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Research article

Food systems for long-term spaceflight: Understanding the role of non-nutrient polyphenols in astronauts' health

Menglan Zhao

School of Health, Tianhua College, Shanghai Normal University, 201800, Shanghai, China

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ABSTRACT

Background: Manned space exploration missions have developed at a rapid pace, with missions to Mars likely to be in excess of 1000 days being planned for the next 20 years. As such, it is important to understand and address the challenges that astronauts face, such as higher radiation exposure, altered gravity, and isolation. Meanwhile, until now the formulation of space food systems has not focused on non-nutrients, and has not considered issues arising from their absence during space missions or the possibility of them to solve the challenges caused by space hazards.
Aims: This study investigates, by systematic review, current space food systems and the potential for non-nutrients, such as flavonoids and polyphenols, to counteract radiation- and low gravity-induced degeneration of bone, vision, muscle strength, immune function and cognition.
Results and discussion: A systematic approach found 39 related animal model studies, and that polyphenol dietary interventions have been shown to mitigate radiation-related physiological problems and cognitive decline, as well as reduce the implications of radiotherapy. From the results of these studies, it appears that berry extracts have a significant effect on preventing cognitive problems through attenuating the expression of NADPH-oxidoreductase-2 (NOX2) and cycloocygenase-2 (COX2) in both frontal cortex and hippocampus and immune system problems caused by radiation similar to that experienced in space. For physiological problems like alteration of blood-testicular barrier permeability and oxidative stress in kidney and liver caused by gamma rays and X-rays, various polyphenol compounds including resveratrol and tea polyphenols have a certain degree of protective effect like enhancing metabolism of heart and decreasing DNA damage respectively. Due to the lack of quantitative studies and the limited number of relevant studies, it is impossible to compare which polyphenol compounds are more effective. Only one study showed no difference in the performances of a blueberry extract-fed group and a control group exposed to Fe irradiation after 12 months.
Conclusion: In conclusion, current animal studies have shown that polyphenols can mitigate radiation damage to some extent, but more research is needed to enable the application of a polyphenol diet to actual space flights.

1. Introduction

A lack of energy from food, or disease resulting from deficiency of one or more nutrients have all contributed to the failure of human exploration in Earth's history. For example, scurvy was found to be associated with inadequate vitamin C during Columbus' voyages

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E-mail address: zlm2581@sthu.edu.cn.

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[1]. As we extend our exploration beyond Earth, the nutritional challenges become even more complex and critical.

Humans have been exploring space for over six decades. In 1957, the first human-made object was launched into space, marking the dawn of space exploration [2]. Following this, John Glenn became the first astronaut to eat in space using an aluminum tube in 1962 [3]. Today, more distant and prolonged space flights are being planned, such as NASA's 'three-step' plan for landing on Mars by the 2030s, involving almost 1000 days in space, while China intends to send manned missions to the moon between 2024 and 2030 [4]. These missions necessitate careful consideration of astronauts' nutritional requirements, which extend beyond those of Earth-bound individuals.

Space travel presents unique hazards, namely altered gravity, radiation, isolation, and confinement, each with potential detrimental consequences (Fig. 1). Therefore, in addition to medical care, nutrients in the food matrix are essential to ensure the health of astronauts in overcoming these space-specific challenges during long flights. While macronutrient recommendations for spaceflight are roughly the same as those for Earth, research has shown certain nutrients to be particularly valuable as countermeasures to space-induced physiological problems. For instance, omega-3 can reduce bone loss to some extent [5] and promote neurogenesis [6].

The particular interest for space travel are polyphenols, a category of compounds found in vegetables, fruit, and tea. Polyphenols are the widest group of phytochemicals [11] and have shown promise in addressing space-specific health challenges. What makes polyphenols especially relevant for astronaut health is their potential protective effects against space-specific hazards, particularly radiation.

Space radiation exposure can increase levels of reactive oxygen species (ROS) [12], inducing neuroinflammation in the brain which is related to physiological functions including behaviour, cognition and the central nervous system (CNS) [7]. This space-specific increase in oxidative stress presents a unique challenge for astronaut health that goes beyond normal terrestrial conditions. Polyphenols, along with other antioxidants like vitamin C, vitamin E, and selenium, have shown potential in reducing oxidative stress caused by space radiation [13,14].

Researchers have begun to explore the protective effects of substances such as ginseng and ginkgo biloba specifically on the damage caused by extra-terrestrial radiation [15–17]. More recently, the protective effects of polyphenols on DNA mutation and oxidative stress caused by gamma radiation and ion radiation during space flights have gained attention [18,19]. This focus on space radiation protection distinguishes the potential benefits of polyphenols for astronauts from their general health benefits on Earth.

It is hypothesized that while supplying nutritional needs for space travel based on Earth/terrestrial standards is important, it may be insufficient to fully address the unique challenges of the space environment. An optimized dietary system that includes non-nutrients such as polyphenols may be necessary to promote health and prevent potential space-induced physiological problems that go beyond normal terrestrial health concerns.

The aim of this review is to examine the role of non-nutrients such as polyphenols in mitigating negative implications caused by space-specific hazards like radiation and altered gravity. These conditions are not typically encountered in everyday life on Earth, making the potential benefits of polyphenols particularly relevant for astronaut health.

