High Altitude Sickness and Antioxidant Interventions

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Abstract

High altitude sickness (HAS) has been one of the important environmental challenges occurring as a result of the failure of the physiological acclimatization to acute hypobaric hypoxia. The prime bodily retort to hypoxia and adaptation linked to HAS comprises hyperventilation, increased systemic blood pressure together with tachycardia (increased heart rate) and increased hemoglobin concentration. These collective retorts enhance the supply of oxygen to the cells by means of alterations in the respiratory, cardiovascular, and hematologic system, thereby boosting the cellular oxygen uptake together with consumption mechanisms. Additionally, in majority of the cases, these bodily responses may not be sufficient, as a result the mount to high elevations and the associated hypoxia culminate in complex medical condition. Diverse strategies for preventing HAS can be employed categorized mainly into pharmacological and non-pharmacological and miscellaneous. Pharmacological interventions comprise drugs like acetazolamide or dexamethasone which have been found to work effectively but also linked with adverse physical secondary effects. Non-pharmacological and miscellaneous interventions are those which are not founded on the administration of drugs and can be categorized into two sets: pre-acclimatization and supplements. Pre-acclimatization and additional methods founded on pressure comprise the employment of hypobaric air breathing to sham higher elevations, positive end-expiratory pressure, and remote ischemic preconditioning. In addition, non-drug approaches, herbs, and natural supplements have been also tested and found to be promising in combating this challenge. Supplements may contain herbal extracts (like *Ginkgo biloba*,

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Rhodiola species, and Coca leaf products), mineral elements (like iron, magnesium), antacids, and hormonal agents (like medroxyprogesterone and erythropoietin). Hypoxia is well known for causing prooxidant/antioxidant disturbances in the cell, thereby resulting in oxidative stress. The key mechanisms through which hypoxia-induced reactive oxygen species (ROS) overgeneration takes place are increased catecholamine manufacture, mitochondrial redox potential diminution together with the stimulation of xanthine oxidase pathway. The scientific observations of a raised risk of ROS and free radical mediated oxidative insult at higher elevation have shown the way to the researchers to suggest nutritional antioxidant interventions such as ascorbic acid, beta-carotene, vitamin E, selenium, alpha-lipoic acid, etc. present in fruits and vegetables and herbal supplements rich in antioxidants like *Ginkgo biloba*, which may be advantageous in combating the problem of HAS. Several antioxidants and their concoction have been tested and have shown mixed results in relation to the effectiveness of antioxidants in averting HAS. Despite the bulk of scientific investigations exploring the beneficial effects as well as the effectiveness of various antioxidants against HAS in different experimental models, the present state of evidence is unable to substantiate or repudiate the use of any antioxidant or a concoction of antioxidant as a definite prophylactic agent. Additionally, an inadequate number of investigations support the effectiveness of antioxidant supplements at higher elevations in easing the difficulty of HAS. Furthermore, there is a dearth of standardized studies in this regard. The variations in the current investigations with regard to experimental design considerations like altitude reached, rate of ascension, degree of pre-acclimatization; antioxidant employed, purity and quality of the antioxidant, the timing, duration, pretreatment, and dosage administered; individual susceptibility, small sample size, etc. cloud the understanding with respect to their efficacy in bringing out the desirable effects. Another challenge in this regard is to identify the appropriate dosage, timing, or combination of antioxidants which will regulate the induced oxidative stress without any deleterious effects on the body and therefore help the body to ease out the symptoms of HAS. Therefore, given the undesirable side effects associated with pharmacological interventions, non-pharmacological antioxidant interventions which are relatively safer and with minimal side effects need more attention in order to combat this challenge of HAS.

Keywords

High altitude sickness · Antioxidants

12.1 Introduction

High altitude sickness (HAS) has been one of the important environmental challenges being faced by mankind since prehistoric times. It mainly occurs as a result of the failure of the physiological acclimatization to acute hypobaric hypoxia.

A huge number of individuals mount to higher elevations for various reasons ranging from occupational deployment, recreation, athletic competition, hobby to name a few. Apart from a considerable reduction in ambient temperature and humidity, the key environmental attributes defining the higher elevations are a significant plunge in barometric pressure resulting in a diminishment in the partial pressure of oxygen at every single point alongside the oxygen transport cascade commencing with the ambient environment to the powerhouse of the cell. Despite the constant oxygen percentage in the ambient air at about 21%, there is a drop in the atmospheric pressure with rise in height, as a result less amount of oxygen is available to the body consequently leading to hypobaric hypoxia (Zafren 2014).

