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Review

Prolonged space flight: Adverse health effects and treatment options with medicinal plants and natural products

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Abstract: Exposure to zero gravity causes many physiological changes which may result to affect the health of people involved in space travel. The current review summarizes current knowledge on the start and progression of space motion sickness, bone loss, muscle loss, cardiovascular disorders, respiratory problems, and neuronal and hormonal problems. Around 70% of astronauts suffer from space adaption syndrome, fluid changes, and head motions. It has also been suggested that otolith asymmetries and Coriolis cross-coupling stimulation are the main causes of space motion sickness. The findings reveal that space flight directly affects the body's normal functioning. Despite an intense training routine, a study of historical data from piloted flights discovered that slow degradation of bone and muscle tissue, along with fluid losses, can eventually lead to kidney stones, musculoskeletal problems, bone fractures, and even problems with other organs of the body. Due to such problems focus is given to curing these problems associated with space travel. Medicines that are used in space and medicinal plants like Spirulina, and Ginseng that are of use for the treatment of these problems associated with space travel are discussed along with the treatment options available for such problems in space and the cautions that must be followed. Also, the herbal medication that can be used in outer space is taken into account. The findings of this study state the necessary precaution that needs to be taken by astronauts in outer space and also provides information for future research to be done on solving these problems.

1. Introduction

Humankind's topmost aspirations include space travel. Since the 1960s, significant advancements in spaceflight technology have been made. The period of space occupancy was extended from minutes to days, months, and even years in some circumstances, thanks to these advancements. From a strictly technical aspect, the duration of spaceflight is a logistical problem that necessitates careful optimization of escape paths with sufficient fuel and nourishment. However, astronauts' (and cosmonauts') biological reactions to space, an environment in which spaceship crews are constantly experiencing weightlessness, offer equally challenging and distinct biomedical problems throughout spaceflight missions. These challenges must be overcome for humans to travel, live, and work in space and on distant planets (1).

One of the most challenging situations for people to endure is space travel. Currently, space astronauts live and work onboard the International Space Station (ISS), but shortly, new space missions to

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the Moon and Mars are planned, which would necessitate extended stays for crew members in outposts in space. There are also ambitious business sectors and government proposals to send humans to space for mining, extra-terrestrial base construction, and other high-risk economic ventures (2).

A long space expedition has so far involved more than 500 individuals. The effects of space travel variables on the anatomy and physiology of humans continue to be a substantial obstacle to human hyperextended missions, notwithstanding the aspiration of deep space travel. The most critical factors are radiation, microgravity, hyperdynamics, and isolation.

This review is being conducted to understand the health effects and adverse effects that are associated with space travel and to check any safety measures available. Most physiological systems are affected by spaceflight effects, which disrupt homeostatic mechanisms. Adaptation to microgravity begins unexpectedly early due to alterations in hormone regulation and cardiovascular system function.

All physiological changes in the body that occur during spaceflight are now considered to be reversible. However, recovering from the microgravity impacts on specific systems takes a long time, far longer than the period of the trip. Many experimental instruments and methodologies have been created to explore the physiological alterations caused by space travel. In recent years, genomic and proteomic techniques have attracted much interest (2). A hypocaloric diet and changes in hormonal status may exacerbate the problem to a significant degree. As a result, muscle and bone mass loss occur, causing health issues throughout the journey and lengthening the recuperation period.

Because of the costly and inherent technical limitations of conducting molecular research on board, the etiology of these changes is currently poorly understood at the molecular and cellular levels (3). Till 2021 nearly 600 astronauts have been to space and this figure is still rising (4). And currently, 10 people are working in space till the data of this review was collected (5).

This review is done to study the problems that astronauts face in outer space as a result of long-term space travel. And the medicines that can be used along with the nutritional supplements that are provided in the space. Medicinal plants that can be used for preventing and curing these problems are studied. This study provides information about the problems in space and the necessary precaution that can be taken to minimize these problems.