With the increasing duration of space missions, particularly those planned for Mars, understanding how to mitigate spaceflight-induced health risks is critical. Current space food systems may not adequately address the need for non-nutrient compounds that have shown promise in countering the negative effects of space-specific hazards. This study aims to fill this gap by investigating the potential benefits of polyphenols in the unique context of space travel and its associated health risks.

As the field of space nutrition evolves, it's important to note the growing body of research in related areas. For instance, recent bibliometric analyses have highlighted trends in metagenomics research related to hot springs [20] and developments in forensic genetics [21]. While these studies don't directly address space nutrition, they underscore the rapid advancements in biotechnology and genetics that may have future applications in understanding and addressing the unique nutritional needs of astronauts in long-duration

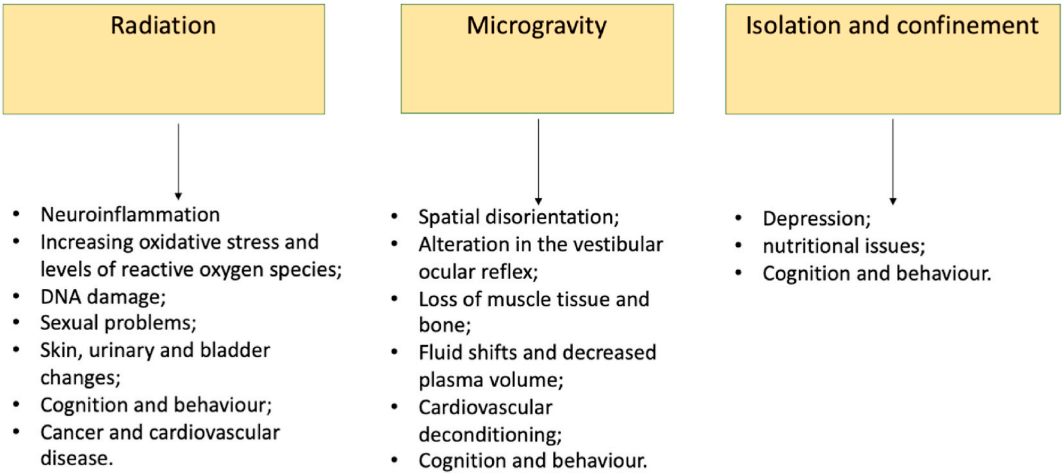

Fig. 1. Possible effects of space hazards on the human body. Note: Information were from Ref. [7,8,9,10].

space missions.

2. Related works

2.1. Early development

Since 1962, when John Glenn first ate applesauce form an aluminium tube in space [3], space food systems have developed steadily, and a new product for the Apollo program - the food bar - was developed, which could be consumed without hands [22]. Not only the quality but also the variety of food has improved. At the same time, astronauts in the Apollo program were the first to have access to hot water [23]. Until now, space food systems have not only been required to meet the nutritional needs of astronauts but must also consider the flavour and shelf life of food, while ensuring food safety and hygiene [24]. The timeline of space food systems indicates that, from initial technological limitations to later technological developments, the variety and quality of food has been continuously improved to meet not only nutritional requirements but also palatability requirements [3].

Regarding current space food systems, they have several elements, including the most basic one: safety, which means food must be free from microbiological, physical, or chemical risks to astronauts. Reliability is also important to prevent problems, and nutrition is an essential element to guarantee astronauts' health. Today, astronauts can eat almost as many kinds of food as they do on Earth, all of which have been specially packaged or processed, such as by dehydration, freezing and irradiation, to meet the special requirements of the weightless environment of space [25]. Space food can be classified as natural form foods (vegetables, fruits and cookies), intermediate moisture foods (applesauce and beef jerky), thermostabilized foods, dehydrated foods and irradiated foods [26]. The International Space Station (ISS) food System has now developed a standard menu to meet astronauts' nutritional needs during space flight, and provides menu cycles for astronauts of 8–16 days [27].

2.2. Macro- and micro-nutrient requirements

Since nutrition status in space is affected by many factors, it is important to monitor astronauts' nutritional status during space flights as it relates to their health, especially with nearly 1000 days planned for Mars missions. There are several ways to monitor astronauts' nutrition, such as using urine and blood tests to determine the amount of each nutrient in the body, or using food frequency

Table 1
Nutrient requirements for a 360-day International Space Station Mission.

Nutrient	Units	Requirement
Energy	KJ (kcal)	WHO[a] equation[b]
Protein	%Total energy consumed	12–15
Carbohydrate	%Total energy consumed	50
Fat	%Total energy consumed	30–35
Fluid	mL/MJ consumed or mL/kcal	238–357 or 1.0–1.5 or 2000 mL/d
Vitamin A	μg retinal equivalent	1000
Vitamin D	mg	10
Vitamin E	mg α-tocopherol equivalent	20
Vitamin K	mg	80
Vitamin C	mg	100
Vitamin B12	mg	2
Vitamin B6	mg	2
Thiamin	mg	1.5
Riboflavin	mg	2
Folate	mg	400
Niacin	NE or mg	20
Biotin	mg	100
Pantothenic acid	mg	5
Calcium	mg	1000–1200
Phosphorus	mg	1000–1200 <1.5 times Ca intake
Magnesium	mg	350
Sodium	mg	1500–3500
Potassium	mg	3500
Iron	mg	10
Copper	mg	1.5–3.0
Manganese	mg	2.0–5.0
Fluoride	mg	4
Zinc	mg	15
Selenium	mg	70
Iodine	mg	150
Chromium	mg	100–200

[a] WHO, World Health Organization.

