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Gene-edited medicinal 'superplants': Advancements for prolonged space travel

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Abstract
Space exploration is an arduous journey, with future explorations extending in duration, increasing the risk for common space-related health issues such as bone density loss due to microgravity, impaired gut microbiota, cardiovascular ailments, and exposure to cosmic radiation. These ailments can be addressed using medicinal plants. Enhancing their efficacy entails employing gene editing to target specific secondary metabolite pathways associated with therapeutic properties. Moreover, gene editing can combine multiple medicinal properties from various plants, culminating in a singular 'superplant' with enhanced therapeutic benefits. This review discusses the current usage of medicinal plants in promoting human health during space travel, the application of gene editing technology in modifying medicinal plants and presents a vision for the utilization of gene-edited medicinal plants in space to mitigate the risk of various space-related health issues.

Keywords: Antimycotic activity, minimum inhibitory concentration, *Argemone mexicana* L.

Introduction
Space travel presents an exciting opportunity to investigate celestial bodies and enhance our understanding of the cosmos as we know it. Alternatively, exploring outer space could become imperative in the event that resources on Earth are depleted, or a catastrophe occurs.

Researchers have spent decades exploring the potential of space exploration, but future missions will require even longer journeys through space. Humanity has made significant strides in space travel, from landing humans on the Moon and launching probes to explore distant planets. However, technological advancements and international collaborations have motivated us to pursue more ambitious space exploration goals. Space missions are constrained on time, storage, water, and food prep, even more so during future missions to the Moon and Mars, which will require extended stays for over twelve months. Space travel is one of the most challenging situations for the human body to endure. The adverse physiological effects of extended space travel are highly variable and continue to be an obstacle in carrying out missions (Bhuyan *et al.*, 2023) [3]. There are a plethora of health issues involved, including microgravity, bone density loss, impaired gut microbiota, and central fluid shift (Simanonok and Charles, 1994; Turroni *et al.*, 2020; Bhuyan *et al.*, 2023) [54, 63, 3].

Longer space travel invariably leads to rising health concerns that can be addressed using medications. However, storing copious amounts of pills and vitamins for unpredictable health concerns is not practical due to limited storage space. Additionally, for extended space travel that may last many years, medications are likely to expire and resupplying may not be possible (Wotring, 2015) [68]. Further, the instability of medications in space environments is a significant concern for long-duration space missions. The harsh conditions of spaceflight, including microgravity, excessive vibration, humidity variation, temperature differences, and continuous radiation, can potentially cause instability in pharmaceuticals. This can lead to reduced potency and effectiveness of medications, which is particularly problematic for extended missions where resupply is not possible (Mehta, 2017) [74]. A new system is urgently needed to address these issues.

Long-term stays in space require a sustainable life support mechanism that can provide fresh food, maintain a clean atmospheric balance, and regenerate resources - all of which can be supplied by plants (Wolff *et al.*, 2014) [67]. Additionally, plants can be used for medicinal purposes. This review summarizes the potential applications of medicinal plants in addressing common space travel ailments, including microgravity, bone density loss, impaired gut

microbiota, and central fluid shift.
Additionally, I propose the development of a medicinal 'superplant' - a multipurpose medicinal plant capable of alleviating multiple symptoms associated with space travel.

Microgravity

Prolonged exposure to microgravity during extended space travel can lead to severe physiological impairments in the human body. Most notably, a microgravity-induced bone loss trend suggests that more bone density and calcium is lost in longer missions. During spaceflight, microgravity conditions "unload" weight bearing bones, triggering increased bone mineral loss leading to secondary osteoporosis (Grimm *et al.*, 2016) [16]. Furthermore, calcium deficiency is common among astronauts, with nearly 50% decrease in calcium intake and absorption during a 3-month long term spaceflight (Smith *et al.*, 1999) [55]. Space travel results in increased bone density in the skull area, while causing significant bone depletion in the upper limbs, lumbar spine, thorax, and lower extremities (Stavnichuk *et al.*, 2020) [58].

