Pulmonary hypertension and the potential of 'drug' repurposing: A case for African medicinal plants

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Pulmonary hypertension (PH) is a haemodynamic disorder in which elevated blood pressure in the pulmonary circulation is caused by abnormal vascular tone. Despite advances in treatment, PH mortality remains high, and drug repurposing has been proposed as a mitigating approach. This article reviews the studies that have investigated drug repurposing as a viable option for PH. We provide an overview of PH and highlight pharmaceutical drugs with repurposing potential, based on limited evidence of their mechanisms of action. Moreover, studies have demonstrated the benefits of medicinal plants in PH, most of which are of Indian or Asian origin. Africa is a rich source of many medicinal plants that have been scientifically proven to counteract myriad pathologies. When perusing these studies, one will notice that some African medicinal plants can counteract the molecular pathways (e.g. proliferation, vasoconstriction, inflammation, oxidative stress and mitochondrial dysfunction) that are also involved in the pathogenesis of PH. We review the actions of these plants with actions applicable to PH and highlight that they could be repurposed as adjunct PH therapies. However, these plants have either never been tested in PH, or there is little evidence of their actions against PH. We therefore encourage caution, as more research is needed to study these plants further in experimental models of PH while acknowledging that the outcomes of such proof-of-concept studies may not always yield promising findings. Regardless, this article aims to stimulate future research that could make timely contributions to the field.

Keywords. Pulmonary hypertension, novel therapeutics, drug repurposing, African medicinal plants, adjunct therapies.

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Synopsis

What the study adds. Pulmonary hypertension (PH) remains a fatal disease, and 80% of the patients live in developing countries where resources are scarce and specialised therapies are often unavailable. Drug repurposing is a viable option to try to improve treatment outcomes.

Implications of the findings. We propose that another form of 'drug' repurposing is the use of medicinal plants, many of which have demonstrated benefits against pathological processes that are also key in PH, e.g. apoptosis, tumour-like growth of cells, proliferation, oxidative stress and mitochondrial dysfunction.

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure ≥20 mmHg when diagnosed with right heart catheterisation,[1] or a right ventricular systolic pressure ≥40 mmHg (in the absence of pulmonary stenosis and acute right heart failure) as measured with transthoracic echocardiography.[2] Approximately 75 million people suffer from PH globally,[3] and it occurs mainly in women.[4] It is associated with several conditions, such as HIV, left heart disease, schistosomiasis, chronic obstructive pulmonary disease and tuberculosis sequelae.[5-7] These conditions increase pulmonary vascular remodelling that results in increased pulmonary vasculature resistance and therefore PH. The current PH treatment regimens have made a significant clinical impact, as they improve clinical outcomes and quality of life to a certain degree.[1] However, they do not cure PH, suggesting that its pathophysiology is not fully understood,[8] and this limited impact of the current drugs on PH highlights a need for better treatment regimens. During the past 5 years, and particularly in the post-COVID-19 period, drug repurposing has been proposed as a novel way to augment the health benefits afforded by current PH drugs.[9] The articles on this topic are too many to list in full, but these three show the importance of the idea.[10-12]

A brief overview of the pathophysiology and treatment of PH

PH has a complex pathophysiology that includes an array of molecular factors and proteins that trigger myriad molecular pathways[13] such as increased proliferation of pulmonary artery smooth-muscle cells (PASMCs) and a cancer-like phenotype characterised by PASMC resistance to apoptosis and excessive proliferation of pulmonary artery

endothelial cells (PAECs).[14] Other pathways include pulmonary inflammation, elevated oxidative stress, lung mitochondrial dysfunction, lung fibrosis and pulmonary vasoconstriction.[14] These pathways ultimately result in obliterative changes to the pulmonary arterioles, including thickening of the intima and medial layers[13] and plexogenic arteriopathy.[15]