2. Space adaptation syndrome

All cosmonauts have specific anomalous sensory reactions during the early phases of microgravity during spaceflights, such as orientation illusions, vertigo, and difficulties with the fixation and tracking of moving objects in the visual field. This state is unpleasant, especially when other autonomic symptoms are present (6).

Space adaptation syndrome SAS is a biological issue affecting human spaceflight that is operationally relevant (7). During the first few days of flight, about 70% of all astronauts and cosmonauts are affected somehow. It can start an hour after entering orbit or microgravity and last for several hours or even a day or two (8).

Around half of the US shuttle and Soviet Salyut astronauts had symptoms, including migraine, severe fatigue, violent puking, disorientation, and abdominal discomfort, usually in the first three to five days of spaceflight. However, cases have been documented for as long as two weeks. The vestibular or visual-vestibular mismatch theory is the most widely accepted idea in SAS pathogenesis (9). The cephalad fluid shift theory is another explanation that explains the origin of SAS, while the exact cause is unknown(10). Decorrelation between sensory stimuli activates SAS. When moving around in a weightless environment, the sensory channels convey conflicting information regarding spatial orientation and physical movement, resulting in nausea and motion sickness (11).

Adrian LeBlanc et al. reported study results of muscle loss of some male crew members where the mission duration was more than two weeks. Evaluation of the crew members was done before the days of launch; on the landing day, the crew members were again checked continuously for up to 1 month. There was a reduction in muscle and bone mass. Nearly 10% of the losses were in the ankle exterior and the back muscles. Other areas like the quadriceps, hamstring, and anterior legs were affected to a certain extent (12).

Robert H. Fitts et al. reported the research results, which showed that muscle atrophy in rats exposed to space flight happened quickly, with up to 37% decreases in muscle mass occurring within one week. Data on humans from Skylab and Mir was collected, and it was discovered that spaceflight lowers the maximal force of limb skeletal muscle and causes leg extensors to atrophy. When the flight is long enough (i.e., more than 200 days), muscles exhibit a similar loss in isokinetic strength of around 30% (13).

Per A. Tesch et al., they have found that during spaceflight, the optimum voluntary knee extensor limb strength decreases by around 3-4% each week, primarily due to muscle atrophy. It also noted that if the quadriceps and gluteus muscles lost roughly 8% of their mass, an almost 10% decline in overall muscle strength(14). Gopalakrishnan et al., in 2010, reported muscle mass changes in four male spacecraft crew members, showed that the calf changed more (by 10 to 16%) than the thigh (by 4 to 7%), but the upper arm did not alter (+0.4 to 0.8%). There were isometric and isokinetic strength changes at the elbow (range: 7.5 to 16.7%), knee (range: 10.4 to 24.1%), and ankle (range: 4 to 22.3%). Despite the durability test's overall post-flight drop in total work (14%), a rise in post-flight resistance to fatigue was seen (15).

James R. Lackner has reported a systematic study of responses to Coriolis cross-coupling stimulation, where a shocking outcome was attained that space adaptation syndrome was occurring because of the decrease in the velocity storage time constant that established why parabolic and space flights were not sensitive to Coriolis cross-coupling stimulation while they were in zero gravity (16). Recently Tsukasa Tominari et al., 2019, used a novel gondola-type centrifugal device. Researchers have reported study findings of mice bred for two weeks in 2G hypergravity or 1G control. The 2G hypergravity altered the calf muscle volume due to higher myogenic gene expression and decreased expression of muscle degradation genes. Additionally, it was discovered that 2G hypergravity altered the humerus, femur, and tibia's bone mass (17).

3. Overall health changes and problems

3.1. Bone loss

There have been reports of space travellers suffering significant bone loss occurring at a rate of 1% to 5% per month since the mid-1970s, which responded only partially to non-pharmacological therapies. Anti-resorptive bisphosphonates and other pharmacological interventions reduce bone loss during flight, but they may impede the slow and occasionally uneven post-flight recovery (18). As a result, astronauts face a significant and unresolved health risk from zero gravity bone loss (19).