[b] WHO equation: accounting for weight, age, sex, and moderate activity levels. Source [36].

questionnaires and food diaries to understand how much food an astronaut is actually intaking [28].

Table 1 indicates the basic requirements of macronutrients and micronutrients for the ISS, covering almost all nutrients, but there is no reference to non-nutrients which can act as antioxidants to modulate metabolic pathways [29]. In addition, in comparison to the recommend daily allowance on Earth, some nutrients like vitamin D, vitamin E, vitamin C and vitamin B12, are almost doubled in the space environment [30]. Vitamin D deficiency may be due to lack of ultraviolet (UV) exposure caused by the spacecraft's UV shielding, which therefore increases the need for adequate vitamin D supplementation in food, being an important nutrient [31]. At the same time, according to the available evidence, astronauts with vision problems also have changes in the circulating metabolites of the one-carbon metabolic pathway, resulting in increased vitamin B12 intake [32]. Even though antioxidants like vitamin C and Vitamin E have been considered, their mechanisms are different to non-nutrients such as polyphenols [33–35]. Cooper et al. (2017) conducted a study to measure the nutritional stability of 109 processed and pre-packaged space foods over 3 years at room temperature, including 24 micronutrients. The study suggested that the level of most micronutrients was inadequate before or during storage. It is predictable that the loss of nutrients from food due to radiation and microgravity in space will be even more severe.

With the continuous development of the space industry, the planned flights to Mars should involve long-duration explorations in space or similar missions, which will bring more challenges, so ensuring sustainable and intact food and nutrition systems is essential to guarantee the health of astronauts.

2.3. Potential non-nutrients requirements

Non-nutrients are a variety of components in food including natural and synthetic compounds, polyphenolic compounds and fibre, food additives and preservatives [37]. Polyphenols - one type of non-nutrients - are believed to provide beneficial effects for neurodegenerative diseases, inflammation, cardiovascular health, type 2 diabetes and cancer [38]. Dietary polyphenols are secondary metabolites of plants found in nature and are mainly found in vegetables and fruits [39]. More than 8,000 phenolic structures are known, of which more than 4,000 flavonoids are recognized [40,41]. As the largest group of phytochemicals, a diet rich in polyphenols has been shown to have health benefits [42].

According to research, the formation of many chronic diseases is related to oxidative stress involving reactive oxygen species. By providing electrons or hydrogen atoms, polyphenols can neutralize free radicals, inhibit the generation of free radicals, reduce the oxidation rate, and thus play an antioxidant role [43]. In addition to affecting free radicals, polyphenols act as auxiliary antioxidants, assisting in the regeneration of some vitamins [44]. However, until now the formulation of space food systems has not focused on non-nutrients, and has not considered issues arising from their absence during space missions. Diets lacking in non-nutrients can have various impacts on human health, which is obviously of great importance for astronauts on space missions [45]. For instance, studies have highlighted the influence of flavonoids on human memory and cognition, as well as a potential role in reducing blood pressure [46,47]. Such studies suggest that by improving blood flow to the brain and peripheral blood flow, flavonoids can reduce risks of both cardiovascular and cerebrovascular diseases. As astronauts must carry out various complicated and technical tasks in unusual high-risk situations, it is crucial that nothing negatively effects their cognitive abilities and potentially endangers their lives and the success of the mission. Likewise, any factors that could affect health during missions, such as high blood pressure and ways to control it, should be explored, for similar reasons. Therefore, consideration of the effects of non-nutrients like fruit-flavonoids and polyphenols is of obvious relevance to space diets and space missions generally.

3. Methodology

3.1. Search strategy

The literature search regarding polyphenols' benefits in terms of countering space radiation-induced physiological problems utilized four electronic databases (Web of Science, PubMed, Scopus and Cochrane), and was run in June 2021. The hypothesis of this research is that non-nutrients such as polyphenols can reduce the risk of radiation injury. The search strategy consisted of two key elements: one being polyphenols including food rich in phenolics, flavonoids and extracts of some foods; and the other being space radiation and simulated irradiation. The search terms were (pomegranate OR flavonoids OR blueberry OR blueberries OR resveratrol OR cocoa OR polyphenols) AND (“proton irradiation'' OR 56Fe OR ″space radiation'' OR “ionizing irradiation”), and they were searched for in the titles and abstracts of papers in all databases. The polyphenols promote health and prevent space-induced physiological problems due to their antioxidant, anti-inflammatory, and neuroprotective properties. These properties help mitigate oxidative stress, which is heightened in space environments due to increased radiation exposure. In order to prevent omission of correlated articles, papers in previous systematic reviews were identified.

