Review Article

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Natural plant products in treatment of pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a severe disease characterized by progressive remodeling of distal pulmonary arteries and persistent elevation of pulmonary vascular resistance (PVR), which leads to right ventricular dysfunction, heart failure, and eventually death. Although treatment responsiveness for this disease is improving, it continues to be a life-threatening condition. With the clinical efficacy of natural plant products being fully confirmed by years of practice, more and more recognition and attention have been obtained from the international pharmaceutical industry. Moreover, studies over the past decades have demonstrated that drugs derived from natural plants show unique advantages and broad application prospects in PAH treatment, not to mention the historical application of Chinese traditional medicine in cardiopulmonary diseases. In this review, we focus on summarizing natural plant compounds with therapeutic properties in PAH, according to the extracts, fractions, and pure compounds from plants into categories, hoping it to be helpful for basic research and clinical application.

Keywords

pulmonary arterial hypertension, natural products, traditional Chinese medicine, treatment, pulmonary vascular resistance

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Pulmonary arterial hypertension (PAH) is a severe disease characterized by progressive pulmonary vascular remodeling[1–3] and an increase in pulmonary vascular resistance (PVR), which may lead to right ventricular dysfunction, heart failure, and death.[4–6] In addition, the prognosis of PAH is still poor and the mortality rate is highly comparable to cancer. Although treatment strategies for this pulmonary vascular disease are improving, it still represents a life-threatening disorder.

There are several drugs available in clinic, such as inhaled nitric oxide (NO), prostacyclin drugs, endothelin receptor antagonists, Phosphodiesterase type 5 inhibitor, and the latest developed soluble guanylate cyclase stimulator.[7–10] Unfortunately, current therapeutics for PAH are limited; most are designed to reduce pulmonary arterial resistance by inducing vasodilatation. The progressive vascular remodeling is still hardly to be reversed. Thus, there is an urgent need for novel therapies.

Historically, natural products from plants and animals were the source of virtually all medicinal preparations. More recently, natural products have been developed as new medicines in clinical practice after convincing clinical trials, particularly as vascular disease treatment agents (Table 1). Furthermore, the utilization of natural products or natural product structures plays an extremely significant

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Table 1. Natural plants for any vascular disease.

Vascular disease	Natural plants	Efficacy	Reference
Atherosclerosis	Ginkgo biloba leaf	• Reduce atherosclerotic nanoplaque formation and size, suppress atherosclerotic lesion development • Reduce intima-media ratio, decrease proliferation and migration of VSMCs, and induce greater apoptosis • Improve glucose homeostasis and circulating adiponectin levels, attenuate the expression of connexin 43 protein and the concentrations of plasma Homo sapiens C-reactive protein	144–147
	Salvia miltiorrhiza Bunge	• Inhibit atherosclerotic lesion formation in aorta • Lower cholesterol and inhibit low density lipoprotein oxidative modification • Downregulate protein expression and activities of matrix metalloproteinase-2 and matrix metalloproteinase-9 through inhibiting nicotinamide adenine dinucleotide phosphate oxidase 4-mediated reactive oxygen species generation	148–151
	Green tea	• Protect apolipoprotein $E^{-/-}$ mice from atherosclerosis through the Jagged 1/Notch pathway • Attenuates atherosclerotic lesion formation and development through decreasing macrophage cholesterol content and MCP-1 expression in macrophages • Reduce total cholesterol, triglycerides, low-density and very low-density lipoprotein cholesterol fractions, and increase high-density lipoprotein	152–154
	Astragalus membranaceus	• Alleviate the extent of atherosclerosis in aorta of apolipoprotein $E^{-/-}$ mice • Suppress the progression of atherosclerotic lesions and the inflammatory reaction • Reduce plasma levels of total cholesterol and low-density lipoprotein cholesterol, increase high density lipoprotein cholesterol levels, and reduce the aortic fatty streak area	155–157
Thrombus and platelet aggregation	Ginkgo biloba leaf	• Inhibit platelet aggregation induced by oxidative stress, platelet activation factor, or collagen • Reduce the plasma levels of thromboxane B2 and prostacyclin metabolites • Inhibit the production of cyclooxygenase-1-mediated thromboxaneA2 in platelets and cyclooxygenase-2-mediated prostaglandin I2 in endothelial cells non-selectively	158,159
	Salvia miltiorrhiza Bunge	• Inhibits thrombosis formation, platelet aggregation • Inhibits platelet adhesion to immobilized collagen by interfering with the collagen receptor $\alpha 2\beta 1$ • Suppress $[Ca^{2+}]^{i}$ mobilization and arachidonic acid liberation	160–165
	Uncaria rhynchophylla	• Inhibit platelet aggregation and antithrombotic • Reduce the thromboxane B2 generation in platelet rich plasma induced by collagen • Suppress the formation of malondialdehyde in platelet suspension stimulated by thrombin and inhibit the release of platelet factor 4	166–168
	Anemarrhena asphodeloides	• Inhibit platelet aggregation, blood coagulation, as well as the formation of a thrombus • Delay the activated time of thromboplastin • Antiplatelet and anticoagulation	169,170
	Panax notoginseng	• Inhibit platelet aggregation and plasma coagulation • Suppress thrombin-induced platelet superficial activation and adhesion in vitro and improve hypercoagulable state in vivo • Over-express peroxisome proliferator-activated receptor γ protein and mRNA and upregulate phosphatidylinositol 3 kinase/protein kinase B through endothelial NOS pathway in platelet	171–173

(continued)

