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Review

The Prospect and Challenges of Repurposing Established Drugs in Pulmonary Arterial Hypertension

Sila Ozlem Sener [1,2], Rateep Nasim [3] and Talat Nasim [1,*]

[1] Translational Medicine Laboratory, School of Pharmacy and Medical Sciences, Faculty of Life Sciences, University of Bradford, Bradford BD7 1DP, UK; silaozlem.sener@sbu.edu.tr
[2] Gulhane Faculty of Pharmacy, University of Health Sciences, 06018 Ankara, Turkey
[3] School of Biosciences, University of Kent, Canterbury CT2 7NU, UK; rn283@kent.ac.uk
* Correspondence: t.nasim@bradford.ac.uk; Tel.: +44-(0)12-7423-6076

Abstract: *Pulmonary* arterial hypertension (PAH) is a progressive disorder caused by the narrowing of small blood vessels in the lungs, which, in the absence of therapies, leads to right heart failure and premature death. No cure for this devastating disorder is known. Current management therapies aim to improve symptoms, and hence, there is a need to identify novel therapeutic interventions. The major objectives of this review are to critically evaluate current treatment strategies and highlight the challenges and prospects of established drugs and natural products for the resolution of PAH.

Keywords: pulmonary arterial hypertension; repurposing drugs; natural products; synthetic compounds

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1. Introduction

A serious medical condition known as pulmonary arterial hypertension (PAH) is characterized by a steady increase in pulmonary vascular resistance and a progressive deterioration of the small pulmonary arteries that may eventually lead to death. A mean pulmonary arterial pressure of at least 25 mmHg at rest or greater than 30 mmHg during exercise and/or a pulmonary vascular resistance of at least 3 Wood units is defined as PAH [1,2]. The incidence of PAH is approximately 1% in the general population, but it can reach up to 10% in those over 65 [3]. The three major medications used to treat PAH are endothelin receptor inhibitors, prostacyclin analogs, and phosphodiesterase-5 (PDE5). These medications' primary aim is to change the proportion of pulmonary circulation vasodilation to constriction. Furthermore, their ability to enhance clinical outcomes is limited, and severe adverse effects can be caused [4].

The process of finding novel medications and obtaining approval for sale typically takes several phases throughout conventional pharmaceutical discovery and development. Hence, developing novel approaches to shorten the drug discovery process is essential. The process of discovering a new drug is known to take ten or even fifteen years of study and significant financial resources [5]. Because of these limitations, "drug repurposing" has emerged as a substitute strategy for finding de novo drug molecules to accelerate the drug development process. This involves looking for new agents for medications that are currently licensed [6].

This study provides an overview of the current medications used in the treatment of PAH and highlights the prospects and challenges of FDA-approved natural and synthetic drugs that may have potential therapeutic benefits for PAH.

2. Current Medications in PAH and Their Limitations

There are currently three main targets for PAH drugs: the endothelin, prostacyclin, and nitric oxide/cGMP pathways (Figure 1). However, the existing drugs associated with these pathways are unable to provide a radical improvement for the treatment of PAH and

instead resolve the symptomatic problems associated with PAH. Additionally, quality of life can be negatively impacted by the severe side effects of these medications [7].

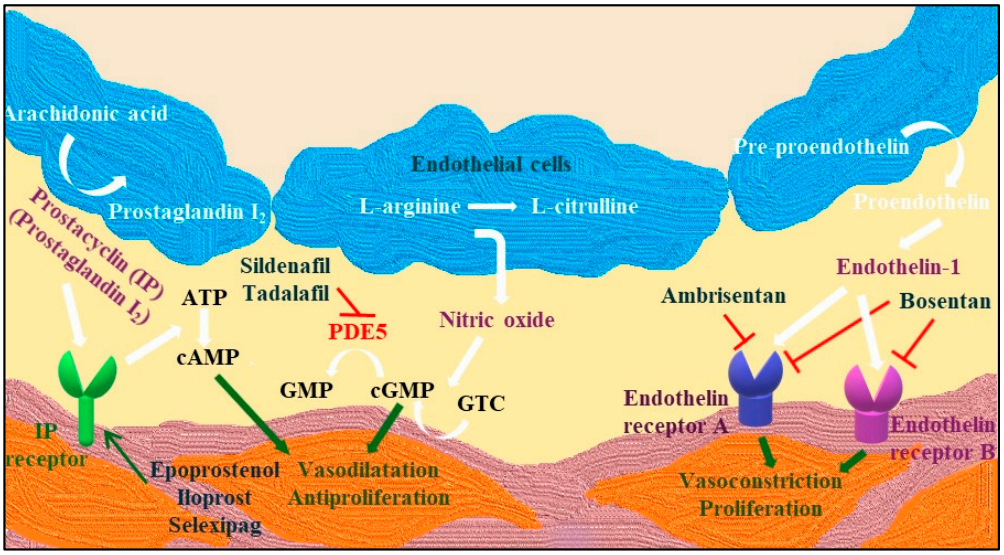

Figure 1. Current medications used in the treatment of PAH. These medications aim to target the endothelin receptor, prostacyclin, and nitric oxide/cGMP-mediated pathways. Blunt red arrows (⊥) indicate inhibition, while sharp green arrows (→) indicate stimulation.