3.1.1. Mechanism of polyphenols mediated outcomes

Polyphenols exert their beneficial effects through various mechanisms across different physiological systems. These mechanisms include:

Antioxidant activity

Polyphenols neutralize free radicals and reduce oxidative stress, which is crucial in protecting cells from damage caused by space radiation [48].

Anti-inflammatory effects

Polyphenols modulate inflammatory pathways, thereby reducing inflammation and potentially preventing chronic diseases [49].

Neuroprotective properties

Polyphenols enhance cognitive functions by protecting neurons, improving synaptic plasticity, and promoting neurogenesis [50].

Cardiovascular benefits

Polyphenols improve endothelial function, reduce blood pressure, and prevent atherosclerosis, which are vital for maintaining cardiovascular health in space [51].

3.2. *Eligibility criteria*

Eligibility criteria were full text available in English, randomised controlled human study, animals or human trials NOT in vitro or cell trials, polyphenols (including all sub-classes and relevant foods, also the only variable) in real space situation or using simulated space radiation and original study published before June 23, 2021.

3.3. *Study selection*

For the obtained articles, the duplicates were first removed, and then eligibility criteria were used to review the titles and abstracts to remove articles that were unrelated or not relevant to the criteria. For the articles that were too unclear, the full text was reviewed with the criteria, and the articles that met the eligibility criteria were included. The process is illustrated in Fig. 2.

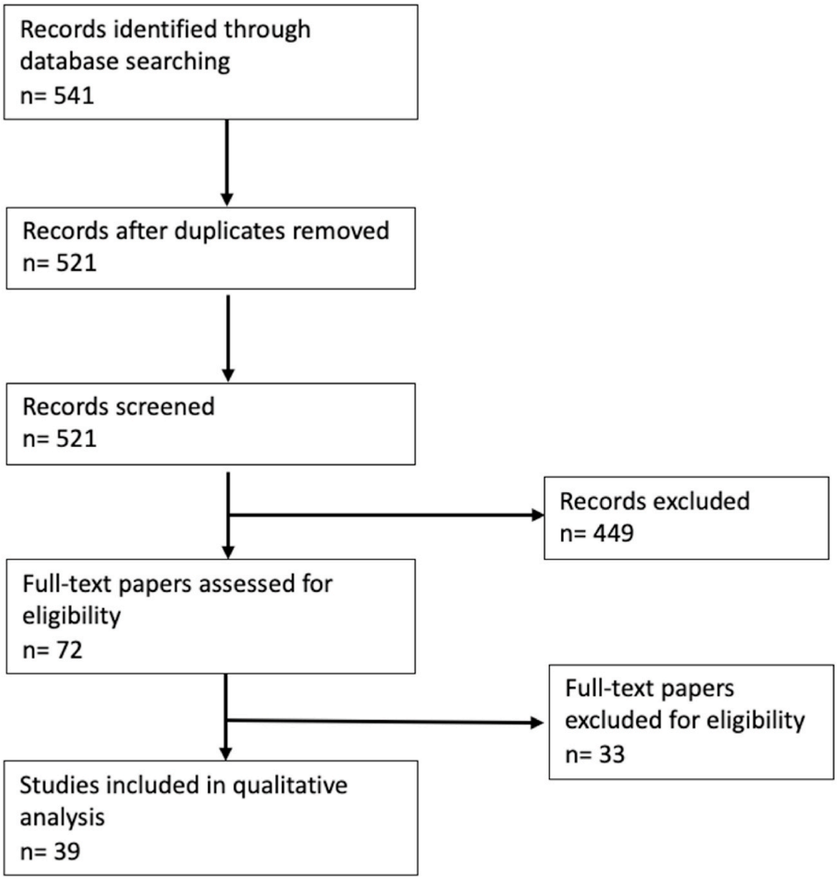

Fig. 2. Prisma flow diagram for selecting articles to be included in a systematic review.

3.4. Data collection

Data collection was conducted by study design, the details of the intervention including dose and time of radiation and type of polyphenols, reported outcomes, and the results in different groups. The Cochrane Collaboration tool was used to assess the bias of each included study on criteria of outcome [52].

4. Results

Through review and screening, there is no human study that compliances the eligibility criteria. The design and results of the 39 studies are presented in three tables. Tables 2–4 present the protective effects of polyphenols on: 1) radiation-induced cognitive and behavioral problems; 2) physiological outcomes and; 3) complications of radiotherapy. All the studies were done *in vivo* on mice or rats. Three types of radiation were used in the studies selected, X-ray, ϒ-ray and ^{56}Fe particles. These 39 studies included polyphenol dietary intervention before exposure and dietary intervention after exposure. The number of studies using X-rays was 3, while there were 28 studies using ϒ-ray and 8 studies using ^{56}Fe particles. Radiation doses varied across all studies, ranging from 0.25 to 22 Gy.

The summary tables (Tables 2–4) contain all data on the protective effects of polyphenols on radiation-induced problems, including cognitive and immune problems, physiological problems caused by oxidative stress and radiotherapy induced damage of normal tissue. Results of all studies showed positive effects of polyphenols or food rich in polyphenols, on the three types of radiation stresses, including hesperidin, resveratrol, pomegranate, blueberry and strawberry, Epigallocatechin-3-gallate, gossypetin. Only Rabin et al.'s study conducted in 2005 showed no difference in performance between the two groups of mice treated with 2 % blueberry extract compared to a control group that was also irradiated. The group treated with 2 % strawberry extract performed better than the control group.