Microgravity conditions also lead to impair cytoskeletal function. Human multipotent stem cells (hMSCs), which are found in adult bone marrow, are important for cytoskeleton integrity. In microgravity conditions, osteoblastic expression in hMSCs are inhibited, reducing osteoblastic differentiation and disrupting the cytoskeleton (Zayzafoon, Meyers and McDonald, 2005) [70]. A similar pattern has been observed in endothelial and glial cells upon exposure to space flight, suggesting that impaired cytoskeletons may contribute to cardiovascular, musculoskeletal, and immune system compromise (Uva *et al.*, 2002; Carlsson *et al.*, 2003; Zayzafoon, Meyers and McDonald, 2005) [64, 70].

Though there are no definite treatments to reverse bone osteoporosis, there are some management techniques. Firstly, exercise leads to the decrease of bone mineral loss, resulting in positive effects of bone loss. This has been determined in several animal models, but current human trials have shown exercise only provides a partial protection against bone mineral loss and requires supplementation with an anti-resorptive. Pharmacologically, protein, calcium, vitamin D, and high intake of alkaline precursors are shown to reduce bone loss (Hajisadeghi *et al*., 2021; Fischer *et al*., 2023) [18, 13].

There have been no successful therapeutic strategies that have prevented osteocyte apoptosis, and future exploration may entail using a CRISPR-Cas 9 knockout for Cx43 or PGE2 biomarkers in apoptotic signaling (Ru and Wang, 2020, p. 20) [48]. Microgravity causes unloading and disuse of the bones speculates the dysfunction of Src/MEK/ERK, autophagy, Wnt/Beta-catenin, AMPJ- PGC1A-ROS axis, NO-sGc-cGMP, PTHrP/PTH1R; VEGF/VEGFR2 pathway, though it is not clear what is the direct cause of osteocyte apoptosis (Ru and Wang, 2020) [48].

Green tea polyphenol supplementation with drinking water has been shown to increase protection of bone mass by reducing inflammation, and downregulating COX-2 and TNF-α could reduce the risk of osteoporosis (Shen *et al.*, 2010) [53].

Future studies should decipher the molecular mechanism by which osteocyte apoptosis occurs in microgravity conditions using animal models and gene editing of pathways.

Gut Microbiota

The gut microbiome plays a key role in immune functions and homeostasis. Impaired balance of microbiota could lead to a myriad of health concerns, including metabolic disorders, increased susceptibility to infectious pathogens, diseases of gut and body organs, and even cancer (Mosca, Leclerc and Hugot, 2016; Sommariva *et al.*, 2020; Shama *et al.*, 2024) [38, 57, 52] Hind-limbed unloaded mice are well-established terrestrial models to simulate microgravity effects, mimicking various physiological changes akin to space travel (Shama *et al.*, 2022) [51]. In a hind-limbed unloaded mice model, microgravity conditions were mimicked over a three-week period; the study reported a decrease in intestinal microbial diversity and increase in pathogenic bacteria (Shama *et al.*, 2022) [51]. As established before, space-induced microgravity environments promote bone density loss and weakened muscles. Taking probiotics has been associated with regaining strength and muscle mass, suggesting that maintaining a healthy gut microbiome leads to improved overall health and maintained muscle strength - combatting common space travel ailments (Giron *et al.*, 2022) [14].

Ceratonia Siliqua, or Carob, extract contains pectin, gums, and polyphenols and has been shown to flourish gut microbiome with its anti-inflammatory properties (Requena *et al.*, 2010; Micheletti *et al.*, 2023) [47, 35]. Polyphenols are secondary metabolites of plants and act as antioxidants, neutralizing reactive oxygen species and improving gut health (Zhang and Tsao, 2016) [71]. Epigallocatechin-3-gallate (EGCG) in green tea has been shown to stimulate production of *Bifidobacterium adolescentis* when metabolized, creating a healthier gut bacteria profile and promoting human health (Liu *et al.*, 2020) [32].

