Ibrahim *et al. Nutrition & Metabolism* (2024) 21:66
https://doi.org/10.1186/s12986-024-00836-6

Nutrition & Metabolism

REVIEW Open Access

Gut matters in microgravity: potential link of gut microbiota and its metabolites to cardiovascular and musculoskeletal well-being

Zeinab Ibrahim[1,2], Naveed A Khan[5], Ruqaiyyah Siddiqui[4,5], Rizwan Qaisar[1,2], Hezlin Marzook[1], Nelson C. Soares[3,6] and Adel B Elmoselhi[1,2*]

Abstract

The gut microbiota and its secreted metabolites play a significant role in cardiovascular and musculoskeletal health and diseases. The dysregulation of the intestinal microbiota poses a significant threat to cardiovascular and skeletal muscle well-being. Nonetheless, the precise molecular mechanisms underlying these changes remain unclear. Furthermore, microgravity presents several challenges to cardiovascular and musculoskeletal health compromising muscle strength, endothelial dysfunction, and metabolic changes. The purpose of this review is to critically examine the role of gut microbiota metabolites on cardiovascular and skeletal muscle functions and dysfunctions. It also explores the molecular mechanisms that drive microgravity-induced deconditioning in both cardiovascular and skeletal muscle. Key findings in this review highlight that several alterations in gut microbiota and secreted metabolites in microgravity mirror characteristics seen in cardiovascular and skeletal muscle diseases. Those alterations include increased levels of *Firmicutes/Bacteroidetes* (F/B) ratio, elevated lipopolysaccharide levels (LPS), increased in para-cresol (p-cresol) and secondary metabolites, along with reduction in bile acids and *Akkermansia muciniphila* bacteria. Highlighting the potential, modulating gut microbiota in microgravity conditions could play a significant role in mitigating cardiovascular and skeletal muscle diseases not only during space flight but also in prolonged bed rest scenarios here on Earth.

Keywords Gut, Microbiota, Metabolites, Microgravity, Cardiovascular, Skeletal muscle, Deconditioning

*Correspondence:
Adel B Elmoselhi
amoselhi@sharjah.ac.ae
[1]Research Institute of Medical & Health Sciences, University of Sharjah, Sharjah 27272, UAE
[2]Basic Medical Sciences Department, College of Medicine, University of Sharjah, Sharjah 27272, United Arab Emirates
[3] Center for Applied and Translational Genomics (CATG), Mohammed Bin Rashid university of Medicine and Health Sciences, Dubai 0000, United Arab Emirates
[4]Institute of Biological Chemistry, Biophysics and Bioengineering, Heriot-Watt University, Edinburgh EH14 4AS,, UK
[5]Microbiota Research Center, Istinye University, Istanbul 34010, Turkey
[6]Laboratory of Proteomics, Department of Human Genetics, National Institute of Health Doutor Ricardo Jorge (INSA), Av Padre Cruz, Lisbon 1649-016, Portugal

Introduction

The human gut microbiota consists of a diverse population of microbes including bacteria, archaea, viruses, fungi, and protozoa, altogether combined with their genomes defined as microbiome [1, 2]. The composition and diversity of the gut microbiome are influenced by the position of the microbiome within the gastrointestinal (GI) tract, and other factors, such as age, dietary habits, and medications [3]. Due to its indispensable role in regulating the immune system, host nutrition, energy metabolism, synthesis of vitamins, fat storage, and influence on human behavior, the gut microbiome is often referred as the last human organ [4]. A gut microbiota acts as an endocrine organ, producing bioactive metabolites that regulate the cardiovascular and skeletal muscle systems [5, 6]. A dysbiosis of the gut microbiota can contribute to cardiovascular and skeletal muscle disorders through secreted metabolites and molecular mechanisms such as inflammation and autophagy [5, 6]. Evidence is lacking in evaluating the risks associated with changes in gut microbiota composition, leaving it unclear whether these changes are responsible for cardiovascular and skeletal muscle deconditioning in astronauts. As a result, future research into the role of gut microbiota in microgravity-related deconditioning and its potential utility as an indication of an astronaut's overall health and well-being will lead to the diagnosis and treatment of potential health concerns [7]. The study of metabolites released by the gut microbiota and how they alter various diseases is critical for better understanding the mechanisms underlying microbiota-induced diseases [8].

Due to a lack of downward pull by gravity, there is a cephalad shift of intravascular volume in microgravity, causing fluid to move from the lower extremities to the upper body [9]. This causes decrease in blood flow, reduced nutrients, and atrophy of the heart. There is also atrophy of the skeletal muscles, particularly in the soleus, gastrocnemius, quadriceps muscles of the lower legs [9, 10]. This demonstrates that cardiovascular deconditioning in microgravity can contribute to skeletal muscle atrophy, Furthermore, muscle atrophy can also result from reduced physical activity and metabolic alterations [11]. Studies have shown that exercise can partially prevent atrophy during microgravity, though it may not be entirely effective, suggesting a need for further research that seeks to develop additional interventions that preserve and maintain the overall health of astronauts in space [10, 12]. A major approach to maintain astronauts' health revolves around the gut microbiome and its secreted metabolites, as those metabolites can change in space and microgravity [13]. An exploration of the metabolome of gut microbiota changes as a result of spaceflight may be useful to assist astronauts in maintaining good health during spaceflight [13].

In this review, we discuss the role of the gut microbiota and the secreted metabolites in cardiovascular diseases (CVDs), and skeletal muscle atrophy. In particular, we focus on the molecular mechanisms associated with cardiovascular and skeletal muscle deconditioning in microgravity environments. Additionally, we explore the potential connection between alterations in gut microbiota in microgravity and their role in the development of cardiovascular diseases (CVDs) and skeletal muscle atrophy.

Gut microbiome in pathophysiology of human health

In healthy individuals, control of pathogenic bacteria in the intestinal tract is due to the homeostatic balance between commensal and potentially pathogenic bacteria. However, changes in microbial composition cause a significant imbalance between beneficial and potentially pathogenic bacteria, resulting in an increased sensitivity to pathogenic insults [14]. The imbalance between commensal and potentially pathogenic bacteria is referred to as "dysbiosis" and is triggered by a disturbance in the microbiota composition, alterations in their location, or alterations in their functional composition and metabolic activities; or the interplay between the microbes and the host health [14]. Potential alterations in gut microbiota balance at qualitative and/or quantitative levels could lead to several diseases [14]. Ian et al. demonstrated that gut microbiome composition is linked to aging which is highlighted by a loss of diversity in the core taxa [15]. Moreover, investigations of fecal samples from individuals of various age groups show that the composition and diversity of the gut microbiota change with age [16]. Lower activity, nutritional pattern, poor immune system and hence recurrent infections, drug usage, and alterations in intestinal function or structure could be contributing factors may contribute to the decline in *Bifidobacterium* and *Lactobacillus*, and an the observed increase in *Enterobacteriaceae* in older adults [17]. A number of approaches have been reviewed elsewhere for studying microorganisms isolated from a particular environment and their secreted metabolites [18, 19].

Intestinal health is usually estimated with a ratio of two dominant phyla *Firmicutes* and *Bacteroidetes* (F/B ratio), which is disturbed in different pathological conditions such as obesity, diabetes, non-alcoholic fatty liver and inflammation [20]. This ratio is commonly used as a marker for obesity and metabolic diseases as obese individuals and obese mice model revealed an increased F/B ratio, owing to ability of *Firmicutes* to extract energy from food, resulting in more efficient calorie absorption and weight gain [21]. This is more evident with increased uptake of high fiber diet which increases the abundance of *Firmicutes* [21]. A high fiber diet increases

the concentration of short-chain fatty acids (SCFAs) in the intestine, which may reduce the risk of developing colorectal cancer [22]. An even more fascinating finding is that the gut microbiome has been linked to the emergence of various types of cancer such as hepatocellular carcinoma (HCC) [23]. Gut-secreted substances like lipopolysaccharides (LPS) activate the toll-like receptor (TLR) signaling pathway, causing chronic inflammation, leading to a risk factor for HCC in humans [23]. Ma et al. showed that bile acid upregulated the expression of CXCL16 expression that regulates the accumulation of NKT cells with an active phenotype that inhibits liver tumor growth [24]. CXCL16 mediates adhesion and phagocytosis of the gut microbiome triggering inflammation [25]. These findings provide a mechanistic link between gut microbiota, serum bile acids, and tumor immune microenvironment.

The gut microbiota has a profound role in chronic inflammatory diseases like inflammatory bowel disease (IBD) which is characterized by chronic and relapsed inflammatory events in the intestine [26]. This results in prolonged ulceration of the colon due to the decrease in the important butyrate producing (*Firmicutes*) bacteria from the families *Ruminococcaceae* and *Lachnospiraceae*, as well as their proteins, indicating the potential involvement of butyrate in IBD, and the use of gut-derived metabolites as a therapeutic target to reestablish intestinal balance [27, 28]. Beyond the GI-tract, microbiota plays a role in the central nervous system (CNS) and blood-brain barrier (BBB) function by secretion of metabolites that will activate inflammatory pathways and lead to diseases such as depression, anxiety, autism, parkinson's disease, and stroke [29]. The gut-brain axis serves as a communication pathway between the gut microbiota, the brain, and the BBB [30, 31]. Signals are exchanged between the central nervous system (CNS) and the enteric nervous system via metabolites produced by the microbiota, which can enter the CNS via a variety of routes, including the vagus nerve [30, 31].

The brain microvascular endothelial cells are held together by tight junction proteins, namely claudin, occludin, and zonula occludens (ZO), which together form an endothelial cell barrier [32]. Notably, in germ-free mice, tight junction proteins claudin-5 and ZO-1 were significantly decreased, indicating a possible relationship between gut microbiota and the BBB [32]. Furthermore, after the administration of sodium butyrate, these tight junction proteins were upregulated [32]. This suggests that sodium butyrate and other microbial-derived metabolites can play a role in regulating host homeostasis, including the integrity of the BBB.Taken together, several studies revealed the potential role of the gut microbiota in various aspects of human health [7, 33]. However, there is still a pressing need for in-depth mechanistic investigations of the gut microbiota to explore their viability as diagnostic and therapeutic targets for various pathological conditions.

Cardiovascular diseases (CVDs) outcomes of gut microbiota

Cardiovascular diseases (CVDs) are considered the leading cause of mortality on a global scale. According to the World Health Organization (WHO), each year, 17.9 million deaths worldwide occur due to CVDs [34]. Unhealthy nutrition, physical inactivity, dyslipidemia, high blood pressure, and obesity are all risk factors for CVDs [35]. Furthermore, gut microbiota has recently emerged as a new risk factor in the field, in which it plays an essential role in regulating cardiovascular function and dysfunction [36]. In this section, we will discuss the role of gut microbiota and its secreted metabolites in cardiovascular function and diseases.

Role of gut microbiota and secreted metabolites in CVDs

Beyond the GI-tract, gut microbiota has been linked to several cardiovascular diseases [37, 38]. The intestinal epithelial barrier, which is maintained by tight junctions expressed between epithelial cells, acts in defending the internal milieu against the adversarial surrounding environment establishing a semi-permeable wall [39]. Several factors, including an unhealthy and fatty diet, genetic susceptibility, intestinal infections, chronic stress, and alcohol consumption, can alter the permeability of the intestinal wall, resulting in leaky gut, primarily through loosening of the tight junctions, as well as due to direct mucosal damage and inflammatory reactions [37]. Therefore, many toxins and harmful metabolites can now enter the systemic circulation and are known to cause CVDs [37]. We further discuss major metabolites such as lipopolysaccharides (LPS), 4 trimethylamine N-oxide (TMAO), Indole-3-Propionic Acid (IPA), uremic toxins, gaseous metabolites, bile acid (BAs), and short-chain fatty acids (SCFAs) involved with gut/CVD axis.

