Chinese medicinal plants for the potential management of high-altitude pulmonary oedema and pulmonary hypertension

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ABSTRACT
Context: Despite the abundance of knowledge regarding high-altitude pulmonary oedema (HAPE) and high-altitude pulmonary hypertension (HAPH), their prevalence continues to be on the rise. Thus, there is an urgent need for newer safer, effective, and relatively economic drug candidates. China is particularly known for the use of medicinal plants.

Objective: This review summarizes the medicinal plants used for HAPE and HAPH in the past 30 years, as well as some potential plants.

Methods: Publications on HAPE and HAPH from 1990 to 2020 were identified using Web of Science, PubMed, SCOPUS, Springer Link, Google Scholar databases, Chinese Clinical Trial Registry and CNKI with the following keywords: ‘medicinal plants,’ ‘hypoxia,’ ‘high-altitude pulmonary oedema,’ ‘high-altitude pulmonary hypertension,’ ‘pathophysiology,’ ‘mechanisms,’ ‘prevention,’ ‘treatment,’ ‘human,’ ‘clinical,’ ‘safety,’ and ‘pharmacokinetics.’

Results: We found 26 species (from 20 families) out of 5000 plants which are used for HAPE and HAPH prevention or treatment. Rhodiola rosea Linn. (Crassulaceae) is the most widely utilized. The most involved family is Lamiaceae, which contains 5 species.

Discussion and Conclusions: We mainly reviewed the medicinal plants and mechanisms for the treatment of HAPE and HAPH, and we also assessed related toxicity experiments, pharmacokinetics and bioavailability. Potential medicinal plants were also identified. Further research is needed to determine the pharmacological effects and active ingredients of these potential medicinal plants.

INTRODUCTION

The population living at a high altitude over 2500 meters above sea level (masl) includes 140 million people worldwide. Additionally, approximately 40 million people visit high-altitude areas for work or travel every year (West et al. 2012). High-altitude pulmonary oedema (HAPE) develops 2 or more days after exposure to altitudes above 3000 masl. At 4500 m within 4 days, the incidence is 0.2% and reaches 2% at 5500 m within 7 days; the incidence increases to 6 and 15% at 4500 m and 5500 m, respectively, within 1–2 days (Bartsch and Swenson 2013). The prevalence of high-altitude pulmonary hypertension (HAPH) is 4.2% in women and 11.8% in men (Negi et al. 2013). HAPE is a noncardiogenic form of pulmonary oedema that is specific to high-altitude hypoxia (Luks 2015). Early-onset HAPE has many clinical manifestations, such as dyspnoea during exercise, reduced exercise performance, dry cough with exertion, and mild fever; advanced illness is characterized by orthopnea, pink frothy sputum, and drowsiness (Bartsch and Swenson 2013). The recent definition of pulmonary hypertension (PH) has been updated to include the concomitant presence of mean pulmonary arterial pressure (mPAP) >20 mmHg, pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance ≥3 WU. HAPH is included in the third category according to the latest classification guide for PH (Simonneau et al. 2019). The common clinical manifestations of HAPH include headache and difficulty breathing and are accompanied by erythrocytosis and pathological manifestations, such as hypoxaemia (Latshang et al. 2017). Some potential risk factors, such as heart failure, which is fatal, present in advanced stages (Latshang et al. 2017). In recent years, tourism to high-altitude locations has become increasingly popular; thus, high-altitude disease has gradually attracted increasing attention.

Approximately, 80% of people worldwide continue to rely on medicinal plants, and the status of medicinal plants in meeting people’s health needs is of great importance (West et al. 2012), because chemical drugs are expensive and have side effects. In the Wilderness Medical Society Practice Guidelines, acetazolamide, nifedipine, sildenafil, salmeterol and dexamethasone are drugs used for the prevention of HAPE; acetazolamide, a diuretic, and dexamethasone are drugs used for the treatment of HAPH. However, acetazolamide lacks data supporting a role in...
HAPE prevention, and it has side effects, such as hypotension and dyspnoea. No recommendation can be made regarding the use of acetazolamide for HAPE prevention and treatment. Salmeterol is often associated with side effects, including tremor and tachycardia, and it is not also recommended (Luks et al. 2019). Further, dexamethasone should never be used for more than 7 days given the risk of adrenal suppression; therefore, it is not recommended by guidelines. As clinical data about the effectiveness of these drugs are limited, there is no recommendation for the treatment of HAPE (Aksel et al. 2019).

Acetazolamide is the first choice for HAP prevention and treatment, and endothelin receptor antagonists and phosphodiesterase 5 blockers are also used for HAP (Mirrakhimov and Strohl 2016); however, these drugs are not the best solutions. Many medicinal plants for preventing and treating HAPE and HAPH have appeared clinically. However, many of them are empirical drugs, and few randomized controlled trials (RCTs) have been conducted. We summarize these with the hope that further research can obtain more scientific clinical data.

Given the growing popularity of medicinal plants, along with the aforementioned limitations of current anti-HAPE and anti-HAPH therapies, research on the mechanisms, safety, efficacy, and cost of natural therapies represents an important scientific endeavour. Medicinal plants have been used for thousands of years in China, and Chinese people have a wealth of clinical experience in medicinal plants. Therefore, this review discusses the progress in research on Chinese medicinal plants in this field. Chinese medicine resources are abundant, and many of them have significant effects on treating HAPE and HAPH (Li et al. 2018).

This article mainly introduces the medicinal plants used in HAPE and HAPH, focussing on their biologically active ingredients, mechanisms of pharmacological actions, safety evaluations, pharmacokinetics, and bioavailability. New drugs for the treatment of HAPE and HAPH with less side effects and low cost may be identified through the summary of these medicinal plants, and the symptoms of patients with altitude sickness can be alleviated.