Treatment options for PH improve PH-related symptoms by targeting these molecular pathways. Drugs include endothelin-1-receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues and prostacyclin-receptor agonists.[16] PH survival without treatment used to average 2.8 years, with survival rates of 68%, 48% and 34% at 1, 3 and 5 years after diagnosis, respectively.[17] However, with treatment, survival rates have improved to 97.2%, 91.5%, 84.2%, 80.2% and 75.9% at 1, 2, 3, 4 and 5 years, respectively.[18] Great strides have therefore been made with regard to PH treatment, but there is room for improvement, as despite these drugs, patients still die from PH. This situation suggests that there is a need for better treatment strategies.[19]

Drug repurposing in PH

The aim of drug repurposing[20] in PH is to reutilise drugs that were traditionally used for other diseases in the hope that they may provide health benefits for PH patients too. Accumulating literature suggests that there is indeed an instrumental role for drug repurposing in PH. For instance, imatinib, a tyrosine kinase inhibitor used in patients with chronic myelogenous leukaemia,[21] has been shown to have vasodilatory properties by blocking the platelet-derived growth factor-activated pathway of vascular remodelling.[22] It can therefore be linked to PH, which develops through a similar mechanism.[23] As a result, imatinib was repurposed for PH and has been shown to improve haemodynamics and pulmonary vascular resistance in PH patients.[24] Other examples are summarised in Table 1.

Repurposing from an African perspective

Most Africans rely on medicinal plants as a source of healthcare.[42] The World Health Organization reports that ~80% of developing countries depend largely on medicinal plants for the treatment of ailments and diseases.[43] Over the years, African traditional plants have received attention for their health benefits, a characteristic that is attributed to their high polyphenol content.[44] There has been a close to 60% increase in the number of research outputs based on the potential health benefits of African medicinal plants in the past decade.[45]

Many of these African medicinal plants have beneficial effects against diseases such as cancer,[46] diabetes,[47] inflammation[48] and bacterial respiratory diseases.[49] However, there is a paucity of studies investigating the potential of African medicinal plants in counteracting PH, and this is a pity, as these plants offer a niche for the discovery of novel therapeutic targets or adjunct therapies for PH. Such discoveries could equate to afforable therapies to assist PH patients in resource-limited developing-world settings. PH drugs are expensive and therefore inaccessible to many patients in developing countries, where most public health healthcare systems cannot afford to foot the high costs of pharmaceutical drugs. There is therefore a continued search for adjunct PH therapies that are effective and affordable.[50] For this purpose, few studies have investigated natural products or traditional herbs as an adjunct therapeutic approach in PH.[51-53] Some medicinal plants from India and Asia show considerable benefit against key aspects of PH pathophysiology,[51-53] but there is a paucity of such studies on African medicinal plants and PH. This is strange, as Africa boasts rich biodiversity and a wide range of plant species that have medicinal properties. We perused the literature for studies that have demonstrated the underlying mechanisms of these African medicinal plants, and we review whether they counteract molecular pathways in other diseases that are also involved in the pathogenesis of PH. We propose that these African medicinal plants could be used against PH and that this may also be observed as a form of 'drug' repurposing. Needless to say, more research is warranted.

Anti-inflammatory effects of African medicinal plants

Inflammation is usually triggered by damage to living tissues resulting from microbial infections, physical damage or defective immune responses.[54] Various mechanisms of action have been proposed to explain the anti-inflammatory activity of medicinal plants. These mechanisms include inhibition of 15-lipoxygenases,[55] elevation of nitric oxide (NO) production,[57] inhibition of phospholipase A_2,[56] and modulation of proinflammatory gene expression.[57] African medicinal plants have become synonymous with anti-inflammatory effects;[48] in fact, *Aspalathus linearis* (also known as rooibos) is a unique South African species that is considered a potent anti-inflammatory agent. Studies have shown that it achieves this action by limiting the cellular release of proinflammatory cytokines (tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6)) in lipopolysaccharide-induced inflammation.[58,59] Similar effects have been shown with the African potato in a rat model of diclofenac-induced inflammation[60] (Table 2).