Lipopolysaccharides (LPS) in CVDs

LPS is a well-known inflammatory inducer that is found in gram-negative bacterial cell walls. In gut dysbiosis, intestinal adhesion proteins are downregulated, allowing LPS to enter systemic circulation. Enzymes in the liver metabolize LPS and excrete it in bile; if this process is disrupted, LPS can successfully enter systematic circulation [40]. In the bloodstream, LPS binds to plasma proteins such as LPS-binding protein (LBP), an acute phase protein that facilitates LPS binding to the TLR4 receptor on target tissues [40]. TLR4 activates numerous pro-inflammatory cytokines and promotes functional maturation of innate immune antigen-presenting cells [41]. Increased blood levels of LPS, which in-turn

activates reactive oxygen species (ROS) and inflammatory pathways, have been associated with the onset of atherosclerosis [42]. Several studies have confirmed and investigated further the mechanisms of LPS-induced atherosclerosis [43–45]. Others focused on targeting inflammation, mainly through TLR4, since it has shown the strongest link between inflammation and atherosclerosis [46]. In a study based on mice model given high-cholesterol diet for six months along with silencing of the TLR4 gene appeared to have decreased the size of atherosclerotic lesions, and lipid content [47]. However, Garshick et al. demonstrated that transplanting aortas from Apoe$^{-/-}$ mice with atherosclerosis into normolipidemic wild-type mice besides administering antibiotics is yet another way to target inflammation [48]. They also discovered that plaque size in Abx-WT recipient mice did not differ from Apoe-/- mice, but there was a 32% reduction in macrophages (CD68-expressing cells), indicating that antibiotics delay atherosclerosis inflammation resolution and that gut microbiota play a role in atherosclerosis inflammation [48]. The increase LPS levels in patients with atherosclerotic cardiovascular disease is mainly explained by the increased levels of *Enterobacteriaceae*, pathogenic and LPS-producing organisms within the *phylum Proteobacteria* [42]. Given that CVD is caused by a several factors, inflammation, as one of them, plays a crucial role in its progression and development, and LPS acts as a bridge between them [49].

Trimethylamine N-oxide (TMAO) in CVDs

Trimethylamine N-oxide (TMAO) is known as a risk factor for cardiovascular diseases [50]. Trimethylamine (TMA) is generated by gut microbiota from *Firmicutes* and *Proteobacteria* phyla through the conversion of L-carnitine or choline, both present in red meats [50]. TMA is then converted to TMAO by flavin-containing monooxygenase isoform-3 enzyme (FMO3) in the liver [42, 51].TMA is primarily produced from dietary choline and carnitine by enzymes such as choline-TMA lyase (CutC), and carnitine oxygenase (CntA), or by the reduction of TMAO to TMA by trimethylamine N-oxide reductase (TorA) [52]. TMAO increases foam cell production in arterial walls via reduced reverse cholesterol efflux, activation of vascular inflammation, platelet aggregation and thrombosis, upregulation of macrophage scavenger receptors, and ROS production, ultimately leading to atherosclerosis [51, 53]. Additionally, Geng.J et al. demonstrated that TMAO promotes foam formation from macrophages via the scavenger receptor CD36 and MAPK/JNK pathway [54]. TMAO inhibition has been shown in several studies to be an effective method of preventing and treating atherosclerosis [55, 56]. These methods include inhibiting the CutC enzyme, or the FMO3 enzyme, which can result in TMA accumulation and trimethylaminuria or fish malodor syndrome [56–58]. Berberine, a Chinese traditional medicine isolated from *Coptidis Rhizoma*, is a more recent approach that downregulates the choline/TMA/TMAO production pathway [59].

Firmicutes phyla that produce TMA (*Clostridium*, *Lactobacillales*, *Eubacterium*, *Anaeroglobus*, *and Roseburia* genera) which are primarily found in the oral and gut cavity, are also reported to be found in atherosclerotic plaques [37]. It is in limelight, recently, that TMAO production and thrombosis potential could be transmitted via a human fecal transplant to a germ-free recipient, providing new insight into targeting TMAO via gut microbiota modulation [60]. Resveratrol (RSV), a naturally occurring polyphenol found primarily in grapes, is widely used to treat a variety of metabolic diseases, including atherosclerosis [61]. It modulates the gut microbiota and increases the F/B ratio, lowering TMAO levels and increasing hepatic bile acid synthesis [61]. These findings suggest that the gut microbiota may be a promising target for pharmaceutical interventions to reduce the risk of CVDs. Moreover, while TMAO negatively impacts cardiovascular health, it improves enzyme kinetics in skeletal muscle but has been associated with insulin resistance [62].

Indole-3-propionic acid (IPA) in CVDs

Lactobacillus reuteri, *Akkermansia*, and *Clostiridum* genus are all involved in the formation of the anti-inflammatory metabolite indole-3-propionic acid (IPA) in the gut through tryptophan metabolism, and it has several advantageous roles, including the ability to reduce inflammation, lipid peroxidation, and free radical generation [63]. It has been shown that IPA exerts cardioprotective role by inhibiting atherosclerosis through promoting macrophage reverse cholesterol transport via regulation of miR-142-5p/ABCA1 pathway which has been demonstrated to be dysregulated in coronary artery disease (CAD) patients [64]. Furthermore, Pulakazhi et al. have shown that IPA modulates vascular function by inhibiting the release of endothelial nitric oxide synthase (eNOS)-dependent NO by activating the pregnane X receptor (PXR), which is a xenobiotic-activated nuclear receptor expressed in many tissues including vascular endothelium and reduces agonist-induced endothelium-dependent vasodilation [65]. Even though IPA has a protective effect on the cardiovascular system, most of these studies were conducted using animal models rather than clinical studies, thus further research is needed to determine the safety and effectiveness of IPA on humans.

Uremic toxins in CVDs

Para-cresol (p-cresol) is a metabolite that biotransforms the amino acids tyrosine and phenylalanine [66]. It is

predominantly produced by *Clostridium difficile*, a leading cause of diarrhea, as well as other strains within the human gut [66, 67]. Next, in the liver and the gut mucosa, aryl sulfotransferases convert p-cresol to the uremic toxin p-cresyl sulfate, and UDP-glucuronyltransferases convert a small fraction to p-cresyl glucuronide [68]. Although some studies show that p-cresol secondary metabolites have a beneficial role, these have also been linked to a variety of conditions including autism spectrum disorders (ASD), colorectal genotoxicity, platelet dysfunction [69–72]. Moreover, p-cresol and its secondary metabolites are associated with CVDs in hemodialysis patients, and exhibit biomarker potential for predicting CVDs in renal diseases [73, 74]. Jing. Y et al., demonstrated that by activating NOX, increasing ROS production, and increasing proinflammatory TNF-a cytokine expression; p-cresyl sulfate, a uremic biomarker, promotes atherogenesis in hemodialysis patients [75, 76]. These findings were consistent with Han. H et al's study on mice that underwent 5/6 nephrectomy and were treated with p-cresyl sulfate, showed increased NOX activation and ROS production, resulting in cardiac apoptosis and diastolic dysfunction [77]. Although p-cresyl glucuronide accounts for a small proportion of total p-cresol, Liabeuf et al. were the first to demonstrate its association with cardiac-related mortality [78]. Furthermore, p-cresol-treated endothelial cells produced macrovesicles, a marker of endothelial dysfunction, by upregulating miRNA-146b-5p and miRNA-223-3p, which influenced senescence, angiogenesis, and migration of mature endothelial cells [79]. Several studies indicate that uremic toxins pose significant risks to the cardiovascular system [80, 81]. Taken together, the molecular effects of uremic toxins on the cardiovascular system must be further explored, as they could be used as therapeutic targets for CVDs.

Gaseous metabolites in CVDs

Gut microbiota can produce gases metabolites such as methane, nitric oxide (NO), and hydrogen sulfide (H_2S), all of which have been linked to the cardiovascular system. Methane is produced as a byproduct by methane-producing archaea, also known as "Methanogenic archaea," when carbon dioxide is converted into methane in the presence of hydrogen [82, 83]. Chen. O et al. found that methane reduces infarct area in a rat model of myocardial infarction (MI) by inhibiting inflammation, apoptosis, and oxidative stress [84]. On other hand, Zaorska. E et al. found no effect on mean arterial pressure and heart rate in normotensive rats [85]. Thus, effect of methane against MI is specific to distinct animal models, but the underlying reason behind which needs to be delineated [85].

NO plays a well-known cardioprotective role, and its dysfunction leads to several cardiovascular diseases [86–88]. The cardioprotective roles of NO includes regulation of blood pressure, inhibition of platelet aggregation and leukocyte adhesion, and prevention smooth muscle cell proliferation; and reduced NO availability leads to endothelial dysfunction [89]. *Lactobacillus* and *Bifidobacterium* strains, as well as other gram-positive bacteria, produce NO from L-arginine by lowering gut pH via bacterial NO synthase (bNOS) [90, 91].

H_2S critically act in regulating cardiovascular diseases like arrhythmias, heart failure, ischaemic myocardial dysfunction and peripheral vascular disease [92]. Sulfate-reducing bacteria (SRB) and bacteria of the desulfhydrase enzyme produce H_2S in the gut lumen [93]. H_2S has been shown to have cardioprotective properties by inhibiting inflammation, oxidative stress, and fibrosis, or through interaction with NO [92, 94]. H_2S is involved in activation of molecular signaling cascades, post-translational modification of proteins and control of redox-dependent responses [92]. Clinically, H_2S based interventions have proved to be beneficial lowering the risk of CVD in animals in animals via the reversal of disease-programming processes [95].

Bile acids (BAs) in CVDs

Primary BA is metabolized into secondary bile acids in the intestines, which reach the systemic circulation and bind to the farnesoid X receptor (FXR), showing a range of pleiotropic effects and may indicate a relationship between the gut microbiota and cardiovascular health [96]. Moreover, it has been reported that treatment with ursodeoxycholic acid (bile acid) in patients with chronic heart failure enhanced peripheral blood flow [97]. Apart from FXR, BA also interacts several other nuclear receptors that influence the gut microbiome physiologically, such as pregnane X receptors (PXR), and constitutive androstane receptors (CAR) [98]. Once activated by BA, these receptors modulate inflammation, blood pressure, and vascular function. Dysbiosis of the gut microbiota reduces BA production, leading to less cholesterol excreted in the feces, as well as higher absorption and plasma levels of low-density lipoproteins, increasing the risk of atherosclerosis and CVD [99]. Moreover, fasting total bile acid can be used as a potential biomarker for CAD as it has been linked to CAD and the severity of the disease, in addition to myocardial infarction (MI) [100]. Taken together, BA is considered a key coordinator between the gut microbiota and the cardiovascular system. However, the exact functioning mechanism of specific BAs-receptor interaction networks is remained to be discovered.

Short-chain fatty acids (SCFAs) in CVDs

SCFAs, such as acetate, and butyrate, among others are examples of beneficial metabolites produced by the gut

microbiota as byproducts of dietary fiber fermentation [101]. Changes in SCFAs were reported to be observed in various cardiovascular diseases including heart failure models [102]. SCFAs are absorbed in the systemic circulation and affect cardiovascular function [103]. For instance, the injection of acetate or butyrate has been demonstrated to reduce blood pressure in hypertension experimental animals [101]. However, there is a decrease in butyrate-producing bacteria (*Clostridium*, *Eubacterium*, *Fusobacterium*, and *Bifidobacterium*) in gut dysbiosis, and thus a decrease in butyrate levels, which is a major energy substrate of colonocytes and could lead to local or systemic inflammations, increase plaque size in atherosclerosis, heart failure, and coronary artery disease [42]. On the other hand, Zhong et al. demonstrated that butyrate significantly accelerated the high phosphate-induced calcification and osteogenic transition of vascular smooth muscle cells (VSMC) in vitro [104]. Furthermore, it dramatically suppressed HDAC expression in VSMCs and triggered fast activation of NF-κB [104]. In summary, SCFAs play a significant role in the pathology of heart failure mainly through HDAC inhibition, mitochondrial function, and improving cardiac inflammatory response.

Role of gut microbiota in skeletal muscle atrophy

Skeletal muscle atrophy

Skeletal muscle comprises of several long and multinucleated fibers that are held together by three layers of extracellular matrix (ECM) [105]. The outer layer, epimysium surrounds the muscle, and is involved in force transmission and insulation of the muscle [105]. The intermediate layer called the perimysium groups muscle fibers into segments called fascicles and contains blood vessels, nerves, and lymphatic ducts [105]. The inner layer or endomysium is important in transmitting the force produced by the muscle to the tendon and eventually to the bone [105]. Muscle atrophy occurs due to a reduction in myofiber size, decreased protein synthesis, and increased protein degradation [105, 106]. The distinctive indicator of skeletal muscle atrophy is the shrinkage in the diameter of the myofibers [106]. Loss of skeletal muscle function and mass can have various adverse effects, such as reduced mobility, fracture risk, falls, and higher death rates [6]. Recent studies have suggested that dysbiosis of the gut microbiota plays an important role in skeletal muscle mass and functions [107]. In this section, we discuss the role of the gut microbiota and its secreted metabolites associated with skeletal muscle atrophy.

