

Review

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Review

# Medicinal Plants in the Space Exploration Era: Challenges and Perspectives

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## Featured Application

This work outlines the potential human health benefits of using medicinal plants in long-duration space missions.

## Abstract

Since the dawn of civilization, humanity has looked to the sky seeking to expand knowledge beyond Earth's boundaries. The last eight decades have witnessed remarkable progress in space exploration paving the way for increasingly longer space journeys and the establishment of human settlements on the Moon and Mars. These achievements have been made possible by advances in multiple scientific disciplines, including the rise of space medicine, astropharmacy, astrobiology, and astrobotany each addressing how biological and technological systems adapt to extraterrestrial environments. Nevertheless, the space environment remains profoundly inhospitable to human life, making the protection of health and the assurance of long-term sustainability a key strategic goal in space exploration programs. Within this multidisciplinary framework, the potential role of medicinal plants remains underexplored. Historically central to healthcare, medicinal plants provide a vast repertoire of bioactive compounds and molecular scaffolds, many of which have inspired modern drugs. This review explores how medicinal plants could contribute to human well-being beyond Earth—not only as sources of therapeutic agents to mitigate space-induced ailments but also as biomanufacturing platforms for on-demand production of pharmaceuticals. Ultimately, medicinal plants could continue to play a pivotal role in supporting human health in space, but it poses new challenges and requires further scientific and technological advances.

**Keywords:** medicinal plants; spaceflight; microgravity; space radiation; astrofarmacy; space farming

## 1. Introduction

Since ancient times, mankind has eagerly looked at the sky with curiosity and ambition to expand knowledge beyond the terrestrial boundaries. The quest for knowledge can be traced back to around 3500 BC in Mesopotamia with the first observations and calculations of the movements of celestial bodies and has led to challenging projects in the modern day including a return to the Moon to establish a permanent outpost and the colonization of Mars [1]. It is amazing to observe how in the last 80 years such great scientific and technological results have been achieved, previously unthinkable. Table S1 shows the milestones in the history of space travel. These incredible results have been initially achieved by an imaginary arm wrestling between Russian (SSP, Roscosmos) and American (NASA) space agencies and later sustained and integrated with the effort of further national space agencies such as ESA (Europe), CSA (Canada), JAXA (Japan) and CMSA (China)

among the others. In addition, several private space technology companies are also contributing, alone and in collaboration with institutional players, to this field: the main contribution of these companies is the development of spacecrafts and launch vehicles (partially or fully reusable) that make actual and future space travels reliable and affordable, regardless of their purpose (scientific, commercial or touristic) [2]. The emergence of these new actors, funded primarily through private capital and characterized by a for-profit orientation and a weak dependance on government-issued needs, come together under the term “New Space” [3].

The successes achieved in space exploration have gone hand in hand with scientific and technological progress in various areas of knowledge such as physics, engineering and computer science among others. However, progressively venturing into low Earth orbit (LEO) and beyond has posed and poses new problems and challenges. From this criticality new opportunities have arisen, in the form of new scientific disciplines. Overall, these disciplines answer the question of how a “system” behaves under the harsh condition of the extraterrestrial environment; thus, space medicine studies the physiological and neuropsychological alterations occurring during space travels that may negatively affect human health [4–6]; astropharmacy studies how the space environment alters the stability and therapeutic efficacy of drugs, developing strategies to mitigate these effects and to produce medicines in space during long-term missions. [7–11]; astrobiology is an interdisciplinary discipline investigating life, in all its aspects, beyond Earth [12,13]; astrobotany studies the physiological adaptations that occur in plants growing in extraterrestrial environmental conditions and develops appropriate horticultural strategies aimed producing fresh food [14–16]. These new sciences, far from being independent, are on the contrary interconnected and put in the spotlight the well-being and survival of humans during spaceflights and future space colonization.

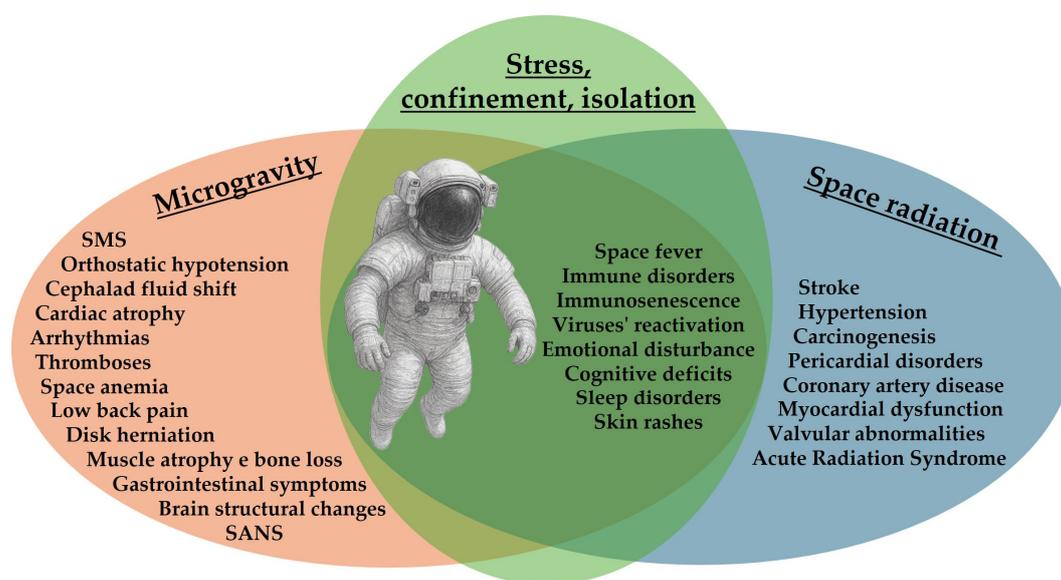
In this complex and in making framework, full of stimulating opportunities and perspectives, a theme remains poorly investigated: what role could medicinal plants play in space exploration and colonization? Historically, the use of medicinal plants has in fact represented a valid therapeutic support to conventional medicine in the management of a wide spectrum of ailments. Besides their direct benefits, phytochemicals, and natural products in general, exhibit a massive scaffold assortment and structural complexity representing an inexhaustible source of pharmacologically active ingredients and lead compounds for rational drug design. Consistently, natural or natural-derived products represented an important fraction of the pharmacological agents approved in the last 40 years [17].

Starting from these assumptions, this review article represents the first attempt to collect and summarize information on the prospects of medicinal plants in the context of long-term space exploration missions. To reach this goal, the review has been organized into four sections. The review starts with an introductory section followed section presenting the state of the art regarding the enormous challenges that the human body faces, both physically and mentally, beyond the Earth boundaries. In the third section, we describe how the space environment modifies the established rules of ground-based pharmaceutical and pharmacology, hindering the effectiveness of therapeutic interventions during space missions. In section 4, we explore the potential role medicinal plants could play in the complex context of space exploration and extra-Earth colonization. Based on current on-Earth knowledge, a tentative proposal will be made regarding which medicinal plants might be useful for alleviating ailments experienced in space. Furthermore, the concept of “medicinal plant” will be used in its broadest sense, discussing the potential use of plants as platforms for biopharmaceutical production on demand. Finally, the concluding section addresses the emerging issues associated with the potential use of medicinal plants in space.

Overall, the opportunity for medicinal plants to maintain a pivotal role also outside Earth boundaries emerges. They may represent both a holistic therapeutic approach consistent with the multifaceted nature of human health risks posed by space exposure and a biomanufacturing tool.

## 2. Space/Flight Hazards

Human beings have evolved over millions of years within the boundary conditions of Earth. It should therefore not be surprising that environmental conditions in LEO are extremely hostile to the human body and can give rise to several physical and mental dysfunctions. Health consequences depend on distance and duration of spaceflight and are often reversible upon return to Earth [4]. Microgravity and space radiation represent the main environmental stressors that alter normal human physiology. Sleep disturbance and several mental health problems can also arise from the intrinsic features of spaceflight such as isolation, confinement, absence of normal day-night cycle, and the prolonged need to perform high-stakes tasks in forbidding environmental conditions. This complex and interconnected set of environmental and psychosocial factors that humans face during space travel is called space exposome. In the following sections, the current state of knowledge about spaceflight-associated health problems will be presented (Figure 1).



**Figure 1.** Main health disturbs induced by space exposome (SANS, Spaceflight-Associated Neuro-ocular Syndrome; SMS, Space Motion Sickness).

### 2.1. Impact of Microgravity on Human Physiology and Health

Gravity is the force by which a planet or any body having mass attracts objects toward its center. An object on Earth's surface is subjected to an acceleration of approximately 1 g (9.81 m/s<sup>2</sup>). It is worth noting that this physical variable remained unchanged during the last four billion years and for this reason gravity can be considered one of the driving forces that shaped life evolution on Earth [5,18]. In space exploration, on the other hand, this staple is missing. The human body transiently experiences high G force during the launch and landing phases, which can reach remarkable values between 3 G and 7 G [19,20]. On the contrary, inside an orbiting spacecraft, astronauts and objects float in a state of microgravity (approximately  $1 \times 10^{-6}$  G). Microgravity ( $\mu$ G) can be defined as a condition of weightlessness occurring when an object is in freefall within a gravitational field. In simple terms, gravitational force is significantly less than those experienced on Earth. Besides  $\mu$ G, it should be also considered that, in future missions that contemplate the possible colonization of the Moon and Mars, humans will be exposed to gravities of 0.17 G and 0.38 G respectively. In these prohibitive environmental conditions, the organism is adversely affected and implements a series of adaptations to counteract the absence of gravity. It emphasizes the importance of investigating the consequences of  $\mu$ G on human physiology and health.

### 2.1.1. Effects of Microgravity on the Cardiovascular System

Exposure to  $\mu\text{G}$  during space travel has been correlated with multiple risks to the cardiovascular system [21–26]. They ultimately represent a physiological adaptive response of the body and may depend at least in part on spaceflight duration [27].

