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Review

Pharmaceutical Solutions for Deep Space Travel and Colonization: Background, Challenges, and Possibilities

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Abstract: Manned missions to Mars and other deep space exploration targets are expected to take place in the next 20 years. These missions will involve prolonged crew exposure to the unique space environment, increasing the risk that astronauts will experience additional physical and psychological health conditions beyond those that would be expected through normal aging on Earth. Thus, there is an acute need to develop therapeutic solutions that can withstand the harsh space environment, while maintaining astronaut health and maximizing crew capabilities to foster successful exploration-class missions. This review covers the nuanced and interdisciplinary challenge that is providing safe and effective pharmaceuticals for future deep space missions. First, the limitations of current pharmaceutical solutions are discussed; the impacts of the space environment on human health and chemical compound stability are covered, along with an evaluation of astronaut medication use on similar missions. Second, potential pharmaceutical solutions and concepts are presented for consideration. Future research should prioritize these and other potential innovations to ensure that our space programs are well equipped to maximize crew safety as astronauts explore deep space objectives.

Keywords: astronaut health; space medicine; pharmaceutical stability; space pharmacy; radioprotection; Mars missions; space exploration and colonization.

1. Introduction

Medicines have constantly evolved throughout history in conjunction with the changing needs of the human race. Herbs, plant components, and other raw natural resources were among the first therapeutic agents used by early humans, who existed in close proximity to each other and their medical supplies. As civilizations eventually advanced and dispersed across new regions, techniques like fermentation were implemented. This and other primitive methods helped humans to preserve crude drugs, and in turn increased human survivability. In modern

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pharmacies, advanced preservation technologies and pharmaceutical engineering have allowed medications to satisfy the shelf life demands of a consumer-driven era. In the near future, as humans attempt to explore deep space, astronauts will be exposed to the hostile space environment for years at a time and will likely be unable to receive physical assistance or supplies from Earth. In preparation for such missions, current pharmaceutical solutions must be adapted once again to meet these new challenges.

Given the evident human-health related risks of space travel, effective medical drug treatments will be an integral component of future missions to Mars and beyond. Hence, this report serves as an overview of the need for new pharmaceutical solutions; the challenges of inventing such solutions; and the possible solutions themselves that may, in whole or in part, help to provide effective medications for deep space travel and colonization. It is hoped that the present review will stimulate collaboration between biomedical, space medicine, and engineering communities, in both the public and private sector, to further investigate and solve these challenges.

2. Materials and Methods

The information used to write this narrative review was obtained from 86 sources. A literature search was conducted using the following three electronic databases: PubMed, the National Aeronautics and Space Administration Technical Reports Server (NTRS), and ScienceDirect. Searches were performed between April 2020 and October 2020. Search terms included “space pharma,” “medications for space,” and “astronaut health and safety,” and these terms were employed in different combinations. One article was sourced following a recommendation from an expert in the field; the bibliographies of relevant articles were also examined for additional pertinent literature. When thematic areas of focus were found to lack coverage by the originally compiled sources, additional efforts were made to locate peer-reviewed articles in Google Scholar and published materials from NASA that could provide further, in-depth information about these areas. Included sources were limited to relevant works with accessible texts and abstracts published in the English language; therefore, the sources reviewed should not be considered comprehensive. All of the sources used to write this narrative review are referenced at the bottom of this document.

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3. Background

The following questions, among others, are helpful to define our current understanding of the interdisciplinary topics converging around the greater, multifaceted challenge that is providing pharmaceuticals for deep space exploration.

- What conditions are astronauts likely to face on upcoming missions, and what human health risks do these conditions entail?
- What medications have been stocked on similar terrestrial and space expeditions; have these medications been effective?
- In what ways are existing therapeutic technologies and their effects altered by the space environment?
- How can current technologies and concepts be applied to provide effective pharmaceuticals and improve astronaut health during future deep space missions?

3.1. Future Space Missions

For centuries, the desire to explore the unknown has been a driving force for mankind's innovation. Such explorations are generally undertaken to increase scientific knowledge, extend human presence, acquire natural and economic resources, and to inspire others in the process. Deep space exploration is no exception.

The National Aeronautics and Space Administration (NASA) has emphasized that one of its main strategic objectives is to "Extend human presence deeper into space and to the Moon for sustainable long-term exploration and utilization" [1][2]. In accordance with this objective, NASA has announced the Artemis missions. The goal of these missions is to send astronauts to the Moon by 2024; beyond this date, NASA aims to create Artemis Base Camp and additional infrastructure on the lunar surface to establish a sustainable lunar presence by the year 2028 [3][4]. Furthermore, these lunar missions will serve to aid and validate the possibility of future deep space missions and the overarching goal to send manned missions to Mars by the 2030's [4][5].

3.2. The Space Environment: Impacts on Human Health and Other Organisms

Before the possibility of space travel, *Homo sapiens* existed within Earth's protective atmosphere as well as an approximately 1-g environment. By contrast, as deep space missions

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take astronauts farther away from Earth's atmosphere and magnetic field, there are several unique pre-flight and post-flight challenges to human health that must be considered. The most clearly identified problematic environmental conditions of spaceflight include, but are not limited to, increased exposure to radiation due to solar particle events (SPEs) and galactic cosmic rays (GCR); microgravity, reduced gravity, and differences between planetary gravitational fields; exposure to celestial dust; and changes to circadian stimuli [6]. There are additional factors which include those directly associated with the artificial spacecraft living environment and associated technologies: crew member relations and confinement within small quarters; geographic isolation from Earth; food appeal, nutritional quality, and degradation; inadequate crew member training; and flaws in technology and mission design (among others) [6][7].

The synergy of environmental and other conditions that astronauts may experience during deep space missions can cause numerous major and minor health effects. Nearly every aspect of human anatomy and health is affected during spaceflight. Microgravity can decrease bone mineral density and lead to early-onset osteoporosis; inadequate, unappealing or degraded food can lead to malnutrition and lower morale; and exposure to radiation could increase the chances of astronauts developing cancer [7]. Current experiments are attempting to further investigate the specific changes that occur to human physiology and the mechanisms by which these changes arise. However, there is still a large amount of uncertainty about the details of these changes, both due to the lack of test subjects available in space and the difficulties associated with conducting experiments in space [8].

It is also known that the immune system is generally weakened or altered during spaceflight [9]. Backing these changes are several studies on the International Space Station (ISS) that have indicated increased salivary stress hormone levels, decreased T and NK cytotoxic effector cell function, and latent herpesvirus reactivation during spaceflight [10]. However, as a result of improved ISS operations and infrastructure, astronaut immunocompetence on the ISS has increased over time. These immunological improvements are thought to be the results of dietary improvements made possible by more frequent ISS resupply, the installation of better exercise equipment, more frequent communication with family members, and other improvements [10]. A remaining problem is that of astronauts on future missions, who will likely be subject to a more confined spacecraft environment for longer time periods, less frequent resupply, and other conditions different from those that improved the ISS.

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Along with the weakening of the immune system, bacteria have displayed changes to gene expression during spaceflight [11]. Increased antibiotic resistance, virulence, and proliferation in pathogens has also been observed [12]. These results, in addition to findings related to the weakening of the astronaut immune system during spaceflight, suggest that astronauts may be more vulnerable to pathogenic infection during deep space missions [12]. Although bacterial infections can be managed with antibiotics, this type of treatment alters commensal bacteria populations as well as microbiota composition. Such changes to the human microbiome and population dynamics may allow for the proliferation of harmful bacteria and opportunistic pathogens whose populations are normally inhibited by the unaltered microbiome [13]. The unique and sterile spacecraft environment and the various hazard prevention systems give rise to microbial exposure levels that are very different from those on Earth [7]. However, the extent to which microbial exposure is altered and the implications of such alterations for human health on future long-duration space missions are still unknown. Future research aimed at understanding changes in human-microbe interactions during spaceflight may contribute to our understanding of similar interactions and relationships on Earth.