Cardiovascular Disease and Cosmic Radiation

In recent years, radiation-induced cardiovascular disease (RICVD) has been a rising concern for those pursuing long-distance space travel. Radiation can interact with genetics and lifestyle factors, potentially exacerbating the risk of RICVD during long-distance space travel (Huff *et al.*, 2022) [21]. Compared to Earth, exposure to high energy protons due to solar particle events and galactic cosmic rays are much higher in space. This leads to concentrated exposure to radiation particles which damage DNA, RNA, and proteins, which put astronauts at a higher risk for RICVD (Moeller *et al.*, 2017; Huff *et al.*, 2022) [37, 21]. The use of antioxidants against radiation- induced tissue damage has long been studied, particularly the use of the Rosmarinic Acid antioxidant has been shown to protect the heart and decrease reactive oxidative species by stimulating antioxidant enzymes and protect the heart (Goudarzi, Fatahi Asl and Shoghi, 2023) [15]. Though this was only studied in rats, human models are still yet to be studied to elucidate the effects of antioxidants in humans.

Supplementing antioxidants in a diet could enhance protection against cosmic radiation in space. One study described how the use of a 2% strawberry extract diet could significantly protect against heavy ion particles common in cosmic radiation than a 2% blueberry extract diet (Rabin, Joseph and Shukitt-Hale, 2005) [46]. Additionally, a single exposure to UV radiation stimulates the release of ROS. Topical application of green tea polyphenol extract epigallocatechin-3-gallate before exposure has been shown to inhibit hydrogen peroxide and nitric oxide production associated with ROS and reverses depletion of antioxidant enzymes such as catalase (Katiyar *et al.*, 2001) [25].

However, the exact treatment and dosage of these remedies against cosmic radiation is highly variable and should be personalized to each astronaut upon further clinical study (Mitrea *et al.*, 2018) [36]. Finally, ferulic acid is typically found in wheat, oats, and rice (Kumar and Pruthi, 2014) [28]. Ferulic acid also preserves antioxidant enzymes and inhibits apoptotic activity in the spleen if administered before radiation exposure by reducing TBARS formation and enhancing catalase activity (Das *et al*., 2016) [10].

Additionally, cardiac arrhythmias are common among long duration spaceflight astronauts, and it has been shown that mitochondrial-associated antioxidants such as resveratrol activate the PI3K/AKT/eNOS pathway and reduce the occurrence of cardiac arrhythmias (Chong *et al*., 2015; Joseph *et al*., 2016) [7, 22].

Medicinal Plants

A medicinal plant contains beneficial nutrients which may serve as precursors to drugs or have therapeutic properties (Sofowora, Ogunbodede and Onayade, 2013) [56]. A plant can be classified as medicinal if it meets one or more of the following conditions: traditional use in formulations like herbal remedies, presence of extractable active compounds for medicinal purposes, culinary use as a spice, fragrant properties combined with medicinal benefits (e.g., ginger), or utilization in the producing materials for medical dressings, such as cotton, jute, and flax (Sofowora, Ogunbodede and Onayade, 2013) [56]. In this article, we primarily focus on medicinal plants in which extracted substances are used for medicinal purposes.

Medicinal plants have been around for years and various methods have already been used to cultivate and enhance their medicinal properties.

Indigenous knowledge

The curation of medicinal plants began through indigenous practices, which contributed to a variety of modern drugs (Gyllenhaal *et al*., 2012) [17]. Rural communities have long used indigenous knowledge to guide their healthcare, energy, and natural resource practices. In some African tribes, medicinal plants have long been conserved by enforcing certain 'taboos', which restricted the harvesting of plants deemed to have medicinal qualities. Conditions included seasonality, timeframe, and cutting in specific areas (Kambizi and Bvenura, 2023) [24]. Ethnobotanical expertise is obtained by personal experience or through oral history over generations. (Aziz *et al*., 2018) [2]. The preparation of medicinal plants varies in cultures and regions of the world. Additionally, different parts of the plant are used to treat different ailments. For instance, *Brassica Rapa* seeds are used for seasonal allergies, the bulb of *Allium cepa* is used to treat digestive issues, and the leaves of *Calotropis procera* alleviate joint pain (Aziz *et al*., 2018) [2]. Various techniques are employed to extract the medicinal qualities of the plant parts. In a study conducted in Woreda Wukro klete Awlaelo located in northern Ethiopia, common preparation methods of medicinal plants include, grinding, crushing, chewing, squeezing, and drinking. Grinding was the most common method of preparation (Mesfin, Tekle and Tesfay, 2013) [33]. Furthermore, Vaidyas in Uttaranchal, India typically crush the medicinal herb into a powder and incorporate it with other ingredients through either cooking, dissolving in liquid, or forming pills for regular supplementation (Kala, Farooquee and Majila, 2005, p. 200) [23].