The most relevant effect caused by  $\mu\text{G}$  on the cardiovascular system is a shift in fluid distribution. On Earth, the upright position under the 1 G force of gravity causes a cephalo-caudal pressure gradient, resulting in a mean arterial blood pressure of  $\sim 200$  mmHg in feet and  $\sim 75$  mmHg in the head [28,29]. Weightlessness in space causes an immediate redistribution of  $\sim 2$  liters of blood and fluids from the lower extremities to the upper body, and arterial blood pressure reaches a uniform value of  $\sim 100$  mmHg [30]. A reduction on circulatory blood volume also occurs due to transcapillary fluid filtration into upper-body interstitial spaces [31,32]. Following these adaptations, the face swells up and the legs become slimmer, a phenomenon commonly known as “puffy face and chicken legs”. Fluid redistribution is accompanied by an increase in stroke volume (the volume of blood pumped out of the left ventricle during each systolic contraction) and cardiac output (the amount of blood pumped by the heart/minute) [33,34]. The hemodynamic rearrangement develops rapidly during short-duration spaceflight but becomes more pronounced during long-duration missions [35].

Alteration in heart size is also commonly observed in astronauts; it is interpreted as a consequence of the reduced effort required by heart functioning in  $\mu\text{G}$  conditions. Long - as well as short - spaceflights have been found to induce a reduction in left ventricular mass [36,37], and to promote cardiac atrophy [38,39]. Moreover, the normal pinecone shape of the heart turns into a more spherical one in absence of gravity, contributing to its reduced efficiency [40].

Overall, these physiological adaptations are among the leading causes of orthostatic hypotension, a condition experienced by astronauts on stand returning from spaceflights. Orthostatic hypotension is characterized by dizziness, lightheadedness, palpitations, weakness and potentially fainting. Upon returning to Earth, the cardiovascular system fails to rapidly readapt to 1 G gravity. Blood pools in the lower extremities, and the reduced cardiac contractility together with the reduced blood volume prevent the cardiovascular system from maintaining adequate pressure and supplying blood to the brain [26,41]. Inadequate vasoconstriction due to  $\mu\text{G}$ -induced dysfunctional autonomic control also contributes to the development of orthostatic hypotension [42–45]. There is evidence that the likelihood of developing orthostatic hypotension is increased after long-term spaceflights [46].

Some astronauts experienced arrhythmias during spaceflights, which may represent a trigger factor of life-threatening events, specifically for future long-term space missions. A direct causal factor has not been identified yet, but the physiological adaptations induced by  $\mu\text{G}$  are responsible, at least in part, in the occurrence of arrhythmia. Biomedical analysis from Apollo, Skylab, Space Shuttle and Mir space programs reported the occurrence of 3 main types of arrhythmias: premature ventricular complexes, ventricular tachycardia and premature atrial complexes [47–50]. Further electrophysiology disfunctions observed in astronauts are atrial fibrillation [51] and prolongation of QT interval [52], specifically after long-term spaceflights.

Finally, studies associated the permanence in  $\mu\text{G}$  environment with the formation of internal jugular vein thromboses [53–56].

The molecular and cellular mechanisms responsible for  $\mu\text{G}$ -induced cardiovascular alterations are beyond the scope of the review; useful information about these specific topics can be found elsewhere [21,22].

### 2.1.2. Effects of Microgravity on the Hematological System

In weightlessness conditions, the reduction on plasma- and total blood volume, resulting from fluid redistribution, is responsible of the so called “space anemia” [57]. Space anemia is a physiological adaptation to  $\mu\text{G}$  characterized by a reduction in erythrocyte and hemoglobin levels, which persist transiently upon return to Earth [58–61]. The extent of anemia and the time required to recover appear to be positively correlated with time spent in space [60,61]. The possible consequences

of space anemia in long-term missions remain a matter of debate but should be carefully examined as it may be responsible for cognitive impairment [62].

### 2.1.3. Effects of Microgravity on the Musculoskeletal System

Microgravity exposure experienced during both short- and long-term spaceflights results in musculoskeletal deconditioning having detrimental health consequences [63,64]. Short exposure to  $\mu\text{G}$  (<30 days) is sufficient to induce lower limbs muscle atrophy [65,66], with a consequent reduction in their functional strength [67,68]. Low back pain [69] and disk herniation [69,70] are additional ailments related to weightlessness. A longer exposure to  $\mu\text{G}$  makes the situation even worse [69,71] and a decrease in the performance of upper limbs was also observed [72].

Like the musculature, the skeletal system is also compromised [64]. Under normal conditions at 1 G, proper bone structure and function are ensured by a fine-tuned balance between bone resorption and formation, promoted by the coordinated action of osteoclasts and osteoblasts [73]. Conversely, in a  $\mu\text{G}$  environment, the lack of mechanical loading disrupts bone homeostasis and bone resorption prevails; this is particularly evident in load-bearing bones. Consistently, a reduction of bone mass and bone mineral density have been observed during long duration missions in space [74–79].

Overall, muscle atrophy and accelerated bone loss are two sides of the same coin, as these structures are anatomically and functionally interconnected. Together, they represent a critical medical problem as they can threaten the health and performance of astronauts during long-duration missions and can have long-term consequences upon return to Earth, increasing, among the other, the risk of fracture and osteoporosis. Complete musculoskeletal recovery after spaceflight is body-area specific and dependent on the length of spaceflight; the time of recovery is longer than spaceflight duration [74,78] and may take more than 2 years for some muscles [80]. Several exercise programs have been developed and tested over time to mitigate the effects of  $\mu\text{G}$  on the musculoskeletal system, but none have been proven to be fully effective [63,81].

### 2.1.4. Effects of Microgravity on the Neurologic System

Research over the past decade has demonstrated that  $\mu\text{G}$  affects the human brain in terms of both structure and function [82,83]. The upward shift of body fluids observed in weightlessness conditions causes a redistribution of cerebrospinal fluid promoting an expansion of ventricular volume, an increase in intracranial pressure and a depression of pituitary dome [84–87]. The extent of changes in the brain produced by  $\mu\text{G}$  increases with the length of time spent in space [84,87,88]; it has also been found that at least 3 years are required for complete recovery [88]. A shift of the brain upwards within the skull [89], and an alteration of white and gray matter volumes have been also observed in several brain areas following long-duration spaceflights [84,85,89].

In addition to structural changes in the brain,  $\mu\text{G}$ -induced cephalic fluid shift is among the causal factors of the so-called spaceflight-associated neuro-ocular syndrome (SANS) [90]. Increasing awareness of SANS and developing appropriate countermeasures to its prevention a priority for space agencies, given its potential debilitating impact on astronaut performance. SANS is in fact a complex syndrome altering astronauts' vision characterized by a spectrum of ophthalmic abnormalities, specifically, optic disc edema, hyperopic refractive alterations (axial hyperopia), posterior globe flattening, choroidal folds, and cotton wool spots (focal regions of ischemic retina) [91]. The disabling potential of this syndrome is demonstrated by studies showing how some of these structural changes can persist for more than 7 years after returning to Earth [92].

During the first phases of adaptation to  $\mu\text{G}$ , humans experience symptoms like seasickness. This phenomenon, called space motion sickness (SMS), is caused by the effects induced by  $\mu\text{G}$  on the vestibular system [93]. Under 1G spatial orientation is driven by integrating sensory information coming from vision -, vestibular - and proprioceptive systems [94]. Conversely, weightlessness affects vestibular signaling due to the inability of the otoliths to detect head position. Otoliths deconditioning leads to dizziness, vertigo, headaches, cold sweating, fatigue, nausea, vomiting [95] and overall is also responsible for sensorimotor deficits such as impaired spatial orientation, balance,

locomotion, gaze control, and eye-head-hand coordination [96–98]. It is worth noting that the brain develops strategies to adapt to weightlessness by increasing the contribution of other sensory systems (visual and somatosensory systems) when vestibular input is compromised [99–104]. The reweighting of sensory systems is also accompanied by neuronal connectivity remodeling and by neuroplasticity processes in different areas of the brain [105–108]. Unfortunately, the neuronal and sensory-functional rearrangements that allow astronauts to adapt to weightlessness have detrimental consequences upon their return to Earth at normal 1G gravity. Consistently, several sensorimotor alterations have been detected postflight such as impairments in balance, posture and locomotion that can increase the risk of fall [109–112], deficits in manual dexterity, dual-tasking, motion perception, and vehicle operation [113]. Full recovery may take several weeks, specifically after long duration spaceflights [109,111,114].

#### 2.1.5. Effects of Microgravity on the Gastrointestinal System and Gut Microbiome

Exposure to  $\mu\text{G}$  has been found to induce several gastrointestinal symptoms such as nausea, vomiting, diarrhea and constipation; however, the data available suggest that these symptoms disappear within the first 30 days of flight [115]. In addition,  $\mu\text{G}$  has been found to promote dysregulation of gut microbiome variety. It is a critical finding since an imbalance in the complex ecosystem of microorganisms in the digestive tract is responsible for the pathogenesis of several ailments [116]. Specifically, microorganisms count increases following permanence in a microgravity environment as well as the Fimicutes/Bacteroides ratio [26,117]. It was confirmed both by a preclinical investigation in mice exposed to space-like conditions [118], and by analysis of twin's gut microbiome [119]. The twin that remained in space for one year showed in fact gut dysbiosis and a reduction on microbiome-derived anti-inflammatory molecules [119]. Permanence under  $\mu\text{G}$  conditions was also associated with a reduction of anti-inflammatory bacterial species [120]. Despite this evidence, the potential health consequences of intestinal dysbiosis during long-term space travel still remain to be investigated.

#### 2.2. Impact of Radiation on Human Physiology and Health

One reason why Earth is such a favorable environment for life is the presence of an atmosphere and a magnetosphere that protect its surface from space radiation (SR) [121,122]. When humans leave Earth and travel beyond LEO, this protection vanishes, and they are exposed to the harmful effects of SR [123–125]. Protecting humans from the harmful effects of SR is therefore considered a critical and priority aspect by NASA's Human Research Program in view of the ambitious space missions of the future [126,127]. On Earth, humans are exposed mainly to electromagnetic radiation, characterized by packets of photons that have energy but are massless and chargeless; at variance, in outer space, they encounter a different kind of radiation that can be defined particle radiation, characterized by energetic particles having mass with or without charge [128]. The main sources of particle radiation in space include the solar particle events (SPEs), the galactic cosmic rays (GCRs) and the trapped particle radiation (TPR) [129]. SPE, commonly known as solar radiation storm, is a periodic phenomenon triggered by the Sun's natural activity during which protons are accelerated into interplanetary space [130]. GCRs originate outside the solar system, mainly from supernova explosions within Milky way; GCRs are composed of about 86%-91% protons, nearly 8%-13% helium ions and for the remaining part of HZE particles, i.e. ions heavier than helium with high charge and energy [131,132]. TPR consists of protons and electrons trapped by geomagnetic fields around Earth in two regions, an inner belt and an outer belt, collectively known as Van Allen radiation belt. The inner and outer belts consist of high-energy protons and electrons respectively [133].