As technology becomes more efficient and cost-effective, the prospect of commercial space travel and "space tourism" becomes more plausible. Several human spaceflight firms like *Blue Origin* and *Space Adventures* plan to or already have sent private customers to space [14], and many companies are already taking bookings for future travel [15]. Professional astronauts must go through extensive training in various areas [16], a demanding selection process, and must meet several physical health requirements [17]. Given that most current information and guidelines about human health during spaceflight have been derived from exceptionally healthy, professional astronauts, the increased presence of "space tourists" on future missions may pose additional healthcare challenges due to changes in chronic condition prevalence, lower health standards, and different training regimens [15]. For these newly participating civilian crew members, cultural differences in medical adherence and beliefs [18], in addition to pre-flight prescription and non-prescription medication use, must be assessed as well. Although the commercialization of spaceflight is still far from mainstream, this newly emerging demographic, possibly influencing the types and quantities of pharmaceuticals taken on future missions, is an important factor to consider when discussing the safety of future space travelers.

The ISS currently provides the best experimental environment for representing conditions that astronauts will experience during deep space missions. Several terrestrial analogs [19], such

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as extended remote expeditions to Antarctica, share similar environmental characteristics—like isolation, confinement, geographical features and mass and volume limitations—with future Mars missions. However, the unique set of conditions that astronauts will experience on future missions will vary. For instance, future Mars missions may incorporate increased extravehicular activities (EVAs), commonly referred to as “spacewalks” [16]. Such mission-specific variables will alter the medical risk profile for missions; therefore, necessary clinical capabilities and medical supplies will vary according to the mission profile and corresponding mission-specific medical conditions list. NASA developed the Space Medicine Exploration Medical Condition List (EMCL) in 2009 as an overarching list of medical conditions most likely to occur during spaceflight missions. The Integrated Medical Model (IMM) is a statistical model that utilizes the Integrated Medical Model Condition List (IMCL), a compilation similar to the EMCL, to perform probabilistic risk analysis with the inputs of crew and mission details and other stored medical database information from previous missions. The IMM quantitatively assesses the likelihood and outcomes of 100 medical conditions (figure 1) [20]. Then, subject matter experts systematically analyze and interpret results from the IMM to compile a mission-specific Accepted Medical Condition List (AMCL) [21]. Unique AMCLs will assist in the identification and prioritization of necessary medical resources for future exploration spaceflights. For future missions, such medical lists and models must be updated, as previous work has focused primarily on missions in low Earth orbit (LEO) [22]. The addition of space tourists will also likely necessitate the expansion of these lists and models.

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Abdominal Injury
Abdominal Wall Hernia
Abnormal Uterine Bleeding
Acute Arthritis
Acute Cholecystitis / Biliary Colic
Acute Compartment Syndrome
Acute Diverticulitis
Acute Glaucoma
Acute Pancreatitis
Acute Prostatitis
Acute Radiation Syndrome
Acute Sinusitis
Allergic Reaction
Altitude Sickness
Angina / Myocardial Infarction
Anaphylaxis
Ankle Sprain / Strain
Anxiety
Appendicitis
Atrial Fibrillation / Flutter
Back Injury
Back Pain (*)
Barotrauma (sinus block)
Behavioral Emergency
Burns secondary to Fire
Cardiogenic Shock secondary to Infarction
Chest Injury
Choking / Obstructed Airway
Constipation (*)
Decompression Sickness Secondary to EVA
Dental: Exposed Pulp
Dental Caries
Dental: Abscess
Dental: Avulsion (tooth loss)
Dental: Crown Loss
Dental: Filling Loss
Dental: Toothache
Depression
Diarrhea
Elbow Dislocation
Elbow Sprain / Strain
Eye Abrasion (from a foreign body)
Eye Chemical Burn
Eye Corneal Ulcer
Eye Infection
Eye Penetration (from a foreign body)
Finger Dislocation
Fingernail Delamination (EVA)
Gastroenteritis
Head Injury
Headache
Headache (CO_2 induced)
Headache (*)
Hearing Loss
Hemorrhoids
Herpes Zoster
Hip Sprain / Strain
Hip / Proximal Femur Fracture
Hypertension
Indigestion
Influenza
Insomnia (*)
Knee Sprain / Strain
Late Insomnia
Lower Extremity Stress Fracture
Lumbar Spine Fracture
Medication Overdose / Reaction
Mouth Ulcer
Nasal Congestion (*)
Nephrolithiasis
Neurogenic Shock
Nose bleed (*)
Otitis Externa
Otitis Media
Paresthesias
Pharyngitis
Respiratory Infection
Retinal Detachment
Seizures
Sepsis
Shoulder Dislocation
Shoulder Sprain / Strain
Skin Abrasion
Skin Infection
Skin Laceration
Skin Rash
Small Bowel Obstruction
Smoke Inhalation
Space Motion Sickness (*)
Stroke (cerebral vascular accident)
Sudden Cardiac Arrest
Toxic Exposure: Ammonia
Traumatic Hypovolemic Shock
Urinary Incontinence (*)
Urinary Retention (*)
Urinary Tract Infection
Vaginal Yeast Infection
VIIIP – Visual Impairment / Increased Intracranial Pressure (*)
Wrist Fracture
Wrist Sprain / Strain

Figure 1. The Integrated Medical Model Condition List (IMCL) [20]. Stars (*) indicate conditions that are related to Space Adaptation Syndrome (SAS).

The numerous ways in which astronaut physical and mental health are at risk during spaceflight are evident. Many medical conditions that arise in space will require the use of pharmaceuticals, and others may require surgery [23]. Crew member safety is a top priority, considering the central role of astronauts and other human passengers within the mission framework. Therefore, effective pharmaceutical solutions are crucial and will greatly increase the probability of mission success.

3.3. Medication Inventory and Consumption During Similar Scenarios

Just as ISS missions and terrestrial analogs can help to predict the conditions and health issues that may arise during deep space missions [19][24], the medical kits used in these past scenarios may be used to provide a framework for those that should be brought on future explorations. The subsection of the ISS medical system that contains medications is the Health Maintenance System (HMS) (figure 2) [25][26].

HMS Organization

- Emergency Medical Treatment Pack (EMTP)
- Oral Medication Pack (OMP)
- Convenience Medication Pack (CMP)
- Topical and Injectable Medication Pack (TIMP)
- Physician Equipment Pack (PEP)
- Medical Supply Pack (MSP)
- IV Supply Pack (ISP)
- Medical Diagnostic Pack (MDP)
- Minor Treatment Pack (MTP)
- Respiratory Support Pack (RSP)
- Crew Contamination Protection Kit (CCPK)
- Crew Medical Restraint System (CMRS)

Figure 2. The HMS consists of twelve subcomponents that are used to assess and maintain astronaut health [25][26][27].

The CMP contains the medications that are most frequently used; the OMP and TIMP contain medications that are used less often; the MDP, MTP, MSP, ISP and PEP are employed for check-ups, minor treatments, and diagnosis; the CMRS is used to physically stabilize a patient for transport and treatment; the CCPK contains items, such as the eyewash, that help to protect crew members from exposure to environmental contaminants; the RSP contains equipment that provides patients with 100% oxygen at a low flow rate; and the primary purpose of the EMTP is to help sustain life under emergency situations [25][26][27]. According to an ISS medical contents list released by NASA in response to an FOIA request in 2016, excluding medical hardware, NASA's ISS medical packs contain approximately 107 distinct medications in total [27].