Methods

In vivo and in vitro studies on Chinese medicinal plants in the management of high-altitude diseases were searched on Web of Science, PubMed, SCOPUS, Springer Link, Google Scholar databases, Chinese Clinical Trial Registry and CNKI from 1990 to 2020. The search terms included: ‘medicinal plants,’ ‘hypoxia,’ ‘high-altitude pulmonary edema,’ ‘high-altitude pulmonary hypertension,’ ‘pathophysiology,’ ‘mechanisms,’ ‘prevention,’ and ‘treatment,’ ‘human,’ ‘clinical,’ ‘safety,’ and ‘pharmacokinetics.’ There were 151 publications on HAPH and HAPE that were reviewed: journal articles (145), dissertations (4), and monographs (2).

Discussion

Medicinal plants, which contain many biologically active ingredients for the treatment of high-altitude diseases, are gradually becoming supplementary or alternative medicines for the treatment of high-altitude diseases. This review focuses on medicinal plants that play a role in the treatment of HAPE and HAPH and their potential therapeutic effects.

In total, 26 species belonging to 19 plant families and 26 plant genera were identified and verified by in vivo (n = 25) and in vitro (n = 6) experiments. Among them, 12 species can be used for HAPE treatment, and 17 species can be used for HAPH treatment. Six species of medicinal plants [Rhodiola rosea Linn. (Crassulaceae), Pueraria lobata (Willd.) Ohwi (Fabaceae), Scutellaria baicalensis Georgi (Lamiaceae), Panax notoginseng (Burkii) F.H.Chen (Araliaceae), Carthamus tinctorius Linn. (Asteraceae), and Ginkgo biloba Linn. (Ginkgoaceae)] show activity in the treatment of HAPE and HAPH. Scientists have discovered their biologically active ingredients and have been able to explain their pharmacological mechanisms of action. Safety assessments, pharmacokinetics and bioavailability studies have also been conducted. In particular, Rhodiola rosea (Rhodiola Capsules, Tibet Yangke Biotechnology Company, China health food approval number G20050750) (Lei et al. 2015), Pueraria lobata (Puerarin Injections, Yantai Zhongce Pharmaceutical Corporation) (Bao 2005), and Ginkgo biloba (Folium Ginkgo Tablets, Dalian Meiluo Pharmaceutical, national medicine permission number Z20064282) (Tsomo 2015) have been well studied and made into preparations.

In addition, there are 31 medicinal plants from 18 families with anti-hypoxic activity, including 8 species of Asteraceae. Many of the anti-hypoxic active ingredients in these plants are unknown, but they may be medicinal plants that could be further studied to explore their potential use for the treatment of HAPE and HAPH.

Medicinal plants considered to have anti-HAPE activity based on in vivo and in vitro studies

There are five theories about the pathogenesis of HAPE (Table 1). (1) There is a change in hemodynamics. Under hypoxia, overactivation of the sympathetic nervous system reduces the synthesis of nitric oxide (NO), while endothelin-1 (ET-1) is over-synthesized, resulting in sustained vasoconstriction (Li et al. 2018). Rhodiola rosea (Qian et al. 2012), Brassica rapa Linn. (Brassicaceae) (Li 2019), Conioselinum anthriscoides (H.Boissieu) Pimenov and Klijuykov (Apiaceae) (Zhang, Deng, et al. 2011) and Polygonum cuspidatum Sieb. et Zucc. (Polygonaceae) (Wang 2011) can inhibit hemodynamic changes by enhancing the release of NO or inhibiting the release of ET-1. (2) There is a change in pulmonary capillary permeability. Under hypoxia exposure, the overexpression of vascular endothelial growth factor (VEGF) increases pulmonary vascular permeability, and proteins and red blood cells then permeate into lung tissue, causing pulmonary interstitial edema (Li et al. 2018). Rhodiola rosea (Lee, Li, et al. 2013), Hippophae rhamnoides Linn. (Elaeagnaceae) (Purushothaman et al. 2011; Zhou et al. 2012), Brassica rapa (Li 2019), and Polygonum cuspidatum (Wang 2011) significantly reduce VEGF levels and improve pulmonary blood-gas barrier permeability. (3) There is decreased fluid clearance in alveoli. The effusion of inflammatory cells in the alveolar spaces is light in rats in the Aesculus chinesis Bunge group (Hai et al. 2011). Aquaporin (AQ) is of great importance in alveolar fluid clearance (Li et al. 2018). Interestingly, AQP expression increased under hypobaric hypoxia conditions but decreased with preventive treatment with Pueraria lobata (Wang, Yan, et al. 2016). (4) There is an inflammatory response. Hypoxia increases the levels of proinflammatory and anti-inflammatory factors in bronchial alveolar lavage fluid (BALF), such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and lactic dehydrogenase (LDH) (Kubo et al. 1996). Rhodiola rosea (Li, Fu, et al. 2013), Pueraria lobata (Wang, Yan, et al. 2016), Hippophae rhamnoides (Purushothaman et al. 2011), Aesculus chinesis
(Hai et al. 2011), Portulaca oleracea Linn. (Portulacaceae) (Alam et al. 2014) and Phloris younghusbandii Mukerj. (Lamiaceae) (Luan et al. 2014) can prevent lung injury of rats exposed to hypoxia via the downregulation of inflammatory cytokines. (5) There is oxidative stress. During hypoxia, the body’s reactive oxygen species (ROS) levels increase, and phospholipase A2 is activated, causing an inflammatory response. Simultaneously, endothelial nitric oxide synthase (eNOS) uncoupling is enhanced, releasing the vasoconstrictor (Li et al. 2017). Rhodiola rosea (Lee, Li, et al. 2013; Lee, Shi, et al. 2015), Epimedium brevicornu Maxim. (Berberidaceae) (Li 2009) and Conioselinum anthriscoides (Zhang 2011) can reduce the damage caused by oxidative stress. Rhodiola rosea and Conioselinum anthriscoides reduce ROS levels, and Rhodiola rosea also attenuates the activation of the adenosine 5’-monophosphate-activated protein kinase-protein kinase C (AMPK-PKC) pathway (Zhang 2011; Lee, Shi, et al. 2013). Epimedium brevicornu mainly regulates oxidative stress markers; after administration, superoxide dismutase (SOD) and LDH activity increased, while malondialdehyde (MDA) and free radical levels decreased (Li 2009) (Table 1).

