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Altitude-induced health challenges: understanding medicine and potential dietary mitigation strategies

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ABSTRACT

The number of people travelling to high-altitude areas or participating in mountain sports is increasing. For individuals visiting such terrains for the first time, the lack of adaptation to the hypobaric hypoxic environment can lead to the deterioration of gastrointestinal function and barriers. In more severe cases, this lack of acclimatisation may lead to acute high-altitude illness. At present, the prevention and treatment of these issues primarily revolve around strategies such as descending to lower altitudes, oxygen supplementation, and medication. However, the available intervention measures to prevent health problems resulting from high-altitude environments remain limited. In this review, we discuss common altitude-related illnesses, including gastrointestinal problems. Moreover, we explore the potential of commonly used medications and dietary supplements in alleviating altitude-related issues. This review can provide a basis for future research on modulating the gut microbiota for mitigating high-altitude illness.

1. Introduction

High-altitude regions are characterised by extreme environmental stress, typically accompanied by hypobaric hypoxia and severe cold. In addition to conditions like acute mountain sickness, high-altitude pulmonary oedema, and cerebral oedema, exposure to high altitudes can lead to pathological issues, such as gastrointestinal haemorrhaging, diarrhoea, vomiting, and upper gastrointestinal haemorrhaging, particularly at altitudes exceeding 5 000 m[1]. Therefore, the impact of high-altitude environments on the human gastrointestinal tract cannot be ignored.

Among the various environments within the human body, the gastrointestinal tract provides a unique ecosystem that can support a rich and diverse microbial community known as the gut microbiota[2]. Compared with the human genome, the genome of this microbiota is believed to be 100 times larger[3]. In many instances, a mutually advantageous symbiotic relationship exists between the host and gut microbiota, where the host provides essential nutrients for the microbes to thrive, while the gut microbiota, to a certain extent, can regulate several physiological functions of the host. For example, the gut microbiota can promote the formation and development of the intestinal immune system[4], strengthen the intestinal barrier[5], and

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regulate the activities of the intestinal tract and central nervous system[6]. Notably, alterations or perturbations to the gastrointestinal milieu can result in detrimental changes in the gut microbiota, termed intestinal dysbiosis. This may lead to physiological decline of the gastrointestinal tract as well as other parts of the body, manifesting as, for example, increased permeability, inflammation of the gastrointestinal tract[7], and higher susceptibility to infectious diseases[8]. In addition, dysbiosis of the gut microbiota has been associated with various chronic diseases, such as obesity[9], cardiovascular disease[10], and colon cancer[11]. Understanding the relationship between intestinal flora and altitude-related diseases may provide a non-pharmacological approach for preventing altitude sickness. This paper reviews the links between altitude-induced changes in the gut and the development of disease, as well as the prevailing pharmacological responses to high-altitude illness, and explores the possibility of modification through dietary means.

2. High-altitude-induced health conditions

The human body exhibits a certain degree of adaptability to the hypobaric hypoxic environment induced by ascending to higher altitudes; however, this acclimatisation typically requires some time. Rapid ascent to high altitudes, exceeding the capacity of the body for acute adaptation, can lead to altitude sickness. Altitude sickness is characterised by a series of syndromes primarily attributable to hypoxia[12], and can be categorised as acute mountain sickness (AMS) and chronic mountain sickness (CMS). AMS can manifest as acute high-altitude reaction (AHAR), high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE), which are often interrelated and can co-occur[13]. With prolonged exposure, AMS can progress to CMS[14], characterised mainly by high-altitude polycythaemia (HAPC) and severe hypoxaemia (SH) (Fig. 1). AMS can occur at any time within hours to 5 days after reaching a certain altitude, and its severity can vary. In severe cases, AMS may be life-

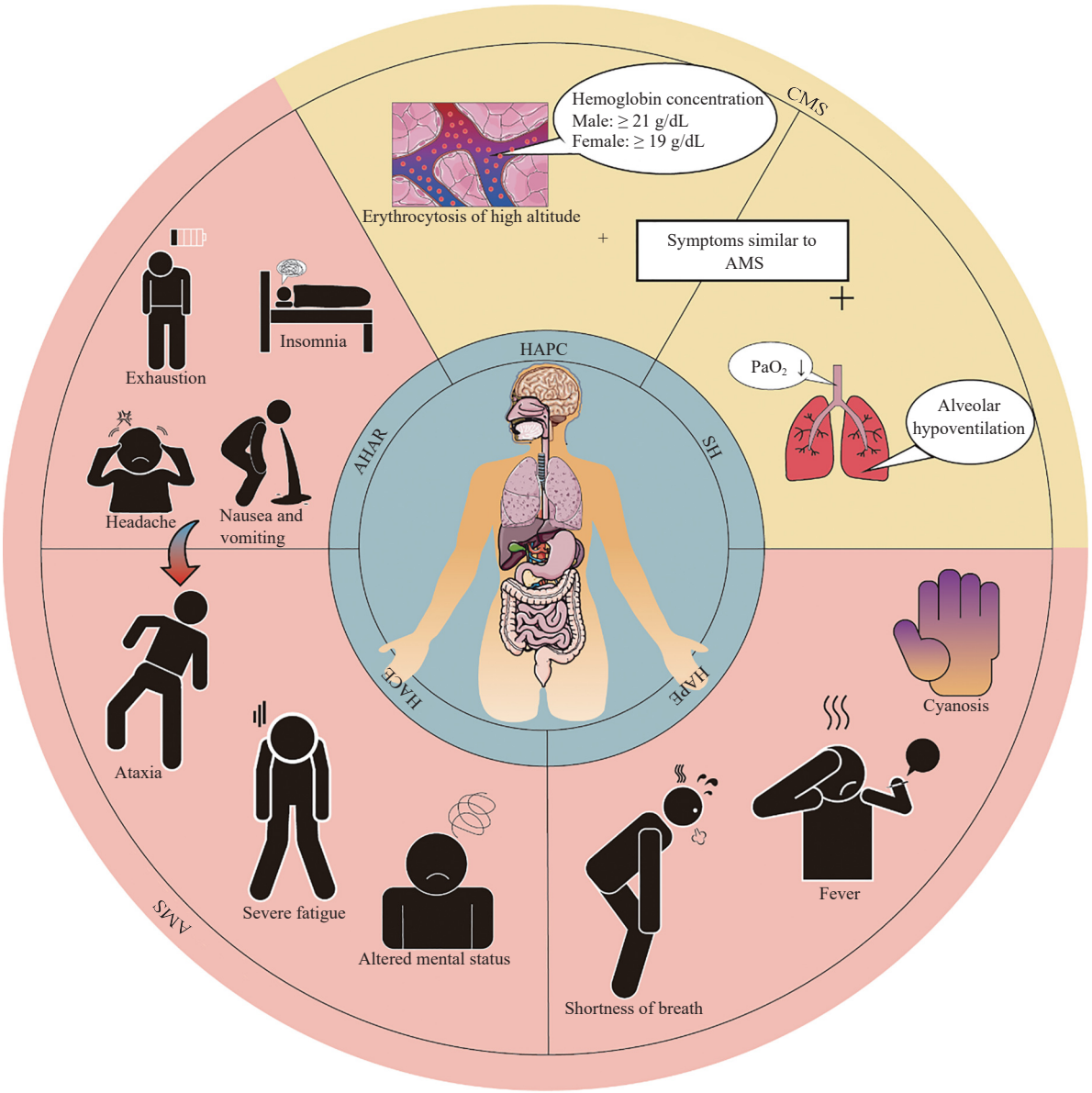

Fig. 1 Forms of altitude sickness and related symptoms. PaO_2, Partial pressure of oxygen.

threatening. Although the pathophysiology of these conditions is well understood, research on prevention and treatment methods remains limited.