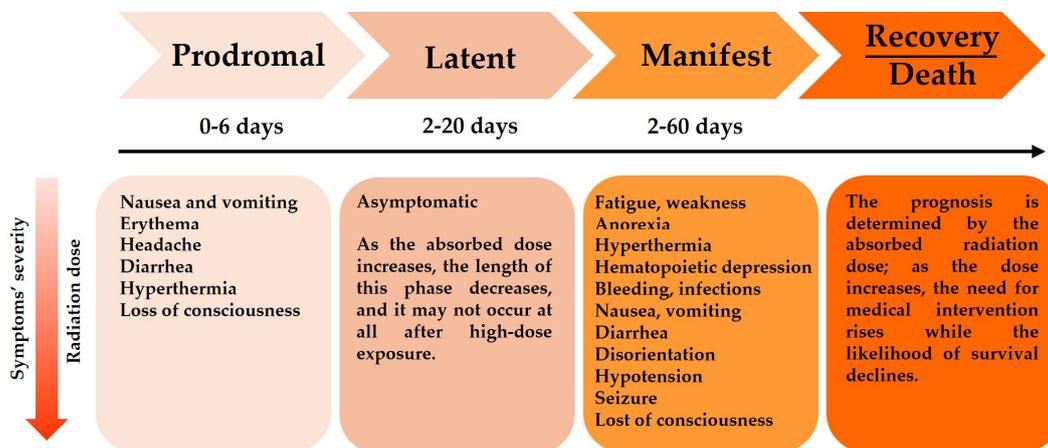
Crew of extended duration missions in deep space will be particularly exposed to the effects of SR. The equivalent dose of radiation in deep space has been estimated at about  $1.84 \text{ mSv day}^{-1}$ , about 280-fold that on Earth [134,135]. The sievert (J/kg) is the estimate of the long-term risks associated with radiation exposure; 1 Sv is approximately equivalent to a 5% excess risk of developing a fatal cancer [136]. For this reason, to limit the health risk associated with SR exposure, space agencies have

established career exposure limits for astronauts that span from 600 mSv to 1000 mSv [137]. Additionally, researchers are actively engaged in finding new strategies to monitor SR exposure and protect astronauts from its harmful effects [138].

Particle radiation in space has medium to high linear energy transfer (LET), overall, the pathological consequences of SR exposure arise from the direct and indirect (via production reactive oxygen species) damage caused by radiation at cellular level that bring to mutations, chromosomal aberrations, functional abnormalities, senescence, and cell death [123,139,140]. In the following sections we summarize the most important studies regarding the potential detrimental effects of SR during space missions on the human body. The limited information available stems from the fact that only astronauts on lunar missions were exposed to significant doses of SR.

### 2.2.1. Acute Radiations Syndromes

One specific health risk that must be considered when planning long-term missions in deep space is the development of acute radiation syndromes [141,142]. Acute radiation syndrome (ARSs) refers to a group of clinical manifestations developing when the human body, or a significant part of it, is exposed to a high dose of ionizing radiation over a short period [143]. Severity, duration and prognosis of ARSs depend on radiation type, exposure duration and dose rate among the others. The main parts of the body involved in this pathology are skin, hematopoietic – , gastrointestinal – and neurovascular – systems. The development of the ARS is divided into 4 phases (figure 2): prodromal, latent, manifest and recovery or death. It should be emphasized that the available information on the development of ARSs is based on observations and clinical studies conducted on humans exposed accidentally or intentionally to ionizing radiation (mainly gamma- and X-ray exposures). These studies have led to the identification of specific exposure limits below which the risk of developing ARS is negligible. For healthy adults, the threshold whole-body dose of radiation acutely delivered is  $\leq 1$  Gy but is lower for children and elderly [141,144].



**Figure 2.** Progression and clinical manifestations of acute radiation syndromes.

During space missions the potential risk of developing ARS is mainly related to SPE, but the real consequences for human health are unknown and are still the subject of intense debate [142,145]. To account for this level of uncertainty, NASA has set a permissible exposure limit for acute radiation effects on blood-forming organs and the circulatory system at 250 mGy-eq over a 30-day period [146]. Note that Gy-eq (gray equivalent) is a unit that accounts for the different effects induced by different types of particle radiation (protons, heavy ions, etc).

### 2.2.2. Effects of Space Radiation on the Cardiovascular System

There is currently little direct evidence of the effects of SR on the cardiovascular system [4,21,25,142]. An epidemiological study has shown an increase in mortality due to cardiovascular diseases in Apollo astronauts (the only humans to have ever traveled beyond the geomagnetosphere)

compared to non-spaceflight astronauts and astronauts who flew only in LEO [147]. However, the limited sample size does not allow to draw strong conclusions. SR has been also found to promote capillary endothelial disfunctions like age-phenotype [148].

The potential risk for cardiovascular health induced by the prolonged exposure to SR can be inferred by studies conducted on Earth [149]. Exposure to ionizing radiation, as for example, during cancer therapy or in atomic bomb survivors have been found to elicit coronary artery disease, myocardial dysfunction, valvular abnormalities, hypertension, stroke and pericardial disorders [126,150–154]. Preclinical in-vitro and in-vivo studies support these epidemiological and clinical findings by showing the potentially hazardous effects of radiation on cells and tissues of the cardiovascular system [142]. Exposure to Fe<sup>56</sup>HZE ion (a major component of GCRs) has been found to induce aberrant structural and functional changes in the aorta of mice and rats resulting in the development of atherosclerotic lesions [155–157]. Moreover, 10 month of <sup>56</sup>FeHZE ion irradiation reduced angiogenesis in mice [158]. In addition, irradiation with multiple ions, in an attempt to simulate GCRs exposure, induced perivascular cardiac fibrosis in rats [159] but only mild changes in mouse heart [160].

Overall, epidemiological and preclinical studies highlight the urgent need to further deepen our understanding of the biological effects of charged particle radiation on the cardiovascular system in order to mitigate the harmful consequences for human health during and after space exploration missions.

### 2.2.3. Carcinogenesis Induced by Space Radiation

It is matter of fact that ionizing radiation is mutagenic and carcinogenic [161]. This evidence comes from epidemiological studies in atomic bomb survivors [162], and in people following accidentally [163] or occupationally exposure to ionizing radiation [164]. Carcinogenesis is mainly triggered by radiation-induced direct and indirect damage to nucleic acids [165,166]; if DNA repair mechanisms are overwhelmed or impaired, unrepaired DNA damage can accumulate causing cancer [166,167].

It is reasonable to assume that SR, characterized by higher LET, increases the carcinogenesis risk [168,169]. Predicting the actual risk for future long-term deep space missions is therefore essential in order to reduce cancer morbidity and mortality in astronauts. Unfortunately, this is complicated by the lack of effective predictive and preclinical models, due to the enormous differences between radiation on Earth and that potentially found in space.

A recent epidemiological study evaluated cancer incidence and mortality in 338 astronauts against US general population [170]. Overall, the study found an increase in the incidence of all types of cancer but a statistically significant decrease in mortality, confirming previous research [171–173]. However, a more detailed analysis revealed a specific statistically significant increase in the incidence of prostate cancer and melanoma although only in the latter case resulted in an increase also in the rate of mortality [170]. In contrast, the incidence and mortality from lung and colon cancer among astronauts were lower than in the general population. The scientific reasons behind these observations are not fully known or understood and are often not directly related to exposure to SR. For example, the observed increase of melanoma incidence and mortality is comparable to that observed in aircraft pilots [174] and seems to be related to UV radiation exposure rather than SR exposure [170,175]. Nevertheless, these data suggest the urge to increase the understanding of the long-term health risks for astronauts exposed to SR.

In vitro and in vivo studies support the idea that we should be concerned about the effects of SR, demonstrating that medium- and high-LET radiation causes damage to nucleic acid and promotes the development of cancer [168,176]. Consistently, exposure to protons or HZE ions (<sup>12</sup>C, <sup>16</sup>O, <sup>28</sup>Si, <sup>48</sup>Ti, <sup>56</sup>Fe) has been found to induce maladaptive genomic and epigenomic responses responsible for the induction of malignant transformation in several cell lines [177–181]. Moreover, the damages caused by high-LET particle radiation have the ability to propagate neighboring non-irradiated cells throughout a phenomenon known as “bystander effect” [182–184].

The carcinogenic activity of particle radiation is confirmed by studies conducted in rodents showing that heavy ion irradiation significantly enhances development and progression of several types of malignancy such as acute myeloid leukemia [185–187], lung cancer [188–190], ovarian tumors [191,192], hepatocellular carcinoma [186,187,193], intestinal tumors [194–197], mammary carcinoma [198,199] and brain tumors [189].

Overall, these findings demonstrate that a deeper understanding of the cancer risk from SR is imperative to safeguarding the health of astronauts on interplanetary and other extended missions. Specifically, SR-induced carcinogenesis should be investigated not only alone but also in the general context of space exposome. Indeed, there is evidence demonstrating an additive effect of SR and  $\mu\text{G}$  in the production of chromosomal aberrations [200,201].

#### 2.2.4. Effects of Space Radiation on the Central Nervous System

The only known effect of space radiation on the central nervous system (CNS) is the perception of light flashes in condition of darkness [202]. This visual illusion has been repeatedly reported by astronauts in several space missions [203–205]; it is the consequence of the interaction of both protons and heavy nuclei with the visual system [206]. Available data suggests that light flashes do not impair astronauts' performance during missions and are not associated with long-term health risks [202].

Besides light flashes, the potential structural and functional alterations of CNS under SR exposure are unknown and unpredictable due to the lack of epidemiological data. A few considerations can be made starting from terrestrial observations of people undergoing cranial radiotherapy or accidentally exposed to radiation, although these data are not easily translatable to the situation in space due to differences in radiation exposure both in terms of type and intensity. The whole brain radiation therapy has been found to cause neurocognitive deficits [207] because of the damaging effects of ionizing radiation on the hippocampus [208]. Furthermore, accidental exposure to ionizing radiation has been associated with an increased risk of Parkinson's disease [209,210].