The human aspect of spaceflight, particularly the physiological changes brought on by the lack of Earth's gravity, is still crucial in determining the viability of long-duration space missions. Long-duration spaceflight has impacts ranging from visual problems to considerable radiation exposure resulting in epigenetic changes and changes in muscle and bone, according to a year-long study conducted by twin astronauts Mark and Scott Kelly (20).

It is generally known that microgravity causes a reduction in weight stress on the skeletal system, resulting in lower bone mineral density (BMD). Dual-energy X-ray absorptiometry is used to calculate the grams of mineral per square inch and density of bone (DXA), which is a reasonably simple method of determining BMD (21). Individuals and individual bones have a wide range of BMD reductions. This heterogeneity was highlighted in a research project on cosmonauts aboard the International Space Station (ISS). Seven of the eight had a drop in BMD in the lumbar vertebrae (2.5-10.6%), all eight had a decrease in BMD in the femur (3-10%), and four of the eight had a 1.7-10.5 percent loss in BMD in the femoral neck. According to a different study, exposure to the zero-gravity environment of space results in losses of 1.1–1.6% in the spine, femoral neck, trochanter, and pelvis, with significant variation across people. Lengthier spaceflight missions necessitate optimal crew member treatments, including osteoporotic drugs and regenerative medicines to mend bone fractures (22).

Furthermore, it appears that the "weight-bearing" bone regions, such as the spine and vertebrae, are the ones that have the highest trabecular bone degradation when one of these illnesses is present. When subjected to situations encouraging bone turnover, non-weight-bearing regions like the skull don't seem to lose bone density (23). Microgravity alters the metabolic milieu of bone, causing site-specific changes in bone remodelling bone production is reduced, and bone resorption is elevated, resulting in considerable brittle bones. After a six-month spaceflight, 5% of the lumbar spine and 10% of the proximal femur's bone can be lost in the pelvic and lower limbs, respectively (24).

Due to the increasing loss of bone density experienced during prolonged spaceflight, bone thinning occurs a particularly severe adverse effect. In this reciprocal free-fall, bones are no longer expected to support the movement or body posture. The skeletal system consequently experiences little to no stress (mechanical strain). The progressive bone loss seen in long-term space residents is thought to be caused by the absence of stress on the bones. Prolonged weightlessness appears to cause a loss in bone mass as osteoblast cell proliferation slows down because the bones are not under strain. There is a net decrease in bone mass due to fewer bone-forming cells and continual bone-destroying activity i.e. osteoporosis (25).

3.2 Muscle loss

The antigravity skeletal muscles weaken over time when individuals are exposed to microgravity. Weight loss due to lower total body fluid volume and musculoskeletal mass has been noted since the first space Gemini mission. Weightlessness causes postural muscles to atrophy due to lack of use, resulting in a reduction in muscular volume, tone, and strength and a reduced ability to deal with physical task capacity. The atrophic response of muscles to weightlessness is quick, occurring within 8-11 days of spaceflight for some astronauts and even within five days for others (26).

The mechanism(s) causing this loss is still unknown, although space flight-induced physical changes in skeletal muscle led to muscle density and strength loss. Muscle atrophy may occur during space travel due to decreased levels of blood hormones like growth hormone (GH)2 or increased levels of catabolic steroid hormones. Therefore, it is anticipated that the causes of muscle loss while space travel will be complicated, involving both local and systemic mechanisms (27). The two main direct effects of muscle loss observed are fatigue and a rising prevalence of lower back pain during and after a flight. Muscle loss occurs early in the flight, although it slows down once the initial response is complete (28).

Long-duration human-crewed spaceflight necessitates the flight crews being subjected to extended durations of antigravity skeletal muscle unweighting. Because many adaptations take days or weeks to complete, the ability to go from microgravity to planetary gravity quickly makes many otherwise beneficial muscle adaptations a liability (29). As demonstrated by research on the Skylab and MIR space stations and flight STS-78 of the Space Shuttle Columbia, proximal muscle fibers are particularly susceptible to deterioration due to zero gravity in both function and structure, respectively, throughout the past 40 years of space study (30).