2.1 AMS

AMS commonly occurs in individuals when they rapidly ascend to altitudes greater than 2 500 m. If individuals reach an altitude of around 4 000 m within a few hours, only a few will remain symptom-free. Mild symptoms of AMS include dizziness, headaches, sleep disturbances, and gastrointestinal discomfort[15]. According to most research, the pathophysiology of AMS is primarily attributable to hypoxia. Hypoxia can lead to problems such as fluid retention, increased vascular permeability, or increased cerebral blood flow, all of which may contribute to the development of AMS. The Lake Louise Scoring System is commonly used to assess AMS and categorise it into mild, moderate, or severe[16].

2.1.1 AHAR

AHAR is characterised by non-specific symptoms and can affect individuals lacking acclimatisation to altitudes exceeding 2 500 m or those ascending to new high-altitude environments. When appropriate measures are taken, these symptoms typically resolve on their own. According to certain viewpoints, AMS represents a mild form of HACE, sharing similar pathophysiological mechanisms[17]. Due to its non-specific clinical symptoms, AHAR can be challenging to diagnose, with both males and females being equally susceptible.

2.1.2 HACE

Symptoms including nausea, headache, lack of response to common anti-nausea and pain-relief medications, and increasing fatigue can indicate the progression of AHAR to HACE[18]. Typical manifestations of HACE include altered mental status and ataxia (loss of control over bodily movements), often accompanied by other forms of high-altitude illness[19]. Early symptoms of HACE can include drowsiness and behavioural changes, with approximately 40%–60% of patients developing ataxia. Patients may also experience gastrointestinal symptoms similar to those of AMS, such as anorexia and vomiting[20]. According to the 2019 updated Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness, HACE is defined as the worsening of AMS with neurological findings such as ataxia, severe fatigue, and altered mental status[21]. Differential diagnoses for HACE primarily include hypoglycaemia, hyponatraemia, hypothermia, migraine, dehydration, carbon monoxide poisoning, drug and alcohol intoxication, stroke, central nervous system space-occupying lesions, and intracranial bleeding.

2.1.3 HAPE

HAPE is a potentially fatal non-cardiogenic pulmonary oedema resulting from severe hypoxia-induced pulmonary vasoconstriction, excessive pulmonary artery pressure, and elevated capillary pressure. It represents the deadliest form of high-altitude illness. Altitude, ascent rate, and an individual's inherent susceptibility are the principal factors governing the occurrence of HAPE. It usually manifests swiftly, within the initial 2–5 days, as individuals ascend to elevations exceeding 2 500–3 000 m, and is less frequently observed below this altitude or after acclimatisation to a specific altitude for 1 week[22]. Initial indications of HAPE encompass diminished exercise tolerance and a non-productive cough, while late-stage symptoms include a bubbling sensation in the chest and the production of white or pink frothy sputum. Clinical features include cyanosis, rapid heart rate, rapid breathing, and a mild increase in body temperature, generally not exceeding 38.5 °C[23]. In an examination of HAPE patients at an altitude of 4 559 m, arterial blood oxygen saturation and oxygen partial pressure were noted to be significantly lower in the patient group than in the healthy control group. Oxygen saturation in the healthy control group ranged from 70% to 85%, with oxygen partial pressure at 40–45 mmHg. In contrast, in the patient group, oxygen saturation was less than 50%, with the average oxygen partial pressure being approximately 20 mmHg. Studies involving right heart catheterisation before treatment or descent in HAPE patients have indicated an average pulmonary artery pressure range of 60–80 mmHg, with the values for some individuals reaching as high as 117 mmHg. Chest computed tomography scans of individuals with HAPE revealed a sporadic and nodular pattern of oedematous areas[24]. In general, individuals with a prior occurrence of HAPE at particular elevations exhibit an increased risk of HAPE recurrence when re-exposed to similar altitudes, indicating potential susceptibility to HAPE. In untreated cases of HAPE, the estimated mortality rate is approximately 50%[25], highlighting its extreme lethality.

2.2 CMS

CMS, also known as Monge's disease, was first discovered by Peruvian physician Carlos Monge. Presently, this condition is characterised as a clinical syndrome that manifests in individuals residing at high altitudes (above 2 500 m) for extended periods[26]. When individuals migrate from lowland to high-altitude regions, they typically experience AMS, which, with prolonged exposure to high altitudes, may progress into CMS[14]. The clinical characteristics of CMS include polycythaemia and hypoxaemia, typically accompanied by pulmonary artery hypertension. The clinical symptoms of CMS gradually ameliorate upon descent to lower altitudes but resurface upon returning to high-altitude regions. The severity of CMS is typically assessed using the internationally recognised Qinghai Score[14]. The notion that a reduction in high-altitude adaptation contributes to the onset of idiopathic central hypoventilation has gained acceptance as a mechanism underlying CMS development. However, the presence of related diseases can also contribute to the occurrence of CMS. Notably, CMS does not occur in isolation; it often co-occurs with various organ-related conditions. In addition to its impact on the respiratory system, CMS can affect the circulatory system and even the digestive system[27].

2.2.1 HAPC

CMS was originally described as HAPC in Andean highland residents[28]. It is defined by a haemoglobin (Hb) concentration of ≥ 21 g/dL for males and ≥ 19 g/dL for females. Approximately 5%–10% of the population residing in high-altitude regions globally is believed to be susceptible to HAPC, and the prevalence increases with age[29].

