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REVIEW

Chinese Herbal Medicine in Hypoxic Pulmonary Hypertension Treatment: Mechanisms, Progress, and Future Directions

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Abstract: Hypoxic pulmonary hypertension (HPH) is a severe subtype of pulmonary hypertension(PH) characterized by chronic lung disease or prolonged hypoxia, leading to pulmonary vascular remodeling and right heart failure. Traditional Chinese Medicine (TCM) has garnered significant attention for its potential therapeutic effects on HPH due to its minimal side effects, multiple target actions, affordability, and cultural acceptance. Recent studies have highlighted the potential of TCM in inhibiting pulmonary artery smooth muscle cell proliferation, modulating inflammation, and oxidative stress. This review aims to explore the mechanisms of action of TCM in treating HPH, focusing on its ability to modulate key signaling pathways involved in pulmonary vascular remodeling, such as PI3K/Akt, Nrf2, NF-κB, and RhoA/ROCK. The goal is to provide a comprehensive overview of the current progress and future directions in the application of TCM for HPH treatment. TCM demonstrates significant therapeutic potential in HPH by modulating signaling pathways involved in inflammation, oxidative stress, and pulmonary vascular remodeling. Key compounds such as taxifolin glycoside, resveratrol, and salidroside have shown promising effects in inhibiting abnormal proliferation of pulmonary artery smooth muscle cells (PASMCs) and reducing oxidative stress. These mechanisms contribute to the overall efficacy of TCM in preventing and treating HPH. By modulating key signaling pathways and exerting anti-inflammatory and antioxidant effects, TCM offers a promising therapeutic approach for HPH. Further research is needed to validate the clinical efficacy and safety of TCM formulations, and to explore the underlying mechanisms through modern scientific methods. The integration of TCM with modern medicine could provide new strategies for the treatment of HPH.

Keywords: hypoxic pulmonary hypertension, Chinese herbal medicine, antioxidant, mechanisms, vascular remodeling, signaling pathway

Introduction

Pulmonary Hypertension (PH): Overview and Pathogenesis

Pulmonary hypertension (PH) is caused by various diseases and mechanisms.[1] It involves structural and/or functional changes in pulmonary blood vessels that increase pulmonary vascular resistance and pulmonary arterial pressure, leading to clinical and pathophysiological syndromes that progress to heart failure or even death.[1] The key features of PH include excessive proliferation of pulmonary artery smooth muscle cells (PASMCs), increased extracellular matrix deposition, and inflammatory factor accumulation in the pulmonary vascular wall, all contributing to elevated pulmonary vascular

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resistance.[2] The diagnostic criteria for PH included mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest as measured by right heart catheterization.[3] Although the 6th World Symposium on PH lowered this threshold to 20 mmHg, this value is higher than that in healthy adults (14.0 ± 3.3 mmHg).[4] Epidemiological studies reported that various PH subtypes affect approximately 1% of the global population, and the prevalence of PH is as high as 10% in individuals older than 65.[5] The increase in smoking and global population aging have increased the prevalence of chronic obstructive pulmonary disease (COPD), which is closely related to smoking. Approximately 90% of patients with COPD have mPAP > 20 mmHg, with the prevalence of PH associated with COPD estimated at 39.2%.[6] On average, there is a 2-year gap between PH symptom onset and diagnosis. Early symptoms are often subtle, and progression can be rapid, leading to an average survival of only 2.8 years for untreated patients.[7] The pathogenesis of PH involves pulmonary arterial remodeling caused by excessive PASMC proliferation and pulmonary arterial endothelial cell (PAEC) injury, leading to immune responses by various cell types (B cells, T cells, neutrophils, dendritic cells).[8] Current treatments include non-pharmacological approaches such as lung transplantation and medications such as prostacyclins (prostaglandin I2, iloprost, or treprostinil), endothelin receptor antagonists (bosentan, ambrisentan, or macitentan), phosphodiesterase-5 (PDE5) inhibitors (sildenafil, tadalafil, or vardenafil), and L-type calcium channel blockers.[1] Despite improvements in pulmonary function and reduced hospitalizations, the 5-year mortality rate remains approximately 50%.[9]

Hypoxia-induced pulmonary hypertension (HPH) is a subtype of PH characterized by chronic lung disease or prolonged hypoxia, with exertional dyspnea as the primary symptom.[10] Current guidelines recommend long-term oxygen therapy as the primary treatment for HPH. However, this therapy only alleviates symptoms, and it does not address oxidative stress, enzyme imbalance, or related issues.[1] With the continuous exploration of reverse pharmacology and pre-clinical and clinical studies, new drugs are gradually emerging. Traditional Chinese medicine (TCM) has received extensive attention because of its advantages including minimal adverse reactions, multiple targets, and effectiveness through multiple pathways. Moreover, TCM is extracted from pure natural plants, thus meeting the requirements of safety and low costs. Currently, many Chinese herbal medicines are being studied clinically for HPH treatment. This paper reviews the use of TCM for HPH treatment over the past two decades, focusing on TCM monomers, compounds, and extracts. It discusses the inhibition of abnormal proliferation of PASMCs via antioxidative pathways and summarizes the mechanisms of action of TCM and its use in HPH treatment strategies.

PH: Pathogenic Factors and Subtypes

The pathogenesis of PH is multifactorial, resulting from the complex interaction of various factors and pathways, including external and internal influences, interactive factors, various vasoactive molecules, multiple ion channels, and multiple signaling pathways (Figure 1).[1] Pulmonary vasoconstriction, pulmonary vascular remodeling (PVR), and in situ thrombosis formation are the main pathological changes in PH, and they are primarily associated with impaired pulmonary vascular endothelial function caused by an imbalance between vasodilators and vasoconstrictors (nitric oxide [NO]/endothelin-1 [ET-1]),[11] abnormal PASMC proliferation, local inflammation accumulation, immune dysregulation, mitochondrial dysfunction, and metabolic reprogramming, among other factors.[12] Excessive PASMC proliferation and resistance to apoptosis leading to vascular remodeling are the primary pathological features of PH.[13,14] PH can be classified into five subtypes based on differences in pathophysiology and treatment strategies:[15] pulmonary arterial hypertension attributable to arterial causes, PH caused by left heart disease, PH attributable to lung diseases and/or hypoxia, chronic thromboembolic PH and other pulmonary artery obstructions, and pulmonary arterial hypertension of unclear multifactorial mechanisms. Each subtype can be divided into numerous subclasses (Figure 1).

HPH: Mechanisms and Current Treatments

HPH is a progressive syndrome triggered by chronic hypoxia or lung disease, and exertional dyspnea is a key symptom.[16,17] The pathogenesis of HPH involves a shift from compensatory functional changes to decompensatory structural damage, progressing from hypoxic pulmonary vasoconstriction (HPV)[18] to PVR.[19]

Under physiological conditions, the pulmonary circulation features high flow, low pressure, and low resistance. During hypoxia, small pulmonary arterioles constrict, thereby redirecting blood flow to well-ventilated lung segments, optimizing gas exchange.[20] If hypoxia is localized, then HPV can improve the partial pressure of oxygen in arterial blood

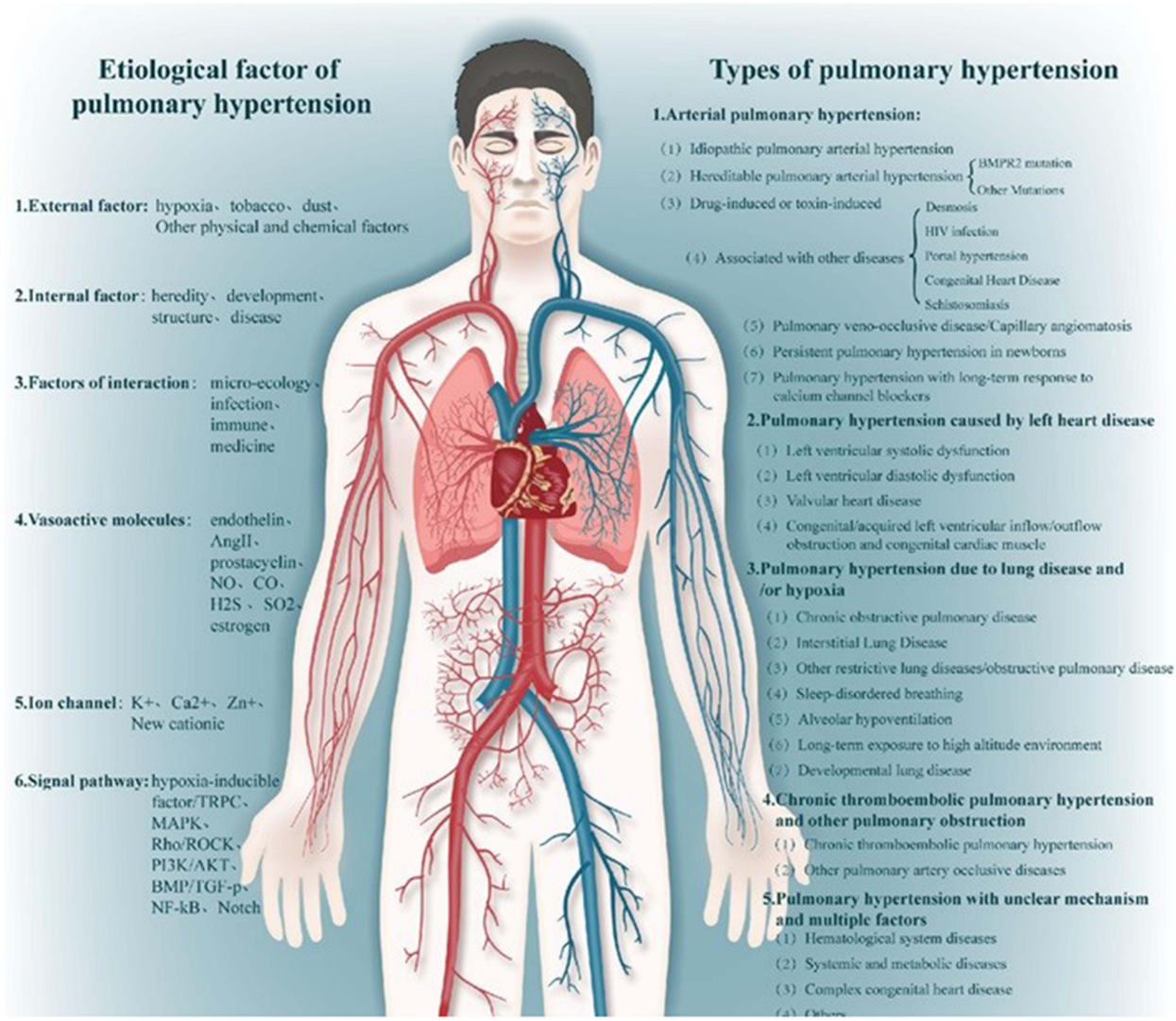

Figure 1 Pathogenic factors and subtypes of pulmonary hypertension.

(PaO_2), most effectively when the hypoxic lung volume is 30%–70%. The impact on PaO_2 can be negligible if the area of vascular constriction is small. Thus, transient HPV can divert blood flow from hypoxic lung segments, serving as a physiological compensatory mechanism to adapt to adverse reactions and protect PaO2.[21] However, prolonged hypoxia causes sustained pulmonary vasoconstriction, leading to increased vascular stiffness, narrowed arterial lumina, and elevated blood viscosity. Consequently, chronic HPV is detrimental, promoting HPH and increasing the workload of the right ventricle.

Continuous functional changes in the pulmonary vasculature inevitably result in structural damage. When hypoxia persists beyond the organism's compensatory capacity, the pulmonary vessels undergo structural remodeling. This process involves several mechanisms. Specifically, pulmonary arteries, composed of the intima, media (PASMCs), and adventitia, generate excess reactive oxygen species (ROS) under prolonged hypoxia. Chemotactic factors such as CCR5 recruit inflammatory factors including interleukin (IL)-1β, IL-6, macrophage migration inhibitory factor, and high mobility group box 1 protein (HMGB1), which accumulate around the vessels.[22] As pulmonary vessels contract, ROS and inflammatory factors enter the pulmonary arterial vasculature, initially causing endothelial cell injury in response to chronic inflammation. Because of impaired endothelial barrier function, there is an imbalance in released vasodilatory substances (such as NO, angiotensin II, thromboxane A2), further exacerbating vascular constriction. Simultaneously, because of changes in vascular morphology, the cellular interstitial spaces widen. Growth factors produced by the intima

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(such as platelet-derived growth factor [PDGF], transforming growth factor-β1 [TGF-β1], fibroblast growth factor-2, and vascular endothelial growth factor [VEGF][23]) interact with PASMCs through these spaces, leading to the abnormal proliferation and migration of these cells.[24] ROS can also promote the activation and expression of multiple growth factors, including phosphatidylinositol 3-kinase (PI3K)/Akt, p38 mitogen-activated protein kinase (MAPK), c-Src, TGF-β1, and VEGF. These growth factors can in turn stimulate ROS production, forming a local positive feedback loop. In addition, the mitochondrial apoptosis pathway mediated by ROS plays a crucial role in pulmonary arterial remodeling. Using rat models of HPH, multiple studies demonstrated that the Bax/Bcl-2 ratio is decreased, mitochondrial membrane potential is increased, permeability is reduced, apoptosome formation is decreased, and cleaved caspase-3 expression is decreased, thereby inhibiting PASMC apoptosis and ultimately causing pulmonary arterial remodeling.[25,26] The development of HPH represents an adaptive response of pulmonary vascular cells to hypoxia, including gene expression changes and structural readjustments in response to long-term hypoxic conditions. The process of PVR involves various factors such as local immune inflammatory responses, oxidative imbalance, the dysfunction of endothelial cells and fibroblasts, and the abnormal proliferation and apoptosis inhibition of PASMCs.[27,28]

HPH represents an adaptive response to chronic hypoxia involving gene expression changes in the pulmonary vasculature that lead to metabolic, functional, and structural readjustments. Endothelial-to-mesenchymal transition (EndMT) also plays a significant role in PVR.[29,30] In chronic lung diseases such as obstructive pulmonary disease or pulmonary fibrosis, hypoxia-sensitive genes are highly expressed, contributing to the progression of HPH.[31,32] This uncontrolled pressure eventually increases the load on the right heart, potentially leading to structural changes or failure, earning HPH the nickname "cancer of cardiovascular diseases"[17] (Figure 2).