Table 1. Continued

Vascular disease	Natural plants	Efficacy	Reference
Hypertension	Ginkgo biloba leaf	• Protect against hypertension with hypercholesterolemia-induced renal injury • Reduce vasospasm and increase relaxation • Suppress renal oxidative stress, nitrosative stress, and inflammation	174–176
	Salvia miltiorrhiza Bunge	• Lower arterial blood pressure under basal conditions in spontaneously hypertensive rat models and relax coronary arteries in a cumulative dose-dependent manner • Decreased the average blood flow velocity in liver in ET-1 induced portal hypertension • Improve cardiac function and reduce arterial blood pressure partially via inhibiting nicotinamide adenine dinucleotide phosphate oxidase and activating the nitric oxide signaling pathway	177–179
	Uncaria rhynchophylla	• Anti-hypertensive, anti-arrhythmic, anti-thrombotic and inhibit platelet aggregation • Lower the blood pressure, improve the structural integrity of vascular endothelium • Decrease the expression of intercellular adhesion molecule 1 and selectin P, block the release of calcium from intracellular stores	180–184
	Ligusticum wallichii Rhizome	• Elicit an effect on vasorelaxation in isolated rat aortas and anti-hypertension in spontaneously hypertensive rat • Reduce portal pressure in portal hypertensive rats	185,186
Ischemia-reperfusion injury	Ginkgo biloba leaf	• Protect against myocardium ischemic/reperfusion injury by decreasing oxidative stress, repressing inflammatory cascade in vivo, and inhibiting toll-like receptor 4/nuclear factor kappa B pathway in rat model • Suppress renal epithelial tubular cell apoptosis • Decrease NO production by inhibiting gene and protein expression and enzymatic activity of inducible NOS	187–190
	Salvia miltiorrhiza Bunge	• Prevent cardiac ischemic/reperfusion injury and improve cardiac function in a rat model of hypertrophy • Protect against neonatal hypoxia-ischemia brain injury in vivo by an increase in the ratio of Bcl-2 to Bax expression • Protect the mitochondrial membrane from the ischemia-reperfusion injury and lipid peroxidation through an electron transfer reaction in mitochondria against forming reactive oxygen radicals	191–193
	Uncaria rhynchophylla	• Protect against cerebral ischemia/reperfusion damage • Significantly reduce infarct volume and improve neurological function after ischemic brain injury through the inhibition of lipopolysaccharide-stimulated production of pro-inflammatory cytokines • Reduce the lipid peroxidation injury of brain cells through inhibiting the NOS activity and increasing the superoxide dismutase activity	194,195
	Ligusticum wallichii Rhizome	• Suppress ischemia-induced ventricular arrhythmias and reduce the infarct size resulting from ischemia/reperfusion injury • Enhance myocardial antioxidant status through induction of heme oxygenase-1 and inhibition of neutrophil and improve the immunity profile in ischemic-reperfusion rats • Protect cells against glutamate-induced apoptosis via the inhibition of oxidative stress and a change in the levels of apoptosis-related proteins, Bcl-2 and Bax	196–199

(continued)

Table 1. Continued

Vascular disease	Natural plants	Efficacy	Reference
	Anemarrhena asphodeloides	• Reduce cerebral ischemia/reperfusion-induced inflammatory cell activation and pro-inflammatory mediator production • Decrease total infarct volume and edema in the ipsilateral hemispheres of ischemia-reperfusion rats • Inhibit increased neutrophil infiltration of ischemic brain tissue • Reduce myeloperoxidase positive cells in striatal and cortical areas	200

Bcl-2, B cell leukemia/lymphoma 2; Bax, Bcl-2-associated protein x; ET-1, endothelin-1; NO, nitric oxide; NOS, nitric oxide synthase.

role in the drug discovery and development process. A detailed analysis of new medicines approved by the U.S. Food and Drug Administration during 1981–2010 revealed that 34% of those medicines based on small molecules were natural products or direct derivatives of natural products, including the stains, tubulin-binding anticancer drugs, and immunosuppressants.[11,12] Furthermore, because of the increasing high cost and lengthy development process of chemical drugs, the natural products industry, characterized by ''naturopathy,'' is thought to become the most promising industry in the global pharmaceutical industry. Interestingly, studies over the past decades have demonstrated that drugs derived from natural plants show unique advantages and broad application prospects in PAH treatment, not to mention the historical application of traditional Chinese medicine (TCM) in cardiopulmonary diseases. Experimental and clinical research revealed that natural products can ameliorate the symptoms and improve prognosis of PAH. Additionally, some natural products selectively improve the pulmonary circulation without affecting systemic arterial pressure. In this review, we will summarize the current knowledge about the natural plant compounds with the potential and promising therapeutic properties in the field of PAH, according to the extracts, fractions, and pure compounds from plants into categories, hoping it will provide useful information for future basic research and clinical application (Table 2).

Alkaloids

Alkaloids are a group of alkaline nitrogenous natural products, which are widely distributed in plants and usually exhibit a broad range of pharmacological activities including anti-tumor, anti-inflammatory, anti-viral, and analgesic.[13–15] Many of them have been used in traditional and modern drug development.

Ligustrazine

Ligustrazine, also known as tetramethylpyazine, is an effective constituent of *Scechwan Lovage Rhizome*. It also exists in the rhizome of *Curcuma aromatica Salisb* and *Jatropha podagrica Hook*. Studies have shown that ligustrazine can significantly reduce mean pulmonary arterial pressure (mPAP), PVR, and the plasma endothelin-1 (ET-1) levels in acute hypoxia-induced pulmonary hypertension (PH) dogs;[16] and meanwhile upregulate NO levels in patients with PAH, through alleviating the damage of pulmonary arterial endothelial cells (PAECs) and restoring the balance between vasoactive factors.[17]

There are several possible contributions to the function of ligustrazine. It is revealed that ligustrazine can inhibit platelet aggregation and prevent thrombosis effectively.[18,19] It has also been discovered that ligustrazine can block the release of reactive oxygen species from lung tissue[20] and moderate the upregulation of hypoxia-inducible factor 1 and vascular endothelial growth factor (VEGF) expression, which consequently reduces hypoxia-induced lung injury.[21] Also, ligustrazine is a Ca^{2+}channel antagonist which can dilate the blood vessels during hypoxia by blocking Ca^{2+} influx.[22,23] This may be one of the principal mechanisms responsible for the protective effect of ligustrazine in patients with PAH.