**Medicinal plants considered to have anti-HAPH activity based on in vivo and in vitro studies**

Scutellaria baicalensis, Panax notoginseng, Carthamus tinctorius and Ginkgo biloba are the most widely studied medicinal plants for HAPH treatment and have been formulated (Table 1). The pathophysiological mechanism of HAPH involves three factors. (1) There is pulmonary vasoconstriction. NO is a key vasodilator, and its reduced availability is of considerable importance in the progression of HAPH (Klinger et al. 2013). At the same time, elevated levels of ET-1 and angiotsin II (Ang II) lead to vasoconstriction (Mishra et al. 2015). Salvia miltiorrhiza Bunge (Lamiaceae) (Wang et al. 2013), Panax notoginseng (Zhao et al. 2015), Allium sativum Linn. (Amaryllidaceae) (Fallon et al. 1998), Conioselinum anthriscoides (Cao et al. 1998), Ginkgo biloba (Berg 2004), and Polygonum cuspidatum (Miao et al. 2012) can reduce pulmonary vasoconstriction. Salvia miltiorrhiza mediates vasorelaxation by increasing cyclooxygenase-2 (COX-2) gene expression, prostacyclin production, and Ca2+ influx and release (Wang et al. 2010, 2015). Moreover, activation of the p38 mitogen-activated protein kinases (p38MAPK) pathway has been demonstrated to be an important underlying mechanism in the generation of HAPH, and Panax notoginseng can reduce the expression of p38MAPK and increase NO synthesis and NO levels in plasma and lung tissue (Zhao et al. 2015). Allium sativum blocks HAPH in vivo through a combination of endothelium-dependent and endothelium-independent mechanisms to affect pulmonary arterial circulation (Fallon et al. 1998). A study showed that (Cao et al. 1998) the role of Conioselinum anthriscoides is related to ET-1. Other studies have reached different conclusions; for example, Conioselinum anthriscoides dilated the pulmonary artery, but it had no effect on the synthesis and release of ET-1 (Liu et al. 1990; Zhang, Deng, et al. 2011). Although there are some inconsistencies in the mechanims, Conioselinum anthriscoides has been widely used in HAPH treatment. In an earlier study (Cheng and Chen 1996), Ginkgo biloba relieved abnormal changes in pulmonary systolic pressure by specifically antagonizing the receptor of platelet-activating factor. Additional follow-up studies (Zhu et al. 2007; Wu et al. 2008) found that Ginkgo biloba increases NO levels and reduces ET-1 levels; moreover, it can significantly upregulate HIF-1α expression. Polygonum cuspidatum regulated NO, Ang II, and ET contents in serum and lung samples to attenuate HAPH (Miao et al. 2012).

(2) There is pulmonary vascular remodelling. In hypobaric hypoxia, the pulmonary vascular wall is thickened, eventually leading to pulmonary vascular remodelling. Scutellaria baicalensis (Huang et al. 2014; Zhang, Niu, et al. 2014; Huang et al. 2013), Sophora flavescens Aiton (Fabaceae) (Zhang, Pu, et al. 2014), Salvia miltiorrhiza (Luo et al. 2013), Carthamus tinctorius (Li et al. 2016), Cistanche desertica M a (Orobanchaceae) (Liu et al. 2016), Polygonum cuspidatum (Miao et al. 2012), Agaricus bitorquis (Quél.) Sacc. (Agaricaceae) (Jiao et al. 2019) and Salvia przewalskii Maxim. (Lamiaceae) (Wang, Wang, et al. 2019) can reduce pulmonary vascular smooth muscle cell (PASMC) proliferation and reverse pulmonary vascular remodelling. Scutellaria baicalensis (Huang et al. 2014; Zhang, Pu, et al. 2014; Huang et al. 2018) inhibits the proliferation of hypoxia-induced PASMCs by upregulating the A2A receptor in the stromal cell derived factor-1/recombinant chemokine C-X-C-motif receptor 4 (SDF-1/CXCR4) signalling pathway or attenuating transforming growth factor-β1 (TGF-β1). The A2A receptor is selectively bound to CXCR4, and the combination of SDF-1 and CXCR4 mediates the phosphoinositide 3-kinase/protein kinase B (PI3K/PKB) signalling pathway to regulate the cell cycle. Salvia miltiorrhiza (Luo et al. 2013) can inhibit the upregulation of S-phase kinase associated protein2 (Skp2), the reduction in the p27 protein in PASMCs and protein kinase B (PKB/AKT) phosphorylation. Salvia miltiorrhiza can also downregulate the increase in TGF-β, inhibit the phosphorylation of SMAD3, inhibit hypoxia inducible factor-1α (HIF-1α) (Li, Mi, et al. 2015; Wang et al. 2015), and ultimately inhibit the proliferation of PASMCs (Zhang et al. 2018). RhoA and Rho kinase represent a primary mechanism of HAPH (Resta et al. 2010), and Salvia miltiorrhiza can mediate the anti-hypoxic effects in the RhoA/ROCK signalling pathway (Wang, Duo et al. 2019). Sophora flavescens significantly inhibits TGF-β1 levels and the expression levels of HIF-1α and nuclear factor-kappa B (NF-κB), and it downregulates hydroperoxide levels in PASMCs. Additionally, Sophora flavescens prevents HAPH through its anti-proliferative effects (Zhang, Niu, et al. 2014). Cistanche desertica (Liu et al. 2016) significantly reduces the expression of VEGF protein in lung tissue, and Polygonum cuspidatum (Miao et al. 2012) reverses remodelling through the PKC pathway. However, the exact mechanism by which Carthamus tinctorius functions is unclear.