2.1. Endothelin Receptor Blockers (ERBs)

Vascular endothelial cells mainly lead to the production and secretion of endothelium (ET-1) in the vessels, which causes a vasoconstrictive effect on pulmonary artery smooth muscle cells. In addition to its vasoconstrictive effect, ET-1 increases smooth muscle cell proliferation. Therefore, ET-1, with antihypertensive potential, constitutes a new therapeutic strategy for the treatment of PAH [8].

2.1.1. Bosentan

Bosentan (Figure 2) is an endothelin receptor antagonist used in the treatment of PAH. Bosentan is a specific and competitive antagonist for both type A and type B endothelin-1 receptors [9,10].The oral administration of bosentan (Tracleer® Actelion Pharmaceuticals, Titusville, NJ, USA) was approved by the FDA in 2001 for the treatment of PAH [11]. Placebo-controlled clinical trials investigating pulmonary hypertension have shown that orally administered bosentan improves exercise ability and improves clinical findings in patients with WHO functional class III or IV symptoms, including limitations of physical activity and heart failure at rest [12–14].

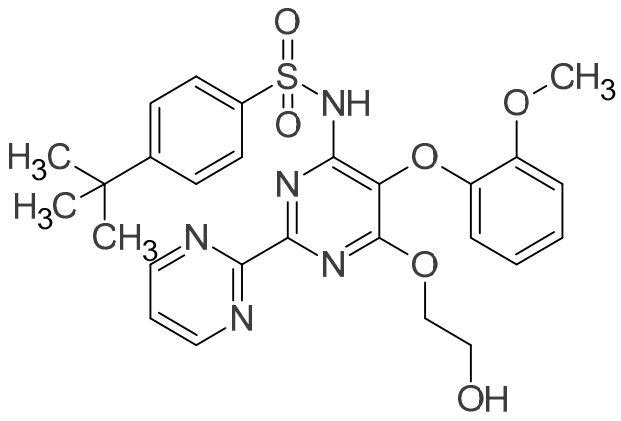

Figure 2. The molecular structure of bosentan.

Birth defects can potentially be caused by bosentan. It also causes hepatotoxic side effects, including abnormal liver function and a high rise in hepatic amino transaminase levels. As a result, bosentan is subject to risk evaluation and mitigation strategies (REMSs) in the US [15].

2.1.2. Ambrisentan

Ambrisentan (Figure 3) is a highly selective and potent endothelin-A receptor antagonist, unlike bosentan, which is a competitive antagonist of both type A and type B endothelin-1 (ET-1) receptors [16,17]. Ambrisentan (Letaris®, Gilead Inc., Foster City, CA, USA) was approved by the FDA in 2007 for the indication of PAH [11,18]. Treatment with ambrisentan was associated with a significant improvement in exercise capacity and a significant delay in the progression to clinical worsening in randomized, placebo-controlled clinical trials [16,17,19].

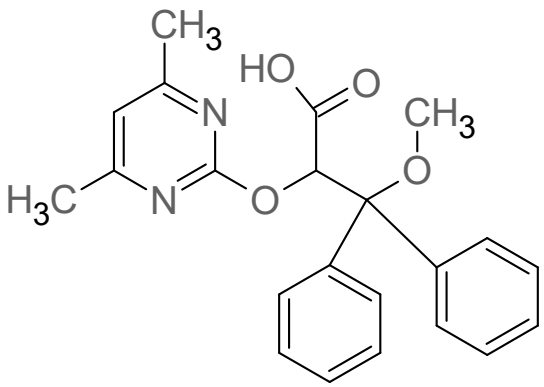

Figure 3. The molecular structure of ambrisentan.

Ambrisentan is covered by the REMS program in women of childbearing age because it has been identified as having the potential to cause serious birth defects [20].

2.2. Phosphodiesterase-5 (PDE5) Inhibitors

The pathogenesis of PAH is characterized by endothelial cell dysfunction. One of the causes of endothelial dysfunction is based on a decreased level of vasodilators, such as prostacyclin and nitric oxide. Phosphodiesterase type 5 (PDE-5) plays a role in the process of inactivating cyclic guanosine monophosphate, the second messenger of the nitric oxide pathway. The level of PDE-5 increases with PAH progression. Thus, PDE-5 inhibitors have introduced a therapeutic approach in the treatment of PAH by increasing the levels of vasodilators, such as nitric oxide [21].

2.2.1. Sildenafil

Sildenafil (Figure 4) is an oral and intravenous selective phosphodiesterase type 5 (PDE5) inhibitor. The selective PDE5 inhibitor promotes the level of cGMP, which, in turn, induces nitric oxide-mediated vasodilation [22]. In patients with idiopathic PAH or PAH with congenital systemic–pulmonary shunts, sildenafil has been shown in clinical trials to improve exercise capacity. Sildenafil (Revatio®, Pfizer Inc., New York, NY) was approved by the FDA in 2005 for the treatment of PAH [11,23].

