evidence-based efficacy continues to increase^[56].

3.3.3 Cosmeceuticals and personal care

The incorporation of Huangjing into cosmetic and personal care formulations is grounded in scientifically validated dermatological benefits associated with its bioactive constituents, primarily their antioxidant, anti-inflammatory, and moisturizing properties. Leveraging its status as a medicinal and edible homologous ingredient, Huangjing facilitates the development of cosmeceuticals that offer multifunctional skin benefits, thereby effectively bridging the gap between topical application and systemic wellness^[118].

Anti-aging and antioxidant serums represent a predominant application category. The efficacy observed in this domain originates from the synergistic action of Huangjing polysaccharides and flavonoids. Specific Huangjing polysaccharide fractions exhibit potent free radical scavenging capacity, effectively

neutralizing DPPH radicals while concurrently elevating the activity of endogenous antioxidant enzymes including SOD and GSH-Px^[46]. Concurrently, Huangjing flavonoids inhibit tyrosinase activity, thereby attenuating melanin overproduction and ameliorating photoinduced hyperpigmentation. These mechanistic properties have been leveraged in high-performance anti-aging serums and targeted periorbital treatments prevalent in East Asian and European markets. Furthermore, the natural antioxidant positioning of flavonoid-based ingredients is substantiated in the European Union through REACH compliance and EU Cosmetics Regulation (EC) No 1223/2009, reinforcing consumer confidence and market access^[119].

Skin brightening and even-toning formulations leverage targeted bioactive compounds, notably Huangjing homoisoflavonoids endemic to the Asparagaceae family and specific phenolic acids, which directly modulate melanogenic pathways. Their amphipathic nature enables integration into cellular lipid bilayers, providing a biophysical mechanism for membrane stabilization and suppression of inflammatory mediators that trigger hyperpigmentation. This mechanistic rationale underpins the development of whitening essences, spot-correcting serums, and brightening moisturizers. In South Korean markets, these ingredients are frequently incorporated into patented polysaccharide-hyaluronic acid complexes, clinically validated for potent free radical scavenging activity, thereby securing competitive differentiation in the saturated dermocosmetic sector^[120].

Barrier repair and enhancement formulations represent a pivotal therapeutic category. Huangjing steroidal saponins—notably dioscin—modulate epidermal homeostasis by upregulating hyaluronic acid synthase expression and augmenting intercellular lipid synthesis, thereby improving stratum corneum hydration and barrier function. Instrumental assessments using corneometry have demonstrated significant increases in skin hydration parameters following topical application of saponin-enriched preparations^[121]. These mechanistic properties are leveraged in restorative creams, barrier repair emulsions, and overnight reparative formulations specifically indicated for sensitive or compromised skin conditions. The emerging paradigm of skinimalism, characterized by minimalist yet high efficacy skincare routines centered on barrier restoration, converges strategically with this therapeutic application, thereby catalyzing both product innovation and consumer market penetration^[122].

The overarching development of Huangjing in cosmeceuticals reflects a holistic “inside-out” philosophy. This approach aligns topical skincare with the systemic health benefits derived from its consumption as a functional food, promoting a synergistic route to skin wellness. By translating traditional knowledge of its nourishing properties into modern, evidence-based cosmetic science, Huangjing is establishing a durable and sophisticated presence in the global personal care industry, meeting the demand for multifunctional, natural, and scientifically credible ingredients.

3.4 Advanced delivery systems for pharmaceutical applications

The pharmacological translation of Huangjing bioactives, including polysaccharides, saponins, and homoisoflavonones, remains constrained by inherent pharmacokinetic limitations, notably low oral bioavailability, poor physicochemical stability, and absence of tissue-specific targeting. To address these barriers, self-microemulsifying drug delivery systems (SMEDDS) have been

employed to enhance the lymphatic transport and intestinal absorption of lipophilic saponins, while cyclodextrin inclusion complexes improve the aqueous solubility and epithelial permeability of flavonoids through host-guest molecular interactions^[123].

