



### Commentary

## Herbal Remedies as an Alternative Medication for Altitude Sickness

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### Abstract

Application of herbal remedies has been applied in the handling of altitude sickness for a long time. But the scientific evidence regarding the effectiveness of herbal medicine is still not enough. The main reason (s) seems associated with the missed target according to Traditional Chinese Medicine (TCM). Herbs in TCM were used to treat and/or relief the disorder (s) after the acute stage of altitude sickness. Therefore, experts in TCM focused the results of Qi deficiency, Blood deficiency and Yin injury. Unfortunately, a meta-analysis of the clinical reports included 364 trials of herbal remedies showed the negative results. Moreover, the popular agent *Rhodiola crenulata* extract named Hong Jing Tian in Chinese has also been evaluated as negative in a crossover trial. Although a high individual variability between cases and a myriad of confounding environmental factors are concerned for the clinical trials, we consider the failure

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associated with the various stage of altitude sickness in volunteers. Therefore, we provide new target and/or direction regarding the application of herbal medication for altitude sickness. Additionally, herbal mixture seems more effective than individual herb in clinical practice. Comments from the present study are going to suggest a new way in the application of herbal remedies for altitude sickness.

**Keywords:** Acute stage; Altitude sickness; Clinical practice; Herbal remedies; Traditional Chinese Medicine (TCM)

### Introduction

More than 38 million people live permanently at altitudes  $\geq 2400$  m, and at least 100 million people travel to high altitude locations each year for individual purpose around the world. Also, the army soldiers have to remain at these higher altitudes on duty for a while or long durations. Gradual ascent to high altitude areas generally leads to acclimatization. These events include respiratory, hematological adaptation resulting in the enhanced oxygen uptake that may delivery to the tissues. Inability to acclimatize leads to High Altitude Pulmonary Edema (HAPE) and High Altitude Cerebral Edema (HACE). Acute Mountain Sickness (AMS) is used to describe the problems in the un-acclimatized persons shortly after ascent to high altitude. It is a health problem with severe and potentially fatal consequences; particularly HAPE and cerebral edema are potentially fatal. It also provides a useful model for studying the pathophysiological process of low oxygen in an otherwise healthy population.

It has been indicated that the high-altitude syndromes are mainly due to the body's responses to hypobaric hypoxia, not due simply to hypoxemia [1]. There is a delay between the onset of hypoxia and the onset of symptoms after ascent (from hours to days). Additionally, not all symptoms are immediately reversed with oxygen. The symptom induced by the experiments between hypobaric hypoxia (simulated high altitude), hypoxia alone and hypobaric normoxia, AMS occurred rapidly showing a greater severity than simulated altitude. However, AMS also occurred in normobaric hypoxia, after a longer exposure with less severe.

AMS is a nonspecific symptom and occurs at altitudes as low as 2000 m<sup>2</sup>. It is a neurologic disorder showing nonspecific symptoms (loss of appetite, fatigue, headache, nausea, weakness, lightheadedness, difficulty in sleeping and dizziness) developing 6 - 12 h after ascent to a high altitude, except sometimes as early as 1 hour. Mild altitude sickness is similar to a hangover it causes headache, nausea and fatigue. However, it should take as a warning sign of risk of the serious forms of altitude sickness: HAPE and HACE. Too rapid an ascent to high altitude without prior acclimatization leads to HAPE. The main symptoms of HAPE including shortness of breath in addition to cough and fever, which are caused by a diminished capacity for alveolar fluid reabsorption. Alveolar hypoxia and resulting tissue hypoxia may initiate HAPE. The hypoxic pulmonary vascular response is enhanced to the development of severe pulmonary hypertension. The causal treatment of HAPE is descent, evacuation, and administration of oxygen [2]. HACE is an encephalopathy whose hallmarks are ataxia and altered consciousness with diffuse cerebral involvement

but generally without focal neurologic deficits. The first signs may be uncharacteristic behavior such as laziness, excessive emotion or violence. Progression to these disorders is rapid. Drowsiness and loss of consciousness occur shortly before death. Papilledema and retinal hemorrhages may also occur. The correlation between HACE and retinopathy has been established although the mechanism (s) remained unclear [3].