Tetrandrine

Tetrandrine (TET) is a bisbenzylisoquinoline alkaloid extracted from the root of *Stephania tetrandra S. Moore*. It also existed in the stem of *Menispermum dauricum DC*, the root of *Stephania cepharantha Hayata*, and *Cyclea barbata (Wall.) Miers*. Xie et al. and Wei et al. found that TET produces multiple pharmacological effects, for instance, protecting myocardial, cerebral, and renal ischemia.[24,25] Remarkably, it also helps to prevent hypoxic PH.

In 2010, Feng et al. reported that TET selectively ameliorated monocrotaline (MCT)-induced PAH in rats by reducing PVR and right ventricular hypertrophy (RVH) without affecting the systemic pressure, thus significantly reversing the damage of pulmonary vascular and lung tissue,[26] which merits TET as a candidate for PAH treatment. Furthermore, in 2014, Feng et al. demonstrated that TET could reverse the elevation of mPAP and the remodeling of small pulmonary arteries, induced by MCT.[27]

TET acts as an antagonist of some vasoconstriction factors such as platelet-activating factor, angiotensin II, and prostaglandin F, which play a significant role in the occurrence and development of PAH. Studies have demonstrated that TET could directly downregulate the expression of

Table 2. Natural plant products for possible PAH treatment.

Category	Natural products	Origin	Efficacy	Mechanism	Subjects	Reference
Alkaloids	Ligustrazine	*Ligusticum wallichii Rhizome*; *Curcuma aromatica Salisb*; *Jatropha podagrica Hook*	Decrease plasma ET-1 level, reduce mPAP and PVR		Dog	16
			Enhance the synthesis and release of NO and suppress those of ET-1; decrease mPAP, internal diameter of right ventricle, and outflow of right ventricle		Human	17
			Attenuate the plate aggregation, reduce thrombus formation and blood viscosity, accelerate blood flow restoration		Rat	18
			Inhibit the platelet aggregation formation and thrombus		Human	19
			Inhibit platelet activation	Inhibit the intracellular calcium ion concentration	Rat	20
	Tetrandrine	*Stephania tetrandra S.Moore*; *Cyclea barbata (Wall.) Miers*; *Menispermum dauricum DC*	Inhibit PASMCs proliferation, improve endothelial function; reduce mPAP and RVH index; reverse pulmonary vascular remodeling and attenuate oxidation in lung	Adjust the imbalance of the NO signaling pathway and change the expression of inducible NOS and cyclic guanosine monophosphate-dependent protein kinase-1.	Rat	27,30
			Inhibit the activity of serum angiotensin enzyme, decrease the amount of angiotensin I converted to angiotensin II, suppress the proliferation of medullar collagen and PASMCs in pulmonary acinar artery, reduce pulmonary vasoconstriction and lower PH			26,28,29,31
				TET is a calcium antagonist that blocks the influx of calcium from vascular smooth muscle, relaxes vascular smooth muscle; it also decreases the content of prostaglandin F2 in the lung, so as to reduce the contractility of the pulmonary vasculature and thus reduce the PH		32
Flavonoids	Ginkgo biloba extracts	*Ginkgo biloba*	Relieve RVH and reduce chronic hypoxic PH	Attenuate the function of PKC signal channel	Rat	40
				Antagonize platelet activating factor, angiotensin and reduce blood viscosity		41
	Puerarin	*Puerarin lobat (Willd) Ohwi*	Inhibit pulmonary vascular remodeling, RVH, and PH	Inhibit the deposition of collagen	Rat	47

(continued)

Table 2. Continued

Category	Natural products	Origin	Efficacy	Mechanism	Subjects	Reference
			Reduce mitochondrial membrane potential, cytochrome C release and caspase-9 activation, inhibit cell growth and apoptosis	Downregulated the expression of elongation factor 2	Rat	48
				Downregulate Bcl-2 and upregulate Bax.	Human	49
Glycosides	Salidroside	*Rhodiola rosea L*	Rhodiola has been shown to be beneficial in high-altitude PH			56
			Reduce mPAP and RVH, attenuate remodeling of pulmonary arterial	Lower VEGF expression	Rat	57
			Inhibit transforming growth factor beta expression and attenuate PH			58
			Reverse hypoxia-induced inhibition of Cytochrome C release from mitochondria into cytoplasm, enhance the cleavage of caspase 3, and increase adenosine A2a receptor expression	Enhance adenosine A2a receptor related mitochondria-dependent apoptosis	Mice	60
			Exert protective effect against PAH via rebalancing cell proliferation and mitochondria-dependent apoptosis of PASMCs	Decrease the expression of cyclin D1 and increase the accumulation of P27 by blocking the protein kinase B/glycogen synthase kinase 3 beta signaling pathway	Rat PASMCs	61
			Inhibit DNA synthesis and proliferation of rabbit PASMCs, reduce pulmonary vascular remodeling	Inhibit upregulation of Ca^{2+} concentration induced by hypoxia in PASMCs	Rabbit	62
			Reverse hypoxia-induced PASMC proliferation and apoptosis resistance, attenuate chronic hypoxia-induced RVH and pulmonary artery remodeling	Inhibit PASMC proliferation via AMPKα-p53-p27/p21 pathway and reverse apoptosis resistance via AMPKα1-P53-Bax/Bcl-2-caspase 9-caspase 3 pathway	Rat	63,64
	Polydatin	*Polygonumcuspidatum Sieb. et Zucc*; *Fallopia multiflora (Thunb.) Harald*	Improve fibrinolytic activity, increase cardiac output, and reduce PAP		Pig	69
			Regulate NO, angiotensin II, ET contents in the serum and lung samples, reverse remodeling, and attenuate hypoxic PH	Attenuate the phosphorylation of PKCα and δ induced by H_2O_2; meanwhile, increase the phosphorylation of PKCε which has antioxidant effects	Rat	70
	Icariin	*Epimedium*	Markedly shorten right ventricle systolic duration and notably prolong diastolic duration and attenuate the		Rat	87

