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Review

Therapeutic Resolution of Pulmonary Arterial Hypertension (PAH) Using Natural Products

Maria Osei-Wusuansa [1], Nura Mohammed [1], Damilola Makanjuola [1], Khaled Habas [1], Sila Ozlem Sener [1,2], Khaled H. Assi [1], Rateep Nasim [3], Sadaf Nawaz [1], Rajendran C. Gopalan [1], Colin W. Wright [1] and M. Talat Nasim [1,4,*]

[1] Translational Medicine Laboratory, School of Pharmacy and Medical Sciences, Faculty of Life Sciences, University of Bradford, Bradford BD7 1DP, UK; m.osei-wusuansa@bradford.ac.uk (M.O.-W.)
[2] Gülhane Faculty of Pharmacy, University of Health Sciences, Ankara 06018, Türkiye
[3] School of Biosciences, Stacey Building, University of Kent, Canterbury CT2 7NJ, UK
[4] Centre for Health, Agriculture and Socio-Economic Advancements (CHASA), Lalmonirhat 5500, Bangladesh
* Correspondence: t.nasim@bradford.ac.uk; Tel.: +44-(0)-12-7423-6076

Abstract: Pulmonary arterial hypertension (PAH) is a progressive and rare condition characterised by the occlusion of pulmonary arterioles, with clinical manifestations resulting from the cross-sectional area reduction of the small pulmonary arteries. The disease is driven by a combination of factors including vasoconstriction, thrombosis, inflammation, proliferation, and the obstructive remodelling of the pulmonary artery walls. Heterozygous mutations in the type II bone morphogenetic protein receptor (BMPR2) underlie the majority of the inherited and familial forms of PAH. Current evidence indicates that in PAH, the BMPR2-mediated-signalling is diminished and the TGFβ signalling is heightened. Even when managed with current therapeutic approaches, the disease eventually results in increased pulmonary vascular resistance, right heart failure, and premature death. Natural products act as vascular disease treatment agents and have been used in clinical practice following compelling clinical trials. The rationale for the selection of natural compounds derives from their multi-targeted approach and synergistic effects. Although novel medicines licenced by the FDA (USA) between 1981 and 2010, constitute approximately 34% natural products or derivatives of natural products, their potentials for the treatment of PAH are not fully explored. The objective of this review is to emphasise the significance of natural products in the therapeutic resolution of PAH.

Keywords: pulmonary arterial hypertension; transforming growth factor-β; bone morphogenetic protein; natural products; pulmonary circulation

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1. Introduction

What Is Pulmonary Arterial Hypertension (PAH)?

Pulmonary arterial hypertension (PAH) is a rare cardiovascular anomaly marked by increased pulmonary vascular resistance (PVR) and elevated blood pressure in the pulmonary arteries [1,2]. It is caused by dysfunctions in endothelial and smooth muscle cells, leading to aberrant vascular proliferation/fibrosis and remodelling (Figure 1). Endothelial and smooth muscle cell dysfunctions alongside inflammation cause an increase in vascular resistance, resulting in right ventricular hypertrophy [3–5].

The elevated pulmonary vascular resistance and pulmonary arterial pressure heighten the right ventricular afterload, which, if left untreated, leads to right ventricular failure and eventual death [6]. For decades, PAH has remained a disease with high morbidity and mortality rates, despite advancements in management and treatment regimens [1]. Consequently, the disease remains incurable and severe and has a progressive characteristic affecting both the right ventricle (RV) and the pulmonary vasculature [2,7]. The disease parameters are clinically defined by a mean pulmonary arterial pressure of >20 mmHg, normal left atrial pressure, and a vascular resistance of ≥3 Woods units [2,8].

