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External Factors Affecting Gastrointestinal Barrier and Mucosal Immunity at High Altitude

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ABSTRACT

High altitude regions above 2,700 meters pose unique physiological challenges to travellers, including hypoxia caused by decreased oxygen levels. Gastrointestinal issues such as nausea, vomiting, and anorexia are common in high altitude sojourners. The gastrointestinal barrier is composed of epithelial cells connected with tight junctions, desmosomes, and covered with a thick layer of mucous. The mucosal and immunological barriers work together to regulate intestinal homeostasis and prevent harmful pathogens from entering the system. Any damage to the gastrointestinal barrier can lead to an increase in permeability which can cause harmful microbial toxins and unwanted substances to enter the bloodstream, triggering an inflammatory response. External factors such as hypoxia and intense physical workouts at high altitude can disrupt the barrier and lead to inflammation and microbial dysbiosis, which changes the normal population of gut microbiota and can cause gastrointestinal discomfort. This review aims to examine the effects of these external factors on the gastrointestinal barrier and highlights the importance of therapeutic and dietary interventions to manage high altitude induced mucosal barrier dysfunction and restore immunological homeostasis of the gut.

Key words: Mucosal immunity; Hypoxia; High altitude; Gut barrier; Inflammation

1. INTRODUCTION

The high altitude environment presents itself as a major challenge to the sojourners travelling there for various purposes including pilgrimage, trekking and safeguarding the border. With a constant increase in altitude, the barometric pressure decreases due to which the partial pressure of oxygen is also reduced leading to hypoxic conditions in the body. Apart from hypoxia, other factors like low temperature, lack of fresh food, drinking water and sanitation make the journey to the high altitude regions a big challenge. A frequently reported illness observed in sojourners travelling to high altitude above 2,700 m is Acute Mountain Sickness (AMS) which is associated with vomiting, anorexia, dyspepsia, nausea, difficulty in sleeping, fatigue and gastrointestinal discomfort[1,2]. Along with AMS, bleeding in the gastrointestinal tract which can manifest into a potentially life-threatening condition is also reported by many individuals travelling to high altitude[3]. The gastrointestinal tract is one of the important systems in the body which gets affected due to extreme environmental stresses at high altitude leading to gastrointestinal tract inflammation[1,4]. Wu, *et al*., published a study in 2007 reporting the incidence of gastrointestinal bleeding in 0.49 % out of 13,502 workers building the Qinghai-Tibetan railroad[3]. The human gut is the major site for the absorption of important nutrients and water whereas the intestinal barrier regulates the homeostasis of the gut by controlling the expression of tight junction proteins and prevents the leakage of harmful toxins and bacteria into the systemic circulation[5]. Hence any injury or damage to the gastrointestinal tract can lead to decreased nutrient absorption which further causes weight loss and fatigue. In association with this, the injury to the intestinal barrier causes increased gastrointestinal barrier permeability due to which the gut becomes leaky and allows the free exchange of toxins, antigens and pro-inflammatory cytokines in the systemic blood leading to an inflammatory response and may cause AMS[6].

The stressful environmental conditions at high altitude constitute a unique challenge to the human body, including a hypoxic environment, altered atmospheric pressure, and extreme cold temperatures. While the physiological adaptations to high altitude have been extensively studied, the impact of high altitude on the gastrointestinal tract barrier and mucosal immunity remains unexplored. Despite the presence of numerous pieces of evidence to suggest the prevalence of gastrointestinal barrier injury at high altitude, a limited amount of research is taken up to study the problem and to identify potential therapeutic treatments for the same. Hence, this review aims to provide a comprehensive overview of the various factors like hypoxia, gut microbiota, physical exercise, medications and diet, which affect the human gastrointestinal barrier at high altitude. Understanding the significance of the

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impact of various external factors upon the gastrointestinal tract at high altitude is crucial for the development of new strategies to mitigate their effect and to develop potential treatments for optimising gut health at high altitude.