In a study examining the association between HAPC and CMS, data collected from residents of La Rinconada, the world's highest city at an altitude of 5 100–5 300 m, revealed that the main contributing factors to HAPC were age and gender[30]. Subsequent research confirmed that oestrogen plays a significant role in regulating red blood cell production, especially under conditions of chronic hypoxia. This explains the lower prevalence of CMS in females and increased prevalence in postmenopausal women[31]. In high-altitude environments, increased red blood cell count is regarded as a compensatory haematological reaction to oxygen deficiency. Typically, a dynamic balance exists between the proliferation and apoptosis of red blood cells, and a decrease in red blood cell apoptosis may be one of the reasons for the excessive buildup of red blood cells[32]. In an early population-based study, the expression of hypoxia-inducible factor 2α (HIF-2α) was observed to be more pronounced in the bone marrow of patients with CMS than in the control group. Additionally, erythropoietin (EPO) concentrations in the bone marrow were strongly correlated with the concentrations of HIF-2α. Furthermore, the study revealed an increased microvessel density in the bone marrow of CMS patients, which was also significantly correlated with Hb levels. These findings suggest that the HIF-2α/EPO pathway within the bone marrow may regulate HAPC and angiogenesis. Additionally, the authors speculated that hypoxia-triggered angiogenesis may result in alterations in the structure and function of the bone marrow, potentially contributing to the development of CMS[33]. A subsequent study by this team indicated that upregulation of the HIF-2α/EPO pathway can lead to excessive erythrocytosis, and the DNA methyltransferase (DNMT) inhibitor 5-azacytidine can reduce red cell lineage proliferation by demethylating the von Hippel-Lindau (VHL) promoter in the bone marrow[34]. Another group of researchers found that overexpression of the endothelial PAS domain-containing protein 1 (*EPAS1*) gene in the bone marrow may promote erythrocytosis, further contributing to HAPC[35]. Overall, these findings suggest that changes within the bone marrow play a pivotal role in the onset of HAPC.

2.2.2 SH

Loss of acclimatisation to high altitudes (> 2 500 m) results in SH and polycythaemia. Hypoxaemia worsens with increased exposure to high-altitude environments. To adapt to hypoxic conditions, pulmonary blood vessels constrict to reduce blood flow and match ventilation to alleviate hypoxaemia[36]. However, persistent hypoxic pulmonary vasoconstriction can progress to pulmonary hypertension or pulmonary heart disease[37]. Recent studies have indicated that individuals with prolonged exposure to hypobaric hypoxic environments experience more severe nocturnal hypoxaemia and higher nighttime blood pressure variability[38]. Current research primarily views hypoxaemia as a cardiovascular change accompanying the development of CMS, and research in this domain is limited. Focusing on the alleviation of hypoxaemia may offer novel perspectives for CMS treatment.

3. Gastrointestinal problems caused by high altitude

3.1 Intestinal barrier damage

Numerous investigations have demonstrated that exposure to elevated altitudes can degrade the integrity of the intestinal barrier, a condition primarily characterised by increased intestinal permeability, villous damage, and inflammation (Fig. 2). In a study exploring the influence of the gut microbiota and host response to increased altitude, 17 healthy males resided at sea level for three weeks before spending an additional three weeks at an altitude of 4 300 m, during which they controlled their diet and lifestyle. The assessment of intestinal permeability involved the quantification of sugar substitute excretion in urine. The results showed that the excretion of lactulose and mannitol at high altitudes was limited compared with that at sea level, and the ratio of lactulose to mannitol excretion increased by approximately 70%, indicating an increase in small-intestine permeability[39]. Additionally, this research group observed a direct correlation between gut microbiota diversity and gastrointestinal permeability[40]. In a study involving male Wistar rats, a significant deterioration of intestinal morphological parameters was found in rats at altitudes of 3 842 and 4 767 m. Furthermore, the high-altitude group exhibited higher levels of HIF-1α and inducible nitric oxide synthase (iNOS), indicating that the expression of HIF-1α and iNOS significantly increased with exposure to low pressure and low oxygen, potentially contributing to intestinal mucosal damage[41]. In another study concerning the impacts of acute hypobaric hypoxia on gastrointestinal function at an altitude of 7 620 m, Sprague-Dawley (SD) rats were divided into control and exposure groups at different times. The exposure groups exhibited varying degrees of intestinal mucosal injury, characterised primarily by increased mucosal permeability, villous rupture, and upregulation of secretory immunoglobulin A (sIgA), proinflammatory cytokines, and proinflammatory markers[42]. By exposing male SD rats to a simulated hypobaric hypoxic environment at 4 000 m for 3 days, a model of intestinal barrier damage was established. After 3 days of exposure, the rats showed thinning of the intestinal epithelial mucosa; significantly reduced villous height, surface area, and mucosal thickness; infiltration of inflammatory cells into the lamina propria and exudation of red blood cells. These findings confirmed that a hypobaric hypoxic environment can compromise the integrity of the intestinal barrier[43].

3.2 Mucosal immune changes

The mucosal immune system represents a segment of the adaptive immune response that is particularly vulnerable to the presence of invasive pathogens and infections. Within the gastrointestinal tract, lymphocytes lining the mucosa play a significant role. This system, known as gut-associated lymphoid tissue (GALT) [44], encompasses various lymphoid tissues, including Peyer's patches in the small intestine, as well as numerous isolated lymphoid follicles. Peyer's patches serve as specialised sites for initiating and propagating immune responses. M cells are specialised epithelial cells found in the intestinal lumen, which can transport antigens to immune-initiating sites[45]. Due to the unique characteristics of M cells, they have attracted significant research interest for the development and enhancement of mucosal immunity.

In an animal experiment, Wistar rats were exposed to a hypobaric chamber at an altitude of 4 767 m. The rats subjected to high-altitude conditions exhibited intestinal damage, with the appearance of double-membrane structures resembling autophagosomes in intestinal epithelial cells after 6 h of exposure, which peaked at 24 h[46]. In

