Review Article

iMedPub Journals
http://www.imedpub.com

Journal of Medical Physics and Applied Sciences
ISSN 2574-285X

2021
Vol. 6 No.5:11

Attenuation of Space Radiation-Induced Damage by an Oral Supplementation with a Mixture of Micronutrients in Astronauts

Kedar N Prasad[1*] and Jae Ho Kim[2]

[1]Department of Radiology, University of Colorado Health Sciences Center, Engage Global Inc. 245 El Faisan Drive, San Rafael, CA 94903, USA
[2]Department of Radiation Oncology, Henry Ford Health System, Detroit, Mi, 48202, United States

***Corresponding author:** Kedar N Prasad, Department of Radiology, University of Colorado Health Sciences Center, Engage Global Inc. 245 El Faisan Drive, San Rafael, CA 94903, USA, E-mail: knprasad@comcast.net

Citation: Prasad NK, Kim HJ (2021) Attenuation of Space Radiation-Induced Damage by an Oral Supplementation with a Mixture of Micronutrients in Astronauts. J Med Phys and Appl Sci Vol.6 No.5: 11.

Abstract

Context: There are no effective radiation protection strategies to protect the astronauts against space radiation while traveling beyond the earth-orbit.

Objectives: The objectives are to characterize space radiation and its ability to produce reactive oxygen species and inflammation that can increase adverse health effects in astronauts. Because of limitation of using a single or a mixture of few antioxidants, it proposes a comprehensive mixture of micronutrients for prevention and mitigation of radiation damage in astronauts.

Methods: Critical analysis of the published studies on space radiation-induced adverse health effects on astronauts and their countermeasures obtained from the PubMed Central was performed.

Results: While traveling beyond the earth-orbit, astronauts are exposed to galactic cosmic rays (GCRs), solar particles events, and (c) electrons and protons trapped in the Van Allen Belts. Space radiation enhances oxidative stress and inflammation that are associated with increased health risks. Administration of a single or a mixture of few antioxidants may not be adequate for radiation protection astronauts. Therefore, a comprehensive mixture of micronutrients for prevention and mitigation of space radiation injury is proposed.

Conclusion: Astronauts travelling beyond the earth orbit are exposed to space radiation, which enhance oxidative stress and inflammation that can produce adverse health effects. A comprehensive micronutrient mixture may prevent and mitigate adverse health effects in astronauts by simultaneously reducing the above cellular deficits.

Keywords: Space radiation; Reactive oxygen species; Inflammations; Micronutrients; HZE particles

Received: August 30, 2021; **Accepted:** September 13, 2021; **Published:** September 20, 2021

Introduction

Yuri Gagarin of the former USSR was the first astronaut (also called cosmonaut) to travel into outer space and successfully completed one orbit of Earth on 12th April, 1961. Since then, astronauts are spending more and more time on space missions. Between 1969-1972, astronauts landed on the lunar surface in 6 of 7 lunar landing missions. They took 8-12 days to reach moon and spent 21-74 hrs on the lunar surface, depending upon the lunar landing missions. In recent years, astronauts are spending up to 6 months or more at the International Space Station (ISS). To live in such a close environment under microgravity, weightlessness, and exposure to low levels of galactic cosmic radiation (GCR) poses increased health risks to astronauts. These risks include space radiation-induced neoplastic and non-neoplastic diseases, microgravity-induced musculoskeletal atrophy, and psychological stress due to living in isolation.

To The next challenging space exploration mission may include travel to the Moon followed by journey to the Mars. It will take 800 to 1,100 days to reach Mars and astronauts may spend 500 days on the surface of Mars, depending on the final mission design [1]. It is expected that astronauts travelling to Mars will be exposed to much higher doses of space radiation, microgravity, and weightlessness than those who spent a 6-month mission on the ISS. Therefore, the risks of adverse health effects in astronauts

are expected to increase much greater than those travelling in the ISS. For the successful space missions, it is imperative to develop safe and effective countermeasures for astronauts on various space missions as well as for astronauts returning to civilian life. In order to accomplish this, it is essential to identify space radiation-induced generation of reactive chemicals that damage the cells.

GCR radiation by virtue of being high linear energy transfer (LET) radiation causes damage by producing dense ionization in biological molecules that cannot be protected by pharmacological or physiological agents. Because exposure to GCR radiation also generates extensive amounts of reactive oxygen species (ROS) along the track, the damage produced by this component of GCR can be protected by scavengers of ROS. One of such scavengers of ROS is antioxidant.

This review briefly describes (a) characteristics of space radiation, (b) production of ROS during GCR radiation, (c) effects of gravity on the production of ROS, (d) adverse health effects of space radiation, and (e) biological strategies for prevention and mitigation of space radiation-induced cellular damage. This review points out the limitations of administration of a single or a mixture of antioxidants only before irradiation for space radiation protection in astronauts. To address these limitations, the review proposes a comprehensive mixture of micronutrients that can be administered orally before and after exposure to irradiation for prevention and mitigation of radiation injury in astronauts during space travel, during stay on the lunar or Mars surface, and during returns to their civilian life.

Literature Review

Characterization of space radiation

The Space radiation is different from the terrestrial form of radiation with respect LET. Terrestrial radiation such as x-rays and gamma-rays are low LET, whereas space radiation such as high energy particles are high LET. Astronauts in the International Space Station (ISS) at the altitudes of 300-400 km and orbital inclination of 51.60 are exposed to three primary sources of space radiation, (a) galactic cosmic rays (GCRs) consist of high energy protons and heavy ions from outside of our solar system, (b) solar particles events (SPEs) during which high energy particles (electron, neutrons, protons, and heavy ion nuclei) are released, and (c) electrons and protons trapped in the Van Allen Belts outside the spacecraft. During SPE, high energy protons arising from the sun within the region of solar magnetic instability are released for a short period of time, while solar wind consists of low energy protons and electrons [2]. The combination of these forms of radiation produces a complex radiation environment inside and outside of the ISS, and the extent of complexity of radiation depends upon the solar cycle, altitudes, and shielding of each module of the ISS [3].

Galactic cosmic radiation (GCR) is made of the nuclei of atoms that have no electrons and travels nearly speed of light. GCR is composed of 85% hydrogen nuclei (protons), 14% helium nuclei, and 1% high-energy and highly charged high atomic number ions called HZE particles that include heavy ions of carbon, iron, or nickel nuclei. Although HZE particles represent very small part of GCR, they exhibit higher ionizing power, greater penetration ability, and inflicting greater biological damage. GCR can easily penetrate through a typical spacecraft as well as through astronaut skin. Humans are protected from GCR because of earth atmosphere and magnetic field, whereas lunar surface is devoid of these protective atmosphere and magnetic field [4]. Therefore, astronauts on the lunar surface are likely to receive more radiation than on the earth.