2. INTESTINAL BARRIER DYSFUNCTION AND MUCOSAL IMMUNITY

Our body is made up of large mucosal epithelial surfaces that protect the host from external environmental stresses. The intestinal barrier present in the gastrointestinal tract is a dynamic structure made up of epithelial cells held together by tight junctions which serves the purpose of blocking the translocation of harmful microbial byproducts and toxins from the intraluminal space to the systemic circulation. In addition to this, it acts as a free passage for the transport of essential nutrients and water into circulation. The specialised goblet cells secrete a thick layer of mucous which covers the apical surface of the epithelial cells of the gastrointestinal tract. This covering of mucous serves as a crucial part of the host's innate immune defence, by serving as the primary barrier against a variety of pathogenic microbes. A recent study reported that the Mucin 2 deficient mice lacking the protein responsible for the production of the mucosal layer displayed enhanced intestinal permeability and increased bacterial translocation in comparison to wild type control[7].

Furthermore, the adjacent intestinal epithelium cells are connected by specialised protein structures known as tight junctions which form a secure seal between the cells to restrict the leakage of unwanted substances across the intestinal epithelium. Al-Sadi reported that the knockdown of Occludin a tight junction protein in Caco-2 cells caused a significant increase in the macromolecule flux across the intestinal barrier, suggesting the pivotal role of tight junction proteins like occludin in regulating intestinal permeability[8]. The secretory immunoglobulin A (sIgA), primarily produced by the plasma cells in the lamina propria, orchestrates the immune responses at the mucosal surface and promotes immune tolerance. On the other hand, the immunological cells like macrophages, T cells and dendritic cells residing inside the lamina propria of the gut as well as the Peyer's patches are essential for the proper maintenance of immune homeostasis of the gut. For instance, the adaptive immune response is alerted when an antigen enters the host system. The antigen is then presented by the dendritic cells to the T cells, which upon activation leads to the differentiation of naive T cells into various T cell subsets, one of which includes Th17 cells. This subpopulation of T cell expresses the transcription factor RORγt which plays a major role in maintaining the immune homeostasis of the gut. These cells play multiple roles in host defence within the gut by producing effector cytokines like IL-17, aiding in neutrophils recruitment and interacting with Tregs to inhibit excessive inflammation. Additionally, the intestinal tract is also rich in a variety of immunological factors which contribute to mucosal immunity[9]. These factors include antimicrobial peptides like defensin which are secreted by the paneth cells and the enterocytes and are known to possess antimicrobial activity. The antimicrobial peptides in association with the cellular barrier act as a protective shield against harmful pathogens and toxins and maintain the homeostasis of the gut. Various genetic, lifestyle and environmental factors can disrupt the intestinal barrier which leads to gastrointestinal dysfunction. The disruption of the intestinal barrier results in increased intestinal permeability which is often reported as a leaky gut[10]. The leaky gut allows the free exchange of toxins and other unwanted molecules with the systemic blood which causes the activation of the immune response which later develops into inflammation (Fig. 1). A disrupted gastrointestinal barrier also fails to sufficiently absorb important nutrients and electrolytes from the diet. Moreover, the damaged intestinal barrier is also correlated with microbial dysbiosis in the gastrointestinal tract[11].

2.1 Effect of Hypoxia on the Gastrointestinal Tract

The hypoxic environment at the high altitude is known to induce many changes to the physiological aspects of the human body. A few of them include damage to the intestinal barrier, epithelial cell injury (due to a decrease

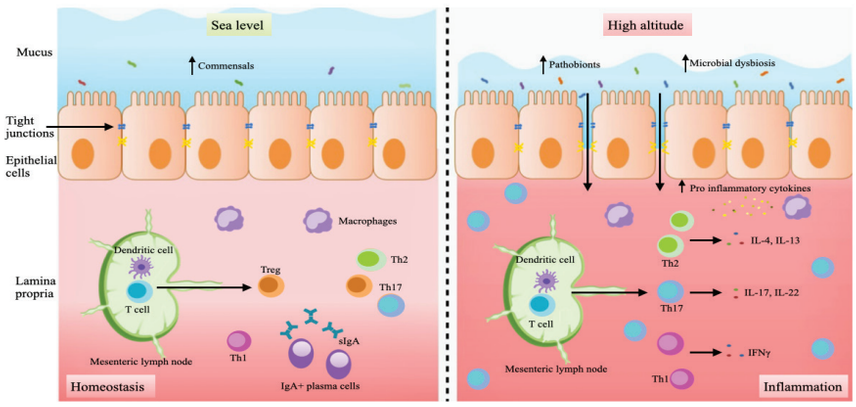

Figure 1. A comparative representation of the intestinal barrier depicting homeostasis and inflammation at sea level and high altitude respectively.