A retrospective examination of American ISS crew member medication use found that sleep medications were used most frequently, with nasal congestion, body pain, rashes, and allergies needing frequent treatment with medications as well; related medication use was reported among submariners and space shuttle astronauts who experienced some conditions that were similar to those present on the ISS [28]. During an earlier ISS mission where medication consumption data was not collected in a standardized fashion, the average number of recorded medication doses consumed, per crew member over the course of one mission, was 12.6; whereas a later investigation, using more standardized data collection techniques, recorded this number to be about 453 medication doses per crew member, over the course of one mission [29]. Such investigations show the importance of proper data collection techniques. On future missions without resupply and medical evacuation capabilities, chronic injuries and conditions may require prolonged medication use and enough stock to last multiple years. Improved medical

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documentation practices have made clear the importance of pharmaceutical availability during spaceflight [30], but medication use during spaceflight is still a knowledge gap [31].

Future studies that are able to gather more consistent medication-use and medical data with the use of systematic collection techniques, such as through a dose-tracking application [29], will enable a better understanding of:

- The most common medical conditions that occur during spaceflights
- Avoidable factors that influence human health conditions in space
- What medications are most frequently used by astronauts before and during missions

3.4. Limitations of Current Solutions

Although reviewing the medicine used in previous scenarios may be used to guide the selection of future medical needs and equipment, there are obvious differences between ISS and terrestrial analog missions and the conditions that astronauts will face on exploration-class missions, like a journey to Mars. The ISS, where crew members usually stay for six months at a time, is in constant LEO and typically maintains an orbital altitude of about 255 miles above the Earth, which allows for the frequent resupply of the ISS multiple times per year [16]. Among the supplies that arrive at the ISS are medications that replace older ones six months before they are set to expire [32]. On the other hand, what NASA expects to be a roughly three-year journey to Mars will not include resupply missions or prompt medical evacuations [33]. Unlike the return time from the ISS which is less than a day, Mars-bound astronauts with major medical issues may have to wait up to several months to return to Earth; this is due to the nearly 34 million miles that lie between the two planets when they are closest [33]. If manned missions to Mars stock all therapeutic agents from the start, without resupply or manufacturing capabilities, medical stock and efficacy must adhere to at least a three-year mission framework.

Along with the lack of resupply and medical evacuation capabilities available on longer duration missions, there is also the possibility of modified pharmaceutical efficacy during spaceflight. Records of previous crew members reporting ineffective medications [28] as well as reports of repeated sleep-promoting medication intake during the night [34] suggest that medication efficacy could be reduced during spaceflight.

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Altered pharmaceutical shelf life during spaceflight may be one cause of this decreased efficacy. Although true product shelf life variability (i.e. between two different tablets from the same bottle) is a direct consequence of imperfect manufacturing, estimated product shelf life can be predicted in part through stability testing [35]. Shelf life is defined by the Food and Drug Administration (FDA) as "the time period during which the product is expected to remain stable, or retain its identity, strength, quality, and purity, when it is properly stored according to its labeled storage conditions" [36]. As of 2019, 87% of the medications on the ISS had shelf lives that were less than two years [37]. This suggests that, if a three-year Mars mission carried and stored pharmaceuticals according to the current setup onboard the ISS, the crew would (according to the labeled medication expiration dates) run out of viable medications before the end of the mission. The FDA has claimed that certain drugs may retain stability even after their labeled expiration dates have passed, but current shelf life extensions are specific to the type of medication and extensive testing is required to ensure the safety of such extensions [36]. Additionally, these shelf life estimates and extensions are based on terrestrial storage environments, where the unique factors that impact cargo during deep space exploration are not present.

Experiments that analyzed the stability of certain medications on the ISS have shown that some medications may degrade faster in space [32][38][39]. One experiment compared the active pharmaceutical ingredient (API) content of ISS-stored medications and ground control medications after 28 months of storage [38]. Overall, after storage in space, several formulations had a lower percent content or potency of API, and medications stored in space failed potency requirements at a consistently higher rate than those on Earth over each storage period interval [38]. Although temperature and humidity parameters on the ISS were similar to those on Earth [38], increased radiation, altered gravity, and vibrational forces were some of the unique environmental factors that impacted the stored medications in space [32]. Medications with slightly different chemical formulations react differently to these factors, so degradation rate, chemical byproduct toxicity limits, and chemical byproduct composition will differ between individual therapeutic agents. Therefore, characterizing specific degradation products and setting corresponding toxicity limits are important steps to be taken before future missions [32].

Past and future experiments focused on pharmaceutical degradation during spaceflight are limited by experimental resources and the multifactorial nature of the spaceflight environment. When experimentalists attempt to limit the number of environmental variables

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acting upon a pharmaceutical sample, there are additional problems that complicate the results. The radiosensitivity of certain chemical compounds in space, for example, is dependent on the specific conditions of the space radiation environment [40]. Due to the difficulties in replicating the space radiation environment on Earth, however, it is difficult to draw conclusions about the impact of the space radiation environment on pharmacological agents [40]. Despite the inherent difficulties of experimentation in space and on Earth, future experiments are necessary before medications used in spaceflight can be held to the same shelf life standards as their terrestrial counterparts. As of now, the usefulness, effectiveness, and safety of individual ISS medications beyond their labeled shelf lives remain a knowledge gap [41].

Spaceflight may also cause pharmacokinetic (PK) and pharmacodynamic (PD) [28] alterations as well. PK refers to a medication's movement throughout the body and how the body processes the medication, while PD relates to the body's biological response to the medication and how the medication affects the body. Alterations in PK and PD could impact the safety and effectiveness of pharmaceuticals used during spaceflight [28]. Some microgravity-induced physiological changes that are thought to impact PK and PD, such as shifts in fluid distribution towards the upper body, can be simulated in human and animal studies such as terrestrial bedrest studies [42] and rodent suspension studies [43]. However, with the current wide-ranging and inconclusive results, the specific spaceflight-induced changes to medication PK and PD are not yet fully understood [44][37][40]. This knowledge gap exists primarily because of the inability of some terrestrial studies to closely simulate the conditions of the spaceflight environment and the differences in experimental design between studies [37]; the limited number of human subjects available in space is also a limiting factor. In the future, compact organ-on-a-chip platforms may serve as more accessible methods of conducting biological and pharmacological studies in space [82]. Addressing such knowledge gaps is essential to improve our understanding as it relates to pharmaceutical efficacy and safety in space.

3.5. Additional Challenges and Considerations

Engineering and logistical challenges also influence the possible scope of pharmaceutical solutions for future missions. For example, just as the harsh space environment has the ability to damage and alter biological organisms, medical devices and electronics are likewise susceptible to damage from conditions like the space radiation environment [46]. Thus, devices that allow for *in situ* pharmaceutical manufacturing must be resistant to such conditions.

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Additionally, due to the weight and volume limitations of the internal spacecraft environment, compact and lightweight technologies are optimal. As of 2015, the cost to launch one gallon of water to the ISS was about $25,000; during the same year, the total savings, per day, that resulted from recycling water on the ISS added up to about $425,000 [16]. These numbers highlight the tremendous financial burden that may be lifted by recycling consumable resources in space. Further, these costs are likely to be greater for future exploration-class missions. Therefore, it is essential to consider solutions that recycle water and other consumables to free up weight and space for other priority cargo. Even more weight and volume savings can be achieved by introducing effective preventative health care measures, making accurate predictions about medication use, and selecting cargo that serves multiple purposes—for instance, identifying viable medications that can be used to treat a variety of conditions.

Although the space environment poses a number of challenges, it does present some characteristics may be advantageous. A better understanding of planetary resources and the advancement of *in situ* resource utilization techniques [47], such as mining water ice on Mars [48], may help to establish long-term resource independence despite infrequent resupply. Additionally, experiments in microgravity have suggested that protein crystallization techniques conducted in the space environment produce larger and more visually flawless crystals than those regularly produced on Earth [49]; these benefits may aid future structure-based drug design and pharmaceutical development efforts, providing a potential alternative for industries conducting similar operations on Earth.