This hypobaric hypoxia generates an array of physiological retorts that enables the climber to endure and acclimatize to the state of diminished oxygen pressure. In cases, where the body is not able to acclimatize due to defective bodily responses, the body succumbs to some or the other forms of HAS. Further, when the rate of ascension exceeds the rate of bodily adaptation it culminates into HAS (Zafren 2014). This quickly rescindable condition is characterized by a group of brain and lung syndromes occurring in individuals as a result of ascend to altitudes greater than approximately 2500 m (above 7000 feet). HAS is considered of two types: acute mountain sickness (AMS) and chronic mountain sickness (CMS), also referred to as Monge's disease (Monge 1942).

The prime bodily retort to hypoxia and adaptation linked to HAS comprises hyperventilation, increased systemic blood pressure together with tachycardia (increased heart rate), and increased hemoglobin concentration (Palmer 2010). These collective retorts enhance the supply of oxygen to the cells by means of alterations in the respiratory, cardiovascular, and hematologic system, thereby boosting the cellular oxygen uptake together with consumption mechanisms (Palmer 2010). Additionally, in majority of the cases, these bodily responses may not be sufficient, as a result the mount to high elevations and the associated hypoxia culminate in complex medical condition (Palmer 2010; Luks et al. 2017), well known as HAS. It can arise at any time ranging from several hours of ascension to post 5 days of ascension with mild to deadly conditions depending upon several physical and biological factors.

12.2 Acute Mountain Sickness (AMS), High Altitude Cerebral Edema (HACE), and High Altitude Pulmonary Edema (HAPE)

AMS is a syndrome characterized primarily by neurological symptoms. Scientific studies have corroborated the elevation in rate of respiration coupled with raised hemoglobin levels with experience to low oxygen pressure at higher altitudes (Palmer 2010; Paralikar and Paralikar 2010; Luks et al. 2017). This reduced pressure and diminished oxygen concentration at higher altitudes generates a set of symptoms comprising of headache, dizziness, shortness of breath, anorexia, or nausea, vomiting, tiredness, and insomnia frequently termed as AMS (Palmer 2010). The

most predominant symptom of AMS is headache which can be considered as a discrete clinical entity. If neglected, the illness may advance to life threatening high altitude cerebral edema (HACE) or pulmonary edema. In severe cases where the brain (HACE) is chiefly affected, symptoms like drowsiness, confusion, unconsciousness or ataxia, impaired motor control can transpire (Imray et al. 2010), whereas when the lungs (high altitude pulmonary edema or HAPE) are disturbed, symptoms like cough or breathlessness appear. If unaddressed, HACE may lead to death as an upshot of cerebral edema. HACE is generally headed by the signs and symptoms of AMS and is often considered as the dangerous form and culmination phase of AMS (Imray et al. 2010; Palmer 2010; Zafren 2014). Further, studies indicate a connection by way of intracranial hypertension amid these syndromes through which they may share a common pathophysiology (Davis and Hackett 2017; Luks et al. 2017). The Lake Louise Questionnaire or Environmental Symptoms Questionnaire can be employed to score the severity of AMS in mountaineers.

Pulmonary alveolar hypoxia is a common term for non-adapted individuals who rapidly travel to high altitudes. It is characterized by the diminished trans-alveolar fluid transport resulting in excessive fluid buildup in the alveoli overstating alveolar hypoxia. This further impedes the gas exchange process consequently instigating the pathological development of HAPE, which is deadliest kind of HAS (Stream and Grissom 2008; Imray et al. 2010). Moreover, HAPE is a condition developing due to hypoxia within 2–4 days of ascent to higher elevations wherein the lungs are distressed as a result of pulmonary edema leading to intricate chain of events. It is described by a set of symptoms such as cough, difficult breathing (dyspnea), and reduced exercise tolerance (Palmer 2010). It is uncommon post 1 week of adaptation to a specific elevation (Palmer 2010). Basically, it generates as a result of the failure of the biological mechanisms to prevent the entry of water into the airspace (Scherrer et al. 2010) resulting in hypoxic pulmonary hypertension which is the distinguishing feature of HAPE. According to Scherrer et al. (2010), the faulty pulmonary nitric oxide production; overstated manufacture of endothelin-1; inflated sympathetic stimulation; and deficient alveolar transepithelial sodium transport have been suggested as the possible mechanisms behind the arbitration of pulmonary hypertension.

