Bioflavonoids as Important Component of Biological Protection from Ionizing Radiation

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ABSTRACT

New advances in the area of deciphering the mechanism for a possible modification of the biological effects of radiation exposure at the genetic level make it possible to distinguish the group of radiation protective agents having their own specific features in the implementation of their beneficial effects. The mechanism of the radioprotective action of bioflavonoids is worthy of a detailed analysis in view of their great biological importance. Radiobiological studies show that antioxidants can reduce the radiation damage to membranes and favor more adequate energy dependent adaptive and reparative processes after the exposure to radiation. Bioflavonoids are significant component of “biological protection” for an enhance of resistance of the body to environmental factors that are adverse for human health, including ionizing radiation, with reducing the risk of carcinogenic effects and decreasing the biological age. The best practical value of bioflavonoids, can be considered as the agents for prophylaxis against the development of oxidative stress. These are the reasons why the administration of natural antioxidants have a pathogenetic justification for exposures to chronic (months, years) low-rate-dose ionizing radiation. These agents were previously and are currently being developed for use during long-term, low-rate-dose exposures to radiation, under conditions of long space missions. Acting as low-dose stressors through a hormetic mechanism and a “substrate” support of adaptive shifts radiomodulators results in an increase in the antioxidant defense of the body and the rearrangement of its functioning in the new environment with the modulation of gene expression of antioxidant response elements by activation of Nrd2/Keap1 and Sirtuin/FoxO pathways and a decrease in the transcription factor NF-κB.

KEYWORDS

Bioflavonoids; Antioxidants; Radiation Protective Agents; Radiomodulators; Low-Dose-Rate Irradiation

1. Introduction

Preventive medicine gives a lot of attention to the role of antioxidants, especially of the natural origin. Radiobiological studies show that antioxidants can reduce the radiation damage to membranes and favor more adequate energy dependent adaptive and reparative processes after the exposure to irradiation. It is important to emphasize that the organism responds to the radiation damage, as to any influence of stress, by mobilizing the antioxidant system. Under conditions of the long-term low-level exposure to radiation, when the antioxidant system of the organism is exhausted, the administration of natural water soluble and fat soluble antioxidants can act as a substrate treatment aimed at compensating the increased need for these compounds [1-3].

Bioflavonoids (natural plant flavonoids, semi-essential nutrients, vitamin P) are significant component of “biological protection” [4,5] for an enhance of resistance of the body to harmful environmental factors, including ionizing radiation, with reducing the risk of carcinogenic effects and decreasing the biological age [6,7].

Flavonoids are the products of the plant vital activity. Tea leaves, buckwheat, Sophora japonica, citrus fruits, rose hips and black chokeberry are especially rich in them. Substantial amounts of flavonoids are contained in black currants, strawberries, raspberries, cherries, sea
buckthorn, some sorts of apples, plums and grapes.

Flavonoids are plant polyphenols. The most important are flavan-3-ols (catechins), flavonols, flavones, neo-flavanones, anthocyanidins, leucoanthocyanidins (flavandiols-3,4), and also chalcone derivatives, dehydro-chalcone and aurone. About 4000 flavonoids have been described. Flavonoids are water-soluble or lipophilic compounds with yellow, orange and red color. Anthocyanines and aurones are plant pigments, and colour flowers and fruits. Humans need several hundred milligrams of bioflavonoids (vitamin P) per day.

In plants, they exist in the form of glycosides and rutinosides. In plants, flavonoids protect the photosynthetic apparatus of the cell against reactive oxygen species during the exposure to the short-wave UV radiation and other forms of oxidative stress (frost, drought, extreme fluctuations of the environmental temperature, etc.) [8,9]. It should be noted that plants growing in the areas contaminated by fallout from Chernobyl have an increased production of anthocyanins [10]. In addition, flavonoids are referred to as protective agents in the plants which are affected by pathogens.

The tissues of the body contain ascorbic acid at a certain concentration; cell membranes contain tocopherols. There is a recirculation of the oxidized and reduced forms of these natural antioxidants, which supports the antioxidative protection of cell membranes. It involves flavonoids, which are the most powerful antioxidants, and the antioxidant system of cells as a whole. Flavonoids reduce ascorbic acid and they also readily form complexes with metal ions, as well as have the antimitogenic activity. Flavanols, flavonols and flavonones inhibit lipid peroxidation [11], including that induced by ionizing radiation, starting with the concentration of more than 10 mcM [12]. Plant flavonoids several times exceed endogenous and exogenous antioxidants in the tissues of animals and humans (vitamin E, glutathione, ascorbic acid, beta-carotenoinds) in their antiradical activity [13, 14]. The unquestionable synergetic effect was observed in quercetin with glutathione and ascorbic acid [15]. The flavonoids possess anti-inflammatory, antioxidant, anti-allergic, hepatoprotective, antithrombotic, antiviral, and anti-carcinogenic activities [16].