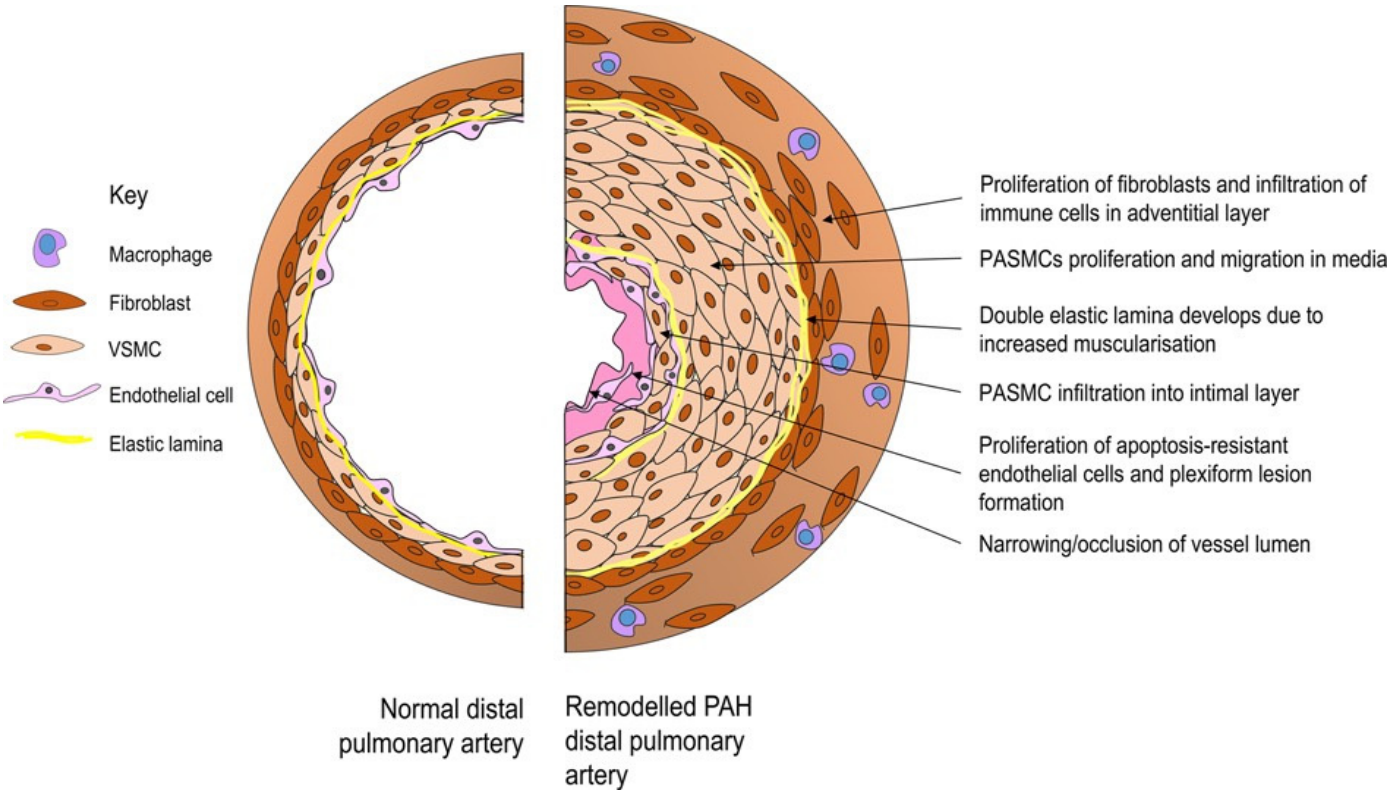


Figure 1. Pulmonary vascular remodelling in PAH: The intima, media, and adventitia—the three layers of vascular cells—are shown in a cross-sectional image of a pulmonary artery. These cells play a role in the vascular remodelling seen in PAH, causing the arterial lumen to constrict or completely block. This raises blood pressure in the pulmonary circulation, which normally has low pressure, and increases right ventricular stress [9].

Around 1 in 67,000 people have PAH. A prevalence of 6.6 and 27 cases per million adults is estimated in the United States and Europe [10]. Patients with PAH are mostly at the age between 30 and 60 years and are most commonly women. Every year, about 500–1000 new cases are diagnosed in the U.S. PAH has a low survival rate, and it has been reported that 67 to 99% of patients only have a 1-year survival rate [11].

Currently, modern therapeutic options have extended patient survival rates by 1–5 years. However, the median survival rate after a PAH diagnosis remains 2.8 years [6]. Lung transplantation remains the only option for long-term survival as there is still no cure for this progressive disease. Current treatment therapies only provide patients with limited additional time before a lung transplant is needed. So far, no effective treatment has been developed [12].

2. Pathogenesis of Pulmonary Arterial Hypertension

PAH is a progressive disorder characterised by the narrowing of the PAs, subsequently leading to increased pulmonary arterial pressure. A combination of genetic, molecular, and environmental factors contributes to the pathogenesis of PAH. These factors include vasoconstriction, thrombosis, pulmonary vascular remodelling, apoptosis resistance, endothelial dysfunction, and chronic inflammation. These severe complications can lead to right ventricular overload, right heart failure, and even death [12].

In PAH, the homeostatic balance between many mediators affecting vascular tone, cellular development, and coagulation in the pulmonary circulation is disrupted by various clinical and pathophysiological mediators. These mediators include serotonin, endothelin-1, and thromboxane A2, which function in the pathogenic triad of thrombosis, cell proliferation, and vasoconstriction contributing to the disease pathogenesis [13,14]. Nonetheless, the

underlying mechanisms by which these mediators contribute to the disease pathogenesis are not entirely understood at the molecular level. The development of PAH has been linked to several distinct molecular processes significantly influenced by environmental risk factors and genetic predisposition [13,15].

2.1. Vasoconstriction

An essential factor in the aetiology of pulmonary hypertension (PH) is pulmonary artery vasoconstriction, which likely occurs early in the disease and may even be reversible [16]. Vasoconstriction is the contraction of the muscular wall of vessels, causing the narrowing of the arteries. This occurs when norepinephrine binds to the α1- and α2-adrenergic receptors. Vasodilation is the relaxation of the muscular wall, resulting in the subsequent widening of blood vessels.

Key agents such as nitric oxide (NO), endothelin-1 (ET-1), serotonin (5-HT), and prostacyclin have a role in PAH and contribute to pathogenesis. NO is a vasodilator and therefore leads to vasodilation and reduced blood pressure. In PAH, there is a reduction in NO production. Subsequently, vasoconstriction occurs and the downregulation of NO leads to increased pulmonary arterial pressure. ET-1 and 5-HT are vasoconstrictors and their elevated levels in PAH patients cause vasoconstriction and vascular remodelling. Overall, these agents contribute to PAH pathogenesis by causing vasoconstriction, vascular remodelling, and vasodilation imbalance.

Vasoactive substances act as vasoconstrictors and vasodilators in the PAs. There is evidence that PAH is associated with the dysregulation of these vasoactive chemicals, including NO, ET-1, 5-HT, and prostacyclin.

Shao et al. (2011) also found that endothelial NO synthase expression levels were lower in PAH patients [16]. This suggests that the vasodilator NO and its second messenger, cyclic guanine monophosphate (cGMP), are less bioavailable in PAH patients. Similarly, prostacyclin and its second messenger, cyclic adenosine monophosphate, are reduced in PAH patients [16].

The lung tissue of patients with PAH showed elevated levels of the endogenous vasoconstrictor ET-1. ET-1 stimulates endothelin A&B receptors on vascular smooth muscle cells (ET1-A) and endothelial cells (ET1-B) [16]. While ET1-B receptors help neutralise circulating ET-1, ET1-A receptors are mainly responsible for vasoconstriction. However, selective antagonists targeting ET1-A receptors have not resulted in more effective treatment outcomes [16].

Treatments targeting PAH have demonstrated clinical efficacy, highlighting the significance of all three pathways linked to vasoconstriction. Crucially, though, none of the therapies can fully treat PAH patients; only few can reduce patients' symptoms and enhance their quality of life [16,17].

2.2. Thrombosis

Thrombosis is the formation of a blood clot within a blood vessel, obstructing the flow of blood. The prevalence of micro-thrombotic events is rising in older adults with chronic illnesses. This is caused by increased von Willebrand factor activity, seen in people with PAH, and insufficient endogenous anticoagulant factors, proteins C and S [15]. Also, thrombotic events in PAH are linked to the activation of tissue factor [18] glycoprotein, abundantly expressed on pulmonary fibroblasts. When TF is exposed following an injury, it forms a complex with Factor VIIa, which triggers the coagulation cascade. This, in turn, catalyses the activation of Factor X, leading to thrombin production. It has been demonstrated that the normal expression of TF in the pulmonary artery wall is significantly elevated in the vascular lesions of patients with PAH [19].