Generation of secondary radiations by HZE particles

Technological evolution Interaction between HZE particles and electrons in target atoms, and fragmentation of the incident HZE particles and target nuclei gives rise to secondary radiations, which include photons, protons, neutrons, alpha-particles, and other heavy ions with lower velocity as well as energetic electrons referred to as delta rays [5,6]. Delta rays due to their long range can irradiate not only direct target cells but also neighboring by stander cells. As a matter of fact, the total dose deposited by delta rays could be as high 30-40% of HZE particles [7,8].

Space radiation facilities available to perform experiments on the earth

The HZE particles of galactic cosmic radiation are difficult to obtain for experiments on the earth. However, the Brookhaven National Laboratory in NY has facility to provide high energy ions from proton to gold, the Gunma University Heavy Ion Medical Center in Japan, and the National Center for Oncological Hadron therapy in Italy have facilities to provide high energy C-ion beam. Heavy-Ion Medical Accelerator in Chiba in Japan can provide high energy beam of He, C, Cr, Fe, Ni, Xe, and the GSI Helmholtz Center for Heavy Ion Research in Germany can provide high energy beam of ions from proton to uranium for biological and shielding experiments.

Studies performed using HZE radiation facilities on the earth

Extensive studies on the adverse health effects of HZE particles utilizing high energy heavy ions have been performed primarily in rodents. However, there are several uncertainties regarding the extrapolation of the results from the above studies to astronauts traveling in lower-earth orbit (LEO) and beyond. They include use of mono-energetic high atomic number ions radiation, higher dose rate, and total dose [9]. The use of sequential irradiation with more than one high energy ions is better than one mono-energetic ion, but it cannot mimic the effects of complex space radiation. In contrast, astronauts are exposed to complex radiation environment of particles and ions, together with microgravity and social isolation. These conditions are difficult to reproduce on the earth for laboratory experiments. Nevertheless, experimental data on the adverse health effects of mono energetic HZE particle in rodents suggest that such effects may be found in astronauts who would stay inside the spacecraft for more than 6 months, who perform extravehicular activities, and who may reside on lunar surface for several days.

GCR radiation doses received by astronauts during extravehicular activities

Astronauts are exposed to higher doses of space radiation during extravehicular activities than during the same period inside the spacecraft despite extravehicular space suits, which provides insufficient shielding against such radiation [10].

Doses received by astronauts on the lunar surface

Between 1969-1072, astronauts successfully landed on lunar surface in 6 of 7 lunar landing missions. The average dose to astronauts at the lunar surface varied from 180 mSv to 1140 mSv (Life Sciences Data Archive at JSC3) **(Table 1)**.

Table 1: Describes time to reach to the moon, time spent on lunar surface, and average dose in rad as well as in mSv (in parenthesis).

Mission	Duration to the moon	Lunar surface duration	Average dose to astronauts
Apollo 11	8 days, 3hrs, 13 mins	21 hrs, 36 mins	0.18 rad (180 mSv)
Apollo 12	10 days, 4 hrs, 31 mins	31 hrs, 31 mins	0.58 rad (580 mSv)
Apollo 14	9 days, 1 min	33hrs, 31 mins	1.14 rad (1140 mSv)
Apollo 15	10 days, 1 hrs, 11 mins	66 hrs, 54 mins	0.30 rad (300 mSv)
Apollo 16	11 days, 1 hrs. 51 mins	71 hrs. 2 mins	0.51 rad (510 mSv)
Slice nr 11	Slice nr 11	Slice nr 11	0.55 rad (550 mSv)

Astronauts in deep space are exposed to both solar particle events (SPE) and galactic cosmic rays (GCR). Dose rates from SPE and GCR are around (0.5 mSv)/day inside the ISS. The average dose to 7 deceased Apollo crew was +/- 5.9 mSv 1.5 mSv (range 1.8 mSv to 11.4 mSv) [11].

The dose to astronauts depends upon the time spent in the spacecraft, extravehicular activities or on the lunar surfaces. Generally, effective dose is low; however, the biological effects are cumulative. High-energy protons and charged particles can damage shielding as well as biological system [3,12]. In recent years, astronauts are spending up to 6 months or more at the International Space Station (ISS). To live in such a close environment under microgravity and weightlessness, exposure to low levels of space radiation poses additional health risks to astronauts. Astronauts received an effective dose in the range of 50-2000 mSv over 6-12 months stay in ISS. Astronauts would receive approximately 290 mSv during an average duration stay of 15.6 days in ISS [13].

Reactive (ROS) production du ring exposure to galactic cosmic radiation

An excellent review has described the involvement of increased oxidative stress and inflammation in damage produced by HZE particles in in vitro and in vivo [14]. High LET HZE particles produce direct effect by ionizing cellular molecules and indirectly by producing reactive oxygen species (ROS) from hydrolysis of water, which generate various oxidizing species such as e-aq (hydrated electron), $^{\bullet}OH$, $H^{\bullet}$, H_2, H_2O_2 [15, 16]. In the presence of oxygen, e-aq and $H^{\bullet}$ species are rapidly converted to superoxide ($O_2^{\bullet}$-) and perhydroxyl ($HO_2^{\bullet}$). Organic radical ($R^{\bullet}$), when combines with O_2, produce Peroxyradical ($RO_2^{\bullet}$) [17]. The burst of these ROS occur along the track of HZE particles [18]. Space radiation can stimulate the activity of inducible nitric oxide synthase in the target cells [19], leading to generation of large amounts of nitric oxide ($^{\bullet}NO$), which can combine with $O_2^{\bullet-}$ to form peroxynitrite (ONNO-), which can damage nucleic acid, lipid, protein, and thiol [20]. Peroxynitrite and other reactive nitrogen species (RNS), when generated during inflammation, can damage nucleic acid, protein and lipid in neighboring bystander cells that can lead to genomic instability or cell death [21].

Unlike low-LET radiations (x-rays, γ-rays), which decrease energy deposition exponentially as a function of tissue penetration, the energy deposit of HZE particles is characterized by a relatively low entrance dose in the target tissue and a sharp maximum deposit at the end of range known as a Bragg peak. Because of the spread of oxidative stress from cells directly targeted with HZE to neighboring non-targeted cells, the increased oxidative stress continues to persist in both targeted and non-targeted cells. This in turn promotes genetic instability that may enhance the risks of long-term late effects including cancer and degenerative disease [14].

ROS production during exposure to microgravity

The interaction between the effects of HZE particles and microgravity in producing ROS is not fully defined. Exposure to microgravity alone contributes to oxidative stress leading to bone loss [22]. The analysis of the urine of astronauts on the Russian space station MIR and on the shuttle for a short-duration missions revealed opposite effect on the levels of oxidative stress during in-flight and post-flight [23]. The levels of oxidative damage were less during in-flight, whereas they increased during post-flight. These results were interpreted to mean that decreased production of ROS was due to the reduced energy production by the astronauts during in-flight, while increased oxidative stress during post-flight was due to decreased antioxidant defense system. Indeed, reduced activities of antioxidant enzymes were detected for several days after space flight [24].