Antioxidant properties of African medicinal plants

African medicinal plants are well known for their ability to scavenge free radicals and activate cell antioxidant defence systems.[64] Their mechanism of action is complex, but reactive oxygen species (ROS) stimulate the translocation of nuclear respiratory factor 2 (Nrf-2) to the nucleus, where it binds to antioxidant response element motifs to enhance redox defence[65] and the elevation of intracellular antioxidant gene and protein expression, as well as the increase of antioxidant enzyme activities.[66] Several African medicinal plants can counteract the deleterious effects of elevated oxidative damage to cell structures, including lipids, proteins and DNA. *Aloe claviflora* is a plant that can scavenge ROS and limit lipid peroxidation,[67] while *Aloe vera* and *Aspalathus linearis* induce antioxidant effects via the Nrf-2 pathway (Table 3).

Close to 90% of cellular ROS is produced by mitochondria,[68] while the same organelles are key role players in the optimal function of cellular antioxidant systems.[69] In the absence of proper mitochondrial regulation, antioxidant capacity is reduced, which leads to the excessive production of ROS that further impair mitochondrial function.[70] *A. vera* has been shown to improve mitochondrial function by reducing ROS production, while *Moringa oleifera* can do the same via an Nrf2/haem oxygenase 1

Table 1. A list of pharmaceutical drugs used for other diseases that could be repurposed for PH (some have recently been tested in a PH context)

Drug	Approved for	Effects in models of PH	References
Imatinib	Chronic myeloid leukaemia	Improves haemodynamics and exercise capacity	Frost *et al.*[24]
Tacrolimus	Solid-organ transplantation	Improves *BMPR2* expression in peripheral blood mononuclear cells of human subjects	Spiekerkoetter *et al.*[25]]
Anastrozole	Breast cancer	Improves 6-minute walk distance and reduces 17β-oestradiol levels	Kawut *et al.*[26]
Paclitaxel	Ovarian cancer	Inhibits pulmonary vascular remodelling by FoxO1-mediated autophagy suppression	Feng *et al.*,[27] Zhao *et al.*[28]
Etanercept	Rheumatoid arthritis	Prevents and reverses monocrotaline-induced PH by reducing inflammatory cell infiltration	Zhang *et al.*[29]
Carvedilol	Congestive heart failure	Reduces right ventricular systolic pressures in patients	Cheong *et al.*[30]
Melatonin	Jet lag	Improves cardiac function, reduces oxidative stress, enhances antioxidant systems, and inhibits pulmonary vascular remodelling	Hung *et al.*,[31] Maarman *et al.*,[32] Wang *et al.*[33]
Hydroxychloroquine	Malaria	Attenuates PH by decreasing proliferation and increases apoptosis of pulmonary artery smooth-muscle cells in pulmonary hypertensive arteries.	Ryan[34]
Anakinra	Rheumatoid arthritis	Reduces inflammation and right ventricular dysfunction in PH via interleukin signalling	Trankle *et al.*[35]
Rituximab	Non-Hodgkin's lymphoma	Improves 6-minute walk distance	Zamanian *et al.*[36]
Sotatercept	Chemotherapy-induced anaemia, multiple myeloma, beta-thalassaemia, and end-stage kidney disease	Improves pulmonary vascular resistance in patients, and reduced N-terminal pro-B-type natriuretic peptide levels	Humbert *et al.*[37]
Dimethyl fumarate	Multiple sclerosis	Improves PH by blocking proinflammatory pathways and reducing the infiltration of immune cells in lung tissue.	Grzegorzewska *et al.*[38]
Fasudil	Angina and cerebral vasospasm	Reduces pulmonary vascular resistance in PH patients	Fujita *et al.*,[39] Fukumoto *et al.*[40]
Nesiritide	Acute decompensated heart failure	Ameliorates pulmonary capillary wedge pressure	Michaels *et al.*[41]]

PH = pulmonary hypertension; FoxO1 = forkhead box protein O1.