These studies examined the benefits of polyphenols from a radiation perspective. The results suggest that polyphenols can mitigate radiation-related cognitive problems and neurocognitive decline. The study also found that polyphenols can improve radiation-induced problems in specific areas of the brain [54]. In addition, blueberry extract can help prevent radiation-induced liver cell damage [8], effectively reducing oxidative stress, and thus have a protective effect on a number of physiological problems involving the liver, kidneys and cardio-metabolism [63,62]. At the same time, a diet rich in polyphenols has been shown to reduce DNA damage and reduce levels of tumour necrosis [66,67,69]. And it can be inferred from all included studies that for cognitive problems, berry extracts and resveratrol have the most significant effect, and for physiological problems they also show a protective effect, as well as tea polyphenols and other polyphenolic compounds.

These studies used many doses of polyphenols and flavonoids, ranging from 5 mg/kg to 200 mg/kg, while the intervention time was

Table 2
Studies on the effect of diet polyphenol intake on outcomes related to cognition and immune system.

Time for assessment	Polyphenol type and dose	Subjects	Radiation type and dose (Gy)	Outcome	Reference
56 days	20 g/kg diet, 2 % blueberry or strawberry extract	Male Sprague-Dawley rats	^{56}Fe, 1.5	Protected hippocampally mediated behaviour and intact striatal function respectively.	[53]
28 days	20 g/kg diet, 2 % blueberry extract	Male Sprague-Dawley rats	^{56}Fe, 0.25	Attenuated protein carbonylation in the hippocampus and frontal cortex.	[54]
90 days	20 g/kg diet, 2 % blueberry or strawberry extract	Rats	^{56}Fe, 1.5	Reduced the accumulation pf p62 and PHF-tau in hippocampus.	[14]
21 days	0.6 mg polyphenols/day from pomegranate	Male and female C57BL/6 mice	γ-ray, 2	Provided neuroprotection from the effects of radiation-induced cognitive and behavioural skill deficits. **Proton irradiation affects males more than females in motor function.**	[19]
3 days	2.5 and 5 mg/kg/day, Epigallocatechin-3-gallate	Adult male Wister rats	γ-ray, 4	Inhibited the increase of protein carbonyl level in the hippocampus and protected the DNA damage and apoptosis in the hippocampus.	[55]
37 days	20 mg/kg, resveratrol	Male C57BL/6 mice	γ-ray, 6	Attenuated the reduction of the level of IL-2, IL-4, IL-7 and IFN-γ.	[56]
56 days	20 g/kg diet, 2 % blueberry or 2 % strawberry	Male Sprague-Dawley rats	^{56}Fe, 1.5 and 2.5	Up regulated some protective stress signal genes in the brain.	[57]
24 days	50 mg/kg, hesperidin	Male albino rats	γ-ray, 5	Attenuated biochemical disorders in brain tissues.	[58]
14 days	20 g/kg diet, 2 % or4% strawberry or blueberry extract	Sprague–Dawley rats	^{56}Fe, 0, 0.5, 0.8, 1, 1.5 and 2	Ameliorated the disruptive effects of neurocognitive performance.	[59]
60 days	20 g/kg diet, 2 % blueberry or strawberry extract	Male Sprague–Dawley rats	^{56}Fe, 1.5	The performance of the radiated animals given blueberry extract did not differ from the radiated animals given the control diet 12 months after irradiation. Radiated animals fed the strawberry performed better than control and blueberry diet animals.	[60]
56 days	20 g/kg diet, 2 % blueberry or strawberry extract	Male Sprague–Dawley rats	^{56}Fe, 1.5	Reduced the effects of oxidative stress of neurochemical and behavioural changes in rats.	[61]

Table 3
Studies of the effect of diet polyphenol intake on outcomes related to physiological problems.