Traditional breeding

Breeding medicinal plants is far more time-intensive than breeding crops. Medicinal plants are more prone to inhibit growth in response to various environmental stresses. Secondary metabolites aid plants in overcoming environmental stresses, and medicinal plants release secondary metabolites such as alkaloids and flavonoids, marking an important distinction between medicinal and crop plant breeding (Wang *et al*., 2020) [66]. The initial domestication of plants was centered around staple crop plants such as wheat, rice, potato, and maize, and neglecting medicinal plants in the process (Niazian, 2019a) [42]. Medicinal plants are naturally highly variable and is one of the reasons traditional breeding methods were used until now, in addition to the low cost and return on investments [Carlen 2011] [17].

Gene editing

Gene editing techniques for medicinal plants have emerged as promising tools for enhancing their therapeutic properties. While the application of these methods to medicinal plants is relatively new, several approaches have shown potential:

- CRISPR-Cas technology has been applied to a few plants notably *Salvia militiorrhiza* and *Cannabis sativa* to produce knockouts and highlight key genes that produce medicinal compounds (Zhou *et al*., 2018) [74].
- TILLING (Targeting-Induced Local Lesions IN Genomes) is a reverse genetic screening technique used to identify mutant genotypes, and while it has not been employed on medicinal plants specifically, it could be used to optimize detection of genes associated with medicinal properties (Niazian, 2019s) [43].
- TALENS (transcription activator-like effector nucleases) are engineered nucleases that induce targeted DNA modifications and achieve more than 10% DNA modification efficiency (Khan *et al*., 2017; Niazian, 2019b; Niazian and Niedbała, 2020) [26, 43]. Many crop plants have used TALENS for yield and quality improvement (Khan *et al*., 2017) [26].

Transgenes

When developing transgenic medicinal plants, it is crucial to ensure that the introduced genes do not interfere with or degrade the plant's important medicinal compounds. The goal is to enhance the plant's therapeutic properties without compromising its existing medicinal value. Most methods for developing medicinal plant transgenes involve agrobacterium-mediated transformation (Trivedi *et al*., 2016) [62]. In one such study, transgenic *Gentiana macrophylla* roots showed over 30-fold increased growth and produced a higher number of alkaloids for pharmaceutical use because of the larger root biomass in the T-DNA of agropine type of Ri plasmids (Tiwari *et al*., 2007) [61]. Thus, the incorporation of transgenes can enhance the overall ability for a medicinal plant to generate therapeutic compounds.

Machine Learning-Assisted Methods

In medicinal plant breeding, machine learning can be used to classify molecular markers, which enable the study of genetic diversity. Convolutional neural networks (CNNs) can be trained to read DNA/RNA sequences and classify genotypes using molecular markers (Niazian and Niedbała, 2020) [43]. In essence, machine learning and deep learning techniques can be used as phenotype prediction tools using genome data, allowing for more efficient medicinal plant breeding outcomes.

Future Directions

Given the harsh environment and storage constraints of space travel, introducing a medicinal 'superplant' would be an ideal way to improve astronaut health. The 'superplant,' would be genetically modified to contain multiple medicinal properties for different space-related ailments in one plant. This novel approach to space health provides a sustainable, regenerative supply of medicinal supplements that could mitigate space-induced ailments more naturally than traditional pharmaceuticals. Rather than relying on reactive treatments, continuous intake of medicinal plant compounds could serve as a key preventative measure for numerous diseases, especially during long-duration space flights.