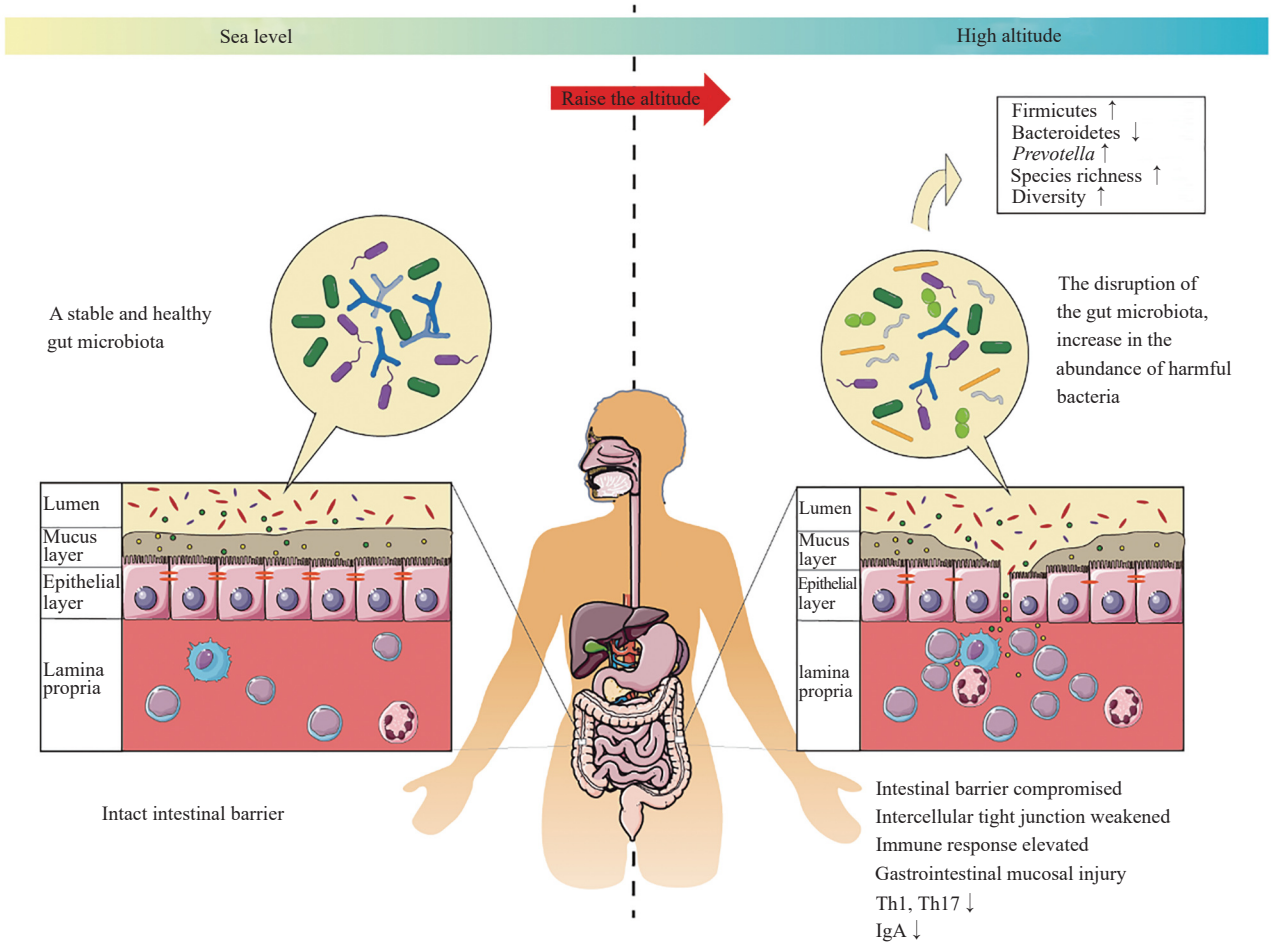

Fig. 2 Gastrointestinal problems caused by high altitude. IgA, immunoglobulin A; Th, T helper.

another experiment, experimental colitis was induced in mice by administering *Citrobacter* through gavage in both normoxic and hypoxic environments for 2 weeks. The results showed a significant decrease in body weight in the hypoxic environment, an increase in pathogens in the faeces, and more severe pathological damage to the colonic tissue. Additionally, the percentages of Th1 and Th17 cells significantly decreased, affirming that reduced oxygen exposure substantially intensified the manifestations and pathological harm in mice, potentially affecting their immune functionality[47]. In a study involving mountaineers, arterial oxygen saturation (SaO_2) values were measured at three distinct altitudes. As expected, the SaO_2 levels were significantly lower at high altitudes than at low altitudes. Furthermore, on the second and fourth days, 28% and 61% of individuals, respectively, exhibited peptic mucosal lesions during endoscopy. This indicates that exposure to elevated altitudes may induce mucosal injuries, even in healthy individuals[48]. Additionally, an earlier study demonstrated that hypobaric hypoxic conditions induce a more pronounced immune stress response, leading to reduced levels of secretory immunoglobulin A (sIgA) in saliva. Even after a 2-week recovery period, the sIgA levels did not return to normal. This indicates that hypoxia affects the mucosal immune system of human subjects[49]. Identifying strategies to mitigate changes in mucosal immunity caused by low-pressure, low-oxygen conditions to prevent injury may be a feasible direction for future research.

3.3 *Gut microbiota alteration*

Different altitudes are associated with different atmospheric oxygen partial pressures, resulting in diverse physiological adaptations associated with hypoxic stress in animals. Several studies have profiled the intestinal microbiota of mammals residing at varying elevations. In a 2017 study focused on the influence of altitude and geography on the gut microbiota of Tibetan populations, researchers analysed the faecal microbiota of 208 Tibetans living at altitudes ranging from 2 800 to 4 500 m through genetic sequencing. The results showed that with increasing altitude, both the diversity and richness of the gut microbiota significantly increased. At higher altitudes, Firmicutes and Actinobacteria were more abundant, while at lower altitudes, Bacteroidetes was more abundant. Additionally, the abundance of the *Bifidobacterium* genus in the gut of populations at higher altitudes was significantly higher than that in populations at lower altitudes[50]. In a similar experiment conducted in 2016, it was found that Han Chinese individuals who had migrated to high-altitude regions exhibited a higher presence of the genera *γ*-Proteobacteria and *Escherichia-Shigella* in their gut microbiota[51]. In a study examining the correlation between the gut microbiota and altitudinal variations in wild house mice, researchers performed DNA extraction and 16S rRNA sequencing of distal cecum samples from 10 house mouse populations totalling 92 house mice from two vertical sample zones in

Ecuador and Bolivia-Brazil. The results showed a trend of greater microbial richness at higher altitudes, although it was not statistically significant. However, a noteworthy positive association was observed between the phylogenetic diversity of Bacteroidetes and altitude[52]. The relative abundance of *Prevotella* significantly increased at altitudes above 2 000 m in both transects. This pattern is similar to that observed in populations of pikas (small mammals related to rabbits) at altitudes ranging from 1 000 to 4 331 m[53] and consistent with observations in humans, as mentioned earlier. In an experimental study examining the influence of altitude on the gut microbiota composition of European mouflon and ibex, the high-altitude cohort was noted to exhibit increased abundance of Firmicutes and decreased abundance of Bacteroidetes compared with the low-altitude group[54]. This distribution pattern is similar to that observed in the gut microbiota of Tibetan human populations. An increased Firmicutes to Bacteroidetes ratio is linked to enhanced host energy absorption. A recent study has demonstrated that hypoxic environments exert rapid and long-lasting effects on the gut microbiota and blood glucose levels in humans[55].

For individuals travelling from low- to high-altitude areas, the gut microbiota is minimally influenced by diet. The decrease in the abundance of several genera, including *Lactobacillus* and *Lactococcus*, is primarily related to the time spent at high altitudes and is not significantly affected by dietary changes. Additionally, individuals with a higher abundance of *Prevotella* at low altitudes are more susceptible to AMS upon ascent to high altitudes[39]. Even after only 6 days of travelling on the Tibetan plateau, the diversity of gut microorganisms in Han Chinese individuals was noted to be significantly decreased. This change persisted even after extended residence at high altitudes, and the diversity did not fully return to normal levels upon returning to lowland areas, indicating the long-lasting and profound impact of high-altitude environments on the host gut microbiota[55]. Similar findings have been observed in experimental rodents, where researchers noted a strong and persistent impact of hypoxia on the β-diversity of the gut microbiota in rats[56].