According to the approximations, around 84% of individuals flying straight to 3860 m are disturbed by AMS (Murdoch 1996). In comparison to AMS, the danger of HACE and HAPE is considerably lesser, with approximations varying between 0.1 and 4.0% (Basnyat and Murdoch 2003). Therefore, HACE and HAPE are though uncommon diseases in comparison to AMS nonetheless they are more deadly, particularly as the elevation rises (Stream and Grissom 2008). Generally, higher the altitude and faster the climb, the higher the possibility of occurrence of HAS. Moreover, depending upon the sensitivity, different individuals respond differently. So, individual susceptibility is yet another risk factor playing an important role in the development of HAS. Apart from these, history of HAS, permanent habitation below 900 m, physical exertion in kids and adults, obesity, and coronary heart disease could be other plausible risk factors behind the development of HAS (Basnyat and Murdoch 2003; Dehnert and Bärtsch 2010).

As far as gender is concerned, both men and women appear to be similarly vulnerable, together, better physical health does not ensure protection against HAS (Palmer 2010). To add, individuals suffering from asthma are strictly recommended to keep their health under control prior to any exertion at higher elevations (CATMAT 2007). Numerous expiries at higher altitudes like on Mt. Everest and other high mountains can be accredited as an upshot of altitude sickness. Furthermore, in general, HAS is a benign disorder troubling the individuals from sea level in case of a ski vacation or climbing in the mountains. The figure of people traveling quickly to higher elevations for work or tourism is increasing day by day. Betterment in transportation facilities for high elevation regions has further contributed to the rising number. Consequently, HAS has emerged as a major environmental health threat and prophylactic interventions are needed to combat this situation.

12.3 Diverse Strategies for Preventing High Altitude Sickness (HAS)

Various interventions have been documented in the scientific literature to escape HAS, particularly AMS (CATMAT 2007; Luks et al. 2010; Seupaul et al. 2012; Zafren 2014). On the whole, the various interventions employed for averting HAS can be categorized into pharmacological and non-pharmacological and miscellaneous (Luks and Swenson 2008; Luks et al. 2010). The Committee to Advise on Tropical Medicine and Travel suggested an accord for HAS, elaborating the preclusion and treatment methods amid various other issues concerning this clinical state (CATMAT 2007).

12.3.1 Pharmacological Interventions

Researchers have also studied diverse pharmacologic interventions to check HAS (Zafren 2014). In this context, drugs like acetazolamide or dexamethasone have been found to work effectively for the deterrence of AMS. Acetazolamide being a diuretic hinders the enzyme carbonic anhydrase, thereby causing an upsurge in renal excretion of potassium and bicarbonate. The induction of metabolic acidosis is the main target behind this prophylactic treatment, thus continuing hyperventilation at higher elevations and augmenting systemic oxygenation that eases AMS symptoms. Acetazolamide is a diuretic that inhibits carbonic anhydrase, producing an increase in renal secretion of potassium and bicarbonate. The aim of prophylactic treatment is to induce metabolic acidosis, thereby maintaining hyperventilation at high altitude and enhancing systemic oxygenation, which decreases the symptoms of AMS. The therapeutic efficacy of steroids, explicitly dexamethasone, has been linked to its antioxidant properties and consequent capacity to uphold the vascular integrity of the blood–brain barrier (BBB) (Hackett et al. 1998), which seems to be principally vulnerable to oxidative insult (Halliwell 1992). Sumatriptan and gabapentin have also been shown to give positive results against AMS but need more research

(Seupaul et al. 2012). However, pharmaceutical prevention has been linked with adverse physical secondary effects, for instance, acetazolamide though effective but triggers complaints like paresthesias, dysgeusia, and diuresis. AMS being a common problem at higher elevations, easily accessible, as well as harmless prophylactic means are wanted.