This aberrant expression on the luminal surface of arteries predisposes individuals to in situ thrombosis and contributes to smooth muscle cell migration and proliferation. Additionally, tissue factor and downstream thrombin signalling facilitate endothelial cell migration and haphazard angiogenesis, contributing to the formation of plexiform lesions.

Further establishing TF as a crucial mediator in the vascular damage of PAH patients, Bakouboula et al. showed elevated TF-expressing endothelial cell microparticles discharged from the pulmonary circulation of PAH patients [19].

2.3. Vascular Remodelling

Vascular remodelling is the alteration of the structure and arrangement of blood vessels, leading to elevated systemic vascular resistance. This remodelling results in the narrowing of the PAs, restricting blood flow from the right ventricle and leading to the hypertrophy of the right ventricular muscle. Subsequently, this results in right heart failure. As mentioned above, key agents such as vasoconstrictors (5-HT and ET-1) and vasodilators (NO and prostacyclin) contribute to vascular remodelling. The reduced production of vasodilators and the increased production of vasoconstrictors lead to increased vasoconstriction and subsequent vascular remodelling. Additionally, genetic factors such as mutations in BMPR2 genes cause abnormal cell proliferation, resulting in remodelling. Furthermore, growth factors such as VEGF contribute to the thickening of the vessel wall, thereby increasing vascular resistance [15,20].

Remodelling within small pulmonary arteries is characterised by excessive cell proliferation in all vascular layers, particularly the uncontrolled pro-proliferative activity of PASMCs. Remodelling is common in both the venous and arterial vascular beds of the pulmonary vasculature. Although the exact aetiology of venule remodelling is unknown, it is known to occur in cases of pulmonary veno-occlusive disease and postcapillary pressure elevation caused by left-sided heart disease. However, growth factors, mitogens, cytokines, ion channels, receptors, neurotransmitters, viruses, and transcription factors all functionally and structurally regulate arterial pulmonary vascular remodelling, even though this process is still not completely understood. BMPR2 is a significant player in the regulation of pulmonary arterial remodelling. In response to specific ligands (BMP-2 and BMP-4), BMPR2 and BMPR1 normally heterodimerize, activating SMADs and Id (inhibitor of differentiation) proteins. These downstream signalling cascades activate cell cycle master regulators, such as p21 or CDKN1A, which limit proliferation, initiate apoptosis, and accelerate cell ageing [15].

2.3.1. Pericyte-Mediated Vascular Remodelling

Pericytes are involved in vascular tone regulation, endothelial cell proliferation, and vessel stabilisation, maturation, and remodelling. Their two-fold increase in the distal PAs from the lungs of individuals with PAH is indicative of this. In a study, pulmonary EC-derived fibroblast growth factor (FGF)-2 and interleukin-6 have been shown to promote pericyte migration and proliferation. Similarly, the isolated PAH lung tissue's TGFβ overexpression promoted the development of smooth muscle-like cells in that tissue [15].

2.3.2. Inflammation and Immunity

The emergence of PAH has been linked to inflammatory responses to immunological processes and infectious organisms, including viruses and parasites. Inflammatory and immunological responders, such as T and B lymphocytes (T lymphocytes kill infected cells or regulate other immune cells while B lymphocytes produce antibodies), mast cells, dendrites, and macrophages, have all been found in pulmonary vascular lesions of patients with PAH. In response to inflammatory stimuli, these inflammatory cytokines cause endothelial and smooth muscle cells to proliferate, migrate, and become resistant to apoptosis, resulting in pulmonary vascular remodelling [15].

2.3.3. Resting Membrane Potential

Potassium channels influence cell migration and proliferation because they control the resting membrane potential of a variety of cell types, including smooth muscle cells. Mutations in the potassium channel subfamily K member 3 gene, KCNK3, were reported in a family of hereditary PAH patients in 2013. Activating this gene in a rat model of PH

reduced right ventricular systolic pressure, enhanced right ventricular hypertrophy, and increased pulmonary vascular wall thickness *in vivo*. Although the exact pathophysiology of KCNK3 in PAH is unknown, its inactivation and decreased expression are believed to contribute to vasoconstriction and pulmonary artery remodelling. This process involves hypertrophy, smooth muscle and endothelial dysfunction, and pulmonary vascular wall thickness [15].

3. Molecular Genetic Basis of Pulmonary Arterial Hypertension (PAH)

Mutations in the BMPR2 gene have been established in numerous clinical studies as the major genetic determinant in the pathogenesis of PAH and account for 53–86% of patients with hereditary PAH, as well as 14–35% of patients with sporadic PAH [8,21,22]. BMPR2 is a receptor kinase that specifically recognises and phosphorylates serine and threonine amino acid residues. It is classified as a member of the transforming growth factor β (TGF-β) superfamily [23].

In both TGF-β and BMP signalling pathways, ligands and receptors specific to their respective pathways initiate signal transduction (Figure 2). In the case of BMP signalling, BMPR2 initiates signal transduction via the receptor SMADs (R-SMADs) SMAD1, SMAD5, and SMAD8. Upon ligand binding, it forms a complex with a type I receptor, namely, ALK3 or ALK1, and phosphorylates R-SMADs. R-SMADs form a complex with common SMAD4 and translocate to the nucleus, to regulate the transcription of target gene ID1 (inhibitor of differentiation) in the case of BMP signalling (Figure 2) [24].