Prevention is known to better than treatment of AMS. Handling of AMS or HACE follows three principles: further ascent should be avoided until the symptoms have resolved, patients with no response to medical treatment should descend to a lower altitude and at the first sign of high altitude cerebral edema patients should descend to a lower altitude. Acetazolamide is introduced as the drug of choice for prophylaxis against AMS. It is recommended to take 125 and 250 mg twice daily while acetazolamide at 125 mg twice daily shows less risk of paraesthesia [4]. It is contraindicated in the patients with liver disease for hepatic coma by interfering with the urinary elimination of  $\text{NH}_3$  acidosis [3]. Dexamethasone, a steroid, is also used to alleviate AMS and it is applied in combination with acetazolamide to decrease the systolic pulmonary artery pressure and incidence of HAPE in adults. However, the adverse effect of steroid shall be careful. Moreover, vasodilators, including Nifedipine and Sildenafil, were also applied to alleviate the symptoms. But side effects have been claimed [3]. Overall, ideal medicine for AMS is still not observed.

### Application of Herbal Remedies in Altitude Sickness

Herbal remedies have been applied in the prophylaxis and handling of high mountain disorders for a long time. According to Traditional Chinese Medicine (TCM), several formulations have been mentioned. It has been recommended that complementary and alternative medicine (especially integrative medicine) contributes to the therapy of AMS [5]. Sea buckthorn, called “Shan-Ji” in Chinese, has been demonstrated to improve high altitude polycythemia in rats [6]. In China, the aborigines of Qinghai-Tibetan plateau maintain a variety of medicinal plants with the ability to alleviate AMS [7]. *Rhodiola algida*, named Hong Jing Tian in Chinese, is the famous Tibetan medicinal plant with anti-AMS effect. It is the first choice in the prevention of AMS when people going to travel to the high altitude [8]. Recently, a traditional Tibetan medicine named Zuo-Mu-A Decoction has also been demonstrated the merit in the prevention of high altitude polycythemia in rats [9]. Ginkgo (*Ginkgo biloba*) and Roseroot (*Rhodiola rosea*) in addition to coca (*Erythroxylum coca*) were famous around the world for AMS [3].

In clinical practice, the randomized clinical trials testing Chinese herbal medicine against AMS were analyzed [10]. Total 364 trials were included but only 9 reports were used in the meta-analysis. These analyses also included Ginkgo leaf tablet and *Rhodiola rosae* (Hong Jing Tian) decoction. However, due to the unclear methodological quality, no positive result obtained. Additionally, *Rhodiola crenulata* extract has also been evaluated as negative for AMS in a crossover trial [8].

Limitations of the clinical trial in the evaluation of AMS or altitude sickness have been concerned, mainly, a high individual variability between cases and a myriad of confounding environmental factors are the reasons [11]. From the small sample sizes ( $n < 30$ ), only large differences or rates can be obtained. Therefore, improvement in the clinical trial for evaluation of AMS or altitude sickness seems

essential. The Strengthening Altitude Research (STAR) project in clinical research, is expected to be an effective way of enhancing research quality [12].

### The Perspective of Herbal Medication in the Handling of Altitude Sickness

In basic research, the used animals were maintained in well-control condition to receive the hypobaric hypoxic manipulation that is hard to mimic the high mountain disorders. Therefore, reports show the effectiveness belong to scientific view only which is far from the clinical practice. For example, *Rhodiola crenulata* extract has also been documented as effective in rats exposed to hypoxia involved a simulated altitude of 8000 m for 9 h [13]. It is fully different from the report in the clinical trial, indicating the critical difference between animal studies and clinical trials in AMS [8].