Time for assessment	Polyphenol type and dose	Subjects	Radiation type and dose (Gy)	Outcome	Reference
28 days	200 mg/kg, blueberry extract	Mature male albino rats	γ-ray, 8	Enhanced antioxidant enzyme activities and reduced lipid per-oxide contents.	[8]
42 days	5 mg/kg/d or 25 mg/kg/d, Resveratrol	The C57Bl/6NCrl female mice	γ-ray, 2	Groups irradiated with resveratrol had enhanced metabolism of heart compared to those irradiated without resveratrol supplementation.	[62]
21 days	100 mg/kg/d, Chrysophyllum. caimito extract	Adult male albino rats	γ-ray, 6	Protected the oxidative stress in liver and kidney tissues; reduced the biochemical disorders of liver and kidney.	[63]
Injection	100 mg/kg, polydatin	Male wild-type C57BL/6 mice	γ-ray, 4	Reduced the level of reactive oxygen species and the concentration of the oxidative products; alleviated testes injury and retained sperm viability.	[64]
15 days	50 mg/kg, quercetin	Adult male Wistar albino rats	γ-ray, 10	Effectively decreased oxidative stress and inflammatory damage to both ileum and colon tissues.	[65]
14 days	50 mg/kg, 100 mg/kg and 200 mg/kg, dark tea extract	Male C57BL/6 mice	γ-ray, 7, 7.5 and 6	Decreased DNA damage and levels of reactive oxygen species and increased the numbers of hematopoietic cells.	[66]
14 days	Mixture of green tea extract (GTE): grape seed extract (GSE) at dose 100: 200 mg/kg	Male albino rats	γ-ray, 5 and 10	Decreased the level of pro-inflammatory cytokines, Tumor necrosis factor-α and C-reactive protein.	[67]
3 days	200 mg/kg, black mulberry extract	Male Wistar rats	γ-ray, 3 and 6	Reduced oxidative stress, e.g. reduced genotoxicity and cytotoxicity.	[68]
3 days	75 mg/kg, naringin	Male Swiss albino mice	γ-ray, 6	Significantly reduced radiation-induced nuclear DNA damage and cell death.	[69]
7–21 days	25 % by weight, dried plum	Male mice	^{56}Fe, 1	Preserved cancellous percent bone volume and reduced the expression of genes related to bone resorption.	[70]
27 days	50 mg/kg Epigallocatechin-3-gallate	Ten-week-old male mice (C57BL/6)	X-ray, 2	Alleviated blood-testicular barrier permeability and inhibit testicular steroidogenesis.	[71]
3 days	30 mg/kg, gossypetin	Swiss albino male mice	γ-ray, 5	Ameliorated oxidative stress in liver and prevented deactivation of redox signaling pathway.	[72]
3 h, inject	0, 10, 20, and 40 mg/kg, apigenin	Male CBA/CaJ mice	γ-ray, 3	Suppressed the activation of NF-kappa B in bone-marrow-derived macrophages and reduced the levels of proinflammatory cytokines.	[73]
5 days	10, 15, 20, 25, 40, and 50 mg/kg, extract of *Panax ginseng*	Male Swiss albino mice	γ-ray, 6, 8 and 10	Protected the membranes from oxidative damage.	[74]
15 days	700 mg/kg/day, Grewia asiatica fruit	Swiss albino mice	γ-ray, 5	Protected DNA and RNA in testis.	[75]
7 days	50 mg/kg and 100 mg/kg, hesperidin	Male Sprague–Dawley rats	γ-ray, 1,3 and 5	Protected hepatic cells from damage and against oxidative stress.	[76]
30min, inject	30 mg/kg RH-3 from Hippophae rhamnoides berries	Swiss albino strain ‘A’ male mice	γ-ray, 5 and 10	Enhanced the spermatogonia proliferation and the stem cell survival and reduce sperm abnormalities.	[77]
21 days	50 and 100 mg/kg Ginkgo biloba extract	Male Wistars rats	γ-ray, 4.5	*Ginkgo biloba* extract significantly reduced the adjusted clastogenic score.	[78]

shorter for the high-dose polyphenol diet intervention [8,68,87]. Dietary intervention studies with blueberry and strawberry extracts usually involved relatively high doses and periods of 4–8 weeks [54,8,53]. Moreover, if the intervention was by injection, the dose was also small, and usually several hours before or after the irradiation [77,73]. However, the intervention dose of polyphenols was also dependent on the type. From these studies, it was observed that epigallocatechin gallate intervention doses were generally small, with 6.25 mg/kg, 12.5 mg/kg and 25 mg/kg used in Ref. [88] and 2.5 mg/kg and 5 mg/kg used in Ref. [55] only 3 days before irradiation, which still had a protective effect on mice that were exposed to radiation.

In the studies on the effects of radiation on cognition, blueberry and strawberry extracts were used as dietary interventions, and the type of radiation used was ^{56}Fe particles. Almost all relevant studies showed that blueberry and strawberry extracts improve the cognitive effects of radiation, including the hippocampus’s influence on behaviour. The only exception was Rabin et al.’s study of 2005, which showed no difference in performance between the two groups of mice treated with 2 % blueberry extract compared to a control group that was also irradiated. The group treated with 2 % strawberry extract performed better than the control group.

All the studies used three main types of radiation: ^{56}Fe radiation, X-rays and ϒ-rays. As Fig. 2 shows, the average doses of these three rays were different, with ^{56}Fe ions having a relatively small radiation dose and ϒ-rays having a relatively large radiation dose, as is shown in Fig. 3.

In addition, the results of Dulcich and Hartman’s [19] study which used ϒ-ray and pomegranate as diet intervention indicate that polyphenols could alleviate radiation-induced cognitive and behavioral deficits, and that radiation affects males more than females in

Table 4
Studies on the effect of diet polyphenol intake on outcomes related to implications of radiotherapy.