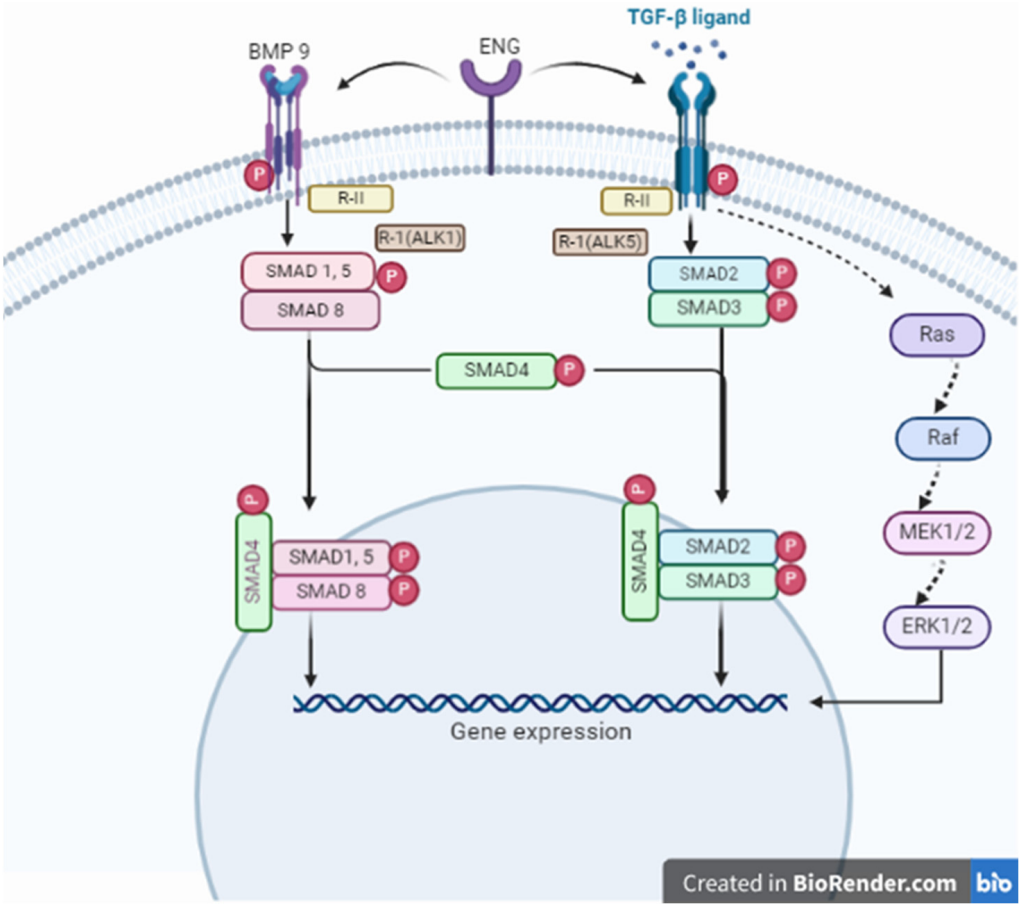


Figure 2. TGF-β/BMP signalling pathways. Type-1 (R-I), type-II (R-II), and recruits' type-3 (ENG) receptors are the receptors that BMP9 and TGF-β ligand bind to, respectively. R-II phosphorylates R-I, which causes ligand-specific gene expression in a SMAD-dependent way. Gene expression is likewise the outcome of the TGF-β/BMP-induced activation of other non-SMAD-dependent signalling pathways (Ras, Raf, MERK, and ERK). Biorender.com was used to create this image.

TGFβR2 couples with ALK5 after ligand stimulation to phosphorylate R-SMADs. SMAD signalling occurs via SMAD2 and SMAD3 (in the case of TGF-β), which also translocate into the nucleus together with common SMAD4 to directly regulate the transcription of target gene Pai1 [22,23]. BMP/TGFβ receptors can bind to ligands and then activate non-SMAD-related pathways essential for vascular system development.

These pathways include phosphatidylinositol 3-kinase (PI3K)—Akt, small Rho-like GTPase pathways in certain cells, and mitogen-activated protein kinases (MAPKs) including p38, Erk, and JNK. Type1/type2 receptor recruitment to signalling complexes or ligand binding to type1/type2 hetero-oligomeric complexes are necessary for the activation of these non-canonical pathways. This alternative signalling pathway is also activated by downregulating the SMAD-signalling pathway [25].

Numerous biological processes including osteogenesis, cell proliferation, and cell differentiation are regulated by BMP signalling. As such, heterogeneous mutations in the BMPR2 gene amplify the pro-proliferative state in pulmonary artery smooth muscle cells (PASMCs) by interfering with BMP, SMAD-dependent, and SMAD-independent signalling [23]. Other novel mutations, such as those in SOX17, EIF2AK4, AQP1, and ATP13A3 genes, have also been identified to cause the development of PAH. However, they represent an infrequent cause of the disease [26].

Additionally, mutations in other TGF-β superfamily members (Table 1) such as BMP9, ALK3, TGFβR2, SMADs 1 and 4, and in ALK3 have also been identified. Genetic mutations in these genes interfere with the SMAD-dependent BMP signalling pathway, resulting in the elimination of the growth-inhibiting effects of BMPs on vascular cells. Also, excessive proliferation and heightened resistance to apoptosis of PASMCs, in response to TGFβ1 ligand stimulation of the TGFβ signalling pathway, have been identified and are likely to be responsible for the reduction in the size of the pulmonary vascular lumen [26,27].

Table 1. TGFβ superfamily members.

Genes	Function	Refs
BMPR2	Member of the type II receptor of the TGFβ superfamily	[6]
SMAD1/5	Regulatory SMAD proteins capable of transducing downstream signalling via the BMP signalling pathway	[22,27]
SMAD4	Common SMAD proteins which form a complex with regulatory SMAD proteins and translocate into the nucleus to regulate gene transcription.	[23,24]
ALK1	Member of the type I receptor of the TGFβ superfamily	[6]
TGFβR2	Member of the type II receptor of the TGFβ superfamily	[28]
ALK3	Member of the type I receptor of the TGFβ superfamily	[28]
SMAD2/3	Regulatory SMAD proteins capable of transducing downstream signalling via the TGFβ signalling pathway	[28]
BMP4/9	Circulating vascular quiescence ligands which stimulate type 1 and 2 receptors of the BMP signalling pathway	[23]
TGFβ1	Circulating vascular quiescence ligand that stimulates type 1 and 2 receptors of the TGFβ signalling pathway	[27]

4. Current Therapeutic Approach in PAH Management and Its Limitations

Over the past two decades, there has been remarkable progress in assessing and managing patients with pulmonary arterial hypertension (PAH). Every PAH medication now available on the market targets one of three universally recognised pathways (nitric oxide, endothelin, or prostacyclin) [13,15]. The advent of targeted therapies for PAH, including prostacyclin and its analogues, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and more recently, a soluble guanylate cyclase activator, have expanded treatment choices and potentially decreased morbidity and mortality. However, none of the existing therapies have achieved a cure for PAH.

According to a study conducted for a year, 22% of PAH patients received prostacyclin [29]. Endothelin receptor antagonists (ERAs) are usually the first line of treatment, although there are no current data suggesting the number of patients on this medication [30]. Phosphodiesterase (PDE) inhibitors were shown to be successful, as was measured by the 6 min walking test. Patients taking a PDE5 inhibitor were able to walk 48 m further in 6 min compared with patients who did not take PDE5 inhibitors [31].