There have been reports that the combination of sildenafil with other drugs, such as nitrates, or the use of sildenafil over a specific dose may cause a sudden and dramatic reduction in systolic blood pressure levels. There have also been studies associating non-arteritic anterior ischaemic optic neuropathy with sildenafil use [24,25].

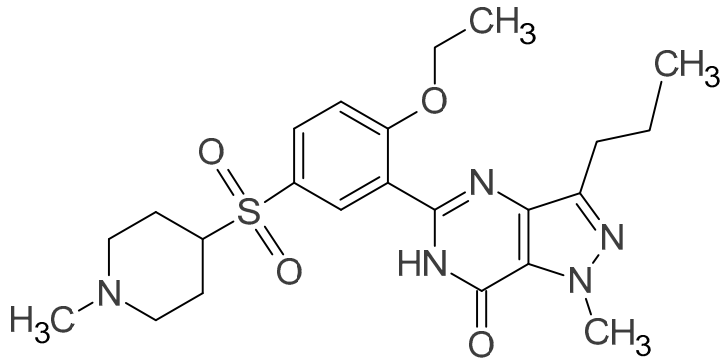

Figure 4. The molecular structure of sildenafil.

2.2.2. Tadalafil

Tadalafil (Adcirca®, Eli Lilly Nederland B.V., BJ Utrecht, Netherlands) (Figure 5) is an oral selective phosphodiesterase type 5 (PDE5) inhibitor that was approved by the FDA in 2009 for PAH treatment. Patients treated with tadalafil showed improved exercise capacity and reduced clinical worsening compared with a placebo in clinical trials of PAH [11,26,27].

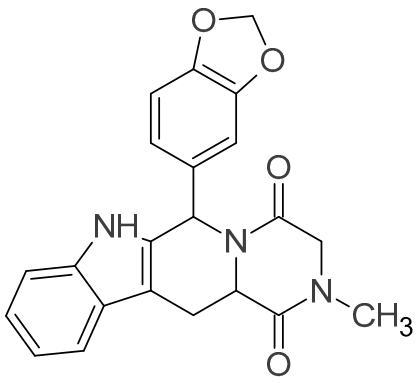

Figure 5. The molecular structure of tadalafil.

Tadalafil treatment may cause side effects such as headache, flushing, nasopharyngitis (including stuffy or runny nose and blocked sinuses), nausea, dyspepsia, stomach pain, myalgia, back pain, and pain in the extremities. Patients who have had an acute myocardial infarction within the last 3 months or who have severe hypotension should not be treated with tadalafil. In addition, like sildenafil, tadalafil has been associated with non-arteritic anterior ischaemic optic neuropathy (NAION) and is contraindicated in patients with NAION-related visual loss [28].

2.3. Prostacyclin Analogs

The level of prostacyclin produced in vascular endothelial cells is decreased in PAH patients. Prostacyclin also has a potent vasodilatory effect and reduces platelet aggregation, inflammation, and vascular smooth muscle proliferation. Therefore, prostacyclin analogs that increase prostacyclin synthesis are one of the important strategies used in the treatment of PAH [29].

2.3.1. Epoprostenol

Epoprostenol (Figure 6) is the pharmaceutical form of a natural prostaglandin, prostacyclin. Epoprostenol is a vasodilator and inhibits platelet aggregation. It is used for the long-term management of PAH. Clinical data have shown that epoprostenol can improve PAH symptoms, including the limitation of physical activity and heart failure at rest. A significant increase in long-term survival in PAH patients has been reported with

epoprostenol [30]. Epoprostenol (Flolan®, GlaxoSmithKline, Philadelphia, PA, US) was approved by the FDA in 1995 [11].

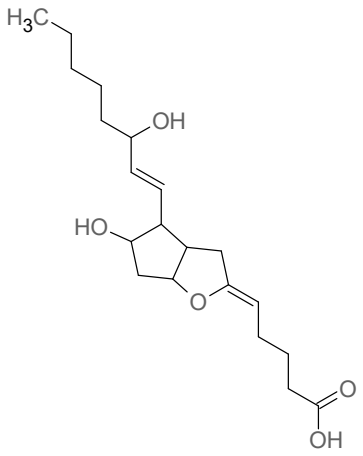

Figure 6. The molecular structure of epoprostenol.

Epoprostenol treatment is associated with common side effects. These include diarrhea, headache, flushing, jaw pain, nausea, vomiting, leg and foot pain [31]. Epoprostenol may also cause a rash, impotence, and decreased appetite. Epoprostenol is available for use by intravenous infusion. The use of intravenous infusion and its short half-life causes side effects such as infection, that is, local infection of the central venous line, bacteremia, and sepsis. Its administration by an intravenous route and its effects are non-specific, resulting in peripheral vasodilation. This situation is directly related to systemic hypotension and coronary steal adverse effects. In addition, the use of intravenous administration in chronic disease has an impact on the quality of life of patients with PAH [32].