Although this is not a comprehensive compilation of such variables that need to be considered, it should be noted that these and other engineering and logistical barriers should influence the design and function of possible solutions.

4. Possibilities

Despite the numerous challenges and nuances of the space environment, there are several potential solutions that may help to provide an effective pharmacy for deep space exploration missions. Some of these solutions can be implemented alone, while others can be combined. These interdisciplinary prospects are categorized into four sections: Improving Pharmaceutical Formulations, Pharmaceutical Storage and Packaging, Manufacturing Therapeutics *In Situ*, and Preventative Measures.

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4.1. Improving Pharmaceutical Formulations

The process of drug discovery and development, from identifying a target through getting approval for marketing, often takes more than 12 years, with an estimated cost of about $2.6 billion on average [50]. Thus, rather than starting from the beginning of this process, improving upon current therapeutic agents by employing excipients and stability enhancement methods will be more effective in improving drug stability while continuing to meet budget and flight deadline commitments. For instance, as it relates to photoprotective agents, excipients with antioxidant capacities may be added to drug formulations. One light stability study showed that, as the concentration of β-carotene was increased in methanol solutions containing the drug nisoldipine (a calcium channel blocker used to treat hypertension), the photodegradation rate of nisoldipine decreased as well [51]. Additionally, drug incorporation into liposomes has been shown to significantly increase drug photostability [52]. Excipients may interact with distinct formulations in different ways, so the safety and effectiveness of excipients in the context of specific formulations must be studied. The stability of Aspirin, for instance, when combined with dextrose, starch, cellulose, or stearate has proven to be greater than in Aspirin formulations including silica or aluminum oxide [53]. Excipient degradation in the space environment, along with PK and PD changes, must be further studied as well.

4.2. Pharmaceutical Storage and Packaging

The photodegradation of pharmaceuticals is commonly mitigated by storing medications in opaque, amber-colored plastic or glass containers that can absorb UV light at wavelengths up to 470 nm [54]. Still, further measures must be taken to protect medications from the other types of radiation that exist in the space environment.

The impacts of radiation can be attributed to the energy that a physical object receives as it is infiltrated by a charged particle. The energy of ionizing radiation in the deep space environment, when compared to that which astronauts currently experience on the ISS, is said to be about five times more severe [55]. This radiation may play a role in the degradation of pharmaceuticals [40]. However, on future Mars trips, resupply capabilities, including those able to replenish degraded food and medical supplies, will be unfeasible [33]. Reports from NASA have mentioned the possibility of shipping food [33] and medical supplies [55] to Mars, pre-mission, to be cached and preserved for astronaut accessibility upon arrival. Additionally, cryopreserving pharmacological agents stored on the Martian surface has been previously

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proposed as a way to mitigate radiation-induced pharmaceutical degradation [56][55]. It has been shown that cryogenic temperatures can reduce radiation damage to biological samples [57]. However, future studies must investigate the effects of cryogenic preservation on additional formulations and test in conditions that more closely resemble those of the space radiation environment [40]. Compacted lunar soil samples have displayed shielding capabilities against space-like radiation conditions [58]; for scenarios that necessitate pharmaceutical storage on the Moon, a barrier made out of this soil material may be a way to mitigate radiation damage to pharmaceuticals. Future studies should determine the viability of Martian soil for similar applications.

Regarding in-flight storage, both pre-established and deployable, “just-in-time” barriers have been proposed as potential radiation shielding solutions [40]. Such structures, by reducing crew exposure to radiation, will mitigate DNA damage, cancer, other health risks [15][44][59], and the use of more medications to treat these conditions. Simultaneously, pharmaceuticals stored in or moved to these protected areas will be subject to reduced exposure as well [55][40]. In order to achieve minimal mass and volume for this type of protective system, some solutions propose using available mass—like food supplies, water, and compacted trash—to provide shelter on an as-needed basis, rather than carrying additional mass for the sole purpose of radiation shielding [59]. One design proposes a solution where astronaut crew quarters are constructed from water-fillable structural panels; such waterwalls would provide additional water storage capability in addition to deployable radiation protection in the case of an SPE [59]. Although predictive models for such solar events are being developed [60], insufficient forecasting capabilities may limit the effectiveness of such deployable barriers, as they may not be established in time. Additionally, deployable barriers will not protect crew members or medications from GCR, which are a constant source of radiation.

Radiation passing through barriers and packaging material can also create secondary particles that may interact with the pharmaceuticals inside [61][40]. Several polyethylene varieties—incorporating boron, water, and tungsten—may be effective at attenuating primary radiation and avoiding secondary radiation [61][62][63]. Specifically, boron carbide composites are lighter than conventional aluminum shields and display improved mechanical properties when compared to high density polyethylene [62].

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Labeled shelf life estimates assume that medications are protected from the environment by their original packaging, but some spaceflight medications undergo pre-flight repackaging in custom containers. This custom packaging saves volume and mass, but could affect pharmaceutical stability by altering exposure to heat, light, humidity, and gases; the packaging itself could interact with the medications as well [32][38][39][64]. The accelerated degradation of medications in previous studies has been attributed to repackaging [32], although the effects of repackaging on pharmaceutical stability are not fully understood [65]. The protective, compatible, safety, and performance capabilities of container closure systems should be decided according to the routes of administration and dosage forms [64].

4.3. Manufacturing Therapeutics *In Situ*

Future missions will likely extend beyond the terrestrial shelf life limits for many of the medications that are currently included in the medical kits in space. Fortunately, there are several prospective technologies that would make it possible for therapeutic agents to be manufactured on site, or *in situ*, and on an as-needed basis.

In one investigation, *Lactuca sativa*, lettuce, is being considered as a potential bioproduction platform for recombinant protein therapeutics including trypsin, parathyroid hormone (PTH), and granulocyte colony-stimulating factor (G-CSF); the process, from production to delivery, is proposed to take less than a day and will produce therapeutics useful in treating burns and skin damage, osteoporosis, and acute radiation syndrome, respectively [66]. After the biologics are produced by the plant, affinity chromatography will be performed with the use of plant-made viral immunosorbent nanoparticles for rapid purification [66]. Without processing, modified plants could provide both nutrients and therapeutic benefits when consumed [67]. However, before doing so, the therapeutic compounds present per unit mass of raw plant material and the consistency of such measurements will need to be characterized in order to mitigate incorrect dose consumption.

Even in the absence of genetic modifications, naturally occurring plant-derived phytochemicals and fungi-derived secondary metabolites have numerous known and unknown medical applications [68][69][70]. Additionally, stressors associated with the space environment may activate cryptic metabolic pathways, which could assist in the discovery and production of new medically-applicable compounds [69]. Systems currently used to cultivate plants on the ISS, such as the Passive Orbital Nutrient Delivery System [71] and the Advanced Plant Habitat [72],

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may enable future missions to grow medicinal plants. After purification, bioactive secondary metabolites could be used to treat infections, reverse pathogenic drug-resistance, and reduce virulence [61]. Such therapeutics may be necessary, given that certain pathogens may display increased proliferation, antibiotic resistance, and virulence in the space environment [12].

Another technology currently in the developmental stage is a device that will contain synthetic microbes capable of producing active pharmaceutical compounds on demand. Devices will be ingested by astronauts, reside in the gastrointestinal tract, and will be able to produce drugs as needed [73]. As an increasing number of microbial therapeutics move into clinical trials, there are still questions about the manufacturing, storage, and delivery of microbial APIs that remain unanswered [74]. Both plant-based and microbe-based manufacturing processes have precursors that are able to last for the duration of the proposed missions and also require less mass and volume because resources will only be consumed as they are needed. In the future, an expanded range of manufacturable biopharmaceuticals may be capable of addressing more health conditions, which may allow for the reduction of medications brought in medical kits. However, the effect of the space environment on plants and bacteria must be further investigated before the long-term safety and effectiveness of such systems can be determined.