4.1. Prostacyclin Analogues

Prostacyclin (PGI_2) belongs to the endogenous proteinoid family. PGI_2 is released by vascular endothelial cells, acting as vasodilators and inhibiting platelet aggregation [32]. The synthesis of PGI_2 is not well understood. However, it is suggested that thromboxane A2 synthase (CYP5A1) catalyses the formation of thromboxane TXA2 from PGH2 (prostaglandin H2), which is synthesised by COX-1 and may be physically related to thromboxane. This is related to the cytochrome P450 superfamily of proteins and is utilised to treat arterial PH. Prostacyclin works by selectively binding to its receptor, activating the G-protein receptor (also known as IP receptor), and increasing intracellular cAMP, which activates the protein kinase [33]. Prostacyclin synthesis is carried out by prostacyclin synthase (CYP8A1), expressed constitutively in endothelial cells, neurons, and glial cells. It catalyses the conversion of PGH2 synthesised by COX-2 to PGI2 [34].

The analogues used in clinic include beraprost, trepostinil, iloprost, and selexipag. Despite being popular treatments for PAH, these drugs have their drawbacks. Beraprost is an approved drug in the United Kingdom (UK) to be used for PAH. However, a drawback of this drug is its ineffectiveness as a persistent treatment, as evaluated by the primary efficacy endpoint [35].

Treprostinil, a prostacyclin analogue, has a direct vasodilation effect on the pulmonary system. Treprostinil is administered by intravenous infusion via a central venous catheter. This is disadvantageous as it can cause a reaction to the catheter or site pain within patients [36].

Another drug used to treat PAH includes iloprost. Antihypertensives, anticoagulants, and non-steroidal anti-inflammatory drugs cannot be taken when patents are on iloprost. This limits the drug's use to patients seeking treatment for multiple conditions. Iloprost is administered via nebulisation every 2 h, making it inconvenient for patients to maintain their normal life [37].

Finally, the drug selexipag is another treatment used for PAH patients, and is an antagonist of the prostacyclin receptor, leading to vasodilation in pulmonary circulation. Patients admitted with selexipag must be cautious of taking other medications. This is because many medications cannot be taken with selexipag due to potential drug interactions [38].

4.2. Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors (PDE inhibitors) are a group of drugs that target specific phosphodiesterase enzymes in certain cells. They have been approved by the FDA for the treatment of chronic obstructive pulmonary disease including erectile dysfunction, pulmonary arterial hypertension, psoriasis, psoriatic arthritis, and atopic dermatitis.

There are four types of PDE inhibitors including PDE-3, PDE-4, PDE-5, and non-specific PDE inhibitors. Intracellular second messenger molecules like cAMP and cGMP are broken down and rendered inactive by the enzyme phosphodiesterase (PDE). By inhibiting the breakdown of cGMP or cAMP and increasing their levels in smooth muscle cells, PDE inhibitors work on their target phosphodiesterase enzymes (PDE-3, PDE-4, and PDE-5), causing relaxation and vasodilation [39].

Nitrites should not be taken alongside PDE-5 inhibitors such as sildenafil, tadalafil, vardenafil, or avanafil since they can cause severe hypotension [40]. Patients with heart failure or bleeding disorders cannot take PDE inhibitors either, due to the mechanism of action the drug's use, as it inhibits platelet aggregation, leading to the worsening of the condition.

4.3. Calcium Channel Blockers

Calcium channel blockers (CCBs) are used as a treatment for PAH; the most used drugs are diltiazem and nifedipine [41]. CCBs work by acting on the vascular smooth muscle, dilating the pulmonary resistance vessels and lowering the pulmonary arterial pressure. CCBs relax blood arteries, increasing the flow of blood and oxygen to the heart while reducing strain [42]. However, CCBs are unsuitable for patients with low cardiac output or high right atrial pressure. Another limitation of CCBs is their low bioactivity, therefore leading to more frequent administration [43].

4.4. Endothelin Receptor Antagonists

Endothelin is a chemical that makes blood arteries constrict. Patients with PAH create an excess of endothelin, which causes the constriction of the blood arteries in the lungs. As a result, blood pressure in the PA increases. Endothelin receptor antagonists (ERAs) are potent vasodilators with antimitotic characteristics, which can specifically dilate and remodel the pulmonary arterial system [44]. Recently, they have emerged as an alternative to traditional therapies for PAH. ERAs work as a target therapy that blocks endothelin receptors [45]. This antagonist works by decreasing the pulmonary vascular pressure, which improves the tolerance and symptoms in patients with PAH. ERAs used in the treatment of PAH include ambrisentan, bosentan, and macitentan (which is currently in phase III clinical trials) [46].

ERAs lower endothelin levels in the blood, minimising the damage caused by an excess level of endothelin. A limitation associated with EAs is liver damage, and therefore patients will usually receive regular blood tests. Despite this, some studies suggest that the liver damage caused by bosentan may occur due to the inhibition of the bile salt export pump. This inhibition leads to the build-up of harmful bile salts inside the liver cells, resulting in damage to the liver cells [47]. However, the exact mechanism by which ERAs cause liver damage remains unclear.

5. Natural Products in the Management of PAH

Studies on natural products that are being considered for PAH medication development have recently been reviewed by [48,49]. Animal models of PAH were given varying amounts of aqueous ethanolic plant extracts and phytochemicals. These phytochemicals comprised iso-flavonoids (genistein), flavonoids (nobiletin, quercetin, baicalain, and epicatechin), alkaloids (berberine, oxymatrine, isorhynchophylline, ligustrazine (tetramethylpyrazine), polyphenols (chlorogenic acid, resveratrol, punicalagin, polydatin, and apple polyphenols) terpenoids (carvacrol), saponins (asiaticoside and ginsenoside), phenolic glycoside (salidroside), natural minerals, and polysaccharides. Most of them demonstrated favourable pharmacological effects on key pathways involved in the development of PAH. Natural products contain many active ingredients which could offer synergistic activity to restore balance in the multiple mechanisms involved in the development of PAH.