2.3.2. Iloprost

Iloprost (Figure 7) is an inhaled prostaglandin used in the treatment of PAH. Iloprost is thought to act in a similar way to epoprostenol. Clinical studies have shown that the use of iloprost significantly improves acute hemodynamic response, cardiac output, pulmonary artery blood pressure, and arterial oxygen saturation in PAH patients compared to the baseline [33,34]. Iloprost (Ventavis®, Actelion Pharmaceuticals, Titusville, NJ, USA) was approved by the FDA in 2002 [11].

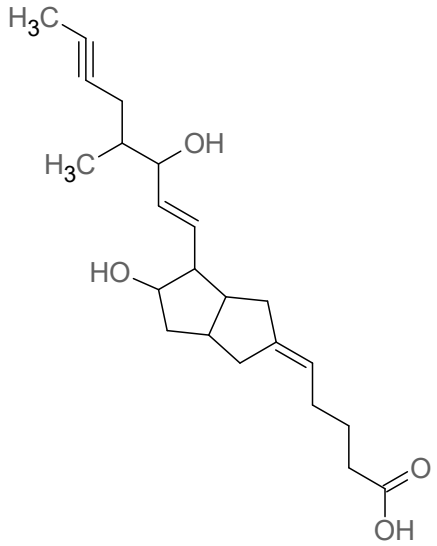

Figure 7. The molecular structure of iloprost.

The most commonly reported adverse effects associated with iloprost treatment are syncope, increased cough, flushing, jaw pain, headache, dizziness, influenza-like syndrome, peripheral edema, hypotension, nausea, and diarrhea [35].

2.4. Prostacyclin IP Receptor Agonists

Selexipag

Selexipag (Figure 8) is an oral selective prostacyclin receptor agonist for the treatment of PAH. A Phase II trial demonstrated a reduction in pulmonary vascular resistance in PAH patients after 17 weeks of treatment. Selexipag was shown to improve disease progression and reduce the need for hospitalization in a Phase III study. Selexipag was approved by the FDA in 2015 [36,37].

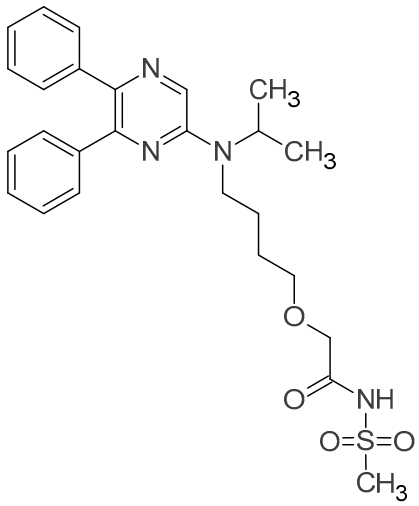

Figure 8. The molecular structure of selexipag.

Consistent with other prostanoid medications, selexipag produces predictable (Table 1), dose-dependent side effects such as headache, flushing, nausea, vomiting, and musculoskeletal discomfort [36].

Table 1. Summary of the current medications used in PAH together with their mode of action and side effects.

Name of the Drug	Mode of Action	Side Effect	References
Bosentan	Endothelin receptor blockers	Birth defects, abnormal liver function, and increasing effects of hepatic amino transaminase	[15]
Ambrisentan	Endothelin receptor blockers	Birth defects	[20]
Sildenafil	PDE5 inhibitors	Reduction in systolic blood pressure and ischemic optic neuropathy	[17,24]
Tadalafil	PDE5 inhibitors	Headache, flushing, nasopharyngitis, and NAION-related visual loss	[28]
Epoprostenol	Prostacyclin analogs	Diarrhea, headache, flushing jaw pain, vomiting, leg and foot pain, decreasing appetite, and coronary steal side effects	[32]
Iloprost	Prostacyclin analogs	Cough, flushing, jaw pain, headache, dizziness, influenza-like syndrome, peripheral edema, hypotension, nausea, and diarrhea	[35]
Selexipag	Prostacyclin IP receptor agonists	Headache, flushing, nausea, vomiting, and musculoskeletal discomfort	[36]

3. The Importance of Repurposing Drugs in PAH

The exploration of new indications for old drugs through drug repurposing results in a reduction in the time-dependent high costs and future potential risks of compounds compared to traditional drug discovery initiatives. The drug repurposing strategy significantly reduces failure rates (45%) in drug development associated with safety or toxicity issues. This strategy also leads to a reduction in the average drug development time of up to 5–7 years. In addition, drug repurposing has the potential to make drugs with a known safety profile directly available to new patient populations [38]. Therefore, repurposing "old" medications is becoming an attractive approach to finding new therapies [7]. This study examined FDA-approved repurposed drugs, including natural, semisynthetic, and synthetic compounds with therapeutic potential for PAH.

4. Natural or Natural-Derived Drugs in PAH Treatment

Currently used drugs for the treatment of PAH remain inadequate for radical improvement. In recent years, products of natural origin have shown promising therapeutic potential in the treatment of cardiovascular diseases and have led researchers to investigate these natural sources in the treatment of PAH [39].