in pH and an increase in reactive oxygen species) and mucosal cell injury which results in inflammation as well as gastrointestinal bleeding. Hypoxia is also known to alter the innate immunity factors which can heighten the inflammatory response at high altitude. Hypoxia at high altitude activates the sympathetic system causing vasoconstriction which may also contribute to intestinal mucosal injury[12]. A limited number of human studies suggest that exposure to hypoxia causes increased intestinal permeability which is associated with gastrointestinal dysfunction. A study conducted on 14 human volunteers travelling to an altitude of 6,300 m reported that intestinal permeability increased during rapid ascent from 60m to 5,570 m[13]. A similar study performed by Karl, *et al*., on 17 male healthy individuals exposed to 4,300 m for 22 days also revealed an increase in intestinal permeability in comparison to sea level[14]. A prevalence of gastrointestinal bleeding was also assessed in 13,502 workers, employed at an altitude of 4,905 m on Mount Tangulla to construct the Qinghai-Tibetan railroad. It was found that around 0.49 % of workers were suffering from acute gastrointestinal bleeding caused due to gastric ulceration and erosion[3].

In 2012, a study found that rats exposed for 3 days to an altitude of 7,000 m in a hypobaric hypoxia chamber led to intestinal barrier injury which further activated an inflammatory response mediated by TLR4 and NF-κB signalling. They also reported a massive increase in the production of pro-inflammatory cytokines IL-6 and TNF-α, which can further exacerbate inflammation[15]. A parallel study performed by Xu, *et al*., on male SD rats exposed for 5 days to an elevation of 7,000 m, reported major damage to the small intestine of rats exposed to hypobaric hypoxia[16]. It was observed that the intestinal mucosal surface of the exposed rats was severely damaged in addition to this the tight junctions forming the intestinal barrier between the intestinal epithelial cells also widened, causing the leakage of unwanted substances into the systemic circulation. A study by Khanna, *et al*., on the rodent model also concluded that exposure to hypobaric hypoxia resulted in a subsequent increase in mucosal damage and barrier permeability. The study also reported an increase in the natural killer cells and dendritic cell population as well as an increased level of secretory immunoglobulin A and pro-inflammatory cytokine IL-17, highlighting the direct effect of hypobaric hypoxia on mucosal immunity[17]. Under a hypoxic environment, the hypoxia inducible factor-1 (HIF-1) signalling gets activated which regulates the expression of hypoxia responsive genes. A group of rats exposed to 3,842-4,747 m for 3 days have increased expression of HIF-1α and iNOS in the small intestine along with swelling and thickening of the intestinal villi[18]. Earlier studies have revealed that the increase in the expression of iNOS and nitric oxide is directly associated with inflammation in the gut and is considered a potential biomarker for the identification of GI tract diseases like IBD[19,20]. A study by Adak, *et al.*, on male albino rats exposed to 4,873 m elevation reports the necrosis of the intestinal epithelial layer with decreased number of goblet cells secreting mucin[21]. There are a limited number of studies which delineate the effect of hypobaric hypoxia on