(3) There is oxidative stress. The oxidative stress response causes changes in ROS, oxidative damage markers (such as MDA), and antioxidants (such as SOD and glutathione (GSH)) (Strapazzon et al. 2016). In addition, haemoglobin interacts with SOD to increase ROS generation, which in turn causes inflammation and endothelial damage (Irwin et al. 2015). Sophora flavescens (Zhang, Niu, et al. 2014) also prevents HAPH through its anti-inflammatory and antioxidant effects; it can significantly upregulate nuclear factor-E2 related factor2 (Nrf2), SOD, and haem oxygenase 1 (HO-1) expression and can downregulate hydroperoxide levels in PASMCs. After treatment with Conioselinum anthriscoides (Zhang 2011) or Urtica dioica Linn. (Urticaceae) (Tolody et al. 2005; Ahmadipour and Khajali 2019), intracellular ROS levels were significantly reduced. Ziziphus jujuba Mill. (Rhamnaceae) (Wang, Wu, et al. 2019) and Terminalia bellirica (Gaertn.) Roxb. (Combretaceae) (Yang, Shi, et al. 2019) may improve the levels of C-reactive protein (CRP), erythropoietin (EPO) in serum.
| Latin binomial                      | Family              | Part used        | Active compounds          | Dose (mg/kg body weight) | Experimental animal model | Pharmaceutical effect                                                                 |
|------------------------------------|---------------------|------------------|---------------------------|--------------------------|----------------------------|----------------------------------------------------------------------------------------|
| *Agaricus bitorquis*               | Agaricaceae         | Fruits           | Polysaccharides           | N/A                      | N/A                        | Lipid peroxidation markers ([lactic dehydrogenase (LDH), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase] levels increased significantly, the formation of serotonin, dopamine, endothelin and acetylcholine were promoted |
| *Allium sativum*                   | Amaryllidaceae      | Whole            | Allicin                   | 100                      | Male SD HAP rats induced by hypoxic Plexiglas glove box | Pulmonary vasoconstriction inhibited significantly                                      |
| *Conioselinum anthriscoides*       | Apiaceae            | Rhizomes         | Ligustrazine              | 80                       | Mongrel HAP dogs induced by hypoxic gas mixture | Pulmonary vasoconstriction and ET-1 release inhibited significantly; Oxidative stress markers (ROS) and ET-1 level inhibited significantly |
| *Panax notoginseng*                | Araliaceae          | Roots and rhizomes | *Panax notoginseng* saponins | 50                       | Male SD HAP rats induced by hypoxic chamber | p38MAPK level in the rat lung decreased significantly, however, NO level in lung tissue and plasma increased significantly |
| *Carthamus tinctorius*             | Asteraceae          | Flowers          | HSYA                      | 25, 50, 75, 100          | Male Wistar HAP rats induced by hypoxic chamber | There was a dose-dependent significant reduction in the proliferation of PASMCs, remodelling of the pulmonary artery at 25,50,100 and 200 mg/kg of extract |
| *Erigeron brevicaespus*             | Asteraceae          | Whole grass      | Breviscapine              | 300, 600, 900            | Clinic                      | Oxidative stress markers (SOD, LD) in the mice lung increased significantly, however, oxidative stress markers (MDA, free radicals) decreased significantly |
| *Epimedium brevicornu*             | Berberidaceae       | N/A              | Total flavonoids          | N/A                      | Male bal b/c HAP mice induced by vacuum chamber | NO and expression of tight junction proteins in lung tissue increased significantly, ET-1, HIF-1α and VEGF levels inhibited significantly |
| *Brassica rapa*                    | Brassicaceae        | Tubers           | P-Coumaric acid           | 400                      | Male ICR HAP mice induced by normal pressure hypoxic chamber | Oxidative stress markers (ROS, MDA, myeloperoxidase (MPO)), ET-1, HIF-1α and VEGF levels in the rat lung alleviated significantly, activation of AMPK-PKC attenuated significantly |
| *Rhodiola rosea*                   | Crassulaceae        | Whole grass      | Salidroside               | 50, 100                  | Male Sprague-Dawley HAP rats induced by hypobaric hypoxia chamber | Oxidative stress markers (ROS, MDA, myeloperoxidase (MPO)), ET-1, HIF-1α and VEGF levels in the rat lung alleviated significantly, activation of AMPK-PKC attenuated significantly |
| *Hippophae rhamnoides*             | Elaeagnaceae        | Leaves           | N/A                       | 50, 100, 200             | Male SD HAP rats induced by decompression chamber | TNF-α, IL-6, IL-10 and monocyte chemotactic protein 1 (MCP-1) levels in BALF, and catecholamine level in plasma, oxidative stress markers (free radical, MDA) reduced significantly, however, oxidative |