Microgravity increased lipid peroxidation in human erythrocyte membrane and decreased blood antioxidant levels in cosmonauts [25,26]. Long-term missions increased triglyceride levels and ratio of HDL/LDL cholesterol (high-density lipoprotein/low-density lipoprotein) [27]. Since space radiation generates extensive amounts ROS and RNS (reactive nitrogen species), it is likely that the combination of space radiation and microgravity together with other space stressors may increase the risk of cardiovascular disease, including atherosclerosis in astronauts.

ROS production during exposure to hypergravity

It is essential to note that astronauts are also exposed to hypergravity during the launch of the spacecraft and upon re-entry to the earth environment, but no significant studies on changes in the levels of oxidative stress have been performed. In rats, increased levels of MDA (malondialdehyde), a marker of oxidative stress, were found in the heart and kidney tissues [28,29]. Exposure to hypergravity increased oxidative stress and decreased the number of Purkinje neurons and impaired motor co-ordination in rat neonates [30].

Induction of inflammation as a response to cellular radiation damage

Ionizing radiation is known to induce chronic inflammation via radiation-induced cell damage [31]. GCR disrupted synaptic integrity and increased neuroinflammation, which persisted 6 months after irradiation in rats [32]. As soon as cell injury irrespective of inducing agents occurs, acute inflammation releases anti-inflammation cytokines at the site of injury to help in the healing process. When the cell damage is repaired, acute inflammation is turned off. In the event, the cell injury is not healed, chronic inflammation, which releases pro-inflammatory cytokines, complement protein, adhesion molecules, and ROS occurs. Space radiation-induced cellular damage caused by ROS can be attenuated by antioxidants; however, injury caused by ionization of vital cell molecules cannot be reduced by antioxidants, therefore, cellular damage persists, which initiates chronic inflammation. Both increased oxidative stress and chronic inflammation play an important role in initiating and progression of space radiation-induced adverse health effects. Thus, decreasing oxidative stress and chronic inflammation at the same time may decrease the acute and late health risks in astronauts. In order to achieve this goal, increasing the levels of antioxidant enzymes as well as dietary and endogenous antioxidant compounds at the same time for neurodegenerative diseases such as Alzheimer's disease have been proposed [33]. The same idea would be applicable to astronaut protection.

Adverse health effects of space radiation

Possible health risks to astronauts include cancer, damage to the central nervous system, cardiovascular disease, cataract, acute radiation sickness, and genetic damage [3,12,34].

Effects of space radiation on the brain function: It is essential that astronauts maintain normal neuronal function during long space journey to Moon or Mars for the success of missions. Effects of HZE particles on the brain function have been investigated primarily on rodents [35]. Exposure to HZE particles increased the presence of dense fibrillary proteins and beta-amyloid fragments in the serum of mice that are associated with Alzheimer's disease [36]. Irradiation of rats with HZE particles induced cognitive dysfunction and behavioral deficits that are linked to the damage of structure and synaptic integrity of the specific region of the brain [37-40]. These adverse neuronal functions persisted over one year, suggesting that HZE particles can cause permanent damage in the brain [32]. Most studies have used mono-energetic HZE particle radiation. One study has investigated the effects of sequential irradiation with protons, 16 O ions, and 28 Si ions on behavioral and cognitive performance in male and female mice [41]. Results showed that mice of both sexes exhibited depressed behavior and impaired cognitive function. In addition, cortical levels of microglia activation marker CD68 (Cluster of Differentiation 68) increased after irradiation in females but not in males indicating the presence of neuroinflammation, while the levels of BDNF (brain-derived neurotrophic factor) decreased after irradiation in males, but not in females. Gut microbiome also changed after irradiation in these mice.

Space radiation on cancer risk: Space radiation can increase the risk of cancer in astronauts during civilian life, especially after long duration flight because of exposure to complex radiation environment of low and high LET radiation together with microgravity inside and outside of the spacecraft. There are no human data available on this issue. However, animal studies suggest that the risk of cancer exists in astronauts exposed to space radiation. Exposure to HZE particles induced malignant lymphoma and harderian gland tumor in the eye's orbit of mice [34, 42]. Also, exposure to proton radiation and Fe-ions radiation induced premalignant changes and malignant tumors of myeloid origin of the bone marrow [42].

Effects of space radiation on DNA damage and chromosomal damage: Galactic cosmic radiation causes dense ionization in DNA along the radiation tracks and induces "complex DNA damage" or clustered DNA damage. This form of DNA damage is difficult to repair when compared to normal DNA damage [43-45]. Gamma-H2AX, a phosphorylated histone protein, is a marker of DNA double-strand breaks (DSBs). Tracks of the gamma-H2AX foci are found in the nuclei of lymphoblast's [46] and fibroblasts in astronauts after space flight [47].This form of DNA damage can lead to cancer or cell death. The frequency of chromosomal anomalies appeared to be higher at post-flight than at pre-flight among astronauts, especially after space flight of longer than 180 days [48,49]. Thus, space radiation can cause genetic instability that can increase the risk of cancer. Simultaneous exposure to microgravity and x-rays or carbon ions increased chromosomal damage more than that observed with microgravity, x-rays or carbon ions alone.

Effects of space radiation on the eye: Astronauts have increased risk of cataract due to exposure to GCR during space travel [50-52]. High LET radiation is known to have a high radiobiological effect (RBE) on the development of cataract.

Effects of space radiation on the immune system: Because of radiation-induced impaired immune system, astronauts have increased risk of serious infections including debilitating dental infection and urinary tract infection [53-58]. Reduction in whole-blood counts following exposure to SPE particles was greater in pigs than in ferrets and mice [59]. Combination of microgravity and SPE radiation can produce additive or synergistic effects on the immune system of murine models [60-63].

Studies on protection of astronauts against galactic cosmic rays

Antioxidants administered before irradiation with HZE particles: Dr. Kennedy and her colleagues at the University of Pennsylvania have performed pioneering studies on radiation protection using high doses of mono-energetic HZE particles from one of the facilities on the earth [34,64]. These studies have utilized one antioxidant or a mixture containing antioxidants and some B-vitamins. There may be several limitations of using one antioxidant in astronauts, although it is effective in protecting rodents against HZE particles radiation. This issue will be presented later in the manuscript. The mixture used in the above studies contains most dietary and endogenous antioxidants, only

2 B-vitamins, selenomethionine and Bowman-Birk inhibitor. This mixture produced significant protection against monoenergetic HZE particles radiation in rodents and cell culture models. For the studies on astronauts, adding other antioxidants, vitamin D3, all B-vitamins may be essential for protection against acute and long-term damage produced by space radiation (see the rationale below).