(continued)

Table 2. Continued

Category	Natural products	Origin	Efficacy	Mechanism	Subjects	Reference
			abnormal hemodynamics of pulmonary artery and right ventricle			
			Attenuate mPAP, RVH index and pulmonary artery remodeling	Decrease the contents of serum angiotensin II, ET, prostaglandin F2, thromboxane A2, and prostaglandin I2, and inhibit the gene expression of angiotensin I converting enzyme, cytochrome c oxidase subunit II, and thromboxane A synthase		88
			Upregulate the expression of endothelial NOS and downregulate the expression of 5-type phosphodiesterase inhibitors, increase the content of NO and cyclic guanosine monophosphate in lung tissue and ameliorate PH	Protect against MCT-induced PAH in rats through increase of NO/cyclic guanosine monophosphate signaling pathway		90
Diterpenoids	Tanshinone IIA	*Salvia miltiorrhiza Bge*; *Salvia sclarea L*; *Salvia przewalskii Maxim*	Recover acute hypoxia-induced downregulation of I_{kv} currents and upregulate the mRNA and protein expression of Kv1.5 and Kv2.1 in PASMCs, reduce right ventricular systolic pressure and RVH, and restrain pulmonary wall remodeling	Reverse the I_{kv} currents through modulate the expression of Kv channels in pulmonary arterioles	Rat	91
			Inhibit cell proliferation	Arrest cells in G1/G0-phase by slowing down the hypoxia-induced degradation of p27 via serine threonine kinase 1/S-phase kinase associated protein 2-associated pathway		92
	Sodium Tanshinone IIA sulfonate		Decrease right ventricular systolic PAP and RVH, attenuate medial wall thickening, PVR and remodeling	Inhibit increase of transient receptor potential superfamily members 1,6 and decrease SOCE through reducing the numbers or activity of SOCC and basal $[Ca^{2+}]$		95
				Stimulate Kv2.1 expression through the regulation of intracellular Ca^{2+} homeostasis		96

(continued)

Table 2. Continued

Category	Natural products	Origin	Efficacy	Mechanism	Subjects	Reference
			Reduce pulmonary artery systolic pressure and Borg dyspnea score, improve exercise capacity, and decrease WHO FC of PH from III or IV down to II		Human	94
	Triptolide	*Tripterygium wilfordii Hook. F.*	Promote the regression of pulmonary artery neointimal formation, attenuate the development of RVH, pulmonary remodeling, and PH	Antiproliferation and anti-inflammatory effects or enhancement of apoptosis in PAECs	Rat	99
				Inhibit the activity of matrix metalloproteinases		100,101
				Effect the balance of matrix metalloproteinase 9/tissue inhibitor of metalloproteinase 1		102
Pyanocoumarins	Praeruptorin A	*Peucedanum Praeruptonrum Dunnon*	Inhibit PASMC proliferation and attenuate PH	Inhibit chronically hypoxic enhancement of basal $[Ca^{2+}]^i$ and SOCE	Rat	114
				Inhibit hypoxia caused Kv1.5 and Kv2.1 mRNA expression down, maintain cell membrane potential balance		117
Stilbenes	Resveratrol	*Polygonum cuspidatum*; *Arachis hypogaea Linn.*; *Fructus Mori* and *Vitis vinifera L.*	Prevent hypoxia-induced human PASMC proliferation, attenuate RVH	Induct the serine threonine kinase 1-dependent inhibition of arginase II.	Human	122
			Attenuate oxidative stress and inhibit inflammatory reaction, improve the function of PAECs, reverse the right ventricle and pulmonary artery reconstruction		Rat	123
			Reduce mPAP and PH	Suppress the expression of MCP-1 and p- p38-mitogen-activated protein kinase expression	Rat	127
Others	Semen lepidii	*Descurainia Sophia (L)*	Enhance myocardial contractility, reduce PH		Rabbit	129
			Increase partial pressure of O_2 and decrease partial pressure of CO_2, reduce mPAP and PVR		Human	130
			Reduce right ventricular systolic and diastolic blood pressure and mPAP		Rat	131 132

(continued)

Table 2. Continued

Category	Natural products	Origin	Efficacy	Mechanism	Subjects	Reference
	Radix Astragali	*Astragalus membranaceus (Fisch) Bge.*; *Astragalus membranaceus (Fisch) Bge.var. Mongholicus (Bge.) Hsiao*	Inhibit proliferation of adventitial cells, hypertrophic of tunica media, muscularization of non-muscular arteries and the structural remodeling of intra-acinar pulmonary arteries and PH	Preserve the endothelial cells, dilate the pulmonary circulation, and improve hemodynamic condition	Rat	134
			Preserve intra-acinar pulmonary arteries wall cells proliferation, dilate pulmonary artery, inhibit intra-acinar pulmonary arteries remodeling, and improve PH			135
			Regulate the concentration of ET-1and NO in pulmonary tissue, reverse the reconstruction of pulmonary vessels partially			136,137
			Decrease the concentration of thromboxane A2 and reverse the remodeling of pulmonary artery partly			138
			Regulate the concentration of superoxide dismutase and oxygen free radicals in pulmonary tissue	Protect pulmonary vascular from hypoxia by anti-oxidant effects		139
			Eliminate oxygen free radicals and reduce blood viscosity		Human	140