Table 2. African medicinal plants (tested in non-PH models) with anti-inflammatory activity that could be repurposed for PH

Plant	Common name	Experimental model	Mechanism	References
Hypoxis hemerocallidea	African potato	Diclofenac-induced inflammation animal model of rats	Inhibition of iNOS and NF-κB	Ojewole[60]
		In vitro model		Zulfiqar *et al.*[61]
Aspalathus linearis	Rooibos tea	Lipopolysaccharide-induced inflammation animal model of mice	Inhibition of proinflammatory cytokines (TNF-α, IL-1β and IL-6)	Ajuwon *et al.*,[58] Lee and Bae[59]
		In vitro model		Lee and Bae[59]
Ximenia caffra	Large sourplum	*In vitro* model	Inhibits the messenger RNA expression of proinflammatory genes (IL-6, iNOS and TNF-α)	Zhen *et al.*[62]
Asparagus africanus	Wild asparagus	Carrageenan-induced rat paw oedema and inflammation in Swiss albino and Wistar rats	Inhibition of inflammation by limiting proinflammatory cytokines	Ojewole[60]
Aloe ferox	Aloe	Carrageenan-induced rat paw oedema and inflammation	Inhibition of inflammation due to a high content of malic acid acylated carbohydrates	Mwale and Masika[63]

PH = pulmonary hypertension; iNOS = inducible nitric oxide synthase; NF-κB = nuclear factor kappa B; TNF-α = tumour necrosis factor alpha; IL-1β = interleukin 1 beta; IL-6 = interleukin 6.

Table 3. African medicinal plants could be repurposed for PH owing to their highly relatable mechanisms of actions against pathways that are key to PH pathogenesis

Plant	Common name	Experimental model	Mechanism	References
Dacryodes edulis	Safou plum	Fructose-STZ diabetes induced rat model	Suppresses the expression of Nrf-2 to induce antioxidant activity	Erukainure *et al.*[74]
Moringa oleifera	Drumstick tree or moringa	*In vitro* model	Suppresses H2O2-induced mitochondrial depolarisation and apoptosis through suppression of the mitochondrial-mediated apoptosis pathway, while it activates the Nrf-2/HO-1 signalling pathway	Kirindage *et al.*[75]
		Lipopolysaccharide-induced inflammation model in mice	Decreased mitochondrial superoxide content, and restoration of the mitochondrial membrane potential in the LPS-induced macrophages	Sailaja *et al.*[76]
Aloe vera	Aloe	*In vitro* model	Attenuates oxidative stress, initiates antioxidant defences, regulates mitochondrial dysfunction and suppresses apoptosis	Xu *et al.*[77]
Aloe claviflora	Aloe	*In vitro* model	Inhibits lipid peroxidation and has ROS scavenging effects	Lindsey *et al.*[67]

PH = pulmonary hypertension; Nrf-2 = nuclear respiratory factor 2; H2O2 = hydrogen peroxide; HO-1 = haem oxygenase 1; LPS = lipopolysaccharide; ROS = reactive oxygen species.

(HO-1) signalling pathway (Table 3). Mitochondrial dysfunction is considered a key component of PH that occurs specifically in PASMCs and PAECs.[71] Potent antioxidants[32,72] that could improve mitochondrial function and mitochondrial regulation have previously been highlighted as therapeutic targets for PH by our group.[13,73] It therefore follows that African medicinal plants may be able to show benefit in PH models by reducing ROS production, limiting oxidative stress and improving mitochondrial function.

Antiprolific effects of African medicinal plants

African medicinal plants have potent antiprolific effects in a wide range of experimental models.[78] A root bark extract of *Zanthoxylum paracanthum* was tested in human breast cancer (HCC1395) and human prostate cancer (DU145) cell lines, where it showed antiprolific activity,[79] but the mechanisms remain poorly understood. The African cherry has demonstrated antiprolific activity in human prostate cancer cells, which is believed to be mediated via reduced apoptosis.[80] Other plants that have similar effects include *Zingiber ocianale* and *Sutherlandia frutescens* in human cancer cell lines[81,82] (Table 4).

In PH, proliferation is a key feature that leads to pulmonary arteriolar remodelling,[83] and because PASMCs and PAECs become resistant to apoptosis, PH has been deemed to have a cancer-like phenotype.[84] Furthermore, impaired apoptosis regulation in these cells is also a major determinant of PASMC proliferation in remodelling.[85] There are myriad mechanisms outside the scope of this review, but impaired apoptosis regulation and cell metabolism are instrumental. Given the evidence that African medicinal plants can induce antiprolific effects, it is therefore likely that that they may also provide benefit against the cancer-like phenotype observed in PH.