Time for assessment	Polyphenol type and dose	Subjects	Radiation type and dose (Gy)	Outcome	Reference
30 min, Inject	150 mg/kg, amifostine	Male C57BL/6 mice	γ-ray, 7.5 and 3	Amentoflavone significantly attenuated radiation-induced oxidative stress and affected gene tumour necrosis factor alpha-induced protein 2.	[79]
6 days	40 mg/kg, resveratrol	Male C57BL/6 N mice	γ-ray, 7	Improved intestinal morphology, decreased apoptosis of crypt cells, maintained cell regeneration.	[80]
14 days	0.2 g/kg tea polyphenols	Female Wistar rats	γ-ray, 15	Attenuated the lesions of submandibular glands and apoptosis of cells was not apparent.	[81]
20 days	50 mg/kg/day, Punica granatum peel extract	Male Sprague Dawley rats	X-ray, 8	Decreased the levels of pro-inflammatory cytokines and lactate dehydrogenase.	[82]
20 days	10 mg/kg/day, resveratrol	Male Sprague Dawley rats	X-ray, 8	Increased the level of glutathione and decreased the level of malondialdehyde and collagen content in the liver and ileum tissues.	[83]
6,48 and 72 h	200 mg/kg Pycnogenol ® , or 300 mg/kg Pycnogenol 200 mg/kg Pycnogenol ® , or 300 mg/kg Pycnogenol 200 mg/kg Pycnogenol ® , or 300 mg/kg Pycnogenol 200 mg/kg or 300 mg/kg, Pycnogenol	Male Wistar rats	15 Gy delivered by Varian Clinic 6/100 γ-ray, 15	Animals receiving treatment with Pycnogenol had better condition of mucosal layers than those without pysnogenol.	[84]
30 min	100 mg/kg, Hesperidin	male Sprague-Dawley rats	γ-ray, 22	The expression of Vascular endothelial growth factor gene was 25-fold overexpressed in comparison to control group.	[85]
7 days	25 mg/kg or 50 mg/kg rutin-enriched coriander extract	Male C57BL/6 (CD45.2) mice	γ-ray, 7, 6 and 4	The survival rate of irradiated mice was significantly improved, and the hematopoietic stem and progenitor cells frequency was increased.	[86]
15 days	300 mg/kg, Moringa oleifera leaf extract	Swiss albino male mice	γ-ray, 5	Prevented the lipid peroxidation and restored the glutathione levels.	[87]
30 days	6.25 mg/kg, 12.5 mg/kg And 25 mg/kg, Epigallocatechin-3-gallate	Male Kunming mice	γ-ray, 6	Increased the immune organ index, then prevented significantly the immune system damage.	[88]

motor function.

In the included studies, there were no cases of poisoning, or side effects, from any polyphenols including chemical agents or food extracts.

5. Discussion

The results so far suggest that substances such as polyphenols and flavonoids may have a protective effect against radiation-related health problems, both physiologically and in age-related cognitive decline. However, to fully consider the positive effects of

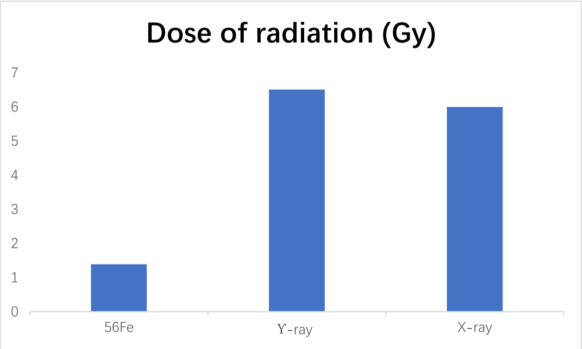

Fig. 3. The average dose of different radiation in all included studies. The average dose of 56 Fe is 1.39 Gy, the average dose of ϒ-ray is 6.51 Gy, the average dose of X-ray is 6.00 Gy.

polyphenols on cosmic rays and possible physiological problems associated with radiotherapy, as well as the risk of secondary cancers, the overall study's strengths and limitations need to be evaluated. During space flight, blood and urine collection, food intake monitoring, and changes in astronauts' body mass are measured to determine their nutritional status. Under the intervention of polyphenols, comparative changes of data can be carried out to understand the role of polyphenols in the space environment, and research on different kinds of polyphenol compounds can also better determine the most effective polyphenols.

5.1. Advantages and prospects

The existing studies have been done on mice and rats because of the unethical nature of human experimentation, and possibly the early stage of the field in this area. However, animal models are difficult to apply to humans because of differences in metabolic rate, lifespan and body mass between humans and animals [89]. The studies included above are designed to optimize the dose of radiation to achieve more valuable results. Most experiments use doses of radiation higher than those experienced by space flight, X-ray tests and everyday high-risk jobs. Radiation exposure is generally acute rather than chronic in studies, depending on the endurance and lifespan of the mice, and the X and gamma rays used in the experiments do not have sustained effects on the central nervous system at low doses, so increasing the dose would yield more accurate results. In addition, the experimental studies need to ensure the lowest doses that can cause the molecular changes *in vivo*, otherwise they are unable to assess whether the polyphenols have effect. According to studies, the 50 % fatality rate radiation dose for rats is 8 Gy, while 50 % fatality rate for humans is 3 Gy, so using high doses of radiation is reasonable and necessary [90].

The aim of this study was to establish a systematic review of the protective effects of polyphenols on the effects of radiation and thus to provide an intervention in the diet of astronauts. The positive effects of polyphenols have been largely confirmed in animal studies.

As for coffee and tea, which represent a lifestyle food for many people rich in polyphenols, they are also good for the human body [91,92]. Adding such foods to space food systems not only helps astronauts feel a sense of home to alleviate the psychological problems associated with long-term space flight, but also combats radiation from space flight because they are rich in polyphenols.