Table 1. Effect of Hypobaric Hypoxia on the gastrointestinal tract

S.No.	Model used	Exposure	Study outcomes	References
1.	Sprague Dawley rats	Hypobaric hypoxia exposure for 7 days at 25,000 ft	Administration of synbiotics for 7 days led to improvement in the intestinal barrier integrity with consecutive decrease in the levels of pro inflammatory cytokines and chemokine.	Khanna, *et al.*,[52]
2.	Sprague Dawley rats	Hypobaric hypoxia exposure for 14 days at 7620 m	An increase in the natural killer cells and dendritic cell population as well as an increased level of secretory immunoglobulin A and pro-inflammatory cytokine IL-17.	Khanna, *et al*.,[17]
3.	17 human volunteers	4,300 m for 22 days	Increased intestinal permeability	Karl, *et al*.,[14]
4.	20 subjects who had past history of HAPE and 18 healthy control	Exposed to 12 % oxygen (FiO_2 = 0.12)	Inflammatory chemokines MCP-1 and MIP-1α were significantly higher in subjects who has past history of HAPE as compared to healthy control group	Mishra, *et al*.,[41]
5.	Male Wistar rats	3,842-4,747 m for 3 days	Increased expression of HIF-1α and iNOS, swelling and thickening of intestinal villi	Zhang, *et al*.,[18]
6.	Male Sprague Dawley rats	7,000 m for 5 days Hypobaric hypoxia	Damage to the small intestine. Increased IL-4 and IFN-γ.	Xu, *et al.*,[57]
8.	Male albino rats	4,873 m	Necrosis of intestinal epithelial layers with decreased goblet cells population	Adak, *et al*.,[21]
9.	Sprague Dawley rats	7,000 m for 3 days Hypobaric hypoxia	Intestinal barrier injury. TLR4 and NF-kB increased. Increase in pro-inflammatory cytokines IL-6 and TNF-α.	Luo, *et al.*,[15]
10.	14 human volunteers	6,300 m for 12 days	Intestinal permeability increased	Dinmore, *et al.*,[13]

the intestinal barrier and immune markers (Table 1), hence in depth, research is required to comprehend the same depth and to identify promising dietary/therapeutic interventions.

2.2 Effect of Physical Exercise on the Gastrointestinal Tract

Exercise or intense physical exertion at high altitude performed under hypoxic conditions presents a unique and stressful physiological challenge to the human body.Over the past few years a limited number of reports have revealed that during intense physical exercise under hypobaric hypoxia, the intestinal barrier suffers intense damage. It was reported by Li, *et al*., that SD rats performing simulated treadmill training exposed to a hypoxic environment at 4,000m revealed disrupted intestinal mucosal barrier and a subsequent increase in the pro-inflammatory cytokines like IL-6 and TNF-α in the small intestine, providing early evidence that exercise at high altitude leads to intestinal dysfunction[22]. A study performed on 9 healthy male volunteers exposed to 4,300m in a hypobaric chamber reported an increase in the markers of intestinal barrier injury such as Claudin-3, fatty acid binding protein and Lipid binding protein. These markers were elevated after 1 hour of exercise in the hypobaric chamber. They also reported that the volunteers engaged in performing physical activity under a stimulated hypoxic environment complained of gastrointestinal problems like nausea and abdominal stitch more in comparison to volunteers performing the same physical activity under a normoxic environment[23].

Hill, *et al*., also reported that running on a treadmill under normobaric hypoxia for 1 hour resulted in increased intestinal barrier permeability as well as an increase in the concentration of cytokines and fatty acid binding protein[24]. A similar study also performed on 9 healthy male subjects performing exercise on a treadmill for an hour under hypoxic environment revealed the presence of increased endotoxin concentration in the plasma[25]. The elevation of endotoxin in the plasma is directly correlated to intestinal barrier injury or disruption of the tight junctions of the gastrointestinal barrier[26]. The leakage of microbial endotoxins like lipopolysaccharide from the intraluminal space to the systemic circulation triggers the activation of the Toll-like receptor 4 signalling pathway, which results in the release of pro-inflammatory cytokines in large amounts. These pro-inflammatory cytokines can induce local inflammation in the gut compromising the integrity of the intestinal barrier and increasing its permeability by contraction of the actin filament due to activating myosin light chain kinase. In contrast to this, a study concluded that performing exercise in a normobaric hypoxia chamber for 60 minutes leads to a decrease in the level of TNFα: IL-1RA ratio and Monocyte chemoattractant protein-1[27]. Hence, studies investigating the impact of performing intensive physical activity at high altitude on the gastrointestinal tract have demonstrated an increase in intestinal permeability caused due to intestinal barrier disruption. However, the exact mechanism underlying the effect needs to be explored in detail.