4.1. Capsaicin

The natural compound, capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) (Figure 9), derived from the fruit of the capsicum plant, has an alkaloid structure [40]. Christian Friedrich Bucholz isolated it in its impure state for the first time. John Clough Thresh obtained it in crystalline form in 1876, and E. K. Nelson clarified its structure in 1919 [41]. Capsaicin binds to the vanilloid receptor subtype 1 ion channel receptor in tissue, which causes a burning sensation. In November 2009, the FDA approved capsaicin (Qutenza®, Averitas Pharma, Morristown, NJ, USA) for the treatment of post-therapeutic neuralgia together with neuropathic pain [42].

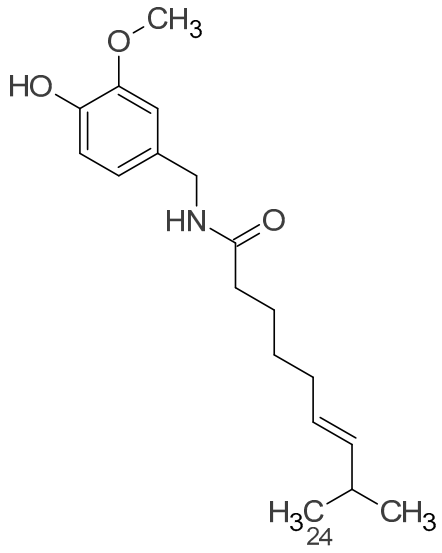

Figure 9. The molecular structure of capsaicin.

Treatment with capsaicin was found to reduce the values of right ventricular systolic pressure and the rate of right ventricular/left ventricle plus septum, right ventricular/body weight, and lung weight/body weight in rats with monocrotaline-induced PAH, thereby alleviating PAH-related symptoms. Furthermore, capsaicin treatment downregulated the p38 (p-p38) MAPK pathway, resulting in alleviated inflammation in PAH [43].

4.1.1. Colchicine

Colchicum autumnale is the first source of the naturally occurring alkaloid colchicine [44]. Colchicine (Figure 10) was approved by the FDA in 2009 for the prevention of gouty arthritis as well as the treatment of acute gout and familial Mediterranean fever [45].

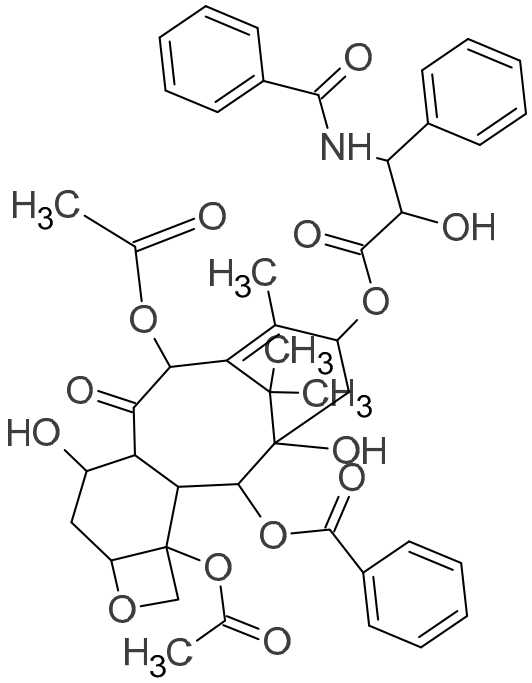

Figure 10. The molecular structure of colchicine.

Right ventricular-specific microtubule derangement, caused by monocrotaline-induced PAH, is characterized by a decrease in junctophilin-2 and t-tubule disarray. Colchicine has been proven to enhance junctophilin-2 expression, reduce microtubule density, and improve t-tubule architecture and right ventricular function. It was demonstrated that adverse pulmonary vascular remodeling in monocrotaline-induced PAH is also reduced by colchicine [46]. In MCT-induced PAH, colchicine or the combined therapy of colchicine–nicorandil led to a decrease in the protein expressions of markers of right ventricle damage and an increase in biomarkers for the preservation of right ventricular function [47].

4.1.2. Paclitaxel

Paclitaxel (Figure 11), also referred to as taxol, is one of the most popular medicinal drug molecules used for cancer treatment. Paclitaxel was first obtained from the bark of *Taxus brevifolia* (Pacific yew tree) in 1963 [48].Through phase I, II, and III clinical trials conducted between 1977 and 1992, it was established that taxol significantly reduced the risk of a varied range of cancer types. FDA authorized taxol in 1992 for the management of advanced ovarian cancer. Taxol was also approved to treat metastatic cancer in 1994 [49].

The activation of autophagy has been implicated in the pathogenesis of PAH. Autophagy is directly associated with forkhead box protein O1 (FoxO1). In MCT-PAH animals, autophagy was activated, and FoxO1 expression increased. Paclitaxel treatment has been proven to reduce FoxO1 phosphorylation, suppress autophagy, and also to reduce elevated right ventricular systolic pressure, right ventricular hypertrophy index, and the percentage of medial wall thickness in MCT-induced PAH rats. In conclusion, paclitaxel inhibits pulmonary vascular remodeling through FoxO1-mediated autophagy suppression. These data suggest that paclitaxel may be a novel therapeutic agent for the prevention and treatment of PAH [50].