Ever since antioxidant research started with ginkgo biloba, concerns have been raised over the last century about the effects of radiation on the central nervous system [93], which can affect astronauts' quality of life after returning from space. Dietary interventions to reduce radiation damage to astronauts' physiological systems are important, so further research into the role of polyphenols in radiation is necessary. At the same time, the impact of radiation is very widespread, such as our daily exposure to ultraviolet light. With the incidence of skin cancer on the rise [94], and studies showing that flavonoids have a protective effect on skin tissue caused by ultraviolet light, this systematic review study becomes more valuable to the wider population [95].

5.2. Limitations

Although the included studies cover many kinds of polyphenols, there are still some polyphenols which have not been taken into consideration, such as capsaicinoids in chili peppers. It would therefore be a bit short-sighted to say that all polyphenols have a protective effect against radiation-induced problems. In addition, without human experiments, the existing body of animal model studies is limited and not large enough.

The tumorigenesis aspect was also not covered in the above studies, and there is some evidence that radiation may cause tumorigenesis [96]. However, since tumor formation is a long-term process, it may be difficult to observe in the short term via animal experiments. As for the astronauts who have experienced space flight, there are no relevant reports after returning to Earth, and it is difficult to completely attribute their subsequent physical condition to space flight. Therefore, the prevention of radiation-induced tumors by polyphenols has not been covered in this study.

In all included studies, animals were given a polyphenol diet before or after radiation, and the extracts used, including blueberries, were preserved in a non-radioactive state, which is not what happens in space. Polyphenols or foods containing polyphenols are exposed to radiation in space, so it is impossible to estimate the actual absorption rate and antioxidant capacity of polyphenols as a result of radiation. In addition, studies have focused on the effects of radiation on the antioxidant capacity of some plants and the DNA damage on seeds in space [97,98]. Although the effects of radiation cannot be proved significantly according to the studies, food should be irradiated together with subjects in future experiments to replicate space conditions.

The possibility of adverse reactions to high doses of polyphenols was not discussed in the experiments. The possible harmful effects of the oestrogen activity of isoflavones and the inhibition of non-haem iron absorption by the consumption of polyphenols should be further studied and evaluated to avoid negative effects [99]. Current studies suggest that understanding nutrient bioavailability is key to further critical assessment of nutrient effects and toxicology [100,101]. Some of the included studies applied dietary interventions after radiation, but most applied dietary interventions before radiation. However, radiation can also affect the gut microbiome, which can affect the absorption of polyphenols or other nutrients [102]. Also, astronauts are exposed to radiation when they eat in space, so the design needs to be adjusted to meet this challenge.

The existing studies used berry extracts or polyphenols as part of the dietary intervention, rather than the food itself. But in fact, the food is not the same as supplements and extracts. Although they guarantee a dose of one or more nutrients, without the matrix of the food that contains trace elements, sometimes the desired effect will not be achieved. In addition, the synergistic effect produced by several nutrients is different from single nutrient effect [103]. Protein bars rich in polyphenols are already being developed at NASA, and this extra compound requires its bioactive agent to be in an active form when it reaches the gastrointestinal tract to ensure effectiveness [104]. Finally, radiation protection drugs such as indralin are already being considered to counter the possible effects of cosmic radiation [105], so foods rich in natural antioxidants should be taken seriously. It is therefore clear that more research is needed on fortified food.

5.3. Gaps between research and reality

On long space flights, the preservation of fresh vegetables and fruits is a problem. Although the research is still in the stage of using extracts, it is necessary to consider the preservation of fresh fruits and vegetables, such as freeze-drying and space-growing methods, since the food itself would not only provide the most complete nutritional system, but also give astronauts a sense of normality. In space cultivation, the main limitation is radiation, which studies have shown can damage a seed's DNA and affect its gene expression [98]. Freeze-drying technology has been used in space flight already, and freeze-dried food actually loses some vitamins and other important biological compounds. But to date it has been a relatively reliable method [106].

3D printing technology has great potential in the food industry. Not only can it create the desired shape and texture, but it can also customize the nutrients [107]. It has not been used in space food systems, so this is one technology that could be considered to provide a richer variety of foods to meet the visual, tactile and nutritional needs of astronauts.

6. Conclusion

The results so far suggest that polyphenol dietary interventions can mitigate the physiological effects of ionizing and gamma radiation, such as oxidative stress, immune system problems, and cognitive problems. This study uniquely addresses the gap in knowledge regarding the role of non-nutrient polyphenols in mitigating spaceflight-induced physiological issues, providing a novel perspective on enhancing astronaut health through diet. Therefore, from a systematic review of animal experiments, it can be concluded that polyphenols have a certain positive effect on radiation-induced problems. For cognitive problems, berry extracts and resveratrol have the most significant effect, and for physiological problems they show a protective effect as well. Trying to add berry extract or resveratrol to an astronaut's diet could have implications for future optimization of nutritional systems in space. At the same time, the conclusion has certain significance for reducing the radiation hazards in space flight, and has reference significance for the damage of surrounding tissues caused by radiotherapy. However, some unconsidered problems need to be solved.

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Declaration of competing interest

The authors declare that they have no competing interests.

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