LPS in skeletal muscle atrophy

The integrity of the intestinal barrier is compromised in gut microbial dysbiosis and loss of diversity, allowing harmful microbial products such as LPS to enter the bloodstream and cause systemic inflammation, metabolic disorders, and decreased muscle function and mass [6]. LPS is well-known for inducing skeletal muscle inflammation by producing pro-inflammatory cytokines and activating inflammatory pathways such as NF-κB [108, 109]. NF-κB contributes to muscle atrophy via various mechanisms, including muscle protein degradation, inflammation, muscle fiber regeneration inhibition, and ROS production [110]. Doyle et al. showed that LPS causes muscle atrophy by activating the transcription ubiquitin ligases atrogin-1/MAFbx and MuRF1, which consider markers for muscle wasting [111, 112]. Few in-vitro studies revealed that LPS decreased membrane-bound TLR4 (inhibitor of κBα), and induced myotube atrophy [113]. On the other hand, stimulated muscle contractions are found to decrease membrane-bound TLR4 and increase soluble TLR4 (sTLR4) ultimately preventing LPS-induced signaling and myotube atrophy [113]. Even though there are a lot of studies done on muscle atrophy and LPS, evidence is still lacking to directly correlate gut microbiota with muscle atrophy which currently seeks wide attention.

IPA in skeletal muscle atrophy

A recent study aimed to investigate the role of *C. sporogenes* and its secreted IPA metabolite in skeletal muscle discovered that IPA regulates the expression of myogenic regulatory factors, effectively promotes muscle weight gain in experimental mice, and protects against inflammation via activating PXR and IPA/miR-26a-2-3p/IL-1β cascade [114]. IPA reduces inflammation not only by activating PXR, which inhibits proinflammatory cytokine secretion, but also by inducing miR-26 A expression, which ultimately downregulates the expression of proinflammatory markers (CCL2, CCL5, IL-1β, and TNFα) and hence TLR4/MyD88/NF-κB signaling pathway [114]. Although there have been few studies on the effect of IPA on skeletal muscle, it appears that IPA has a potential therapeutic utility as a nutritional intervention to reduce inflammation within atrophied skeletal muscle, yet further studies is needed in this field. Thus, IPA could be a potential therapeutic target or candidate for preventing the imbalance in muscle protein metabolism associated with muscle atrophy.

Uremic toxins in skeletal muscle atrophy

Due to cytotoxic effects, p-cresol usually accumulates in patients with chronic kidney disease and during hemodialysis; increasing the risk of cardiovascular disease, morbidity, and mortality [115]. Patients with chronic kidney disease experience significant loss of muscle mass, strength, and function, a condition associated with aging known as sarcopenia [116]. The results of incubating murine cultured myoblasts with combinations of uremic

toxins derived from indoxyl sulfate, and p-cresol, both produced by gut microbiota, showed that uremic toxins inhibit cell proliferation, increases apoptosis, inhibit myogenic differentiation, and promote muscular fibrosis; confirmed using rat model-based studies [117]. Other mechanisms through which indoxyl sulfate might cause skeletal muscle atrophy include increase in ROS, increase in inflammatory cytokines, phosphorylation of ERK, JNK, and p38, as well as an activation of the muscle atrophy F-box (MAFbx) [118, 119]. It is essential to conduct more in vivo research on the effects of uremic toxins on skeletal muscle atrophy models.

Gaseous metabolites in skeletal muscle atrophy

In this section, we will explore the influence of metabolites, such as methane, NO, and H2S, on skeletal muscle atrophy. Although methane production is a critical metabolite in reducing the pressure of hydrogen required in ruminal fermentation, it can lead to a reduction in gross energy. As a result, developing strategies to reduce methane emissions is critical [120]. Lovastatin, a secondary metabolite produced during fungal growth that inhibits methane emission, caused myopathy and skeletal muscle damage in goats [120]. Moreover, RSV, the naturally occurring polyphenol, also could reduce methane production, but unlike lovastatin, it prevents muscle loss, reduces aging-related muscle loss, and improves exercise performance [121]. Further research needs to investigate the direct role of enteric methane in skeletal muscle atrophy. NO on the other hand, have benefical role in the skeletal muscle, as studies found that NO and its precursor L-Arginine amino acid play a protective and important role in skeletal muscle through increasing protein accumulation and muscle development via the mTOR pathway, regulating autophagy, and mitochondrial unfolded protein response [122, 123]. Furthermore, NO treatment of an atrophied skeletal muscle model in mice prevented muscle mass loss which further confirms the protective role of NO in skeletal muscle [124]. Lastly, H_2S has been found to regulate inflammatory responses and redox signaling pathways in a variety of tissues including muscles. The anti-inflammatory and antioxidant characteristics of H_2S prevent muscle loss caused by immobilization conditions such as prolonged bed rest or unloading, and muscle fibrosis [125, 126]. Furthermore, it can reduce endoplasmic reticulum (ER) stress protein markers, a condition known to cause muscle atrophy due to reduced capacity of proper protein folding [127, 128]. These findings suggest the therapeutic potential of H_2S to treat patients with disuse-associated muscle atrophy.

Taken together, Investigating how gaseous metabolites such as methane, NO, and H2S affect muscle metabolism, inflammation, and oxidative stress could provide useful insights into muscle atrophy and novel therapies.

Bile acids (BAs) in skeletal muscle atrophy

Bile acid has been shown in studies to modulate skeletal muscle by binding to the farnesoid X receptor (FXR), which produces fibroblast growth factor (FGF) 19 and activates the protein kinase (ERK) signaling pathway and its downstream targets to increase muscle mass [129]. Similarly, Qiu et al. discovered that depleting the gut microbiota with an antibiotic cocktail (Abx) caused skeletal muscle atrophy due to microbial dysbiosis and altered bile acid metabolism in the intestine, which was characterized by the inhibition of FGF15 signaling [130]. A decrease in FGF15 causes skeletal muscle atrophy by inhibiting muscle protein synthesis via the ERK1/2 pathway [107]. Studies have also shown that bile acids like Cholic acid and Deoxycholic acid decrease the fiber diameter and MHC protein levels, and there is an increase in atrogin-1, MuRF-1, and oxidative stress [130]. The protective function of bile acid has been investigated in several studies suggesting the potential use of bile acid against skeletal muscle atrophy [107, 130].

SCFA in skeletal muscle atrophy

SCFAs have been shown to affect protein metabolism in skeletal muscle tissues as well as improve muscle mass retention [131]. Moreover, a study on the role of SCFA in Chinese children aged 6–9 years found an association between intestinal microbiota and SCFA in skeletal muscle mass and function [132]. In vitro studies have shown that acetate improves glucose uptake and fatty acid metabolism while increasing the expression of GLUT4 and myoglobin [133]. Other studies have revealed that butyrate enhances metabolism and prevents age-related muscle loss [134]. In diabetic nephropathy mice models, butyrate alleviated muscle atrophy, promoted PI3K/Akt/mTOR signaling, and suppressed oxidative stress and autophagy in skeletal muscle [135]. Thus, butyrate exerts protective effects on muscle atrophy by enhancing intestinal barrier function and activating the FFA2 receptor-mediated PI3K/Akt/mTOR pathway [135]. Furthermore, SCFA administration to germ-free mice was shown to partially reduce skeletal muscle dysfunction caused by gut microbiota depletion, implying a robust role of gut microbiota and SCFA in skeletal muscle mass and function [136].

Microgravity

The term "microgravity" describes a condition known as "weightlessness" that happens only in space [137]. Even though 'g' is not equal to zero, the term "microgravity" is used because gravitational force is minimal and close to zero (ug) [137]. Astronauts are known to experiences various stressors in microgravity environments including cardiovascular deconditioning such as cephalad fluid shift, decrease of left ventricular mass, and decrease

of ventricular stroke volume [138, 139]. Upon returning to earth, these changes become more evident in the form of orthostatic intolerance, increased heart rate, and reduced physical capacity [138]. Generally, reduced physical capacity is partly due to muscle weakness and wasting, also known as "muscle deconditioning," caused by microgravity and prolonged bed rest [140, 141]. During microgravity, a fluid shift from the lower to the upper body may impair gastrointestinal function, resulting in changes in gut microbiota composition, which is linked to several diseases [142]. However, the impact of gut microbiota composition and its secreted metabolites in microgravity-induced disorders like cardiovascular and muscles deconditioning is not well investigated yet. Several changes that occur due to microgravity resemble those associated with prolonged bed rest; thus, research in the field of microgravity has applications not only in space but also on Earth as it provides insight into the mechanisms involved in deconditioning [143].

Cardiovascular deconditioning in microgravity

Microgravity environment and its effects on human health has become an evolving field in research due to the increase interest in space travel [144]. Changes in cardiovascular system are among the major and critical adaptations to the microgravity environment resulting in cardiac remodeling [145]. The structural renewal or reorganization of live tissue is referred to as tissue remodeling [145]. Cardiac remodeling is characterized as a series of molecular and cellular changes that manifest clinically as changes in the cardiac size, mass (hypertrophy or atrophy), form (heart wall geometry and thickness), post- injury function, and it is attributed to ventricular dysfunction [146]. Though asymptomatic initially, it can progress to signs and symptoms similar to heart failure [146]. A rodent hindlimb unloading (HU) model demonstrated a decrease in heart weight, reduced left ventricular ejection fraction (LV-EF), and decreased LV-FS (fractional shortening), indicating altered heart function in simulated microgravity [147]. Likewise, after 10 days in space, astronauts reported a 9.1% decrease in LV mass [147–149]. At this point, it is important to review further details of cardiac outcomes due to the effect of microgravity.

Molecular mechanisms of cardiac remodeling due to simulated microgravity

At molecular level, HU mice have shown an upregulation in cardiac remodeling markers such as HDAC4, and ERK [149]. HDAC4 is expressed in the heart and is important in regulating heart function and ischemia injury [150]. One of the targets of HDAC4 is myocyte enhancer factor 2 (MEF2) transcription factor, which is inhibited by HDAC4 through binding and catalyzing local histone deacetylation [151]. Studies showed that MEF2 is involved in cardiomyocyte remodeling through activation of its target myotonic dystrophy protein kinase (DMPK) which will lead to a loss of sarcomere structure [152]. HDAC4 was phosphorylated in HU mice, resulting in its export to the cytoplasm followed by subsequent activation of MEF2 and its downstream target genes involved in pathological cardiac remodeling [149].

ERK1/2 activation mediates both pathological and physiological cardiac remodeling. Exercise results in physiologic cardiac hypertrophy: rats swimming 90 min per day for 12 weeks showed increased expression of ERK and p90RSK which are responsible for cell growth and protein synthesis [153]. ERK phosphorylation at threonine 188, on the other hand, causes abnormal hypertrophy in pressured mouse models, human heart failure, and patients with fast-progressing aortic valve stenosis; however, further research is required to determine the molecular mechanism and the differences between pathological and physiological cardiac remodeling [154]. In hypertension, angiotensin II is the primary effector hormone (AngII), which causes physiological vasoconstriction and regulates blood pressure [154].Furthermore, elevated AngII amounts following myocardial infarction and throughout ventricular hypertrophy indicate that AngII promotes abnormal cardiac cell growth [154]. Mechanical stretch increases ERK-induced hypertrophy in an AngII-associated manner, mainly through ERK stabilization of the insulin-like growth factor II receptor (IGF-IIR) protein [154]. ERK5, the last classic MAPK subfamily, is activated by both growth and stress stimuli; thus, it plays a role in sarcomere elongation [154]. Recently, it has been established that ERK5 contributes an important role in the development of damaging hypertrophy [155]. Pressured mice with cardiomyocyte-specific ERK5 deletion demonstrated decreased hypertrophic response and activation of apoptosis markers [154, 156]. HU mice following 28 days of unloading showed upregulation of phosphorylated ERK [147]. This increase in p-ERK coupled with an increase in heart mass remained after seven days of recovery indicating the role of ERK in both physiological and pathogenic cardiac remodeling [147].

Apoptosis has also been linked to pathogenic cardiac remodeling associated with LV dysfunction, ischemia-reperfusion and myocardial infarction (MI) [157]. Additionally, the loss of cardiomyocytes due to apoptosis can contribute to congestive heart failure [157]. Elevated levels of apoptosis were observed in cardiac transplantation patients with idiopathic dilated cardiomyopathy, highlighting a connection between apoptosis and end-stage heart failure [158]. Studies in endothelial cells exhibited that cardiovascular disease highly correlates with the microgravity-induced impact on endothelial cell (EC) proliferation, survival, and apoptosis [158]. This finding

is cell- type specific as HUVEC and bovine aortic endothelial cells (BAEC) cells proliferated faster compared to microvascular endothelial cells (HMEC) [159–161]. In porcine endothelial cells (PAEC), studies with simulator models of microgravity expressed upregulation of TP53, FASLG, and BAX genes together with a downregulation of BCL2 and PCNA genes [162]. Even though large set of studies in-vitro and in-vivo have been carried out, it is still unclear how cardiac apoptosis is triggered by microgravity. Moreover, regulation of apoptotic pathways when cardiac cells adapt to the microgravity environment is yet to be deciphered.