AMPK, adenosine monophosphate-activated protein kinase; Bcl-2, B cell leukemia/lymphoma 2; Bax, Bcl-2-associated protein x; ET-1, endothelin-1; FC, functional class; Kv, voltage-gated K^+; MCT, monocrotaline; mPAP, mean pulmonary arterial pressure; NO, nitric oxide; PAEC, pulmonary arterial endothelial cell; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PASMC, pulmonary artery smooth muscle cell; PKC, protein kinase C; PVR, pulmonary vascular resistance; RVH, right ventricular hypertrophy; SOCC, store-operated calcium channel; SOCE, SOCC-mediated store-operated Ca^{2+} entry; TET, Tetrandrine; WHO, World Health Organization.

platelet-derived growth factor and basic fibroblast growth factor in rats with PAH, thus inhibiting vascular smooth muscle cell (VSMC) proliferation, relieving pulmonary vascular remodeling, and consequently attenuating the development of PAH.[28,29] Furthermore, TET improves the function of PAECs and remits mPAP by attenuating the expression of inducible nitric oxide synthase (NOS) and upregulating the expression of protein kinase 1 in the lung tissue of PAH rats. TET also increases the activity of superoxide dismutase in lung tissue, accelerates the scavenging of oxygen free radicals, and prevents the impairing of lung function cells.[30] It is generally accepted that hypoxic vasoconstriction can be inhibited by Ca^{2+} channel blockers via blood vessels dilatation. TET is thought to be a weaker calcium channel antagonists and studies have suggested that TET can turn down Ca^{2+} influx by blocking Ca^{2+} channels, which partly contributes to the protective effect of TET in PAH.[31,32]

Flavonoids

Flavonoids are widely distributed in plants and berries, such as *Ginkgo biloba Linn*, *puerarin lobata*, *Crataegus pinnatifida*, and *Vitis vinifera*. Modern pharmacological studies have revealed that these compounds possess obvious pharmacological effects in the cardiovascular and endocrine system.[33–35] Many preparations have been utilized as medicines, such as puerarin-based Yufeng Ningxin tablets and ginkgo preparations of Tianbao Ning.[36]

Ginkgo biloba extracts

Nowadays, Ginkgo biloba extracts (GBEs) are widely used in treating cardiovascular diseases for their outstanding pharmacological effects. The main active components of GBEs are flavonoids and diterpenoids. Ginkgo biloba flavonoids have strong anti-oxidation and free-radical scavenging effects. Diterpenoids, such as Ginkgolide B, can also reduce the generation of free radicals.[37]

Also, GBEs exert promising effects on improving acute lung injury (ALI) via downregulating the c-Jun N-terminal kinase and protein kinase B-dependent nuclear factor κB activation pathway.[38] Moreover, they inhibit platelet activation and aggregation induced by platelet factors and therefore have the potential to improve blood circulation.[39]

Studies have shown that Ginkgo biloba can reduce chronic hypoxic PH and relieve RVH, which is partly related to the attenuation of the function of the protein kinase C (PKC) signal channel.[40] It is also reported that Ginkgo Plus significantly reduces the hypoxia-induced increase of mPAP and PVR as well as the ratio of right ventricular weight vs. left ventricular plus septal weights.[41] GBEs alleviate the apoptosis of endothelial cells (ECs) caused by hydrogen peroxide.[42] In addition, they stabilize inflammatory cells and show anti-inflammatory effect by decreasing the release of inflammatory mediators.[43] Furthermore, GBEs may decrease the concentration of NO and increase superoxide dismutase activity in plasma accompanied by the downregulation of inducible NOS expression.[44] Consequently, GBEs indirectly decrease the injury of pulmonary vascular ECs and improve PAH.

Puerarin

Puerarin is isolated from the dried roots of puerarin lobata (Willd.) Ohwi. It dilates blood vessels, decreases myocardial oxygen consumption, and improves myocardial ischemia.[45,46] Recently, Li et al. observed that puerarin could improve pulmonary vascular remodeling in rats with PH by inhibiting the deposition of collagen.[47] A study also showed that puerarin exerted protective effects in MCT-induced PAH rats.[48] Furthermore, puerarin can induce the release of cytochrome C, activate caspase-9, downregulate B cell leukemia/lymphoma 2 (Bcl-2), and upregulate Bcl-2-associated protein x (Bax) expression. It can scavenge oxygen free radicals and inhibit the proliferation of smooth muscle cells (SMCs). Studies have also confirmed that puerarin induces human pulmonary artery smooth muscle cells (PASMCs) apoptosis via a mitochondria-dependent pathway.[49]

Glycosides

Many Chinese herbal medicines contain glycosides such as ginseng, liquorice, Rhodiola, Polygonum cuspidatum, etc., which are effective ingredients with powerful activities.

Salidroside

Medicinal plant *Rhodiola rosea L* is a kind of perennial herb; it contains salidroside, tyrosol, flavonoid compounds, amino acids, trace elements, and other ingredients. Rhodiola mainly possesses effects of anti-aging, anti-anoxia, anti-fatigue, anti-depressants, and anti-radiation.[50–53] It can also enhance immunity, regulate the nervous system, and protect the cardiovascular system.[54,55] Above all, Rhodiola has great therapeutic potential.