Unlike other forms of PH, HPH lacks specialized targeted drugs. Treatment primarily relies on consensus-driven combination therapies, as recommended by domestic and international experts. The Diagnosis and Treatment Guidelines for Pulmonary Arterial Hypertension in China (2021 Edition) recommend long-term oxygen therapy for HPH caused by

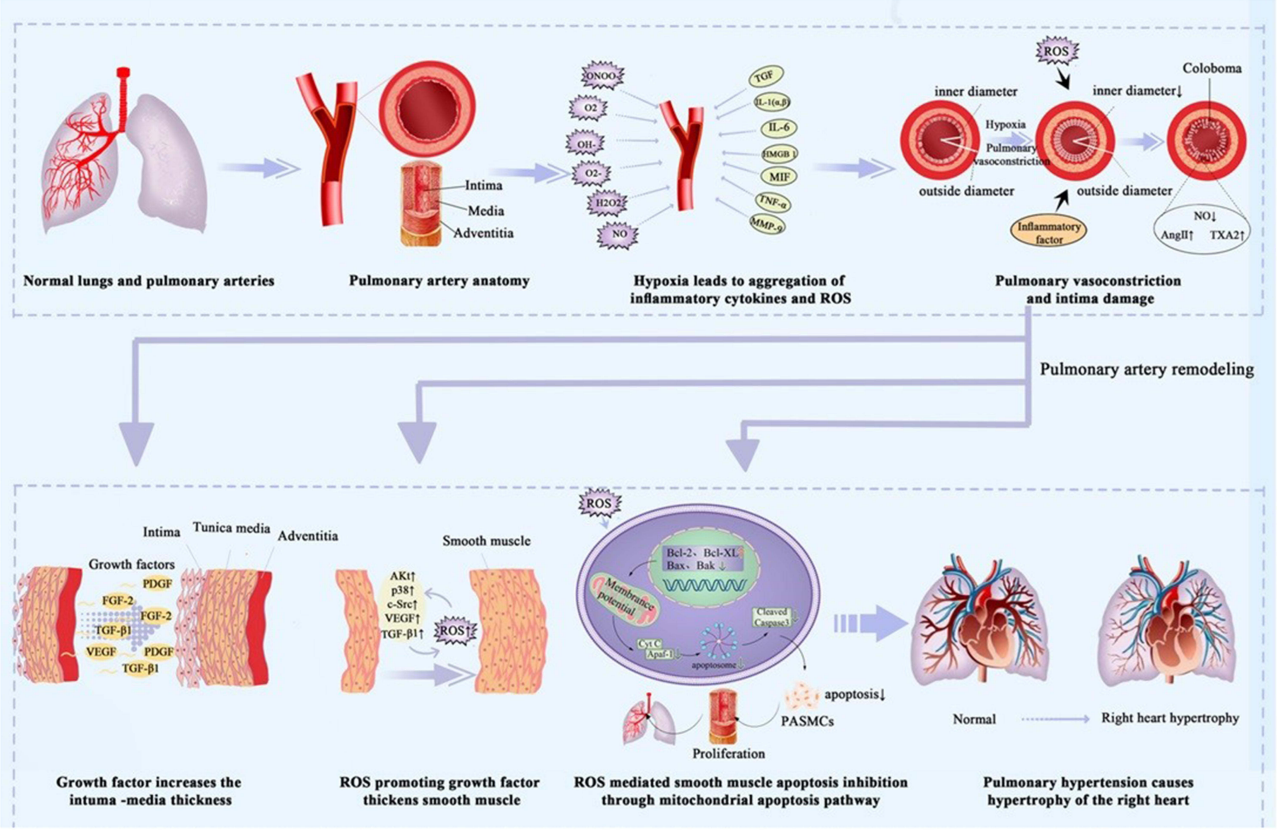

Figure 2 Pathogenesis of HPH.

lung diseases and/or hypoxia.[1] Nevertheless, these combinatorial regimens elevate risks of adverse effects and impose substantial economic burdens, underscoring the unmet need for superior therapeutic options.[4]

TCM offers promising potential for HPH treatment. TCM is known for its wide range of pharmacological activities, including anti-cancer, antioxidant, neuroprotective, anti-inflammatory, and anti–COVID-19 effects.[33] Research has demonstrated that herbal TCMs can protect against HPH by reversing the abnormal proliferation of PASMCs caused by hypoxia,[34,35] thereby reducing pulmonary arterial pressure.

Chinese Herbs: Compounds, Monomers, and Derivatives

TCM originated in early human history, rooted in the long-term interactions of the Chinese people with nature. The legend of Shennong, known as the "Divine Farmer" or "Emperor of Medicine" symbolizes the beginnings of TCM during the Neolithic Age. During this period, primitive agriculture emerged, and people began to understand the medicinal properties of various crops and natural substances. Over generations, ancient scholars documented and clinically applied approximately 12,000 medicinal plants, leading to TCM's widespread recognition and global influence.[36]

Today, more than 80% of the population in developing countries relies on traditional herbal medicine for basic healthcare.[37] TCM is typified by its unique medicinal substances and its multi-level, multi-target therapeutic effects, which have garnered international attention. However, because of the complexity of TCM components and limited analytical methods, only a few TCM products, such as sodium tanshinone IIA sulfonate (STS), beetroot juice, epicatechin, tetramethylpyrazine phosphate, and rosuvastatin combined with garlic extract, have been approved by the FDA and CFDA for therapeutic use.[38] Although large-scale randomized controlled trials have not provided convincing evidence of its therapeutic effects, TCM is widely used in routine medical care and preclinical research. TCM is applied in forms such as decoctions (herbal soups made by boiling medicinal herbs in water and then straining out the residue), powders (ground into powder form and encapsulated), pills, ointments, tinctures, tablets, infusions, and injections.

Chinese Herbal Compounds (CHCs)

CHCs, as multi-component natural medicines, offer multi-target efficacy and synergistic effects across multiple pathways, differing fundamentally from Western medicine in HPH diagnosis and treatment.[39] CHC prescriptions often focus on promoting qi and blood circulation, improving fluid metabolism, and resolving phlegm.[40] Various CHC forms (decoctions, capsules, injections) are widely used in pre-clinical HPH models, displaying effectiveness in delaying or inhibiting disease progression.

For example, Tongxinluo is a CHC that reduces hypoxia-induced endothelial damage by downregulating intercellular adhesion molecules (ICAM-1, ICP-1), hypoxia-inducible factor 1α (HIF-1α), VEGF, and ET-1 while regulating eNOS and iNOS expression, thus increasing NO activity in HPH rats.[41,42] Another study demonstrated that San-huang-xie-xin-tang, composed of Huanglian (*Coptis chinensis* Franch.), Huangqin (*Scutellaria baicalensis* Georgi), and Dahuang (*Rheum palmatum* L.), significantly reduces U46619-induced arterial hypertension by downregulating PDE5, Rho kinase (ROCK) II, and cyclooxygenase-2 (COX-2) and upregulating soluble guanylate cyclase 1 (sGC1).[43] Lu et al reported that Qiliqiangxin capsules composed of Huangqi (*Astragalus membranaceus* (Fisch.) Bunge), Renshen (*Panax ginseng* C.A. Mey.), Wutou (*Aconitum carmichaelii* Debeaux), Danshen (*Salvia miltiorrhiza* Bunge), Rougui (*Cinnamomum cassia* (L.) J.Presl), Honghua (*Carthamus tinctorius* L.), Gangliao (*Polygonum aviculare* L.), and Chenpi (*Citrus reticulata* Blanco) directly restore mitochondrial function and structure, modulate apoptosis pathways, and reverse right ventricular remodeling attributable to HPH.[44] Wu et al conducted network pharmacology analysis, revealing that the Qishen Yiqi formula targets therapeutic pathways in pulmonary arterial hypertension and significantly modulates PI3K-Akt, MAPK, and Hif-1 signaling pathways.[45]

Highly cited studies from China also highlighted CHCs such as Xuefu Zhuyu decoction and Qibai Pingfei lung capsules, which improve PVR and reduce inflammation by modulating pathways such as PI3K/Akt and JAK1/STAT3.[46,47] Details of the composition and mechanisms of CHCs are presented in Table 1.

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Table 1 The Mechanism of Action of Chinese Herbal Compounds and the Diseases They Treat

Compound	Ingredients	Mechanisms	Study Type	Play a Therapeutic Role in the Following Diseases	References
Tongxinluo	Ginseng, leech, scorpion, native turtle, centipede, cicada, red peony, incense, frankincense, sour jujube kernel (fried), sandalwood, borneol, etc.	IL-6↓, tumor necrosis factor (TNF)-α↓, calcineurin ↓, nuclear factor of activated T cells (NFATc3)↓, ICAM-1↓, ICP-1↓, HIF-la↓, VEGF↓, ET-1↓, iNOS↓ eNOS↑, NO↑, K^+↑	Animal experiment, clinical trial	Ischemic stroke, Atherosclerotic cerebrovascular disease	[41,42]
Sanhuang Xiexin decoction	*Coptis, Scutellaria*, rhubarb	PDE-5↓, ROCKII↓, COX-2↓ sGCa1↑, sGCβ1↑	Animal experiment	Chronic gastritis, Metabolic syndrome and type 2 diabetes, Oral ulcer, Liver disease	[43]
Qiliqiangxin capsule	*Astragalus*, cassia twigs, ginseng, aconite, *Draba, Alisma*, bamboo, orange peel, safflower, *Salvia miltiorrhiza*, Xiangjia peel	TGF-β1/Smad3↓, TNF-α↓, PVR↓, myofibroblasts↓ peroxisome proliferator-activated receptor γ ($PPAR_{\gamma}$)↑, PAECs↑	Animal experiment	Chronic heart failure, Arrhythmia	[44]
Xuefu Zhuyu decoction	*Angelica sinensis*, Shengdi, Chuanxiongxiong, peach kernel, safflower, *Fructus aurantii*, red peony root, bupleurum, licorice, *Platycodon, Achyranthes papyrus, Draba nemorosa, Astragalus, Salvia miltiorrhiza*	ET-1↓, proliferating cell nuclear antigen (PCNA)↓, PASMCs↓ NO↑, PAECs↑, caspase 3↑	Animal experiment, clinical trial	Coronary Heart Disease, Heart Failure, Chronic Obstructive Pulmonary Disease。	[46]
Qibaipingfei capsule	*Astragalus membranaceus*, Chuanxiongxiong, Schisandrae, Dilong, *Allium macrostemon, Draba nemorosa*, raw sun-dried ginseng	ET-1↓, IL-6↓, TNF-α↓, calcineurin↓, NFATc3↓ NO↑, K^+↑, anti-inflammatory↑, PAECs↑	Animal experiment	Chronic Obstructive Pulmonary Disease	[47,48]
Sandalwood powder with three flavors	Sandalwood, nutmeg, jujube	p27Kip1↓, PCNA↓, α-SMA↓, cyclin D1↓, CDK4↓, PASMCs↓	Animal experiment	Cardiovascular disease, Diabetes mellitus, Gastric ulcer	[49]
Compound Xiebai capsule	*Allium macrostemon*, melon wilt, *Pinellia, Coptis*, white wine	NF-kB↓, caspase 3↓, vascular cell adhesion molecule-1 (VCAM-1) ↓, ICAM-1↓ anti-inflammatory↑, Bcl-2↑, PAECs↑	Animal experiment	Chronic Obstructive Pulmonary Disease, Chronic Bronchitis, Severe Pneumonia	[50]
Feixin decoction	Peach kernel, safflower, Red peony, *Salvia miltiorrhiza*	HIF-1α↓, VEGF↓, PASMCs↓	Animal experiment	Novel Coronavirus Pneumonia (COVID-19)	[51]
Seven Dragon Heavens	Notoginseng, earth dragon, *Rhodiola*	HIF-1a↓, ET-1↓, IL-1β↓, TNF-a↓, VEGF↓ NO↑, anti-inflammatory↑	Animal experiment	Chronic Obstructive Pulmonary Disease, Chronic Pulmonary Heart Disease, Pulmonary Interstitial Fibrosis	[52]
Tuckahoe licorice soup	Tuckahoe, licorice, ginger, laurel branch	TGF-β1↓, p53↓, PCNA↓, PASMCs↓	Animal experiment	Arrhythmia, Rheumatic Heart Disease, Rheumatoid Arthritis	[53]
Breviscapine injection	Cedrin, a small amount of breviscapine and other flavonoid glycosides	ET-1↓, PASMCs↓, PKC↓ PAECs↑, NO↑	Animal experiment, clinical trial	Acute cerebral infarction, Coronary heart disease with angina pectoris	[54]

Notes: Most CHC formulations used for HPH treatment remain in the experimental animal stage, whereas only a small portion are applied clinically. Because of the lack of guidelines and regulations on dosage and drug stability, strict control is necessary for the clinical application of CHCs. The ↑ and ↓ symbols in the table indicate increased or decreased expression levels of the corresponding factors/proteins, respectively.