Skeletal muscle deconditioning in microgravity

Skeletal muscle, constituting roughly half of body weight, not only facilitates body movements but also plays essential roles in heat generation, blood sugar regulation, amino acid storage, and modulation of in-vivo physiological functions, showcasing its adaptability and plasticity in response to diverse environmental and disease-related factors [163, 164]. Traditionally recognized as a contractile organ, skeletal muscle also plays pivotal roles in metabolic regulation, glucose storage, and endocrine signaling, functioning as a secretory organ that releases an array of growth factors and cytokines [163, 164]. However, in the microgravity environment, significant alterations in skeletal muscle structure and function have been observed [165]. Despite exercise programs being implemented in space, studies by Fitts et al. reveal substantial losses in fiber mass, force, and power, indicating that exercise alone in microgravity fails to prevent muscle atrophy, underscoring the imperative need for further interventions, including pharmaceutical agents, to mitigate muscle wasting [165]. A simulated microgravity environment provides insight into skeletal muscle atrophy's molecular causes, which may provide therapeutic targets to mitigate muscle waste during space travel.

Molecular mechanisms of skeletal muscle atrophy due to simulated microgravity

At the molecular level, the inflammatory process is a major pathologic factor contributing to skeletal muscle dysfunction [166]. It interferes with muscle homeostasis and myogenesis, and contributes to skeletal muscle atrophy [166]. Forkhead box class O (FoxO) transcription factors are activated by inflammation, which leads to the activation of the ubiquitin-proteasome system (UPS), particularly lysosomal proteolysis, inducing muscle atrophy [166]. Baek et al. demonstrated that subjecting C2C12 myoblasts cell line to simulated microgravity utilizing 3D clinorotation increased FOXO transcriptional activity and resulted in lower myocyte size via stimulation of atrophy genes [167]. In addition, inflammation mediated by NF-κB can lead to increased expression of muscle ring finger 1 (MuRF1), which is E3 ubiquitin ligase inducing muscle atrophy [168]. Moreover, MuRF1 plays a role in remodeling both cardiac and skeletal muscle [169]. MuRF1 targets the crucial sarcomere proteins and hence plays an important role in the breakdown and destruction of the skeletal muscle contractile machinery [170]. MuRF1 expression increases in microgravity models, the progressive muscular atrophy in HU conditions [170]. Micro-RNAs are also predicted to have important role in eliciting inflammation in microgravity models of muscle atrophy. Studies showed that pathways controlled mainly by let-7a and miR-1, miR-125b-5p, miR-95-5p, miR-222-3p are involved in skeletal muscle response to microgravity, and highlight the important role played by inflammation in muscle atrophy [171]. Moreover, the microgravity environment also affects the gut microbiota compensation; we will discuss in the following sections these changes that happen in microgravity and compare them with the changes in gut microbiota in conditions like CVDs and skeletal muscle atrophy. Figure 1 summarizes these changes.

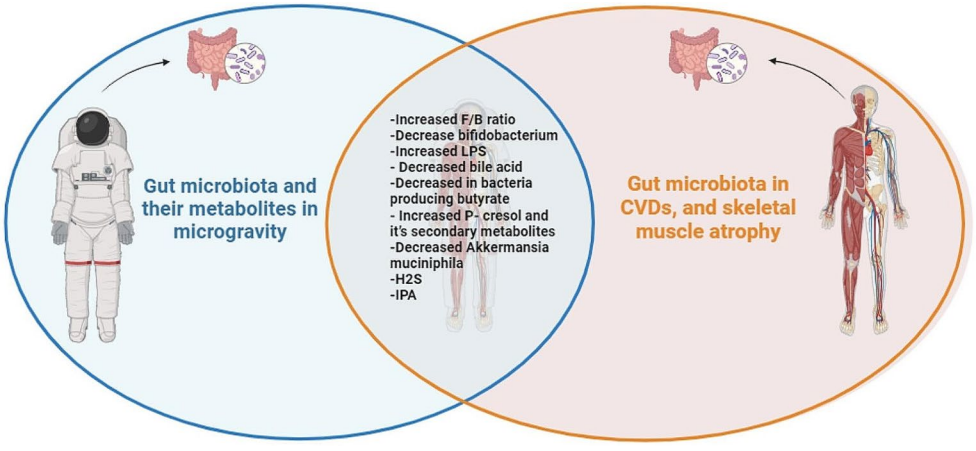

Fig. 1 Common changes in microbiota and its secreted metabolites in microgravity, and in CVDs and skeletal muscle atrophy

Gut microbiota dysbiosis in the microgravity environment, CVDs, and skeletal muscle atrophy

The national aeronautics and space administration (NASA) recently conducted an interesting study whereby the gut microbiome of an astronaut and his twin who remained on Earth were compare [172]. Alterations in the gut microbiome and its metabolites were detected during his 1-year mission aboard the International Space Station (ISS) that were not seen in his twin on Earth during the same time [172]. These changes include a higher F/B ratio in space, a decrease in IPA which has anti-inflammatory effects, a reduction in bile acid, and a significant increase in p-cresyl sulfate and p-cresyl glucuronide [172]. Moreover, in a study of 15-day and 35-day spaceflight missions, results revealed a fluctuation between the subjects, with *Firmicutes* abundance gradually increasing and *Bacteroides* abundance gradually decreasing after 15 days in space [173]. This variability in their results is primarily due to the small sample size [173]. Similarly, coronary artery disease, stroke, and heart failure have all been linked to a higher F/B ratio, suggesting a possible relationship between changes in gut microbiota in the microgravity environment and changes of gut microbiota in various CVDs [42]. Furthermore, due to its protective effect on the cardiovascular system and skeletal muscle, the decrease in IPA levels seen in the astronaut could be responsible for cardiovascular and skeletal deconditioning.

Similar to NASA twin study, Michael A. S et al., showed that plasma p-cresol glucuronide and p-cresol sulfate levels were higher in one of the monozygotic twins who spent 340 days aboard the ISS compared to his identical twin (ground subject) [174]. P-cresol not only has adverse effects on the cardiovascular system, but it also alters the gut microbiome, favoring the survival of pathogens such as *Clostridia*, and inhibits butyrate producers, in addition to depleting the hepatic sulfur pool, which affects drug metabolism, and endogenous metabolites [174]. Since this metabolite is found in the microgravity environment, CVDs, and skeletal muscle abnormalities, it suggests a robust potential risk factor. Therefore, relationship between this metabolite and microgravity-induced cardiovascular and skeletal muscle deconditioning, as well as potential mitigation strategies, must be investigated.

In a study using a HU mouse model, revealed a decrease in the abundance of gut *Bifidobacterium* spp. and *Akkermansia muciniphila* within 3 days of HU, along with an increase in LPS-binding protein and inflammation, however; supplementation of *Bifidobacterium* spp. inhibited the endotoxemia [175]. The reduction in *Bifidobacteria* observed in HU mice might increase the risk of cardiovascular diseases, as discussed previously [42]. *Bifidobacteria* are known to produce anti-inflammatory metabolites such as butyrate, and their reduction can lead to systemic inflammation and an elevated risk of cardiovascular diseases. [42]. Furthermore, *Akkermansia muciniphila* is known as gut microbial marker in healthy individuals, and for its protective role in cardiovascular and skeletal muscle health, thus; its decrease in HU mice may explain the possible microgravity-related cardiovascular and skeletal muscle deconditioning that takes place [176, 177]. Lastly, HU mice showed increase in LPS-binding protein and inflammation, LPS is known to activate reactive oxygen species (ROS), inflammatory pathways, and it has been associated to the onset of atherosclerosis [42]. ROS can produce arrhythmias, cardiac remodeling by apoptosis and necrosis, smooth muscle hypertrophy, and endothelial cell oxidative injury [42, 178]. Besides CVDs, patients with low muscle mass also have a high abundance of gram-negative bacteria with LPS [179].

In the "MARS500 study," where 6 astronauts were kept within an analog Mars-surface habitat for 520 days, there was a decrease in butyrate-producing bacteria such as *Faecalibacterium prausnitzii* after one year, with reduction in anti-inflammatory bacteria such as *Ruminococcus bromii*, and *Lactobacillus acidophilus* [180]. As previously discussed, butyrate has a protective role in both skeletal muscle atrophy and CVDs [135, 181].

In addition to its protective role in cardiovascular and skeletal muscle atrophy, as mentioned above, H2S treatment enhanced osteoblast surface and maintained mechanical strength in simulated microgravity [182]. Additionally, it reduced IL-6 levels in serum, skeletal muscle, and tibiae [182].

In a recent study on rhesus macaques, researchers positioned the animals in head-down tilted bed rest (HDBR) at a 6° angle for six weeks to induce muscle atrophy [183]. Using metagenomics analysis of fecal samples, they identified several bacterial genera associated with abnormal amino acid metabolism in atrophied muscle: *Oligella*, *Sporosarcina*, *Citrobacter*, *Weissella*, *and Myroides* [183]. Additionally, they discovered several genera related with immune dysfunction (*Klebsiella*, *Kluyvera*, *and Bifidobacterium*) [183]. This highlights the significance of the gut microbiota in skeletal muscle function and implies that the host-microbiota interaction involves inflammatory and metabolic pathways, potentially leading to diverse abnormalities [183].

Overall, dysbiosis of the gut microbiota in microgravity has been reported in many studies [8, 184]. However, little research has been conducted on the consequences and the effects of these changes in the gut microbiota and its secreted metabolites on the entire body system of the astronauts, although it was known that the gut microbiota and its secreted metabolites have been reported to have cardiovascular and skeletal muscle effects. The similarities between gut microbiota dysbiosis in microgravity and those occurring in cardiovascular disease

and skeletal muscle atrophy suggest that gut microbiota and their secreted metabolites could be the underlying cause of microgravity-induced cardiovascular and skeletal deconditioning. In Table 1, different metabolites and their role in CVD, skeletal muscle atrophy, along with the effect of microgravity on the levels of these metabolites, are outlined.

Gut microbiota modulation

Gut microbiota balance and health can be modulated through the administration of prebiotics, probiotics and postbiotics [185]. Probiotics consist of live microorganisms, prebiotics are compounds utilized by these microorganisms, and postbiotics are bioactive metabolites produced when beneficial gut microbes metabolize prebiotics or from bacterial cell wall components after cell wall damage, all contributing to our health [30, 186, 187]. Considering that *Lactobacillus casei* strain Shirota (LcS) has the potential to boost innate immunity and balance the microbiota in the intestinal tract, its stability in capsules containing freeze-dried LcS was evaluated over a period of one month on the International Space Station (Probiotics Package) [188]. As a result, it was discovered that LcS retained its viability and fundamental probiotic qualities for one month, even though most astronauts spend longer periods in space [188]. Several studies have found that prebiotics supplementation improves the health of humans in several ways, including improving memory, upregulating anti-inflammatory cytokines and downregulating proinflammatory cytokines, and improving lipid metabolism and glucose homeostasis in type 2 diabetics [189–191]. It has also been found that prebiotics reduce the effects of oxidative stress and inflammation, which are known to increase the risk of CVD [42, 192]. Additionally, Postbiotics have been demonstrated to protect against a wide range of diseases, including cancer, autoimmune diseases, inflammatory disorders, and

Table 1 The role of different metabolites in CVDs, skeletal muscle atrophy, and the possible link to microgravity findings