Rhodiola can significantly inhibit VSMC proliferation and contraction, and reduce the concentration of plasma ET-1 in rats with PH. It is also suggested that Rhodiola inhibits ET-1 expression and promotes the synthesis and the release of NO by affecting pulmonary vasculature selectively. Furthermore, Rhodiola can alleviate the imbalance of systolic and diastolic pulmonary arterial pressure. It also lowers mPAP, alleviates RVH, and improves PH which may be associated with the declined expression of VEGF in the pulmonary arteriolar wall.[56,57] In addition, Rhodila has a notable effect on high-altitude environment-induced PH rats, and inhibition of transforming growth factor beta-1 expression is one of the possible mechanisms.[58]

Adenosine A2a receptor, which is one of the G protein coupled receptors, shows the effects of anti-inflammation after being activated by adenosine and analogues under

physiological and pathological conditions.[59] Moreover, studies have shown that the Salidroside, as a main pharmacological ingredient of Rhodiola, can increase the expression of Adenosine A2a receptor in PASMCs, reversing the downregulated ratio of Bax and Bcl-2 induced by hypoxia. Furthermore, it also promotes the release of mitochondrial cytochrome C into the cytoplasm, accelerates the elimination of caspase 9 via mitochondrial pathway, and thus enhances apoptosis. In addition, Salidroside can reverse the remodeling of pulmonary arterial pressure induced by chronic hypoxia and therefore alleviate the mPAP.[60]

Also, Salidroside inhibits platelet-derived growth factor-BB-induced proliferation and DNA synthesis of PASMCs by blocking the process of G0/G1 to S phase. This may be related to decreasing the expression of cyclin D1 and increasing the accumulation of p27 by blocking the protein kinase B/glycogen synthase kinase-3β signaling pathway.[61] In recent years, the relationship between adenosine monophosphate-activated protein kinase (AMPK) and lung disease has increasingly caught the attention of researchers. The current studies suggest that AMPK also plays a vital role in treating lung cancer, bronchial asthma, PAH, and other pulmonary diseases. Besides, Salidroside inhibits the increase of G2/M phase cells induced by hypoxia via AMPKα1-P53-P27/P21 pathway. Accordingly, the proliferation and DNA synthesis of PASMCs are inhibited.[62] In addition, Salidroside lowers the levels of P21 and P27, upregulates P53, and mediates apoptosis by regulating the expression of Bax and Bcl-2 via AMPKα1-P53-Bax/Bcl-2-caspase 9-caspase 3 pathway. Consequently, the imbalance of PASMCs proliferation and apoptosis are restored, the pulmonary arterial remodeling is inhibited and the chronic hypoxia-induced PH[63] is relieved via AMPKα1-P53 pathway.[64]

Polydatin

Polygonum cuspidatum Sieb. et Zucc is a TCM which is mainly used for treating chronic bronchitis, traumatic injury, and damp-heat jaundice clinically.[65,66] Polydatin (PD) is the main active ingredient extracted from *Polygonum cuspidatum Sieb. et Zucc* and *Fallopia multiflora (Thunb.) Harald* with the pharmacological effects of suppressing myocardial cell contraction and platelet aggregation, anti-oxidation, and anti-shock.[67,68] It is reported that PD significantly reduces PAP in hypoxic animals and it can increase cardiac output and improve fibrinolytic activity.[69] Moreover, Miao et al. observed that PD can alleviate hypoxic PH and reverse remodeling, which attributes to a protective role in treating oxidative stress injury via PKC signaling pathway.[70] On the one hand, PD attenuates the phosphorylation of PKCα and δ induced by H_2O_2; meanwhile, it increases the phosphorylation of PKCε which has antioxidant effects.[71] On the other hand, PD alleviates lung injury[72] through inducing apoptosis and inhibiting proliferation by depressing the cell cycle, upregulating Bax, and downregulating Bcl-2.[73] However, the exact mechanism of PD reducing the mPAP needs to be further researched and confirmed.

Icariin

Icariin (ICA), a typical flavonol glycoside isolated from the Chinese medical herb Epimedium and has been reported to have abundant pharmacological effects, including antidepressant,[74–76] anti-inflammation,[77,78] anti-oxidative stress,[79–81] heart failure inhibition,[82] cardiovascular protection,[83] and sexual and immune function enhancement.[84–86]

In 2016, Li et al. confirmed that ICA could alleviate the abnormal hemodynamics of the pulmonary artery and right ventricle in PAH model rats induced by MCT, with systolic PAP, diastolic PAP, mPAP, right ventricular systolic pressure, right ventricular diastolic pressure, mean right ventricular pressure reduced, right ventricular preload decreased, compensatory enhancement of right ventricular systolic and diastolic function eased, and right ventricular maximum dP/dt and right ventricular minimum dP/dt absolute value dropped. Furthermore, ICA can slow down the heart rate and prolong the cardiac cycle of PAH model rats. Also, the length of the diastolic period in the cardiac cycle increases gradually following the increase in ICA administration dosage; therefore, it is conducive to improve cardiac function.[87] In addition, ICA treatment is reported to significantly attenuate mPAP, RVH index, and pulmonary artery remodeling, and to decrease the contents of serum angiotensin II, ET, prostaglandine F2α, thromboxane A2, and prostacyclin, and to inhibit the gene expression of angiotensin converting enzyme, cyclooxygenase-2 and thromboxane A2 synthetase.[88] Moreover, Li et al. found that ICA administration could increase the contents of NO and cyclic guanosine monophosphate by improving expression of endothelial NOS[89] and inhibition of 5-type phosphodiesterase in lung tissue of the MCT-injected rats. That is to say, ICA may be effective in protecting against MCT-induced PAH in rats through the increase of NO/cyclic guanosine monophosphate signaling pathway.[100]

Diterpenoids

Diterpenoid compounds mostly exist in the form of resins, lactones, or glycosides in nature. Tanshinone compounds and triptolide are the main tricyclic diterpenes that affect PAH.