Extensive studies on micronutrients, phytonutrients, and selenium when administered before monoenergetic HZE particles irradiation in animal and cell culture models have been performed. A few such studies are described here.

Treatment of human cells in culture with selenome-thionine for 18 hrs. Before irradiation prevented monoenergetic HZE particles-induced rise in increased oxidative stress as well as it reduced lethality of irradiated cells [65]. Administration of diet containing vitamin A one week before accelerated ^{56}Fe ion-irradiation significantly reduced the expression of inflammation-related genes and reduced the incidence of cancer by half in rats [66]. Irradiation of hippocampal cells in culture with 1 Gy of high energy ^{56}Fe ions produced extensive amounts of free radicals [67]. Treatment of these cells with alpha-lipoic acid before or after irradiation markedly attenuated the levels of ROS. Treatment of middle-aged mice with alpha-lipoic acid 3 weeks before irradiation with 3 Gy of ^{56}Fe ions reduced radiation-induced impairment of special memory retention ability [68]. Supplementation with diet rich in polyphenolic compounds from blueberry or strawberry extract 8 weeks before irradiation with 1.5 Gy or 2 Gy of energetic ^{56}Fe ions protected against radiation-induced behavior impairment [69].

Dietary supplementation with a mixture of antioxidant containing n-acetylcysteine (NAC), coenzyme Q10, glutathione, alpha-lipoic acid, vitamin C, vitamin E succinate, B-vitamins (B1-thiamine, B3-niacin), BBI (Bowman-Birk inhibitor), and selenomethione in various combinations before irradiation provided protection against monoenergetic HZE particles radiation in mice and cell culture models [34,42]. One CT scan, which delivers 10 mGy of gamma-radiation, induced double-strand DNA breaks (DSBs) in the peripheral lymphocytes of patients. Administration of a mixture of multiple antioxidants (a commercial preparation) 60 minutes before the CT scan reduced the number of cells with DSBs by over 50% [70].

Antioxidants administered after irradiation with gamma-radiation: Family of vitamin E, administered before irradiation is more effective than alpha-tocopherol in providing radiation protection in animal models [71]. This micronutrients also effective when administered after irradiation [72]. For an optimal radiation protection, timing of administration after irradiation is very important. Dietary supplementation with a mixture of antioxidants (selenomethionine, sodium ascorbate, N-acetylcysteine, alpha-lipoic acid, vitamin E succinate, and coenzyme Q10) when administered 24 hrs after total body irradiation with gamma-radiation provided better radiation protection than that administered immediately after irradiation [73]. Similar observations were reported in another study [74]. Diet supplemented with dried plum powder reduced space radiation and microgravity-induced bone loss by decreasing oxidative stress and inflammation in mice [75].

Limitations of administering antioxidants only before or after irradiation

In most studies, antioxidants were administered before or after irradiation. Existence of long-lived free radicals after irradiation [76] suggested that post-irradiation treatment with antioxidants together with pre-irradiation treatment would be useful in optimally reducing radiation damage. However, timing of post-irradiation treatment is important. Post-irradiation treatment with antioxidants soon after irradiation may interfere the action of anti-inflammatory cytokines that are released to help in the repair of cellular damage in the early of phase of tissue repair. Studies on rodents have shown that administration of antioxidant mixture 24 hours after irradiation provide better protection than that administered soon after irradiation [73,74]. No studies have been performed to evaluate the effectiveness of antioxidants when administered orally before and after irradiation in the same animal or cell culture models.

Limitations of administering a single antioxidant for radiation protection in astronauts

The administration of a single antioxidant is effective in prevention or mitigation of radiation injury in animal models; it may not provide radiation protection in the astronauts because of several limitations. Some of them are described here.

(a) Space radiation produces high levels of ROS and RNS. Administration of a single antioxidant in a high internal oxidative environment of astronauts would be oxidized, which then would act as a pro-oxidant rather than as an antioxidant [75].

(b) Different antioxidants are distributed differently in the sub-cellular compartments of cells, all of which must be protected. Administration of a single antioxidant cannot accumulate in all parts of the cell in sufficient amounts to provide adequate protection in astronauts [76].

(c) Vitamin E is more effective scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure of the cells [77]. Therefore, administration of one antioxidant may not provide adequate protection in whole body.

(d) Elevation of both antioxidant enzymes and dietary and endogenous antioxidant compounds are needed to achieve maximal protection against radiation-induced oxidative and inflammatory damage. This is due to the fact that they act by different mechanisms. Antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes destroy H_2O_2 by catalysis, converting them to harmless molecules such as water and oxygen. Administration of a single antioxidant cannot achieve this goal.

(e) Administration of a single antioxidant cannot protect both the aqueous and lipid compartments of the cell against radiation injury.

(f) Different antioxidants increase the production of different protective proteins in the cells by altering the expression of different microRNAs [78]. For example, some antioxidants can activate Nrf2 by upregulating miR-200a that inhibits its target protein Keap1, whereas others activate Nrf2 by down-regulating miR-21 that binds with 3'-UTR Nrf2 mRNA [79]. Thus, different antioxidants activate Nrf2 (Nuclear Factor-Erythroid-2-Related Factor 2) by different mechanisms. Administration of a single antioxidant cannot accomplish the above objective.

Administration of a single antioxidant compound failed to yield expected benefits that were observed in animal models. For examples, administration of vitamin E alone produced no effect in patients with Parkinson's disease [80,81]. It also had no effect on cognitive function in patients with Alzheimer's disease, but it produced minimal benefits in early phase of this disease [82,83]. Administration of beta-carotene alone in male heavy tobacco smokers increased the risk of lung cancer [84]. These studies suggest that administration of a single antioxidant is unlikely to provide any significant protection against space radiation in astronauts.

How to simultaneously reduce oxidative stress and inflammation

In order to reduce oxidative stress and inflammation at the same time, it is essential to simultaneously enhance the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds [85]. Oral supplementation with a mixture of antioxidants can increase the levels of dietary and endogenous antioxidant compounds; however, enhancing the levels of antioxidant enzymes requires an activation of a nuclear transcriptional factor Nrf2. A brief description of activation processes is presented here.

Processes of Activation of Nrf2: Under normal physiological conditions, activation of Nrf2, one of the nuclear transcriptional factors, requires ROS. Activated Nrf2 dissociates itself from Keap1-CuI-Rbx1 complex and migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of cytoprotective enzymes including antioxidant enzymes [86, 87]. It appears that during prolonged oxidative stress commonly observed in human chronic diseases, activation of Nrf2 becomes resistant to ROS [88,90]. This is evidenced by the fact that increased oxidative stress continues to occur in chronic diseases despite the presence of Nrf2. However, some antioxidants such as vitamin E [91], alpha-lipoic acid [92], curcumin [93], resveratrol [94,95], omega-3-fatty acids, [96,97], glutathione [98], n-acetylcysteine [99], and coenzyme Q10 [100] activate ROS-resistant Nrf2.