Arnauld E. Nicogossian et al. (1992) reported long-term physiological acclimatization to space during the early 1970s Skylab program. Despite protective precautions, data from Skylab revealed a 20–25% decrease in led strength and endurance, while statistics from the 1987 Mir missions of 160–, 175–, and 326–day missions revealed muscle atrophy in the 25–40% range after a flight. Total body calcium loss of 3–4 percent every month and calcareous bone resorption at a rate of approximately 5 percent per month are two osteoporosis-related consequences (31).

Laurence Vico et al. have reported a mean bone loss of 17% in the cancellous tibia at the end of a group's 1-month flight, but no significant changes in the tibial cortices or either radius envelope. After the mission, one cosmonaut revealed 1.5% bone loss in the tibial cancellous bone, with no notable improvement after recuperation. The actual BMD was unaffected by previous cumulative periods spent in space. Tibial bone loss remained during recovery, implying that the recovery time would be longer than the mission duration (32).

A 2011 study by Roy Yuen-chi Lau and Xia Guo on 11 astronauts revealed that cancellous bone lost more than cortical bone. After six months in space, the 11 astronauts' cancellous BMD decreased on average by 5.4%, while the range of reductions ranged from 0.4% to 23.4% (33).

The Wnt/β-catenin signaling cascade is significant in microgravity-induced bone loss, as shown by Xin Chen et al. in 2019. Canonical Wnt communication prevents bone resorption by fostering osteoblast growth and activity while reducing bone resorption. The Wnt signaling pathway is inhibited by the antagonists' sclerostin and Dick Kopf-related protein 1 (Dkk-1), which bind to two co-receptors, low-density lipoprotein receptor-related proteins 5 and 6 (LRP5, 6). These findings, in essence, demonstrated that the Wnt-catenin signaling pathway is essential for maintaining bone homeostasis in microgravity (34).

3.3 Cardiovascular problems

During space travel, the human cardiovascular system undergoes significant changes that can cause some disorders in the body. In space, humans have been continuously exposed to ionizing radiation. Radiation exposure is a significant risk for individuals on any journey to the Moon and Mars. Before engaging in prolonged space travel, it is crucial to comprehend the long-term impacts of radiation on human health. Ionizing radiation is a general term for any electromagnetic wave or particle capable of removing an atom or molecule from the substance it passes through. The exposure to radiation in space is substantially different from that on Earth. During such missions, astronauts will be exposed to high-energy ions, vibrant protons from galactic cosmic radiation (GCR), lesser energy protons from solar flares events, secondary neutrons, protons, and heavy ions generated by the substance that shields spacecraft during exploratory missions. Studies indicate that ionizing radiation exposure has increased coronary damage risk (35).

So far, most space science research has been done on people in Low Earth Orbit (LEO) who have experienced microgravity. The intrathoracic tension is noticeably reduced due to this low gravity, which causes the thorax to expand and encourages blood flow into the brain. The neurological and endocrine systems have been suggested to be affected by elevated cerebrovascular pressure, which can change the baroreceptor response. Additionally, in response to aberrant information, the vestibular system stimulates the parasympathetic nervous system, which can result in spatial adaption syndrome and its accompanying symptoms of dizziness, sickness, and confusion (36). Another result is the well-known cosmetic occurrence of "puffy face" as well as "chicken legs," in which it has been shown that the surface tissue thickness of the forehead increases by up to 7% while the tibia reduces by up to 15% (37).

3.4 Respiratory problems

Studies are carried out to determine how ionizing radiation affects the lungs. It was discovered that oxidative radiation exposure seriously damaged the lungs' cell structure (38). The lung still performs well in weightlessness despite the modifications that occur when gravity is absent. Even after six months in space, lung function does not appear to decline upon returning to Earth because, unlike many other organ systems, the lung does not appear to undergo structural adaptation changes when gravity is removed (39).