Tanshinone IIA

Tanshinone IIA is a main constitute of *Salvia miltiorrhiza Bge*, *Salvia sclarea L*, and *Salvia przewalskii Maxim*. Luo et al. reported that Tanshinone IIA could inhibit cell proliferation and pulmonary vasoconstriction. Furthermore, it can alleviate the downregulation of voltage-gated K^+(Kv)1.5 and Kv2.1 in messenger RNA (mRNA) and protein levels induced by chronic hypoxia and upregulate the

level of Kv-mediated currents in PASMCs, which leads to reduced mPAP.[101] There were also reports that Tanshinone IIA inhibited hypoxia-induced PASMC proliferation through arresting the cells in the G1/G0-phase by slowing down the degradation of p27 via protein kinase B/S-phase kinase associated protein 2-associated pathway.[102] Meanwhile, Tanshinone IIA inhibits the binding of non-canonical nuclear factor-κB and activator protein-1 to DNA, thus suppressing tumor necrosis factor (TNF)-α-mediated migration of SMCs.[103]

Sodium Tanshinone IIA Sulfonate is a water-soluble derivative of Tanshinone IIA. Wang et al. have identified that Sodium Tanshinone IIA Sulfonate exerts promising effects on treating PH,[104] including lowering mean right ventricular systolic pressure, and relieving RVH and pulmonary arterial wall thickness.[105] In addition, it is well-known that intracellular Ca^{2+} plays a crucial role in the complex mechanisms of VSMC contraction and proliferation. Store-operated calcium channel (SOCC) is mainly composed of canonical transient receptor potential superfamily members and the expression of transient receptor potential superfamily member 1,6 are upregulated selectively by chronic hypoxia. Recently, studies indicated that the upregulation of SOCC induced by hypoxia is the main reason for the imbalance of calcium ions in SMCs. Consequently, the results indicate that Sodium Tanshinone IIA Sulfonate reduces SOCC-mediated store-operated Ca^{2+} entry (SOCE) by inhibiting the chronic hypoxia-induced expression upregulation of transient receptor potential superfamily member 1,6 in remote PASMCs of rat.[105] Thus, it lowers the concentration of intracellular calcium, dilates pulmonary vasculature, and decreases mPAP.[106]

Triptolide

Triptolide is the active component of TCM *Tripterygium wilfordii Hook*. *F*., which exhibits a variety of pharmacological effects, such as anti-inflammatory and immune suppression.[107,108] Research shows that Triptolide can alleviate the development of PH and RVH, and promote regression of pulmonary arterial neointimal formation, possibly through the inhibition of matrix metalloproteinases activity.[109–111] Moreover, it attenuates the development of PH and RVH in rats receiving MCT injection. Effects on the expressions of matrix metalloproteinases-9 and tissue inhibitor of metallopmteinase-1 may play an important role in facilitating the regression of vascular remodeling.[112] Furthermore, it also can improve the early inflammatory infiltration of PAH and reduce inflammation reaction. In addition, Triptolide may improve the MCT-induced PAH by inhibiting cell proliferation and inducing apoptosis.[113]

Pyranocoumarins

Pyranocoumarin compounds are widely found in the plant kingdom, especially in angiosperms such as *Umbelliferae*, *Rutaceae*, *Leguminosae*, etc., with biological activities of anti-acquired immunodeficiency syndrome, anti-tumor, and cardiovascular disease treatment.[104,105]

Praeruptorin A

Peucedanum Praeruptonrum Dunnon, a well-known TCM, is mainly used for the treatment of respiratory diseases in people. In the 1980s and 1990s, Wang et al. found that *Peucedanum Praeruptonrum Dunnon* and its extracts had therapeutic effects on PAH animals. Not only can they reduce mPAP and ameliorate pulmonary circulation of a PAH animal model, but they can also suppress pulmonary inflammation.[106,107] The following studies demonstrated that *Peucedanum Praeruptonrum Dunnon* can reduce mPAP without influencing the systemic artery pressure and can decrease the right heart index and thickness of small pulmonary artery media significantly. It was also reported that the composition of tenascin-C decreased significantly in pulmonary vasculature of rats upon treatment with *Peucedanum Praeruptonrum Dunnon*.[108] Several angular-type pyranocoumarins, such as Praeruptorin A, B, C, D, and E, have been identified as the main components of *Peucedanum Praeruptonrum Dunnon*.[109] Among them, Praerutorin A is considered to be the bioactive component, which showed relaxant effect on ex vivo pulmonary arteries.[110]

It is well accepted that chronic hypoxia increases the basic calcium concentration of PASMCs in both hypoxia PH rats and cell models. SOCC-induced SOCE enhancement is the main reason for the imbalance of intracellular Ca^{2+} concentration.[111–113] Previous studies reported that Praerutorin A could significantly decrease the enhancement of basal Ca^{2+} and SOCE in distal PASMCs of rat, which might suppress cell proliferation and improve PAH.[114]

Also, the expression and function reduction of the potassium channel, especially the voltage-dependent K^+ channel causes a series of pulmonary vascular pathological changes in the pathogenesis of PAH. Particularly, abnormal expression and function of Kv 1.5 and Kv 2.1 channel are key factors for PASMC proliferation and apoptosis, which ultimately lead to pulmonary vascular remodeling.[115,116] Furthermore, it was confirmed that Praerutorin A obviously suppressed the downregulation of Kv 1.5 and Kv 2.1 mRNA expression caused by hypoxia in rats PASMCs, which may maintain the balance of cell membrane potential, consequently inhibiting cell proliferation and ameliorating PAH.[117]

Stilbenes

The stilbene compound is a general term for a class of substances which have a polystyrene nucleus or a polymer thereof. Stilbene compounds have a variety of biological activities. In addition to the already known antibacterial effects, in recent years it has been found that some stilbene

compounds possess lipid-lowering, expansion of coronary blood vessels and inhibition of platelet aggregation, and anti-hypertensive and anti-tumor effects.[118]

Resveratrol

Resveratrol (RES) is a kind of polyphenol mainly derived from *polygonum cuspidatum*, *Arachis hypogaea Linn*, *Fructus Mori*, and *Vitis vinifera L*. It exists free-form or as a corresponding glycoside in two geometric isomers: cis- (Z) and trans– (E), both of which have anti-oxidative activity.[119] RES is a new type of compound which can protect ECs and show antioxidant and anti-inflammatory effects on systemic circulatory system.[120] Furthermore, it can be used for the prevention and treatment of a variety of cardiovascular diseases, including PH.[121]

Recently, Chen et al. confirmed that RES, the deglycosylation form of polydatin, could prevent hypoxia-induced human PASMC proliferation and attenuate RVH through the phosphoinositide 3 kinase -protein kinase B signaling pathway.[122] It was also suggested that resveratrol could improve endothelial function, attenuate oxidative stress, and inhibit inflammatory reaction, while suppressing vascular reconstruction in MCT-induced PAH rats. RES also alleviates mPAP by controlling the proliferation of SMCs and the vascular remodeling. [123] Accordingly, RES achieves the purpose of prevention and treatment of PAH by playing a vasodilation role.