Targeting Space-Induced Health Risks Through Genetic Engineering

In the previous discussion of space-related ailments, a common biological factor contributing to microgravity-induced osteoporosis, impaired gut microbiota, and cardiovascular disease from cosmic radiation is the activation of ROS. In the human body, the Nrf2-ARE pathway regulates the detoxification process using antioxidants and eliminates ROS (Nguyen, Nioi and Pickett, 2009) [41]. Thus, the primary focus of the 'superplant' is to contain high amounts of ROS antagonists which upregulate the NRF2-KEAP1 pathway in the body.

NRF2 is a key gene involved in activating cytoprotective genes against ROS species, and KEAP1 is a key negative regulator of NRF2, degrading NRF2 in unstressed conditions and stabilizing it during defense responses (Yamamoto, Kensler and Motohashi, 2018) [69]. However, NRF2 is stabilized upon KEAP1 degradation. Additionally, the medicinal plant should over-express secondary metabolites that facilitate nuclear translocation of NRF2 to upregulate cytoprotective genes and provide antioxidant benefits.

Polyphenols as Natural NRF2 Activators

Several natural compounds can serve as NRF2 activators by promoting its nuclear translocation, leading to the transcription of cytoprotective genes such as glutathione S-transferases (GSTs) and glutathione reductases (GRs) (Yamamoto, Kensler and Motohashi, 2018; Talebi *et al.*, 2021; Liu *et al.*, 2022) [69, 60, 31].

Green tea catechins are one class of polyphenols that are able to induce the NRF2-KEAP1, enhancing cellular defense mechanism.

Additionally, phenolic acids like ferulic acid and chlorogenic acid, commonly present in fruits, along with flavonoids such as catechins and epicatechins, are notable for their potent antioxidant activity. These compounds have the capability to translocate NRF2 and enhance the expression of antioxidant enzymes like heme oxygenase-1 (HO-1) and catalase (CAT) (Kumar and Goel, 2019; Qader *et al.*, 2020) [27, 45]. There is a rising interest in identifying botanical NRF2 activators due to its extreme promise in treatment of several human diseases.

Leveraging Gene Editing to Enhance Medicinal Plant Properties

To create a functional medicinal 'superplant,' gene editing technology should be employed to consolidate multiple medicinal plant properties into one plant and to enhance secondary metabolite production.

However, before gene editing technology can be applied, the medicinal plant needs to be fully sequenced. Currently, medicinal plant genome sequencing is severely lacking compared to crop plants and organisms with mostly fully sequenced genomes, preventing many pathways and genes that control secondary metabolite production from being identified (Alami *et al.*, 2022) [1]. Using bioinformatics and functional genomics could radically accelerate medicinal plant sequencing and gene targeting to improve elucidate secondary metabolite biosynthesis pathways. Modern plant metabolomics is a newly emerging tool used to uncover biosynthetic pathways (Sumner *et al.*, 2015) [59]. Using such screening tools, it would be ideal to identify key metabolic pathways and genes involved in secondary metabolite production and allow for a targeted gene editing approach. Another approach is TILLING (Targeting-Induced Local Lesions IN Genomes), a reverse genetic screening technique used to identify mutant genotypes, and while it has not been employed on medicinal plants specifically, it could be used to optimize detection of genes associated with medicinal properties (Niazian, 2019a) [42].

Tandem duplication (TD) and whole-genome duplication (WGD) could be used to enhance secondary metabolite and antioxidant function and TD has been demonstrated successfully in poppy and tea plants (Alami *et al.*, 2022) [1].

Cis-regulatory sequences such as transcriptional enhancers are able to increase transcription rate and expression rate with transcriptional factors (Schmitz, Grotewold and Stam, 2021) [50]. In Pea plants, the PetE enhancer upregulates genes of interest through induced histone acetylation. This hyper-acetylation increases transcription rates by recruiting more transcription activators (Chua, Watson and Gray, 2003) [8].

CRISPR-Cas 9 systems could be employed to target gene activation and improve nutritional content using sgRNA and Cas9, which creates a double stranded break whereby natural reannealing would induce mutations and gene knockouts (Sathee *et al.*, 2022) [49]. This approach could be used to downregulate the ROS signaling pathway. In rice, OsSRT1 overexpression leads to increased stress tolerance and decreased ROS expression (Huang *et al.*, 2019) [20]. Similarly, by identifying key ROS regulators in medicinal plants, appropriate gene regulation would allow the 'superplant' to better tolerate space environment stress.