(continued)
| Latin binomial          | Family          | Part used | Active compounds                  | Dose (mg/kg body weight) | Experimental animal model | Pharmaceutical effect                                                                 | Indication                                                                 | References                       |
|------------------------|-----------------|-----------|-----------------------------------|--------------------------|---------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------|
| *Pueraria lobata*      | Fabaceae        | Roots     | Puerarin                          | 100                      | Male SD HAPE rats induced by hypobaric chamber | IL-1β and TNF-α levels in BALF, and AQP in the rat lung decreased significantly, activation of NF-κB and IκB suppressed significantly | HAPE                                                                                   | (Wang, Yan, et al. 2016)          |
| *Sophora flavescens*   | Fabaceae        | Roots     | Oxymatrine                        | 50                       | Male SD HAPH rats induced by hypoxic chamber | PASMCs Proliferation, HIF-1α and NF-κB levels inhibited significantly, hydroperoxide, ROS level and pulmonary vasoconstriction attenuated significantly, however, oxidative stress markers (SOD, GSH, Nrf2, HO-1) levels increased significantly | HAPH                                                                                   | (Zhang, Niu, et al. 2014)         |
| *Ginkgo biloba*        | Ginkgoaceae     | Leaves    | Ginkgolide B                      | 200; 5                   | Male SD HAPE rats induced by hypobaric chamber, Male Wistar HAPH rats induced by hypoxia chamber | BALF protein concentration increased significantly, Antagonising the receptor of Platelet activating factor | HAPE; HAPH                        | (Cheng and Chen 1996; Berg 2004) |
| *Dracocephalum tanguticum* | Lamiaceae     | Whole grass | N/A                               | 1000, 3000, 5000         | SD HAPH rats induced by hypoxic hypobaric chamber | Oxidative stress markers (MDA) in rat lung tissues, mPAP and RVH levels decreased significantly, however, oxidative stress markers (SOD, GSH-Px) activities increased significantly | HAPH                                                                                   | (Li, Yang, Li, et al. 2015)      |
| *Phlomis youngusbandii* | Lamiaceae       | Roots     | Phenylethanoid glycosides         | 50, 200, 400              | HAPE rats induced by animal decompression chamber | Oxidative stress markers (SOD, GSH) in the mice lung increased significantly, however, oxidative stress markers (MDA), IL-1β and TNF-α decreased significantly | HAPE                                                                                   | (Luan et al. 2015)                |
| *Salvia miltiorrhiza*  | Lamiaceae       | Roots     | Danshensu and Tanshinone          | 160                      | Male SD HAPH rats induced by hypoxic chamber | TGF-β level and phosphorylation of smad3 attenuated significantly, HIF-1α level inhibited significantly | HAPH                                                                                   | (Wang et al. 2015; Zhang et al. 2018) |
| *Salvia przewalskii*   | Lamiaceae       | Whole     | N/A                               | 500, 1000, 2000          | Male SD HAPH rats induced by an altitude of 4260 m | mPAP, RhoA, ROCK1, ROCK2 levels decreased significantly | HAPH                                                                                   | (Wang, Wang, et al. 2019)        |
| *Scutellaria baicalensis* | Lamiaceae     | Roots     | The flavonoid baicalin extracted  | 60                       | Male A<sub>x</sub>R<sup>−/−</sup> or Bal b/c WT HAPH mice induced by hypoxia | Hemodynamic changes and pulmonary arterial remodelling alleviated significantly, CXCR4 and SDF-1 levels, activation of PI3K and AKT phosphoryl attenuated significantly, HIF-1α and AHR expression inhibited significantly (time and dose dependent) | HAPH                                                                                   | (Huang et al. 2014; Huang et al. 2018) |

(continued)
| Latin binomial          | Family                  | Part used     | Active compounds | Dose (mg/kg body weight) | Experimental animal model                          | Pharmaceutical effect                                                                 | Indication                                      | References                  |
|------------------------|-------------------------|---------------|------------------|--------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------|
| *Cistanche deserticola* | Orobanchaceae           | Flowers       | Echinacoside     | 12.5, 25, 50             | Male and female Wistar HAPH rats induced by Northwest special environment artificial experiment cabin | VEGF level in the rat lung reduced significantly                                      | HAPH                                          | (Liu et al. 2016)            |
| *Polygonum cuspidatum*  | Polygonaceae            | Rhizomes      | Polydatin        | 20, 40, 80; 5, 10, 20    | SD HAPE rats induced by hypobaric hypoxic chamber; Male Sprague-Dawley HAPH rats induced by hypobaric hypoxic chamber | PaO₂ and arterial oxygen saturation (SaO₂) levels increased significantly, however, VEGF level reduced significantly; Remodelling of the pulmonary artery attenuated significantly, however, NO level and NOS activity increased significantly | HAPE; HAPH                                    | (Wang 2011; Mao et al. 2012) |
| *Portulaca oleracea*    | Portulacaceae           | Whole grass   | Ethanol extract  | 100, 200, 400             | Male bal b/c HAPE mice induced by hypobaric chamber | Oxidative stress markers (ROS, MDA) in the mice lung and activation of the NF-κB pathway reduced significantly, however, oxidative stress markers (GSH, SOD) increased significantly | HAPE                                          | (Yue et al. 2015)            |
| *Ziziphus jujuba*       | Rhamnaceae              | Fruits        | N/A              | 6.25                      | Male and female SD HAPH rats induced by hypoxic hypobaric chamber | CRP, EPO, VEGF levels in serum decreased significantly, the inflammatory reaction inhibited significantly | HAPH                                          | (Wang, Wu, et al. 2019)      |
| *Gardenia jasminoides*  | Rubiaceae               | Fruits        | Gardenia Yellow pigment | 500                  | Male and female bal b/c HAPE mice induced by plateau low pressure hypoxic animal experiment chamber | N/A                                                                                   | HAPE                                          | (Mao et al. 2017)            |
| *Aesculus chinensis*    | Sapindaceae             | Fruits        | Sodium aescinate | 5                        | SD HAPE rats induced by hypoxic hypobaric chamber   | TNF-α level reduced significantly, however, partial pressure of carbon dioxide (PaCO₂) and partial pressure of oxygen (PaO₂) levels increased significantly | HAPE                                          | (Hai et al. 2011)            |
| *Urtica dioica*         | Urticaceae              | Stems and leaves | Essential oil   | N/A                  | HAPH broilers induced by an altitude of 2100m | Oxidative stress markers (SOD, catalase (CAT)) level increased significantly | HAPH                                          | (Ahmadipour and Khajali 2019) |
**Table 2.** The grade of human evidence for the most common plants.

