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Author(s): Anthony C. Muscatello

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Nutritional Supplements as Radioprotectors— A Review and Proposal

Anthony C. Muscatello
Los Alamos National Laboratory
Los Alamos, NM 87545
Mailing Address: Rocky Flats Environmental Technology Site
P.O. Box 4013, T130A
Golden, CO 80401

Abstract

The scientific literature contains several reports that show nutritional substances, such as vitamins, minerals, and phytochemicals (plant chemicals), provide substantial radioprotective effects in animal studies. Incorporating these substances to the human diet, already voluntarily practiced by a large segment of the population, in addition to providing other favorable health effects, may also provide a radioprotective effect. This potential radioprotective effect would be very useful in mitigating the effects of occupational radiation exposure to astronauts (especially future Mars explorers), airline crews, nuclear workers, both commercial and government, and populations exposed to nuclear accidents, e.g. Chernobyl. This paper reviews the existing evidence of radioprotective effects by nutritional supplements and proposes that their efficacy be evaluated, first with animal studies, followed by human tests with astronauts and cosmonauts on long-term missions, such as to the Mir space station and the International Space Station (ISS).

1. Introduction

In the early 1950s, Lushbaugh and co-workers at the Los Alamos Scientific Laboratory (1,2) found that fresh aloe vera gel was very effective in aiding the healing of beta radiation-induced skin burns induced by exposure of rabbits to radioactive strontium. Healing times were cut to less than half. This discovery has led to the isolation of the active component of aloe vera gel, acemannan. A key discovery in more recent years is that administration of acemannan has shown strong radioprotective effects in rats subjected to sublethal doses of radiation (3). Acemannan is currently commercially available as a nutritional supplement, and acts as an immune system stimulant/modulator. Acemannan has been found to be non-toxic (4).

Hall (5) has reviewed chemical radioprotectors, with an emphasis on their use in radiotherapy. Amifostine (WR-2721) appears to be the best synthetic chemical radioprotector for radiotherapy. The structure of amifostine is $\text{NH}_2(\text{CH}_2)_3\text{NHCH}_2\text{CH}_2\text{SPO}_3\text{H}_2$. Hall reports that Apollo astronauts probably carried WR-2721 to the moon to protect themselves from high-energy protons in case of a solar flare once outside the Earth's protective magnetic field. The astronauts would have been exposed to an estimated dose of several Gray (Gy), equivalent to several hundred rads, a potentially fatal dose. WR-2721 provides a Dose Reduction Factor (DRF) of two to three and would greatly reduce the health effects of a solar event. Unfortunately, chemical

radioprotectors are toxic at levels close to the effective dose (6). The dose-limiting toxicity of amifostine is hypotension, or low blood pressure. WR-2721 also has a serious limitation in that it provides radioprotection to the bone marrow, the gut, and the salivary glands, but it provides poor protection to the lungs, and no protection to the brain.

As will be shown below, there are non-toxic natural products such as acemannan, which provide radioprotection, potentially as good or better than chemical radioprotectors. This proposal recommends that a systematic evaluation of a group of commercially available nutritional supplements (nutraceuticals) be performed to determine their efficacy in providing radioprotection of humans, especially in the context of future Mars exploration. Any other beneficial health effects should also be evaluated.

2. Mechanism of Radioprotection

Hall (5, p. 184) describes the accepted mechanism of radioprotection. Briefly, radiation absorption by living cells induces the production of free radicals. Normally, oxygen in the cells reacts with the free radicals producing highly reactive oxygenated free radicals, leading to the breaking of chemical bonds and cell damage. Radioprotectants scavenge the free radicals before they can react with oxygen, allowing restitution of the original target molecule.

There is a limitation to the effectiveness of free radical scavenger radioprotectors. According to Hall (5, p. 185), "...they are effective against the indirect action of x-rays and have little effect with high linear energy transfer radiations in which direct action is dominant. Since the indirect action accounts for about two thirds of the biological effect of x-rays, a perfect protector that scavenged all of the free radicals could have a dose reduction factor approaching 3." However, the radioprotector effect is not completely described by this simple mechanism. Again according to Hall (5, p. 185), "This simple description of the mechanism of action of sulfhydryl radioprotectors is intellectually satisfying, but it is clearly not the whole story since radioprotectors of this class have more effect with densely ionizing radiations (such as neutrons) than would be expected. Other factors must be involved that are not fully understood." This is in reality a positive development for radioprotection for spacefarers because much of the hazard is from particulate radiation such as protons and cosmic rays, which have high linear energy transfer (LET). Otherwise it would appear to be more difficult to provide radioprotection against such radiation.