12.3.2 Non-Pharmacological and Miscellaneous Interventions

Non-pharmacological and miscellaneous interventions are those which are not founded on the administration of drugs and can be categorized into two sets: pre-acclimatization and supplements. Pre-acclimatization and additional methods founded on pressure comprise the employment of hypobaric air breathing to sham higher elevations, positive end-expiratory pressure, and remote ischemic preconditioning (Burse and Forte 1988; Launay et al. 2004; Dehnert et al. 2014; Berger et al. 2017). The risk of HAS escalates with a non-adapted mountaineer mounting to higher elevations greater than 2500 m (Paralikar and Paralikar 2010). Moreover, with increased individual susceptibility, an individual may suffer from AMS even below 2500 m at intermediate elevations like 2100 m (Davis and Hackett 2017). Further, the ascent speed together with exertion are the chief modifiable intermediaries of AMS risk. Therefore, though tough and unviable, gradual ascent or regulated rate of ascension, with regard to meters mounted per day has been suggested as one of the best ways of escaping HAS (CATMAT 2007; Paralikar and Paralikar 2010; Luks et al. 2014; Zafren 2014). While scheduling the rate of ascension, the elevation at which mountaineers sleep is of prime significance than the elevation attained during arousal (Luks et al. 2014). In gradual ascent, the mountaineers, especially individuals lacking prior altitude exposure, evade swift mounting to elevations more than 3000 m. Usually, they halt and stay at 2500–3000 m for 2–3 nights before mounting higher, using an additional night for adaptation every 600–900 m in case of ongoing climb. The main components in acclimatization are directed at safeguarding the availability of oxygen to body tissues and organs by way of optimum oxygen tension of the arterial blood (Bärtsch and Saltin 2008). Climbing to higher altitudes during daytime and coming back to lower elevations for rest assist in acclimatization (CATMAT 2007). Hypobaric and hypoxia chambers which change the amount of fractional inspired oxygen (FIO_2) or positive end-expiratory pressure (PEEP) imitating the effects of acclimatization could be appealing and extensively acknowledged for high elevation mountaineers as they would save time, transportation and effort in staging locations (Burse and Forte 1988; Dehnert et al. 2014; Launay et al. 2004). Additional interventions founded on remote ischemia in order to safeguard the brain could restore injury from subsequent ischemic slurs, because of its influences on vasoactive and inflammatory pathways (Berger et al. 2017; Pérez-Pinzón et al. 1997). To add, prior experience also aids in better acclimatization to the prevailing conditions. The

knowledge and cognizance of AMS among the climbers have also been found to be effective in diminishing the prevalence of AMS (Gaillard et al. 2004). According to Vardy et al. (2005) cognizance among the climbers about the true signs and symptoms along with the prevention methods for AMS deters its occurrence.

In addition to drugs, non-drug approaches, herbs, and natural supplements have been tested and found to be promising in combating this challenge. Supplements may contain herbal extracts (like *Ginkgo biloba*, *Rhodiola* species, and Coca leaf products), mineral elements (like iron, magnesium), antacids and hormonal agents (like medroxyprogesterone and erythropoietin) (Roncin et al. 1996; Dumont et al. 1999; Gertsch et al. 2002, 2004; Chow et al. 2005; Moraga et al. 2007; Leadbetter et al. 2009; van Patot et al. 2009; Panossian et al. 2010; Seupaul et al. 2012; Chiu et al. 2013; Talbot et al. 2011; Ke et al. 2013; Heo et al. 2014; Ren et al. 2015). Iron supplement has been also shown to act as a prophylactic agent in diminishing the frequency of AMS in case of swift ascension to higher elevations in healthy participants (Talbot et al. 2011). The shielding effects of iron supplements have been attributed to its influence on the pathological and physiological responses to hypoxia, specifically those produced due to iron deficit (Ren et al. 2015). Moreover, the ability of iron supplements in alleviating pulmonary hypertension which may be caused due to acute scarcity of iron has been suggested as the mechanism behind its protective effect (Burtscher et al. 2004). Iron is a vital ingredient for the formation of human blood, and individuals lacking iron suffer from a disease known as anemia. In order to meet the deficiency, intravenous iron solutions such as dextran iron, ferrous gluconate, and iron sucrose have been employed in medical settings. Among these, iron sucrose which is a multi-core of iron (III)-hydroxide in sucrose has been indicated to be comparatively safer with minimal allergy risk together with least occurrence of undesirable effects (Hörl 2007). Contradictory results have also been reached. A preliminary research conducted by Ren and his colleagues (2015) utilized iron sucrose as intravenous iron supplementation in order to determine its efficacy in preventing AMS. The study revealed that intravenous iron supplementation has no substantial shielding effect in averting AMS.