Biofortification to Enhance Nutritional Content

Biofortification is the process of enhancing the nutritional quality of food crops by increasing the content of vitamins, minerals, and amino acids. Biofortification could be employed to increase the plant's nutritional quality without compromising its crucial characteristics. Selenium (Se) is a crucial trace element in boosting the immune system, and its deficiency is known to cause weakened immune systems and even cancer (Brown and Arthur, 2001) [4]. Deficiency is largely attributed to the lack of Se in plant soil and consequently in the plant itself. Attempts to restore selenium concentration in plants has been attempted with biofortification. This has been tested on a medicinal plant *Plantago ovata* with Se biofortification, and results demonstrated an increase of production of polyphenols and overall antioxidant content (Dey and Raychaudhuri, 2023) [12]. Similar results have been shown in other medicinal plants such as *Plantago asiatica* and Iranian Borage (Hosseinzadeh Rostam Kalaei, Abdossi and Danaee, 2022; Liao and Zhu, 2022) [19, 30]. This is largely explained due to the increase of ROS under Se-stress signaling. To date, biofortification has no2w3wt been tested on medicinal plants under space conditions such as microgravity and extended radiation exposure. If testing Se-biofortification, it should be noted how space-induced stressors and genetic mutations would interact with Se-stress signaling, and if this combination may change expression levels of polyphenols.

Engineering Space-Resilient Plants

Plants with existing rich levels of antioxidants may not require gene editing for metabolite production but may need modification to support stressors in space. Thus, the second approach would be to edit the plant to better withstand stressors and create space environments that enable the growth of the plants while maintaining its nutrient content.

There are several concerns of growing plants in space, and there is much still unknown. Unique concerns to growing plants in space is exposure to ionizing radiation, which could alter gene expression, and microgravity, which severely alters plant physiology (Vandenbrink and Kiss, 2016; De Micco *et al.*, 2023) [65, 11]. A study found that secondary metabolite production of Cannabis was enhanced in a simulated microgravity setting (Darigh *et al.*, 2022) [9]. High temperature stress and concentrated ultraviolet-B light environments stimulate an increase of secondary metabolites and phenols (Naghiloo *et al.*, 2012; Li *et al.*, 2020) [39, 29]. Further testing of medicinal plants rich in antioxidants such as green tea containing epigallocatechin-3-gallate, should be tested in a microgravity environment to corroborate the finding of enhanced secondary metabolite function. Additionally, very few plants are being grown in space, only leafy vegetables, and little to no medicinal plants have been tested. A third approach would be to gene-edit plants that have already been grown in space to express more polyphenols and antioxidants. Overexpression of transcription factors in tomato plants have been used to increase expression of anthocyanin, a pigment found to be a protective agent against human diseases (Butelli *et al.*, 2008; Nguyen *et al.*, 2023, p. 20) [5, 41]. Strawberries, an antioxidant rich fruit, have been cultivated in space with great potential for survival in a harsh space environment. As mentioned earlier, a strawberry extract supplement diet aids in protection against cosmic radiation and associated heavy ion buildup. Overexpression of FaMAPK5 and FaMAPK10 in strawberries leads to increased anthocyanin enzyme activity (Zhang *et al.*, 2021; Zhang and Zhang, 2022) [73, 72]. Utilizing such a modification would be essential for space travel, especially in situations of limited cultivation opportunities where each fruit should be optimized for nutrition.