3.5 Neuronal problems

The CNS and the human body are generally affected by ionizing radiation, hypo-magnetic fields, and gravitational overloads during space travel. Ionizing radiation in space has a significant impact on neurons. Ionizing radiation specifically impacts the developing neural precursor cells and elevates inflammatory mediators in the central nervous system (40). The network of neurons responsible for secreting different neurotransmitters is connected to the damage to the neurons (41). Our findings raise the intriguing possibility that lengthy space travels may alter brain activity due to neuronal remodelling and inadequacies in the decomposition of waste. Intriguingly, compared to his identical twin who remained on Earth, the astronaut twin who spent an entire year aboard the International Space Station (ISS) showed a post-flight loss in brain performance, according to a recent National Aeronautics and Space Administration (NASA) twins investigation (42,43).

3.6 Hormonal changes

Selective morphological changes were brought on by space travel in the pituitary's corticotropes and gonadotrophs. After extended space travels (>14 days), growth hormone and TSH levels declined while prolactin levels increased. Plasma levels of ACTH remained unchanged (5-7 days) (44). Thyroxine and triiodothyronine, two thyroid hormones, are decreased in space, which may indicate mild hypothyroidism. Epinephrine, norepinephrine, and dopamine are the main mediators of the sympathetic nervous system, which appears to be more active in space (45).

3.7 Digestion

Food availability, the food's freshness, exposure to radiation, and nutrient sources are the main factors that affect the nutrition availability of the astronauts. Moreover, the weightlessness of the zero-gravity environment may give rise to indigestion problems. Also, the antigravity environment causes the epithelial cells of the lining of the intestine to disrupt, this causes the protection of bacteria and viruses from food contamination to decrease, even after returning to earth's environment (46).

3.8 Psychological problems

The main problem the astronauts face is sleeplessness more than any other problem. Study reports showed that sleeplessness is the most common of all the conditions faced by astronauts (46). Radiation, light-dark cycles, the effects of microgravity on the environment, and other variables can change sleep habits. Other theories include decreased tissue perfusion brought on by sleep apnea flare-ups, malfunctioning lymphatic drainage systems, or poor brain perfusion. Other psychological alterations likely related to insomnia include mood swings, altered neurocognitive performance, and increased stress levels (47).

3.9 Eye problems

Astronauts exhibit similar nerve fiber layer hemorrhages to those seen in idiopathic intracranial hypertension, including optic disc edema, globe curvature, choroidal and retinal folding, alterations in hyperopic vision impairment, and so on. Years after they had returned to Earth, a few crew members still had issues (48).

4. Treatment Strategies

For readapting to Earth's gravity, an experiment was performed where the astronauts were exposed to a centrifuge of 11/2 h 3g. After about 6 hr the astronauts were able to readapt to normal gravity hence decreasing the symptoms of space adaptation syndrome (49).

4.1 For bone loss

For bone loss and muscle loss problems in space, astronauts carry out daily exercises in space to reduce the effect of microgravity(50). Moreover, the nutritional requirement of the astronauts is increased with the necessary supplements of calcium, vitamin, iron, phosphorus, etc. Drugs like antiresorptive agents and anabolic agents are used to decrease osteoclast and also increase bone formation (51).

Antiresorptive drugs mainly, biphosphates are drugs that reduce osteoclast by binding to hydroxyapatite crystals in the bone matrix by acting as pyrophosphates (51). Some of the drugs that are being used are bisphosphonates pamidronate, zoledronic acid, and ibandronate are structural analogs of inorganic pyrophosphate. A study done in 2013 on ISS astronauts showed that astronauts who exercised daily and were given a daily dosage of alendronate showed significantly less bone loss compared to the ones who only exercised (18).

An anabolic agent i.e., recombinant teriparatide (rhPTH [1-34] [Forteo]) is the first drug anabolic drug to be used for osteoporosis. Teriparatide act on the receptors of parathyroid hormone (PTH), thus inhibiting the action of PTH i.e. mobilizing skeletal calcium into blood serum (52).