An activation of Nrf2 alone is not sufficient to increase the levels of antioxidant enzymes. Activated Nrf2 must bind to ARE to increase the transcription of cytoprotective enzymes including antioxidant enzymes. It is interesting to note that the binding ability of Nrf2 to ARE was impaired in aged rats and this defect was restored by supplementation with alpha-lipoic acid [92]. It is unknown whether the binding ability of activated Nrf2 would be impaired in astronauts during prolonged stay inside the spacecraft or long after space journey when they adopt civilian life.

It has been reported that activation of Nrf2 decreases oxidative stress as well inflammation [101,102]. Many antioxidant compounds also attenuate inflammation [103-108]. Levels of oxidative stress and inflammation are closely linked. Inflammatory responses are necessary for healing of oxidative damage of the cells, and it turned off after healing is complete. However, oxidative damage of cells is not healed, chronic inflammation responses occur. Such inflammatory responses release ROS, pro-inflammatory cytokines, adhesion molecules and complement proteins, all of which are toxic to the cells.

Proposed mixture of micronutrients for reducing adverse health-effects of space radiation

A comprehensive mixture of micronutrients containing vitamin A, mixed carotenoids, vitamin C, alpha-tocopheryl acetate, alpha-tocopheryl succinate, vitamin D3, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, omega-3 fatty acids, curcumin, resveratrol, all B-vitamins, and minerals selenomithionine, and zinc for prevention and mitigation of space radiation is proposed [33,85]. This mixture would increase the levels of antioxidant enzymes by activating the ROS-resistant Nrf2 and enhancing the levels of dietary and endogenous antioxidant compounds. Such a micronutrient mixture may optimally reduce oxidative stress and chronic inflammation at the same time, and thereby, provided maximal protection against space radiation in astronauts. The question arises whether any mixture of antioxidants has produced beneficial effects in human diseases. Two clinical studies support the value of a mixture of micronutrient in producing beneficial effects in certain human diseases in which oxidative stress and inflammation plays a major role in their pathogenesis. For example, administration of multiple micronutrients reduced the risk of cancer in men [109] and delayed the progression of HIV disease by prolonging the time period for initiating the anti-viral therapy [110]. Therefore, it is likely that the proposed micronutrient mixture may reduce the adverse effects of space radiation by reducing oxidative stress and inflammation at the same time in astronauts during as well as after space journey. Pre-clinical studies administering this micronutrient mixture before and after exposure to HZE particles radiation should be performed to test its effectiveness in radiation protection.

Discussion and Conclusion

The approach of methodology is theoretical. The data was collected from the secondary sources like published books, articles etc. Critical analysis of the published studies on space radiation-induced adverse health effects on astronauts and their countermeasures obtained from the PubMed Central was performed.

Astronauts are exposed to space radiation during travel into low-earth orbit and beyond. Three primary sources of space radiation include (a) galactic cosmic rays (GCR) consists of high energy protons, Helium nuclei, and high-energy and highly charged ions called HZE particles that include heavy ions of carbon, iron, or nickel nuclei released from outside of our solar system, (b)

solar particles events (SPEs) during which high energy particles (electron, neutrons, protons, and heavy nuclei) are released, and (c) electrons and protons trapped in the Van Allen Belts outside the spacecraft. The combination of these forms of radiation produces a complex radiation environment inside and outside of the International Space Station (ISS). Despite extravehicular space suits, astronauts are exposed to higher doses of space radiation during extravehicular activities than during the same period inside the spacecraft. The risk of cancer, brain damage, cardiovascular disease, cataract, and genetic damage after exposure to space radiation exist in astronauts. Space radiation produces damage by ionizing vital molecules in the cells and by generating extensive amounts of ROS along radiation track. Although administration of a single or a mixture of few antioxidants prevents and mitigates ROS-induced radiation damage in animal and cell culture models, they may not provide an optimal protection in astronauts. The reasons for this discrepancy have been discussed. Therefore, a comprehensive mixture of micronutrients containing dietary and endogenous antioxidants, resveratrol, curcumin, n-acetylcysteine, and minerals selenomethione and Zn is proposed for prevention and mitigation of space radiation injury in the astronauts during space travel as well as during civilian life. The proposed micronutrient mixture can be prepared in the form of paste and placed in a tube for the astronauts while travelling in space or spending time on the lunar surface. Astronauts can resume micronutrient mixture in capsules when they return to civilian life.

Conflict of Interest

The author is Chief Scientific Officer of Engage Global of Utah. This company sells nutritional products to consumers.

References

1 Drake BG, Hoffman SJ, Beaty DW (2010) Human exploration of Mars, design reference architecture 5.0. In2010 IEEE Aerospace Conference. IEEE Access 8: (1-24).

2 Rahman M, Di L, Yu E, Lin L, Zhang C, et al. (2019) Rapid flood progress monitoring in cropland with NASA SMAP. Remote Sensing 11(2): 359-366.

3 Furukawa S, Nagamatsu A, Nenoi M, Fujimori A, Kakinuma S, et al. (2020) Space radiation biology for "Living in Space". BioMed research international.

4 Lioyd CW (2008)The radiation challenge. In: NASA.

5 Cucinotta FA, Wilson JW, Shinn JL, Badavi FF, Badhwar GD (1996) Effects of target fragmentation on evaluation of LET spectra from space radiations: Implications for space radiation protection studies. Radiat Meas. 26(6):923-934.

6 Emfietzoglou D, Papamichael G, Nikjoo H (2017) Monte Carlo electron track structure calculations in liquid water using a new model dielectric response function. Radiat Res 188(3):355-368.

7 Cucinotta FA, Nikjoo H, Goodhead DT (1998) The effects of delta rays on the number of particle-track traversals per cell in laboratory and space exposures. Radiat Res 150(1):115-119.

8 Gonon G, Groetz JE, De Toledo SM, Howell RW, Fromm M, et al. (2013) Nontargeted stressful effects in normal human fibroblast cultures exposed to low fluences of high charge, high energy (HZE) particles: kinetics of biologic responses and significance of secondary radiations. Radiat Res 179(4):444-457.

9 Chancellor JC, Blue RS, Cengel KA, Auñón-Chancellor SM, Rubins KH, et al. (2018) Limitations in predicting the space radiation health risk for exploration astronauts. NPJ Microgravity 4(1):1-1.

10 Hu S, Kim MH, McClellan GE, Cucinotta FA (2009) Modeling the acute health effects of astronauts from exposure to large solar particle events. Health Phys 96(4):465-476.