African medicinal plants that have been tested in models expressing features of PH

Some African medicinal plants have been reported to induce therapeutic effects either in PH models or in experimental models that express certain key features of PH, including right ventricular hypertrophy, lung fibrosis, pulmonary inflammation, pulmonary artery vasoconstriction and endothelial cell proliferation (Table 5). These plants can reduce inflammation in PH models by decreasing inflammation factors such as nuclear factor kappa B (NF-κB), TNF-α, and type 1 and type 2 T-helper (Th1 and Th2) cytokines.[88] African medicinal plants have polyphenols that give these plants the ability to counteract the features listed here, through potent antioxidant actions. Some of these plants can increase antioxidant enzyme activities of superoxide dismutase, catalase and glutathione peroxidase, while others can regulate mitochondrial function as a means to limiting ROS production.[89,90] Other plants induce vascular relaxation by increasing NO and endothelial NO synthase expression (Table 5). Extracts of these plants have also been reported to counteract vascular remodelling in PH models, doing so by suppressing epithelial-mesenchymal transition through the transforming growth factor beta 1 (TGF-β1)/Smad pathway,[91] which decreases the expression of p38 mitogen-activated protein[92] and causes reduction of endothelin 1.[93]

Challenges and recommendations

Several challenges exist concerning the use of medicinal plants for the treatment of human diseases. It must be acknowledged that African medicinal plants often have pleiotropic effects,[102] and establishing a single mechanism is difficult. Other challenges include poor bioavailability,[103] nonspecific or pleiotropic actions,[42] mitohormesis,[104] drug interactions,[105] and poor pharmacokinetics[106] and lack of accurate/effective dosage and

Table 4. African medicinal plants (tested in non-PH models) with antiprolific and apoptosis activity for smooth-muscle cell remodelling that could be repurposed for PH

Plant	Common name	Experimental model	Mechanism	References
Curculigo orchioides Gaertn	Golden eye grass or black musli	In a human breast cancer cell line (MCF-7)	Induced anti-cancer effects by increasing cell death of cancer cells	Singh[86]
Sutherlandia frutescens	Cancer bush	LS180 colorectal cancer mini-tumours	Induced anti-cancer effects by limiting cancer cell metabolism	Gouws *et al.*[81]
Fagaropsis angolensis	Murumu or dale	Throat and colon cancer cell lines (Hep2 and CT-26.CL-25)	Induced antiprolific effects via the actions of polyphenols	Gaobotse *et al.*[87]
Zanthoxylum paracanthum	Kokwaro (Rutaceae)	Cancer cell lines (HCC1395, DU145, Vero E6)	Induced antiprolific activity	Kaigongi *et al.*[79]
Prunus africana	African cherry	Human prostate cancer cells (PC3)	Induced antiprolific activity possibly mediated via an increase in apoptosis	Komakech *et al.*[80]

PH = pulmonary hypertension.

Table 5. A list of African medicinal plants that have demonstrated to have therapeutic actions in models that express features of PH