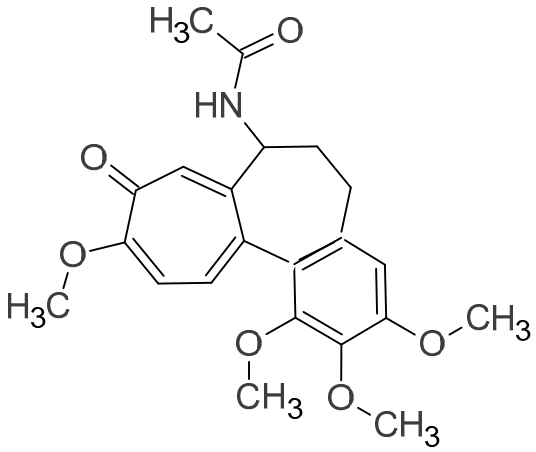

Figure 11. The molecular structure of paclitaxel.

4.1.3. Rapamycin

Triene macrolide rapamycin (Figure 12) is derived from several actinomycetes, such as *Actinoplanes* sp., *Streptomyces hygroscopicus*, and *Streptomyces iranensis*. Studies have shown that it has the potency to prevent kidney transplant rejection as an independent remedy or in combination with cyclosporine, giving rise to its therapeutic relevance. In 1999, the FDA approved it as an oral immunosuppressant for organ transplantation [51].

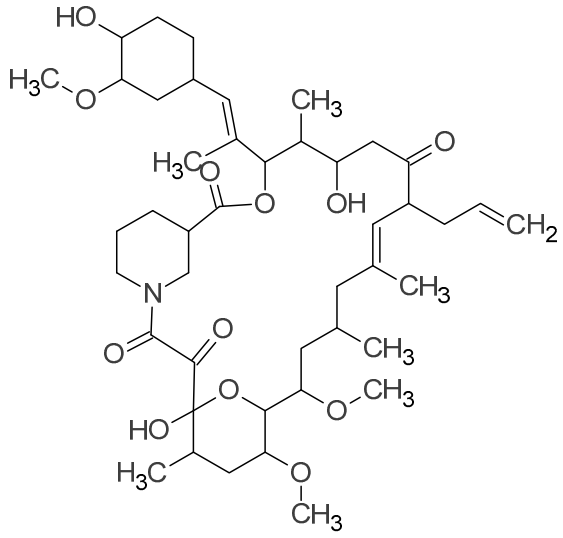

Figure 12. The molecular structure of rapamycin.

Rapamycin, in both free and nanoparticle forms, has been shown to cure PAH development, PAH-induced pulmonary arteriole thickness, and ventricular remodeling via its efficacy on the mTOR pathway [52].

4.1.4. Tacrolimus

A macrolide immunosuppressant called tacrolimus, which is a calcineurin inhibitor, was isolated in *Streptomyces tsukubaensis*. Tacrolimus was approved by the FDA in 1993 for use in liver and kidney transplants after it was proven to be an effective first-line immunosuppressive agent [51].

Tacrolimus increases the production of the inhibitor of the differentiation-1 (*id*-1) gene by blocking calcineurin and sequestering FK-binding protein 12, which, in turn, stimulates SMAD1/5 and MAPK signaling and further promotes BMPRII-mediated signaling [7]. A randomized placebo-controlled trial (Phase IIb) revealed that tacrolimus improved 6 min

walking distances (Table 2), serological and echocardiographic markers, and peripheral blood mononuclear cells, with reduced BMPR2 expression associated with PAH [53].

Table 2. The summary of the natural drugs that can be repurposed in PAH together with their mode of action and developmental stages.

Name of the Drug	Mode of Action	Developmental Stage (e.g., Animal Models, Clinical Trials, etc.)	References
Capsaicin	Inhibition of p38 (p-p38) MAPK pathway	Monocrotaline-induced PAH in rats	[43]
Colchicine	Improvement of junctophilin-2 expression	Monocrotaline-induced PAH in rats	[46]
Paclitaxel	Reduction in FoxO1 phosphorylation	Monocrotaline-induced PAH in rats	[50]
Rapamycin	Inhibitory effects on mTOR pathway	Monocrotaline-induced PAH in rats	[52]
Tacrolimus	Reduction in BMPR2 expression	Phase IIb trial	[53]

5. Synthetic Drugs in PAH Treatment

In addition to natural sources, research on the use of synthetic drugs in the treatment of PAH is ongoing. Anakinra and etanercept are among these synthetic drugs [11].

5.1. Anakinra

Anakinra (Figure 13) is an IL-1 receptor antagonist (IL-1Ra) and causes a reduction in inflammation by blocking the activity of the receptors for both IL-1a and IL-1b [54]. Anakinra was approved by the FDA for rheumatoid arthritis treatments in 2001 [55].