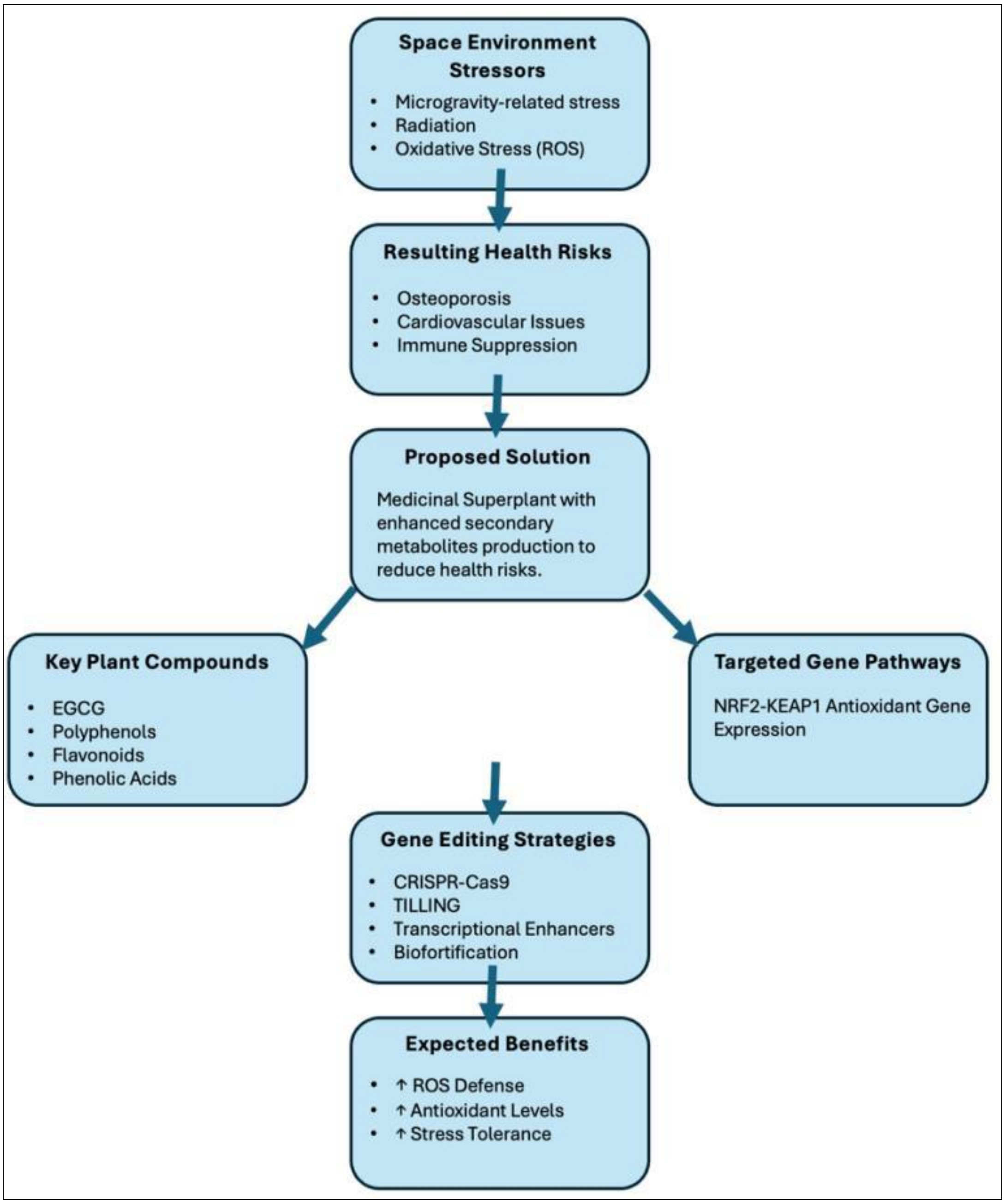

Fig 1: Summary of Medsicinal Superplant Concept for Space Travel

Conclusion

Human space travel is a complicated venture, especially so for long-duration space flights. Given storage constraints and extended time periods, the use of chemical medications may not be the most effective tool to manage space travel ailments. In this review, we have outlined the various types of space ailments such as microgravity, bone-density loss, impaired gut bacteria biome, and cardiovascular health and possible use of medicinal plant treatment for each. We presented the possibility of developing a medicinal 'superplant' using gene-editing mechanisms, creating a viable medicinal supplement suitable for space travel. To our knowledge, there has been no research study to date that introduces this possibility.

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