| Latin binomial                  | Indication | Route | Dosage          | Toxicity     | Interacting drug and comments                                                                 | References                       |
|--------------------------------|------------|-------|-----------------|--------------|------------------------------------------------------------------------------------------------|----------------------------------|
| Aesculus chinensis             | HAPE       | i.v.  | 10–40 mg/day    | N/A          | N/A Docetaxel: neutropenia and sepsis; Ritonavir: gastrointestinal toxicity; Warfarin: antiplatelet effect; NSAIDs: antiplatelet effect; Ticlopidine: antiplatelet effect | (Zhou et al. 2005)               |
| Allium sativum                | HAPH       | p.o.  | 600 mg id       | N/A          | (Valli and Giardina 2002; Cox et al. 2006; Chen et al. 2011)                                       |
| Carthamus tinctorius           | HAPH       | p.o.  | N/A             | N/A          | (Chua et al. 2015; Hu and Wang 2019)                                                               |
| Ginkgo biloba                  | HAP; HAPH  | p.o.  | 500 mg tid      | Moderately toxic |                                                                                                    | (Valle et al. 2012; Maniscalco et al. 2019) |
| Panax notoginseng              | HAPH       | p.o.  | 300 mg tid      | N/A          | (Hu and Wang 2019)                                                                                |
| Polygonum cuspidatum           | HAP; HAPH  | N/A   | N/A             | Abortion     | (Chuenjid et al. 2018; Xiao et al. 2019; Zhang 2019a)                                              |
| Pueraria lobata                | HAP; i.v.  | 20–200 mg/day | N/A          |             |                                                                                                    |
| Rhodiola Rosea                 | HAP;       | p.o.  | 240 mg tid      | No           | Paroxetine: mild serotonin syndrome                                                               | (Lei et al. 2015; Ishaque et al. 2012; Maniscalco et al. 2015) |
| Salvia miltiorrhiza            | HAP;       | p.o.  | 225 mg id; 60 mg/day; 1 g tid; 1 g tid; 5 mg/day; 70 amg tid | Slightly toxic | Aspirin: antiplatelet effect; Warfarin: antiplatelet effect; Ca²⁺-eine: CYP1A2 activity; Fexofenadine: induction of intestinal P-glycoprotein; Midazolam: reduce the absorption of midazolam; Rosuvastatin: reduce the absorption of rosuvastatin; Clopidogrel: inhibit CES1A | (Chen et al. 2017; Hu and Wang 2019; Xiao et al. 2019; Yang, Hasegawa, et al. 2019) |