Moreover, anti-inflammatory effects of RES may be associated with lower expression of inflammatory factors such as interleukins and TNF-α.[124] Studies have shown that monocyte chemoattractant protein-1 (MCP-1) recruits huge amounts of inflammatory cells for the injured part after ALI to form positive feedback.[125] At the same time, a series of inflammation-related mediators are generated to cause pulmonary vascular EC damage and mPAP increase.[126] RES significantly decreases the mRNA and protein levels of MCP-1. It suggests that RES can reduce the recruitment of monocytes and alleviate the injury of PAECs caused by inflammatory cells and inflammatory mediators. Previous studies have demonstrated that p38-mitogen-activated protein kinases is the key upstream molecule to generate MCP-1. Experimental results have also revealed that RES suppresses the expression of MCP-1 mainly by limiting the activation of p-p38-mitogen-activated protein kinases. Hence, those effects of RES mitigate PAH eventually.[127]

Other natural products

Semen lepidii

Semen lepidii, the seeds of *Descurainia Sophia (L)*, have been used in TCM to relieve cough, prevent asthma, reduce edema, and promote urination.[128] Studies have shown that the compound capsule of *Semen lepidii* evidently decreases rabbit PH induced by 5-hydroxytryptamine in vivo and increases the contraction amplitude of myocardial, that is, enhances myocardial contractility.[129] So it seems that *Semen lepidii* have effects of improving cardiac output and lowering mPAP and PVR.[130] Furthermore, it is observed that *Semen lepidii* can improve arterial blood gas in PAH rats.[131]

Mustard glucoside and G-sitosterol, the active ingredients of *Semen lepidii*, can relieve cough, relax bronchial smooth muscle, and remit bronchial spasm. Moreover, research has found that the Hlvetivoside of *Semen lepidii* distinctly decreases MCT-induced right ventricular systolic and diastolic blood pressure, as well as mPAP.[132]

Radix Astragali

Radix Astragali, the traditional Chinese herb, is the root of *Astragalusmembranaceus (Fisch) Bge*. or *Astragalusmembranaceus (Fisch) Bge.var.Mongholicus (Bge.) Hsiao*, which has been used as folk herbal medicine in China for many years. Several experimental and clinical studies have provided evidence of its extensive pharmacological effects, including regulating blood pressure and treating nervous, respiratory, and endocrine diseases.[133]

Although accumulative data have shown that *Radix Astragal* was beneficial for the treatment of PAH,[134] its mechanisms were multifaceted, and mainly included the following: (1) inhibition of the remodeling of intra-acinar pulmonary arteries and the hyperplasia of collagen;[135] (2) decrease in the content of ET-1 and increase in the content of NO, improving the expression level of NOS, maintaining the balance of NO/ET-1;[136] (3) intervening with mRNA expression of collagen in right ventricle;[137] (4) lowering the concentration of thromboxane A2 in pulmonary tissue and reversing the reconstruction of pulmonary vessels;[138] (5) regulating the concentration of superoxide dismutase and oxygen free radical in pulmonary tissue, preserving pulmonary vasculature from hypoxia stimulation by the action of antioxidant;[139] and (6) exerting impact on the other of vasoactive substances.[140]

Perspectives

With the clinical efficacy of natural plant products being fully confirmed from years of practice, they have received more recognition and attention from the international pharmaceutical industry. Proved by numerous studies, natural plant products such as TET have great potential in the treatment of PAH. There are numerous advantages of natural plant products. They are green and with lower economic costs compared with chemical drugs. Natural product treatment is a multi-target and multi-link system with a unique advantage in the therapy of complex diseases, while chemical drugs are primarily for a single target. Meanwhile, some natural plant products exhibit selective functions on pulmonary circulation with no significant effect on system circulation. Hence, there is a good prospect

and potential development value for natural plant products in PAH therapy.

From the literature reported so far, we summarize the achievements of this field in PAH. (1) Pre-clinical studies and traditional clinical practices have revealed that a number of natural plant products, such as tetrandrine, ligustrazine, salidroside, etc., harbor potential in PAH therapy. (2) Some natural plant products, such as ligustrazine, Qingning oral solution, Astragalus, etc., show selective effects in pulmonary circulation and cardiac function. (3) Multiple mechanisms have been involved in the treatment of PAH by natural plant products. For example, Rhodiola inhibits the secretion of ET-1 and promotes the synthesis and release of NO from PAECs, while ligustrazine has an antagonistic effect of Ca^{2+}.

However, these studies are preliminary and have limitations. (1) Some natural products can reduce systemic blood pressure and even cause hypotensive reactions. (2) Generally, the effects of nature plant products are weaker than chemical medicines in PAH treatment; they are reasonably compatible and doses should be considered seriously. (3) Experimental and clinical studies with large numbers of subjects are still insufficient to form treatment standards in the utilization of nature plant products. (4) Some plants are reported as showing toxicity in system and pulmonary vasculature, such as MCT, Ergotamine,[141] and pyrrolizidine alkaloids[142] contained in the Senecio and Crotalaria plants.[143] The multifunction of natural plant products should be considered carefully.

In summary, natural products have great potential in the treatment of PAH, but the specific mechanisms need further study. We are looking forward to the next efficient medicine for PAH treatment. We also believe that natural products have broad prospects and great value in the future.

Conflict of interest

The authors declare that there is no conflict of interest.

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