These existing reports demonstrate that high-altitude environments considerably affect both the diversity and composition of the gut microbiota of the host. Furthermore, multiple experiments have indicated that this effect is primarily related to the altitude at which the host resides and is not significantly influenced by dietary factors. Given these observations, the potential of modulating the gut microbiota to alleviate or prevent health issues arising from high-altitude conditions remains a promising subject for further investigation.

4. Strategies for adaptation to high-altitude illnesses

4.1 AMS management strategies

4.1.1 Preventive measures

Rather than treating high-altitude illnesses, preventive measures are often considered the first step. Gradual ascent is the most effective prevention method because the primary risk factors for high-altitude illnesses are altitude and ascent rate. Gradual ascent allows individuals more time to adapt to the changes in altitude[21]. Research has shown that staying at 2 200 m for 6 days before ascending to 4 300 m can reduce the probability and severity of AMS[57]. A report from 2019 indicates that the mechanisms underlying the impact of acclimatisation strategies on alleviating AMS are not yet fully understood. However, based on research results and clinical experience, gradual altitude gain remains the preferable choice for preventing AMS[58].

Acetazolamide and dexamethasone are also used to prevent HACE. However, dexamethasone use is associated with several side effects. In particular, when used for more than 2 weeks, dexamethasone may lead to weight gain, high blood pressure, acne, dermatitis, vascular and connective tissue thinning, avascular necrosis of bones, gastrointestinal ulcers, and long-term mental disturbances. Additionally, the side effects associated with dexamethasone use may overlap with the symptoms of AMS and HACE, rendering diagnosis highly challenging[59]. Therefore, acetazolamide has become a more common choice for many climbers, although the potential side effects of long-term medication use must not be overlooked.

The simplest method for preventing HAPE is to ascend to higher altitudes in a gradual manner. Research has shown that a rapid ascent to high altitudes can lead to an increase in pulmonary artery pressure, with an inverse relationship observed between arterial oxygen partial pressure and oxygen saturation. In contrast, staged increases in altitude result in a considerably smaller rise in pulmonary artery pressure, and this increase is not correlated with oxygen parameters. This observation demonstrates the preventive benefits of gradual or staged ascents to higher altitudes. Although the sample size of reported experiments has typically been small, gradual altitude ascent still appears to be the most efficacious preventive approach. This approach is not limited to HAPE but also exhibits some efficacy in preventing other high-altitude illnesses.

Some studies have also shown that ibuprofen may be a potentially viable option for preventing AMS. Although its effectiveness may not be as pronounced as acetazolamide, considering the availability and tolerability of the medication, consuming ibuprofen (600 mg, 3 times a day) may be a reasonable approach.

Despite the emergence of alternative medications for preventing AMS, research in this area remains limited, and their feasibility requires further investigation. Additionally, considering the potential side effects of medications like dexamethasone, such as exacerbated gastrointestinal bleeding[60], exploring non-pharmacological methods for preventing or treating AMS is also a promising direction for future research.

4.1.2 Clinical treatment

Once a high-altitude illness is diagnosed, the priority should be to descend to a lower altitude. Descending by 300–1 000 m is the most effective treatment for the majority of high-altitude illnesses. The actual descent required may vary from person to person, but unless environmental factors interfere, individuals should descend until their symptoms disappear[20-21].

Medicines such as acetazolamide and dexamethasone are also very commonly used in the prevention and treatment of altitude illnesses (Table 1). Acetazolamide is a traditional diuretic used clinically for oedema treatment and represents the primary medication for preventing AMS and HACE. Research has shown that acetazolamide can effectively prevent AMS. A meta-analysis demonstrated that all doses of acetazolamide (250, 500, 750 mg/day) are efficient in preventing AMS, with 250 mg/day being the minimum effective dose[61]. In a review involving 16 trials with 2 301

participants, acetazolamide reduced the risk of AMS by nearly half[62]. Although a recent study found that a dose of 125 mg/day was no less effective than 250 mg/day, it may be because the study population had a lower incidence of AMS, limiting the ability to distinguish the effects of lower doses[63]. Current recommendations suggest consuming acetazolamide one day before ascending to a higher altitude, at a dose of 125 mg twice a day, and continuing until descending to a lower altitude.

Table 1
Effectiveness of mainstream medicine in the prevention or treatment of altitude sickness.

Treatment	Altitude	Usage	Dose	Result	Reference
Acetazolamide	Rapid ascent to 4 300 m from 2 000 m over 2 h	Prophylactic use	250 mg/day, 125 mg twice a day (bid)	Lower incidence of AMS Placebo: 45% Acetazolamide: 14%	[92]
Acetazolamide	From 2 100 m to 4 200 m after a 5- to 10-day ascent	Clinical use	250 mg orally	The alveolar to arterial oxygen pressure difference: Acetazolamide: (−0.8 ± 1.2) mmHg Placebo: (3.3 ± 2.3) mmHg	[93]
Acetazolamide	Ascent from 2 860 m to 4 800 m followed by an appropriate ascent profile	Clinical use	125 mg bid	No use for HAPE	[94]
Acetazolamide ibuprofen	Rapid ascent from 1 240 m to 3 788 m over 2 h	Prophylactic use	Acetazolamide: 125 mg bid Ibuprofen: 600 mg three times a day (tid)	The incidence of AMS Acetazolamide: 62.2% Ibuprofen: 51.1%	[95]
Acetazolamide, budesonide	Ascent from 1 240 m to 3 810 m over 4 h	The first dose was taken before ascent and the second dose was taken about 8 h after starting ascent	Acetazolamide: 125 mg bid Budesonide: 180 μg bid	The incidence of AMS Acetazolamide: 43% Budesonide: 73% Placebo: 63%	[96]
Acetazolamide	Ascent from 3 440 m to 4 928 m over 6 days	Prophylactic use	125, 375 mg bid	The incidence of AMS 125 mg bid: 24% 375 mg bid: 21% Placebo: 46%	[97]
Acetazolamide	Ascent from 1 400 m to 5 200 m	Prophylactic use	62.5, 125 mg bid	The incidence of AMS 62.5 mg bid: 55.3% 125 mg bid: 60%	[63]
Dexamethasone	Ascent from 2 500 m to 4 800 m	Clinical use	4 mg each time	Mean reaction time: 2 500 m: (1.20 ± 0.36) s 4 800 m: (1.40 ± 0.37) s Dexamethasone: (1.26 ± 0.32) s	[98]
Dexamethasone	Ascent from < 800 m to 3 100 m	Prophylactic use	8 mg/day	The incidence of AMS/ARAHE Dexamethasone: 22% Placebo: 24% PaO_2 Dexamethasone: 9.6 kPa Placebo: 10.6 kPa	[99]
Acetazolamide, dexamethasone	Ascent from 3 800 m to 5 790 m	Prophylactic use		The incidence of AMS Acetazolamide: 72% Non-acetazolamide: 70% Individuals reported an improvement in AMS symptoms 12 h after dexamethasone treatment	[100]
Dexamethasone	Ascent from 490 m to 4 559 m	Before ascent at 4 559 m, or started on day 2 at 4 559 m only	8 mg bid	Dexamethasone taken before ascent prevents severe hypoxemia and sleep disturbances, while dexamethasone taken 24 h after arrival at 4 559 m increases oxygenation and deep sleep	[101]
Nifedipine	Ascent from 490 m to 4 559 m	Clinical use	20 mg/(6 h)	Symptoms like shortness of breath and/or chest pressure were relieved within 1 h Pulmonary artery pressure (mmHg) Controls: 63.5 ± 14.9 Pretreatment: 133.7 ± 19.8 Nifedipine treatment: 1 h: 73.7 ± 13.8 14.6 h: 58.2 ± 5.0 34.7 h: 65.5 ± 11.7	[64]
Nifedipine	First stage: 6 days, 2 700−3 600 m Second stage: 4 days, 3 600 −4 500 m	Clinical use	30 mg bid	No additional benefit in the resolution of HAPE	[65]
Tadalafil, dexamethasone	Ascent from 490 m within 24 h and stay for 2 nights at 4 599 m	Prophylactic use	Tadalafil: 10 mg bid Dexamethasone: 8 mg bid	The incidence of HAPE Placebo: 7/9 Tadalafil: 1/8 Dexamethasone: 0/10 The incidence of AMS Placebo: 8/9 Tadalafil: 7/10 Dexamethasone: 3/10	[67]