Chinese Herbal Monomers (HMs) and Their Derivatives: Mechanisms

The therapeutic mechanism of HMs involves reducing inflammatory and vascular growth factor levels, regulating Ca^{2+} and K^+ channels, restoring mitochondrial function, and controlling signaling pathways to achieve pulmonary artery vasodilation, protect endothelial function, and reverse PVR.[55]

Anti-Inflammatory

Inflammation plays a crucial role HPH development, with lesions in patients with HPH containing chemotactic factors and inflammatory mediators such as TNF, IL-6, IL-1β, and TGF-β1.[12] In HPH rat models, inflammatory cells, including T cells, B cells, macrophages, dendritic cells, and mast cells, infiltrate around pulmonary vessels and contribute to PVR.[56] These immune cells are correlated with disease severity and survival, making them potential therapeutic targets for HPH.[57]

Monocyte chemoattractant protein-1 (MCP-1), also known as CC-motif chemokine ligand 2 (CCL2), belongs to the CC chemokine family. MCP-1 promotes the progression of inflammation by attracting inflammatory factors to migrate and infiltrate the local microenvironment. Activation of the NF-κB pathway increases MCP-1 expression and stimulates the proliferation of PASMCs.[58] Resveratrol can downregulate MCP-1 by inhibiting the NF-κB signaling pathway, thereby reducing damage to PAECs and suppressing abnormal PASMC proliferation.[59,60] The NF-κB signaling pathway is a classical anti-inflammatory pathway widely targeted in PH treatment. Puerarin, betaine, and baicalin can also alleviate the accumulation of inflammatory factors around pulmonary arteries by inhibiting the NF-κB pathway, thereby improving pulmonary artery obstruction caused by pulmonary vascular resistance and mitigating PH.[61–64] Elevated expression of inflammatory factors such as TNF-α, IL-6, and IL-1β is commonly observed around the pulmonary arteries in PH. These inflammatory factors accelerate the remodeling process and disrupt local immune balance.[65] Allicin (*Allium sativum* L.) and grape seed proanthocyanidins can reduce the expression of related inflammatory factors in the lungs of mice, alleviating perivascular inflammation and inhibiting HPV and PVR.[66,67]

Oxidative Stress

Oxidative stress occurs when the balance between oxidation and antioxidants is disrupted in a low oxygen environment, leading to an oxidative state. This imbalance, driven by free radicals, plays a key role in disease development. When ROS, central to oxidative stress, accumulate beyond the capacity of antioxidant systems, they induce neutrophil infiltration, protease secretion, and the production of oxidative intermediates.[68] In HPH, ROS accumulation is linked to pulmonary microvascular endothelial dysfunction, growth factor feedback, and mitochondrial apoptosis pathways, all contributing to HPH progression and right heart failure.[69–71] NADPH oxidase, a major ROS source, can induce PVR directly or through ROS generation.[72,73] Given the role of oxidative stress in HPH, natural herbal antioxidant therapies have emerged as promising prevention and treatment options.

Nuclear factor E2-related factor 2 (Nrf2), the main antioxidant response regulator, reduces oxidative stress by controlling antioxidant enzymes such as heme oxygenase-1 (HO-1).[74] Salvianolic acid A reduces intracellular ROS production, inhibits TGF-β1 and EndMT, and counters PVR by activating the Nrf2/HO-1 pathway.[75] The synergistic action of NADPH oxidase (NOX) and VPO1 exacerbates oxidative damage in HPH.[76] MLB and trimethoxy stilbene, a new resveratrol analog, prevent PVR and right heart failure in HPH rats by inhibiting oxidative stress and inflammation via the NOX/VPO1 pathway and extracellular signal-regulated kinase (ERK) signaling.[77,78] Resveratrol further regulates the MAPK/ERK1 and PI3K/Akt pathways, enhances the Nrf2/thioredoxin-1 (Trx-1) axis, inhibits HIF-1α expression, and reduces hypoxia-induced ROS production. Ligustrazine exerts anti-inflammatory, antioxidant, and anti-PASMC proliferation effects in HPH by inhibiting the ROS/HIF/VEGF pathway and modulating the ROS/iNOS/PKG axis.[79,80]

Ion Channels

Ion channel dysfunction, especially Ca^{2+} and K^+ channel dysfunction, plays a critical role in HPH progression.[81] Elevation of the intracellular calcium concentration ($[Ca^{2+}]i$) is a major factor in PVR development.[82] Prolonged hypoxia and inflammation impair K^+ channel activity in PASMCs, leading to membrane depolarization and voltage-gated Ca^{2+}

channel activation, thereby increasing [Ca^{2+}]i and causing vasoconstriction.[83] Thus, strategies to reduce [Ca^{2+}]i and restore K^+ channel function are key to treating HPH, with natural herbal medicines and its derivatives often targeting these ion channels.

Danshensu IIA induces pulmonary vasodilation by inhibiting calcium influx, suppressing intracellular calcium release, and activating K^+ channels.[84] TRPC channels regulate [Ca^{2+}]i by facilitating calcium influx or modulating membrane potential.[81] Under hypoxic conditions, TRPC1 and TRPC6 expression is increased in PASMCs, thereby enhancing store-operated calcium entry (SOCE). STS reduces SOCE and basal calcium levels by inhibiting elevated TRPC1 and TRPC6 expression in rats with HPH, alleviating pulmonary vascular resistance, and improving pulmonary vascular and right ventricular remodeling.[85] Calcium-sensing receptors (CaSRs) are crucial for regulating [Ca^{2+}]i, vasoconstriction, and PASMC proliferation. Ligustilide inhibits CaSR activation in PASMCs and reduces [Ca^{2+}]i.[86] Hypoxia reduces Kv1.5 and Kv2.1 expression in small pulmonary arteries, lowering IKV currents in PASMCs.[87] STS significantly inhibits the hypoxia-induced proliferation of PASMCs by affecting the expression of Kv2.1.[88] Eulophia maculata (*Eulophia maculata* (Lindl.) Rchb.f.) extract reduces extracellular calcium levels, inhibits adrenaline-induced intracellular calcium release, and suppresses PDE5, thereby enhancing pulmonary vasodilation.[89] Pretreatment with *Rhodiola tangutica* (Maxim.) S.H.Fu upregulates K^+ channel protein expression, inhibits Ca^{2+} channel protein expression, and suppresses hypoxia-induced PASMC proliferation.[90]

Apoptosis Regulation

Dysregulated apoptosis represents a core pathological mechanism in pulmonary vascular remodeling (PVR) associated with hypoxic pulmonary hypertension (HPH). Imbalanced apoptosis and proliferation across major pulmonary vascular cell types, particularly pulmonary arterial endothelial cells (PAECs) and smooth muscle cells (PASMCs), are central to disease progression, exhibiting paradoxical effects that contribute to its complexity.[91]

Apoptosis of PAECs serves as a trigger of HPH. This process is a key early event in HPH pathogenesis. Chronic hypoxia, inflammatory cytokines (eg, TNF-α, IL-1β), and oxidative stress directly induce PAEC apoptosis.[22] This compromises endothelial barrier function and vasoregulation, reducing vasodilatory factors (eg, NO, prostacyclin) while increasing vasoconstrictors (eg, ET-1, TXA2), exacerbating vasoconstriction.[23] Critically, apoptotic debris and inflammatory mediators from dying PAECs activate local inflammation, recruiting immune cells and promoting the release of growth factors (eg, PDGF, TGF-β) and cytokines. These signals drive the phenotypic shift of adjacent PASMCs from a contractile to a proliferative/secretory state, characterized by excessive proliferation, migration, and apoptosis resistance, ultimately leading to fixed PVR and elevated pulmonary artery pressure.[24] Thus, PAEC apoptosis initiates and sustains a pathological vascular cycle, making its inhibition a key therapeutic target. Active compounds from traditional herbs, such as Astragaloside IV (AST IV),[92] Salvianolic acid A (SalA),[38] and Resveratrol,[93] demonstrate protective effects against hypoxia/inflammation-induced PAEC apoptosis in HPH. They enhance endothelial survival and NO bioavailability via pathways like PI3K/Akt and Nrf2/HO-1 activation.

PASMC apoptosis resistance constitutes the structural basis for PVR.[94] Characterized by downregulated pro-apoptotic proteins (eg, Bax) and upregulated anti-apoptotic proteins (eg, Bcl-2) under hypoxia, this phenomenon reduces the Bax/Bcl-2 ratio, stabilizes mitochondrial membrane potential, and suppresses mPTP opening, apoptosome formation, and Caspase-3 activation.[95] Concurrent activation of pro-survival pathways (eg, PI3K/Akt, ERK) further enhances PASMC viability, enabling sustained proliferation and accumulation that directly drives medial hypertrophy, vascular obliteration, and increased resistance. Herbal agents including AST IV,[96] Puerarin,[97] Baicalin,[98] Apigenin[99] and Salidroside[100] counter this resistance by modulating apoptotic protein expression (eg, reducing Bcl-2/Bax ratio, activating Caspase-3) through pathways such as the mitochondrial pathway (Salidroside via A2aR), AMPKα1/p53/Bax/Bcl-2/caspase cascade, HIF-1α/Kv1.5 signaling, or PI3K/Akt inhibition, thereby inducing PASMC apoptosis and attenuating medial thickening.

Therapeutic Implication of Dual Regulation

The paradoxical effects of apoptosis in PAECs (detrimental) versus PASMCs (protective resistance) necessitate treatment strategies capable of bidirectional regulation, ie protecting PAECs from apoptosis while inducing apoptosis in hyperproliferative PASMCs. Thus, effective HPH management requires: Preserving endothelial integrity and function by

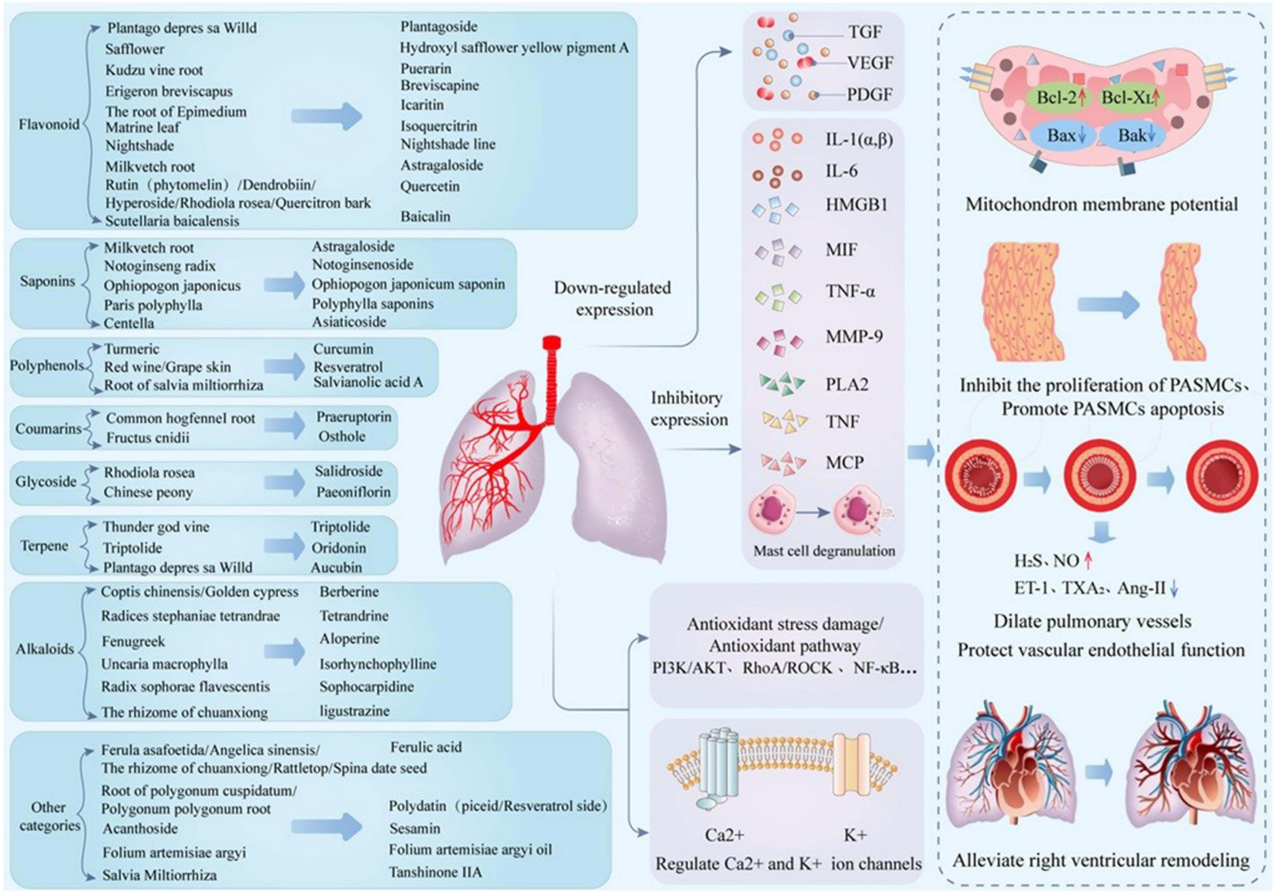

Figure 3 Mechanisms underlying HPH treatment by TCMs.

reducing PAEC apoptosis; Selectively inducing apoptosis in apoptosis-resistant, proliferating PASMCs. Many herbal compounds exhibit this dual potential through pleiotropic actions – antioxidant, anti-inflammatory, and pathway modulation – simultaneously protecting endothelium and promoting PASMC apoptosis. Future research should delineate the specific molecular mechanisms of different compounds in cell-specific apoptosis regulation, assess their relative contributions to restoring pulmonary vascular homeostasis, and explore potential synergies. Harnessing this cell-specific apoptosis modulation is central to developing more effective and safer herbal therapies for HPH (Figure 3).