5.1. Medicinal Plants Eliciting Beneficial Effects for Treatment of PAH

5.1.1. *Allium sativum* (Garlic)

The aqueous extract of *A. sativum* has vasorelaxant properties that are capable of halting PAH progression in hypoxia-induced rats [50]. In another study, rats administered monocrotaline (MCT) were given fermented garlic extract (FGE) to determine their effects on pulmonary arterial hypertension. Weight, arterial stiffness, and atrial natriuretic peptide levels were all elevated in the right ventricle by MCT treatment, but not in the left ventricle. FGE reversed these effects as well as medial hypertrophy and pulmonary arteriole endothelial dysfunction. FGE also attenuated the pulmonary fibrosis brought on by the lung's translations of the proteins PKG, MCT, and eNOS and enhanced the lung translations of VCAM-1 and MMP-9. An accessible inhibitor of guanylyl cyclase (sGC) was also inhibited by FGE. This study shows that FGE has cardioprotective benefits on MCT-induced rats [51].

5.1.2. *Allium macrostemon*

The usage of A. macrostemon's volatile oil in PAECs has been shown to boost eNOS production and serine 1177 phosphorylation [52]. Additionally, A. macrostemon's volatile oil relaxes pulmonary arteries via triggering the intracellular Ca^{2+}/PKA/eNOS signalling cascade. Consequently, the oil (containing the active ingredient DMDS) can raise PAH via triggering the Ca^{2+}/PKA/eNOS signalling pathway.

5.1.3. *Berberine vulgaris*

The main active constituent of B. vulgaris is berberine (BBR). BBR mitigated monocrotaline-induced PAH by inhibiting the endothelin-1 system, which was implicated in the development of PAH [53]. In another investigation, BBR therapy reversed the hypoxia-induced decrease in BMPR2 expression and the phosphorylation of P-SMAD1/5 proteins. BBR also reversed the hypoxia-induced elevation in TGF-β and the phosphorylation of P-SMAD2/3 proteins. Since BBR therapy restored the decreased expression of PPARγ caused by persistent hypoxia, the protective effect might be achieved by modulating PPARγ expression. Furthermore, BBR therapy had a strong protective effect against the hypoxia-induced proliferation of PASMCs by blocking the expression of Trx1 and its target gene β-catenin [54–56], and researchers claimed that PAH is primarily driven by protein phosphatase 2A (PP2A), and BBR might mitigate PAH through PP2A signalling pathways, providing a potential treatment strategy for PAH. In monocrotaline-induced PAH, BBR reversed the rise in Bcl-2 expression, raised the Bax-to-Bcl-2 ratio, and decreased the amount of muscularised resistance vessels and pulmonary vascular remodelling, according to [57,58].

5.1.4. *Crataegus rhipidophylla*

The fruits, leaves, and flowers of *C. rhipidophylla* contain beneficial substances such as epicatechin, hyperoxide, and chlorogenic acid. When broiler chickens with PH caused by high altitude were given *Crataegus rhipidophylla* (Hawthorn) extract, the amount of enzymes responsible for liver damage, such as ALT (Alanine transaminase) and AST (Aspartate transaminase), decreased concurrently with an increase in the expression of proteins like albumin and globulin [59].

5.1.5. *Eulophia macrobulbum*

All compounds identified in the 50% ethanolic extract of *E. macrobulbum* are phenanthrene derivatives [60]. It has been demonstrated that the treatment of ethanolic extract and its active compound, 1-(4′-hydroxybenzyl)-4,8-dimethoxyphenanthrene-2,7-diol, using isolated PAs from MCT-induced PAH rats, improved pulmonary artery relaxation mediated through endothelial NO [61]. The compound also reduced Ca^{2+}-mobilisation and reduced pulmonary artery wall thickness and right ventricular hypertrophy.

5.1.6. *Mimosa pigra*

The characterisation of the phytochemical profile and phytotoxic activity of *M. pigra* showed that flavonoids, tannins, phlobatannins, alkaloids, and saponins were present in the methanolic extract of the plant [62]. When hypoxia-induced PAH rats were treated with *M. pigra* extracts, it enhanced endothelial NO synthase and restored the endothelium to normal function [63].

5.1.7. *Kelussia odoratissima*

Sesquiterpenes and phthalides are the active ingredients in the essential oil of *K. odoratissima* leaves [64]. The study conducted on broiler chickens with PH treated with this extract yielded positive results in terms of body weight gain, as well as a rise in NO levels and the heterophil/lymphocyte ratio, and a decrease in serum MDA levels [65]. The treatment of the broiler chickens with these chemicals resulted in the upregulation of SOD1 and iNOS and the reduction in ET-1 gene expression in the heart tissue.

5.1.8. *Terminalia arjuna*

The main components of *T. arjuna* include minerals, polyphenols, sterols, tannins, triterpenoids, saponins, and flavonoids [66]. In MCT-induced PAH rats, the aqueous extract of *T. arjuna* stem bark halted the decline in the relative weight of the lungs. The antiapoptotic effect of *T. arjuna* in pulmonary hypertensive rats was demonstrated by its association with a decrease in the Bcl2/bax ratio, a reduction in RV hypertrophy and the percentage molecular weight of the pulmonary artery, a decrease in lipid peroxidation and NOX1 protein expression in the lung, and an increase in SOD and CAT [67,68].

5.1.9. *Trifolium pratense*

T. pratense harbours several therapeutic compounds such as polyphenols (isoflavone and flavonoids), volatile compounds, and essential mineral elements [69]. *T. pratense* exhibits phytoestrogen activity and can raise serum NOS and NO levels [70]. It has been showed that feeding PAH broiler chickens with the isoflavones of *T. pratense* extract lowered ET-1 levels in the serum and lungs and boosted NOS secretion [71].

5.1.10. *Withania somnifera*

Phytochemical analysis showed that *W. somnifera* contains alkaloids. *W. somnifera* is also rich in numerous valued secondary metabolites such as steroids, alkaloids, flavonoids, phenolics, saponins, and glycosides [72]. *W. somnifera* therapy lowered RVP and RVH as well as PCNA expression in MCT-induced PAH rats. *W. somnifera* therapy increased the production of procaspase 3, which in turn triggers apoptosis in pulmonary arteries. Furthermore, *W. somnifera* therapy lowered the amount of ROS in lung tissue and raised IL-10 levels, demonstrating anti-inflammatory activities [73]. Moreover, *W. somnifera* raised the expression of eNOS and reduced the expression of HIF-1a in lung tissue (HIF-1a rises in hypoxia), eliciting a potential therapeutic application in hypoxia-induced PAH.