11 Bailey V (1975) Radiation measurement and instrumentation. In Biomedical Results of Apollo. In: NASA.

12 Rask J, Vercoutere W, Navarro BJ, Krause A (2008) Space Faring: The Radiation Challenge. NASA 3(8):9.

13 Delp MD, Charvat JM, Limoli CL, Globus RK, Ghosh P (2016) Apollo lunar astronauts show higher cardiovascular disease mortality: possible deep space radiation effects on the vascular endothelium. Scientific reports 6(1):1-1.

14 Li M, Gonon G, Buonanno M, Autsavapromporn N, De Toledo SM, et al. (2014) Health risks of space exploration: targeted and nontargeted oxidative injury by high-charge and high-energy particles. Antioxid Redox Signal 20(9):1501-1523.

15 Paretzke HG (1987) Radiation track structure theory. Kinetics of non-homogeneous processes.

16 LaVerne JA (2000) Track effects of heavy ions in liquid water. Radiat Res 153(5):487-496.

17 Meesungnoen J, Jay-Gerin JP (2011) Radiation chemistry of liquid water with heavy ions: Monte Carlo simulation studies. Charged particle and photon interactions with matter: recent advances, applications, and interfaces. Boca Raton: Taylor & Francis 355-400.

18 Muroya Y, Plante I, Azzam EI, Meesungnoen J, et al. (2006) High-LET ion radiolysis of water: visualization of the formation and evolution of ion tracks and relevance to the radiation-induced bystander effect. Radiat Res 165(4):485-491.

19 Mikkelsen RB, Wardman P (2003) Biological chemistry of reactive oxygen and nitrogen and radiation-induced signal transduction mechanisms. Oncogene 22(37):5734-5754.

20 Wardman P (2009) The importance of radiation chemistry to radiation and free radical biology (The 2008 Silvanus Thompson Memorial Lecture). Br J Radiol 82(974):89-104.

21 McBride WH, Chiang CS, Olson JL, Wang CC, Hong JH, et al. (2004) A sense of danger from radiation. Radiat Res 162(1):1-9.

22 Kondo H, Limoli C, Searby ND, Almeida EA, Loftus DJ, et al. (2009) Shared oxidative pathways in response to gravity-dependent loading and gamma-irradiation of bone marrow-derived skeletal cell progenitors. Radiat Biol , radiol. 47(3):281-285.

23 Stein TP, Leskiw MJ (2000) Oxidant damage during and after spaceflight. Am J Physiol Endocrinol Metab AM J PHYSIOL-ENDOC M 278(3):375-382.

24 Stein TP(2002) Space flight and oxidative stress. Nutr. 18(10):867-871.

25 Markin AA, Popova IA, Vetrova EG, Zhuravleva OA, Balashov OI (1997) Lipid peroxidation and activity of diagnostically significant enzymes in cosmonauts after flights of various durations. Aviation, Space, and Environmental Medicine 31(3):14-18.

26 Soulsby M, Johnson E, Akel N, Agarwal R, Gaddy D, et al.(2011) PANCREATIC HISTOLOGY AND ASSOCIATED BIOCHEMICAL CHANGES IN RATS ON HIND-LIMB SUSPENSION. InAIP Conference Proceedings. American Institute of Physics 1326(1): 93-99.

27 Markin A, Strogonova L, Balashov O, Polyakov V, Tigner T (1998) The dynamics of blood biochemical parameters in cosmonauts during long-term space flights. Acta astronautica 42(1-8):247-53.

28 Zhang Z, Zhan H, Geng XC (2001) The progress on+ Gz stress-induced injuries of the cardiac structure and function and their mechanisms. Space medicine & medical engineering 14(5):378-381.

29 Li M, Gonon G, Buonanno M, Autsavapromporn N, De Toledo SM, (2014). Health risks of space exploration: targeted and nontargeted oxidative injury by high-charge and high-energy particles. Antioxid Redox Signal 20(9):1501-1523.

30 Mao XW, Nishiyama NC, Pecaut MJ, Campbell-Beachler M, Gifford P, et al. (2016) Simulated microgravity and low-dose/low-dose-rate radiation induces oxidative damage in the mouse brain. Radiat Res 185(6):647-657.

31 Multhoff G, Radons J (2012) Radiation, inflammation, and immune responses in cancer. Front Oncol 2:58.

32 Parihar VK, Allen BD, Caressi C, Kwok S, Chu E, etal. (2016) Cosmic radiation exposure and persistent cognitive dysfunction. Sci Rep 6(1):1-4.

33 Prasad KN (2016) Simultaneous activation of Nrf2 and elevation of antioxidant compounds for reducing oxidative stress and chronic inflammation in human Alzheimer's disease. Mech Ageing Dev 153:41-47.

34 Kennedy AR, Davis JG, Carlton W, Ware JH (2008) Effects of dietary antioxidant supplementation on the development of malignant lymphoma and other neoplastic lesions in mice exposed to proton or iron-ion radiation. Radiat Res 169(6):615-25.

35 Jandial R, Hoshide R, Waters JD, Limoli CL (2018) Space–brain: The negative effects of space exposure on the central nervous system. Surg. Neurol. Int 9.

36 Cherry JD, Liu B, Frost JL, Lemere CA, Williams JP, et al (2012). Galactic cosmic radiation leads to cognitive impairment and increased aβ plaque accumulation in a mouse model of Alzheimer's disease. PloS one 7(12):53275.

37 Britten RA, Jewell JS, Miller VD, Davis LK, Hadley MM, et al. (2016) Impaired Spatial Memory Performance in Adult Wistar Rats Exposed to Low (5–20 cGy) Doses of 1 GeV/n 56Fe Particles. Radiat Res 185(3):332-337.

38 Britten RA, Jewell JS, Duncan VD, Hadley MM, Macadat E, et al. (2018) Musto AE, Tessa CL. Impaired attentional set-shifting performance after exposure to 5 cGy of 600 MeV/n 28Si particles. Radiat Res 189(3):273-282.

39 Haley GE, Yeiser L, Olsen RH, Davis MJ, Johnson LA, et al. (2013) Raber J. Early effects of whole-body 56Fe irradiation on hippocampal function in C57BL/6J mice. Radiat Res 179(5):590-596.

40 Rabin BM, Hunt WA, Joseph JA, Dalton TK, Kandasamy SB (1991). Relationship between linear energy transfer and behavioral toxicity in rats following exposure to protons and heavy particles. Radiat Res 128(2):216-221.

41 Raber J, Yamazaki J, Torres ER, Kirchoff N, Stagaman K, et al. (2019) Combined effects of three high-energy charged particle beams important for space flight on brain, behavioral and cognitive endpoints in B6D2F1 female and male mice. Front Physiol 10:179.

42 Kennedy AR, Wan XS (2011) Countermeasures for space radiation induced adverse biologic effects. Adv. Space Res. 48(9):1460-1479.

