COMMENTARY

A promising heterocyclic nucleus is beta-carboline

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ABSTRACT

New therapeutic medications and methods are urgently required for the treatment of Pulmonary Hypertension (PH), a deadly and chronic condition. The active ingredients of traditional Chinese medicine, Scutellaria baicalensis Georgi, baicalein and baicalin, have a variety of pharmacological effects. The use of baicalin and baicalein as a therapy for PH has been suggested by a number of research using in vitro and in vivo models of the disease. The anti-inflammatory response, inhibition of pulmonary smooth muscle cell proliferation and endothelial-to-mesenchymal transformation, stabilization of the extracellular matrix, and mitigation of oxidative stress are just a few of the potential mechanisms underlying the beneficial effects of baicalin and baicalein treatment on PH. These substances pharmacokinetics have also been examined. Baicalin and baicalein should continue to be researched as natural remedies because of their therapeutic potential.

INTRODUCTION

A cardiovascular condition known as Pulmonary Hypertension (PH) causes pulmonary vasoconstriction, remodeling, and in situ thrombosis as well as several other pathological alterations that increase vascular resistance and progressively raise Pulmonary Artery Pressure (PAP). Right ventricular hypertrophy, right heart failure, and mortality are all consequences of the right ventricular afterload rise in PH. Targeted agents have long been used in the treatment of PH. The quality of life of patients with PH is considerably improved by a variety of targeted treatments that cause pulmonary vasodilation, such as endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclin analogs. With 1-year, 3 year-, and 5-year survival rates of 85.5%, 66.7%, and 53.6%, respectively, patients with PH still have a dismal prognosis and a high mortality rate. The clinical care of PH is also difficult, adding to the disease's burden. Thus, it is essential to create more potent pharmacotherapies to treat PH. A class of disorders known as PH have intricate pathological processes including numerous signaling pathways and pathological alterations. Long-term therapy is frequently necessary for patients with PH, and adverse effects, notably drug-induced liver damage, cannot be ignored. The positive effects of natural products on the prevention and treatment of PH have recently come to light in new research. Pharmacokinetic studies have shown that baicalin can be partially hydrolyzed in the gastrointestinal tract, and its hydrolysates and prototype drugs can enter the hepatoenteric circulation before being ultimately excreted via urine and bile. Baicalin and baicalein mutually transform during absorption in vivo. Furthermore, it is discovered that their entry into the cell is mediated through carrier-mediated transmembrane transport. Intestinal bacteria's glucuronidase is essential for hydrolyzing baicalin into its aglycon form, baicalein, which is then absorbed. UDP-glucuronic acid transferase can change baicalein into baicalin. It is interesting that baicalein absorbed better than baicalin in vivo in every section of the gastrointestinal tract. However, after ingesting baicalein, baicalin is the primary substance that enters the bloodstream. Baicalin has a low bioavailability, so scientists have created novel baicalin preparations with greater absorption, higher bioavailability, and a wide range of clinical application possibilities. Examples of these preparations include nano/micro scale baicalin delivery systems. Patients with PH must take long-term medications, hence baicalin and baicalein's safety must be established before they can be used in clinical settings. A multi-dose escalation program was

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used to study the pharmacokinetics, safety, and tolerability of baicalein, and it was discovered that several oral doses of the drug in the 200 to 800 mg range were both secure and well tolerated, with neither nephrotoxicity or hepatotoxicity. Baicalin (500 m g) and cyclosporine A (200 m g) are both well tolerated in adult subjects, according to the pharmacokinetics of a single dosage injection of baicalin on cyclosporine A in healthy volunteers. Multiple pathways and factors are frequently involved in the complex pathogenesis of PH. Pulmonary vasoconstriction, pulmonary vascular remodeling, and in situ thrombosis are, generally speaking, the three main pathogenesis-related processes. Pulmonary Vasoconstriction (also known as HPV) causes blood to flow to better ventilated areas in an acutely hypoxic environment, maintaining a sufficient ventilation/flow ratio in the lungs. However, under long-term hypoxia, the pulmonary vasculature may undergo irreversible remodeling. The proliferation of Pulmonary Artery Smooth Muscle Cells (PASMCs) in the middle and outer layers of the pulmonary artery is one sign of this irreversible remodeling, which also causes luminal narrowing and PH. The main triggers for pulmonary vasoconstriction include hypoxia, inflammation, and the resulting imbalance between vasodilator and vasoconstrictor factors. Additionally, it has been suggested that PASMCs with high intracellular Ca2+ concentrations are crucial for pulmonary vasoconstriction. One of the key pathways that causes chronic inflammation and PH. A localized hypoxic microenvironment brought on by an imbalance in oxygen supply and demand in the lungs can cause fibroblasts to secrete a variety of inflammatory substances, including macrophage chemo-kines, stimulating factors, and adhesion proteins. These substances also encourage the infiltration of other inflammatory cells, including monocytes, lymphocytes, and dendritic cells, which causes inflammation to grow in the tiny pulmonary arteries. The class of models for researching PH known as MCT-induced PH models is commonly used. MCT specifically affects the pulmonary vascular endothelium after being converted by the liver enzyme P450 monooxygenase. This persistent inflammation in the pulmonary vasculature causes pulmonary vascular remodeling and elevated PAP. Numerous studies have demonstrated that animal models of MCT-induced PH reveal numerous inflammatory cell infiltration and increased levels of inflammatory markers. An inflammatory and oxidative stress-activated transcription factor with widespread biological activity is known as Nuclear Factor-B (NF-B). The NF-B signaling pathway is crucial for the remodeling of the pulmonary arteries. A complex clinical process involving pulmonary arteriolar contraction and remodeling of the vascular wall characterizes PH, a pulmonary vascular disease. Vasodilators comprise the majority of the clinically available medications for PH now on the market. Although they partially succeed in limiting PASMC proliferation, they eventually fail to halt the process of pulmonary vascular remodeling. Therefore, it is increasingly necessary to create medications for PH that work through innovative methods. For the treatment of PH, our group has been thoroughly analyzing new compounds derived from natural products. According to our research, puerarin, salvianolic acid A, resveratrol, and genistein can slow the pathological development of PH through different mechanisms than the ones used by the current treatments.