Table 1 (*Continued*)

Treatment	Altitude	Usage	Dose	Result	Reference
Dexamethasone	Ascent from 490 m to 4 559 m over 24 h	Prophylactic use	8 mg bid	Maximal oxygen consumption (VO_2 max) Control: (61 ± 6)% Dexamethasone: (70 ± 9)% O_2 pulse (VO_2/heart rate) Control: (68 ± 7)% Dexamethasone: (77 ± 11)%	[68]
Acetazolamide, *N*-acetylcysteine	CMS at 4 380 m	Clinical use	Acetazolamide: 250 mg/day *N*-acetylcysteine: 1 200 mg/day	CMS score: Acetazolamide: fell by 34.9% *N*-Acetylcysteine: fell by 34.0%	[70]
Fe(III)-Hydroxide sucrose	At 4 340 m	Clinical use	200 mg intravenous infusions	PASP: Reduced by 6 mmHg	[71]

Note: ARAHE, altitude-related adverse health effects; PASP, pulmonary artery systolic pressure.

Dexamethasone is another medicine that can serve as an alternative to acetazolamide, especially for patients who are unable to endure acetazolamide. The typical dosage for dexamethasone is 2 mg orally every 6 h or 4 mg twice a day. It is recommended to start taking dexamethasone on the first day of ascent to higher altitudes or when rapidly ascending to higher altitudes[20]. Some experts even suggest a combination of acetazolamide and dexamethasone for individuals, such as military personnel or rescue workers, who must rapidly ascend to altitudes above 3 500 m[21].

Nifedipine, a type of calcium channel blocker, is an effective medication for preventing HAPE. In early experiments, the administration of nifedipine was observed to markedly lower pulmonary artery pressure among patients, with no significant side effects[64]. This suggests that nifedipine likely prevents HAPE by lowering the pulmonary artery pressure. However, most of these experiments were conducted in the previous century. In 2012, a study involving 110 Indian soldiers with HAPE found that nifedipine, when used alongside descending to lower altitudes and receiving supplemental oxygen, did not have an additional effect in relieving HAPE[65]. Therefore, the actual effectiveness of nifedipine remains debatable. Tadalafil has also been reported to have a preventive effect on HAPE but not on AMS. In some susceptible individuals, tadalafil may even exacerbate AMS, although the exact mechanism remains unclear[66]. Some evidence suggests that taking 8 mg of dexamethasone every 12 h has a certain preventive effect on HAPE. However, the small sample sizes in these experiments limit the generalisability of these findings[67]. In another study, dexamethasone was found to significantly enhance the maximum oxygen consumption. Individuals taking dexamethasone exhibited an 18% higher maximum oxygen consumption compared with the control group. Such an increase can enhance an individual's ability to uptake oxygen in a hypoxic environment, providing a possible explanation for the preventive effect of dexamethasone[68]. Although other medicines can also prevent HAPE, the relevant clinical data are limited, and these medicines are thus not yet suitable for direct use in HAPE prevention. Acetazolamide is an effective medication for preventing AMS and HACE but does not have relevant experimental data to support its use in HAPE prevention.

Although no specific research has confirmed the role of oxygen supplementation in treating high-altitude illness, extensive clinical experience has highlighted that oxygen supplementation may be a promising strategy for treating high-altitude-related illnesses.

Overall, in the treatment and prevention of high-altitude illnesses, the control of altitude and intake of oxygen remain the primary and most feasible approaches. When rapid altitude ascent is unavoidable, medication may be an option, albeit with potential side effects. Exploring alternative methods for prevention and treatment that can replace such medications represents a promising research direction.

4.2 CMS management strategies

Considering that CMS typically occurs in individuals who reside at or spend extended periods at high altitudes, our recommendation for preventing CMS is to engage in regular physical exercise to enhance cardiovascular fitness. Additionally, we advise individuals with respiratory conditions to minimise their time spent at high altitudes as much as possible[26].

Similar to the strategies for managing AMS, descending to lower altitudes and oxygen supplementation remain the primary recommended options. However, continuous oxygen therapy is necessary for CMS patients. Additionally, some research suggests that oxygen therapy is particularly effective for severe CMS cases[69]. Acetazolamide also exhibits a certain degree of efficacy in alleviating CMS symptoms, as it can reduce polycythaemia and significantly improve patients' CMS scores. *N*-Acetylcysteine has also shown potential in improving CMS scores, although its impact on polycythaemia is not significant[70]. Iron, as an essential component of Hb synthesis, may play a role in alleviating CMS. Early studies suggested that iron supplementation can alleviate hypoxia-induced pulmonary hypertension, while iron deficiency may exacerbate it[71]. Therefore, iron supplementation may be considered beneficial for alleviating CMS. However, subsequent research has indicated that excess iron supply can potentially promote HAPC[72].

Considering the feasibility and simplicity of the abovementioned methods for alleviating CMS, exploring dietary approaches for CMS mitigation may be a promising avenue for future research.