The potential detrimental effects of SR on cognitive function also come from in vivo studies, in which laboratory animals can be irradiated with heavy ions. Although these studies are affected by technical and procedural limitations, they overwhelmingly reported that exposure to HZE particles disrupt cognitive behaviours in rats and mice [83,211]. Interestingly, cognitive deficits in rodents have been observed not only at high doses but also in the range of doses predicted for a mission to Mars [212–216] based on measures made by the Curiosity rover [135,217]. Overall, these findings suggest that the potential effects of SR on astronauts' cognitive performance deserve greater attention and further investigation to preserve their health and to ensure the success of future long duration Mars missions.

### 2.3. *Other Risk for Human Health Induced by Space Exposome*

This section summarizes the risks to human health during space travel that cannot be traced back to a single environmental cause but are caused by the totality of the space exposome. This also includes the stress astronauts face when they have to perform complex tasks and maneuvers in a highly hostile environment, far from home and loved ones, and often with minimal margins for error.

#### 2.3.1. Immunological Dysfunctions Following Spaceflights

The immune system is a structured defense network that evolved on Earth to protect the organism from endogenous and exogenous dangers. [218]. Once in contact with the complex and unknown set of stressors of the space exposome, human immunity reacts abnormally [219,220]. Consistently, during spaceflights several alterations on innate and adaptive immunity have been observed in astronauts, such as change in maturation, proliferation and function of several immune cell lines [221–229], dysregulation in cytokine secretion [119,225,228,230–236], changes in the human antibody repertoire [237], alteration in stress hormones levels [224,234,238]. These immunological

dysfunctions occur during both short-duration and long-duration spaceflights, and some have been found to persist even after returning to Earth. Interestingly, there is evidence to suggest that the immune system has the ability to adapt to space conditions after repeated missions [229,239].

The dysregulation of the immune system following spaceflights may have several consequences. Overall, stressful conditions of the space exposome trigger a process of premature immunosenescence [234] characterized by an enhanced pro-inflammatory state resembling that observed during aging, a condition known as inflammaging [240] that may expose the organism to several immune-related diseases. Consistently, several infectious diseases have been reported in post fly medical debriefs [241]. Moreover, the sum of functional immune alterations can be considered responsible, at least in part, for the development of space fever [242] and to the reactivation and shedding of latent viruses in astronauts [233,238,243–249] who generally remain in asymptomatic state.

Unlike the human body, microbes appear to find a favorable environment in space [250]. Bacteria displayed increased grow rate [251,252] and virulence [253–255], as well as, enhanced antibiotic resistance [256–259] during spaceflight. A similar increase in virulence and resistance to antifungal agents have been observed in several strains of fungi [260–263].

Overall, the dysregulation of human immune responses, combined with the increased virulence of pathogens observed during spaceflight, poses a serious health risk to astronauts and could hinder the success of long-duration space missions.

### 2.3.2. Neuro-Behavioural Alterations During Spaceflights

One of the greatest challenges during long-term space missions is the need to maintain high levels of alertness and performance efficiency while dealing with multiple stressors never experienced on Earth. This requires a huge effort and can cause mental health problems [6,264–266]. It is important to emphasize that, in this context, the concept of "mental health problems" should not be understood as a true diagnosable mental disorder, but rather as neurobehavioral symptoms that can cause distress in astronauts and have a negative impact on the success of the mission [6]. The main neurobehavioral problems observed during spaceflight are cognitive deficits and sleep disorders. In section 2.2.4, we discussed the potential role of space radiation in altering astronauts' cognitive performance.

Sleep loss and disturbance are symptoms commonly observed during spaceflights [267]. Sleep disturbances are therefore considered a critical factor during long-term missions, as they can negatively impact astronauts' performance, alertness, emotional state and concentration, thus increasing the risk of operational errors and the success of mission objectives [267,268]. This is not surprising considering that sleep homeostasis, regulated both by internal and external factors, has evolved over time to adapt human physiology to terrestrial environmental conditions. Conversely, during spaceflight numerous factors contribute to sleep disruption, such as the lack of the natural 24-hour light-dark cycle,  $\mu$ G, uncomfortable environmental conditions in spacecraft and space stations (light conditions, noise, temperature), the use of uncomfortable sleeping bags, alterations in the circadian pacemaker (body temperature and cortisol levels), cognitive overload and high workload [6,269–276]. Evidence has consistently shown that both the duration and quality of astronauts' sleep are adversely affected during spaceflight. The average daily sleep time measured in astronauts on several space missions was about 6 hours or less, an amount of time lower than that observed pre- and post-flight [268,277,278]. Overall, sleep duration in space is lower than that recommended to maintain good health and optimal performance [279]. Furthermore, sleep during space missions is of poor quality and shallower. Sleep recordings have shown that the structure and duration of REM and NREM sleep have been altered during spaceflight [269,280]. A study also found that sleep during spaceflight was interrupted by an average of 4.6 awakenings per night, lasting an average of 6.5 minutes [272]. Finally, the impact of sleep disorders is confirmed by the high number of astronauts who had to take sleeping pills during space missions [278,281]. Besides pharmacological intervention several countermeasures are under investigation to restore sleep homeostasis during space missions

such as optimization of work-rest phases, improvement on spacecraft/spaceship environment, light therapy and human intestinal flora therapy [267,282].

An additional issue that should be considered during long-duration space missions is the emotional response of individuals [266]. Although no data is available reporting emotional impairments in astronauts during spaceflight, evidence from ground-based analogues (submarines, polar stations, or space mission simulations) suggests the potential emergence of emotional and psychosocial disturbance [283–285]. Several stressors have been identified as potentially contributing to altered human emotional states and social conflict in space: confinement, social isolation, homesickness, habitat design, cultural barriers, individual personality, and crew dynamics [284,286–291].

Overall, scientific research has brought to light the strong impact of space stressors on human mental health and the consequent need to develop appropriate countermeasures in the planning of long-term space missions.

### 2.3.3. Dermatologic Alterations During Spaceflights

The skin is the largest and outermost organ in the body and performs multiple physical, chemical, physiological, and immunological functions [292]. It is therefore reasonable to expect that the skin is highly sensitive to environmental stressors such as those found in space [293]. The most common dermatologic symptoms evidenced during spaceflight are skin rashes [294–297], dryness [297,298], itching [297,298], peeling (mainly in hands and feet) [294,297] and skin sensitivity [296,297]. Evidence exists also in the development of erythema and skin sensitivity upon landing after 340 days spent in space [299].

The triggers of skin diseases are not yet fully identified and understood. A clinical case has highlighted the possibility that dermatitis may arise due to the reactivation of the herpes simplex virus (HSV-1) during long-duration spaceflights [300]. Poor hygiene [297], the use of no-rinse personal care products [296,299,301] or disinfecting wipes [302], low humidity in the spacecrafts [296,301], and the prolonged contact with constricting suits used during extravehicular activities [303] are also considered responsible, at least in part, of the dermatologic manifestations observed during space missions.

Two longitudinal studies have attempted to identify changes in skin structure and physiology that might explain astronauts' skin reactions in space: the SkinCare and Skin-B studies. The SkinCare study evidenced a thinning of the stratum corneum (the outermost layer of the epidermis) and a decrease on skin elasticity [304], but unfortunately, the Skin-B study fails to confirm these results [297]. A further study reported a thinning of the living layer of the epidermis, a decrease in melanin concentration and a general decrease in skin cell metabolism [295]. The conflicting results gathered from these 3 studies can be largely attributed to the limited sample size used (1-6 subjects).

Overall, this evidence suggests that much more research is needed to clarify the causes and mechanisms of skin disorders observed in space, although it is worth emphasizing that skin disorders during spaceflight do not currently represent a critical issue that could hinder the success of a space mission.

## 3. Pharmacological Interventions in Space

In the previous section we described how human physiology, which evolved to adapt to terrestrial environmental conditions, is challenged by the space exposome. As a result, multiple health dysfunctions occur during spaceflights that require appropriate drug treatment [302]. From this need, a new discipline arises, astropharmacy, an emerging interdisciplinary field dedicated to understanding and addressing the pharmaceutical and pharmacological issues associated with human spaceflight. Broadly speaking, the harsh conditions found in space profoundly affect drug stability, pharmacokinetics (PK), pharmacodynamics (PD), and overall clinical outcomes [8]. Moreover, as human missions extend beyond LEO toward the Moon, Mars, and possibly farther, the

capacity to develop, transport, store, protect and even manufacture pharmaceuticals in situ represents critical aspects to support astronaut health during long-duration missions [9].

The traditional pharmaceutical supply chain relies heavily on regular resupply, cold-chain logistics, and stable environmental conditions, all of which are compromised in space. For long-duration missions, autonomous pharmaceutical strategies must replace Earth-dependency. This includes developing formulations with extended shelf life, understanding altered drug metabolism in space, and utilizing advanced technologies such as 3D printing and synthetic biology, [7].

Astropharmacy also intersects with multiple scientific disciplines, such as pharmacology, pharmacognosy, systems biology, materials science, and aerospace engineering. Furthermore, it plays a critical role in safeguarding astronaut health by ensuring medication availability and efficacy for acute and chronic conditions, psychological support, immune regulation, and radioprotection [305]. The field is not only foundational to space medicine but also serves as a testing ground for innovations that may translate back to Earth-based pharmaceutical challenges, especially in remote or extreme environments.

### 3.1. Medical Care in Spaceflight

On board the International Space Station (ISS), astronauts have access to a carefully designed medical kit intended to address the most common health issues encountered during long-duration missions. The kit is organized into color-coded packages, each serving a specific purpose: white for “convenience” medicines used for frequent conditions, red for “emergency” medicines, purple for “oral” medicines, and brown for “topical and injectable” treatments. Within these kits are FDA-approved drugs, including analgesics, anti-infectives, local anesthetics, antiallergics, corticosteroids, hormones, and medications targeting gastrointestinal, neurological, cardiovascular, and respiratory diseases [10].