Chinese HMs and Their Derivatives: Classification

In preclinical HPH treatment, different CHCs often exhibit similar therapeutic effects, mainly because of similarities in key HMs or their classification. For instance, although the compositions of Qili Qiangxin capsules[44] and Qibai Pingfei capsules[47,48] differ, both CHCs share *Astragalus* as a key HM,[101] a flavonoid known for its immunomodulatory, cardiotonic, hypotensive, and anti-viral properties. Consequently, both CHCs reduce inflammation and modulate the NO pathway, providing anti-inflammatory and endothelial-protecting effects. Key HMs in CHC such as plantain, rhodiola, and peony (*Paeonia lactiflora* Pall.) contain potent antioxidants such as catalpol,[102] salidroside,[103] and paeoniflorin,[104] which belong to the glycoside class and share the mechanisms of clearing ROS and activating antioxidant pathways. The mechanisms of various Chinese herbal monomers are shown in Table 2.

Flavonoids in Chinese HMs

Flavonoids, a group of organic compounds found abundantly in plants, are characterized by a flavan nucleus, and they exhibit anti-inflammatory, antioxidant, anti-angiogenic, anti-microbial, and anti-viral effects.[150] They also reduce vascular fragility, improve vascular permeability, and regulate lipid and cholesterol levels in vascular diseases.[151]

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Table 2 The Pharmacological Mechanisms of Various Components in Chinese Herbal Medicines and the Diseases They Treat

Classification	Component	Molecular Formula	Action Object	Dose/ Concentration	Mechanisms of Action	Effect	Play a Therapeutic Role in the Following Diseases	Refs
Flavonoid	Breviscapine	$C_{21}H_{18}O_{12}$	Patients with patient	50 mg/day (i.v.)	ET-1↓, NO↑	Regulating vasomotor factors	Cardio-cerebrovascular disease, Hepatic fibrosis, Chronic kidney disease	[105]
Flavonoid	Puerarin	$C_{21}H_{20}O_9$	SD rats, PAECs	80 mg/kg (P.O.) 30 mol/L	LC3B-II↓, BECN-1↓, ATG5↓, SQSTM1↑, BMPR2/Smad↑, PPARγ/PI3K/Akt↑	Inhibiting PASMC proliferation, inhibiting oxidative stress	Ischemic heart disease, Cerebral infarction, Diabetes mellitus	[106,107]
Flavonoid	Genistein	$C_{15}H_{10}O_5$	PASMCs, SD rats	50 mol/L 60 mg/kg	ROS↓, SOD↑, H_2O_2↑, EPO/EPOR↑, NO↑	Inhibiting oxidative stress	Cancer, Obesity	[108]
Flavonoid	Baicalein	$C_{15}H_{10}O_5$	SD and Wistar rats	100 mg/kg (P.O.) 100 mg/kg (P.O.) 20, 100, 200 mg/kg	TNF-α↓, IL-1β↓, IL-6↓, NF-κB p65↓, BMPR2↑, BMP-4↑, BMP-9↑, Smad1/5/8↑, AKT/ERK/NF-κB↓	Inhibiting inflammatory response	Diabetes mellitus, Atherosclerosis, Hypertension	[62,109,110]
Flavonoid	Quercetin	$C_{15}H_{10}O_7$	PASMCs	60 mol/L	MMP2↓, MMP9↓, Bax/Bcl-2↑; cyclin B1↓	Inhibiting PASMC proliferation	Chronic Obstructive Pulmonary Disease, Allergic Asthma, Rheumatoid Arthritis	[111]
Flavonoid	Isoquercetin	$C_{21}H_{20}O_{12}$	PASMCs	30 mol/L	PCNA↓, α-SMA↓, cyclin D1↓, CDK4↓, p-PDGF-Rβ↓	Inhibiting PASMC proliferation	Amyotrophic lateral sclerosis (ALS), Sickle cell anemia	[112]
Flavonoid	Dihydromyricetin	$C_{15}H_{12}O_8$	PASMCs	100 mg/kg	MMP9↓, p-STAT3↓	Inhibiting PASMC migration	Diabetes mellitus, Alcoholic liver disease, Ulcerative colitis	[113]
Flavonoid	Apigenin	$C_{15}H_{10}O_5$	SD rats	50, 100 mg/kg	Cytochrome C (Cytc)↑, Bax↑, Bcl-2↓, caspase-3↑, caspase-9↑, HIF-1α-KV1.5↓	Inhibiting PASMC proliferation	Diabetes mellitus, Gastric ulcer, Alcoholic liver injury	[99]
Alkaloid	Ligustrazine	$C_8H_{12}N_2$	SD rats and patients with HPH	100 mg/kg (P.O.) 120 mg/day (i.v.) 40, 80, 160 mg/kg	HIF-1α↓, basal $[Ca^{2+}]i$↓, SOCE↓, TRPC1↓, TRPC6↓, ET-1↓, NO↑, PI3K/AKT regulation	Regulating calcium homeostasis, regulating vasomotor factors, inhibiting inflammatory response	Angiitis, Angina pectoris, Sepsis	[114,115]
Alkaloid	Tetrandrine	$C_{38}H_{42}N_2O_6$	SD rats	50 mg/kg (i.p.)	iNOS↓, PKG-1↑, SOD↑, MDA↓	Inhibiting oxidative stress	Chronic Obstructive Pulmonary Disease, Pulmonary Arterial Hypertension, Rheumatoid Arthritis	[116,117]
Alkaloid	Berberine	$C_{20}H_{18}NO_4$	PASMCs	20, 100 mol/L	p-PP2Ac/t-PP2Ac↓, p-Akt/Akt↓, p-ERK1/2↓, p-P38↓, PCNA↓, BMPR-II↑, P-Smad1/5↑, TGF-β↓, p-Smad2/3↓, PPARγ↑	Inhibiting PASMC proliferation, inhibiting inflammatory response	Diabetes mellitus, Atherosclerosis, Chronic Kidney Disease	[118,119]
Alkaloid	Betaine	$C_5H_{11}N_{02}$	SD rats	100, 200, 400 mg/kg	MCP-1↓, ET-1↓, NF-κB↓, TNF-α↓, IL-1β↓	Inhibiting inflammatory response	Hyperhomocysteinemia, Multiple sclerosis, Alzheimer's disease	[120]
Alkaloid	Aloperine	$C_{15}H_{24}N_2$	SD rats and PASMCs	25, 50, 100 mg/kg 50 mol/L	G0/G1 phase arrest; NF-κB↓, RhoA↓, ROCK1↓, ROCK2↓, ROCK↓	Inhibiting PASMC proliferation, inhibiting inflammatory response	Pulmonary Arterial Hypertension, Cancer, Eczema	[121,122]
Glycoside	AST IV	$C_{41}H_{68}O_{14}$	SD rats	10, 30 mg/kg 40, 80 mg/kg	TNF-α↓, IL-1β↓, HIF-1α↓, VEGF↓, NLRP-3/calpain-1↓, caspase-1↓, ASC↓, IL-18↓, IL-1β↓, Bcl-2↓, ERK↓, HIF-1α↓, VEGF↓, caspase-3↑, caspase-9↑, Bax↑	Inhibiting PASMC proliferation, inhibiting inflammatory response	Hand-foot-and-mouth disease, Alcohol-associated Liver Disease, Insulin Resistance	[92,97,123,124]

Glycoside	Salidroside	$C_{14}H_{20}O_7$	BALB/C mice and PASMCs	32 mg/kg (P.O.) 500 mol/L	Bax/Bcl-2↑, caspase 9↑, cleaved caspase-3↑, A2aR↑, AMPKα1↑, p53↑, p27↓, p21↓, PCNA↓, caspase-3↑, NF-κB↓, Nrf2/HO-1↑	Promoting apoptosis, inhibiting PASMC proliferation	Alzheimer's disease, Parkinson's disease, Epilepsy	[100,125,126]
Glycoside	Asiaticoside	$C_{48}H_{78}O_{19}$	PASMCs and PAECs	50 mol/L	TGF-β1↓, p-Smad2/3↓, ET-1↓, NO↑, cGMP↑, p-Akt/Akt↑, p-eNOS/eNOS↑	Inhibiting inflammatory response, regulating vasomotor factors	Alzheimer's disease, Parkinson's disease, Acute lung injury	[127,128]
Glycoside	Notoginsenoside R1	$C_{47}H_{80}O_{18}$	PASMCs	8, 40, 100 mol/L	p-ERK/t-ERK↓, ERK1↓, ERK2↓	Improving pulmonary vascular remodeling	Ischemic brain injury, Alzheimer's disease, Depression	[103,129,130]
Glycoside	Polydatin	$C_{20}H_{22}O_8$	PASMCs	100 ng/mL	EndMT↓, N-cadherin↓, β-catenin↓, vimentin↓, TAGLN↓, PECAM1↑	Inhibiting PASMC proliferation	Ischemic cerebrovascular disease, Myocardial ischemia, Shock	[131]
Glycoside	Icariin	$C_{33}H_{40}O_{15}$	SD rats	40 mg/kg (P.O.)	NO↑, eNOS↑, cGMP↑, PDE5↓	Regulating vasomotor factors	Rheumatoid arthritis, Osteoporosis, Cardiovascular disease	[132]
Polyphenol	Resveratrol	$C_{14}H_{12}O_3$	SD rats	40 mg/kg (P.O.) 25 mg/kg 40 mg/kg	TNF-α↓, IL-1β↓, IL-6↓, PDGF-α/β↓, SphK1/S1P/NF-κB↓, MAPK/ERK1↓, PI3K/AKT↓, HIF-1α↓, Nrf-2/Trx-1↓	Inhibiting inflammatory response, inhibiting oxidative stress	Diabetes mellitus, Alzheimer's disease, Cancer	[93,133–136]
Polyphenol	Danshensu	$C_9H_{10}O_5$	PASMCs	30 g/mL	TGF-β/Smad3 pathway regulation	Inhibiting PASMC proliferation	Coronary heart disease, Angina pectoris, Myocardial ischemia	[137]
Polyphenol	Salvianolic acid A	$C_{26}H_{22}O_{10}$	SD rats	3 mg/kg (P.O.) 0.3, 1, 3 mg/kg	AST↓, ALT↓, NT-proBNP↓, RVSP↓, ET-1↓, BMPR2↑, Smad1/5↑, Nrf2/HO-1↑, ROS↓, TGFβ1↓, EndMT↓	Improving pulmonary vascular remodeling, inhibiting oxidative stress	Cardiovascular disease, Chronic kidney disease, Cerebral infarction	[38]
Polyphenol	MLB	$C_{36}H_{28}Mg_{016}$	SD rats	5, 15 mg/kg	HIF-1α↓, NF-κB↓, MCP-1↓, PCNA↓, CDK4↓, cyclin D1↓, ROCK1, 2↓, NOX/ROS/ERK↓, NOX2↓, NOX4↓	Inhibiting inflammatory response, inhibiting oxidative stress	Cancer, Kidney disease, Pulmonary arterial hypertension	[138,139]
Terpene	Paclitaxel	$C_{47}H_{51}NO_{14}$	SD rats	5 mg/kg (i.v.)	p27Kip1↑, p-FoxO1↓, RVSP↓, LC3A↓, LC3B↓	Inhibiting autophagy	Cancer	[140,141]
Terpene	Dihydroartemisinin	$C_{15}H_{24}O_5$	HPAECs	60 mol/L	ROS↓, NO↑, SOD↑	Inhibiting HPAEC proliferation	Rheumatoid arthritis, Lupus nephritis, Systemic lupus erythematosus	[142]
Terpene	Triptolide	$C_{20}H_{24}O_6$	PASMCs	1 mol/L	Bsg↓, CyPA↓, ROS↓	Inhibiting inflammatory response, inhibiting oxidative stress	Rheumatoid arthritis, Systemic lupus erythematosus	[143]
Terpene	Glycyrrhizin	$C_{42}H_{62}O_{16}$	SD rats	50 mg/kg (i.p.)	HMGB1↓, ET-1↓	Inhibiting inflammatory response	Peptic ulcer, Metabolic-associated fatty liver disease, Acute lung injury	[144]
Quinone	STS	$C_{19}H_{17}NaO_6S$	SD rats and PASMCs	10 ng/mL 10, 30 mg/kg	mTOR↓, eIF2α↓, c-Myc↓, IL-6↓, IL-8↓, TNF-α↓, PI3K/AKT/mTOR↓, TRPC↓, SOCE↓, $[Ca^{2+}]i$↓, PKG/PPAR-γ↑, Bcl-2↓, Bax↑	Inhibiting PASMC proliferation, inhibiting inflammatory response, ion channels	Hormone-dependent breast cancer, Hormone-dependent prostate cancer, Osteoporosis	[84,85,145–147]
Quinone	Thymoquinone	$C_{10}H_{12}O_2$	SD rats	16 mg/kg (P.O.)	PCNA↓, α-SMA↓, MMP2↓, Bax/Bcl-2↑, cleaved caspase-3↑	Inhibiting pulmonary arterial remodeling	Ischemic cerebrovascular disease, Cerebral stroke	[148]
Quinone	Hydroxysafflor yellow AA	$C_{27}H_{32}O_{16}$	Wistar rats	10 mg/kg (i.p.)	ANXA5↑, SRC↑, PGR↑, EGFR↑, PPARG↑, ESR1↑	Inhibiting PASMC proliferation, inhibiting oxidative stress	Ischemic cerebrovascular disease, Cerebral stroke	[149]

Note: The ↑ and ↓ symbols in the table indicate increased or decreased expression levels of the corresponding factors/proteins, respectively.