43 Sage E, Shikazono N (2017) Radiation-induced clustered DNA lesions: Repair and mutagenesis. Free Radic Biol Med FREE RADICAL BIO MED 107:125-135.

44 Hada M, Wu H, Cucinotta FA. mBAND (2011) analysis for high- and low-LET radiation-induced chromosome aberrations: a review. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 711(1-2):187-192.

45 Hada M, Georgakilas AG (2008) Formation of clustered DNA damage after high-LET irradiation: a review. J Radiat Res 49(3): 203-210.

46 Ohnishi T, Takahashi A, Nagamatsu A, Omori K, Suzuki H, (2009) Detection of space radiation-induced double strand breaks as a track in cell nucleus. Biochem Biophys Res Commun 390(3):485-488.

47 Moreno-Villanueva M, Wong M, Lu T, Zhang Y, Wu H (2017) Interplay of space radiation and microgravity in DNA damage and DNA damage response. NPJ Microgravity 3(1):1-8.

48 George K, Rhone J, Beitman A, Cucinotta FA (2013) Cytogenetic damage in the blood lymphocytes of astronauts: effects of repeat long-duration space missions. Mutat Res Genet Toxicol Environ Mutagen 756(1-2):165-169.

49 Maalouf M, Durante M, Foray N (2011)Biological effects of space radiation on human cells: history, advances and outcomes. J Radiat Res 52(2):126-146.

50 Rastegar Z, Eckart P, Mertz M (2002) Radiation-induced cataract in astronauts and cosmonauts. Graefes Arch Clin Exp Ophthalmol 240(7):543-547.

51 Chylack Jr LT, Peterson LE, Feiveson AH, Wear ML, Manuel FK (2009) NASA study of cataract in astronauts (NASCA). Report 1: Cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. Radiat Res 172(1):10-20.

52 Cucinotta FA, Manuel FK, Jones J, Iszard G, Murrey J, et al. (2001) Space radiation and cataracts in astronauts. Radiat Res 156(5):460-466.

53 Crucian BE, Choukèr A, Simpson RJ, Mehta S, Marshall G (2018) Immune system dysregulation during spaceflight: potential countermeasures for deep space exploration missions. Front Immunol 9:1437.

54 Crucian B, Sams C (2009) Immune system dysregulation during spaceflight: clinical risk for exploration-class missions. J Leukoc Biol 86(5):1017-1018.

55 Guéguinou N, Huin-Schohn C, Bascove M, Bueb JL, Tschirhart E, et al. (2009) Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit?. J Leukoc Biol 86(5):1027-1038.

56 Taylor GR, Zaloguev SN (1977) Medically important micro-organisms recovered from Apollo-Soyuz Test Project (ASTP) crew members. Life Sci Space Res 15:207-212.

57 Pierson DL, Stowe RP, Phillips TM, Lugg DJ, Mehta SK (2005) Epstein–Barr virus shedding by astronauts during space flight. Brain, behavior, and immunity 19(3):235-242.

58 Pierson DL, Mehta SK, Magee BB, Mishra SK (1995) Person-to-person transfer of Candida albicans in the spacecraft environment. Med. Mycol. MED MYCOL 33(3):145-50.

59 Sanzari JK, Wan XS, Wroe AJ, Rightnar S, Cengel KA, et al. (2013) Acute hematological effects of solar particle event proton radiation in the porcine model. Radiat Res 180(1):7-16.

60 Sanzari JK, Romero-Weaver AL, James G, Krigsfeld G, Lin L, et al. (2013) Leukocyte activity is altered in a ground based murine model of microgravity and proton radiation exposure. PloS one 8(8):71757.

61 Sanzari JK, Wilson JM, Wagner EB, Kennedy AR (2011) The combined effects of reduced weightbearing and ionizing radiation on splenic lymphocyte population and function. Int. J Radiat Biol 87(10):1033-1038.

62 Li M, Holmes V, Zhou Y, Ni H, Sanzari JK, et al. (2014) Hindlimb suspension and SPE-like radiation impairs clearance of bacterial infections. PLoS One 9(1):e85665.

63 Zhou Y, Ni H, Li M, Sanzari JK, Diffenderfer ES,et al. (2012) Effect of solar particle event radiation and hindlimb suspension on gastrointestinal tract bacterial translocation and immune activation 7(9):44329.

64 Kennedy AR (2014) Biological effects of space radiation and development of effective countermeasures. Life Sci Space Res 1:10-43.

65 Kennedy AR, Ware JH, Guan J, Donahue JJ, Biaglow JE, et al. (2004) Selenomethionine protects against adverse biological effects induced by space radiation. Free Radic Biol Med 36(2):259-266.

66 Burns FJ, Tang MS, Frenkel K, Nádas A, Wu F,et al. (2007) Induction and prevention of carcinogenesis in rat skin exposed to space radiation. Radiat Environ Biophys 46(2):195-199.

67 Limoli CL, Giedzinski E, Baure J, Rola R, Fike JR (2007) Redox changes induced in hippocampal precursor cells by heavy ion irradiation. Radiation and Environmental Biophysics 46(2):167-172.

68 Villasana LE, Rosenthal RA, Doctrow SR, Pfankuch T, Zuloaga DG, et al. (2013) Effects of alpha-lipoic acid on associative and spatial memory of sham-irradiated and 56Fe-irradiated C57BL/6J male mice. Pharmacol Biochem Behav 103(3):487-493.

69 Rabin BM, Shukitt-Hale B, Joseph J, Todd P (2007) Diet as a factor in behavioral radiation protection following exposure to heavy particles. Gravit Space Biol Bull 18(2).

70 Kuefner MA, Brand M, Ehrlich J, Braga L, Uder M, et al. (2012) Effect of antioxidants on x-ray–induced γ-H2AX foci in human blood lymphocytes: preliminary observations. Radiology 264(1):59-67.

71 Singh VK, Beattie LA, Seed TM (2013) Vitamin E: tocopherols and tocotrienols as potential radiation countermeasures. J Radiat Res 54(6):973-988.

72 Satyamitra MM, Kulkarni S, Ghosh SP, Mullaney CP, Condliffe D,et al. (2011) Hematopoietic recovery and amelioration of radiation-induced lethality by the vitamin E isoform δ-tocotrienol. Radiat Res 175(6):736-745.

73 Brown SL, Kolozsvary A, Liu J, Jenrow KA, Ryu S,et al. (2010) Antioxidant diet supplementation starting 24 hours after exposure reduces radiation lethality. Radiat Res 173(4):462-468.

74 Wambi C, Sanzari J, Wan XS, Nuth M, Davis J,et al. (2008) Dietary antioxidants protect hematopoietic cells and improve animal survival after total-body irradiation. Radiat Res 169(4):384-396.