4.3 Potential of dietary approaches in alleviating high-altitude-related issues

Given the side effects associated with medicines like acetazolamide, dexamethasone, and nifedipine, which are commonly used in the prevention and treatment of high-altitude illnesses, exploring alternative methods that can provide relief from these conditions is a promising direction. Approximately 80% of the global population benefits from medicinal plants and some of these medicinal plants can be used as dietary supplements in specialised foods[73]. Although

many of these remedies are based on traditional knowledge, certain medicinal plants such as *Rhodiola rosea* and *Panax notoginseng* have demonstrated beneficial effects in alleviating high-altitude illnesses (Table 2).

For example, *Rhodiola* has been noted to effectively mitigate pulmonary arterial hypertension induced by chronic hypoxia in SD rats[74]. Additionally, *Rhodiola* extract can preserve the integrity of the alveolar-capillary barrier by reducing plasma ET-1 and VEGFs, thereby alleviating HAPE[75]. Recent research also suggests that the active component of *Rhodiola*, salidroside, has the potential to ameliorate cerebral oxidative stress-induced harm, inflammatory reactions, and disruption of the blood-brain barrier caused by hypobaric hypoxia[76]. The effective component of *P. notoginseng* (Sanqi), notoginsenoside R1 (NG-R1), has been proven to have effects similar to those of dexamethasone in improving cardiac pathological damage in rats with high-altitude heart injury. NG-R1 can activate the ERK1/2-P90RSK-Bad pathway to prevent high-altitude-induced cardiac injury and inhibit apoptosis[77]. Notably, *Ginkgo biloba* has been observed to prevent early-stage HAPE[78]. Promoting the overexpression of brain-derived neurotrophic factor (BDNF) and

Table 2
Dietary supplements with potential mitigating effects on altitude sickness.

Supplement	Experimental subjects	Altitude	Dose	Result	Mechanisms	Reference
Rhodiola algid	Male SD rats	Exposure to a 4 500 m environment for 4 weeks	62.5, 125, 250 mg/kg	Compared with the normal group, administration of ACRT reduced mPAP, right ventricular hypertrophy, pulmonary small artery wall thickness, and damage in ultrastructure induced by hypoxia in rats		[74]
R. crenulata extract (RCE)	Male SD rats	Exposed to 8 000 m in a simulated hypobaric hypoxia chamber at room temperature for 9 h	50, 100 mg/kg	RCE can reduce alveolar-capillary barrier dysfunction to alleviate pulmonary edema induced by hypobaric hypoxia	Reducing plasma ET-1 and VEGFs. Downregulate the proteins expression of p-NF-κB-p65, NOD-like receptors family pyrin domain containing 3 (NLPR3) (NLRP3), cleaved-Caspase-1 and ASC	[75]
Salidroside (active ingredient from *R. crenulate*)	Male BALB/c mice	Exposed to 7 000 m of hypobaric hypoxia in an animal decompression chamber	20, 50 mg/kg	Salidroside can attenuate hypobaric hypoxia-induced cerebral oxidative stress injury, inflammatory responses and the blood-brain barrier damage		[76]
RCE	39 participants	Exposed to 25 000 feet by wearing a medical-grade poly vinyl chloride oxygen breathing mask supplied with 7% oxygen for 30 min	627 mg/capsule, 2 capsule were taken in 48 h	RCE pretreatment significantly prevented hypoxia-induced reductions in SpO_2 levels, DST, WCST, and TMT. In addition, RCE attenuated the AMS-like symptoms		[82]
Notoginsenoside R1 (NG-G1)	Male SD rats	Exposed to 6 000 m in a simulated hypobaric hypoxia chamber for 48 h	50, 100 mg/kg	NG-R1 can improve abnormal cardiac electrical conduction and alleviate high-altitude-induced tachycardia	Activation of the ERK1/2-P90 RSK-Bad signaling pathway	[77]
G. biloba extract	36 participants who reside at sea level	Ascent to 3 696 m	80 mg bid	The incidence of AMS GBE: 0% Acetazolamide: 36% Placebo: 54%		[83]
G. biloba extract	44 participants who reside between 1 400 and 1 600 m	Ascent from 1 600 to 4 300 m within 2 h	120 mg bid	The incidence of AMS GBE: 7/21 Placebo: 13/19	Promoting the overexpression of BDNF. Activating the CaMKII/ERK/CREB signaling pathway	[84]
G. biloba extract	Male SD rats	Exposed to 380 mmHg in a simulated hypobaric hypoxia chamber for 24 h	200 mg/kg	Protein concentrations in BALF: Control: (19.8 ± 2.6) mg/dL GBE: (11.6 ± 0.9) mg/dL Protein concentrations of pleural fluid: Control: (4.9 ± 0.16) g/dL GBE: (4.0 ± 0.13) g/dL		[78]
Danshen (*S. miltiorrhiza*) dripping pills	58 inhabitants residing in Beijing (average altitude of 46 m)	Ascent to Tibet at an altitude above 3 000 m for 11 days	90 mg tid	AMS score: Placebo: 3.79 CDDPS: 2.31 SaO_2: Placebo: 85.72% CDDPS: 87.86%	Suppressed NF-κB and up-regulated Nrf2 might play significant roles	[85]
Compound Danshen Dripping Pills (CDDPS)	141 male adults who reside at an altitude of 250 m or lower	Ascent to 4 000 m	135 mg tid	The incidence of AMS: CDDPS: 48.6% Placebo: 67.6% Metabolic equivalents: CDDPS: (9.93 ± 1.18) METs Placebo: (9.31 ± 1.52) METs		[86]

Note: ACRT, bioactive fraction from *R. algid* ; mPAP, mean pulmonary arterial pressure; DST, short-term and working memory capacity; WCST, cognitive flexibility, and selective attention; TMT, executive functioning; GBE, *G. biloba* extract; BALF, bronchoalveolar lavage fluid; MET, metabolic equivalents; ET-1, endothelin-1; VEGFs, vascular endothelial growth factors; ERK, extracellular signal-regulated protein kinases; Nrf2, nuclearfactor erythroid 2-related factor 2; NF-κB, nuclear factor kappa-B; SpO_2, peripheral oxygen; P90RSK, p90 ribosomal S6 kinase; CaMK II, calcium/calmodulin-stimulated protein kinase II; CREB, cyclic-AMP response binding protein.

activating the CaMKII/ERK/CREB signaling pathway may be a potential approach to reduce brain damage caused by high-altitude environments[79]. In rat studies, Danshen was found to alleviate hypoxia-induced tachycardia. Ethanol extracts of Danshen at different concentrations can alleviate hypoxia-induced tachycardia and oxidative stress, suggesting its potential in mitigating cardiorespiratory issues caused by hypoxia[80]. Suppressed NF-κB and up-regulated Nrf2 might play significant roles in the mechanisms of Danshen[81].