An experimental study demonstrated that breviscapine can stimulate NO production by increasing the expression of protein kinase G1 (PKG-1) and activate the NO signaling pathway to improve pulmonary vascular dilation. Additionally, breviscapine significantly improved right ventricular hypertrophy in HPH rats by inhibiting calcium influx and activating calmodulin.[105] The natural flavonoid compound puerarin inhibits abnormal PASMC proliferation by arresting the cell cycle at the G1 phase and improve PVR. Additionally, the reduced expression of the cell cycle-related proteins cyclin A, cyclin E, and cyclin D1 is also attributed to puerarin-induced autophagy.[106] Another in vitro study revealed that puerarin improves hypoxia-induced pulmonary vascular contraction and oxidative stress by activating the BMPR2/Smad and PPARγ/PI3K/Akt signaling pathways, which reduces ROS and ET-1 levels in hypoxia-induced HPAECs.[107] In antioxidant therapy research for HPH, genistein restored the imbalance of ROS and H_2O_2 in hypoxia-induced PASMCs from the source and improved oxidative balance in the body through the EPO/EPOR signaling pathway.[108] Baicalein (baicalin) intervention in rats with HPH can reduce the levels of inflammatory factors such as TNF-α, IL-1β, and IL-6, improving the local inflammatory storm caused by hypoxia. Subsequent studies suggested that baicalein can exert its anti-inflammatory properties by modulating the NF-κB and BMP/Smad pathways.[62,109] Furthermore, the ability of baicalein to improve PVR might involve the synergistic action of multiple pathways, including the TNF-α/BMPR2, MAPK/matrix metalloproteinase-9 (MMP-9) signaling pathway, Akt/eNOS, ERK, and NF-κB signaling pathways.[110] Quercetin, another common flavonoid compound, was found in in vitro experiments to inhibit abnormal PASMC proliferation and induce PASMC apoptosis by blocking the tyrosine receptor kinase A/AKT signaling pathway.[111] Additionally, its homologous compound isoquercetin also exerted protective effects on HPH rats, with potential mechanisms related to the PDGF receptor β signaling pathway.[112] In summary, flavonoid compounds improve HPH by modulating vascular constriction factors, exerting anti-inflammatory and antioxidative effects, and inhibiting abnormal PASMC proliferation.

Alkaloids in Chinese HMs

Alkaloids, nitrogen-containing organic compounds found in plants in the Polygonaceae, Fabaceae, Apocynaceae, and Solanaceae families, are key active ingredients in many TCMs. With more than 3000 types identified, these compounds exhibit diverse biological activities, including anti-cancer, anti-angiogenesis, anti-inflammatory, and anti-proliferative effects.[152,153] Recently, their therapeutic potential in HPH has gained attention. Mechanistically, alkaloids can prevent and treat HPH through anti-inflammatory, antioxidant, and autophagic processes, promoting PASMC apoptosis, disrupting the cell cycle, and inhibiting cell proliferation and migration.[118,119]

For example, ligustrazine delays PVR in HPH by modulating PASMC calcium homeostasis and regulating vasoactive factors (ET-1, NO)[114] while also inhibiting PASMC proliferation by blocking the PI3K/Akt signaling pathway, thereby preventing cell cycle progression from G0/G1 to S phase.[115] Tetrandrine, another alkaloid, significantly reduces pulmonary arterial pressure in rats with HPH by stimulating endothelial NO production by NOS via PKG-1 and blocking myocardial Ca^{2+} channels, thereby delaying right ventricular hypertrophy.[116,117] Berberine, a natural alkaloid organic compound extracted from the herb *Coptis chinensis*, was found in recent studies to primarily treat HPH by modulating the BMPR2 and TGF-β pathways and inhibiting the Trx1/β-catenin pathway. Another study demonstrated that berberine inhibits PASMC proliferation induced by adrenaline primarily via the PP2A pathway, and these findings were validated in both patients with HPH and animal models.[118,119] Betaine, a biogenic amine from goji berries (*Lycium barbarum* L.), was originally used as a dietary supplement, and it was revealed in preclinical studies of HPH to possess notable anti-inflammatory effects. It regulates the levels of inflammatory factors such as NF-κB, TNF-α, and IL-1β, thereby improving mPAP.[120] Aloperine, extracted from the Chinese herbal medicine *Sophora alopecuroides* L., exerts significant protective effects against vascular diseases. Both in vitro and in vivo HPH studies indicated that aloperine suppresses PASMC proliferation and reduces mean mPAP through modulating the RhoA/ROCK and NF-κB pathways.[121,122]

Glycosides in Chinese HMs

The study of glycosides began in the early 19th century with the discovery of amygdalin in 1830. Glycosides are organic compounds characterized by a glycosidic bond between a monosaccharide or oligosaccharide and another molecule such as alcohol, sugar, purine, or pyrimidine. This unique structure gives them notable stability, water solubility, and bioavailability.[154] Glycosides play a crucial role in drug development, with many TCMs, such as *Plantago*,[102]

Rhodiola,[103] and *Peony*,[104] containing effective glycosides. Research indicates that glycosides exert therapeutic effects through pathways involving inflammation, oxidative stress, cell proliferation, apoptosis, cell cycle progression, and ion channels. Their anti-inflammatory and antioxidant effects are particularly valuable in HPH treatment.

AST IV, a glycoside isolated from *Astragalus membranaceus*, has displayed anti-inflammatory effects in rats with HPH, reducing vasoconstrictive and inflammatory factors (ET-1, Ang II, TNF-α, and IL-6) and mitigating PVR by inhibiting the NLRP-3/calpain-1 pathway.[97,123] In vitro, AST IV suppressed T follicular helper cell responses, expanded T follicular regulatory cell responses, and regulated the Notch signaling pathway, thereby reversing remodeling progression.[92,124] Furthermore, AST IV has been demonstrated to exert cardioprotective effects by regulating calcium ion homeostasis, suppressing cardiomyocyte apoptosis in rats with HPH, and delaying right ventricular remodeling.[155] The efficacy of the traditional Chinese herb *Rhodiola rosea* in treating HPH has been confirmed.[125] However, its specific mechanisms of action are unclear, prompting in-depth research into its key active component salidroside. Salidroside promoted PASMC apoptosis via an A2aR-related mitochondrial-dependent pathway, thereby alleviating HPH.[100] Additionally, salidroside inhibited chronic hypoxia-induced PASMC proliferation via the AMPKα1/p53/p27/p21 pathway and reversed resistance to apoptosis through the AMPKα1/p53/Bax/Bcl-2/caspase 9/caspase 3 pathway.[126] Therefore, apoptosis modulation is considered a key mechanism of salidroside in treating HPH. Asiaticoside, a saponin monomer isolated from the traditional Chinese herb *Centella asiatica* (L.) Urb., primarily treats HPH by blocking TGF-β1/SMAD family member 2/3 signaling to induce PASMC apoptosis,[127] and it can also prevent endothelial cell apoptosis by regulating the NO pathway.[128] Recent studies revealed that notoginsenoside R1 extracted from *Panax notoginseng* (Burkill) F.H.Chen inhibits hypoxic pulmonary vasoconstriction induced by low oxygen and high carbon dioxide levels by attenuating ERK pathway activation.[129] Notoginsenoside R1 also prevents HPH by modulating the p38 MAPK pathway.[130] Other glycosides such as icariin, epimedium glycoside, and paeoniflorin have also displayed therapeutic effects against HPH. For instance, icariin effectively inhibits EndMT by blocking HIF-2α/Arg1 signaling, thereby improving pulmonary endothelial dysfunction and PVR.[131] Epimedium glycoside improves HPH by inhibiting the TGF-β1/Smad2/3 pathway,[132] and paeoniflorin ameliorates HPH by improving BMPR2 downregulation-mediated EndMT.[30]

In summary, glycosides compounds influence HPH by modulating inflammation, oxidative stress, cell apoptosis, and vascular constriction, with their apoptosis-modulating and antioxidant effects being particularly significant. Aucubin, a β-D-glucopyranoside, is as a potential HPH therapy target because of its strong antioxidant and detoxifying properties, minimal toxicity, and ability to reduce oxidative stress and enhance antioxidant enzyme activity.[102,156–158] However, its relevance to pulmonary vascular diseases remains unexplored, indicating promise for future research.

Polyphenols in Chinese HMs

Phenolic acids, secondary metabolites widely found in plants, possesses a range of biological activities, including anti-inflammatory, anti-microbial, anti-cancer, anti-allergic, anti-viral, and anti-thrombotic effects.[159–161] As natural antioxidants, they hold promise in TCM and as resources for developing new drugs and products. However, further research is needed to determine their safety, efficacy, and mechanisms of action for specific applications. Recently, phenolic acids have attracted interest as potential therapeutic agents for preventing and treating HPH.

Resveratrol, a non-flavonoid polyphenolic compound, is synthesized by plants in response to stress, injury, infection, or UV radiation. It is found in various plants, especially grapes, *Polygonum cuspidatum*, and peanuts. Resveratrol exhibits anti-inflammatory, antioxidant, anti-proliferative, and anti-fibrotic properties.[162] Its therapeutic effects on the cardiovascular system have led to its widespread use in preclinical HPH studies. Sphingosine-1-phosphate (SphK1/S1P) signaling induces PVR by activating NF-κB and upregulating cyclin D1. Resveratrol reverses this process by inhibiting the SphK1/S1P/NF-κB/Cyclin D1 signaling pathway.[133] Resveratrol activates the PI3K/AKT signaling pathway to inhibit the expression of arginase II induced by hypoxia, thereby preventing PASMC proliferation.[93,134] In terms of antioxidation, resveratrol regulates the MAPK/ERK1 and PI3K/Akt pathways, enhances the NRF2/Trx-1 axis, suppresses HIF-1α expression, and reduces hypoxia-induced ROS production, concurrently decreasing the levels of TNF-α, IL-1β, and IL-6 in rat lungs.[135] Furthermore, resveratrol can achieve similar therapeutic effects by inhibiting the RhoA/ROCK signaling pathway, activating SIRT1, and suppressing Th17 cell differentiation.[136] Furthermore, resveratrol can prevent right

ventricular hypertrophy and cardiac fibrosis in patients with HPH while also reducing acetylation levels in the right ventricle.[163] Phenolic acids extracted from HMs such as (salvianolic acid A) and magnesium lithospermate B (MLB) have displayed significant efficacy in treating HPH. Danshensu inhibits PASMC proliferation, with its protective effects involving regulation of the TGF-β/Smad3 pathway.[137] Salvianolic acid A delays PVR by activating the BMPR2/Smad pathway while inhibiting apoptosis and EndMT.[38] MLB exerts its therapeutic effects on HPH by inhibiting the NOX/ROS/ERK and NOX/VPO1 pathways.[138,139] MLB also inhibits hypoxia-induced EndMT and downregulates HIF-1α, MCP-1, NF-κB, PCNA, CDK4, and other factors, thereby halting disease progression. These findings suggest that polyphenolic natural antioxidants could effectively improve HPH.

Terpenes in Chinese HMs

Terpenoids, a class of naturally occurring organic compounds, are known for their distinctive aromas and are found in many herbal medicines with expectorant, anti-tussive, anti-spasmodic, diaphoretic, insecticidal, and analgesic effects. Terpenoids can be isolated from natural sources through distillation, direct steam distillation, freezing, and extraction. Terpenoids exhibit a range of biological activities including antioxidant, anti-inflammatory, and anti-microbial properties.[164]

Paclitaxel, is a terpenoid known for its anti-proliferative effects against vascular diseases, and it is FDA-approved for preventing restenosis caused by drug-eluting stents.[165] In HPH studies, paclitaxel exerted beneficial effects in model mice, which were attributed to the upregulation of p27Kip1 and shortening of the cell cycle.[140] Another study indicates that paclitaxel exerts protective effects against HPH by inhibiting FoxO1-mediated autophagy.[141] Dihydroartemisinin, derived from *Artemisia annua* L., is a potent antimalarial drug, and it also improves endothelial cell proliferation and migration while reducing oxidative stress by lowering ROS levels in hypoxia-induced pulmonary arterial hypertension.[142] Basigin (Bsg) is a transmembrane glycoprotein that promotes myofibroblast differentiation, cell proliferation, and MMP activation. Triptolide improves right ventricular dysfunction in HPH model animals by inhibiting Bsg and its ligand CyPA, suppressing PASMC proliferation, and reducing ROS and inflammatory cytokine levels.[143] HMGB1 is a pro-inflammatory cytokine governing tissue remodeling and angiogenesis in pulmonary arterial hypertension. Glycyrrhizin, a terpenoid compound, improves HPH-induced right ventricular systolic pressure elevation and right ventricular hypertrophy, reduces pulmonary inflammation, and delays PVR by inhibiting HMGB1.[144]

Quinones in Chinese HMs

Quinone compounds are bioactive molecules found in plants, including naphthoquinones, benzoquinones, and anthraquinones. Their unsaturated cyclohexadienedione structure makes them essential in the electron transfer chain of biological oxidation. This redox property underpins their roles in regulating apoptosis, autophagy, proliferation, and angiogenesis.[166] STS is a notable quinone that alleviates HPH by reducing $[Ca^{2+}]i$ and restoring K^+ channel activity.[84,85] STS also inhibits hypoxia-induced abnormal PASMC proliferation by modulating pathways such as mTOR/eIF 2α,[145] PI3K/AKT/mTOR,[146] and PKG/PPARγ,[147] thus regulating pulmonary inflammation and edema. In another in vitro experiment, thymoquinone induced apoptosis in PDGF-BB–induced PASMC proliferation by enhancing the mitochondrial-dependent apoptotic pathway associated with p38 MAPK and regulating the expression of apoptosis genes (Bax, Bcl-2). Hydroxysafflor yellow A (HSYA), a key component of traditional Honghua medicine, has anti-inflammatory, antioxidant, and anti-thrombotic effects. A network pharmacology study revealed that HSYA can inhibit PASMC proliferation and PVR and reduce pulmonary arterial wall thickness and muscularization by modulating genes such as ANXA5, SRC, PGR, EGFR, PPARG, and ESR1, thereby improving HPH.