Leveraging enhanced systemic exposure, active targeting strategies have been strategically implemented to achieve site-specific accumulation, particularly in oncological and inflammatory indications. The inherent immunomodulatory and antineoplastic activities of Huangjing polysaccharides and saponins, mediated *via* TLR4/NF- κ B and PI3K/Akt signaling cascades, furnish a mechanistic foundation for the rational design of ligand-conjugated delivery platforms that selectively home to immune cells or tumor microenvironments. Complementarily, stimuli-responsive systems engineered for triggered release under pathological conditions, exemplified by acidic pH or elevated enzymatic activity, confer additional spatial and temporal precision in therapeutic delivery^[124].

A distinctive advantage of Huangjing polysaccharide-based carriers resides in their intrinsic pharmacological activity that extends beyond passive drug transport. The structural attributes of these polysaccharides, encompassing molecular weight distribution and monosaccharide composition, facilitate the self-assembly of stable nanocomplexes and direct biological interactions. This carrier-as-drug paradigm is substantiated by documented synergistic anti-inflammatory and antioxidant effects between Huangjing polysaccharides and saponins *in vivo*, complemented by the established anti-fatigue and immunomodulatory properties inherent to the carrier material^[125].

Collectively, Huangjing polysaccharides constitute an optimal foundational material for intelligent drug delivery systems by virtue of their natural origin, favorable biocompatibility, tunable physicochemical properties, and intrinsic bioactivity. Future research priorities should encompass the rational design of multi-stimuli-responsive platforms for controlled release, mechanistic elucidation of synergy between carrier and drug payloads, and the establishment of standardized scalable manufacturing processes to advance these systems toward clinical translation. The convergence of these advanced delivery technologies with the characterized bioactivities of Huangjing constituents is poised to unlock the full therapeutic potential of this traditional medicinal resource^[126, 127].

4 Quality control

The analyses in preceding chapters underscore a central paradox: despite vibrant innovation activity and increasingly well-defined health mechanisms, the translation of Huangjing potential into stable, high-value global products remains impeded. Germplasm heterogeneity, empirical processing methodologies, and inadequate quality standards constitute pivotal bottlenecks that sever the critical link between scientific insight and market-ready consistency. As a multi-sourced medicinal herb, Huangjing faces persistent quality control challenges encompassing raw material variability, insufficient process standardization, absence of original-constituent correlation models, and inadequate long-term toxicological data. These deficiencies precipitate substantial fluctuations in active compound profiles, exemplified by polysaccharide content variations ranging from 7.73% to 27.64% across germplasm resources, while simultaneously exacerbating adulteration risks throughout the supply chain.

Therefore, establishing an integrated quality control framework encompassing origin traceability, processing standardization,

constituent fingerprinting, and safety assessment has become imperative for sectoral advancement. Such a system, aligned with modern scientific and industrial imperatives, would fundamentally reconcile traditional empirical practices with evidence-based standardization, thereby ensuring batch-to-batch consistency and facilitating global market access for this traditional medicinal resource^[128].