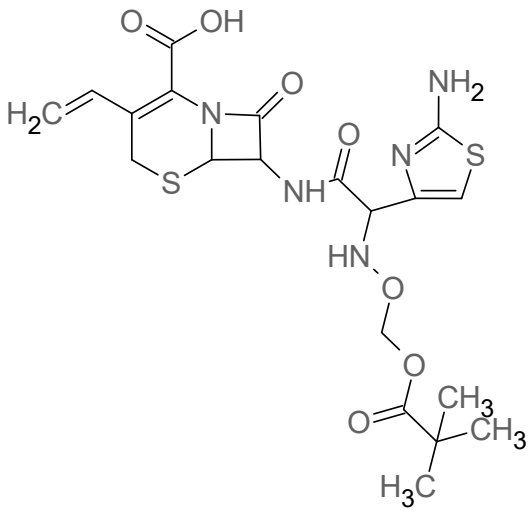

Figure 13. The molecular structure of anakinra.

A Phase IB/II pilot study evidenced that anakinra provides achievable and safe treatment for PAH patients with right ventricular failure through the blocking of IL-1 [56].

5.2. Etanercept

Etanercept (Figure 14) is a competitive inhibitor of TNF-α, a pro-inflammatory cytokine that plays a major role in psoriasis and psoriatic arthritis. The first FDA-approved medication for psoriatic arthritis was etanercept. Etanercept is also indicated for the treatment of adolescent polyarticular-course rheumatoid arthritis and rheumatoid arthritis [57].

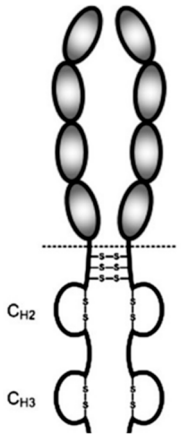

Figure 14. Structure of etanercept [58].

Etanercept has been shown to prevent and reverse MCT-induced PAH by reducing inflammation through its TNF-a antagonist effect [59].

5.3. Rosiglitazone

Rosiglitazone (Figure 15) is a thiazolidinedione glucose-lowering agent that regulates glucose control by improving hepatic and peripheral insulin sensitivity and may also contribute to the preservation of pancreatic β-cell function [60]. The FDA approved rosiglitazone in May 1999 for use either alone or with metformin or sulphonylurea, along with diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus [61].

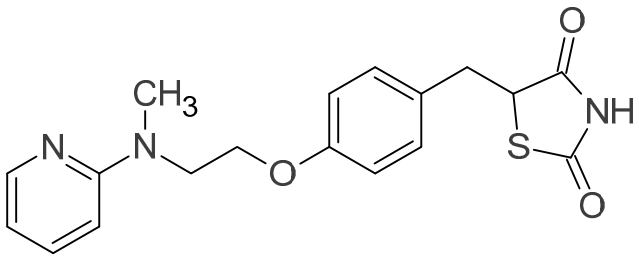

Figure 15. Molecular structure of rosiglitazone.

Rosiglitazone has been proven to regulate the expression of the key molecular markers lactate dehydrogenase and alkaline phosphatase in human PAH-affected endothelial cells and PASMC, which is implicated in the progression of PAH. Rosiglitazone has also been evidenced to cause dose-dependent inhibition in the proliferation of PASMCs [62]. Thus, rosiglitazone may have the potential to be evaluated as a drug to be repurposed in PAH treatment. However, the FDA placed restrictions on the use of rosiglitazone in September 2010. Even if the limitations were lifted once more in November 2013, as the FDA Drug Safety Communication that was released states, "some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains" [63]. Therefore, when assessing rosiglitazone as a repurposing medication, potential cardiovascular side effects need to be considered.

5.4. Ranolazine

The FDA approved ranolazine (Figure 16) as a medication in 2006 for the treatment of chronic angina pectoris in patients who do not respond adequately to other anti-anginal agents, including amlodipine, β-adrenoceptor antagonists, or nitrates. It acts through a variety of pharmacological processes, one of which is probably the decreased oxygen consumption caused by the suppression of the late inward sodium current [64].

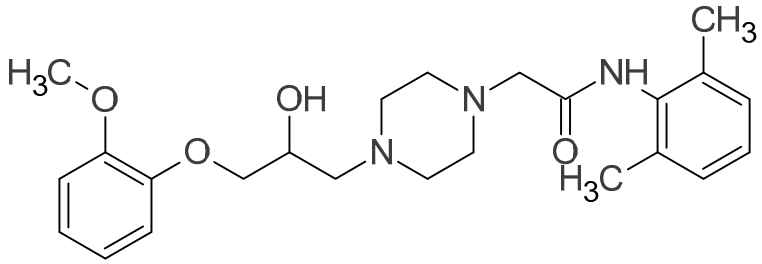

Figure 16. Molecular structure of ranolazine.

MCT-induced PAH rats treated with ranolazine showed improved plasma brain natriuretic peptide (BNP) levels, RV hypertrophy, and RV pressure, as well as reduced intracellular calcium overload. In addition, ranolazine reduced doxorubicin-induced cardiotoxicity in animal models by scavenging oxidative stress [65].