Hormonal supplements are supposed to elevate the hypoxic ventilatory responses by means of improving the oxygen saturation and diminishing the hematocrit level together with the induction of red blood cell formation (Heo et al. 2014; Milledge and Cotes 1985). Hypoxia-induced erythropoietin (EPO) production is closely linked with adaptation to higher elevations. However, the release commences after 1–2 days of altitude exposure and it takes weeks to cause a rise in hemoglobin. (Milledge and Cotes 1985). EPO which is a glycoprotein has been found to be helpful against AMS by triggering the manufacture of red blood cell in the body together with a reduction in plasma volume, thereby causing a rise in the arterial O_2 concentration (Heo et al. 2014).

12.4 Cellular Antioxidant System and its Alteration in Relation to HAS

Hypoxia is well known for causing prooxidant/antioxidant disturbances in the cell, thereby resulting in oxidative stress (Magalhães et al. 2004; Pialoux et al. 2009). The key mechanisms through which hypoxia-induced reactive oxygen species (ROS) overgeneration takes place are increased catecholamine manufacture, mitochondrial redox potential diminution together with the stimulation of xanthine oxidase pathway (Mazzeo et al. 1998; Kehrer and Lund 1994). The production of free radicals which are extremely energized molecules possessing either one or more than one unpaired electron in their atomic orbital (Halliwell 1994) may further be a part of the cause in the intricate pathophysiology of HAS (Bailey and Davies 2001). Free radicals are generated in the body as a result of the cellular metabolism utilizing molecular oxygen. Though physiologically vital in controlled amounts, but then again, when in surplus could trigger and promulgate membrane destabilization and cell injury. Studies have connected the free radicals in a range of pathologies, especially lung disease like respiratory distress syndrome and a range of central nervous system complaints produced as a result of neurodegeneration, ischemia, or trauma (Halliwell and Gutteridge 1999). Nonetheless, it remains to be elucidated that they are the reason or simply an outcome of disease pathology. The oxidative insult caused as a result of these free radicals is however deterred by the efficient antioxidant defense system equipped with several enzymatic and non-enzymatic antioxidants. However, this antioxidant defense system is overwhelmed during mounting to high elevation (Bailey and Davies 2001). Numerous investigations have documented increased markers of oxidative stress as a result of high altitude exposure (Vasankari et al. 1997; Chao et al. 1999; Pfeiffer et al. 1999; Bailey et al. 2001; Joanny et al. 2001). To support this, Bailey et al. (2001) have indicated marked rise in lipid peroxidation and intracellular myofiber proteins soon afterward rise to 5100 m height. These upsurges were predominantly noticeable in volunteers developing AMS. Additionally, studies have shown that individuals from higher elevations have lower GPX activity (Imai et al. 1995). Further, the activity and effectiveness of GPX depend on the fitness of the thiol system. Glutamylcysteinylglycine which is continually manufactured by the glutamyl cycle is one among the key thiol/antioxidant source of the cell. Exposure to higher elevations results in diminishment of reduced glutathione (GSH) concentrations and elevation in oxidized glutathione concentrations (Ilavazhagan et al. 2001; Joanny et al. 2001) indicating the diminution in antioxidant capacity. Apart from hypobaric hypoxia, additional environmental factors contributing to the cumulative load of oxidative stress at higher elevations include exposure to ultra violet radiations, cold, diet poor in antioxidants, etc. depicted in figure 1 (Bailey and Davies 2001). However, the injury caused due to hypoxia-induced oxidative stress at higher elevations can be lessened by an antioxidant intervention, thereby reducing the toll of HAS (Askew 2002).

12.5 Role of Antioxidant Interventions and Prophylactic Benefits in HAS

The scientific observations of a raised risk of ROS and free radical mediated oxidative insult at higher elevation have shown the way to the researchers to suggest nutritional antioxidant interventions such as ascorbic acid, beta-carotene, vitamin E, selenium, alpha-lipoic acid, etc. present in fruits and vegetables and herbal supplements rich in antioxidants like *Ginkgo biloba*, which may be advantageous in combating the problem of HAS (Bailey et al. 2001; Gertsch et al. 2002; Askew 2002; Moraga et al. 2007; Panossian et al. 2010; Talbot et al. 2011; Seupaul et al. 2012; Chiu et al. 2013; Ke et al. 2013; Heo et al. 2014; Ren et al. 2015). Several antioxidants and their concoction have been tested against HAS. Studies have obtained mixed results in relation to the effectiveness of antioxidants in averting HAS, some observed beneficial effects (Roncin et al. 1996; Bailey and Davies 2001; Ilavazhagan et al. 2001; Schmidt et al. 2002; Gertsch et al. 2002; Moraga et al. 2007; Lee et al. 2013a, b), whereas others did not report any benefit (Pfeiffer et al. 1999; Gertsch et al. 2004; Chow et al. 2005; Baillie et al. 2009; Ke et al. 2013; Chiu et al. 2013).