4.2 For muscle loss

Though the main physiology behind muscle atrophy is still unknown, it is believed that due to a decrease in gravitational force, the tension on the muscles and bones is decreased, which decreases the strength of the muscles and starts muscle atrophy (28).

A study done in 2020 showed that treatment with myostatin antibody YN41 blocked the reduction of muscle grip strength caused due to zero gravity conditions in space (53). Another study was done where a subcutaneous implant of the nanofluidic delivery system of the drug Formoterol (nF-FMT) was implanted and tested on zero gravity exposed mice. Results showed a decrease in muscle atrophy compared to the vehicle control group (54).

4.3 For cardiovascular problems

Cardiovascular problems mainly arise due to radiation exposure and also due to the absence of gravity blood needs to be pumped with more force to reach the lower extremities. This increases stress on the heart.

Pharmacological treatments available are ACE inhibitors – captopril, xanthine-derivative pentoxifylline combined with α-tocopherol are used. But data on the usage of these compounds are limited (55). But the main measures that can be taken are to shield the radiation as much as possible, continue physical exercise, and intake nutraceuticals and antioxidants (56).

4.4 For respiratory problems

Though respiratory problems are not common in space, due to the absence of gravity the lung capacity decreases and also the position of the diaphragm is displaced. Protection from ionizing radiation is important. Special space suits are developed so that there is no damage to the body of astronauts due to these rays (57).

4.5 For neuronal problems

No specific drugs are used for neuronal problems that arise due to space travel. But precautions are taken to shield the radiation as much as possible. Dietary supplements and antioxidant intake is very essential to control the damage of neurons due to space travel.

4.6 For hormonal problems

During the first few days of the space flight, there is an increase in proinflammatory cytokine IL-6 which increases protein breakdown and as a result, there is muscle loss (58). Also due to the increase in the activity of PTH hormone recombinant forms of PTH hormones are used to decrease bone reabsorption (52). There is also an increase in the levels of antidiuretic hormone (ADH) during space flight (59). Diuresis is induced by loading water or sodium chloride, and due to acetylcholine-induced vasodilation, the concentration of electrolytes remains balanced. Erythropoietin is also seen to decrease in astronauts in long-duration space flights. Thus, the level of RBC decreases in the blood (59). Iron supplements are given along with folic acid to the astronauts.

4.7 For digestion

Food is generally given in very calculated amounts to the astronauts. The food carrying capacity remains limited and thus limited food and nutrition can cause a problem. Due to weightlessness the signals generated in the stomach for digestion due to weight are disturbed and this causes problems in digestion (60). The gut microbiome is greatly reduced in outer space which creates problems in food digestion. For this pre and probiotics are given to the astronauts regularly (61). Calculated nutrients and proper supplements are essential for the proper maintenance of the digestive system.

4.8 For psychological problem

Psychological problems may arise due to isolation and a quiet environment of space. For this astronauts are given proper training pre-flight to maintain their mental condition in isolation. (62). Medical kits in spacecraft contain medication for depression, sleeplessness, anxiety, and fatigue (63).

4.9 For eye problem

For the protection of the eye, astronauts were sunglasses with a dark color lens and thin protective gold coating. There are special devices that decrease intracranial pressure and reduce the chances of glaucoma (63).

5. Medicinal plants used in space

Nutritional requirements in space contain calcium, iron, vitamin A, vitamin C, riboflavin, thiamine, vitamin D, vitamin E, magnesium, zinc, fiber, and pantothenic acid. There are many herbal preparations available to meet the nutritional requirements in space as well as for maintaining the mental and physiological state of astronauts (64).