The main categories include treatments for motion sickness, such as meclizine and promethazine, and a range of pain relievers including acetaminophen, ibuprofen, hydrocodone, and, in specific situations, ketamine. Sleep disturbances — which occur about ten times more frequently in space than on Earth — are managed with melatonin, zolpidem, and modafinil. Respiratory problems and allergic reactions are treated with decongestants, antihistamines, and injectable epinephrine for emergencies. The kit also contains gastrointestinal drugs such as bismuth subsalicylate, loperamide-based anti-diarrheals, stool softeners, acid reflux medications, and anti-nausea treatments. In addition, it includes antibiotics such as azithromycin and tobramycin, antivirals like valacyclovir, antifungals, corticosteroids, hormones, and medications for chronic or acute conditions such as high blood pressure, seizures, and anxiety (table 1) [306,307].

**Table 1.** Spacecraft formulary drugs.

Category	API (Active Pharmaceutical Ingredients)	Main Uses in Space
<b>Motion sickness</b>	Scopolamine; Promethazine; Meclizine; Dimenhydrinate	Prevention and treatment of space motion sickness (nausea, vomiting, dizziness) due to adaptation to microgravity
<b>Pain management</b>	Acetaminophen (Paracetamol); Ibuprofen; Aspirin; Tramadol; Oxycodone	Relief of muscle pain, headache, joint or exercise-related pain, and minor acute or chronic pain
<b>Sleep aids/Alertness</b>	Zolpidem; Melatonin; Diphenhydramine; Modafinil; Caffeine	Regulation of disturbed circadian rhythms; sleep promotion; alertness maintenance during long shifts or after disrupted sleep

<b>Respiratory/allergy</b>	Loratadine; Cetirizine; Pseudoephedrine; Fluticasone; Albuterol (Salbutamol)	Management of allergies, nasal congestion, respiratory irritation, and cough in the closed spacecraft environment
<b>Gastrointestinal</b>	Omeprazole; Ranitidine; Loperamide; Ondansetron; Metoclopramide	Treatment of nausea, reflux, diarrhea, constipation, and other digestive disturbances linked to microgravity and space diet
<b>Anti-infectives</b>	Amoxicillin; Ciprofloxacin; Azithromycin; Mupirocin; Clotrimazole	Prevention and treatment of bacterial, skin, or urinary infections during space missions
<b>Anti-inflammatory / Hormonal</b>	Prednisone; Hydrocortisone; Dexamethasone; Naproxen	Management of acute inflammation, allergic reactions, edema; modulation of immune response in-flight
<b>Chronic conditions</b>	Levothyroxine; Insulin; Amlodipine; Metoprolol; Sertraline	Management of preexisting chronic conditions (hypertension, diabetes, hypothyroidism, anxiety/depression) during long-duration missions

Not all treatments are related to spontaneous symptoms: at least 10% of drug use is necessary to treat consequences linked to specific operational activities, including extravehicular operations, exercise protocols, or adjustments to work schedules [302]. Statistics indicate that the most frequently used medications aboard the ISS are those for insomnia, pain, nasal congestion, and allergies — a trend similar to that seen in Shuttle missions and in terrestrial ambulatory medicine, although with a significantly higher reliance on sleep aids in orbit [268,308]. Certain events, such as two treatment failures in cases of skin rashes, raise questions about the efficacy or suitability of some drugs in microgravity. These findings suggest that operational adjustments — for example, in internal lighting, shift management, or the design of exercise equipment and extravehicular suits — could help reduce the overall need for pharmacological interventions [309].

### 3.2. Stability and Degradation of Pharmaceutical Compounds in Space

Drug stability is profoundly affected by the extraterrestrial environment. Studies conducted on the ISS have revealed that many medications degrade more rapidly in space than on Earth [310]. Environmental conditions like elevated levels of radiation, variable temperatures, and phase separation triggered by  $\mu\text{G}$  can lead to both chemical and physical degradation of pharmaceuticals [311]. In particular, radiation may disrupt molecular structures by breaking chemical bonds and forming reactive oxygen species, which can oxidize active pharmaceutical ingredients (APIs) [312].

Additionally,  $\mu\text{G}$  influences sedimentation and dissolution behavior in multi-phase drug formulations, particularly those involving suspensions or emulsions [311]. The degradation of critical medications—including antibiotics, antihistamines, analgesics, and cardiovascular agents—has raised concerns about their long-term efficacy during missions exceeding six months [10]. Research has shown that some drugs fall below potency thresholds within 12–18 months of storage in space [313].

To address these concerns, pharmaceutical packaging is being redesigned with radiation-shielding materials, oxygen-absorbing inserts, and thermal insulation. Lyophilized or powdered formulations are being evaluated as more stable alternatives [312]. Moreover, predictive modeling of drug degradation kinetics under space-like conditions is helping to inform pre-mission planning and pharmaceutical inventory management strategies [7].

### 3.3. Pharmacokinetics and Pharmacodynamics in Altered Physiology

The human body undergoes profound physiological changes during spaceflight, and these changes strongly influence pharmacokinetics (PK) and pharmacodynamics (PD). Fluid redistribution leads to decreased plasma volume and altered drug concentrations. Gastrointestinal motility and transit time are affected, potentially impacting drug absorption profiles. Additionally, microgravity-induced alterations in hepatic enzyme activity and renal clearance pathways modify drug metabolism and excretion [8].

These alterations complicate dosing regimens and therapeutic monitoring. For example, altered gastric emptying may delay oral drug absorption, while altered cytochrome P450 enzyme expression may unpredictably increase or decrease hepatic metabolism [314]. Intramuscular injections may cause erratic absorption due to alterations in muscle mass and perfusion.

Therefore, space-specific PK/PD data are essential for rational dosing strategies. However, most of the existing data are derived from animal models or short-term human studies [315]. The use of wearable biosensors and point-of-care diagnostic devices can facilitate personalized medicine in space.

These challenges underscore the need to integrate pharmacogenomics, physiologically-based pharmacokinetic (PBPK) modeling, and AI-based simulations to predict individual drug responses in [316]  $\mu\text{G}$ . Creating a database of space-adapted drug profiles is a key goal for future missions.

### 3.4. In-Situ Pharmaceutical Manufacturing

Due to the logistical limitations of resupplying medications from Earth, in-situ pharmaceutical manufacturing (ISPM) is a core focus of astropharmacy. ISPM includes technologies such as 3D printing of oral solid dosage forms, microfluidic synthesis of small molecules, and bioengineered microbial platforms [9]. These systems must be compact, modular, and capable of operating in low-resource environments.

3D printing of personalized tablets has been demonstrated with active ingredients and controlled-release matrices, enabling on-demand medication production tailored to individual astronauts [317]. Microbial production platforms, particularly engineered *E. coli*, *Saccharomyces cerevisiae*, and *Chlamydomonas reinhardtii*, are being designed to synthesize essential drugs such as acetaminophen and insulin [318]. These biotechnological systems offer low-energy, renewable production pathways suitable for closed-loop life support systems.

The use of plants as bioreactors is another promising avenue. By integrating gene circuits into fast-growing crops, it is possible to generate complex molecules like vaccines, hormones, and enzymes [319,320]. This approach, known as molecular pharming, merges with the fields of synthetic biology and astrobotany, and holds promise for decentralizing drug manufacturing during interplanetary travel.

### 3.5. Regulatory and Operational Challenges

Establishing pharmaceutical manufacturing and usage protocols in space presents a host of regulatory, safety, and operational hurdles. Current pharmacopoeial standards—such as those from the USP, EMA, and WHO—are designed for terrestrial conditions and must be adapted for space. Stability testing, shelf-life validation, and quality control processes must be redefined under microgravity and radiation exposure [7,306].

Moreover, regulatory frameworks need to encompass bioengineered medications and biomanufacturing systems. Issues surrounding microbial containment, gene transfer risks, and biosafety must be addressed, particularly when using genetically modified organisms in closed habitats. Validation protocols for 3D printed or biosynthetically derived pharmaceuticals must ensure reproducibility, sterility, and potency [321,322].

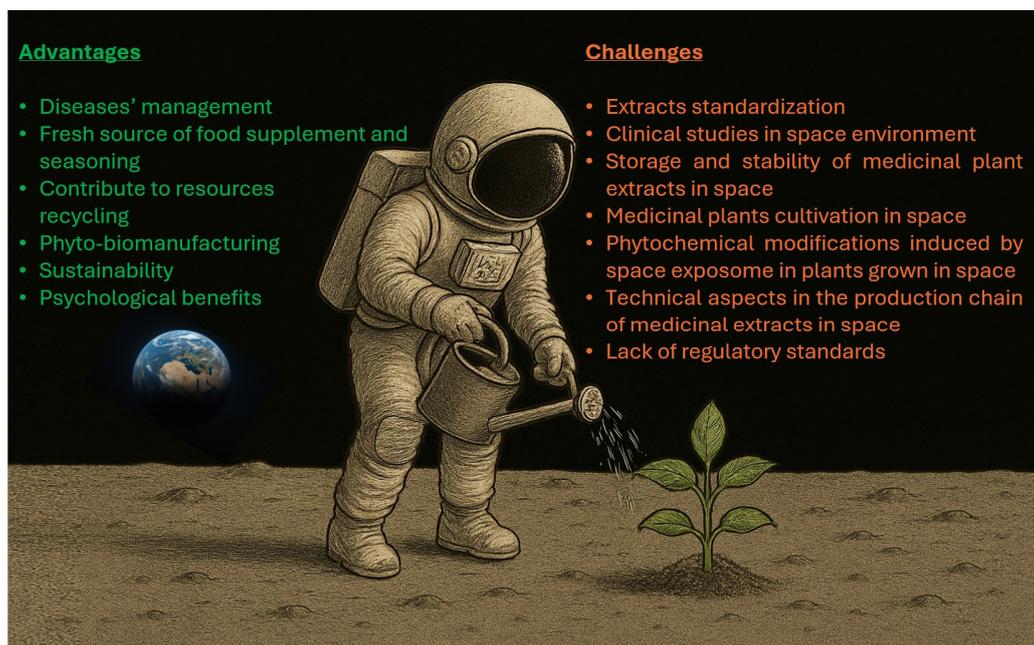
Operationally, space pharmacology requires trained personnel or highly automated systems capable of identifying adverse drug events, preparing formulations, and conducting real-time

diagnostics. Artificial intelligence and telemedicine may support clinical decision-making, but onboard systems must also allow for autonomy in case of communication delays [323].