2.3 Effect of High Altitude on Microbial Dysbiosis

A vast and dynamic population of microbes are known to inhabit the human gastrointestinal tract which plays a crucial role in maintaining gut homeostasis. More than one hundred trillion microorganisms belonging to different families of bacteria colonise the human gut forming a complex symbiotic relationship with the host.

The gastrointestinal tract provides an ambient environment for the microbiota to thrive whereas the microbiota in exchange benefits the host by providing protection against pathogenic bacteria as well as maintaining the gut barrier integrity.The mutual homeostatic relationship between the gut microbiota and the host is disturbed due to various environmental stresses like hypoxia, which leads to microbial dysbiosis. The environmental induced alteration in the population of gut microbiota is known to manifest in various gastrointestinal related disorders like Inflammatory Bowel Disease (IBD) and colitis. It is well reported that *Akkermansia muciniphila* is a mucin degrading bacteria that protects the human intestine from inflammation induced damage by strengthening the integrity of the gastrointestinal tract barrier. The abundance of *A. muciniphila* is reported to be decreased in SD rats when exposed to hypobaric hypoxia leading to microbial dysbiosis. Hence, the use of *A. muciniphila* as a probiotic to treat gastrointestinal problems at high altitude is suggested by multiple reports[28,29].

Another study performed on C57BL/6J mice exposed to high altitude for 1 to 4 weeks reported that the environmental stress contributes to microbial dysbiosis which further leads to gut barrier injury aggravating damage to the gastrointestinal tract[30]. A study done using phenotypic and bioinformatic analysis revealed that the proportion of aerobic bacteria decreased with a subsequent increase in anaerobic bacterial population in rats exposed to high altitude hypoxia. In addition to this, the study also reported a major decrease in the abundance of *Akkermansia* in the high altitude hypoxia group[31]. Kleessen, *et al.*, in 1994 reported that in a group of people travelling to the Himalayas at an altitude above 5,000 m, the population of gram negative pathogenic bacteria like *E. coli* increases with a subsequent decrease in the population of *Bifidobacterium*[32].

Several reports point towards the beneficial role of *Bifidobacterium* in enhancing the integrity of the intestinal barrier in inflammatory disease models like IBD[33,34]. Hence a striking decrease in the abundance of both *Akkermansia* and *Bifidobacteria* might aggravate the symptoms of mucosal and intestinal barrier injury associated with high altitude. Accordingly, dysbiosis in the microbial population of the gastrointestinal tract induced due to exposure to high altitude causes the

disruption of the fine balance between the commensal and pathogenic microorganisms which modulates the immune response, regulates the expression of tight junction proteins as well as influences the production of mucous. The evidence thus far indicates that exposure to high altitudes can lead to alterations in microbial diversity, as well as changes in the relative abundance of specific microbial taxa, potentially playing a role in disturbing gastrointestinal homeostasis.

2.4 Effect of Medication on Gastrointestinal Tract at High Altitude

A hypoxic environment at high altitude may cause illnesses like AMS, High Altitude Pulmonary Edema (HAPE), High Altitude Cerebral Edema (HACE) and gastrointestinal problems. Common physiological conditions like AMS can be managed effectively with rest and decent, but HACE and HAPE require the administration of medications like acetazolamide, dexamethasone, non-steroidal anti-inflammatory drugs, sildenafil or nifedipine[1,35]. For the management of symptoms associated with HAPE and HACE, a corticosteroid medicine known as dexamethasone is administered orally or intravenously at high altitude. This drug relieves inflammation and vasogenic edema as it reduces the production of inflammatory cytokines[36]. A recent study showed that the use of corticosteroids on intestinal organoids culture ameliorates damage to the intestinal barrier caused by proinflammatory cytokines and restores the epithelial barrier function suggesting the gastroprotective role of corticosteroid drugs[37].