Plant	Experimental model of PH	Mechanism	References
Terminalia arjuna	Monocrotaline-induced PH rat model	Reduces right ventricle hypertrophy and medial wall thickness of pulmonary arteries through the decrease of lipid peroxidation, and NADPH oxidases protein expression in the lung and increases superoxide dismutase and catalase activity	Kapoor *et al.*,[94] Pawar and Bhutani[95]
Moringa oleifera Lam.	Monocrotaline-induced PH rat model	Increases superoxide dismutase levels	Chen *et al.*[96]
Securigera securidaca L.	Broiler chicken reared at high altitude	Prevents the inactivation of NO through scavenging of superoxide ions	Ahmadipour[97]
Allium sativium (garlic)	Acute hypoxic pulmonary vasoconstriction	Increases the action of endothelial NO synthase, thereby relaxing the vascular smooth muscles	Fallon *et al.*[98]
Allium macrostemon Bunge	Isolated pulmonary artery	Initiates Ca2+/protein kinase A and endothelial NO synthase signalling pathway in endothelial cells	Han *et al.*[99]
Trifolium pratense L.	Broiler chicken reared at high altitude	Increases NO synthase secretion	Jiang and Yang[93]
Mimosa pigra L.	Hypoxia-induced PH in rats	Elevates NO production and decreases pulmonary artery pressure in hypoxia-induced PH	Rakotomalala *et al.*[92]
Centella asiatica	Hypoxia-induced PH in rats	Activates the NO-mediated signals by enhancing the phosphorylation of serine/threonine-specific protein kinase/eNOS, thus promoting NO production and protecting endothelial cells from hypoxia-induced apoptosis	Wang *et al.*[100]
Acacia senegal	Waterpipe smoke exposure	Prevents pulmonary inflammation and DNA damage, and restores the impairment of lung function via prevention of expression of NF-κB that induced an overexpression of Nrf2 in mice	Nemmar *et al.*[101]
Artemisia herba-alba Asso.	Broiler chicken	Down-regulates and up-regulates Th1 and Th2 cytokines, respectively, in chronic multisystemic inflammation in Algerian patients	Messaoudene *et al.*[88]
Trifolium pratense L.	Broiler chicken	Reduces endothelin 1 in lung tissues	Jiang and Yang[93]
Mimosa pigra L.	Hypoxia-induced PH in rats	Decreases the expression of p38 mitogen-activated protein, thus ameliorating the proliferative endothelial cells of the lung tissue in rats	Rakotomalala *et al.*[92]
Aloe ferox	Paraquat-induced pulmonary fibrosis in mice	Attenuates pulmonary fibrosis by suppressing the EMT process through the TGF-β1/Smads/p38 pathway	Zhang *et al.*[91]

PH = pulmonary hypertension; NADPH = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; Ca2+ = calcium ions; eNOS = endothelial nitric oxide synthase; NF-κB = nuclear factor kappa B; Nrf2 = nuclear respiratory factor 2; Th1 = type 1 T-helper; Th2 = type 2 T-helper; EMT = epithelial-mesenchymal transition; TGF-β1 = transforming growth factor beta 1.

dose conversion from experimental studies to human trials.[107,108] However, great advances have been made in trying to overcome these challenges in experimental studies or clinical trials, such as the use of inductively coupled plasma-optical emission spectrophotometry[103] and nanoparticles[109] to improve, for example, bioavailability. The latter has had considerable success in previous studies. A point of caution is needed here, as conventional methods of nanoparticle production use polyvinyl alcohol, polyethylene glycol, and D-alpha-tocopheryl polyethylene glycol 1000 succinate as stabilisers during synthesis. However, these are toxic, and researchers have been searching for stabilisers that are non-toxic. Studies have shown that plant extracts can also be used as stabilisers for the fabrication of stable poly (lactide-co-glycolide) nanoparticles.[110] We recommend that future studies test poly (lactide-co-glycolide) nanoparticles that have been enriched with a medicinal plant extract to enhance cellular uptake and increase bioactivity.[111] Most medicinal plants or herbs contain several bioactive compounds,[112] making it difficult to know which compounds in an extract have been loaded onto the nanoparticle, so it may be challenging to ensure consistent experimental outcomes across studies. We are of the opinion that where all or most of the individual compounds in an extract have been successfully captured onto nanoparticles, it may still provide significant health benefits or remarkably improve the actions of nanoparticles.[113,114]

Conclusion

Drug repurposing offers a relatively novel approach to achieving better treatment outcomes in PH. Drugs that could be repurposed for PH include melatonin, anakinra, rituximab and nesiritide. African medicinal plants also have potential as adjuvant therapies for PH, as they have been reported to have few to no side-effects and the ability to counteract instrumental pathways or vascular remodelling, which makes them attractive therapeutic targets for PH. They may improve the quality of life of patients suffering from PH and could offer an affordable adjuvant in resource-limited settings. Viable options include *A. linearis*, *Allium sativium*, *Trifolium pratense* L., *Mimosa pigra* L. *and Aloe ferox.* However, the majority of these plants have never been tested in an experimental PH model, so our proposition is hypothetical at best. Regardless, we believe that future studies should investigate these and other African medicinal plants in appropriate models of PH, to test their efficacy and effectiveness. Perhaps one day we will be able to put Africa's diverse flora to good use in PH research.

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