Livesey and Reed (7) discuss radioprotection in detail, especially regarding the role of oxygen, further explaining the simplified mechanism described by Hall. Lett (8), for example, states "Cells are more sensitive to sparsely ionizing radiations when irradiated in the presence of oxygen rather than nitrogen...a phenomenon known since 1923. For mammalian cells, the difference in sensitivity, which is measured as an oxygen enhancement ration (OER) is approximately 3 at an LET of $\sim 1 \text{ keV } \mu\text{m}^{-1}$ and disappears progressively as the LET is increased over the range 20-200 $\text{keV } \mu\text{m}^{-1}$..." Irrespective of the detailed mechanism, much useful empirical work has shown that naturally occurring substances show radioprotective effects. Some of the more recent studies are described below.

3. Radioprotection by Carbohydrate Molecules

Roberts and Travis (9) have shown that a "wound dressing gel [containing acemannan extracted from aloe leaves] reduces acute radiation-induced skin reactions in C3H mice if applied daily for at least 2 weeks beginning immediately after irradiation." The mice were irradiated on the thigh with single doses of gamma rays ranging from 30 to 47.5 Gy (3000

to 4,750 rads). Skin damage reduction by topical application of the acemannan-containing gel was significant compared to no gel, personal lubricating jelly, and healing ointment. These authors note that "acemannan ... induces secretion of several cytokines, including tumor necrosis factor and interleukin-1. Some of these cytokines are thought to regulate wound healing and might also affect acute radiation injury." These results show that acemannan has a strong post-irradiation radioprotective effect.

A similar study (10) that showed no effect of an aloe vera gel on women receiving radiation therapy did not use the same stabilized gel as Roberts and Travis (9). Without stabilization, an enzyme from the leaves of the aloe vera plant destroys the acemannan and no healing effect is observed (1,2).

As noted above, a study of acemannan (3) showed that it exhibits a pre-irradiation radioprotective effect on mice exposed to 7 Gy of radiation. The radioprotective effect was observed as a hematopoietic (blood-formation) effect in the irradiated mice when administered at 1 mg per animal. Higher and lower doses were not as effective. The authors note that acemannan "is a polydispersed beta-(1,4)linked acetylated mannan isolated from the *Aloe barbadensis* plant. It has multiple therapeutic properties including activity in wound repair and as a biological agent for the treatment of neoplasia in animals as well as the ability to activate macrophages."

A carbohydrate which is similar to acemannan, glucan, has been tested for its pre- and post-irradiation radioprotective effect on mice (11). Glucan is "a beta-1,3 polysaccharide immunomodulator isolated from the inner cell wall of the yeast *Saccharomyces cerevisiae*" (11). Patchen *et al.* found glucan to be an effective radioprotector in that injection of 75 mg/kg 20 hr before irradiation of mice with 8 g Gy of ⁶⁰Co radiation gave 100% survival of the mice vs. 100% lethality without treatment. The mechanism of radioprotection is probably induction of macrophage production and release of interleukin-1 (IL-1). The macrophages are activated by the glucan and "both nonspecifically defend the host against opportunistic infections and produce and release several cytokines capable of stimulating the proliferation of protected hematopoietic progenitor cells." In other words, the glucan stimulates the immune system and protects the blood-forming cells that are otherwise very susceptible to radiation damage. Acemannan probably has a similar radioprotective effect since it is well known to modulate the immune system as well (12-16). Injection is likely not necessary to obtain a radioprotective effect since acemannan has been shown to be readily absorbed after injection (17).

Another polysaccharide similar to acemannan, mannuronan that is produced by the bacterium *Pseudomonas aeruginosa*, has also shown a radioprotective effect (18). Injection of 1 mg/kg body weight increased survival of lethally irradiated mice from 0% at 40 days to 80% survival. Other tests showed the mannuronan stimulated production of interleukin-1, interleukin-6 and colony stimulating factor. These immune system and repair system factors likely account for the prevention and repair of damage from radiation.