Metabolite	Role in the cardiovascular system	Role in skeletal muscle atrophy	Effect of microgravity on this metabolite	References
LPS	LPS stimulates ROS production and activates inflammatory pathways that are linked to the onset of atherosclerosis.	Causes skeletal muscle atrophy by activating atrogin-1/MAFbx and MuRF1 and induces inflammation by activating NF-κB.	HU mice showed higher plasma LPS-binding protein.	[42, 108, 112, 175].
TMAO	TMAO causes atherosclerosis by increasing foam cell formation in artery walls.	improves enzyme kinetics in skeletal muscle but has been associated with insulin resistance.	-	[51, 62].
IPA	Promote macrophage reverse cholesterol transport.	Regulates the expression of myogenic regulatory factors, promotes muscle weight gain, and protects against inflammation	NASA twin study showed that astronauts had decreased levels of IPA.	[64, 114, 172].
p-cresol	Induce endothelial dysfunction by upregulating miRNA-146b-5p and miRNA-223-3p	Cell proliferation is inhibited, apoptosis is increased, myogenic differentiation is inhibited, and muscular fibrosis is promoted when combined with indoxyl sulphate.	Plasma p-cresol glucuronide and p-cresol sulfate levels were higher in one of the monozygotic twins who spent 340 days aboard the ISS.	[79, 117, 174]
Methane	Decreases the size of the infarct in a rat model of myocardial infarction (MI) by preventing oxidative stress, apoptosis, and inflammation	Methane inhibition leads to skeletal muscle myopathy.	-	[84, 120]
Nitric Oxide (NO)	Cardioprotective role and its malfunction leads to a variety of cardiovascular diseases.	NO treatment to skeletal muscle atrophy mice model resulted in decreased muscle mass loss.	-	[86, 124]
Hydrogen Sulfide (H2S),	Cardioprotective effect by inhibition of inflammation, oxidative stress, and fibrosis, or interaction with NO.	H2S's anti-inflammatory and antioxidant properties protect against muscle loss caused by prolonged bed rest or unloading, as well as muscular fibrosis. Inhibits ER stress protein markers.	H2S treatment improved the osteoblast surface, maintained mechanical strength in simulated microgravity.	[92, 94, 125–127, 182]
Bile acid	Patients with chronic heart failure who received bile acid treatment had increased peripheral blood flow.	Bile acid enhances muscle mass via binding to FXR, which produces FGF19 and activates the protein kinase (ERK) signaling pathway.	A NASA twin investigation found that astronauts had reduction in bile acid than his identical twin who remained on Earth.	[96, 100, 172]
SCFA	Butyrate reduction led to inflammation, increased plaque size in atherosclerosis, heart failure, and coronary artery disease.	SCFA treatment in germ-free mice reduced skeletal muscle dysfunction induced by gut microbiota depletion.	MARS500 study showed a decrease in butyrate-producing bacteria.	[42, 136, 180]

cardiovascular diseases, in addition to enhancing skeletal muscle mass and function [193–195].

As previously discussed, postbiotics (metabolites) have a variety of roles in cardiovascular and skeletal muscle health and disease. It also protects against pathogens, improves the epithelial barrier, and regulates inflammatory and immunological responses. Despite their lower ability to alter intestinal metabolism or gene expression, postbiotics are considered safer, more stable, and less likely to lead to antibiotic resistance than probiotics, whose half-life is shorter, their effects are heterogeneous, and they are more likely to cause infections [196].

The microgravity environment has been observed to impair the immune system, making the administration of probiotics harmful [197]. Administration of prebiotics and postbiotics overcomes the limitations of probiotics [196, 197]. Since NASA and other space agents are planning for long-term space missions to Mars and the Moon, it is critical to keep the crew healthy to complete the mission successfully [198]. Further research on the role of prebiotics, probiotics, or postbiotics and their use as therapeutic interventions to countermeasure and/or prevent microgravity-related disorders should be conducted to achieve this goal, emphasizing their viability and mechanism of action.

Moreover, exercise is one strategy to control gut microbiota, since it has been proven to increase beneficial microbial species, enrich microflora diversity, and promote the growth of commensal bacteria [199–201]. Furthermore, exercise particularly resistance training in microgravity environment serves as an essential intervention for preventing the negative effects of muscle atrophy, maintaining musculoskeletal health and functional capacity among astronauts during long-term missions [202]. Despite the significance of exercise in alleviating microgravity-induced skeletal muscle deconditioning, exercise alone is not exclusively successful in preserving muscle structure and function, emphasizing the significance of other effective intervention measures [202].

Concluding remarks and future perspectives

Numerous cardiovascular and musculoskeletal diseases are associated with microbial composition of the gut microbiota and its associated metabolites. Microgravity environments have also been observed to have several adverse effects on the cardiovascular system, skeletal muscle, and gut microbiota composition. Throughout this review, we investigated the similarities between changes in gut microbiota and its secreted metabolites in microgravity and those known to cause cardiovascular diseases and skeletal muscle atrophy. We concluded that gut microbiota and their secreted metabolites may partly be responsible for microgravity-related cardiovascular and skeletal muscle deconditioning. Furthermore, it is essential to note that depending on the type of bacteria, and the levels/type of metabolites secreted will determine whether it has a protective effect on cardiovascular and skeletal muscle or not. As a result, the best approach to restore normal gut flora balance is personalized modulation of the gut microbiota. Compared to probiotics, postbiotics or metabolites are considered safer alternative for gut microbiota regulation in space, although their discrete mechanism is not entirely understood. To use metabolites as therapeutic targets in space, it is important to have comprehensive knowledge of these metabolites. Future studies should be designed to address critical questions, such as: (1) Is there a direct correlation between metabolites secreted by gut microbiota and abnormalities induced by microgravity? (2) What mechanisms underlie the ability of these metabolites to trigger cardiovascular and skeletal muscle deconditioning in a microgravity environment? (3) Could compensating for these metabolites improves the cardiovascular and skeletal muscle function in a microgravity environment?

To address these research questions, additional studies in both simulated and realistic microgravity environments are warranted.

Author contributions

ABE and ZI and NAK conceived the idea. ZI and RS and NAK and ABE reviewed literature and prepared the first draft of the manuscript. RQ and HM and NCS and RS and ABE corrected the manuscript. All authors read and approved the final manuscript.

Funding

ZI is partially supported by College of Graduate Studies, University of Sharjah, and ABE by Competitive Research Grant number 230110901140, University of Sharjah, UAE. RS and NAK are supported by the Air Force Office of Scientific Research (AFOSR), USA, Grant number FA9550-23-1-0711.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 February 2024 / Accepted: 27 July 2024
Published online: 09 August 2024

References

1. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449(7164):804–10.
2. Peroni DG, Nuzzi G, Trambusti I, Di Cicco ME, Comberiati P. Microbiome Composition and its impact on the development of allergic diseases. Front Immunol. 2020;11:700.
3. Dekaboruah E, Suryavanshi MV, Chettri D, Verma AK. Human microbiome: an academic update on human body site specific surveillance and its possible role. Arch Microbiol. 2020;202(8):2147–67.
4. Amon P, Sanderson I. What is the microbiome? Arch Dis Child Educ Pract Ed. 2017;102(5):257–60.

5. Chen X, Zhang H, Ren S, Ding Y, Remex NS, Bhuiyan MS, et al. Gut microbiota and microbiota-derived metabolites in cardiovascular diseases. Chin Med J (Engl). 2023;136(19):2269–84.
6. Li G, Jin B, Fan Z. Mechanisms involved in gut microbiota regulation of skeletal muscle. Oxid Med Cell Longev. 2022;2022:2151191.
7. Ramos-Nascimento A, Grenga L, Haange SB, Himmelmann A, Arndt FS, Ly YT, et al. Human gut microbiome and metabolite dynamics under simulated microgravity. Gut Microbes. 2023;15(2):2259033.
8. Yuan L, Zhang R, Li X, Gao C, Hu X, Hussain S, et al. Long-term simulated microgravity alters gut microbiota and metabolome in mice. Front Microbiol. 2023;14:1100747.
9. Lee PHU, Chung M, Ren Z, Mair DB, Kim DH. Factors mediating spaceflight-induced skeletal muscle atrophy. Am J Physiol Cell Physiol. 2022;322(3):C567–80.
10. Tanaka K, Nishimura N, Kawai Y. Adaptation to microgravity, deconditioning, and countermeasures. J Physiol Sci. 2017;67(2):271–81.
11. Chen X, Ji Y, Liu R, Zhu X, Wang K, Yang X, et al. Mitochondrial dysfunction: roles in skeletal muscle atrophy. J Transl Med. 2023;21(1):503.
12. Comfort P, McMahon JJ, Jones PA, Cuthbert M, Kendall K, Lake JP, et al. Effects of Spaceflight on Musculoskeletal Health: a systematic review and Meta-analysis, considerations for Interplanetary Travel. Sports Med. 2021;51(10):2097–114.
13. Tesei D, Jewczynko A, Lynch AM, Urbaniak C. Understanding the complexities and changes of the astronaut microbiome for successful long-duration space missions. Life (Basel). 2022;12(4).
14. DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current understanding of Dysbiosis in Disease in Human and Animal models. Inflamm Bowel Dis. 2016;22(5):1137–50.
15. Jeffery IB, Lynch DB, O'Toole PW. Composition and temporal stability of the gut microbiota in older persons. ISME J. 2016;10(1):170–82.
16. Azcarate-Peril MA, Sikes M, Bruno-Barcena JM. The intestinal microbiota, gastrointestinal environment and colorectal cancer: a putative role for probiotics in prevention of colorectal cancer? Am J Physiol Gastrointest Liver Physiol. 2011;301(3):G401–24.
17. Kim M, Benayoun BA. The microbiome: an emerging key player in aging and longevity. Transl Med Aging. 2020;4:103–16.
18. Zhang L, Chen F, Zeng Z, Xu M, Sun F, Yang L, et al. Advances in Metagenomics and its application in environmental microorganisms. Front Microbiol. 2021;12:766364.
19. Mohd Kamal K, Mahamad Maifiah MH, Abdul Rahim N, Hashim YZH, Abdullah Sani MS, Azizan KA. Bacterial metabolomics: Sample Preparation methods. Biochem Res Int. 2022;2022:9186536.
20. Vaiserman A, Romanenko M, Piven L, Moseiko V, Lushchak O, Kryzhanovska N, et al. Differences in the gut Firmicutes to Bacteroidetes ratio across age groups in healthy Ukrainian population. BMC Microbiol. 2020;20(1):221.
21. Magne F, Gotteland M, Gauthier L, Zazueta A, Pesoa S, Navarrete P et al. The Firmicutes/Bacteroidetes ratio: a relevant marker of gut dysbiosis in obese patients? Nutrients. 2020;12(5).
22. Mirzaei R, Afaghi A, Babakhani S, Sohrabi MR, Hosseini-Fard SR, Babolhavaeji K, et al. Role of microbiota-derived short-chain fatty acids in cancer development and prevention. Biomed Pharmacother. 2021;139:111619.
23. Zhang C, Yang M, Ericsson AC. The potential gut microbiota-mediated treatment options for Liver Cancer. Front Oncol. 2020;10:524205.
24. Ma C, Han M, Heinrich B, Fu Q, Zhang Q, Sandhu M et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science. 2018;360(6391).
25. Diegelmann J, Seiderer J, Niess JH, Haller D, Goke B, Reinecker HC, et al. Expression and regulation of the chemokine CXCL16 in Crohn's disease and models of intestinal inflammation. Inflamm Bowel Dis. 2010;16(11):1871–81.
26. Haneishi Y, Furuya Y, Hasegawa M, Picarelli A, Rossi M, Miyamoto J. Inflammatory bowel diseases and Gut Microbiota. Int J Mol Sci. 2023;24(4).
27. Vijay A, Valdes AM. Role of the gut microbiome in chronic diseases: a narrative review. Eur J Clin Nutr. 2022;76(4):489–501.
28. Geirnaert A, Calatayud M, Grootaert C, Laukens D, Devriese S, Smagghe G, et al. Butyrate-producing bacteria supplemented in vitro to Crohn's disease patient microbiota increased butyrate production and enhanced intestinal epithelial barrier integrity. Sci Rep. 2017;7(1):11450.
29. Zhu S, Jiang Y, Xu K, Cui M, Ye W, Zhao G, et al. The progress of gut microbiome research related to brain disorders. J Neuroinflammation. 2020;17(1):25.
30. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203–9.
31. Garcia-Cabrerizo R, Carbia C, KJ OR, Schellekens H, Cryan JF. Microbiota-gut-brain axis as a regulator of reward processes. J Neurochem. 2021;157(5):1495–524.
32. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6(263):263ra158.
33. Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, et al. Human gut microbiota in health and disease: unveiling the relationship. Front Microbiol. 2022;13:999001.
34. Organisation WH. Cardiovascular Diseases 2022 [https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1
35. Bays HE, Taub PR, Epstein E, Michos ED, Ferraro RA, Bailey AL, et al. Ten things to know about ten cardiovascular disease risk factors. Am J Prev Cardiol. 2021;5:100149.
36. Ascher S, Reinhardt C. The gut microbiota: an emerging risk factor for cardiovascular and cerebrovascular disease. Eur J Immunol. 2018;48(4):564–75.
37. Novakovic M, Rout A, Kingsley T, Kirchoff R, Singh A, Verma V, et al. Role of gut microbiota in cardiovascular diseases. World J Cardiol. 2020;12(4):110–22.
38. Nesci A, Carnuccio C, Ruggieri V, D'Alessandro A, Di Giorgio A, Santoro L et al. Gut microbiota and Cardiovascular Disease: evidence on the metabolic and inflammatory background of a Complex Relationship. Int J Mol Sci. 2023;24(10).
39. Barbara G, Barbaro MR, Fuschi D, Palombo M, Falangone F, Cremon C, et al. Inflammatory and microbiota-related regulation of the intestinal epithelial barrier. Front Nutr. 2021;8:718356.
40. Violi F, Cammisotto V, Bartimoccia S, Pignatelli P, Carnevale R, Nocella C. Gut-derived low-grade endotoxaemia, atherothrombosis and cardiovascular disease. Nat Rev Cardiol. 2023;20(1):24–37.
41. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. Cytokine. 2008;42(2):145–51.
42. Feng D, Christensen JT, Yetman AT, Lindsey ML, Singh AB, Salomon JD. The microbiome's relationship with congenital heart disease: more than a gut feeling. J Congenital Cardiol. 2021;5.
43. Caesar R, Fak F, Backhed F. Effects of gut microbiota on obesity and atherosclerosis via modulation of inflammation and lipid metabolism. J Intern Med. 2010;268(4):320–8.
44. Verhaar BJH, Prodan A, Nieuwdorp M, Muller M. Gut microbiota in hypertension and atherosclerosis: a review. Nutrients. 2020;12(10).
45. Page MJ, Kell DB, Pretorius E. The role of Lipopolysaccharide-Induced cell signalling in chronic inflammation. Chronic Stress (Thousand Oaks). 2022;6:24705470221076390.
46. Huang B, Chen H, Fan M. Inhibition of TLR4 signaling pathway: molecular treatment strategy of periodontitis-associated atherosclerosis. Med Hypotheses. 2008;70(3):614–7.
47. Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, et al. Lack of toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. Proc Natl Acad Sci U S A. 2004;101(29):10679–84.
48. Garshick MS, Nikain C, Tawil M, Pena S, Barrett TJ, Wu BG, et al. Reshaping of the gastrointestinal microbiome alters atherosclerotic plaque inflammation resolution in mice. Sci Rep. 2021;11(1):8966.
49. Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, et al. Inflammation and cardiovascular disease: from mechanisms to therapeutics. Am J Prev Cardiol. 2020;4:100130.
50. Canyelles M, Borras C, Rotllan N, Tondo M, Escola-Gil JC, Blanco-Vaca F. Gut microbiota-derived TMAO: a causal factor promoting atherosclerotic Cardiovascular Disease? Int J Mol Sci. 2023;24(3).
51. Steinke I, Ghanei N, Govindarajulu M, Yoo S, Zhong J, Amin RH. Drug Discovery and Development of Novel therapeutics for inhibiting TMAO in models of atherosclerosis and diabetes. Front Physiol. 2020;11:567899.
52. Jameson E, Quareshy M, Chen Y. Methodological considerations for the identification of choline and carnitine-degrading bacteria in the gut. Methods. 2018;149:42–8.
53. Lee Y, Nemet I, Wang Z, Lai HTM, de Oliveira Otto MC, Lemaitre RN, et al. Longitudinal plasma measures of trimethylamine N-Oxide and risk of atherosclerotic Cardiovascular Disease events in community-based older adults. J Am Heart Assoc. 2021;10(17):e020646.
54. Geng J, Yang C, Wang B, Zhang X, Hu T, Gu Y, et al. Trimethylamine N-oxide promotes atherosclerosis via CD36-dependent MAPK/JNK pathway. Biomed Pharmacother. 2018;97:941–7.