Fischer, *et al*., reported that treating the Caco-2 cells with dexamethasone resulted in enhanced expression of Claudin-4 and a simultaneous decrease in intestinal permeability[38]. In addition to dexamethasone, a carbonic anhydrase inhibitory drug called acetazolamide which is known to possess diuretic properties is widely used for the prevention and treatment of high altitude illnesses[39].

The drug acetazolamide works by inhibiting the enzyme carbonic anhydrase which causes a decrease in the reabsorption of bicarbonate in the kidneys, the elimination of bicarbonate through urine prevents the build up of acid in the body, thereby restoring the acid base imbalance and counteracting against the respiratory alkalosis observed at high altitude[40,41]. A study performed on rats administered with 100-200 mg/kg acetazolamide subcutaneously observed that the intake of acetazolamide induced severe gastric ulceration and reduced mucus secretion[42]. In contrast to this, another study reported that the use of acetazolamide prevented ethanol induced gastric mucosal lesions in Wistar rats by stimulating the biosynthesis of prostaglandins[43]. In addition to this, several studies also report the gastric cytoprotective role of acetazolamide in a rodent model[44,45]. Another medicine which is prophylactically used in the treatment of HACE is nifedipine. The drug nifedipine acts by inhibiting the entry of calcium into smooth muscle cells by blocking the working of L-type calcium channels[46]. This results in systemic vasodilation and a decrease in pulmonary arterial pressure due to which the blood flow improves and alleviates the symptoms of HACE and HAPE. A report suggests that a couple of patients developed gastric mucosal damage after ingesting nifedipine[47].

Another study reported that the use of nifedipine prevented ethanol induced gastric mucosal damaged[48]. A limited number of studies delineate the direct effect of medications used in the treatment of high altitude illness on the gastrointestinal tract. It is also essential to note that the effect of these medications on the gastrointestinal tract may vary from person to person depending on the individual susceptibility, acclimatization to the altitude and presence of any pre-existing gastrointestinal condition which can influence the severity and manifestation of the effect of the medicine. Dexamethasone can cause gastric irritation, while acetazolamide may lead to gastrointestinal disturbances. Nifedipine, although directly not affecting the gastrointestinal tract may have side effects that can cause intestinal distress. Thus, further research is required to gain in depth knowledge of the effect of these medications on the gastrointestinal tract.

2.5 Effect of Diet on the Gastrointestinal Mucosal Barrier at High Altitude

Diet is known to play a significant role in regulating gut homeostasis and in maintaining the integrity of the intestinal barrier. However, at stressful environmental conditions like high altitude the dietary habits of the sojourners often undergo consequential changes due to limited fresh food supply, which can affect the gastrointestinal tract in multiple ways. Hence several dietary supplements are reported to protect the intestinal barrier from high altitude induced distress. As discussed earlier due to exposure to high altitude the normal gut microbiota suffers dysbiosis which may exaggerate intestinal inflammation further leading to intestinal barrier injury. Hence supplementation with probiotics which constitutes live beneficial microbes has been demonstrated to restore the intestinal barrier[49].

A report revealed that the administration of probiotics *(Bifidobacterium and Lactobacillus)* to brown Norway rats subjected to malnutrition led to decreased serum endotoxin levels and bacterial translocation as well as the microbial homeostasis of the gut was also restored[50]. In accordance with this, another study also reported the beneficial role of *Lactobacillus* probiotic in strengthening the intestinal barrier as well as in maintaining the integrity of the tight junctions in both Caco-2 intestinal epithelial cell line and in SD rats[51]. Furthermore, the increasing use of synbiotics, a mixture of probiotics and prebiotics, has emerged as a game changer in the world of gastrointestinal health. Synbiotics offer a synergistic approach to promoting a healthy gut microbiome. It was reported by Khanna, *et al*., that the administration of synbiotics to SD rats for 7 days exposed to hypobaric hypoxia, led to a remarkable improvement in the intestinal barrier injury with consecutive decreases in the levels of pro inflammatory cytokines and chemokine[52].