Another possible application from the field of biotechnology is microfluidics, a compact, portable, and modifiable solution for the purification and microparticle encapsulation of drug products through the use of fluid manipulation [75]. Cell-free transcription and translation methods housed in microfluidic systems also present an opportunity for *in vivo* biopharmaceutical production [76].

Finally, recent advances in three-dimensional pharmaceutical printing technologies further expand the possibilities for on-site therapeutics manufacturing and the personalization of pharmaceutical dose, shape, and dissolution characteristics [77].

4.4. Preventative Measures

Whether it be through adequate nutrition, exercise, greenspaces, or other “countermeasures," improving crew members’ baseline health status by alleviating the negative health effects of the space environment [78] will lessen the drug types and dosages that must be consumed by crew members throughout the length of a given mission. For instance, adequate nutrient and phytochemical consumption is known to improve immune function and decrease the

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risks for pathogenic infection [79]. However, while ISS crew members receive periodic resupplies of fresh food [33], providing a healthy diet for future Mars missions will be difficult, as some critical nutrients may degrade well within the mission timeline [33]. Taking dietary supplements, like those for vitamin D, may improve nutritional intake and astronaut health, although these may degrade over the course of a mission [80]. The ability to successfully grow plants onboard future spacecraft may provide astronauts with whole foods and nutrients [81][80] and simultaneously mitigate the degradation issues related to storage. As it pertains to exercise, crew members have performed in-flight routines dating back to the Apollo missions; although participants reported positive perceived health benefits, the type and duration of exercise needed to have a positive impact on human health in the space environment is unclear [82] and must be further investigated. On the psychological side, as with similar journeys to extreme terrestrial destinations, there are numerous mental stresses that have the potential to impact astronauts during spaceflights and colonization efforts [83]. Along with several other countermeasures proposed by NASA, plants and greenhouse environments have been considered as a way to potentially improve astronaut psychological well-being by providing sensory stimulation and a reminder of Earth [84].

While the ISS uses a telemedicine-based health advising system, Earth-to-Mars communications could take up to 44 minutes roundtrip [33]. Therefore, receiving real-time medical advice from experts on Earth will be unfeasible during future missions. Consequently, there will be an increased dependence on fellow crew members and automated systems for healthcare advice, including medication dose, type, and general consumption recommendations for acute conditions. Furthermore, the automation of future mission medical systems may serve as a preventative health measure in itself—for example, automated in-flight degradation analysis [37] and dose-tracking methods [29] may prevent crew members from consuming dangerous, degraded medications and consuming incorrect quantities. Additionally, crew member pharmacogenetic profiles could expand the opportunities for the personalization of medicine; by assessing an astronaut's individual genetic compatibility with the available medications, adverse reactions, therapeutic ineffectiveness, and incorrect dose administrations could be avoided [85]. Advanced crew member health monitoring systems may allow for the earlier detection of health conditions; this could prevent untreated conditions from developing into more severe cases. Finally, automated systems may reduce the burden of in-flight medical responsibilities for crew members and allow them to allocate time for other tasks, possibly leading to a work environment that is less stressful [86]. Future studies should test the effectiveness and viability of such

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physical and psychological health risk mitigation strategies in the context of the space environment and specific mission architecture.

5. Discussion

Before scrutinizing and building upon prospective solutions, several knowledge gaps should be addressed in order to elucidate the specific limitations of current therapeutic agents and determine what features are desired in ideal solutions. It is imperative that future research efforts aim to gather detailed in-flight medication use data, investigate the negative impacts of the space environment on human health, and quantify changes in the safety and efficacy of specific pharmaceuticals after exposure to the space environment. Currently, published information on these topics is insufficient; relevant government agencies, the private sector, and international partners should be mobilized immediately to identify and prioritize these and other similar issues, such that necessary investigations and relevant solutions can be executed in time to support upcoming space missions. Clarifying and expanding upon the ways in which the general public can collaborate with such efforts would also be helpful to stimulate innovation through crowdsourcing. Time is of the essence, as the ISS, currently an unparalleled environment for conducting experiments in the space environment, is expected to be decommissioned in less than a decade. This defines a tight window to promote, design, and deliver key experiments that will underpin future solutions.

In addition to government space programs, future “space tourism” industries will need to provide safe and effective medications for their customers. Furthermore, research and innovation in this seemingly niche domain may have impactful terrestrial applications in remote military, scientific, and cultural settings. For example, rural villages and isolated scientific research outposts may benefit from longer-lasting pharmaceuticals that allow for less frequent resupplies and fewer wasted medications. These and other commercial spin-off opportunities for social impact and return on investment should incentivize the private sector to collaborate.

A major milestone for humanity is expected to take place in the next 20 years, as astronauts on a manned mission to Mars will become the very first humans to step foot on another planet. Ultimately, if we hope to realize our dream of extending human presence deeper into space, safe and effective pharmaceuticals will support astronaut health and thereby hold a central role in improving the probability of successful missions.

References:

1. National Aeronautics and Space Administration. (2020). *FY 2020 Volume of Integrated Performance.* https://www.nasa.gov/sites/default/files/atoms/files/nasa_fy2020_volume_of_integrated_performance.pdf
2. National Aeronautics and Space Administration. (2018). *NASA Strategic Plan 2018.* https://www.nasa.gov/sites/default/files/atoms/files/nasa_2018_strategic_plan.pdf
3. Warner, C. (2020, August 10). NASA Perseveres Through Pandemic, Looks Ahead in 2020, 2021. Retrieved September 15, 2020 from https://www.nasa.gov/feature/nasa-perseveres-through-pandemic-looks-ahead-in-2020-2021
4. National Aeronautics and Space Administration. (2020). *NASA's Plan for Sustained Lunar Exploration and Development.* https://www.nasa.gov/sites/default/files/atoms/files/a_sustained_lunar_presence_nspc_report4220final.pdf
5. U.S. Office of Space Commerce. (2010). *National Space Policy of the United States of America.* https://history.nasa.gov/national_space_policy_6-28-10.pdf
6. McPhee, J. C., & Charles, J. B. (2009). *Human Health and Performance Risks of Space Exploration Missions.* National Aeronautics and Space Administration. https://humanresearchroadmap.nasa.gov/Evidence/reports/EvidenceBook.pdf
7. National Aeronautics and Space Administration. (2019). *Human Research Program Integrated Research Plan.* (Report No. HRP-47065). https://humanresearchroadmap.nasa.gov/Documents/IRP_Rev-Current.pdf
8. Wotring, V. E. (2012). Introduction. *Space Pharmacology* (pp. 1–5). Springer-Verlag New York. https://doi.org/10.1007/978-3-319-56637-5_68-1
9. Crucian, B. E., Choukèr, A., Simpson, R. J., Mehta, S., Marshall, G., Smith, S. M., Zwart, S. R., Heer, M., Ponomarev, S., Whitmire, A., Frippiat, J. P., Douglas, G. L., Lorenzi, H., Buchheim, J., Makedonas, G., Ginsburg, G. S., Ott, C. M., Pierson, D. L., Krieger, S. S., … Sams, C. (2018). Immune System Dysregulation During Spaceflight: Potential Countermeasures for Deep Space Exploration Missions. *Frontiers in Immunology*, *9*. https://doi.org/10.3389/fimmu.2018.01437
10. Crucian, B. E., Makedonas, G., Sams, C. F., Pierson, D. L., Simpson, R., Stowe, R. P.,