4.1 Raw material heterogeneity and origin effects

The inherent genetic and chemotypic complexity of Huangjing germplasm resources fundamentally compromises quality consistency, given that the ChP recognizes three distinct species, namely *P. sibiricum*, *P. kingianum*, and *P. cyrtoneuma*, as interchangeable medicinal sources despite pronounced interspecific variations in bioactive constituents. Notably, *P. cyrtoneuma* exhibits the highest polysaccharide content up to 27.64%, substantially exceeding *P. kingianum* at 15.12% and *P. sibiricum* at 16.26%, whereas *P. cyrtoneuma* from Guizhou Liuzhi demonstrates markedly elevated flavonoid levels at 1.91% in biennial cultivation, contrasting with 0.66% in quinquennial material and merely 0.14% in *P. sibiricum*. These disparities originate from ecological factors profoundly modulating secondary metabolic pathways. Firstly, suboptimal temperature and light stress in high-altitude cultivation zones activates polysaccharide biosynthesis as an adaptive physiological response. Secondly, intercropping under forest canopy with 40%–60% shade density enhances soil organic matter accumulation and modulates rhizosphere microbial communities, thereby elevating saponin and polysaccharide levels relative to open-field cultivation^[129]. Thirdly, soil physicochemical properties profoundly modulate secondary metabolic pathways. Zinc availability influences metallothionein-related gene expression and may enhance cyclopeptide biosynthesis in specific cultivation systems. Furthermore, light quality directly regulates photosynthetic efficiency and tuber development. Experimental studies confirm that blue light significantly enhances chlorophyll synthesis and electron transport rates in *P. cyrtoneuma* and *P. sibiricum*, promoting subterranean tuber biomass accumulation, whereas red light induces photoinhibition and plant mortality in *P. cyrtoneuma* under extended exposure^[130,131]. Current quality standards exhibit critical limitations due to their exclusive reliance on polysaccharide content, stipulated at a minimum of 7.0% calculated as anhydrous glucose according to the ChP, as a singular quality indicator. This approach neglects quantitative requirements for saponins, flavonoids, and other bioactive compounds that contribute to the therapeutic efficacy and functional properties of Huangjing. Furthermore, the absence of quantifiable climate-soil-constituent correlation and prediction models impedes the translation of geographical advantages into standardized cultivation protocols, thereby compromising the consistency and traceability of medicinal materials across diverse production regions^[117,132]. Compounding these issues, deficient quality control and traceability systems intensify quality fluctuations, as total saponin content exhibits substantial variation among *Polygonatum* species and processing methods. Furthermore, adulteration with morphologically similar substitutes, notably *P. odoratum* (Yuzhu), introduces significant safety hazards and therapeutic inconsistencies. Collectively, these intrinsic variations and standardization shortcomings not only compromise raw material consistency but also impede downstream processing standardization, ultimately undermining

reliable quality assessment and safety assurance across the supply chain^[133,134].

4.2 Standardization challenges

4.2.1 Processing standardization bottlenecks

Modern research has elucidated efficacy-enhancing mechanisms underlying Huangjing processing. Polysaccharide cleavage into oligosaccharides enhances bioavailability, while Maillard reaction products including 5-hydroxymethylfurfural contribute to antioxidant activity^[135]. However, fundamental tensions persist between cultural heritage preservation and international standardization. China's intangible cultural heritage-certified *Jiu Zheng Jiu Shai* (Nine-Steamming-Nine-Sunning) technique mandates bamboo containers and natural sun-drying, whereas contemporary industrial standards permit metal utensils and mechanical drying, creating implementation challenges across global supply chains.

Three primary bottlenecks hinder standardization. First, species-process compatibility gaps remain unresolved. *P. kingianum* requires low-temperature prolonged processing to preserve polysaccharide activity, whereas *P. cyrtoneuma* benefits from high-temperature short-duration steaming (100 °C) to enhance flavonoid transformation^[27]. Despite China-led international standards regulating DNA barcoding identification and composition thresholds, these lack tiered process parameters even though response surface methodology demonstrates precise parameter tunability^[136]. Second, compositional degradation during industrialization poses significant challenges. Elevated-temperature hot-air drying causes substantial flavonoid reduction and 5-hydroxymethylfurfural loss^[137]. Although optimized low-temperature extraction techniques significantly shorten traditional processing cycles while improving saponin retention, these methods require supplementary near-infrared spectroscopy (NIR)-based real-time monitoring to maintain active component stability. Third, fragmented quality control data impede holistic optimization, as evidenced by disconnected datasets across cultivation, processing, and quality assessment stages. Establishing integrated quality markers (Q-markers) incorporating polysaccharide molecular weight distribution (10–100 kDa for immunomodulatory activity), fructose-glucose ratios, steaming-induced phenylpropanoids, and advanced chromatographic tracking methods would enable end-to-end data integration^[138,139].

Modern control systems address these challenges by quantifying critical processing nodes while bridging traditional practices with compliance to international standards including European Union functional ingredient requirements and FOSHU regulations.