Many other reports of radioprotection by polysaccharides are available (19-29). There are also many reports on the radioprotective effect of cytokines alone (30-44). Use of polysaccharides instead of the cytokines is likely to be a more economic and safer method of radioprotection because the cytokines themselves are more expensive and are toxic at radioprotective doses (6). In fact, Landauer *et al.*(6) found glucan to cause a severe locomotor decrement when injected into mice at the dose found to have a radioprotective effect (250 mg/kg). Acemannan does not show such toxicity up to 200 mg/kg in mice (4) and may well be a superior choice for radioprotection studies in humans subjected to radiation in space.

4. Radioprotection by Vitamins

As with polysaccharides, there are many studies of the radioprotective effects of vitamins (45-63), primarily with vitamins A, C, E, and beta-carotene. These vitamins achieve radioprotection primarily by acting as low-toxicity antioxidants and free radical scavengers (46). It is not necessary to go into further detail here. The interested reader can explore the field using the references supplied. Suffice it to say that the evidence that vitamins provide a radioprotective effect is not in doubt and examination of their efficiency in humans is justified.

5. Radioprotection by Flavinoids

A few studies of plant flavinoids as radioprotectors have been performed (64-67). These compounds found in tea, vegetables, and fruits also work as anti-oxidants and scavenge free radicals and hydroxyl radicals that cause much of the damage to cells from radiation. Shimoi et al. (64) has studied the antioxidant activity of various fruits and vegetables. These authors found that the strength of the antioxidant behavior correlated well with the radioprotective effect for carrot, broccoli, grape, tomato, apple, and aloe. This study used the juices of these foods and therefore vitamins, minerals, and other compounds that show radioprotective effects would be present. Nevertheless, this study shows a direct connection between food components and radioprotection. Shimoi et al. also studied tea extracts that showed the radioprotective effect of the flavinoids alone. Again, these and related compounds in whole foods and vegetables show radioprotective effects which should be evaluated in humans.

VI. Radioprotection by Metals and Minerals

Several studies of radioprotection by metals and minerals are available (68-75). Sorenson (68) has reviewed the field and notes "Understanding the metabolism of essential metalloelements and its role in responding to radiation injury as mediated by immunomodulating cytokines offers a new approach to protection against hematopoietic and gastrointestinal syndromes and perhaps cardiovascular and central nervous system syndromes. Copper, iron, manganese, and zinc compounds have radioprotective activity..." In other words, metals are essential nutrients for the formation of various enzymes important to cell functions and having the metal ions present assists the body in resisting and repairing radiation damage. Minerals not considered nutritional until recent years, such as selenium, also show radioprotective effects (69). As above, these substances should be evaluated in tests with humans who would receive radiation doses in the course of already planned space flight.

VII. Radioprotection by Other Naturally Occurring Substances

Many other substances have been found to have radioprotective effects (76-102). These substances range from compounds as common as caffeine, to those as unfamiliar as indomethacin, to oriental medicinal herbs. Evaluation of these substances is outside the scope of this proposal because of the wide variety of materials. Some of these substances no doubt derive their radioprotective effects from the presence of the nutritional substances discussed above and are to a degree duplicative.

VIII. Other Health Benefits

In recent years, the evidence has become overwhelming that phytochemicals, compounds in foods from fruits and vegetables that are not known to have traditional nutritive value,

are very important in prevention and reversal of several diseases (103-111). In addition, the National Aeronautics and Space Administration (NASA) has found that space flight causes viral shedding and decreases in immune function (112). Space Shuttle astronauts have not exhibited detrimental effects of the stress of space flight beyond those attributed to microgravity. However, "a Mars mission...could take 30 months...[and] the already observed decline in cell-mediated immune function on short flights could translate to an increased reactivation of herpesvirus...and an increase in infections." Inactive herpesvirus infection is known to be present in most of the adult population, including, presumably, astronauts. The immune system modulation of acemannan and positive health effects of other phytochemicals in nutritional supplements should greatly decrease the odds of viral shedding and infections.