55. Jing L, Zhang H, Xiang Q, Shen L, Guo X, Zhai C, et al. Targeting trimethylamine N-Oxide: a New Therapeutic Strategy for alleviating atherosclerosis. Front Cardiovasc Med. 2022;9:864600.
56. Wang Z, Roberts AB, Buffa JA, Levison BS, Zhu W, Org E, et al. Non-lethal inhibition of Gut Microbial Trimethylamine production for the Treatment of Atherosclerosis. Cell. 2015;163(7):1585–95.
57. Shih DM, Wang Z, Lee R, Meng Y, Che N, Charugundla S, et al. Flavin containing monooxygenase 3 exerts broad effects on glucose and lipid metabolism and atherosclerosis. J Lipid Res. 2015;56(1):22–37.
58. Zhu Y, Li Q, Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide. APMIS. 2020;128(5):353–66.
59. Ma SR, Tong Q, Lin Y, Pan LB, Fu J, Peng R, et al. Berberine treats atherosclerosis via a vitamine-like effect down-regulating Choline-TMA-TMAO production pathway in gut microbiota. Signal Transduct Target Ther. 2022;7(1):207.
60. Skye SM, Zhu W, Romano KA, Guo CJ, Wang Z, Jia X, et al. Microbial Transplantation with Human Gut commensals containing CutC is sufficient to transmit enhanced platelet reactivity and thrombosis potential. Circ Res. 2018;123(10):1164–76.
61. Chen ML, Yi L, Zhang Y, Zhou X, Ran L, Yang J, et al. Resveratrol attenuates Trimethylamine-N-Oxide (TMAO)-Induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. mBio. 2016;7(2):e02210–15.
62. Krueger ES, Lloyd TS, Tessem JS. The Accumulation and Molecular effects of Trimethylamine N-Oxide on metabolic tissues: it's not all bad. Nutrients. 2021;13:8.
63. Konopelski P, Mogilnicka I. Biological Effects of Indole-3-Propionic Acid, a Gut Microbiota-Derived Metabolite, and Its Precursor Tryptophan in Mammals' Health and Disease. Int J Mol Sci. 2022;23(3).
64. Xue H, Chen X, Yu C, Deng Y, Zhang Y, Chen S, et al. Gut Microbially Produced Indole-3-Propionic Acid inhibits atherosclerosis by Promoting Reverse Cholesterol Transport and its Deficiency is causally related to atherosclerotic Cardiovascular Disease. Circ Res. 2022;131(5):404–20.
65. Pulakazhi Venu VK, Saifeddine M, Mihara K, Tsai YC, Nieves K, Alston L, et al. The pregnane X receptor and its microbiota-derived ligand indole 3-propionic acid regulate endothelium-dependent vasodilation. Am J Physiol Endocrinol Metab. 2019;317(2):E350–61.
66. Paroni R, Casati S, Dei Cas M, Bignotto M, Rubino FM, Ciuffreda P. Unambiguous characterization of p-Cresyl Sulfate, a protein-bound Uremic Toxin, as biomarker of heart and kidney disease. Molecules. 2019;24(20).
67. Saito Y, Sato T, Nomoto K, Tsuji H. Identification of phenol- and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites. FEMS Microbiol Ecol. 2018;94(9).
68. Gryp T, Vanholder R, Vaneechoutte M, Glorieux G. p-Cresyl Sulfate. Toxins (Basel). 2017;9(2).
69. Chang MC, Wang TM, Yeung SY, Jeng PY, Liao CH, Lin TY, et al. Antiplatelet effect by p-cresol, a uremic and environmental toxicant, is related to inhibition of reactive oxygen species, ERK/p38 signaling and thromboxane A2 production. Atherosclerosis. 2011;219(2):559–65.
70. Al Hinai EA, Kullamethee P, Rowland IR, Swann J, Walton GE, Commane DM. Modelling the role of microbial p-cresol in colorectal genotoxicity. Gut Microbes. 2019;10(3):398–411.
71. Bermudez-Martin P, Becker JAJ, Caramello N, Fernandez SP, Costa-Campos R, Canaguier J, et al. The microbial metabolite p-Cresol induces autistic-like behaviors in mice by remodeling the gut microbiota. Microbiome. 2021;9(1):157.
72. Stachulski AV, Knausenberger TB, Shah SN, Hoyles L, McArthur S. A host-gut microbial amino acid co-metabolite, p-cresol glucuronide, promotes blood-brain barrier integrity in vivo. Tissue Barriers. 2023;11(1):2073175.
73. Meijers BK, Bammens B, De Moor B, Verbeke K, Vanrenterghem Y, Evenepoel P. Free p-cresol is associated with cardiovascular disease in hemodialysis patients. Kidney Int. 2008;73(10):1174–80.
74. Meijers BK, Claes K, Bammens B, de Loor H, Viaene L, Verbeke K, et al. p-Cresol and cardiovascular risk in mild-to-moderate kidney disease. Clin J Am Soc Nephrol. 2010;5(7):1182–9.
75. Jing YJ, Ni JW, Ding FH, Fang YH, Wang XQ, Wang HB, et al. p-Cresyl sulfate is associated with carotid arteriosclerosis in hemodialysis patients and promotes atherogenesis in apoE-/- mice. Kidney Int. 2016;89(2):439–49.
76. Aronov PA, Luo FJ, Plummer NS, Quan Z, Holmes S, Hostetter TH, et al. Colonic contribution to uremic solutes. J Am Soc Nephrol. 2011;22(9):1769–76.
77. Han H, Zhu J, Zhu Z, Ni J, Du R, Dai Y, et al. p-Cresyl sulfate aggravates cardiac dysfunction associated with chronic kidney disease by enhancing apoptosis of cardiomyocytes. J Am Heart Assoc. 2015;4(6):e001852.
78. Liabeuf S, Glorieux G, Lenglet A, Diouf M, Schepers E, Desjardins L, et al. Does p-cresylglucuronide have the same impact on mortality as other protein-bound uremic toxins? PLoS ONE. 2013;8(6):e67168.
79. Guerrero F, Carmona A, Obrero T, Jimenez MJ, Soriano S, Moreno JA, et al. Role of endothelial microvesicles released by p-cresol on endothelial dysfunction. Sci Rep. 2020;10(1):10657.
80. Falconi CA, Junho C, Fogaca-Ruiz F, Vernier ICS, da Cunha RS, Stinghen AEM, et al. Uremic toxins: an alarming Danger concerning the Cardiovascular System. Front Physiol. 2021;12:686249.
81. Tonelli M, Karumanchi SA, Thadhani R. Epidemiology and mechanisms of Uremia-related Cardiovascular Disease. Circulation. 2016;133(5):518–36.
82. Roccarina D, Lauritano EC, Gabrielli M, Franceschi F, Ojetti V, Gasbarrini A. The role of methane in intestinal diseases. Am J Gastroenterol. 2010;105(6):1250–6.
83. Buan NR. Methanogens: pushing the boundaries of biology. Emerg Top Life Sci. 2018;2(4):629–46.
84. Chen O, Ye Z, Cao Z, Manaenko A, Ning K, Zhai X, et al. Methane attenuates myocardial ischemia injury in rats through anti-oxidative, anti-apoptotic and anti-inflammatory actions. Free Radic Biol Med. 2016;90:1–11.
85. Zaorska E, Gawryś-Kopczyńska M, Ostaszewski R, Koszelewski D, Ufnal M. Methane, a gut bacteria-produced gas, does not affect arterial blood pressure in normotensive anaesthetized rats. bioRxiv. 2021:2021.03.31.437828.
86. Hermann M, Flammer A, Luscher TF. Nitric oxide in hypertension. J Clin Hypertens (Greenwich). 2006;8(12 Suppl 4):17–29.
87. Chouchani ET, Methner C, Nadtochiy SM, Logan A, Pell VR, Ding S, et al. Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I. Nat Med. 2013;19(6):753–9.
88. Erdmann J, Stark K, Esslinger UB, Rumpf PM, Koesling D, de Wit C, et al. Dysfunctional nitric oxide signalling increases risk of myocardial infarction. Nature. 2013;504(7480):432–6.
89. Naseem KM. The role of nitric oxide in cardiovascular diseases. Mol Aspects Med. 2005;26(1–2):33–65.
90. Sobko T, Reinders CI, Jansson E, Norin E, Midtvedt T, Lundberg JO. Gastrointestinal bacteria generate nitric oxide from nitrate and nitrite. Nitric Oxide. 2005;13(4):272–8.
91. Van de Vermeiren J, Verstraete W, Boeckx P, Boon N. Nitric oxide production by the human intestinal microbiota by dissimilatory nitrate reduction to ammonium. J Biomed Biotechnol. 2009;2009:284718.
92. Kolluru GK, Shackelford RE, Shen X, Dominic P, Kevil CG. Sulfide regulation of cardiovascular function in health and disease. Nat Rev Cardiol. 2023;20(2):109–25.
93. Murros KE. Hydrogen Sulfide Produced by Gut Bacteria May Induce Parkinson's Disease. Cells. 2022;11(6).
94. Li Z, Polhemus DJ, Lefer DJ. Evolution of Hydrogen Sulfide therapeutics to treat Cardiovascular Disease. Circ Res. 2018;123(5):590–600.
95. Wilkie SE, Borland G, Carter RN, Morton NM, Selman C. Hydrogen sulfide in ageing, longevity and disease. Biochem J. 2021;478(19):3485–504.
96. Troseid M, Andersen GO, Broch K, Hov JR. The gut microbiome in coronary artery disease and heart failure: current knowledge and future directions. EBioMedicine. 2020;52:102649.
97. von Haehling S, Schefold JC, Jankowska EA, Springer J, Vazir A, Kalra PR, et al. Ursodeoxycholic acid in patients with chronic heart failure: a double-blind, randomized, placebo-controlled, crossover trial. J Am Coll Cardiol. 2012;59(6):585–92.
98. Little M, Dutta M, Li H, Matson A, Shi X, Mascarinas G, et al. Understanding the physiological functions of the host xenobiotic-sensing nuclear receptors PXR and CAR on the gut microbiome using genetically modified mice. Acta Pharm Sin B. 2022;12(2):801–20.
99. Masenga SK, Hamooya B, Hangoma J, Hayumbu V, Ertuglu LA, Ishimwe J, et al. Recent advances in modulation of cardiovascular diseases by the gut microbiota. J Hum Hypertens. 2022;36(11):952–9.
100. Li W, Shu S, Cheng L, Hao X, Wang L, Wu Y, et al. Fasting serum total bile acid level is associated with coronary artery disease, myocardial infarction and severity of coronary lesions. Atherosclerosis. 2020;292:193–200.
101. Battson ML, Lee DM, Weir TL, Gentile CL. The gut microbiota as a novel regulator of cardiovascular function and disease. J Nutr Biochem. 2018;56:1–15.
102. Yukino-Iwashita M, Nagatomo Y, Kawai A, Taruoka A, Yumita Y, Kagami K et al. Short-chain fatty acids in Gut-Heart Axis: their role in the Pathology of Heart failure. J Pers Med. 2022;12(11).
103. Hu T, Wu Q, Yao Q, Jiang K, Yu J, Tang Q. Short-chain fatty acid metabolism and multiple effects on cardiovascular diseases. Ageing Res Rev. 2022;81:101706.