75 Steczina S, Tahimic CG, Pendleton M, M'Saad O, Lowe M, et al. (2020) Dietary countermeasure mitigates simulated spaceflight-induced osteopenia in mice. Scientific reports 10(1):1-2.

76 Waldren CA, Vannais DB, Ueno AM (2004) A role for long-lived radicals (LLR) in radiation-induced mutation and persistent chromosomal instability: counteraction by ascorbate and RibCys but not DMSO. Mutat. Res. – Fundam Mol Mech Mutagen 551(1-2):255-265.

77 Vile GF, Winterbourn CC (1988) Inhibition of adriamycin-promoted microsomal lipid peroxidation by β-carotene, α-tocopherol and retinol at high and low oxygen partial pressures. FEBS letters 238(2):353-356.

78 Prasad KN, Bondy SC (2017) MicroRNAs in hearing disorders: their regulation by oxidative stress, inflammation and antioxidants. Front Cell Neurosci 11:276.

79 Wu H, Kong L, Tan Y, Epstein PN, Zeng J, et al. (2016) C66 ameliorates diabetic nephropathy in mice by both upregulating NRF2 function via increase in miR-200a and inhibiting miR-21. Diabetologia 59(7):1558-1568.

80 Shoulson I, Parkinson Study Group (1998) DATATOP: a decade of neuroprotective inquiry. Ann Neurol 44(1):160-166.

81 en la enfermedad de Parkinson N (1993) Impact of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 328:176-183.

82 Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, et al. (1997) A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 336(17):1216-1222.

83 Chapman J (2014) Current drug information: Vitamin E and Alzheimer's disease. AJP: Aust J Pharm 95(1126):92-93.

84 Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330(15):1029-1035.

85 N Prasad K, C Bondy S (2014) Inhibition of early upstream events in prodromal Alzheimer's disease by use of targeted antioxidants. Curr Aging Sci 7(2):77-90.

86 Hashimoto M, Yoshimoto M, Sisk A, Hsu LJ, Sundsmo M, et al. (1997) NACP, a synaptic protein involved in Alzheimer's disease, is differentially regulated during megakaryocyte differentiation. Biochem Biophys Res Commun 237(3):611-616.

87 Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, et al. (2006) Supplemental and dietary vitamin E, β-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst Monogr 98(4):245-254.

88 Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, et al. (2007) Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol 2007 Jan 1;66(1):75-85.

89 Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, et al. (2009) Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. Proc Natl Acad Sci 106(8):2933-2938.

90 Lastres-Becker I, Ulusoy A, Innamorato NG, Sahin G, Rábano A, et al.(2012) α-Synuclein expression and Nrf2 deficiency cooperate to aggravate protein aggregation, neuronal death and inflammation in early-stage Parkinson's disease. Hum Mol Genet 21(14):3173-3192.

91 Xu F, Li J, Ni W, Shen YW, Zhang XP (2013) Peroxisome proliferator-activated receptor-γ agonist 15d-prostaglandin J2 mediates neuronal autophagy after cerebral ischemia-reperfusion injury. PloS one 8(1):55080.

92 Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, et al.(2004) Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci 101(10):3381-3386.

93 Trujillo J, Chirino YI, Molina-Jijón E, Andérica-Romero AC, Tapia E, et al. (2013) Renoprotective effect of the antioxidant curcumin: Recent findings. Redox Biol 1(1):448-456.

94 Steele ML, Fuller S, Patel M, Kersaitis C, Ooi L, et al. (2013) Effect of Nrf2 activators on release of glutathione, cysteinylglycine and homocysteine by human U373 astroglial cells. Redox Biol 1(1):441-445.

95 Kode A, Rajendrasozhan S, Caito S, Yang SR, Megson IL, et al.(2008) Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol 294(3):478-488.

96 Gao L, Wang J, Sekhar KR, Yin H, Yared NF, et al. (2007) Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3J. Biol Chem 282(4):2529-2537.

97 Saw CL, Yang AY, Guo Y, Kong AN (2013) Astaxanthin and omega-3 fatty acids individually and in combination protect against oxidative stress via the Nrf2–ARE pathway. Food Chem Toxicol 62:869-875.

98 Song J, Kang SM, Lee WT, Park KA, Lee KM, et al. (2014) Glutathione rescues brain endothelial cells from hydrogen peroxide-induced oxidative stress by activating Nrf2 expression 23(1):93-103

99 Ji L, Liu R, Zhang XD, Chen HL, Bai H, et al. (2010) N-acetylcysteine attenuates phosgene-induced acute lung injury via up-regulation of Nrf2 expression. Inhal Toxicol 22(7):535-542.

100 Beriat GK, Ezerarslan H, Akmansu SH, Aksoy S, Ay S, et al. (2011) Comparison of efficacy of different treatment methods in the treatment of idiopathic tinnitus. Kulak burun bogaz ihtisas dergisi: KBB= Journal of ear, nose, and throat 21(3):145-53.

101 Kim J, Cha YN, Surh YJ (2010) A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. Mutat Res - Fundam Mol Mech Mutagen 690(1-2):12-23.

102 Li W, Khor TO, Xu C, Shen G, Jeong WS, et al. (2008) Yu S, Kong AN. Activation of Nrf2-antioxidant signaling attenuates NFκB-inflammatory response and elicits apoptosis. Biochemical pharmacology 76(11):1485-1489.

103 Abate A, Yang G, Dennery PA, Oberle S, Schröder H (2000) Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. Free Radic Biol Med 29(11):1135-1142.

104 Fu Y, Zheng S, Lin J, Ryerse J, Chen A (2008) Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Mol Pharmacol 73(2):399-409.

105 Cho JY, Rhee MH, Hong S, Kwon M, Kim SH, et al. (2007) Neuroprotective effect of curcumin is mainly mediated by blockade of microglial cell activation. Die Pharmazie-Int J Pharm Sci Res 62(12):937-942.

106 Rahman S, Bhatia K, Khan AQ, Kaur M, Ahmad F, et al. (2008) Topically applied vitamin E prevents massive cutaneous inflammatory and oxidative stress responses induced by double application of 12-O-tetradecanoylphorbol-13-acetate (TPA) in mice. Chem Biol Interact 172(3):195-205.

107 Suzuki YJ, Aggarwal BB, Packer L (1992) α-Lipoic acid is a potent inhibitor of NF-κB activation in human T cells. Biochem Biophys Res Commun 189(3):1709-1715.

108 Zhu J, Yong W, Wu X, Yu Y, Liu C, et al. (2008) Anti-inflammatory effect of resveratrol on TNF-α-induced MCP-1 expression in adipocytes. Biochem Biophys Res Commun 369(2):471-477.

109 Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, et al. (2012) Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA 308(18):1871-1880.

110 Baum MK, Campa A, Lai S, Martinez SS, Tsalaile L, et al. (2013) Effect of micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana: a randomized clinical trial. JAMA 310(20):2154-2163.