Chinese Herbs Improve HPH Through Antioxidant Signaling Pathways

Chronic hypoxia-induced oxidative stress is a key factor in HPH development. Although the exact mechanisms of HPH are not fully understood, international guidelines recognize chronic hypoxia as a primary trigger. Compared with other modeling methods, cellular or mouse models generated via long-term hypoxia are more consistent with oxidation- and inflammation-related indicators in clinical patients with HPH.[167]

ROS, as markers of oxidative stress, influence cellular growth, proliferation, transcription factor activity, and apoptosis. Additionally, ROS act as second messengers, activating various signal transduction pathways that can lead to cellular and tissue damage, organ dysfunction, and even carcinogenesis.[168] Therefore, targeting oxidative stress at its source is a vital strategy for HPH therapy.

Previous sections discussed various HPH treatment strategies, including strategies targeting anti-inflammatory and antioxidant pathways, ion channel modulation, and signaling pathways, as well as the inhibition of EndMT. Herbal medicines play a significant role in regulating oxidative stress through signaling pathways and restoring the ROS balance, potentially reversing the disease at its root. Research has established that Ros have strong links with excessive PASMC proliferation, PVR progression, and right heart failure.[169] Thus, exploring the influence of herbal medicines on signaling pathways, PVR, and antioxidant activity could offer new therapeutic approaches for HPH. The following sections of this article summarize the mechanisms by which herbal medicines regulate signaling pathways, exert antioxidant effects, inhibit abnormal PASMC proliferation, and reverse PVR.

Oxidation

Oxygen is essential for cellular signaling, gene expression, growth, development, and apoptosis, primarily through its role in glucose metabolism, which provides energy for bodily functions.[170] Hypoxia-induced oxidative stress occurs when harmful stimuli lead to the excessive production of ROS by oxidases in mitochondria and the endoplasmic reticulum. This stress surpasses the antioxidant capacity of the body, resulting in neutrophil infiltration, increased protease secretion, and damage to DNA, proteins, lipids, and other macromolecules, ultimately causing cell necrosis and apoptosis.[171] To counteract ROS damage, organisms have evolved a self-antioxidant defense system comprising enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), as well as non-enzymatic antioxidants including vitamin C, vitamin E, coenzyme Q, lipoic acid, and glutathione.[172] SOD, CAT, and GSH-Px are indicators of ROS levels in HPH cell and animal models, as they reflect the degree of oxidative stress. Normally, ROS production and elimination are balanced. However, in HPH, prolonged hypoxia in pulmonary arteries causes ROS levels to exceed the body's clearance capacity. To compensate, the body constricts pulmonary blood vessels to enhance oxygenation. When this constriction surpasses the compensatory limit, irreversible PVR occurs.[173] Recent studies found that various natural herbs can effectively reduce ROS levels in HPH models through multiple signaling pathways. This reduction delays or reverses the abnormal proliferation of PASMCs and decreases PVR, leading to lower mPAP and protecting right heart function (Figure 4).

Antioxidant Signaling Pathways

Signaling pathways are key regulators of cellular homeostasis, physiological processes, development, the determination of cellular fate, and disease progression, and they are potential therapeutic targets. Understanding these pathways is fundamental to studying biological functions and disease mechanisms and developing new treatments.[175] Antioxidant signaling pathways, representing significant branches of these pathways, are crucial for regulating cellular responses to oxidative stress, protecting cells from oxidative damage. These effects are conferred through regulating the activity and expression of antioxidant enzymes, scavenging free radicals, maintaining redox balance, and activating antioxidant response genes such as Nrf2. This activation promotes the expression of antioxidant stress genes, including antioxidant enzymes and heat shock proteins, which enhance cells' antioxidant capacity.[176] Additionally, oxidative stress can trigger cellular apoptosis and inflammatory responses. Antioxidant signaling helps to regulate these processes by modulating the expression and activity of relevant signaling molecules, thereby maintaining cellular stability.[177]

The PI3K/Akt signaling pathway, a classic antioxidant pathway, plays a crucial role in HPH treatment by mediating antioxidation, anti-inflammation, inhibition of abnormal PASMC proliferation, and vasodilation while also protecting endothelial cells. PI3K activation leads to the phosphorylation and activation of Akt, which in turn regulates downstream targets involved in antioxidant defense. Phosphorylated Akt activates transcription factors such as NF-κB and Nrf2, which bind to antioxidant response elements (AREs) in the promoter regions of antioxidant enzyme genes. This process increases the transcription of antioxidant enzymes such as SOD, CAT, and GSH-Px, helping to eliminate ROS that accumulate around pulmonary artery vessels because of chronic hypoxia.[178]

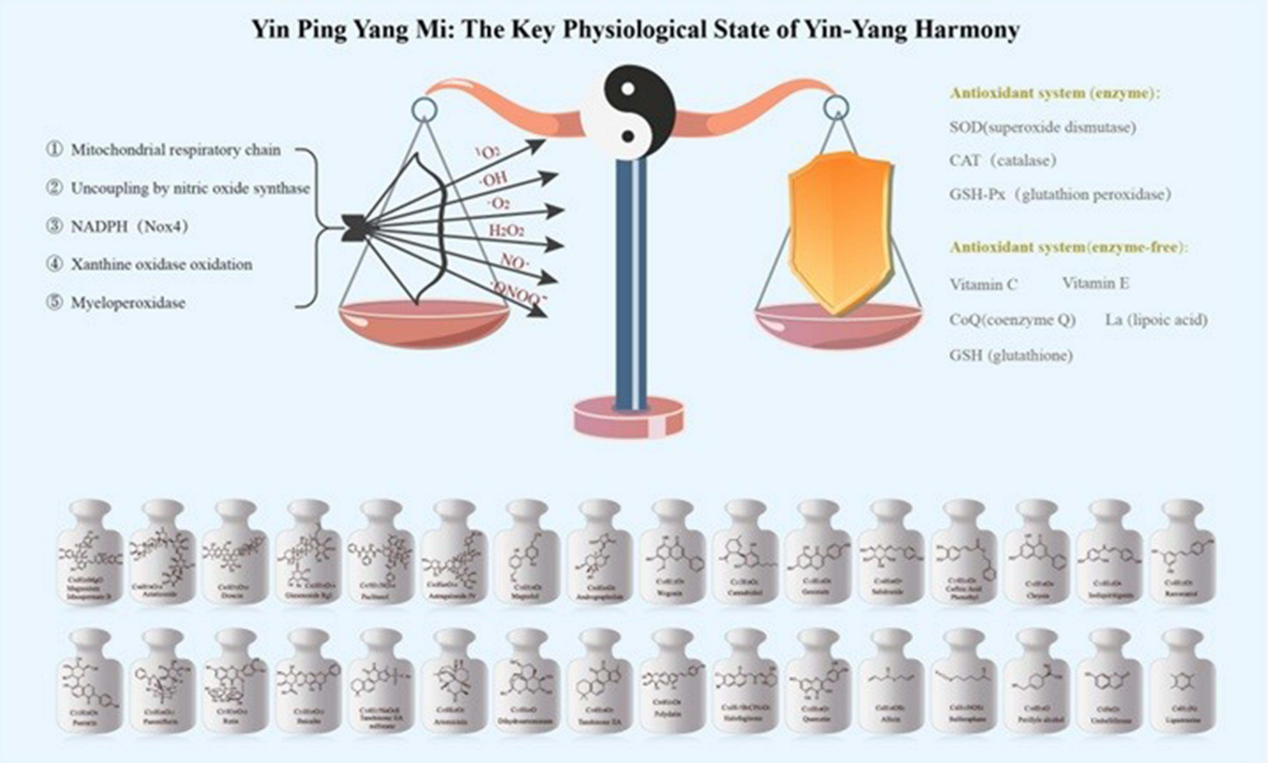

Figure 4 Antioxidant effects of Chinese herbal medicines. ① There are many types of ROS. Those primarily involved in oxidative stress include singlet oxygen ($^1O_2$), hydroxyl radical ($^·HO$), superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and peroxynitrite ($ONOO^-$), whereas those mainly participating in cellular signaling pathways are O_2 and H_2O_2. ② Intracellular ROS are generated through various pathways:[174] primarily by O_2^- generated by the mitochondrial respiratory chain; ROS generated through the uncoupling process of nitric oxide synthase (NOS); oxidative enzymes such as NOX generate ROS by donating electrons to oxygen molecules, and NOX4 is primarily located in mitochondria, serving as a major source of ROS; xanthine oxidase oxidation produces uric acid accompanied by the generation of ROS; and reactions catalyzed by myeloperoxidase also result in ROS production. ③ Monomers of TCM antioxidants: MLB, asiaticoside, dioscin, ginsenoside Rg1, paclitaxel, AST IV, magnolol, andrographolide, wogonin, cannabidiol, genistein, salidroside, caffeic acid phenethyl, chrysin, isoliquiritigenin, resveratrol, pucrarin, paeoniflorin, rutin, baicalin, STS, artemisinin, dihydroartemisinin, tanshinone IIA, polydatin, halofuginone, quercetin, allicin, sulforaphane, perillyl alcohol, umbelliferone, ligustrazine.

Additionally, the Akt pathway can affect the mitochondrial apoptosis pathway by regulating the activity of apoptosis-related protein kinases such as Bax, Bcl-2, and Bad through phosphorylation, thereby controlling cellular apoptosis. These mechanisms collectively help cells manage oxidative stress, maintain redox balance, and protect against oxidative damage. In patients with COPD, macrolide antibiotics reduce chronic inflammation caused by oxidative stress by activating Nrf2 via the PI3K/Akt pathway. This activation decreases secretion by airway epithelial cells, inhibits smooth muscle cell proliferation, improves airway remodeling, and enhances lung function.[179]

During HPH progression, impairment of the NO pathway increases pulmonary vascular constriction, worsening the disease. NO is a key vasodilator synthesized in pulmonary vascular endothelial cells from L-arginine by eNOS. NO then enters PASMCs, in which it activates sGC, which converts GTP into cGMP. This process leads to PASMC relaxation, pulmonary vasodilation, and reduced mPAP.[180] eNOS activity is regulated by phosphorylation and the intracellular redox state. Most TCMs activate the NO pathway via the PI3K/Akt signaling pathway in hypoxic models, counteracting oxidative damage and promoting vasodilation. Genistein, a plant estrogen from soybeans, effectively prevents and treats HPH by activating the PI3K/Akt/NO pathway and enhancing the EPO/EPOR system.[181]

ERK, a member of the MAPK family, plays a key role in cell growth, differentiation, and proliferation. The ERK pathway is typically activated by receptor-triggered molecular cascades, starting with the activation of Ras, followed by Raf kinase, and cumulating in ERK activation. Once active, ERK enters the nucleus to regulate gene transcription by phosphorylating transcription factors and nuclear proteins, thus influencing cellular functions and fate.[182] In HPH, excessive ERK activation affects PASMC survival by altering the expression of cell survival factors and apoptotic regulators, leading to abnormal PASMC proliferation. Cysteine-rich 61 (CCN1), a protein in the CCN family, is crucial

for regulating proliferation, differentiation, apoptosis, angiogenesis, and fibrosis. AST IV counters abnormal PASMC proliferation and PVR by inhibiting CCN1 and reducing ERK pathway activation.[183]

The Nrf2 signaling pathway is a critical defense mechanism against oxidative stress. Under normal conditions, Nrf2 is bound to Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm and is degraded via the ubiquitin–proteasome degradation pathway, thereby maintaining low Nrf2 levels. During oxidative stress, inhibition of Keap1 or structural changes of Nrf2 allow Nrf2 to escape, translocate to the nucleus, and bind to AREs with cofactors such as Maf proteins. This binding activates the transcription of genes encoding antioxidant enzymes, detoxification enzymes, heat shock proteins, and apoptosis regulators, such as NAD(P)H:quinone oxidoreductase 1 (NQO1), HO-1, and glutamate–cysteine ligase.[184] Some natural herbal medicines can activate the Nrf2 pathway by stabilizing the Nrf2–Keap1 complex or enhancing Nrf2 translocation, with Akt phosphorylation also contributing to this activation. Sulforaphane, a potent Nrf2 activator, has been demonstrated to prevent right ventricular dysfunction and remodeling in mice with HPH and right ventricular inflammation and fibrosis. Furthermore, an in vivo study demonstrated that SFN alleviates SuHx-induced PVR, inflammation, and fibrosis by activating the Nrf2/NQO1 pathway.[185] Overall, the Nrf2 pathway serves as a vital defense system for cells, playing a key role in maintaining cellular homeostasis and protecting against oxidative and toxic stresses.