5.1.11. *Moringa oleifera*

Fresh leaves of *M. oleifera* were found to consist of phenolics such as isoquercetin, catechin, tannic acid, gallic acid, quercetin, apigenin, and rutin [74]. Ref. [55] observed that treatment with M. oleifera in MCT-induced PAH rats resulted in increased SOD levels and decreased pulmonary pressure alongside pulmonary artery wall thickness. *M. oleifera* also reduced arterial blood pressure in anaesthetised rats by relaxing small resistance arteries, primarily by stimulating the eNOS-NO-sGC pathway [74].

5.1.12. *Salvia miltiorrhiza*

Salvia miltiorrhiza Bge is the source of sodium tanshinone IIA sulfonate, an active ingredient that is often used as a medicinal product. Administering an aqueous extract of *S. miltiorrhiza* to rats suffering from PH may enhance haemodynamic parameters like mPAP and RVSP. Additionally, it downregulated the expression of TGF-β1 in lung tissue, which is one of the key elements in causing vascular remodelling and subsequent PAH progression. It also boosted NO and 6-Keto-PGF1a and decreased ET-1 and TXB2 levels in the plasma. In PAH development, vasoactive chemicals such as vasorelaxants (PGI2 and NO) and vasoconstrictors (ET-1 and TXA2) are out of balance due to endothelial damage. These findings imply that *S. miltiorrhiza* may be used as a PH treatment since it raises NO levels while lowering the lung tissue expression of ET-1, TXA2, and TGF-β1, thereby improving haemodynamic indicators [75].

5.1.13. *Segurigera securidaca*

Flavonoids present in *S. securidaca* can scavenge superoxide anions, hence shielding NO from inactivation. *S. securidaca* treatment may enhance haemodynamic parameters and reduce the electrocardiogram's R, S, and T wave amplitudes, as indicated by this finding. This plant can lessen oxidative stress by lowering MDA levels [76].

5.1.14. *Rhodiola tangutica (Maxim.) S.H. Fu*

The phytochemical analysis of *R. tangutica* revealed the presence of phenylethanols, flavonoids, and terpenoids. Research on hypoxia-induced PH in rats [77] found that using the bio-actively enriched fraction of *R. tangutica* can boost the expression of PCNA, CDK4, and Cyclin D proteins while decreasing the expression of mPAP, RV/BW, RV/LV+S, haematocrit, and p27Kip1 protein. When the cell cycle transitions from the G0/G1 phase to the S phase, these three proteins play crucial functions.

There is increasing evidence that reducing proliferation, oxidative stress, and inflammation and increasing apoptosis reverses pulmonary remodelling, hypertrophy, and the progression of PAH. The reviewed natural products exert their effects on pathways that promote apoptosis and reduce the negative impact of PAH induced in animal models. Many of these plant extracts have demonstrated beneficial effects in the signalling pathways investigated by the authors. These effects are based on the upregulation of BMPR2, BAX, and caspase-3 (apoptosis inducers) and the reduced expression of TGFβR2, cyclin D1, CDK 4 and 6, PP2AC, PDGF-BB, PCNA markers, and anti-inflammatory proteins. However, there is no substantial evidence of their precise mechanisms of action.

Table 2 below shows the summary of the examined plants in addition to their activities.

Table 2. Natural products evaluated for the treatment of PAH.

Activity	Plants/Compounds	Proposed Mechanism of Action	Refs
Antiproliferative	Berberine	Berberine inhibits the proliferation and migration of PASMCs, thereby reducing medial wall thickness in hypoxic rats *in vivo* and hypoxic PASMC *in vitro* models.	[49,78,79]
	Genistein	Genistein drives the phosphorylation and activation of eNOS via the ERK1/2, PI3K/Akt, and AMP/PKA signalling pathways in MCT rat models *in vivo* and MCT HPASMCs.	[49,80]
	Quercetin	Quercetin reduces cell migration as well as inhibiting the expression of cyclin B1 and PCNA which suppresses the TrkA/ACT signalling pathways, hence decreasing proliferation in both hypoxic and MCT rat models *in vivo*.	[49,81,82]
Antioxidant	Magnesium lithospermate B	In hypoxic *in vivo* rat and *in vitro* PASMC models, this natural product decreased NOX2, NOX4, ERK, ROS, H_2O_2, and Cyclin D1 levels.	[49,83,84]
	M. oleifera	The ethanolic extract of *Moringa oleifera* increases SOD expression and decreases PABP levels in an *in vivo* rat model.	[49,85]
	T. pratense	Isoflavones from *Trifolium pratense* inhibit the expression of ET-1 and promote the expression of iNOS in PAH broiler chicken models *in vivo*.	[49,71]
Vasodilating effect	Apple polyphenol	Apple polyphenol decreased mean pulmonary arterial pressure, pulmonary vascular resistance, and cytosolic calcium levels in PASMCs via increasing nitric oxide and endothelial nitric oxide synthase levels in hypoxia *in vivo* rat and *in vitro* PASMC models.	[49,86]
	A. sativum	The aqueous extract of *Allium sativum* increases nitric oxide, thus promoting vasodilation in hypoxia *in vivo* rat models.	[49,50]
	K. odoratissima	Leaves and shoots from *Kelussia odoratissima* increased nitric oxide and decreased the expression of ET-1 in *in vivo* broiler chicken model, hence exhibiting its vasodilatory property.	[49,65]