The establishment of a dedicated space pharmacopeia and international regulatory consensus will be essential. NASA, ESA, and other space agencies are currently engaging with pharmacological societies to draft guidelines and protocols for extraterrestrial pharmaceutical operations [323].

#### 4. Role of Medicinal Plants in Space Pharmacy

In section 3, we described how astropharmacy helps astronauts prevent and treat ailments caused by the harmful environmental conditions that can be encountered during space missions [324,325]. Starting from this evidence, we wonder which role medicinal plants can play in maintaining astronauts in good health. We hypothesize that medicinal plants, long utilized on Earth for their therapeutic and symbolic value, may maintain their potential applications also outside Earth boundaries (Figure 3) [326,327]. Their phytochemical diversity, ability to be cultivated in controlled environments, and multifunctional benefits make them suitable candidates for enhancing astronaut health and mission sustainability, specifically in the context of long-term space travels and in the future extraterrestrial colonization missions (Moon and Mars) [328]. Overall, it is expected that the use of medicinal plants, alone or in combination with modern medicine, can result in effective and safer treatments [329]. Accordingly, based on the most common medical problems encountered by astronauts in space and the main drugs used to treat them, we have selected 17 medicinal plants that could have beneficial effects on human health during a space mission (table2) [330]. Ultimately, paragraph 4.1 of the review aims to provide a tentative answer to the question: if you were planning to colonize a distant planet, what medicinal plants would you bring with you?



**Figure 3.** Advantages and challenges in the use of medicinal plants during spaceflight and long duration space missions.

Section 4.3 emphasized that plants can not only be used as medicines but can also potentially serve as candidates for onboard biomanufacturing platforms through plant genetic engineering and tissue culture techniques [331–333]. This could contribute to reduce the dependency on Earth-based pharmaceutical supply chains and opens the door for real-time, mission-specific drug production [334].

The psychological benefits of plants in space environments also deserve emphasis (section 4.4), since it has been found that interaction with plants reduce stress and improve mood in humans [335,336]. Plants could then provide a living connection to Earth, offering multifunctional asset for

future space missions by providing nutritional, pharmacological, psychological, and ecological advantages, supporting human health and creating a more hospitable habitat.

#### 4.1. Therapeutic Potential of Phytochemicals in Space Medicine

##### 4.1.1. Use of Medicinal Plants as Alternative Medication for Sleep Disorders

As previously described, sleep disturbance during space missions represents a common and critical concern for astronauts. Consequently, a large proportion of them (70%-80%) reported the acute ( $\leq 7$  days) or recurring ( $> 7$  day) use of sleep-promoting agents [278,302]. Zolpidem, zaleplon, melatonin, temazepam, quetiapine fumarate and eszopiclone are the main hypnotics used by astronauts [278,302].

Starting from evidence coming from folk medicine, it has been found that many phyto-preparations elicit hypnotic effects in preclinical models of insomnia [337,338]. Sleep-promoting activity in plants can arise from many different parts of the plant, including leaves, roots, bark, fruits, seeds, and flowers, and is generally induced by modulation of the GABAergic neurotransmission system. Interestingly, the therapeutic potential of some of these herbs has been confirmed by clinical trials and the most promising are *Valeriana officinalis* L., *Crocus sativus* L., *Lavandula angustifolia* Mill. and *Melissa officinalis* L. (table 2) [337,338]. The main properties of each plant as well as the preclinical and clinical evidence supporting their therapeutic potential are described in the supplemental materials file.

Numerous preclinical studies support the promising beneficial effects of other medicinal plants in alleviating sleep disorders, but clinical evidence of their efficacy is limited and needs to be further confirmed. Among them the most promising are: *Matricaria chamomilla* L., *Aloysia citrodora* Palau, *Citrus aurantium* L., *Lactuca sativa* L. and *Ziziphus jujuba* Mill [337,339].

##### 4.1.2. Use of Medicinal Plants as Alternative Medication for Pain

There is evidence that during space missions, astronauts often experience pain (muscle, joint, and back) and headaches that require medication [302]. Ibuprofen was the most used analgesic followed by acetaminophen and NSAIDs [302].

The plant kingdom has been very generous with pharmacologists, giving them powerful painkillers and anti-inflammatory agents, such as morphine (*Papaver somniferum* L.), delta(9)-tetrahydrocannabinol and cannabidiol (*Cannabis sativa* L.) and salicin (*Salix alba* L.). Despite the potential harmful side effects associated with their use, these natural compounds have represented a real game changer in pain management.

Interestingly, these compounds represent only the tip of the iceberg of the immense repertoire of medicinal plants with potential low to moderate analgesic activity [340,341]. The most promising herbs which may be used adjuvant for pain relief are *Capsicum annum* L., *Curcuma longa* L., *Zingiber officinale* Roscoe, *Salix* genus, *Harpagophytum procubens* (Burch.) DC. ex Meis, *Harpagophytum zeyheri* Decne. and *Boswellia serrata* Roxb. (table 2). The main features of each plant, together with the available preclinical and clinical findings that support their therapeutic potential, are provided in the supplemental materials file.

Finally, although numerous preclinical studies suggest that additional medicinal plants may help relieve pain and inflammation, clinical evidence remains scarce and requires further validation. Among them the most promising are: *Arnica montana* L. (muscle pain) and *Tanacetum parthenium* (L.) Sch.Bip. (migraine) [340].

##### 4.1.3. Use of Medicinal Plants as Alternative Medication for Space Motion Sickness

A high percentage of astronauts experience symptoms attributable to SMS, particularly during the first few days in space and upon return to Earth [93]. Current medical approaches to treating SMS primarily involve promethazine and scopolamine (a plant-derived alkaloid from the Solanaceae

family), although these medications may cause adverse effects including urinary retention, sedation, drowsiness, and amnesia [93,302].

**Table 2.** Medicinal plants selected for their potential therapeutic utility during space missions.

Ailment	Medicinal plant	Main active ingredients	Pharmacological effects	Clinical studies
Sleep disturbance	<i>Valeriana officinalis L.</i>	Sesquiterpenes (valerenic acid), valepotriates, alkaloids [342,343]	Hypnotic, antioxidant, antimicrobial, anti-inflammatory, sedative, anxiolytic, spasmolytic, anticonvulsant, cytoprotective, neuroprotective activity [343]	[344–351]
	<i>Crocus sativus</i>	Crocin, safranal and picrocrocin [352]	Hypnotic, antioxidant, anti-inflammatory, anxiolytic, antidepressive, antiepileptogenic, neuroprotective activity [353,354]	[355–358]
	<i>Lavandula angustifolis</i> Mill	Linalool, linalyl acetate [359]	Hypnotic, analgesic, stress relieving, anxiolytic, anti-inflammatory activity [360,361]	[362–370]
	<i>Melissa officinalis L.</i>	Volatile compounds, triterpenes, phenolic acids, and flavonoids [371]	Antioxidant, anti-inflammatory, hypnotic, antidepressive, neuroprotective, nootropic activity [372,373]	[374–379]
	<i>Capsinum annum L.</i>	Capsaicin, carotenoids [380]	Analgesic, antioxidant, anti-inflammatory, antifungal, antimicrobial, gastroprotective, antihyperlipidemic, immunomodulatory activity [380]	[381–386]
Pain	<i>Curcuma longa L.</i>	Curcumin, demethoxycurcumi, and bisdemethoxycurcumin [387]	Analgesic, antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, hepatoprotective activity [388,389]	[390–393]
	<i>Zingiber officinale</i> Roscoe	Phenolic compounds (gingerols, shogaols, paradols, zingerone), terpenes (zingiberene, $\alpha$ -curcumene, $\beta$ -sesquiphellandrene) [394]	Analgesic, antiarthritic, anti-inflammatory, antioxidant, gastroprotective, hepatoprotective activity [395]	[396–399]
	Willow bark	Salicin, flavonoids, tannins proanthocyanidins [400]	Analgesic, antiarthritic, anti-inflammatory, antimicrobial activity [400]	[401–404]
	<i>Harpagophytum procumbens</i> (Burch.) DC.	Iridoid glycosides (harpagoside, harpagide, procumbide, 8-O-p-Coumaroylharpagide) [405]	Analgesic, antioxidant, anti-inflammatory, antimicrobial, anti-diabetic activity [406]	[407–412]
	<i>Boswellia serrata</i> Roxb	Boswellic acid [413]	Analgesic, antiarthritic, anti-inflammatory, antioxidant, anticancer, neuroprotective activity [413]	[414–418]

SMS	<i>Zingiber officinale</i> Roscoe	Phenolic compounds (gingerols, shogaols, paradols, zingerone), terpenes (zingiberene, $\alpha$ -curcumene, $\beta$ -sesquiphellandrene) [394]	Analgesic, antiarthritic, anti-inflammatory, antioxidant, gastroprotective, hepatoprotective activity [395]	[419–423]
Skin diseases	<i>Aloe vera</i> (L.) Burm. f.	Polysaccharides (acemannan), anthraquinones, enzymes, vitamins, minerals [424]	Antioxidant, wound-healing modulatory, immunomodulatory, anti-inflammatory, antimicrobial, gastroprotective [424,425]	[426–431]
	<i>Curcuma longa</i> L.	Curcumin, demethoxycurcumin, and bisdemethoxycurcumin [387]	Analgesic, antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, hepatoprotective activity [388,389]	[432–435]
Ailment	Medicinal plant	Main active ingredients		Clinical studies
Skin diseases	<i>Calendula officinalis</i> L.	Triterpenoids, flavonoids, saponins, carotenoids, and essential oils [436]	Wound-healing modulatory, anti-inflammatory, antioxidant, antimicrobial, anti-fungal, anti-cancer and analgesic activity [436]	[437–441]
	<i>Camellia sinensis</i> (L.) Kuntze	Polyphenols (epigallocatechin gallate), purine alkaloids [442]	Antioxidant, anticancer, antidiabetic, neuroprotective, immunomodulatory activity [442,443]	[444–447]
	<i>Hypericum perforatum</i> L.	Naphthodianthrone (hypericin), phloroglucinols (hyperforin), flavonoids (rutin, quercetin, hyperoside) [448,449]	Wound-healing modulatory, antioxidant, anti-inflammatory, antimicrobial, anticancer and antidepressant [448,450]	[451–454]
	<i>Panax ginseng</i> Meyer	Triterpene saponins (ginsenosides), polysaccharides, peptides, alkaloids, polyacetylenes, phenolic compounds [455]	Anti-inflammatory, anti-fatigue, antioxidant, immunomodulatory, neuroprotective, cardioprotective activity [456]	[457–463]
Stress	<i>Rhodiola rosea</i> L.	Phenylpropanoids (rosavins), phenylethanoid derivatives (salidroside and tyrosol), flavonoids, monoterpenes, triterpenes, phenolic acids [464,465]	Anti-fatigue, antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anxiolytic, antidepressant and nootropic activity [465].	[466–473]
	<i>Withania somnifera</i> (L.) Dunal	Steroidal lactones (withanolides), alkaloids, sitoindosides, flavonoids, saponins [474]	Anti-inflammatory, antioxidant, anxiolytic, immunomodulatory, neuroprotective, antitumoral and anti-fatigue [475–477]	[478–489]

SMS, Space Motion Sickness.