The NADPH pathway is vital for cellular antioxidant defense, as NADPH provides reducing power for various redox reactions. It is primarily synthesized by enzymes such as glucose-6-phosphate dehydrogenase and isopentenol-2,4-diol-1,4-dehydrogenase, which help to maintain the reduced state of antioxidant molecules such as GSH and Trx. These molecules are essential for scavenging free radicals and mitigating oxidative damage.[186] Additionally, NADPH supports the synthesis of reduced thiol and sulfur compounds, further bolstering cellular antioxidant capacity. Many HMs enhance resistance to oxidative stress and treat HPH by modulating the NADPH pathway. Wogonin, a key component of *Scutellaria baicalensis*, is known for its anti-inflammatory, anti-angiogenic, and anti-fibrotic properties. In a network pharmacology study, researchers identified 40 potential targets of wogonin in the treatment of HPH. Their analyses, supported by in vitro experiments, suggest that wogonin's anti-proliferative effects are mediated through the regulation of the HIF-1/NOX4 pathway.[187]

NF-κB is a nuclear transcription factor involved in regulating inflammation, immune responses, and apoptosis.[188] In its inactive state, NF-κB is bound to inhibitor of κB (IκB) in the cytoplasm. External signals, such as inflammatory mediators, cytokines, or oxidative stress, trigger the phosphorylation and degradation of IκB by specific kinases (eg, IKK). This process releases NF-κB, allowing it to translocate to the nucleus, bind DNA, and activate gene transcription. The PI3K/Akt pathway can also activate NF-κB. Activated NF-κB induces the expression of inflammation-related genes, including inflammatory mediators (IL-1β, TNF-α), cell adhesion molecules (ICAM-1, VCAM-1), and pro-inflammatory chemokines (IL-8).[189] Additionally, NF-κB influences the proliferation, differentiation, and survival of immune cells, which are crucial for normal immune function. Many TCMs inhibit NF-κB activity, thereby reducing inflammatory factor levels around pulmonary vessels in HPH and improving the local microenvironment. Andrographolide, a TCM with anti-inflammatory, antioxidant, and anti-proliferative properties, regulates oxidative stress through the NOX/Nrf2 pathway and inflammation via NF-κB. It inhibits increases in $[Ca^{2+}]i$, blocks ROS production, and prevents the upregulation of IL-6, IL-8, ET-1, and VEGF in PASMCs, thereby reversing PVR in patients with HPH.[190]

The RhoA/ROCK pathway is essential for cellular signal transduction, as it regulates various processes such as cytoskeletal remodeling, cell motility, cell proliferation, and gene transcription. The pathway centers on RhoA, a small GTPase, and ROCK, a protein kinase. RhoA, activated by external stimuli, regulates ROCK, which then phosphorylates substrates such as myosin and actin. This affects cellular contraction, morphology, and signaling. Aberrant activation of the RhoA/ROCK signaling pathway is linked to various diseases, including vascular conditions and tumor metastasis.[191] In HPH, RhoA/ROCK pathway activation promotes PASMC proliferation, migration, and contraction, leading to vascular constriction and increased pulmonary arterial resistance, thereby worsening the disease. RhoA/ROCK pathway inhibition is a potential treatment strategy for HPH. Studies reported that ROCK inhibitors, such as fasudil, can reduce pulmonary vascular resistance, improve vascular remodeling, and decrease the right ventricular load, thus enhancing patient outcomes. Sage (*Salvia officinalis* L.), a traditional TCM with anti-bacterial, anti-viral, antioxidant, and anti-thrombotic properties, improved antioxidant enzyme activities and repair tissue damage in hypoxia-preconditioned mice

with HPH. Sage achieved this by downregulating factors such as HIF-1α, PCNA), Bcl-2, CDK4, cyclin D1, and P27Kip1, as well as inhibiting pro-inflammatory cytokines and the RhoA/ROCK pathway.[192] Thus, the RhoA/ROCK signaling pathway is crucial for HPH treatment, and further research might lead to new therapeutic advancements.

The mitochondrial apoptosis pathway is a major mechanism of programmed cell death, guiding cells toward apoptosis by regulating mitochondrial structure and function. Apoptotic signals increase mitochondrial outer membrane permeability, causing the release of specific apoptotic inducers such as Cytc into the cytosol. Cytc then binds to other apoptotic proteins, such as apoptosis-inducing factor, to form complexes that activate caspases, including caspase-9, initiating a caspase cascade.[193] This cascade leads to apoptosis, which is characterized by DNA degradation, cell membrane rupture, cytoplasmic condensation, and apoptotic body formation. Hypoxia decreases mitochondrial membrane potential, disrupts the electron transport chain, and increases free radical production, thereby damaging mitochondrial function. This disruption can alter intracellular Ca^{2+} homeostasis, leading to high Ca^{2+} concentrations, which activate mitochondrial permeability transition pores and further increase outer membrane permeability. Regulatory factors such as Bcl-2 family proteins within mitochondria are involved in this pathway. TCMs often regulate Bcl-2 family proteins, such as Bax and Bak, through antioxidant signaling pathways, influencing mitochondrial outer membrane permeability and mediating PASMC apoptosis[194] (Figure 5).

Clinical Translation Challenges and Current Status of Clinical Trials

While robust preclinical studies (including in vitro and in vivo models) compellingly demonstrate the potential of numerous Traditional Chinese Medicine (TCM) monomers, extracts, and formulas in treating hypoxic pulmonary hypertension (HPH) – with mechanisms involving anti-inflammatory, antioxidant, and anti-proliferative effects on pulmonary artery smooth muscle cells (PASMCs), promotion of PASMC apoptosis, protection of endothelial function, and regulation of ion channels and signaling pathways – significant challenges remain in translating these promising preclinical findings into clinical practice. Currently, the efficacy and safety of TCM for HPH still require rigorous validation through well-designed clinical studies.

Limitations of Preclinical Studies and Translation Barriers

The translational potential of current preclinical evidence for human pulmonary hypertension (HPH) faces significant limitations and hurdles. Widely used rodent models, employing chronic hypoxia or monocrotaline (MCT), successfully capture key pathological hallmarks like pulmonary vascular remodeling and right ventricular hypertrophy. However, they fail to recapitulate the full complexity, heterogeneity, and protracted course of human HPH.[195] Moreover, inherent species differences in drug metabolism, receptor sensitivity, and immune responses between rodents and humans can lead to divergent pharmacological outcomes, while the predominant use of young, healthy animals inadequately models the common clinical scenario of HPH patients with significant comorbidities (eg, COPD, OSAHS, interstitial lung disease) and age-related factors.[195] Compounding this, preclinical studies often utilize high drug dosages and non-clinically relevant routes of administration (eg, intraperitoneal injection), creating a disconnect with feasible human therapeutic regimens; establishing a clinically applicable safe and effective therapeutic window necessitates systematic pharmacokinetic and toxicological bridging studies. Furthermore, research predominantly focuses on single phytochemicals or derivatives (eg, salidroside,[100,126] sodium tanshinone IIA sulfonate,[84,85] resveratrol,[93,133,134] astragaloside IV[92,123,124]), whose mechanisms are relatively tractable, yet this contrasts sharply with clinical practice utilizing complex traditional Chinese medicine (TCM) formulas (eg, Tongxinluo[41,42] or Qili Qiangxin Capsule[44]). The intricate synergistic, additive, or antagonistic interactions within these multi-component mixtures pose substantial challenges for standardization, quality control, mechanistic elucidation, and complicate clinical validation due to their inherent multi-target nature. Critically, the relatively short duration of preclinical studies hinders comprehensive evaluation of potential long-term adverse effects, such as organ toxicity and drug interactions, associated with TCM constituents, especially given their broad biological activities; long-term safety profiles in HPH patients remain largely undefined. Finally, a fundamental misalignment exists in endpoints: preclinical investigations rely heavily on surrogate metrics like hemodynamics (eg, right ventricular systolic pressure, RVSP), histology (eg, vascular remodeling severity, RV hypertrophy index), and molecular biomarkers (eg, protein expression, cytokine levels), whereas clinical trials prioritize patient-centric outcomes

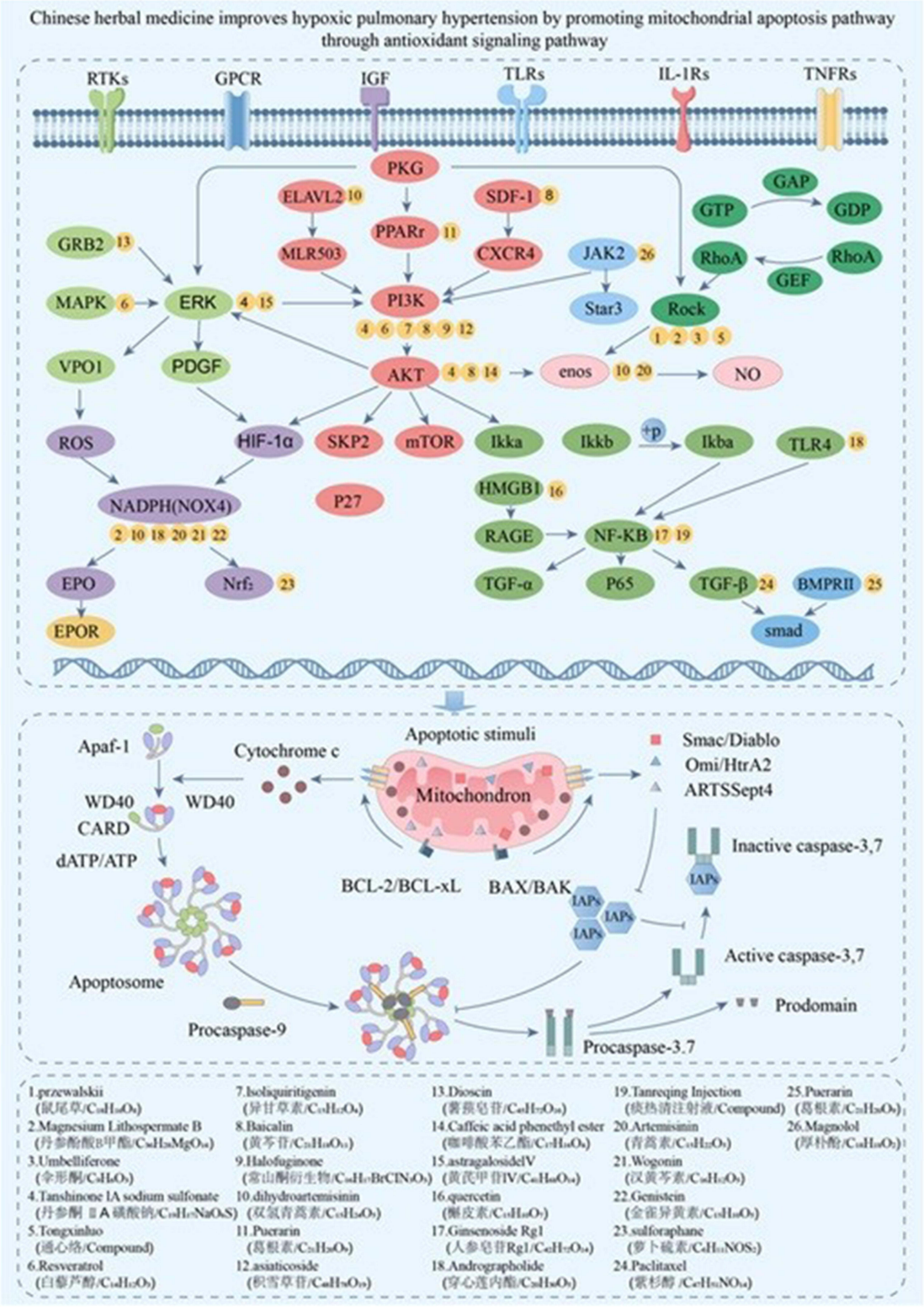

Figure 5 Chinese herbal medicine trigger mitochondrial apoptosis through signaling pathway to relieve abnormal proliferation of pulmonary artery smooth muscle in hypoxic pulmonary hypertension.

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including exercise capacity (eg, 6-minute walk distance, 6MWD), functional class (WHO FC), quality of life, time to clinical worsening, survival, and hemodynamics measured via clinically applicable methods (eg, echocardiography, right heart catheterization).[196] This discordance constitutes a major translational barrier.