104. Zhong H, Yu H, Chen J, Mok SWF, Tan X, Zhao B, et al. The short-chain fatty acid butyrate accelerates vascular calcification via regulation of histone deacetylases and NF-kappaB signaling. Vascul Pharmacol. 2022;146:107096.
105. Dueweke JJ, Awan TM, Mendias CL. Regeneration of skeletal muscle after eccentric Injury. J Sport Rehabil. 2017;26(2):171–9.
106. Sandri M. Protein breakdown in muscle wasting: role of autophagy-lysosome and ubiquitin-proteasome. Int J Biochem Cell Biol. 2013;45(10):2121–9.
107. Qiu Y, Yu J, Li Y, Yang F, Yu H, Xue M, et al. Depletion of gut microbiota induces skeletal muscle atrophy by FXR-FGF15/19 signalling. Ann Med. 2021;53(1):508–22.
108. Frost RA, Nystrom GJ, Lang CH. Lipopolysaccharide regulates proinflammatory cytokine expression in mouse myoblasts and skeletal muscle. Am J Physiol Regul Integr Comp Physiol. 2002;283(3):R698–709.
109. Andreakos E, Sacre SM, Smith C, Lundberg A, Kiriakidis S, Stonehouse T, et al. Distinct pathways of LPS-induced NF-kappa B activation and cytokine production in human myeloid and nonmyeloid cells defined by selective utilization of MyD88 and Mal/TIRAP. Blood. 2004;103(6):2229–37.
110. Li H, Malhotra S, Kumar A. Nuclear factor-kappa B signaling in skeletal muscle atrophy. J Mol Med (Berl). 2008;86(10):1113–26.
111. Doyle A, Zhang G, Abdel Fattah EA, Eissa NT, Li YP. Toll-like receptor 4 mediates lipopolysaccharide-induced muscle catabolism via coordinate activation of ubiquitin-proteasome and autophagy-lysosome pathways. FASEB J. 2011;25(1):99–110.
112. Lee D, Goldberg A. Atrogin1/MAFbx: what atrophy, hypertrophy, and cardiac failure have in common. Circ Res. 2011;109(2):123–6.
113. Ducharme JB, Fennel ZJ, McKenna ZJ, Nava RC, Deyhle MR. Stimulated myotube contractions regulate membrane-bound and soluble TLR4 to prevent LPS-induced signaling and myotube atrophy in skeletal muscle cells. Am J Physiol Cell Physiol. 2023;325(1):C300–13.
114. Du L, Qi R, Wang J, Liu Z, Wu Z. Indole-3-Propionic Acid, a functional metabolite of Clostridium sporogenes, promotes muscle tissue development and reduces muscle cell inflammation. Int J Mol Sci. 2021;22(22).
115. Brocca A, Virzi GM, de Cal M, Cantaluppi V, Ronco C. Cytotoxic effects of p-cresol in renal epithelial tubular cells. Blood Purif. 2013;36(3–4):219–25.
116. Souza VA, Oliveira D, Mansur HN, Fernandes NM, Bastos MG. Sarcopenia in chronic kidney disease. J Bras Nefrol. 2015;37(1):98–105.
117. Alcalde-Estevez E, Sosa P, Asenjo-Bueno A, Plaza P, Olmos G, Naves-Diaz M, et al. Uraemic toxins impair skeletal muscle regeneration by inhibiting myoblast proliferation, reducing myogenic differentiation, and promoting muscular fibrosis. Sci Rep. 2021;11(1):512.
118. Enoki Y, Watanabe H, Arake R, Sugimoto R, Imafuku T, Tominaga Y, et al. Indoxyl sulfate potentiates skeletal muscle atrophy by inducing the oxidative stress-mediated expression of myostatin and atrogin-1. Sci Rep. 2016;6:32084.
119. Changchien CY, Lin YH, Cheng YC, Chang HH, Peng YS, Chen Y. Indoxyl sulfate induces myotube atrophy by ROS-ERK and JNK-MAFbx cascades. Chem Biol Interact. 2019;304:43–51.
120. Leo TK, Garba S, Abubakar D, Sazili AQ, Candyrine SCL, Jahromi MF et al. Naturally produced Lovastatin modifies the histology and Proteome Profile of Goat skeletal muscle. Anim (Basel). 2019;10(1).
121. Ma T, Wu W, Tu Y, Zhang N, Diao Q. Resveratrol affects in vitro rumen fermentation, methane production and prokaryotic community composition in a time- and diet-specific manner. Microb Biotechnol. 2020;13(4):1118–31.
122. De Palma C, Morisi F, Pambianco S, Assi E, Touvier T, Russo S, et al. Deficient nitric oxide signalling impairs skeletal muscle growth and performance: involvement of mitochondrial dysregulation. Skelet Muscle. 2014;4(1):22.
123. Wang R, Li K, Sun L, Jiao H, Zhou Y, Li H, et al. L-Arginine/nitric oxide regulates skeletal muscle development via muscle fibre-specific nitric oxide/mTOR pathway in chickens. Anim Nutr. 2022;10:68–85.
124. Anderson JE, Zhu A, Mizuno TM. Nitric oxide treatment attenuates muscle atrophy during Hind limb suspension in mice. Free Radic Biol Med. 2018;115:458–70.
125. Zhao L, Liu X, Zhang J, Dong G, Xiao W, Xu X. Hydrogen Sulfide alleviates skeletal muscle fibrosis via attenuating inflammation and oxidative stress. Front Physiol. 2020;11:533690.
126. Xu M, Liu X, Bao P, Wang YJ, Lu J, Liu YJ. H(2)S protects against Immobilization-Induced muscle atrophy via reducing oxidative stress and inflammation. Front Physiol. 2022;13:844539.
127. Lu F, Lu B, Zhang L, Wen J, Wang M, Zhang S, et al. Hydrogen sulphide ameliorating skeletal muscle atrophy in db/db mice via muscle RING finger 1 S-sulfhydration. J Cell Mol Med. 2020;24(16):9362–77.
128. Ibrahim Z, Ramachandran G, El-Huneidi W, Elmoselhi A, Qaisar R. Suppression of endoplasmic reticulum stress prevents disuse muscle atrophy in a mouse model of microgravity. Life Sci Space Res (Amst). 2022;34:45–52.
129. Mancin L, Wu GD, Paoli A. Gut microbiota-bile acid-skeletal muscle axis: (trends in Microbiology, corrected proof). Trends Microbiol. 2023;31(3):322.
130. Abrigo J, Gonzalez F, Aguirre F, Tacchi F, Gonzalez A, Meza MP, et al. Cholic acid and deoxycholic acid induce skeletal muscle atrophy through a mechanism dependent on TGR5 receptor. J Cell Physiol. 2021;236(1):260–72.
131. Frampton J, Murphy KG, Frost G, Chambers ES. Short-chain fatty acids as potential regulators of skeletal muscle metabolism and function. Nat Metab. 2020;2(9):840–8.
132. Chen F, Li Q, Chen Y, Wei Y, Liang J, Song Y, et al. Association of the gut microbiota and fecal short-chain fatty acids with skeletal muscle mass and strength in children. FASEB J. 2022;36(1):e22109.
133. Maruta H, Yoshimura Y, Araki A, Kimoto M, Takahashi Y, Yamashita H. Activation of AMP-Activated Protein Kinase and Stimulation of Energy Metabolism by Acetic Acid in L6 Myotube cells. PLoS ONE. 2016;11(6):e0158055.
134. Walsh ME, Bhattacharya A, Sataranatarajan K, Qaisar R, Sloane L, Rahman MM, et al. The histone deacetylase inhibitor butyrate improves metabolism and reduces muscle atrophy during aging. Aging Cell. 2015;14(6):957–70.
135. Tang G, Du Y, Guan H, Jia J, Zhu N, Shi Y, et al. Butyrate ameliorates skeletal muscle atrophy in diabetic nephropathy by enhancing gut barrier function and FFA2-mediated PI3K/Akt/mTOR signals. Br J Pharmacol. 2022;179(1):159–78.
136. Lahiri S, Kim H, Garcia-Perez I, Reza MM, Martin KA, Kundu P, et al. The gut microbiota influences skeletal muscle mass and function in mice. Sci Transl Med. 2019;11:502.
137. Huang B, Li DG, Huang Y, Liu CT. Effects of spaceflight and simulated microgravity on microbial growth and secondary metabolism. Mil Med Res. 2018;5(1):18.
138. Antonutto G, di Prampero PE. Cardiovascular deconditioning in microgravity: some possible countermeasures. Eur J Appl Physiol. 2003;90(3–4):283–91.
139. Vernice NA, Meydan C, Afshinnekoo E, Mason CE. Long-term spaceflight and the cardiovascular system. Precis Clin Med. 2020;3(4):284–91.
140. Fovet T, Guilhot C, Stevens L, Montel V, Delobel P, Roumanille R et al. Early deconditioning of Human Skeletal Muscles and the effects of a thigh Cuff Countermeasure. Int J Mol Sci. 2021;22(21).
141. Jollet M, Nay K, Chopard A, Bareille MP, Beck A, Ollendorff V et al. Does physical inactivity induce significant changes in human gut microbiota? New answers using the dry immersion Hypoactivity Model. Nutrients. 2021;13(11).
142. Turroni S, Magnani M, Kc P, Lesnik P, Vidal H, Heer M. Gut microbiome and space travelers' health: state of the art and possible Pro/Prebiotic strategies for long-term space missions. Front Physiol. 2020;11:553929.
143. Hargens AR, Vico L. Long-duration bed rest as an analog to microgravity. J Appl Physiol (1985). 2016;120(8):891–903.
144. Krittanawong C, Singh NK, Scheuring RA, Urquieta E, Bershad EM, Macaulay TR et al. Human Health during Space Travel: state-of-the-art review. Cells. 2022;12(1).
145. Baran R, Marchal S, Garcia Campos S, Rehnberg E, Tabury K, Baselet B et al. The Cardiovascular System in Space: focus on in vivo and in Vitro studies. Biomedicines. 2021;10(1).
146. Azevedo PS, Polegato BF, Minicucci MF, Paiva SA, Zornoff LA. Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. Arq Bras Cardiol. 2016;106(1):62–9.
147. Zhong G, Li Y, Li H, Sun W, Cao D, Li J, et al. Simulated Microgravity and Recovery-Induced remodeling of the Left and right ventricle. Front Physiol. 2016;7:274.
148. Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, et al. Cardiac atrophy after bed rest and spaceflight. J Appl Physiol (1985). 2001;91(2):645–53.
149. Summers RL, Martin DS, Meck JV, Coleman TG. Mechanism of spaceflight-induced changes in left ventricular mass. Am J Cardiol. 2005;95(9):1128–30.
150. Zhang LX, Du J, Zhao YT, Wang J, Zhang S, Dubielecka PM, et al. Transgenic overexpression of active HDAC4 in the heart attenuates cardiac function and exacerbates remodeling in infarcted myocardium. J Appl Physiol (1985). 2018;125(6):1968–78.
151. Zhao X, Sternsdorf T, Bolger TA, Evans RM, Yao TP. Regulation of MEF2 by histone deacetylase 4- and SIRT1 deacetylase-mediated lysine modifications. Mol Cell Biol. 2005;25(19):8456–64.
152. Damanafshan A, Elzenaar I, van der Samson-Couterie B, van den Bourajjaj M, et al. The MEF2 transcriptional target DMPK induces loss of sarcomere structure and cardiomyopathy. Cardiovasc Res. 2018;114(11):1474–86.