Ginseng belongs to the family Araliaceae, found in the Northern part of China and some other parts of Asia. Three species of ginseng are medicinally important namely Korean ginseng, Chinese ginseng, and American ginseng. Phytochemicals like saponins(ginsenosides Rb1, Rd, Re, Rg1, Rg2, Rh1), polysaccharides (dextran, arabinogalactan, galactose, galacturonic acid, arabinose), amino acids(arginine, glutamic acid, aspartic acid, glycine, leucine), and volatile oils(n-hexadecanoic acid, falcarinol) have been identified in *Panax ginseng*(65). In China, the China Astronaut Research and Training Centre has studied the effect of ginseng on the cognitive defects of astronauts in space. Research is going on the effect of individual ginsenosides in the area of treatment of cognitive defects (66). *Panax ginseng* is also been used commercially in various formulations by different companies. Some of the marketed products are Ginseng Rouge Face Soap, Alpspure Ginseng tablets for energy, and Ginseng Bravo Tea.

In another study, Chinese herbal medicinal formulas Hachimi-jio-gan (*Rehmanniae radix*, *Corni fructus*, *Dioscoreae rhizome*, *Alismatisrhizome*, Hoelen, *Moutan cortex*, *Cinnamon cortex*, *Aconiti tuber*) (Table 1) (67) and Hochu-ekki-to (*Astragali radix*, *Ginseng radix*, *Atractylode rhizome*, *Angelicae radix*, *Zizyphi fructus*, *Aurantii nobilispericarpium*, *Bupleuri radix*, *Glycyrrhizae radix*, *Cimicifugae rhizome*, *Zingiberis rhizome*) (Table 2) (68) are been tested for zero gravity-induced problems. Results suggested that these formulations can decrease the level of ADH in the blood of astronauts in outer space (69).

Table 1 List of plants and phytochemicals of Hachimi-jio-gan-

Plants	Secondary metabolites
Rehmanniae radix	Catalpol, Rehmannioside A, Rehmannioside B, Rehmannioside C, Ajugol, Geniposide, Genistic acid
Corni fructus	Morroniside, Loganin, Cornuside, Caffeic acid, coumaric acid, Quercetin 3-O-glucuronide
Dioscoreae rhizome	Crysanthemin, Dihydrodioscorine, Phytic acid, Procynidin B1, Sapogenin, Discoeine, Cortisone, Tannin

Alismatis rhizome	Alisol O, Alisol S 23-acetate, Alisol H
Poria cocos	Pachymic acid, Tumulosic acid, Eburicoic acid, Trametenolic acid, Pinicolic acid A, Pinicolic acid E
Moutan cortex	Paeoniflorin, Oxypaeonifkorin, Galloyloxypaeoniflorin, mudanpioside A, B, C, D, H, J
Cinnamomi cortex	Cinnamic acid, Cinnamaldehyde, α-Pinene, β-Phenethyl cinnamate, β-Pinene, α-Caryophyllene, Cinncassiol D4, Cinncassiol E
Aconiti tuber	Aconite, Benzoylmesaconine, Mesaconitine, hypaconitine, Heteratisine, Heterophyllisine, Atidine, Isotisine

Studies have shown that natural antioxidant products like aloin which is an anthraquinone glycoside which is prepared from the latex of plants belonging to the genus Aloe especially *Aloe ferox*, and Ginkgolide A which is a unique class of diterpenoids obtained from the plants of *Ginkgo biloba* reduces the reactive oxidant species against Spaceflight-associated neuro-ocular syndrome (SANS) which is caused by an increase in intracranial pressure and cephalad fluid shift produced by both low-dose radiation and high-dose radiation (70).

Spirulina which is dried biomass of *Arthrospira platensis* which is an oxygenic photosynthetic bacterium in fresh and marine water is been used as an anti-inflammatory, and antioxidant as well as boost the immune system of the astronauts and has been used by NASA as a supplementary food for astronauts. It can inhibit the release of histamine from mast cells and maintain anti-inflammatory activities (71). Consumption of spirulina also decreases cholesterol and triglyceride levels.