Current Evidence from Clinical Trials

The current clinical evidence supporting Traditional Chinese Medicine (TCM) for human pulmonary hypertension (HPH) treatment is markedly limited by a critical shortage of high-quality, large-sample randomized controlled trials (RCTs). Available evidence predominantly originates from exploratory investigations, small-scale trials, observational data, or studies targeting broader pulmonary hypertension (PH) cohorts that may incidentally include subsets of HPH patients. Regarding Chinese Herbal Compounds (CHCs), Qiliqiangxin Capsules[44] (approved by China's NMPA for chronic heart failure) have shown promise in exploratory and small RCTs for improving cardiac function, exercise capacity, and quality of life in PH patients, including those with left heart or lung disease etiologies, with proposed mechanisms involving ventricular remodeling amelioration, diuresis, and anti-inflammatory/neuroendocrine modulation; however, robust RCTs dedicated specifically to HPH populations are absent. Similarly, while preclinical studies of Tongxinluo Capsules[41,42] (primarily indicated for coronary heart disease and ischemic stroke) in animal HPH models suggest benefits via endothelial protection, anti-inflammation, anti-oxidation, and attenuated pulmonary vascular remodeling, clinical research specifically evaluating its efficacy in human HPH remains exceedingly scarce. For other CHCs such as Xuefuzhuyu Decoction[46] or Qibaipingfei Capsules,[47] systematic clinical trial data supporting their use in HPH are largely unavailable, as research has been predominantly confined to animal models. Concerning Chinese Herbal Monomers/Extracts, Breviscapine Injection[54] (Scutellarin, approved for ischemic cardio-cerebrovascular diseases) has limited low-quality clinical reports suggesting potential symptomatic or hemodynamic benefits in connective tissue disease-associated PAH or chronic cor pulmonale, yet no dedicated studies adequately evaluate its role in HPH. Sodium Tanshinone IIA Sulfonate (STS),[145–147] another angina-approved agent, possesses microcirculation-improving and potential anti-remodeling properties; preliminary small studies exploring it as adjuvant therapy for PH/PAH hint at possible benefits in exercise tolerance and hemodynamics, but high-quality RCTs specifically powered for HPH assessment are similarly absent. Potential benefits observed for other monomers like Aucubin[102] in preclinical settings await validation through formal clinical investigations in HPH patients. In summary, although preliminary data and mechanistic plausibility suggest potential utility for certain TCM compounds and monomers in HPH management, the clinical evidence landscape remains fragmented and critically constrained by the profound absence of adequately designed, sufficiently powered RCTs specifically enrolling HPH cohorts. This fundamental evidence gap precludes definitive conclusions regarding their efficacy and safety profiles within this distinct patient population.

Critical Knowledge Gaps and Future Directions

Given the profound methodological limitations and the current state of clinical evidence outlined previously, the clinical translation of Traditional Chinese Medicine (TCM) for human pulmonary hypertension (HPH) faces critical challenges and mandates focused future research. The most fundamental gap remains the acute need for rigorously designed, large-sample, multicenter, placebo-controlled randomized controlled trials (RCTs) dedicated to evaluating the efficacy (using primary endpoints such as 6-minute walk distance [6MWD] and time to clinical worsening) and long-term safety profiles of specific TCM interventions (whether monocomponent agents or standardized complex formulas) within well-defined HPH populations, characterized by precise inclusion criteria reflecting underlying lung disease etiology and PH severity alongside standardized treatment protocols. Addressing the inherent heterogeneity among HPH patients, arising from diverse etiologies, varying disease severities, and distinct comorbidities, requires future research to actively pursue patient stratification strategies leveraging biomarkers of inflammation, oxidative stress, vasoactive factors, and advanced imaging phenotypes to identify specific subgroups most likely to derive benefit from particular TCM therapies. Concurrently, the limited efficacy of current standard therapies (eg, long-term oxygen therapy, pulmonary disease management) underscores the critical importance of exploring TCM as an adjuvant to conventional or emerging Western pharmacotherapies within integrated combination strategies; research must rigorously evaluate potential synergistic effects, safety profiles, and long-term outcomes of such combinations. The inherent complexity of TCM

formulations necessitates an unwavering commitment to ensuring batch-to-batch consistency, stability of active constituents, and safety through the development and stringent enforcement of comprehensive quality standards and Good Manufacturing Practices (GMP). Furthermore, bridging the translational divide requires embedding mechanistic investigations (eg, biomarker analyses, advanced imaging to assess vascular remodeling) within clinical trials to validate whether mechanisms identified preclinically hold true in humans and provide a biological rationale for observed clinical effects. Given the chronic, progressive nature of HPH, the persistent efficacy of any TCM intervention must be evaluated through long-term follow-up studies spanning several years, incorporating assessments of sustained clinical benefits, impacts on survival, and systematic surveillance for potential late-emerging adverse effects including hepatic, renal, and immunomodulatory consequences. Finally, complementing objective clinical measures, a dedicated emphasis on patient-reported outcomes (PROs) focusing on improvements in dyspnea, fatigue levels, functional capacity in daily activities, and overall health-related quality of life is essential to fully capture the therapeutic value of TCM from the patient perspective.

Deficiencies and Prospects

Currently, diagnostic examinations for PH include right heart catheterization, blood gas analysis, X-ray, computed tomography (CT), and echocardiography. Of these, right heart catheterization is the only invasive procedure that provides direct hemodynamic assessment of the pulmonary artery and right ventricle through peripheral venous access, making it the gold standard for diagnosing PH. However, invasive procedures carry risks such as infection and mortality, and human error can alter normal pulmonary vascular and cardiac functions in animal models,[196] potentially leading to unnecessary resource waste.

Among non-invasive methods, blood gas analysis can only assess hypoxemia and the acid-base status without quantifying disease progression. Chest X-ray and CT can observe the size and diameter of pulmonary arteries to assess disease progression, but such changes are negligible in mouse models. Echocardiography uses tricuspid regurgitation velocity to estimate pulmonary artery pressure via the Bernoulli equation; however, even the smallest animal ultrasound probes are significantly larger than the radiation area of a mouse's cardiovascular system. Furthermore, all of these tests detect established pulmonary arterial hypertension, but they cannot identify high-risk individuals or monitor disease progression in animal models.

Focusing on the disease itself, chronic hypoxia often leads to ROS accumulation in the lungs, and ROS levels around the pulmonary vasculature in HPH can reflect disease progression to some extent. Therefore, targeting ROS and synthesizing probes to monitor the progression of HPH represent novel examination and monitoring approaches.

In recent years, significant research has explored the use of probes in medical biology, particularly for acute kidney injury (AKI), a condition with high incidence and mortality rates. Early diagnosis is critical for AKI treatment and prognosis. Although traditional urinalysis methods enable non-invasive molecular-level diagnoses of AKI, their sensitivity remains insufficient. Vanin-1 is considered as an early and sensitive biomarker of AKI. Recent studies developed CL-Pa as a novel chemiluminescent probe targeting vanin-1. This probe significantly aids in the early diagnosis of AKI and assessment of the efficacy of anti-AKI drugs.[197] Another study on atherosclerosis reported a novel small-molecule fluorescent probe capable of sequentially imaging and detecting gamma-glutamyl transferase and hypobromous acid. This probe both accurately identifies the locations of mature plaques and successfully predicts the occurrence of atherosclerotic plaques before they become detectable by conventional immunofluorescence or visual inspection. This technology enables imaging of the locations of mature atherosclerotic plaques and provides early indications of plaque formation.[198] In conclusion, chemical fluorescent probes possess high sensitivity, real-time capability, and intuitiveness. When combined with appropriate targets, they hold promise for quantifying the progression of HPH in disease models and providing early diagnosis.

In recent years, network pharmacology, bulk RNA-seq, single-cell sequencing, and spatial transcriptomics have flourished in biomedical research, but they have yet to be widely applied in the treatment of HPH with TCM. Network pharmacology is an emerging branch of pharmacology based on the principles of systems biology. It reveals the efficacy, toxicity, and metabolic characteristics of drugs through the construction and analysis of biological networks. The research methods of network pharmacology include constructing a multi-layer biological network of "drug–component–target–

disease" and utilizing gene functional annotation and pathway enrichment analysis to investigate the mechanisms of drug action in depth. For instance, in a study of the TCM compound Shenkang injection (SKI) in the treatment of diabetes, researchers screened 280 drug targets from the TCMSP database and identified 1197 diabetic kidney disease (DKD) targets from five disease databases: GenGards, OMIM, Drugbank, TTD, and Disgenet. They performed a protein-protein interaction (PPI) network analysis of the intersection, ultimately identifying 118 overlapping targets. The PPI analysis identified core targets such as NOS3, PTGS2, CASP3, CCL2, CXCL8, HIF1A, and AKT1. In the "drug-component-target-disease" network, quercetin, kaempferol, and luteolin exhibited the highest degrees of interaction, suggesting they are the key active components of SKI in the treatment of DKD.[199] This method both predicts the material basis and mechanisms of TCM efficacy and elucidates the rules of drug combinations and formula compatibility, providing new insights for the complex system research of TCM. Furthermore, the applications of network pharmacology in the field of TCM include identifying potential active ingredients in single herbs or formulas, thus elucidating the mechanisms of action of TCM or formulas and interpreting the scientific connotations of compatibility contraindications in TCM. The advent of single-cell sequencing has enabled researchers to gain deeper insights into cellular heterogeneity, which is challenging to achieve with traditional sequencing technologies. Additionally, single-cell sequencing technology can measure mRNA levels in individual cells, providing insights into the gene expression status of those cells. In cancer research, single-cell sequencing can assist in identifying the roles of different cell types within the tumor microenvironment and their influence on treatment responses in tumor development. In a study on liver cancer,[200] single cell RNA-seq revealed unique immune characteristics of early recurrent hepatocellular carcinoma, including a reduction in Treg counts and an increase in dendritic cell counts. In addition, CD8+ T cells exhibited an innate-like functional impairment state characterized by low cytotoxicity and a low clonal expansion phenotype, and early-relapse tumors exhibited low proliferative capacity and high immune evasion ability. Recurrent malignant cells can disrupt antigen presentation by dendritic cells via the PD-L1/CD80 and CTLA4/CD80 axes and recruit innate $CD161^+$ $CD8^+$ T cells through the CCL20/CCR6 axis, thereby creating a dysfunctional anti-tumor immune response in early recurrent hepatocellular carcinoma. These findings provide a theoretical and experimental basis for improving the efficacy of immunotherapy in liver cancer and identifying strategies to prevent recurrence and metastasis.

Conclusions

This comprehensive analysis establishes that Traditional Chinese Medicine (TCM) exerts multi-target therapeutic effects against hypoxic pulmonary hypertension (HPH) through synergistic modulation of critical pathological pathways. Bioactive components—including Qiliqiangxin compound formulations, salidroside, resveratrol, and sodium tanshinone IIA sulfonate—concurrently ameliorate oxidative stress by activating Nrf2/HO-1 and PI3K/Akt signaling to reduce ROS accumulation; suppress inflammatory cascades via NF-κB inhibition to lower TNF-α, IL-6, and MCP-1 levels; reverse pulmonary vascular remodeling through regulation of K^+/Ca^{2+} channels, induction of PASMC apoptosis, and inhibition of abnormal proliferation via AMPK/p53 and RhoA/ROCK pathways; and protect endothelial function by activating BMPR2/Smad signaling and the NO-sGC-cGMP axis. Critically, TCM's holistic approach addresses HPH's multifactorial complexity more effectively than monotherapies by concurrently targeting complementary disease mechanisms.

Nevertheless, clinical translation faces significant challenges: inconsistent quality control in compound preparations risks batch-dependent efficacy variations, pharmacokinetic uncertainties of multi-component systems impede dosage optimization, and rigorous validation of long-term safety and efficacy in human HPH remains limited. Future research should prioritize three critical domains: standardizing bioactive constituents using chromatographic fingerprinting techniques; validating novel targets such as Aucubin-mediated redox balance through advanced methodologies like single-cell sequencing and spatial transcriptomics; and accelerating clinical innovation via ROS-responsive diagnostic probes, network pharmacology-guided TCM combinations, and randomized trials benchmarking TCM against existing therapies.

In summary, TCM represents a promising paradigm for HPH treatment by integrating multi-target efficacy with holistic intervention. Bridging its empirical foundation with modern scientific rigor—through standardized compound development, mechanism-driven target discovery, and tailored clinical validation—will catalyze the development of next-generation HPH therapies that synergize therapeutic potency with regulatory robustness.

Abbreviations

AREs, antioxidant response elements; AKI, acute kidney injury; AST IV, Astragaloside IV; AMPK, AMP-activated protein kinase; Bsg, Basigin; COPD, chronic obstructive pulmonary disease; CHCs, Chinese herbal compounds; COX-2, cyclooxygenase-2; HMs, Chinese herbal monomers; CCL2, CC-motif chemokine ligand 2; CaSRs, Calcium-sensing receptors; Cytc, Cytochrome C; CT, computed tomography; CAT, catalase; DKD, diabetic kidney disease; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; EndMT, Endothelial-to-mesenchymal transition; GSH-Px, glutathione peroxidase; HPH, Hypoxic pulmonary hypertension; HPV, hypoxic pulmonary vasoconstriction; HSYA, Hydroxysafflor yellow A; HIF-1α, hypoxia-inducible factor 1α; HMGB1, high mobility group box 1 protein; HO-1, heme oxygenase-1; [Ca2+]I, intracellular calcium concentration; IκB, inhibitor of κB; Keap1, Kelch-like ECH-associated protein 1; MCP-1, Monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; MLB, magnesium lithospermate B; mPAP, mean pulmonary arterial pressure; Nrf2, Nuclear factor E2-related factor 2; NFATc3, nuclear factor of activated T cells; NQO1, NAD(P)H:quinone oxidoreductase 1; NO, nitric oxide; PH, Pulmonary hypertension; PASMCs, pulmonary artery smooth muscle cells; PAEC, pulmonary arterial endothelial cell; PDE5, phosphodiesterase-5; PVR, pulmonary vascular remodeling; PaO2, pressure of oxygen in arterial blood; PPARγ, proliferator-activated receptor γ; PCNA, proliferating cell nuclear antigen; PKG-1, protein kinase G1; ROS, reactive oxygen species; ROCK, Rho kinase; STS, sodium tanshinone IIA sulfonate; sGC1, soluble guanylate cyclase 1; SphK1/S1P, Sphingosine-1-phosphate; SKI, Shenkang injection; SOD, superoxide dismutase; SOCE, store-operated calcium entry; TNF, tumor necrosis factor; TCM, Traditional Chinese medicine; Trx-1, thioredoxin-1; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule-1.

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Disclosure

The authors declare that they have no conflict of interest.

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