We do believe that the effective herbal remedies were applied but it was not developed in the scientific view, probably as the ethnomedicine supplied to the traveler (s). In addition to the concerns above, the limitation of single herb shall be conducted because it seems useful in scientific research only. In clinical practice, the herbal mixture will be more helpful than a single herb to alleviate the altitude sickness. For example, Hsiao Chin Lon Tang has been identified to improve the patients with Chronic Pulmonary disorder to Heart Diseases (CPHD) [14]. The main herb Ma-Huang in Hsiao Chin Lon Tang has been demonstrated as antioxidant that is known to produce merits in hypoxia including AMS [15]. Additionally, combined dosing with ephedrine, the active principle in Ma-Huang, and the endothelin receptor antagonist ambrisentan produced a distinct ergogenic effect on the simulated high altitude in rats better than the single compound alone [16]. Bai Shao, white peony root, is another important herb in Hsiao Chin Lon Tang and the active principle paeoniflorin has been demonstrated to improve the ling injury in MRL/lpr mice [17]. Also, paeoniflorin is found to support heart function in rats with acute cardiac infarction [18]. Although the scientific view has supported the potential of Hsiao Chin Lon Tang, clinical research is still less performed in the handling of altitude sickness.

High Altitude Disease (HAD) is the most common sickness in areas with altitudes over 3000 m. A four-period prevention model has been suggested in military view [19]. Generally, prevention of HAD is focused on the ascension period but lacked the whole health prevention, particularly for the descent population. Otherwise, experts in TCM handle HAD according to the result of Qi deficiency, Blood deficiency and Yin injury. The hypoxia endurance is expected to be improved mainly after enhancing Qi-Blood-Yin. Therefore, *Codonopsis pilosula*, *Rhodiola rosea*, milkvetch root *Poria cocos* compound, *Dracocephalum heterophyllum*, *Dracocephalum tanguticum* Maxim, *Astragalus*, *Cordyceps sinensis*, *Acanthopanax* and *Rosa acicularis* were mentioned in the applications [19]. However, as described above, the negative results were reported for them from the clinical trials [10]. It indicates the target seems not suitable.

HAD could be divided into the stage of short-term changes that occur with the acute response to hypobaric hypoxia and another stage of longer-term acclimatization and adaptation. The acute syndromes of HAD including AMS, HAPE and HACE that are fatal and related to the speed of ascent. Acetazolamide is the most commonly used agent for the amelioration of AMS [20]. Interestingly, acetazolamide increases the minute ventilation and leads to improvements in

arterial blood gases. An increase in Central Chemoreceptor (CCR) output by acetazolamide has been indicated to associate with the increase in minute ventilation [20]. Additionally, peripheral chemoreceptor afferent activity rises hyperbolically as hypoxia increases. Acetazolamide may reduce the peripheral chemoreceptor activity that could be another merit in AMS. Another carbonic anhydrase inhibitor, benzolamide, causes a leftward shift in the HCVR curve and reduces the symptoms of AMS [21]. Therefore, herbs that may produce a similar effect are expected to be useful in the handling of AMS.

Acute exposure to severe hypoxia causes damage to heart and lung tissues due to the excessive production of free radicals [22]. Telomerase Reverse Transcriptase (TERT) was positively correlated with telomere length and the levels of Hypoxia-Inducible Factor1 $\alpha$  (HIF-1 $\alpha$ ). In response to hypoxia, the expression of TERT and HIF-1 $\alpha$  was significantly upregulated [23]. Herbal medicine may play a potential anti-apoptotic role of HIF-1 that could protect cells against apoptosis under hypoxia [23]. However, they are required to develop in the near future for application in AMS.

## Conclusion

Taken together, it seems essential to change the target in research of herbal medication for altitude sickness. Application of herbs for improvement through enhancing Qi-Blood-Yin seems not suitable in the cases of acute attack, data from clinical trials indicated. Therefore, we proposed that if the new targets were possible to selectively increase the expression of Telomerase Reverse Transcriptase (TERT) and Hypoxia-Inducible Factor1 $\alpha$  (HIF-1 $\alpha$ ); this strategy might provide therapeutic benefit in the pathologic condition. Basically, many useful molecules contained in herbs are required to develop and the herbal mixture will be more useful than a single herb in the handling of altitude sickness.

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