5.5. Anastrozole

The aromatase inhibitor anastrozozole (Figure 17) was approved by the FDA and several countries for the first-line treatment of postmenopausal women with early-stage, hormone-receptor-positive breast cancer. Additionally, it was authorized in the EU and other countries for use in the adjuvant treatment of breast cancer in women who had already completed two-to-three years of adjuvant tamoxifen treatment [66].

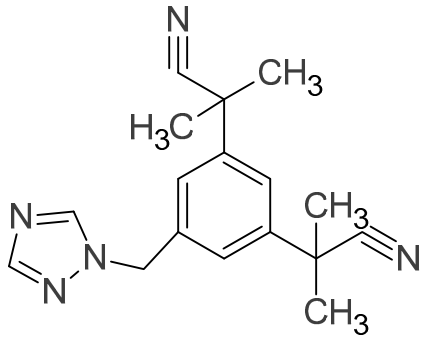

Figure 17. Molecular structure of anastrozole.

It has been demonstrated in animal models that inhibiting the conversion of androgens to estrogen using an aromatase inhibitor suppresses PAH. As a result, research on treatments is usually focused on eliminating the effects of estrogen. In a randomized controlled trial, the use of anastrozole, a breast cancer aromatase inhibitor that prevents androgens from being converted to estrogen, was assessed in 18 patients with PAH. The results showed decreased levels of circulating estrogen and a substantial increase in 6MWD of +26 m compared to −12 m in controls [67].

5.6. Sorafenib

The FDA approved sorafenib (Figure 18) for the treatment of individuals with incurable hepatocellular carcinoma and advanced renal cell carcinoma. Additionally, the EMEA approved its use for the treatment of patients with advanced renal cell carcinoma and hepatocellular carcinoma who do not respond adequately to prior interferon-a or interleukin-2-based therapy or who are considered inappropriate for this type of therapy [68].

In rat models, sorafenib has demonstrated beneficial effects in PAH, such as decreased RV hypertrophy and PA and RV pressures. A small human trial comprising nine patients—seven with severe refractory PAH and two with pulmonary veno-occlusive disease (PVOD)—showed that sorafenib medication improved mPAP in six patients and the WHO Functional Class in eight patients [67].

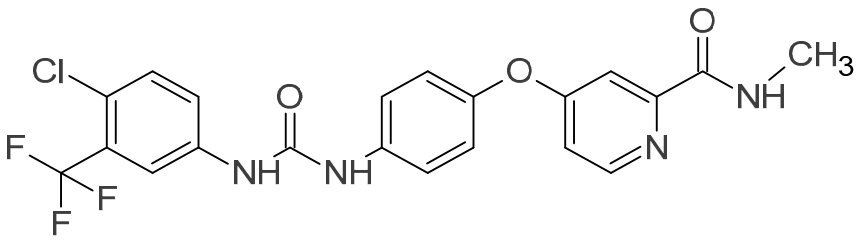

Figure 18. Molecular structure of sorafenib.

6. Challenges of Repurposing Drugs in PAH

Drug repurposing has become more popular recently, but there are fewer applications than expected due to several implementation-related issues. Prospective start-ups have an uphill battle in providing relevant data to regulatory authorities as there are no set regulations for the repurposing of drug candidates. Furthermore, using a repurposed drug for a new disorder also raises patent issues. Finding cost-effective and profitable areas to explore is important for pharmaceutical companies. However, there is no guarantee that the repurposing of a drug for a rare or under-utilized condition will result in a significant financial return. It may, therefore, be more practical for the industry to focus on a more specific and proven scientific target [5].

PAH is a relatively rare disease. There are many approved therapies for its treatment, even if they cannot provide radical improvement. Thus, repurposing drugs for PAH poses significant challenges. As mentioned above, pharmaceutical companies tend to invest in more common diseases rather than rare ones, and this perception of "market saturation", can make it difficult to advance a promising therapy into later stages of clinical development for PAH [11].

7. Conclusions

The recent discovery of innovative drugs that, more specifically, target the pathophysiological processes involved in PAH has become important in identifying novel treatment strategies for PAH. Although PAH symptomatic drugs have long provided patients with tolerable symptom relief, higher mortality rates continue to pose a major treatment obstacle. Current treatments induce a global financial burden, and the long-term survival rate of patients with current medications is still below average. In addition, current therapies are associated with severe side effects that affect PAH patients' quality of life. Therefore, the next generation of PAH therapies is needed to improve long-term survival and eliminate the side effects of current therapies.

Taking a drug from discovery to use in clinical practice is a long and challenging process. As mentioned earlier, repurposing drugs possesses advantages over de novo drug development as they require fewer safety data and basic science studies. In addition, initiatives to repurpose drugs can allow them to be used in the clinic without the need to obtain FDA approval, saving even more time and costs.

This review highlights five natural or natural-derived agents and two synthetic agents that are FDA-approved for their potential use in PAH. These agents have shown preliminary evidence of efficacy in the treatment of PAH. However, further formulation, toxicological, and clinical studies will be required to demonstrate their superior efficacy in comparison with current PAH treatments.

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