Smith, S. M., Zwart, S. R., Krieger, S. S., Rooney, B., Douglas, G., Downs, M., Nelman-Gonzalez, M., Williams, T. J., & Mehta, S. (2020). Countermeasures-based Improvements in Stress, Immune System Dysregulation and Latent Herpesvirus Reactivation onboard the International Space Station - Relevance for Deep Space Missions and Terrestrial Medicine. *Neuroscience and Biobehavioral Reviews*, *115*, 68–76. https://doi.org/10.1016/j.neubiorev.2020.05.007

11. Wilson, J. W., Ott, C. M., Höner zu Bentrup, K., Ramamurthy, R., Quick, L., Porwollik, S., Cheng, P., McClelland, M., Tsaprailis, G., Radabaugh, T., Hunt, A., Fernandez, D., Richter, E., Shah, M., Kilcoyne, M., Joshi, L., Nelman-Gonzalez, M., Hing, S., Parra, M., … Nickerson, C. A. (2007). Space flight alters bacterial gene expression and virulence and reveals a role for global regulator Hfq. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(41), 16299–16304. https://doi.org/10.1073/pnas.0707155104
12. Frippiat, J. P., Crucian, B. E., de Quervain, D. J., Grimm, D., Montano, N., Praun, S., Roozendaal, B., Schelling, G., Thiel, M., Ullrich, O., & Choukèr, A. (2016). Towards human exploration of space: The THESEUS review series on immunology research priorities. *NPJ Microgravity*, *2*, 16040. https://doi.org/10.1038/npjmgrav.2016.40
13. Theriot, C. M., Koenigsknecht, M. J., Carlson, P. E., Jr, Hatton, G. E., Nelson, A. M., Li, B., Huffnagle, G. B., Z Li, J., & Young, V. B. (2014). Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to Clostridium difficile infection. *Nature Communications*, *5*, 3114. https://doi.org/10.1038/ncomms4114
14. Benjamin, S. (2018). Exploration to Exploitation: An Industry Analysis of Suborbital Space Tourism. *New Space*, *6*(1), 87–98. https://doi.org/10.1089/space.2017.0041
15. Grenon, S. M., Saary, J., Gray, G., Vanderploeg, J. M., & Hughes-Fulford, M. (2012). Can I take a space flight? Considerations for doctors. *BMJ (Clinical research ed.)*, *345*, e8124. https://doi.org/10.1136/bmj.e8124
16. Dempsey, R. (2017). *The International Space Station: Operating an Outpost in the New Frontier*. National Aeronautics and Space Administration. https://www.nasa.gov/sites/default/files/atoms/files/iss-operating_an_outpost-tagged.pdf
17. National Aeronautics and Space Administration. (2011). *Astronaut Selection and Training* [Fact Sheet]. https://www.nasa.gov/centers/johnson/pdf/606877main_FS-2011-

11-057-JSC-astro_trng.pdf

18. McQuaid, E. L., & Landier, W. (2018). Cultural Issues in Medication Adherence: Disparities and Directions. *Journal of General Internal Medicine*, *33*(2), 200–206. https://doi.org/10.1007/s11606-017-4199-3
19. Mars, K. (2019, May 16). About Analog Missions. Retrieved August 2, 2020 from https://www.nasa.gov/analogs/what-are-analog-missions
20. Myers, J., Boley, L., Foy, M., Goodenow, D., Griffin, D., Keenan, A., Kerstman, E., Melton, S., McGuire, K., Saile, L., Shah, R., Garcia, Y., Sirmons, B., Walton, M., & Reyes, D. (2015). *Integrated Medical Model Overview* [Conference Presentation]. NASA HRP Investigator's Workshop, Galveston, TX, United States. https://ntrs.nasa.gov/api/citations/20150002713/downloads/20150002713.pdf
21. Blue, R., Nusbaum, D., & Antonsen, E. (2019). *Development of an Accepted Medical Condition List for Exploration Medical Capability Scoping.* (Report No. JSC-E-DAA-TN69936). National Aeronautics and Space Administration. https://ntrs.nasa.gov/api/citations/20190027540/downloads/20190027540.pdf
22. National Aeronautics and Space Administration. (2020, November). *Risk of Adverse Health Outcomes & Decrements in Performance due to inflight Medical Conditions.* NASA Human Research Roadmap. https://humanresearchroadmap.nasa.gov/risks/risk.aspx?i=95#
23. Hodkinson, P. D., Anderton, R. A., Posselt, B. N., & Fong, K. J. (2017). An overview of space medicine. *British Journal of Anaesthesia*, 119(suppl_1), i143–i153. https://doi.org/10.1093/bja/aex336
24. National Aeronautics and Space Administration. (2012). *Analog Missions and Field Tests* [Fact Sheet]. https://www.nasa.gov/pdf/541196main_Analogs_FactSheet_508.pdf
25. Clement, B. M. (2011). *Crew Health Care System (CHeCS) Design Research, Documentations, and Evaluations.* (Report No. JSC-CN-23601). National Aeronautics and Space Administration. https://ntrs.nasa.gov/api/citations/20110011351/downloads/20110011351.pdf
26. Gonzalez, S. M. (2010). *Health Maintenance System (HMS) Hardware Research, Design, and Collaboration.* (Report No. JSC-CN-22352). National Aeronautics and Space Administration.

https://ntrs.nasa.gov/api/citations/20100042371/downloads/20100042371.pdf

27. *National Aeronautics and Space Administration Emergency Medical Procedures Manual for the International Space Station* [partial]. (2016). Governmentattic. https://www.governmentattic.org/19docs/NASA-ISSmedicalEmergManual_2016.pdf
28. Wotring, V. E. (2015). Medication use by U.S. crewmembers on the International Space Station. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *29*(11), 4417–4423. https://doi.org/10.1096/fj.14-264838
29. Wotring, V. E. (2017). *Dose Tracker Application for Monitoring Crew Medication Usage, Symptoms, and Adverse Effects During Missions* [Task Book Report]. National Aeronautics and Space Administration. https://taskbook.nasaprs.com/tbp/tbpdf.cfm?id=11174
30. Mulcahy, R., Bayuse, T., Pattarini, J. M., & Blue, R. S. (2019). *Operational Impact of an Onboard Pharmacy: Mission Impact and Risk Considerations* [Conference Presentation]. Aerospace Medical Association Annual Scientific Meeting, Las Vegas, NV, United States. https://ntrs.nasa.gov/api/citations/20190025093/downloads/20190025093.pdf
31. National Aeronautics and Space Administration. (2020, November). *Pharm-501: We need to accurately characterize when astronauts use medications in space, why they use them, how they use them, whether they work, and if they cause any problems.* NASA Human Research Roadmap. Retrieved August 3, 2020 from https://humanresearchroadmap.nasa.gov/Gaps/gap.aspx?i=738
32. Nimon, J. (2011, November). *Preparing to Stock the Medicine Cabinet for Long-Duration Missions.* International Space Station Program Science Office. https://www.nasa.gov/mission_pages/station/research/news/Medication_ISS.html
33. NASA Office of Inspector General. (2015). *NASA's Efforts to Manage Health and Human Performance Risks for Space Exploration.* (Report No. IG-16-003). National Aeronautics and Space Administration. https://oig.nasa.gov/docs/IG-16-003.pdf
34. Barger, L. K., Flynn-Evans, E. E., Kubey, A., Walsh, L., Ronda, J. M., Wang, W., Wright, K. P., Jr, & Czeisler, C. A. (2014). Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *Lancet Neurology*, *13*(9), 904–912. https://doi.org/10.1016/S1474-4422(14)70122-X
35. Capen, R., Christopher, D., Forenzo, P., Ireland, C., Liu, O., Lyapustina, S., O'Neill, J.,