In this connection, herbal supplements, like *Ginkgo biloba*, possess powerful antioxidant effect and cause arterial vasodilation, indicative of a link with nitric oxide (NO) and potential in hemodynamic disorders reducing free radicals generation as a consequence of hypoxia (Kleijnen and Knipschild 1992). *Ginkgo biloba* is well recognized as a herbal supplement owing flavonoid-mediated antioxidant capacity that has been found to safeguard important processes and structures of the cell, for instance, Na/K-ATPase function, ATP generation by mitochondria, and lipid membranes from the onslaught of oxidative stress (Du et al. 1999; Pierre et al. 1999). Therefore, it has also been tested as a novel prophylactic instrument for the deterrence of AMS. Numerous scientific investigations have suggested the prophylactic use of *Ginkgo biloba* against AMS (Roncin et al. 1996; Gertsch et al. 2002; Moraga et al. 2007). Animal studies conducted on rat models have also revealed its efficacy in averting HAPE (Berg 2004). Studies have indicated that NO may be involved in the pathophysiology of AMS by facilitating hypoxia-incited cerebral vasodilation (Roach and Hackett 2001; Van Mil et al. 2002; Moraga et al. 2007) and *Ginkgo biloba* is suggested to act as an NO forager, thereby diminishing NO concentrations in the cell (Marcocci et al. 1994). Additionally, a research carried out by the group of Moraga et al. (2007) indicated the efficacy of *Ginkgo biloba* in moderating the occurrence of AMS and stimulates a rise in oxygen saturation when administered 24 h prior to the start of ascend as well as continually during ascend to higher altitudes in subjects with no prior experience of mountaineering. The diminution in NO generation as a result of the inhibition of the enzyme NO synthase facilitated by *Ginkgo biloba* could be the reason behind the decline in AMS symptoms, thus lessening cerebral perfusion and penetrability of the blood–brain barrier (Schilling and Wahl 1999). Moreover, *Ginkgo biloba* may also check the activity of the enzyme phosphodiesterase, consequently increasing the relaxation of parietal smooth muscles and causing vasodilation of parietal vessels which in line

enhances tissue perfusion and reduces local hypoxia (Marcocci et al. 1994). Additional probable modes of actions of *Ginkgo biloba* may comprise rise in endogenous antioxidants, diminution in free radical generation together with diminished lung leak during hypoxia (Louajri et al. 2001; Naik et al. 2006).

In contrast, many studies have not been able to show the prophylactic effect of ginkgo against AMS symptoms (Gertsch et al. 2004; Chow et al. 2005; Ke et al. 2013). In a randomized, double-blind, placebo-controlled study conducted by Gertsch et al. (2004) on 614 healthy volunteers receiving ginkgo, acetazolamide, acetazolamide and ginkgo in concoction, or placebo, did not report any significant effect of ginkgo in decreasing the count or austerity of AMS in comparison to placebo. Further, the concoction of acetazolamide and ginkgo resulted in a marginally significant diminution in the effectiveness of acetazolamide. The occurrence of AMS as documented by the researchers was 34% in control placebo group, 12% in acetazolamide, 35% for ginkgo, and 14% in ginkgo and acetazolamide concoction. Together, the fraction of patients with heightened austerity of AMS was found to be 18% for placebo, 3% for acetazolamide, 18% for ginkgo, and 7% for ginkgo and acetazolamide concoction. The authors anticipated the reason behind the failure of ginkgo as a prophylactic agent compared to preceding findings with positive effects to be its administration at the time of enrollment at a high baseline elevation contrasted with giving the medication at sea level prior to mounting. Additional explanations behind these differences could be the differences in experimental protocol and design; timing, duration and dosage administered; variation in altitude at which *Ginkgo biloba* is started; time of high altitude exposure along with quality and purity of *Ginkgo biloba*. In this line, Leadbetter et al. (2009) showed another cause for disparity to be the differences in the composition of the *Ginkgo biloba* extract. This group of researchers compared *Ginkgo biloba* extract from two varied sources and realized the difference in composition and their capacity to lessen the frequency and austerity of AMS. Zafren (2014) suggested the reason behind the differing outcomes reached in different investigations to the variance in constitution of Ginkgo since it lacks standard formulation, together with, the difference in its sources.