The nutritional supplements that are the subject of this proposal have show remarkable health effects (113-115). Significant improvement was observed in a wide variety of health conditions, including dyslexia, hepatitis C, periodontal disease, asthma, Tay-Sachs disease, chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, diabetes, ADHD, lupus and menopause. One study (116) demonstrated that a proprietary mixture of the eight essential saccharides and acemannan greatly improved the survival rate of mice implanted with Norman Murine Sarcoma, a form of cancer, from <10% at 50 days to 47.6% and 66.7% in two trials. Mice were injected weekly with 1 mg/kg body weight with the glyconutritional supplement.

As noted by McAnalley and Venum (117), "Harper's Biochemistry [(118)] lists eight monosaccharides commonly found in the structures coating our cells." Table 1 lists the eight monosaccharides that the human body uses to produce glycoproteins. Only two of the eight, glucose and galactose, are present in the normal western diet. The body can synthesize the rest, but the synthesis is complex and may not always function properly. Supplementation with the other six monosaccharides should lead to improved health or maintenance of health.

Table 1. Eight Essential Monosaccharides

N-acetylneuraminic acid
N-acetylgalactosamine
galactose
glucose
N-acetylglucosamine
xylose
fucose
mannose

IX. Composition of Nutritional Supplements

Tables 2-6 show the composition of the nutritional supplements recommended by this proposal as listed on the product containers. As seen in these tables, these products contain standardized amounts of many the radioprotective substances discussed above in addition to other nutrients. Supplementation of the diets of those exposed to radiation, whether astronauts, cosmonauts, airline crews, nuclear workers, or nuclear accident victims would be expected lead to radioprotection and recovery as well as maintenance of health. Confirmation of this hypothesis remains to be accomplished.

Table 2. Glyconutritional Supplement

Ambrotose™Complex (naturally occurring plant polysaccharides, including freeze-dried aloe vera gel extract = Manapol® powder)

Table 3. Vitamin and Mineral Supplement

<u>Vitamins</u>	“Profile 1”	“Profile 2”	“Profile 3”
A	2,500 I.U.	15,000 I.U.	7,500 I.U.
B1	27 mg	2 mg	7 mg
B12	18 mcg	125 mcg	68 mcg
B2	24 mg	5 mg	8 mg
B6	26 mg	2 mg	10 mg
Beta Carotene	1,000 I.U.	5,000 I.U.	2,500 I.U.
Bioflavinoids	95 mg	56 mg	75 mg
Biotin	36 mcg	57 mcg	52 mcg
C	187 mg	130 mg	170 mg
Choline	19 mg	55 mg	40 mg
D	400 I.U.	170 I.U.	210 I.U.
E	30 I.U.	62 I.U.	50 I.U.
Folic Acid	400 mcg	200 mcg	300 mcg
Inositol	11 mg	25 mg	20 mg
K	90 mcg	50 mcg	90 mcg
Niacinamide	30 mg	38 mg	32 mg
P.A.B.A.	5 mg	7 mg	6 mg
Pantothenic acid	5 mg	29 mg	23 mg
<u>Minerals</u>			
Boron	150 mcg	500 mcg	300 mcg
Calcium	10 mg	75 mg	60 mg
Copper	20 mcg	700 mcg	300 mcg
GTF Chromium	150 mcg	50 mcg	80 mcg
Iodine	3 mcg	100 mcg	30 mcg
Iron	5 mg	2.0 mg	3.5 mg
Magnesium	50 mg	10 mg	25 mg
Manganese	12 mg	2 mg	8 mg
Molybdenum	70 mcg	70 mcg	70 mcg
Potassium	75 mg	7 mg	12 mg
Selenium	15 mcg	15 mcg	15 mcg
Silicon	500 mcg	2.5 mcg	2 mcg
Vanadium	10 mcg	10 mcg	10 mcg
Zinc	7 mg	15 mg	10 mg
Ambrotose™ complex	25 mg	25 mg	25 mg

It should be noted that the vitamins and minerals listed in Table 3 are claimed to be in a more absorbable form with enhanced bioavailability. The three “Profiles” refer to the three basic metabolic profiles of the population which arise from differing historical diets and genetic propensities for different populations. Each “Profile” is supposed to better support that particular metabolic rate.