The efficacy of these medicinal plants, proven in experimental animals for alleviating high-altitude-related diseases, has also been demonstrated in clinical studies. Daily intake of capsules containing 627 mg of *R. rosea* extract significantly mitigates the reduction in saturation of SpO_2 levels caused by hypoxia, improves short-term and working memory capacity, cognitive flexibility, executive function, and alleviates symptoms of acute mountain sickness[82]. Early consumption of *G. biloba* or its extract has been found to partially prevent or alleviate the severity of AMS. A dose of 80 mg/12 h of *G. biloba* extract is sufficient to reduce the incidence of AMS and is more effective than acetazolamide. However, the effectiveness of *G. biloba* extract in preventing AMS may be influenced by the source and composition of the product[83-84]. Research has found that *Salvia miltiorrhiza* (Danshen) can effectively prevent AMS and alleviate its clinical symptoms without specific side effects, particularly after rapid altitude ascent. This may be related to CDDPs's ability to reduce heart rate and myocardial oxygen consumption, while increasing hemoglobin levels, hematocrit, and antioxidant factors[85-86]. Currently, there are numerous medicinal plant products available on the market for mountaineering enthusiasts and tourists visiting high-altitude areas, including oral liquids, tablets, and capsules, which have received positive feedback from users. However, there is still a lack of systematic real-world studies on the actual efficacy of these products, which is a key issue that future research needs to address.

Probiotics have gained popularity as dietary supplements in recent years. The Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) define probiotics as follows: 'Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.' In contrast, prebiotics predominantly consist of dietary fibres, which are indigestible dietary constituents capable of promoting the proliferation of particular microorganisms in the intestinal tract, thereby positively affecting the host's well-being[87].

Indeed, recent research has found significant differences in the gut microbiota of Tibetan residents residing at different altitudes. Additionally, cultural background significantly shapes the constitution of the gut microbiota in the human body. Thus, gut microbiota appears to be a potential intervention target for high-altitude illnesses[50-51].

Administration of synbiotics to rats about to be exposed to hypobaric hypoxia has been noted to significantly reduce the levels of isothiocyanate fluorescein-glucose and zonulin in rat serum. Moreover, synbiotic-treated rats exhibited a significant reduction in proinflammatory cytokine levels in their bodies, demonstrating that synbiotics can improve the intestinal barrier function and reduce the inflammatory response caused by hypobaric hypoxia exposure[88]. Another study has demonstrated that the intake of probiotics or prebiotics can alleviate left ventricular hypertrophy in rats subjected to hypobaric hypoxic conditions. Although the precise mechanisms remain to be elucidated[89], these discoveries indicate the potential of targeting the gut microbiota as a therapeutic strategy for addressing high-altitude maladies.

The results of an experiment focusing on the development of chicken breeds in plateau regions showed that although the supplementation of probiotic additives to the feed did not improve the production performance of broiler chickens, the treatment group of chicks showed a significant reduction in ascites and mortality due to coccidiosis[90]. An earlier study showed that birds reared in a simulated high-altitude environment had poorer intestinal development. However, when prebiotics (such as fungal powder) were added to their feed, the level of intestinal development in birds raised under simulated high-altitude conditions became similar to that of birds raised at local altitudes[91].

In general, research on the use of probiotics or prebiotics to alleviate high-altitude illness in humans remains limited, likely because of small sample sizes and the absence of targeted probiotic formulations. However, the relevant studies in animals have provided promising results. In the future, more animal studies are needed to further explore the feasibility and mechanisms of different species of probiotics in alleviating high-altitude illnesses. At the same time, applying these specifically developed probiotic formulations to clinical trials will help us better understand the role of probiotics in mitigating these conditions. Although there are currently no clinical trials results available regarding the dosage of probiotics for alleviating high-altitude illnesses, based on the dosage range used for addressing other health issues, a daily intake of 10^9-10^{10} CFU should be acceptable. Overall, the consumption of probiotics and prebiotics may be a potential strategy for the prevention or treatment of high-altitude illnesses.

5. Concluding remarks and future perspectives

High-altitude illness has emerged as a major concern for tourists, athletes, and individuals travelling to high-altitude regions. Although our understanding of high-altitude illness and prevention strategies has become increasingly comprehensive, we still face several challenges. Gradual ascent is a traditional but effective method for preventing high-altitude illness, yet in most cases, we do not have sufficient time for altitude acclimatization. To address acute high-altitude illness caused by rapid ascent in a short period, pharmacological interventions have become a viable option. Medications are available to prevent or alleviate its effects, however, the side effects of these medicines cannot be ignored. Therefore, exploring safer methods such as dietary interventions to replace pharmacological interventions is of great significance for the mitigation and prevention of high-altitude illness. Historically, certain medicinal plants, including *Rhodiola*, have been considered effective options for addressing high-altitude illness. Although recent scientific studies have validated these traditional beliefs, variations in the origin and processing methods of these plants may affect the levels of active ingredients in medicinal plant extracts, leading to inconsistent efficacy in preventing and alleviating high-altitude illness. Therefore, detailed analysis of the specific active components and mechanisms of these medicinal plants, as well as in-depth research on their dose-response relationship, is key to further promoting these safer interventions on a wider scale. An increasing number of studies have shown that hypoxic conditions at high altitudes can rapidly and persistently alter the gut microbiota. The dysbiosis of gut microbiota caused by the high-altitude environment may be closely related to high-altitude illness. Moreover, differences in the gut microbiota of residents at varying altitudes suggest that it

may play a role in individual adaptation to high-altitude environments. However, considering the differences in lifestyle and dietary habits among different ethnic groups, further research is needed to fully understand the impact of high-altitude environments on the gut microbiota. Moreover, existing correlation studies have not truly identified the key gut microbes that may lead to high-altitude illness. Understanding how to maintain the stability of these key gut microbes' abundance will also help explore the deeper mechanisms by which different medicines or medicinal plants can prevent or mitigate high-altitude illness.

Probiotics is a direct and effective means of modulating gut microbiota. Although numerous studies have demonstrated their beneficial effects in addressing various health issues, studies on the using probiotics to alleviate high-altitude illnesses started relatively late due to the unique conditions of high-altitude environments and the limited attention from researchers. Some positive research results in experimental animals provide promising indications for the use of probiotics to prevent or alleviate high-altitude diseases. In the future, researchers need to further elucidate the specific mechanisms or pathways through which probiotics exert beneficial effects on high-altitude diseases. This will also help us better understand the role of gut microecology in maintaining human physiological homeostasis under extreme environmental conditions. Additionally, substantial clinical evidence is required to demonstrate the efficacy of probiotics in alleviating high-altitude diseases. The ultimate goal is to identify and develop probiotic formulations suitable for high-altitude environments, providing a novel, safe, and effective dietary supplement for local residents or newcomers to high-altitude regions.

Conflict of interest

Gang Wang is an editorial board member for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare no conflicts of interest.

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