Patterson, N., Quinlan, M., Sandell, D., Schwenke, J., Stroup, W., & Tougas, T. (2012). On the shelf life of pharmaceutical products. *AAPS PharmSciTech*, *13*(3), 911–918. https://doi.org/10.1208/s12249-012-9815-2

36. *Expiration Dating Extension*. Retrieved September 19, 2020 from https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/expiration-dating-extension
37. Blue, R. S., Bayuse, T. M., Daniels, V. R., Wotring, V. E., Suresh, R., Mulcahy, R. A., & Antonsen, E. L. (2019). Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding. *NPJ Microgravity*, *5*, 14. https://doi.org/10.1038/s41526-019-0075-2
38. Du, B., Daniels, V. R., Vaksman, Z., Boyd, J. L., Crady, C., & Putcha, L. (2011). Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. *The AAPS Journal*, *13*(2), 299–308. https://doi.org/10.1208/s12248-011-9270-0
39. Wotring, V. E. (2016). Chemical Potency and Degradation Products of Medications Stored Over 550 Earth Days at the International Space Station. *The AAPS Journal*, *18*(1), 210–216. https://doi.org/10.1208/s12248-015-9834-5
40. Blue, R. S., Chancellor, J. C., Antonsen, E. L., Bayuse, T. M., Daniels, V. R., & Wotring, V. E. (2019). Limitations in predicting radiation-induced pharmaceutical instability during long-duration spaceflight. *NPJ Microgravity*, *5*, 15. https://doi.org/10.1038/s41526-019-0076-1
41. National Aeronautics and Space Administration. (n.d) *Pharm02: We do not know how long medications may be safe and effective beyond their expiration dates.* Human Research Roadmap. Retrieved August 27, 2020 from https://humanresearchroadmap.nasa.gov/gaps/gap.aspx?i=541
42. Saivin, S., Pavy-Le Traon, A., Cornac, A., Güell, A., & Houin, G. (1995). Impact of a four-day head-down tilt (-6 degrees) on lidocaine pharmacokinetics used as probe to evaluate hepatic blood flow. *Journal of Clinical Pharmacology*, *35*(7), 697–704. https://doi.org/10.1002/j.1552-4604.1995.tb04110.x
43. Gandia, P., Saivin, S., Lavit, M., & Houin, G. (2004). Influence of simulated weightlessness on the pharmacokinetics of acetaminophen administered by the oral route: a study in the rat. *Fundamental & Clinical Pharmacology*, *18*(1), 57–64.

https://doi.org/10.1046/j.1472-8206.2003.00220.x

44. Wotring, V. E. (2011). *Evidence Report: Risk of Therapeutic Failure Due to Ineffectiveness of Medication.* https://humanresearchroadmap.nasa.gov/Evidence/reports/Pharm.pdf
45. Jodat, Y. A., Kang, M. G., Kiaee, K., Kim, G. J., Martinez, A., Rosenkranz, A., Bae, H., & Shin, S. R. (2018). Human-Derived Organ-on-a-Chip for Personalized Drug Development. *Current Pharmaceutical Design*, *24*(45), 5471–5486. https://doi.org/10.2174/1381612825666190308150055
46. Zheng, Y., Ganushkina, N. Y., Jiggens, P., Jun, I., Meier, M., Minow, J. I., O'Brien, T. P., Pitchford, D., Shprits, Y., Tobiska, W. K., Xapsos, M. A., Guild, T. B., Mazur, J. E., & Kuznetsova, M. M. (2019). Space Radiation and Plasma Effects on Satellites and Aviation: Quantities and Metrics for Tracking Performance of Space Weather Environment Models. *Space Weather: the International Journal of Research & Applications*, *17*(10), 1384–1403. https://doi.org/10.1029/2018SW002042
47. Muscatello, A. C., & Santiago-Maldonado, E. (2012). *Mars In Situ Resource Utilization Technology Evaluation* [Conference Paper]. 50th AIAA Aerospace Sciences Meeting, Nashville, TN, United States. National Aeronautics and Space Administration. https://ntrs.nasa.gov/api/citations/20120001775/downloads/20120001775.pdf
48. Hoffman, S., Andrews, A., & Watts, K. (2016). *"Mining" Water Ice on Mars: An Assessment of ISRU Options in Support of Future Human Missions* [Presentation]. National Aeronautics and Space Administration. https://ntrs.nasa.gov/api/citations/20160013682/downloads/20160013682.pdf
49. McPherson, A., & DeLucas, L. J. (2015). Microgravity protein crystallization. *NPJ Microgravity*, *1*, 15010. https://doi.org/10.1038/npjmgrav.2015.10
50. Mohs, R. C., & Greig, N. H. (2017). Drug discovery and development: Role of basic biological research. *Alzheimer's & Dementia (New York, N. Y.)*, *3*(4), 651–657. https://doi.org/10.1016/j.trci.2017.10.005
51. Mielcarek, J., Grobelny, P., & Szamburska, O. (2005). The effect of beta-carotene on the photostability of nisoldipine. *Methods and Findings in Experimental and Clinical Pharmacology*, *27*(3), 167–171. https://doi.org/10.1358/mf.2005.27.3.890873
52. De Luca, M., Ioele, G., & Ragno, G. (2019). 1,4-Dihydropyridine Antihypertensive

Drugs: Recent Advances in Photostabilization Strategies. *Pharmaceutics*, *11*(2), 85. https://doi.org/10.3390/pharmaceutics11020085

53. Ager, D. J., Alexander, K. S., Bhatti, A. S., Blackburn, J. S., Dollimore, D., Koogan, T. S., Mooseman, K. A., Muhvic, G. M., Sims, B., & Webb, V. J. (1986). Stability of aspirin in solid mixtures. *Journal of Pharmaceutical Sciences*, *75*(1), 97–101. https://doi.org/10.1002/jps.2600750124
54. Janga, K. Y., King, T., Ji, N., Sarabu, S., Shadambikar, G., Sawant, S., Xu, P., Repka, M. A., & Murthy, S. N. (2018). Photostability Issues in Pharmaceutical Dosage Forms and Photostabilization. *AAPS PharmSciTech*, *19*(1), 48–59. https://doi.org/10.1208/s12249-017-0869-z
55. Jaworske, D. A., & Myers, J. G. (2016). *Pharmaceuticals Exposed to the Space Environment: Problems and Prospects* [Technical Memorandum]. (Report No. E-19193). National Aeronautics and Space Administration. https://ntrs.nasa.gov/api/citations/20160003684/downloads/20160003684.pdf
56. Antonsen, E., Bayuse, T., Blue, R., Daniels, V., Hailey, M., Hussey, S., Kerstman, E., Krihak, M., Latorella, K., Mindock, J., Myers, J., Mulcahy, R., Reed, R., Reyes, D., Urbina, M., Walton, M., Archibald, R., Barratt M., Ameen, M., … Zoldak, J. (2017). *Evidence Report: Risk of Adverse Health Outcomes and Decrements in Performance due to In-Flight Medical Conditions.* National Aeronautics and Space Administration. https://humanresearchroadmap.nasa.gov/Evidence/reports/Medical.pdf
57. Meents, A., Gutmann, S., Wagner, A., & Schulze-Briese, C. (2010). Origin and temperature dependence of radiation damage in biological samples at cryogenic temperatures. *Proceedings of the National Academy of Sciences, USA*, *107*(3), 1094-1099. https://doi.org/10.1073/pnas.0905481107
58. Miller, J., Taylor, L., Zeitlin, C., Heilbronn, L., Guetersloh, S., DiGiuseppe, M., Iwata, Y., & Murakami, T. (2009). Lunar soil as shielding against space radiation. *Radiation Measurements*, *44*(2), 163-167. https://doi.org/10.1016/j.radmeas.2009.01.010
59. Simon, M. A., Cerro, J., & Clowdsley, M. (2013). *RadWorks Storm Shelter Design for Solar Particle Event Shielding* [Conference Paper]. AIAA SPACE 2013 Conference and Exposition, San Diego, CA, United States. National Aeronautics and Space Administration.