These conflicting evidences concerning the efficacy of *Ginkgo biloba* cloud our understanding. Recent reviews indicate the insufficiency of available data with regard to the effectiveness of *Ginkgo biloba* in safeguarding against AMS and thus more larger randomized controlled investigations are needed to fill the gaps (Tsai et al. 2018). With regard to the safety of *Ginkgo biloba*, the current scientific literature indicates that it is harmless, however, it is still not clear whether it bears the capacity to prevent AMS or not. Low dose of acetazolamide is presently the best prophylaxis against AMS. Given the composite nature and inconsistency of *Ginkgo biloba* extract, it is doubtful to be reliably active in averting AMS and hence cannot be suggested as a dependable prophylaxis for AMS (van Patot et al. 2009; Zafren 2014).

Another well-accepted phytoadaptogen employed against HAS is *Rhodiola* species. Genus *Rhodiola* belonging to the family Crassulaceae has been a treasured

medicinal plant for combating HAS in Asian and European countries for thousands of years (Panossian et al. 2010; Hung et al. 2011; Lee et al. 2013a). Globally over 90 species are available and they are well recognized for their great antioxidant activities. Different species possess different amounts of the bioactive elements and therefore differ in their therapeutic usage in the native areas. Among all the recognized *Rhodiola* species, *Rhodiola crenulate* (*R. crenulata*) has been utilized as an antidote for AMS in Tibet since prehistoric times (Lee et al. 2013a, b). This species of *Rhodiola* was found to display great antioxidant activity and alleviated hypobaric hypoxia-induced pulmonary edema in rodents (Lee et al. 2013a). According to latest findings, Na/K-ATPase plays a significant part in the clearance of alveolar fluid. Studies have revealed that the inhibition as well as the knockdown of Na/K-ATPase expression appreciably diminished the clearance of alveolar fluid in rodent models (Icard and Saumon 1999; Looney et al. 2005). Salidroside and tyrosol have been identified as the two bioactive constituents of *R. crenulata* possessing antioxidant, anti-fatigue, anti-inflammatory, and anti-depression properties. The probable mode of action behind the ability of *R. crenulata* in mitigating pulmonary edema in rodent models could be the inhibition of hypoxia-induced Na/K-ATPase endocytosis and preservation of the integrity of alveolar-capillary barrier and pulmonary sodium transport (Lee et al. 2013a). Salidroside and tyrosol are considered as the key bioactive ingredients responsible for the effectiveness of *Rhodiola* species. In this regard, Lee et al. (2013b) through their study confirmed the antioxidant capacity of *Rhodiola crenulata* extract and its bioactive compounds tyrosol and salidroside in the control of Na, K-ATPase endocytosis as well as ROS generation in reaction to hypoxia through similar mechanisms, thereby indicating the important part played by these compounds in the shielding effects of *Rhodiola crenulata* in averting oxidative stress-related illnesses. Other researches have also exhibited beneficial effects of *Rhodiola* in preventing HAS in animal as well as human models (Lee et al. 2013b). Contrary scientific evidences have also been reached which clouds the understanding regarding the ability and efficacy of *Radiola* species in combating HAS. In this connection, Chiu et al. (2013) conducted a randomized, double-blind, placebo-controlled, crossover trial in healthy adult subjects randomized to two treatment series with 800 mg *R. crenulata* extract purified from the rhizome or placebo every day for 1 week prior to mounting and 2 days in the course of climbing, before crossing over to the alternative treatment afterwards a 3 month wash-out period. The researchers did not report any significant change in terms of the occurrence of AMS (as described by a Lake Louise score $\geq$3, counting headache together with no less than one of the indications of nausea or vomiting, fatigue, dizziness, or difficulty sleeping) between the two treatment series, i.e. individuals taking *Rhodiola*-placebo and those taking placebo-*Rhodiola* (all 60.8%; adjusted odds ratio (AOR) = 1.02, 95% confidence interval (CI) = 0.69–1.52). The prevalence of severe AMS in *Rhodiola* extract vs. placebo set was found to be 35.3% vs. 29.4% (AOR = 1.42, 95% CI = 0.90–2.25), thus indicating the ineffectiveness of *Rhodiola* extract in lessening the occurrence or severity of AMS.