Vitamin D deficiency is unlikely observed at high altitude unless a prolonged duration of stay at extreme altitude especially in winter when the temperature drops upto minus 45 ^{0}C and a human can't survive without covering his full body to protect against extreme cold resulting in a decreased synthesis of previtamin D3. The role of supplementation of vitamin D can play an important role in preventing the upregulation of inflammation, decreasing TNF-α expression, and restoring tight junction protein and claudin 2 protein leading to the repair of the intestinal epithelial barrier and restoring gut homeostasis[53].

Glutamine, a non essential amino acid has also gained considerable attention in the past few years as a potential supplement for defending the intestinal barrier from injury[54]. The role of glutamine in protecting the intestinal barrier is multifaceted. Glutamine modulates the expression of tight junction proteins, which are integral for intestinal barrier functioning. Bertrand, *et al.*, reported that the glutamine treatment for patients suffering from IBD revealed enhanced expression of tight junction protein Claudin-1 in the intestinal mucosa[55]. Another study reported that the treatment of intestinal porcine epithelial cells with 2mmol glutamine caused an enhancement in tight junction proteins like zonulin 1, zonula occludin and claudin 4[56].

The effect of glutamine on the gastrointestinal tract when administered to rats exposed to hypobaric hypoxia was elucidated by Xu, *et al.*, in 2014. They reported that when rats were administered glutamine supplement (5g/kg) three days before exposure to hypobaric hypoxia and 5 days during the exposure, a reduction in hypoxia induced intestinal barrier damage was observed with a constitutive decrease in the levels of pro-inflammatory cytokines like IL-6, IFN-γ and TNF-α[57]. The research on prebiotics (compounds in food that foster the growth of beneficial microbiota) has suggested the beneficial effects on gastrointestinal health. During the digestion of prebiotics such as non digestible polysaccharides and dietary fibres by anaerobic bacteria in the gut, a number of metabolites like butyrate, acetate and propionate are produced in the human gut[58]. These metabolites or short chain fatty acids (SCFA) play a crucial role in maintaining the gastrointestinal health[59].

A study suggests that SCFA plays a protective role in maintaining the function of intestinal barrier by inhibiting the activation of the NLRP3 inflammasome.[94] In addition to this, another study revealed that SCFA treatment was able to alleviate ethanol induced intestinal barrier injury in Caco-2 cells by activation of AMPK signalling pathway[60]. Hence due to microbial dysbiosis at high altitude the abundance of SCFA can also be affected which can aggravate intestinal barrier dysfunction, therefore supplementation with SCFA in dietary form can attenuate the intestinal barrier dysfunction at high altitude. Even though a large number of studies discuss the gastroprotective role of various dietary supplements, only a few studies have focused on the benefits of nutritional supplements on gastrointestinal-barrier dysfunction observed at high altitude. Therefore, various other dietary supplements can be explored, which can be used as potential agents in treating and restoring the gastrointestinal barrier integrity at high altitude.

3. CONCLUSION

Sojourn to the high altitude presents a unique challenge to human physiology, including the gastrointestinal tract. The intestinal barrier is composed of a complex variety of structures such as the intestinal epithelial cells, the mucous layer, the immune cells, junctional proteins and the gut microbiota. Any damage or injury to any one component of the intestinal barrier leads to gastrointestinal distress. The injury to the intestinal barrier causes the translocation of harmful toxins from intraluminal space to the systemic circulation which can elicit an inflammatory response. The hypoxic environment at high altitude may compromise the intestinal barrier integrity and increase intestinal permeability through multiple ways. In addition to this, other external factors like performing physical exercise at high altitude, dietary modifications and medication to treat high altitude related illnesses significantly affect microbial homeostasis as well as the gastrointestinal barrier functioning and integrity. Hence understanding these effects is crucial for developing strategies to mitigate gastrointestinal barrier injury and to optimise mucosal immunity at high altitude. Thus, additional investigation is needed to explore the mechanism involved and to develop targeted interventions to protect the gastrointestinal barrier in individuals sojourning to high altitude.

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