153. Yeves AM, Villa-Abrille MC, Perez NG, Medina AJ, Escudero EM, Ennis IL. Physiological cardiac hypertrophy: critical role of AKT in the prevention of NHE-1 hyperactivity. J Mol Cell Cardiol. 2014;76:186–95.
154. Gallo S, Vitacolonna A, Bonzano A, Comoglio P, Crepaldi T. ERK: a key player in the pathophysiology of Cardiac Hypertrophy. Int J Mol Sci. 2019;20(9).
155. Tusa I, Menconi A, Tubita A, Rovida E. Pathophysiological impact of the MEK5/ERK5 pathway in oxidative stress. Cells. 2023;12(8).
156. Rose BA, Force T, Wang Y. Mitogen-activated protein kinase signaling in the heart: angels versus demons in a heart-breaking tale. Physiol Rev. 2010;90(4):1507–46.
157. Wakabayashi H, Taki J, Inaki A, Shiba K, Matsunari I, Kinuya S. Correlation between apoptosis and left ventricular remodeling in subacute phase of myocardial ischemia and reperfusion. EJNMMI Res. 2015;5(1):72.
158. Goldblatt ZE, Cirka HA, Billiar KL. Mechanical regulation of apoptosis in the Cardiovascular System. Ann Biomed Eng. 2021;49(1):75–97.
159. Carlsson SI, Bertilaccio MT, Ballabio E, Maier JA. Endothelial stress by gravitational unloading: effects on cell growth and cytoskeletal organization. Biochim Biophys Acta. 2003;1642(3):173–9.
160. Versari S, Villa A, Bradamante S, Maier JA. Alterations of the actin cytoskeleton and increased nitric oxide synthesis are common features in human primary endothelial cell response to changes in gravity. Biochim Biophys Acta. 2007;1773(11):1645–52.
161. Cotrupi S, Ranzani D, Maier JA. Impact of modeled microgravity on microvascular endothelial cells. Biochim Biophys Acta. 2005;1746(2):163–8.
162. Morbidelli L, Monici M, Marziliano N, Cogoli A, Fusi F, Waltenberger J, et al. Simulated hypogravity impairs the angiogenic response of endothelium by up-regulating apoptotic signals. Biochem Biophys Res Commun. 2005;334(2):491–9.
163. Afroze D, Kumar A. ER stress in skeletal muscle remodeling and myopathies. FEBS J. 2019;286(2):379–98.
164. Mukund K, Subramaniam S. Skeletal muscle: a review of molecular structure and function, in health and disease. Wiley Interdiscip Rev Syst Biol Med. 2020;12(1):e1462.
165. Fitts RH, Trappe SW, Costill DL, Gallagher PM, Creer AC, Colloton PA, et al. Prolonged space flight-induced alterations in the structure and function of human skeletal muscle fibres. J Physiol. 2010;588(Pt 18):3567–92.
166. Huang Z, Fang Q, Ma W, Zhang Q, Qiu J, Gu X, et al. Skeletal muscle atrophy was alleviated by Salidroside through suppressing oxidative stress and inflammation during denervation. Front Pharmacol. 2019;10:997.
167. Baek MO, Ahn CB, Cho HJ, Choi JY, Son KH, Yoon MS. Simulated microgravity inhibits C2C12 myogenesis via phospholipase D2-induced Akt/FOXO1 regulation. Sci Rep. 2019;9(1):14910.
168. McKinnell IW, Rudnicki MA. Molecular mechanisms of muscle atrophy. Cell. 2004;119(7):907–10.
169. Heras G, Namuduri AV, Traini L, Shevchenko G, Falk A, Bergstrom Lind S, et al. Muscle RING-finger protein-1 (MuRF1) functions and cellular localization are regulated by SUMO1 post-translational modification. J Mol Cell Biol. 2019;11(5):356–70.
170. Cadena SM, Zhang Y, Fang J, Brachat S, Kuss P, Giorgetti E, et al. Skeletal muscle in MuRF1 null mice is not spared in low-gravity conditions, indicating atrophy proceeds by unique mechanisms in space. Sci Rep. 2019;9(1):9397.
171. Teodori L, Costa A, Campanella L, Albertini MC. Skeletal muscle atrophy in simulated microgravity might be triggered by Immune-related microRNAs. Front Physiol. 2018;9:1926.
172. Garrett-Bakelman FE, Darshi M, Green SJ, Gur RC, Lin L, Macias BR et al. The NASA Twins Study: a multidimensional analysis of a year-long human spaceflight. Science. 2019;364(6436).
173. Liu Z, Luo G, Du R, Sun W, Li J, Lan H, et al. Effects of spaceflight on the composition and function of the human gut microbiota. Gut Microbes. 2020;11(4):807–19.
174. Schmidt MA, Meydan C, Schmidt CM, Afshinnekoo E, Mason CE. Elevation of Gut-Derived p-Cresol During Spaceflight and its Effect on Drug Metabolism and Performance in Astronauts. bioRxiv. 2020:2020.11.10.374645.
175. Wang Y, Zhao W, Shi J, Wang J, Hao J, Pang X, et al. Intestinal microbiota contributes to altered glucose metabolism in simulated microgravity mouse model. FASEB J. 2019;33(9):10140–51.
176. Byeon HR, Jang SY, Lee Y, Kim D, Hong MG, Lee D, et al. New strains of Akkermansia muciniphila and Faecalibacterium prausnitzii are effective for improving the muscle strength of mice with immobilization-Induced muscular atrophy. J Med Food. 2022;25(6):565–75.
177. Rodriguez-Daza MC, de Vos WM. Polyphenols as drivers of a homeostatic gut microecology and Immuno-metabolic traits of Akkermansia muciniphila: from mouse to Man. Int J Mol Sci. 2022;24(1).
178. Munzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. Impact of oxidative stress on the heart and vasculature: part 2 of a 3-Part series. J Am Coll Cardiol. 2017;70(2):212–29.
179. Yamamoto K, Ishizu Y, Honda T, Ito T, Imai N, Nakamura M, et al. Patients with low muscle mass have characteristic microbiome with low potential for amino acid synthesis in chronic liver disease. Sci Rep. 2022;12(1):3674.
180. Turroni S, Rampelli S, Biagi E, Consolandi C, Severgnini M, Peano C, et al. Temporal dynamics of the gut microbiota in people sharing a confined environment, a 520-day ground-based space simulation, MARS500. Microbiome. 2017;5(1):39.
181. Amiri P, Hosseini SA, Ghaffari S, Tutunchi H, Ghaffari S, Mosharkesh E, et al. Role of Butyrate, a gut Microbiota Derived Metabolite, in Cardiovascular diseases: a comprehensive narrative review. Front Pharmacol. 2021;12:837509.
182. Yang M, Zhang K, Zhang X, Zhang Z, Yin X, He G, et al. Treatment with hydrogen sulfide donor attenuates bone loss induced by modeled microgravity. Can J Physiol Pharmacol. 2019;97(7):655–60.
183. Zhang P, Shao L, Zhang J, Wang L, Pang X, Tao W, et al. Microbiota–muscle/immune interactions in rhesus macaque under simulated microgravity revealed by integrated multi-omics analysis. JCSM Rapid Commun. 2022;5(2):212–25.
184. Han Y, Shao D, Han C, Huang Q, Zhao W. Response of human gut microbiota under simulated microgravity. Appl Microbiol Biotechnol. 2022;106(13–16):5221–31.
185. Liu Y, Wang J, Wu C. Modulation of Gut Microbiota and Immune System by Probiotics, Pre-biotics, and post-biotics. Front Nutr. 2021;8:634897.
186. Park M, Joung M, Park JH, Ha SK, Park HY. Role of postbiotics in Diet-Induced Metabolic disorders. Nutrients. 2022;14(18).
187. Leeming ER, Johnson AJ, Spector TD, Le Roy CI. Effect of Diet on the gut microbiota: rethinking intervention duration. Nutrients. 2019;11(12).
188. Sakai T, Moteki Y, Takahashi T, Shida K, Kiwaki M, Shimakawa Y, et al. Probiotics into outer space: feasibility assessments of encapsulated freeze-dried probiotics during 1 month's storage on the International Space Station. Sci Rep. 2018;8(1):10687.
189. Servin-Casas GA, Romo-Araiza A, Gutierrez-Salmean G, Martinez-Solis E, Ibarra-Garcia AP, Cruz-Martinez Y, et al. Memory improvement in senile rats after prebiotic and probiotic supplementation is not induced by GLP-1. CNS Neurosci Ther. 2022;28(12):1986–92.
190. Shokryazdan P, Faseleh Jahromi M, Navidshad B, Liang JB. Effects of prebiotics on immune system and cytokine expression. Med Microbiol Immunol. 2017;206(1):1–9.
191. Mahboobi S, Rahimi F, Jafarnejad S. Effects of Prebiotic and Synbiotic supplementation on glycaemia and lipid Profile in Type 2 diabetes: a Meta-analysis of Randomized controlled trials. Adv Pharm Bull. 2018;8(4):565–74.
192. Oniszczuk A, Oniszczuk T, Gancarz M, Szymanska J. Role of Gut Microbiota, Probiotics and Prebiotics in the Cardiovascular diseases. Molecules. 2021;26(4).
193. Liu Y, Alookaran JJ, Rhoads JM. Probiotics in Autoimmune and Inflammatory disorders. Nutrients. 2018;10(10).
194. Homayouni Rad A, Aghebati Maleki L, Samadi Kafil H, Fathi Zavoshti H, Abbasi A. Postbiotics as Promising Tools for Cancer Adjuvant Therapy. Adv Pharm Bull. 2021;11(1):1–5.
195. Han S, Seo KH, Gyu Lee H, Kim H. Effect of Cucumis melo L. peel extract supplemented postbiotics on reprograming gut microbiota and sarcopenia in hindlimb-immobilized mice. Food Res Int. 2023;173(Pt 2):113476.
196. Ma L, Tu H, Chen T. Postbiotics in Human Health: a narrative review. Nutrients. 2023;15(2).
197. Enrico C. Space nutrition: the key role of nutrition in human space flight. 2016.
198. Fajardo-Cavazos P, Nicholson WL. Shelf Life and simulated gastrointestinal tract survival of selected commercial Probiotics during a simulated round-trip journey to Mars. Front Microbiol. 2021;12:748950.
199. Monda V, Villano I, Messina A, Valenzano A, Esposito T, Moscatelli F, et al. Exercise modifies the gut microbiota with positive Health effects. Oxid Med Cell Longev. 2017;2017:3831972.
200. Quiroga R, Nistal E, Estebanez B, Porras D, Juarez-Fernandez M, Martinez-Florez S, et al. Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. Exp Mol Med. 2020;52(7):1048–61.

201. Longoria CR, Guers JJ, Campbell SC. The interplay between Cardiovascular Disease, Exercise, and the gut Microbiome. RCM. 2022;23(11).
202. Moosavi D, Wolovsky D, Depompeis A, Uher D, Lennington D, Bodden R, et al. The effects of spaceflight microgravity on the musculoskeletal system of humans and animals, with an emphasis on exercise as a countermeasure: a systematic scoping review. Physiol Res. 2021;70(2):119–51.

Publisher's Note