Ginger rhizome extract is a common natural remedy used on Earth to prevent symptoms of motion sickness, and several clinical studies have provided promising evidence of its efficacy [419–423,490]. While the precise mechanism is still not fully understood, ginger may alleviate certain symptoms by preventing gastric dysrhythmias and increasing plasma vasopressin [421].

#### 4.1.4. Use of Medicinal Plants as Alternative Medication for Skin Diseases

Skin diseases, including eczema, psoriasis, acne, dermatitis, and wound infections, are among the most common human disorders and significantly impact physical, social, and psychological well-being [491]. In the context of spaceflight, however, astronauts face additional and distinctive dermatological challenges. During both short- and long-duration missions they report erythema, burning or itching skin, dryness, increased sensitivity, delayed wound healing, thinning of the epidermis and dermis, changes in skin microbiota, and higher susceptibility to infections [293,492,493]. Conventional treatments rely heavily on corticosteroids, antibiotics, antifungals, and immunosuppressants; while effective, they are often associated with adverse reactions such as skin thinning, microbial resistance, and systemic toxicity [494]. In recent decades, there has been a growing interest in the use of medicinal plants as complementary or alternative approaches for skin care and dermatological therapy [495]. Plants are a rich source of bioactive compounds with anti-inflammatory, antioxidant, antimicrobial, and wound-healing properties that can contribute to restoring skin homeostasis.

The most promising medicinal plants used for dermatological conditions are *Aloe vera* (L.) Burm. f., *Calendula officinalis* L., *Curcuma longa* L., *Camellia sinensis* (L.) Kuntze and *Hypericum perforatum* L. provide compelling evidence of their dermatological benefits, supported by both traditional use and modern clinical validation (table 2). These plants act through multiple mechanisms, including modulation of inflammatory pathways, enhancement of wound healing, and protection against oxidative stress. The main features of each plant, together with the available preclinical and clinical findings that support their therapeutic potential, are provided in the supplemental materials file.

Finally, despite folk claims and encouraging preclinical findings, clinical evidence for additional medicinal plants in skin health remains insufficient. Among them, the most known are: *Matricaria recutita* L., *Azadirachta indica* A. Juss., *Oenothera biennis* L., *Glycyrrhiza glabra* L. and *Centella asiatica* (L.) Urb. [496,497].

#### 4.1.5. Potential Use of Adaptogens to Increase Resilience

In Section 2 we have described as deep space missions pose serious physical and psychological challenges to astronauts. Safeguarding human health and performance is then a critical objective, requiring the development of strategies that enhance mental, physical, and emotional resilience. Adaptogen plants may hold significant promise in this scenario, with their believed ability to boost mental and physical strength. An adaptogenic plant, or adaptogen, is a natural substance, usually derived from herbs, that non-specifically helps the body adapt to stress, restore balance, and improve resilience to physical, emotional, or environmental stressors [498]. Adaptogenic plants are also expected to exhibit minimal side effects and provide a mild stimulatory effect without disrupting sleep quality or excessively accelerating energy metabolism [498]. The adaptogenic effect results from a synergistic interaction among multiple bioactive compounds that act simultaneously engaging various biological pathways. Overall, this multi-targeted mechanism supports homeostasis by modulating the nervous, endocrine, and immune systems, enhancing the body's capacity to adapt to stress and promoting well-being.

The most investigated medicinal herbs for their adaptogenic activity are *Panax ginseng* Meyer, *Rhodiola rosea* L. and *Withania somnifera* (L.) Dunal (table 2). Details on each plant's properties and supporting preclinical and clinical evidence are available in the supplementary material file.

Other plants have been traditionally recognized for their adaptogenic properties, but the extent of clinical evidence substantiating these claims is minimal. Among them the most relevant and promising are *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (commonly known as Siberian ginseng) [499] and *Schisandra chinensis* (Turcz.) Baill. [500].

#### 4.2. Phyto-Biomanufacturing: Synthetic Pharmacognosy for In Situ Production of Active Compounds

Besides the direct use of plant extracts for medicinal purposes, plants could be also useful as biomanufacturing platform. Phyto-biomanufacturing refers to the utilization of plants as biofactories to produce pharmacologically active compounds [331,333,501,502]. In the context of long duration space missions, this concept becomes particularly valuable as a means of ensuring pharmaceutical self-sufficiency [503,504]. Given the high costs, restricted payload capacity, and degradation risks of storing conventional pharmaceuticals in hostile environments, producing therapeutics in situ through plant-based systems could provide a sustainable and flexible alternative, paralleling advances already achieved with microbial platforms [505,506].

The intersection of pharmacognosy and synthetic biology could revolutionize the therapeutic potential of phytopharmaceuticals in space missions [507]. Pharmacognosy provides the foundation for understanding the chemical diversity and pharmacological potential of natural products, it also ensures that the bioactivity, safety, and pharmacokinetics of these engineered compounds are well understood [508]. Analytical tools from pharmacognosy – such as LC-MS/MS, NMR, and bioassays – are essential for characterizing plant extracts, confirming compound identity, and assessing efficacy [509]. The integration of these disciplines ensures a balance between innovation and therapeutic reliability [503,504]. Synthetic biology offers the tools to manipulate and enhance these pathways, enabling precise, scalable, and tailored therapeutic production [510]. Medicinal plants naturally synthesize a wide range of secondary metabolites including alkaloids, terpenoids, and polyphenols, which form the basis of many conventional drugs. Advances in metabolic engineering now enable enhanced synthesis of these compounds by modulating specific biosynthetic pathways. For example, metabolic engineering has been employed to increase artemisinin production in *Artemisia annua* and morphine precursors in *Papaver somniferum* [511,512]. These techniques can be extended to compact, fast-growing plants suitable for space cultivation.

In addition, innovative tools such as CRISPR-Cas9 and pathway reconstruction, further expand the possibilities of phyto-biomanufacturing [513]. Plants can be engineered to express therapeutic proteins such as vaccines, antibodies, and hormones [513,514]. Instead of storing large volumes of pre-manufactured drugs, a compact cultivation unit could be used to grow engineered plants that produce specific drugs on demand [333,510]. For instance, plants expressing recombinant human insulin or granulocyte colony-stimulating factor (G-CSF) could become part of a decentralized medical supply strategy during missions to Mars or lunar habitats [515]. Likewise, space-grown *Nicotiana benthamiana* expressing monoclonal antibodies or vaccines could be harvested, purified, and administered to astronauts within a closed-loop system [516,517].

Alongside whole-plant systems, tissue culture and plant cell suspension systems could offer an additional and alternative method of producing bioactive molecules in confined space habitats [518,519]. These systems can operate in bioreactors, providing high yields of specific molecules without the need to grow whole plants [516]. Such approaches minimize biomass requirements and allow for precise control of growth conditions and compound standardization [519]. The development of portable and compact phytoreactors designed for space environments is an active and promising area of research [520].

Overall, phyto-biomanufacturing may then represent a transformative approach to space pharmacy, merging plant science with biotechnology to create efficient and sustainable therapeutic platforms. By leveraging the natural synthetic capacity of plants, future space missions could achieve greater autonomy, reduce mission risk, and enable personalized, mission-specific pharmacotherapy. In other words, the synergy between synthetic biology and pharmacognosy transforms medicinal plants into programmable platforms for space medicine.

#### 4.3. Psychological and Environmental Benefits for Astronauts

In addition to their pharmacological applications, medicinal plants could provide profound psychological and environmental benefits during space missions. As previously described, the confined, isolated, minimalist and monotonous nature of extraterrestrial habitats – such as spacecraft,

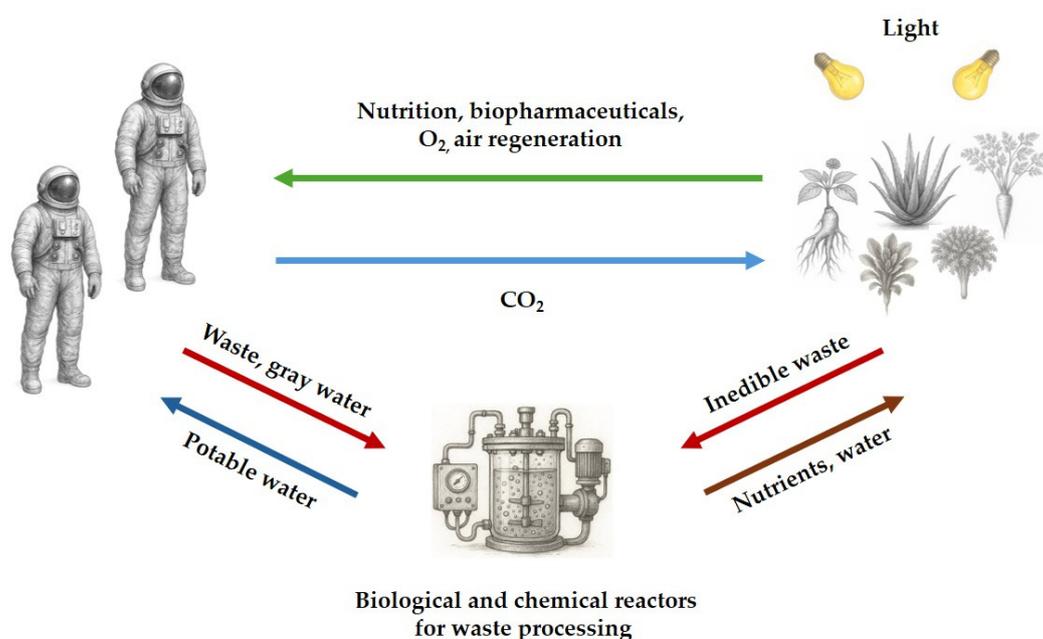
space stations, or future lunar and Martian outposts—can lead to heightened stress, mood disorders, and cognitive fatigue among astronauts [266]. Integrating green environments into these habitats may significantly alleviate such effects.