**Safety of medicinal plants**

One particularly important point for research is the emergence of toxicity, although it is rare. Toxicological research has shown that *Rhodiola rosea* (Gupta et al. 2008; Aiello et al. 2017), *Hippophae rhamnoides* (Sagg et al. 2007; Zhao et al. 2017), Gardenia yellow pigment (Mao et al. 2017), baicilin (Martinez Medina et al. 2017), *Salvia miltiorrhiza* (Wang et al. 2012) and *Cistanche deserticola* (Gao et al. 2016) have no acute or subacute toxicity in rats. The LD50 values were 28.6 mL/kg in *Rhodiola rosea*, 10 g/kg in *Hippophae rhamnoides* and 64 g/kg in *Salvia miltiorrhiza*. However, Danshen injection at high dosages has potential vascular toxicity, so it should not be used far beyond its recommended clinical dosage (Wang, Zhao et al. 2016). An acute toxicity study of the methanolic extract of *Portulaca oleracea* in mice revealed that it is moderately toxic with a lethal dose (LD50) value of 1853 mg/kg (Iranshahy et al. 2017). *Sophora flavescens* is slightly toxic, and the intramuscular injection of oxymatrine in mice was found to be lethal at 256.74 mg/kg, with an intravenous LD50 value of 144.2 mg/kg (He et al. 2015). *Panax notoginseng* saponins have cytotoxic, neurotoxic, and cardiotoxic effects; a dose of 450 mg/kg showed toxicity in the liver and kidney (Wang, Guo et al. 2016). Toxicological studies of hydroxysafflor yellow A (HSYA) in mice and rats have shown mild nephrotoxicity (Liu et al. 2016), reproductive toxicity (Mirhoseini et al. 2012), neurological teratogenicity and cytotoxicity (Nobakht et al. 2000). Another study in mice revealed that taking safflower extract during the lactation period may be toxic for infants and have neuro-, nephro- and hepatotoxic effects. Therefore, it is better for lactating mothers to refrain from its use (Abdolrasool et al. 2013). The main side effect of allicin is damage to the gastrointestinal tract; one of the studies showed that the LD50 value in mice was 309 mg/kg for males and 363 mg/kg for females (Amagase et al. 2001; Amagase 2006; Yun et al. 2014). A clinical pharmacokinetic study found that HSYA may cause different toxicities in men and women. Therefore, when using HSYA, sex differences should be properly considered. Matrine has lethal effects on sperm and should be used cautiously for men (Li et al. 2019). Two clinical studies (Gertsch et al. 2004; Chow et al. 2005) have shown that *Ginkgo biloba* is superior to the positive drug acetazolamide in terms of side effects, but it is not effective at preventing acute mountain sickness compared with placebo. Moreover, many clinical trials-case reports have described serious bleeding events and adverse cardiac events. In addition, *Ginkgo biloba* might elicit toxic and cancer-related consequences in rodents, and although such events were not observed in human subjects, its safety for long-term use in humans is still controversial (Shaito et al. 2020).
| Latin binomial    | Family            | Part used                      | Active compounds            | Possible anti-hypoxia molecular mechanisms and pathways                                                                 | References                                      |
|------------------|-------------------|--------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Angelica sinensis | Apiaceae          | Roots                          | Polysaccharide              | The PI3K/AKT and janus kinase 1/signal transducer and activator of transcription 3 (JAK1/STAT3) pathways were activated   | (Pan and Zhu 2018)                             |
| Apocynum venetum  | Apocynaceae       | Leaves                         | Total flavon                | Lipid peroxidation markers (LDH) increased significantly                                                                 | (Sun et al. 2011)                              |
| Aralia chinensis  | Araliaceae        | N/A                            | Total glucosides            | Oxygen tension in tissues increased significantly and acid-base balance was regulated                                     | (Zhou and Jiang 1991)                         |
| Bletheroecoccus senticosus | Araliaceae     | Roots, rhizomes and stems       | Water extract                | N/A                                                                                                                   | (Rong 2014)                                    |
| Panax ginseng     | Araliaceae        | Roots, stems and leaves         | Ginsenoside; Ginsenoside Rg1| HIF-1α, EPO, Caspase-3 mRNA expressions affected significantly, the internal oxygen balance in rat tissues was regulated, erythropoiesis was promoted, and anti-apoptosis; Phosphorylation of key kinases and expression of HIF-1α in the PI3K/AKT/mTOR pathway increased significantly | (Li, Ma, et al. 2013; Qin et al. 2018)          |
| Panax quinquefolius| Araliaceae        | N/A                            | N/A                         | N/A                                                                                                                   | (Wang 2001)                                    |
| Ophiopogon japonicus | Asparagaceae     | Roots                          | Poly saccharide              | N/A                                                                                                                   | (Xu and Chen 1996)                            |
| Aster souliei     | Asteraceae        | Inflorescences                  | Total flavon                | Oxidative stress markers (SOD, CAT, GSH, GSH-Px, total antioxidant capacity (T-ADG) content increased significantly, however, oxidative stress markers (MDA, ROS, free radical) content reduced significantly, lipid peroxidation was inhibited, the activity of antioxidant enzymes in cells was maintained | (He et al. 2016; Jing et al. 2016)              |
| Chrysanthemum     | Asteraceae        | N/A                            | N/A                         | HIF-1 up-regulated significantly and TnT expression inhibited significantly                                                                 | (Chen 2019)                                    |
| Cremanthodium humile | Asteraceae       | Flowers                        | Ethanol extract              | The decrease of oxidative stress markers (SOD, CAT, GSH-Px) activity inhibited significantly, oxidative stress markers (MDA, ROS) content reduced significantly, the body’s antioxidant enzyme activity was maintained and free radical metabolism was regulated | (Jing et al. 2015)                            |
| Inula japonica    | Asteraceae        | N/A                            | Total flavon                | Oxidative stress was improved                                                                                         | (Zang et al. 2013)                            |
| Leuzea uniflora   | Asteraceae        | Roots                          | Extract                     | Oxidative stress was improved                                                                                         | (Zhang et al. 2005)                            |
| Pyrethrum tattienense | Asteraceae      | Whole grass                    | Total flavon                | Lipid peroxidation markers (LDH, LD), and oxidative stress markers (SOD) activity increased significantly, however, oxidative stress markers (MDA, free radical) content, plasma lactic acid content and blood lactate levels reduced significantly, anaerobic glycolysis was promoted; Lipid peroxidation markers LDH, lactic acid (LAC) levels increased significantly, however, ATP content and ATPase activity decreased significantly | (Ma et al. 2011; Zhao et al. 2018)              |
| Saussurea involucrata | Asteraceae      | N/A                            | Extract; Petroleum ether extract | N/A                                                                                                                   | (Jiang et al. 2016)                           |
| Silybum marianum  | Asteraceae        | N/A                            | Silymarin                   | The HIF-1 signalling pathway was inhibited                                                                            | (Deep et al. 2017)                             |
| Incarvillea youngusbandii | Bignoniaceae | Roots                          | Extract                     | N/A                                                                                                                   | (Chen et al. 2012)                            |
| Astragalus mongholicus | Fabaceae        | N/A                            | Extract; Formononetin       | Oxidative stress markers (SOD, GSH) levels, arterial oxygen partial pressure, arteriovenous partial pressure difference and arterial oxygen saturation increased significantly, however, oxidative stress markers (MDA) content reduced significantly, the elevation of catecholamine level inhibited significantly; VEGF, HIF-1α expressions reduced significantly | (Zhao and Wu 2012; Wu et al. 2016)             |
| Glycyrrhiza uralensis | Fabaceae        | N/A                            | Flavonoid; Glycyrrhizic acid| N/A                                                                                                                   | (Lau et al. 2014; Ge et al. 2017)               |
| Oxytropis ochocephala | Fabaceae        | Whole grass                    | Ethanol extracts             | Oxidative stress markers (SOD, GSH-Px) content increased significantly, however, Oxidative stress markers (free radical) content decreased significantly | (Jiang et al. 2016)                           |
| Castanea mollissima | Fagaceae         | Shells                         | Water extract                | Oxidative stress markers (SOD) level increased significantly, however, oxidative stress markers (MDA) content reduced significantly | (Xu et al. 2012)                              |
| Gentiana scabra    | Gentianaceae      | Roots                          | Water extract                | N/A                                                                                                                   | (Jin and Xu 2005)                              |
| Crocus sativus     | Iridaceae         | N/A                            | Crocetinate acid; Crocin     | N/A                                                                                                                   | (Singer et al. 2000; Ghotbeddin et al. 2020)   |

(continued)
Table 3. Continued.

| Latin binomial | Family                  | Part used | Active compounds | Possible anti-hypoxia molecular mechanisms and pathways                                                                 | References                                      |
|---------------|-------------------------|-----------|------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| *Isodon japonicus* | Lamiaceae               | Stems and leaves | Total two terpenes | Microcirculation was improved (Li et al. 2012)                                                                          | (Li et al. 2012; Zhou et al. 2017; Zhang 2019b) |
| *Menispermum dauricum* | Menispermaceae         | Rhizomes  | Alkaloid         | N/A (Shao et al. 2019)                                                                                                 | (Zhou et al.2017; Zhang 2019b)                 |
| *Gastrodia elata* | Orchidaceae             | Tubers    | Gastrodin; Root Extract | Lipid peroxidation markers (LDH, LA), oxidative stress markers (GSH, glutathione reductase (GR), CAT), and HSp70 levels increased significantly, however, oxidative stress markers (MDA), ET-1, inducible nitric oxide (iNOS), and HIF-1α levels reduced significantly | (Tang et al.2012)                             |
| *Papaveraceae* | N/A                     | Alkaloid   | N/A              | Anti-inflammatory cytokines levels increased significantly, however, pro-inflammatory cytokines levels reduced significantly, inflammatory responses inhibited significantly | (Li 2013)                                      |
| *Corydalis solida* | Polygonaceae            | N/A       | Rhein            | Oxidative stress markers (ROS) production reduced significantly, phosphorylation of AKT and glycogen synthase kinase-3β (GSK3β) increased significantly, P38 level was down-regulated, AKT/GSK3β/p38 pathway increased significantly | (Liu et al.2018)                               |
| *Argentina anserina* | Rosaceae               | Roots     | N/A              | Anti-inflammatory cytokines levels increased significantly, however, pro-inflammatory cytokines levels reduced significantly, inflammatory responses inhibited significantly | (Tang et al.2012)                             |
| *Dimocarpus longan* | Sapindaceae            | Fruit cores | N/A              | Lipid peroxidation markers (LDH) level increased significantly; oxidative stress markers (Nrf2, HO-1) and phase II antioxidant enzymes increased significantly, however, VEGF expression decreased significantly, HIF-1α expression was stable | (Hu et al. 2012)                               |
| *Lycium chinense* | Solanaceae              | Fruits, leaves | Polysaccharide; leaf decoction of *Lycium chinense* (Zhang et al.1991; Mathew and Sarada 2018) | Intestinal permeability was greatly improved (Li, Yin, et al.2015). hara et al. (2012) | (Li et al. 1999; Wang and Wei 2012) |
| *Zingiber officinale* | Zingiberaceae        | Rhizomes  | Water extract; curcumin | Lipid peroxidation markers (LDH) level increased significantly; oxidative stress markers (Nrf2, HO-1) and phase II antioxidant enzymes increased significantly, however, VEGF expression decreased significantly, HIF-1α expression was stable | (Zhao et al. 2016)                             |