4.2.2 Quality assessment limitations and safety risks

Standardization deficiencies directly contribute to safety concerns, with current quality control systems exhibiting three systemic limitations due to overreliance on single chemical markers such as polysaccharide content thresholds. First, significant false-positive risks emerge because the common adulterant *P. odoratum* contains comparable polysaccharide levels but lacks bioactive saponins while retaining the irritant verbascoside, which remains undetected by current standards^[140]. Second, synergistic mechanisms remain overlooked; Huangjing polysaccharide-saponin interactions enhance stability^[141], whereas conventional HPLC fingerprinting captures only limited saponin diversity, thereby missing high-potency low-abundance

constituents. Third, molecular identification limitations persist; standard chloroplast barcodes exhibit high interspecific homology within *Polygonatum*, and their discriminatory power is further compromised in processed rhizomes where genomic DNA degradation impedes polymerase chain reaction (PCR) amplification^[142]. Consequently, more discriminatory techniques such as sequence characterized amplified region (SCAR) markers derived from start codon-targeted polymorphisms remain excluded from pharmacopeial standards despite their demonstrated efficacy in authenticating other medicinal plant species^[143].

Safety research gaps further amplify risks. Acute toxicity studies demonstrate that processed Huangjing rhizome median lethal dose (LD₅₀) values exceed 20 g/kg in mice, while subchronic dosing induces intestinal mucosal alterations^[140]. Contamination presents serious concerns, with recent surveys indicating that wild and cultivated Huangjing resources exhibit varying degrees of heavy metal accumulation, particularly cadmium. Emerging biotic threats further compromise safety, exemplified by the first report of *Agroathelia delphinii*-induced rhizome rot in cultivated *P. cyrtoneura*, which affected approximately 40% of plants in outbreak fields^[144]. This pathogen not only reduces raw material supply but may also facilitate secondary metabolite accumulation, including potential phytotoxins, thereby exacerbating chemical contamination risks^[145].

The 5-hydroxymethylfurfural controversy epitomizes a dose-dependent efficacy-toxicity paradox. While this Maillard reaction product exhibits bioactivity at processing-relevant concentrations, its sulfotransferase-mediated metabolite 5-sulfooxymethylfurfural correlates with DNA adduct formation in mammalian systems^[146]. The absence of harmonized international standards creates regulatory fragmentation, with divergent approaches between precautionary EU limits, Japanese FOSHU functional-claim regulations, and Chinese manufacturer-dependent oversight^[147]. Resolution requires reconstructing quality control through integrated technological approaches. Source control employs unmanned aerial vehicle remote sensing for cultivation parameter monitoring^[148], while pathogen surveillance integrates rhizosphere microbiome analysis to prevent rot epidemics^[149]. Processing optimization utilizes kinetic modeling and spectroscopic monitoring, supplemented by molecular docking for saponin-CYP3A4 interaction prediction and functional bioactivity assessment^[150]. This integrated framework systematically addresses technical barriers to global compliance.

5 Future prospects

The future trajectory of the Huangjing industry is defined by the imperative to transition from a resource-centric model to an innovation-driven high-value sector. This evolution must be underpinned by a dual strategy that rigorously integrates scientific standardization with strategic cultural globalization. To achieve this, the industry must systematically address the interconnected challenges of germplasm heterogeneity, quality standard deficiencies, and technological limitations.

The establishment of a scientifically robust three-dimensional Q-marker system is paramount. Such a system directly responds to the critical limitations of relying on single chemical markers such as polysaccharide content alone^[151]. By integrating foundational specifications (e.g., polysaccharide molecular weight distribution), mechanism-informed biofunctional indicators (e.g., macrophage phagocytosis rate), and technology-driven

authenticity verification, it provides the necessary framework for ensuring product consistency, safety, and efficacy on a global scale. Concurrently, overcoming technological bottlenecks requires the convergence of synthetic biology and intelligent manufacturing. Engineered production platforms, exemplified by yeast strains achieving high saponin titers, offer a solution to raw material variability and enable the high-value single-compound development pathway^[152]. Complementing this, AI-controlled processing and advanced traceability systems are essential for standardizing traditional methods like Nine-Steam-Nine-Sunning, thereby ensuring product compliance and building trust across the supply chain^[151].