Consistently, several studies recommended to include plant life in space habitats of future missions [6,521].

Plants are known to have positive effects on human psychological health [335,336,522,523]. This evidence is one of the founding elements of the concept of biophilia, the innate human tendency to seek connection with nature and other forms of life [524]. Studies in confined and isolated environments on Earth, such as Antarctic stations [525], or during COVID-19 pandemic [526] confirmed this evidence. Even passive interaction with plants—visual contact, scent, or caring for them—has been shown to foster psychological well-being [522]. The act of growing and tending to plants could offers astronauts a form of leisure and emotional grounding, promoting mindfulness and mitigating feelings of isolation [527]. Moreover, as described in the supplemental material file, species like *Lavandula angustifolia* and *Melissa officinalis* could contribute to mental wellbeing with their aromatic properties [379,528]. To maximize health benefits provided by plants, it would be desirable to select multipurpose species that combine therapeutic properties with high aesthetic or olfactory value. [336,529]. Future research may then explore genetically enhanced plants designed to emit specific volatile organic compounds (VOCs) for mood enhancement [530].

From an environmental standpoint, plants help regulate atmospheric composition. Through photosynthesis, they absorb carbon dioxide and release oxygen, contributing to air revitalization within closed-loop life support systems [531,532]. Moreover, transpiration from plant leaves can contribute to humidity regulation and water recycling [533]. The integration of medicinal plants into Bioregenerative Life Support Systems (BLSS) adds a functional layer to habitat sustainability (figure 4) [532].

In summary, plants can be seen not just as a pharmaceutical or nutritional resource but as a potential integral component of a supportive space habitat. Their contributions to psychological resilience, environmental stability, and multisensory enrichment make them invaluable allies in the human pursuit of long-duration extraterrestrial exploration.



**Figure 4.** Schematic diagram of Bioregenerative Life Support Systems (BLSS).

## 5. Challenges and Future Perspectives

Life in space puts a strain on the physical and mental health of humans. In light of the anticipated rise in space exploration and the potential establishment of human settlements on the Moon and Mars, it is crucial to gain a comprehensive understanding of how the human body responds and adapts to the space environment, as well as to develop effective pharmacological interventions suited to such extreme conditions. Within this scenario, medicinal plants have the potential to continue serving as a natural and effective means of supporting human well-being in extraterrestrial environments. Recognizing the untapped potential of this understudied domain, we have then assembled a preliminary selection of medicinal plants that may offer solutions to the most pressing medical needs reported during space missions and that may be helpful in the first phases of extraterrestrial colonization. Our vision is that this provisional list can be validated and expanded over time based on the progress of clinical trials conducted on Earth with multiple promising medicinal plants from our rich ecosystem.

We recognize that, much like other stages of space missions, incorporating medicinal plants into space-based healthcare presents complex challenges and raises important questions. Some of these issues parallel those already encountered and studied on Earth, others are exclusive to space conditions.

1. Beyond traditional claims, the therapeutic use of plant extracts requires rigorous clinical studies to establish both efficacy and safety [534,535]. It is important to note that clinical studies conducted on Earth typically involve either the general population or specific subpopulations of diseased individuals [535]. In contrast, astronauts represent a highly specialized population, and due to the physiological alterations associated with spaceflight, the effectiveness of plant-derived therapies remains to be determined [536]. Future preliminary testing in astronauts during spaceflight are then welcome.
2. Studies of plant extracts—both preclinical and clinical—have often shown inconsistent findings in efficacy, dosing, and side effects. These inconsistencies largely stem from variations in plant matrix, cultivation practices, environmental conditions and extraction techniques [537]. Standardization of the entire production process is thus critical to ensure batch-to-batch consistency in terms of active compounds concentrations and reliable pharmacological outcomes, on Earth and ever more so in space.
3. There is also the strategic decision of whether to rely on Earth-manufactured plant preparations or develop the capacity for on-demand production in space. It may mainly depend on the target of the mission and its duration. In short-duration spaceflights or during the early phases of extended missions, the use of Earth-prepared formulations appears to be the more practical and preferred option. It is important to note that, similar to conventional pharmaceuticals [311], plant extracts are susceptible to degradation. However, the stability of plant-derived compounds in space environments remains largely uncharacterized. To fill this gap, future studies should be finalized to verify physical and chemical stability of plant extracts directly in space [538] or in ground-based spaceflight analogues [539]. In the meantime, medicinal extracts may benefit from current strategies under investigation to improve and prolong drug stability in space, such as: the use or radioprotective packaging materials (i.e. high-density polyethylene composites) [7,311,540]; the storage of extracts at low temperatures ( $\leq 80^{\circ}\text{C}$ ), since it has been found that cold preserve pharmaceuticals from radiation-induced damages [541,542]. Moreover, it has been demonstrated that some excipients and antioxidants provide protective effects to medicines exposed to radiation [311]; it is then conceivable that the presence of antioxidant-active constituents in medicinal plant extracts mitigates the detrimental influence of space radiation.

At variance, in the context of extended space exploration and off-Earth settlements, the autonomous and continuous production of fresh plant material constitutes an asset of considerable strategic importance. Predictably, the magnitude of the challenge is proportional to the importance of the outcome. Within this framework, the possibility of growing plants in

the space environment for human alimentation is the most studied aspect, specifically in terms of feasibility [14,15,543]. Physical and storage constraints in both spacecraft and planetary colonies, as well as the costs of transporting materials into space, pose critical problems in space agriculture. Consequently, closed-loop cultivation systems are being designed and studied that can maximize plant biomass yields while minimizing dedicated space and optimizing resources (energy, water, and nutrients) through the almost complete recycling of waste [14,15]. Collectively referred to as BLSS, these systems pursue the ambitious goal of reproducing Earth-like biogeochemical cycles by fostering mutualistic interactions among humans, plants, and microbes in space [544]. Consequently, integrating medicinal plants into BLSS represents a promising avenue for achieving long-term sustainability and crew health on future missions. In other words, cultivating edible vegetables alongside medicinal plants into BLSS could provide a sustainable source of both nutrition and natural therapeutics. However, further progress in understanding the changes in plant physiology induced by the spatial exposome is essential [16,545,546].

While growing plants in space is possible, albeit complicated, further challenges remain. Not all medicinal plants are suitable for space farming, at least in this pioneering phase. As an example, fast-growing and compact herbaceous plants are likely easier to cultivate and thus preferable to tree species. However, the greatest gap in knowledge concerns the effects of the space environment on the chemical composition of medicinal plants. Experimental evidence indicates that the exposure of several plant seeds to space environment can induce genetic modifications, leading to alterations in the chemical composition of the plants that develop from them [547–551]. It should be emphasized that in these studies, seed germination and plant cultivation were carried out on Earth once the seeds returned from space. The mutagenic effect of the space environment is so strong that it has given rise to a new technique called space mutation breeding, aimed at artificially improving crops [552]. The influence of extraterrestrial conditions on plant physiology and chemistry is not necessarily adverse but requires it to be fully investigated and understood. To put it differently, future studies will have to investigate the phytochemistry of medicinal plants that have completed their entire life cycle in space, which does not necessarily overlap with that observed on Earth. This will allow the accurate reassessment of the efficacy-to-safety ratio of the plant extracts produced in space.

Not least of all, the entire production chain of medicinal plant extracts—including biomass harvesting and processing, solvent extraction, purification, chemical analysis, and storage—constitutes an exceptionally challenging process to implement in the space environment, whether aboard spacecraft or in extraterrestrial habitats. It requires rethinking the entire process to adapt to the different restrictions imposed by space environmental conditions, such as limited space and microgravity, while maintaining efficiency, reliability and reproducibility. Ideally, the process should be fully automated and include an appropriate waste management component aimed at minimizing waste production. This problem can be circumvented at least in part and where possible by using medicinal plants as fresh functional foods (food enriched of biologically active constituents) to supplement the diet of human in space [327].

4. From a regulatory perspective, space agencies, product regulators and international health organizations need to develop standards for the safe use of space-grown medicinal products. It will therefore be critical to develop guidelines for herbal product production and classification, biosafety characterization, dosage validation, interaction with conventional therapies, and determination of stability.

## 6. Conclusions

In conclusion, plants have the potential to become central to future space health and nutrition systems. Their versatility, therapeutic range, safety and compatibility with regenerative life support frameworks make them ideal candidates for deep-space missions to help ensure physical and psychological well-being in a sustainable manner and independent of Earthly supplies. Continued

investment in integrative, cross-disciplinary research is, however, essential to unlock their full potential and pave the way for a new era of bio-botanical medicine beyond Earth.

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## Abbreviations

The following abbreviations are used in this manuscript:

SSP	Space Soviet Program
NASA	National Aeronautics and Space Administration
ESA	European Space Agency
CSA	Canadian Space Agency
JAXA	Japan Aerospace eXploration Agency
CMSA	China Manned Space Agency
LEO	Low Earth Orbit
SANS	Spaceflight-Associated Neuro-ocular Syndrome
SMS	Space Motion Sickness
$\mu$ G	Microgravity
SR	Space Radiation
SPEs	Solar Particle Events
GCRs	Galactic Cosmic Rays
TPR	Trapped Particle Radiation
HZE	high (H), atomic number (Z), and energy (E)
LET	Linear Energy Transfer
ARSs	Acute Radiation Syndrome
CNS	Central Nervous System
PK	PharmacoKinetic
PD	PharmacoDynamic
ISS	International Space Station
APIs	Active Pharmaceutical Ingredients
PBPK	Physiologically-Based Pharmacokinetic
ISPM	In-Situ Pharmaceutical Manufacturing
USP	United State Pharmacopeia
EMA	European Medicines Agency
WHO	World Health Organization
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
G-CSF	Granulocyte Colony-Stimulating Factor
BLSS	Bioregenerative Life Support Systems

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