Table 4. Phytochemical Supplement

Ambrotose™Complex
(naturally occurring plant polysaccharides, including
freeze-dried aloe vera gel extract = Manapol®)
Flash-dried broccoli, Brussels sprouts, cabbage, carrot,
cauliflower, garlic, kale, onion, papaya, pineapple,
tomato, and turnip

Table 5. Phytoestrogen Supplement

Dioscorea (wild yam 10:1)
Glutamic acid
Cellulose,
Arginine
Calcium carbonate
Beta sitosterol
Stearic acid
Silica
Ambrotose™Complex

Table 6. Digestive Supplement

Essential fibers blend	whole oat fiber black currant seed fiber psyllium seed husk fiber flax seed fiber Irish moss carrageenan Konjac glucomannan calcium monohydrogen phosphate plant cellulose
Essential oils and botanicals blend	fenugreek seed fennel seed ginger root rosemary leaf neroli orange blossom peppermint leaf
Essential enteric ecology and flora growth promotants blend	Dahlulin (patented inulin and fructo- oligosaccharides from tubers of <i>Dahlia variabilis</i>)
Essential enteric ecology and flora growth promotants blend (cont.)	galacto-oligosaccharides mannan-oligosaccharides beta glucans Ambrotose™ complex fractionated vegetable oil

Table 6. Digestive Supplement (cont.)

Essential fatty acids blend	caprylic acid rice bran concentrate linoleic and oleic acid soy phosphatides omega-6 concentrate
Essential live probiotic flora blend	Lactobacillus sporogenes L. acidophilus L. plantarum L. rhamnosus L. casei Bifidobacterium bifidum
Essential plant enzymes blend	amylase (starch digestant) lipase (fat digestant) celluase (fiber digestant) protease (protein digestant) saccharase (sugar digestant) lactase (milk sugar digestant)

The phytoestrogen supplement provides primarily plant sterols that the body can use to produce hormones as needed. The digestive supplement provides fiber and intestinal flora that may be difficult for astronauts to maintain on long missions.

The author of this proposal has taken the nutritional supplements for over one and one-half years and has noted the health benefits listed in Table 7.

Table 7. Health Benefits Noted by the Author (Age 47)

Objective health benefits	Fewer colds (down from 4-5 per yr. to 1-2) Milder colds (no cold medicines required) No flu (down from 1 per 1-2 yr.) Disappearance of several small skin growths Greatly reduced occurrence of racing heart
Subjective health benefits	Improvement in 23 yr. old knee injury Less muscle pain during stair climbing Increased strength (arm and back)

X. Summary and Proposal

The literature has a large number of reports of the radioprotective effects of nutritional substances and the mechanisms of the protection are fairly well established. The time appears to be appropriate for the evaluation of the radioprotective effects of a group of commercially available nutritional supplements that have shown remarkable health benefits. The possibility that the combined effects of these supplements will exceed the radioprotective effect of any one is high because other studies of the effect of combinations of radioprotectants have shown a synergistic effect (119-121).

Tests on animals, which are relatively easy to perform, should precede human tests and

could demonstrate the efficacy of the specific supplements identified in this proposal when given orally instead of by injection. It may turn out that oral consumption of nutritional supplements give radioprotection against lower levels of radiation and that higher levels of radiation may be better treated by timed injections, as noted in several studies above. Thus, astronauts could take the supplements on a regular basis for normal levels of radiation during a Mars mission and have injectible forms available in case of a solar flare.

The idea of using nutritional substances to protect spacefarers is not new. However, because of their demonstrated effectiveness and lack of toxicity, the supplements identified in Tables 2-6 should be systematically evaluated as radioprotectants on astronauts or cosmonauts on long-duration missions during which significant radiation doses will accumulate. The methodology to evaluate the effect has yet to be determined, but may well lie in evaluation of microscopic changes in the blood that can occur even at relatively low doses. The effects should be compared for a crew member taking the supplements to another crew member as closely matched as possible who is not taking the supplements. Evaluation of radioprotective effects in other populations undergoing radiation exposure (such as airline crews or nuclear workers) or already having been irradiated (nuclear accident victims, etc.) is also recommended to determine if radioprotective benefit will accrue for them as well.

Even though the radiation dose to the crew of a Mars mission will not be excessive if shielding and a solar flare shelter are provided, enough concern over their exposure has been raised to justify attempts to minimize health effects. The nutritional substances reviewed in this proposal are likely to provide radioprotective and other health benefits that should enhance the probability of a successful mission.

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