Table 2. *Cont.*

Activity	Plants/Compounds	Proposed Mechanism of Action	Refs
Apoptotic effect	*W. somnifera*	Hydro-alcoholic extract from the root of *Withania somnifera* inhibited TNF-α and NF-kB in MCT rat models *in vivo*. This extract also increased procaspase-3 and eNOS levels in this model *in vivo*.	[49,73]
	Carvacrol	Carvacrol inhibited the expression of the anti-apoptotic factor Bcl2 and promoted the expression of the apoptosis inducers BAX and caspase-3 *in vivo* in a hypoxic rat model, thus exhibiting its apoptotic properties.	[49,87]
	Salidroside	In hypoxic *in vivo* rat and *in vitro* PASMC models, salidroside inhibited BCl2 expression levels and increased Caspase 3 and BAX expression levels, thus exhibiting apoptotic properties.	[49,88]
Anti-inflammatory	Astragalus polysaccharides	This compound inhibited inflammatory mediators IL-6, IL-1β, and TNF-α in *in vivo* MCT rat models.	[49,89]
	Oxymatrine	MCT and hypoxia *in vivo* rat/*in vitro* PASMC models showed inhibited IL-6, SDF-1, TGF-β, and VEGF expression levels, with oxymatrine supressing inflammation in these models.	[49,90]
	Resveratrol	Resveratrol inhibited the PI3K/AKT signalling pathway via inhibiting phosphorylated AKT *in vitro* in hypoxic PASMCs as well as decreasing the expression of inflammatory mediators IL-6 and IL-1β.	[49,91,92]
Anti-vascular remodelling	*C.rhipidophylla*	The flavonoid-enriched extract of *Crataegus rhipidophylla* increased nitric oxide levels in broiler chickens *in vivo*.	[48,49,59]
	S.miltiorrhiza	The aqueous extract/root from *Salvia miltiorrhiza* reduced pulmonary arterial pressure, ET-1 levels, and TGFβ1 in MCT rat models *in vivo*. The extract from this natural product also increased nitric oxide and prostacyclin levels in hypoxic and MCT rat models *in vivo*.	[49,75,93]
	Asiaticoside	In hypoxic *in vivo* rat and *in vitro* HPAEC and PASMC models, asiaticoside functioned by suppressing ET-1 expression and inhibiting ET-1 secretion while facilitating NO synthesis and release from PAECs. Asiaticoside also inhibited TGFβ1, TGFβR1, TGFβR2, and Smad2/3 signalling in these hypoxic models.	[49,94,95]

5.2. Side Effects, Safety, and Synergy of Natural Products

Preclinical research on most of these natural products is still in its preliminary stages, and there is no proof of their efficacy or safety. Their precise doses, pharmacological interactions, and adverse effects have not been well investigated or recorded. Clinical trials are being conducted on epicatechin, beetroot root juice, tetramethylpyrazine, and sodium tanshinone IIA sulfonate as potential PAH treatments [96]. Sodium tanshinone IIA sulfonate is a water-soluble salt solution of sulfonated tanshinone IIA. Throughout the years, a plethora of scholarly works have documented its effectiveness in the management of cardiovascular ailments. Notably, no known side effects have been documented [97].

According to a different study, combining Aconiti Lateralis, Radix Praeparata, and Fritillariae Thunbergii Bulbus significantly improves MCT-induced PAH. The inhibition of the PDK1/Akt/PDE4D axis and the activation of the βAR-Gs-PKA/CaMKII signalling pathway caused an increase in heart injury [98]. The application of ginseng was reported to have improved the safety of this combination therapy [99].

The synergy of natural products with conventional therapy has not been ascertained due to insufficient data about the efficacy and safety of natural products in PAH therapy. Recently, rosuvastatin combined with garlic extract was proposed by the Chinese clinical trial registry [96].

6. Future Perspectives and Research Opportunities

In the past two decades, PAH research has undergone a remarkable transformation, which significantly contributed to the development of new therapies and advancements in early diagnosis. However, there are currently no available therapies that provide a cure, so the search for new treatment strategies continues. Based on recent progress in comprehending the molecular pathophysiology of this multifaceted disease, numerous potential therapeutic targets are currently being investigated. The primary objective of these drugs is to intervene in the disease process, with the goal of enhancing long-term survival rates. The current array of treatments, including natural compounds, has been employed to promote BMP signalling, tyrosine kinase signalling, bromodomain (BRD) proteins, sex hormones, and other innovative approaches, such as gene therapy targeting pulmonary vascular remodelling. These interventions are at various stages of development. Indeed, there is an urgent need for new clinical trials involving novel drugs that offer improved efficacy and fewer side effects. This has led to a more precise targeting of the underlying mechanisms of PAH and the exploration of innovative formulations, such as sustained-release or inhalable medications. Studying optimal combinations of existing drugs or novel compounds can further improve PAH management, potentially leading to reduced adverse effects compared to high-dose monotherapies. This approach may have the potential to produce treatments that are both more effective and better tolerated.

The therapeutic targeting of the TGFβ and BMP pathways holds significant promise for the development of disease-modifying drugs, especially in the context of PAH. These pathways play critical roles in cellular processes such as growth, differentiation, and apoptosis, which are implicated in the pathogenesis of PAH.

7. Conclusions

PAH is a condition closely associated with structural vessel anomalies and inadequate pulmonary vascular function, resulting in elevated blood pressure. Current treatments for PAH include prostacyclin and its analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. While these therapies have improved the quality of life and life expectancy for PAH patients, their effectiveness remains insufficient for the radical treatment of PAH. Moreover, the side effects and costs of these treatment approaches limit their effectiveness. The current study discusses the therapeutic potential of natural products for resolving PAH. Products of natural origin are important sources for the research and development of new drugs for the prevention and management of PAH. Recent research has shown that natural products have therapeutic value in the treatment of PAH through mechanisms involving antioxidant, anti-inflammatory, anti-vascular remodelling, vasodilating, and apoptosis-promoting effects. Prominent natural sources for the treatment of PAH include epicatechin, beetroot juice, tetramethylpyrazine, and sodium tanshinone IIA sulfonate. Natural products may create a synergistic effect in the therapeutic effectiveness. The combined use of Aconiti Lateralis Radix Praeparata, and Fritillariae Thunbergii Bulbus has proven to be effective in the treatment of PAH. Similarly, the combined application of ginsengs has been found to be effective in the treatment of PAH. In the development of drugs from natural products, the therapeutic effect must be supported and confirmed by integrating interdisciplinary studies including pharmacognosy, pharmacology, toxicology, medical biochemistry, biochemistry, and cellular and molecular biology. Different profiles of natural-origin products, such as extracts or effective metabolites, have been reported to be beneficial for treating PAH. Extracts obtained from natural sources contain many different metabolites that have synergistic or antagonistic effects on each other. For this reason, in drug development from the natural extract, one of the most important limiting

factors is the determination of the effective dose. To determine the effective dose of the extract, the most effective metabolite must be identified through further biological activity-guided fractionation studies, followed by standardisation and preclinical toxicity and drug safety studies.

Hence, despite the discovery of effective extracts and metabolites for PAH therapy, preclinical research on these natural sources is still in its early stages, and there is insufficient information on their safety, therapeutic doses, pharmacological interactions, or side effects. Therefore, additional multidisciplinary research is required to support the medical advantages of natural products identified for the treatment of PAH.

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