Table 2 List of Plants and Secondary metabolites of Hochu-ekki-to

Plants	Secondary metabolites
Astragali radix	Astragaloside IV, Cycloastragenol, Astragalus polysaccharide, calycosin-7-O-β-D-glucoside, calycosin
Ginseng radix	Ginsenoside, Protopanaxadiol, Protopanaxatriol, ocotillol, oleanolic acid
Atractylodes rhizome	Atractylenolide III, Atractylon, Atractylodin
Angelicae radix	Protocatechuic acid, Phthalic acid, p-hyfroxybenzioic acid, vanillic acid, ferulic acid, Caffeic acid
Zizyphi fructus,	Rutin, Ursolic acid, Scopoletin, Jujubeside A, Jujubeside B, betullinic acid
Aurantii nobilis pericarpium	Limonene, α-Bergamotene, β-Bisbolene, β-Caryophyllene, Linalool acetate
Glycyrrhizae radix	Glycyrrhizic acid, Glycerrhetinic acid, Liquiritin, isoliquiritin
Cimicifuga rhizome	Cimifugin, hydrocinnamic acid, caffeic acid, ferulic acid, isoferulic acid

Zingiberis rhizome	Gingerols, shogoals, paradols, zingerone, gingerenone-A etc
Bupleuri radix	3-methylbutanal, Saikosaponins a, c and d, quercetin, isorhamnetin, rutin

Triphala an Ayurvedic preparation consists of *Emblica officinalis*, *Terminalia bellirica*, and *Terminalia chebula* and the mint extract is effective against radiation-induced problems of astronauts in space (72). Numerous secondary metabolites have been identified from these plants, including polyphenols, alkaloids, glycosides, amino acids, and tannins. *Emblica officinalis* contains gallic acid, ellagic acid, chebulinic acid, Emblicanin-A, Emblicanin-B, Quercetin, and Phyllantine (73,74). *Terminalia bellirica* contains β-cetosterol, ellagic acid, chebulaginic acid, cardenolide, Argungenin, beleric acid, and bellericoside (75) *Terminalia chebula* contains β-cetosterol, termilignan, gallic acid, ellagic acid, chebulaginic acid, quercetin, kamferol, palmitic acid, and linoleic acid (76).

6. Conclusion

In this study, we conducted an analysis and summation of the literature on space adaption syndrome, bone and muscle loss, and cardiovascular, pulmonary, and neurological impacts of spaceflight on astronauts. It has been demonstrated that spaceflight has negative consequences on the human body at many different levels, including the heart, lungs, and brain. Long-time exposure to ionizing radiation in space has considerably affected the body. Space flight causes significant changes in the organs but also causes many functional changes in the body. These changes are seen to cause adverse effects on the body's normal functioning.

Long-time stay in space causes significant loss of muscle, osteoporosis, disturbance in posture, and considerable damage to other major body organs. Ebullism, hypoxia, hypocapnia, and decompression sickness are all possible outcomes of space exploration. In combination, the environment's high-intensity photons and atomic nuclei can potentially cause biological mutation and disintegration. The astronaut faces the danger of going into cardiac arrest and passing away of hypoxia if the body does not receive sufficient oxygen. In the absence of gravity, the lungs' regular gas exchange process results in the evacuation of all gasses from circulation, especially oxygen. The loss of awareness occurs when the deoxygenated blood reaches the brain after 9 to 12 seconds. Proper diet, exercise, and regular intake of supplements can decrease the chances of such problems. This review states all the pharmacological problems of astronauts, that are associated with space travel and zero gravity environment. It also gives the treatment and precautions that are available. To protect the astronauts from these hazards, NASA has designed suitable protective equipment, suits, and vehicles. The amount of ionizing radiation is cancelled up to the level possible by the equipment. Intravenous GH and moderate periodic exercise were found to help diminish muscular atrophy when taken simultaneously and not when used alone. Additionally, steps should be taken to compensate for the body's protein, water, and other nutrients. Proper diet, cleanliness, and exercise should be maintained to properly function and reduce health-related problems in space. Also, the use of plant-based herbal medicines that are in the experimental phase are described, which are can regulate the physiological function of the body in outer space. But finally, these changes are unavoidable, and long-term space flights may cause permanent health hazards to the astronauts, even though all necessary precautions are taken.

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Conflict of Interest

We wish to confirm that there is no known conflict of interest associated with this publication.

Authors contribution

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