Coca leaf, coca tea, and other coca-derivatives have been traditionally utilized by locals for preventing AMS (Salazar et al. 2012; Luks et al. 2014; Zafren 2014). According to anecdotal reports, coca-derivatives are nowadays also being employed by the mountaineers in Asian and African countries for the same (Luks et al. 2014). However, there is a shortage of scientific data proving its efficacy against AMS (Luks et al. 2010; Zafren 2014). In fact, mechanisms have been proposed through which it may raise the risk of AMS. The influence of catecholamine gush in the cardiovascular system may expound part of the pathophysiology (Salazar et al. 2012).

Antioxidants such as ascorbic acid possesses the ability to counteract aqueous superoxide, peroxyl, and alkoxyl radicals and can indirectly produce alpha-tocopherol (Bendich et al. 1986). The fat-soluble alpha-tocopherol is perhaps the most significant chain-breaking antioxidant having the capacity to forage peroxyl radicals. At the same time, alpha-lipoic acid which is both water and lipid soluble possesses the ability to reduce hydroxyl, peroxyl, ascorbyl, and chromanoxyl radicals. It also owns the power to increase the intracellular concentration of glutathione and restore ascorbate and alpha-tocopherol (Packer et al. 1997). Therefore, it is thought as a vital patron to the antioxidant defense mechanism. Bailey and Davies (2001) conducted a randomized double-blind placebo-controlled trial to examine the effectiveness of the concoction of water and lipid soluble antioxidant vitamins. The combination comprised of L-ascorbic acid, dl alpha-tocopherol acetate, together with alpha-lipoic acid, chiefly picked because of their capacity to check lipid peroxidation. The study reflected the physiological effectiveness of chronic antioxidant supplementation by reducing the prevalence as well as the severity of AMS, betterment in resting arterial oxygen saturation, and rise in caloric intake and further suggesting the influential part of oxygen free radicals in the pathophysiology. The authors attributed the decline in AMS prevalence to the diminution in the free radical facilitated cerebral edema as a result of the enhancement in vascular integrity of the BBB. This mode of action could also elucidate the findings of another placebo-controlled research which revealed relatively lower AMS scores after the treatment with *Ginkgo biloba* extract (Egb 761) (Roncin et al. 1996). An antioxidant concoction comprising vitamin E, beta-carotene, ascorbic acid, selenium, alpha-lipoic acid, N-acetyl 1-cysteine, catechin, lutein, and lycopene was also found to be effective in decreasing the oxidative injury caused due to high elevation (Schmidt et al. 2002). Findings from animal studies also stand in support of the potential of antioxidants in effectively reducing the cerebral/pulmonary edema induced experimentally in animal models (Armstead et al. 1992). Oral vitamin E supplementation in rats exposed to hypoxic exposure of 7576 m remarkably decreased the lipid peroxidation (Ilavazhagan et al. 2001). Baillie et al. (2009) on the contrary did not report any benefit of antioxidant intervention employing a concoction of L-ascorbic acid, alpha-tocopherol acetate and alpha-lipoic acid against diminishing the occurrence or austerity of AMS. Pfeiffer et al. (1999) also did not report any benefit from a mixture of antioxidants containing beta-carotene, vitamin E, vitamin C, selenium, and zinc in averting oxidative injury to the biomolecules.

Despite the bulk of scientific investigations exploring the beneficial effects as well as the effectiveness of various antioxidants against HAS in different experimental models, the present state of evidence is unable to substantiate or repudiate the use of any antioxidant or a concoction of antioxidant as a definite prophylactic agent. Additionally, an inadequate number of investigations support the effectiveness of antioxidant supplements at higher elevations in easing the difficulty of HAS. Furthermore, there is a dearth of standardized studies in this regard. The variations in the current investigations with regard to experimental design considerations like altitude reached, rate of ascension, degree of pre-acclimatization; antioxidant employed, purity and quality of the antioxidant, the timing, duration, pretreatment, and dosage administered; individual susceptibility, small sample size, etc. cloud the understanding with respect to their efficacy in bringing out the desirable effects. Another challenge in this regard is to identify the appropriate dosage, timing or combination of antioxidants which will regulate the induced oxidative stress without any deleterious effects on the body and therefore help the body to ease out the symptoms of HAS. Therefore, given the undesirable side effects associated with pharmacological interventions, non-pharmacological antioxidant interventions which are relatively safer and with minimal side effects need more attention in order to combat this challenge of HAS.

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