https://ntrs.nasa.gov/api/citations/20170002287/downloads/20170002287.pdf

60. Zhong, Q., Wang, J., Meng, X., Liu, S., & Gong, J. (2019). Prediction Model for Solar Energetic Proton Events: Analysis and Verification. *Space Weather*, *17*(5), 709–726. https://doi.org/10.1029/2018SW001915
61. Putcha, L., Taylor, P. W., & Boyd, J. L. (2011). Biopharmaceutical challenges of therapeutics in space: formulation and packaging considerations. *Therapeutic Delivery*, *2*(11), 1373–1376. https://doi.org/10.4155/tde.11.115
62. Harrison, C., Burgett, E., Hertel, N., & Grulke, E. (2008). Polyethylene/Boron Composites for Radiation Shielding Applications. Polyethylene/Boron Composites for Radiation Shielding Applications. *AIP Conference Proceedings*, *969*, 484-491. https://doi.org/10.1063/1.2845006
63. AbuAlRoos, N. J., Azman, M. N., Baharul Amin, N. A., & Zainon, R. (2020). Tungsten-based material as promising new lead-free gamma radiation shielding material in nuclear medicine. *Physica Medica*, *78*, 48–57. https://doi.org/10.1016/j.ejmp.2020.08.017
64. U.S. Food and Drug Administration. (1999). *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics.* https://www.fda.gov/media/70788/download
65. Raimi-Abraham, B. T., Garcia Del Valle, A., Varon Galcera, C., Barker, S. A., & Orlu, M. (2017). Investigating the physical stability of repackaged medicines stored into commercially available multicompartment compliance aids (MCAs). *Journal of Pharmaceutical Health Services Research: an Official Journal of the Royal Pharmaceutical Society of Great Britain*, *8*(2), 81–89. https://doi.org/10.1111/jphs.12176
66. McDonald, K. (2020). *A Plant-Based Platform for 'Just in Time' Medications* [Task Book Report]. National Aeronautics and Space Administration. https://taskbook.nasaprs.com/tbp/tbpdf.cfm?id=13952
67. Lei, L. (2019). Lettuce-manufactured pharmaceuticals. *Nature Plants*, *5*(7), 646. https://doi.org/10.1038/s41477-019-0484-y
68. Mahdi, J. G., Mahdi, A. J., Mahdi, A. J., & Bowen, I. D. (2006). The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential. *Cell Proliferation*, *39*(2), 147–155. https://doi.org/10.1111/j.1365-2184.2006.00377.x

69. Countryman, S. (n.d). *Influence of microgravity on the production of Aspergillus secondary metabolites (IMPAS) – a novel drug discovery approach with potential benefits to astronauts' health.* National Aeronautics and Space Administration ISS Program Science Office. https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=1164
70. Kuete, V., & Efferth, T. (2010). Cameroonian medicinal plants: pharmacology and derived natural products. *Frontiers in Pharmacology*, *1*, 123. https://doi.org/10.3389/fphar.2010.00123
71. Zhang, Y. (n.d) *Veggie PONDS.* National Aeronautics and Space Administration ISS Program Science Office. https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=7581
72. Dufour, N. F. (n.d). *Advanced Plant Habitat.* National Aeronautics and Space Administration ISS Program Science Office. https://www.nasa.gov/mission_pages/station/research/experiments/explorer/Investigation.html?#id=2036
73. Langer, R. (2020). *Just in Time Medications from Gastrointestinal Resident Microbial Systems* [Task Book Report]. National Aeronautics and Space Administration. https://taskbook.nasaprs.com/tbp/tbpdf.cfm?id=13957
74. Jimenez, M., Langer, R., & Traverso, G. (2019). Microbial therapeutics: New opportunities for drug delivery. *The Journal of Experimental Medicine*, *216*(5), 1005–1009. https://doi.org/10.1084/jem.20190609
75. Li, W., Zhang, L., Ge, X., Xu, B., Zhang, W., Qu, L., Choi, C. H., Xu, J., Zhang, A., Lee, H., & Weitz, D. A. (2018). Microfluidic fabrication of microparticles for biomedical applications. *Chemical Society Reviews*, *47*(15), 5646–5683. https://doi.org/10.1039/c7cs00263g
76. Damiati, S., Mhanna, R., Kodzius, R., & Ehmoser, E. K. (2018). Cell-Free Approaches in Synthetic Biology Utilizing Microfluidics. *Genes*, *9*(3), 144. https://doi.org/10.3390/genes9030144
77. Jamróz, W., Szafraniec, J., Kurek, M., & Jachowicz, R. (2018). 3D Printing in

Pharmaceutical and Medical Applications - Recent Achievements and Challenges. *Pharmaceutical Research*, *35*(9), 176. https://doi.org/10.1007/s11095-018-2454-x

78. Mars, K. (2019, June). *About Human Health Countermeasures (HHC).* National Aeronautics and Space Administration. https://www.nasa.gov/hrp/elements/hhc/about
79. Wu, D., Lewis, E. D., Pae, M., & Meydani, S. N. (2019). Nutritional Modulation of Immune Function: Analysis of Evidence, Mechanisms, and Clinical Relevance. *Frontiers in Immunology*, *9*, 3160. https://doi.org/10.3389/fimmu.2018.03160
80. Cooper, M., Perchonok, M., & Douglas, G. L. (2017). Initial assessment of the nutritional quality of the space food system over three years of ambient storage. *NPJ Microgravity*, *3*, 17. https://doi.org/10.1038/s41526-017-0022-z
81. Meinen, E., Dueck, T., Kempkes, F., & Stanghellini, C. (2018). Growing fresh food on future space missions: Environmental conditions and crop management. *Scientia Horticulturae*, *235*, 270–278. https://doi.org/10.1016/j.scienta.2018.03.002
82. Scheuring, R. A., Jones, J. A., Novak, J. D., Polk, J. D., Gillis, D. B., Schmid, J., Duncan, J. M., & Davis, J. R. (2008). The Apollo Medical Operations Project: Recommendations to improve crew health and performance for future exploration missions and lunar surface operations. *Acta Astronautica*, *63*(7–10), 980–987. https://doi.org/10.1016/j.actaastro.2007.12.065
83. Pagel, J. I., & Choukèr, A. (2016). Effects of isolation and confinement on humans-implications for manned space explorations. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *120*(12), 1449–1457. https://doi.org/10.1152/japplphysiol.00928.2015
84. Simon, M., Whitmire, A., Otto, C., & Neubek, D. (2011). *Factors Impacting Habitable Volume Requirements: Results from the 2011 Habitable Volume Workshop* [Technical Memorandum]. (Report No. JSC-CN-25231) National Aeronautics and Space Administration. https://ntrs.nasa.gov/api/citations/20110023287/downloads/20110023287.pdf
85. Stingl, J. C., Welker, S., Hartmann, G., Damann, V., & Gerzer, R. (2015). Where Failure Is Not an Option - Personalized Medicine in Astronauts. *PLOS ONE*, *10*(10), e0140764. https://doi.org/10.1371/journal.pone.0140764
86. James, K. L., Barlow, D., Bithell, A., Hiom, S., Lord, S., Oakley, P., Pollard, M., Roberts, D., Way, C., & Whittlesea, C. (2013). The impact of automation on pharmacy

 doi:10.20944/preprints202011.0724.v1

staff experience of workplace stressors. *The International Journal of Pharmacy Practice*, *21*(2), 105–116. https://doi.org/10.1111/j.2042-7174.2012.00231.x