The development of intelligent multifunctional delivery platforms represents a crucial technological frontier, directly addressing the core challenges of low bioavailability and lack of targeting specificity inherent to many Huangjing bioactives. Advanced strategies including SMEDDS and cyclodextrin inclusion complexes enhance oral absorption^[153]. Furthermore, active targeting systems such as ligand-conjugated nanoparticles and stimuli-responsive platforms enable precise delivery to pathological sites^[154]. Integrating these smart delivery technologies with the proposed Q-marker system and sustainable production practices will be pivotal for developing next-generation Huangjing-based pharmaceuticals and nutraceuticals with superior clinical translatability^[135].

Scientific and technological advancement must be coupled with proactive cultural and market integration strategies. The commercial success of international competitors in creating premium branded products underscores the value of cultural resonance. Therefore, pursuing international recognition for intangible cultural heritage, such as traditional processing techniques, and developing culturally informed product narratives are not peripheral but central to value capture in the global wellness market. A structured translational pipeline is recommended to bridge these domains. This involves preclinical development of intelligent delivery systems to enhance bioavailability and targeting, clinical validation focused on conditions with strong preclinical evidence such as metabolic or immune disorders, and advocacy for harmonized international standards that recognize functional Q-markers and modern delivery platforms^[155].

In conclusion, the sustainable future of Huangjing depends on establishing a synergistic framework. This requires implementing precision quality control grounded in a multidimensional Q-marker system. Concurrently, the adoption of disruptive technologies is essential to enable consistent and scalable production. Furthermore, advanced delivery solutions must be developed to overcome existing bioavailability and targeting challenges. Finally, strategic cultural valorization will be integral to this process. Together, these interconnected strategies will transform Huangjing into a globally competitive, evidence-based health resource. This integrated approach not only fulfills national health initiative objectives but also establishes a replicable model for the modernization and global integration of medicinal-food homologous resources, ensuring their relevance and impact in the evolving landscape of global health.

6 Conclusion

The sustainable modernization of Huangjing depends on resolving core translational challenges, including germplasm variability, inadequate quality standards, and technological

limitations. These interconnected issues must be addressed through a comprehensive, multidimensional strategy. The principal bioactivities of this herb derive from synergistic interactions between polysaccharides and saponins, consistent with established market claims for fatigue relief and immune support. Progress necessitates adopting emerging biotechnologies, such as synthetic biology and intelligent manufacturing, to enhance production efficiency, consistency, and traceability. Critically, quality assessment must advance from reliance on single chemical markers toward a holistic, function-based quality-marker system integrating specifications, bioactivity, and authentication. Ultimately, modernization relies on a dual approach combining scientific standardization with cultural valorization, supported by a diversified intellectual property strategy encompassing formulations, extracts, and single compounds. This transformation shifts the industry from resource-based competition to innovation-driven integration within the global health landscape, reinforcing the role of Huangjing in national health initiatives and the broader modernization of traditional medicine.

Data availability

All data needed to support the conclusions in this review are presented in the manuscript. Additional data related to this paper may be requested from the corresponding author upon request.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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Author contribution statement

Yu-Ting Wang: Conceptualization, data curation, writing – original draft, writing – review & editing. **Li Soo Wong:** Data curation, validation, writing – original draft. **Yu Ding:** Data curation, validation, writing – original draft. **Jia-Rui Feng:** Data curation, validation. **Li-Li Liu:** Project administration, resources. **Da-Wei Song:** Project administration, funding acquisition. **Kang-De Bao:** Conceptualization, supervision, funding acquisition, writing – review & editing, project administration, corresponding author. **Zheng Xiang:** Conceptualization, supervision, writing – review & editing, project administration, corresponding author. All the authors have approved the final manuscript.

Informed consent

Not applicable.

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Use of AI statement

None.

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