They may cause adverse reactions in patients, and both clinical evidence and experimental studies in this field are limited (Table 2). Although clinical administration of common plants usually does not result in any significant adverse effects in humans, systemic toxicity and safety issues urgently need further attention and study. Large Randomized Controlled Trials (RCTs) are required to assess the potential of these medicinal plants as an alternative to current treatments for HAPE or HAPH. Moreover, drug interactions in HAPE or HAPH patients must be noted because they can lead to overdosing or undertreatment, resulting in severe clinical consequences.

**Bioavailability of medicinal plants constituents**

Formulating drugs with different doses and modes of administration can improve their absorption. The oral bioavailabilities of baikalin, echinacoside and polydatin were very low, leading to limited clinical use. Changing the route of administration, such as parenteral administration, or the dosage of a drug can improve its bioavailability. The bioavailability of the baicalin nanoemulsion is approximately 1.67-fold greater than that of its monomer (Zhang, Lv, et al. 2011; Zhao et al. 2013). The oral bioavailability of HSYA is approximately 1.2% (Jin et al. 2016), but when it was formulated as solid lipid nanoparticles, the oral bioavailability was 3.97-fold higher than that of the previous form (Zhao et al. 2018). The absolute bioavailability of echinacoside is only 0.83% (Jia et al. 2006); however, when it was incorporated into a phospholipid complex, the absorption of the drug was greatly improved (Li, Yang, Yang, et al. 2015). There are very few human pharmacokinetics studies. The study of pure HSYA preparations in healthy Chinese volunteers indicated that sex differences should be considered in dosage recommendations in clinical use (Li, Yin, et al. 2015).

Although we have seen advances in the development and treatment for HAPH and HAPE, there is still a problem. There is no direct indicator or uniform standard against which to compare treatment effects on HAPE or HAPH, which causes some trouble in formulating clinical medications. For different patients, doctors may not know which choice of medicinal plant is better, which may delay the treatment of the disease and cause serious consequences.

**Potential medicinal plants considered to have anti-hypoxic activity**

Another 31 identified species of medicinal plants have anti-hypoxic activities such as *Gastrodia elata* Blume (Orchidaceae), *Apocynum venetum* Linn. (Apocynaceae), and *Leuzea uniflora* (L.) Holub (Asteraceae) (Table 3). These medical plants can act on the key pathways and genes essential for the pathogenicity of HAPE or HAPH. Considering their active antioxidant components and other pharmaceutical effects, we can further explore whether these medicinal plants can be used to prevent or treat HAPH and HAPE. These potential medicinal plants related to the pathogenesis of plateau diseases have not yet been developed and used clinically. We hope to discover that they have important therapeutic effects on plateau diseases, which will bring new hope for the effective treatment of HAPE and HAPH.
Conclusions

This review summarizes the past 30 years of research into Chinese medicinal plants for the treatment of HAPH and HAPE. Based on the identified plants and their bioactive components, we found that there are not sufficient numbers of medicinal plants that have been used for HAPH and HAPE; however, many studies identify potential medicinal plants, and most of them have considerable research value. The in vivo studies briefly explain the pharmacological effects and the mechanisms of action. However, there are still some medicinal plants with unclear biologically active ingredients.

A better understanding of these remedies could guide physicians to recommend them. However, the pathogenesis of HAPH and HAPE is not completely clear, and the available treatments need to be improved. More research on the discovery and mechanisms of bioavailability, efficacy, and pharmacokinetics of medicinal plants and on the development of additional new treatment models for the clinical treatment of these high-altitude diseases should be the future focus. This review summarizes 26 species of medicinal plants for HAPH and HAPE treatment and 31 species with potentially active ingredients. Few drugs are now available to treat HAPH and HAPE completely and effectively, and drug candidates are needed. Therefore, more in-depth studies are important for providing additional choices for HAPH and HAPE patients, especially options that can improve patient survival, exhibit few side effects and are inexpensive. While many questions about these medicinal plants remain unanswered and much work needs to be done before we determine their place in treating HAPE and HAPH, we believe that this article provides us a good perspective on the pros and cons of medicinal plants.

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Author contributions

Xin Chen, Yonghe Hu: Conceptualization, Methodology, Software.

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Tingting Wang, Xin Chen, Jun Hou, Wenjing Xiao, Longfu Zhou: Visualization, Investigation.

Xin Chen, Yonghe Hu, Yaolei Zhang, Li Yuan, Xiaoqiang Yin: Supervision.

Tingting Wang, Xin Chen, Yonghe Hu: Validation.

Tingting Wang: Writing, Reviewing and Editing.

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