2. Anti-Radiation Effect of Bioflavonoids

Flavonoids mitigate the radiation damage to DNA in vitro which is registered by the reduction of chromosomal aberrations (CA) in the bone marrow, in all probability, due to their anti-radical activity [17]. Quercetin is able to accumulate in mitochondria and bind to the DNA molecule [18].

The mechanism for the action in vitro of dry wine is the same, primarily due to catechins (30 - 100 mg/L) and procyanidins from the grape seeds which are found in its composition [19,20]. Alcohol in the composition of dry wine does not prevent the realization of the effect of bioflavonoids. Catechins from tea also reduce the DNA damage, with epigallocatechin from green tea being the most active (in the ratio of up to 400 mg/L) [21,22]. A similar action is typical for flavonones naringenin from grapefruit [23], apigenin [24], luteolin [25], and lignans [26].

Radiation protective effects of flavonoids on the reduction of the CA levels of the bone marrow were also observed in the experiments in vivo when they were used before and after exposures of mice to irradiation [27,28]. Bioflavonoids can exert a radiation protective effect detected by the test of the increased survival rate of animals exposed to lethal doses of radiation. This result was obtained following the administration of anthocyanins [29] and isoflavone genistein [30,31], flavonol quercetin [32] and the extract from the fruit of black chokeberry [33]. The radiation protective effect of genistein is associated with the induction of G-CSF and IL-6 [34]. Genistein can have a favorable effect on the reduction of the radiation damage to the lungs [35].

The best practical value of bioflavonoids, can be considered as the agents for prophylaxis against the development of oxidative stress. These are the reasons why the administration of natural antioxidants have a pathogenetic justification for exposures to chronic (months, years) low-rate-dose ionizing radiation [2,36]. These agents were previously and are currently being developed for use during long-term, low-rate-dose exposures to radiation, under conditions of long space missions [37-40]. Since these substances have low toxicity and do not have side effects at the administered doses, they can be used repeatedly, lifelong if necessary, with alterations in the cycles of metabolic correction and substrate therapy depending on the appearance of symptoms of chronic oxidative stress. The realization of the action of natural antioxidants takes a certain period of time, so the effect is enhanced following the repeated their administration [41]. A peculiar feature of pharmaco-dynamics of the preparations comprising the “biological shield” is that the modifications in the radiation resistance of the organism under their impact do not happen immediately, but gradually over repeated administration, more often within 2 weeks, and can be maintained at the elevated level during the entire course of treatment and prevention [42,43]. When the preventive measures are well tolerated, they can be repeated without any loss of their effectiveness.

3. The Mechanism of Protective Effectiveness of Bioflavonoids against Ionizing Radiation Exposure

The theoretical basis for the research into the mechanism of increasing the resistance of the organism to environ-
mental chronic stress under the influence of pharmacological agents is from a classic study by Selye [44] and additional research in this area, including studies investigating into the formation of different adaptive stages, depending on the strength and duration of the impact of adverse environmental factors [45-47].

The fundamentally important characteristic feature of the pharmacological agents that enhance the nonspecific resistance of the organism is the fact that their optimal effect can be formed due to the slowly proceeding structural rearrangements manifesting themselves as the alteration and complication of the adaptive phases of “activation” and “training” supported by the definite rhythm of repeated exposures to low doses of an adaptogen [45].

Acting as low-dose stressors through a hormetic mechanism and a “substrate” support of adaptive shifts radiomodulators results in an increase in the antioxidant defense of the body and the rearrangement of its functioning in the new environment with the modulation of gene expression of antioxidant response elements by activation of Nrf2/Keap1 and Sirtuin/FoxO pathways and a decrease in the transcription factor NF-κB [48-50]. According to their action, these agents are to some extent opposite to drugs noted in [1] as classical mitigators (e.g., vaccines, LPS, pro-inflammatory cytokines) which have pro-inflammatory properties and whose mechanism is based on the activation of the transcription factor NF-κB (Table 1).

The repeated administration of vitamin complexes results in the increase of the body resistance to harmful environmental factors, including radiation exposure. This is associated with the activation of the pituitary-adrenal system. For example, ascorbic acid, whose action is stimulated by flavonoids, is a cofactor for the synthesis of adrenaline and glucocorticoids [51,52]. The basis of the pathogenetic mechanism for their action lies in the stimulation of the neuro-immuno-endocrine system with the activation of individual axes of regulation (pituitary-adrenal, hypothalamic-thymic, and pituitary-thyroid), whose predominance depends on the nature, dose, and pattern of administration of a pharmaceutical agents. Of example, estrogenic flavonoids (genistein) have immunostimulant action [53,54]. A direct substrate regulation of the antioxidant system and biosynthetic processes, which are important for the post-radiation reparation of the tissues of the body, is also possible when natural antioxidants are used as nutrient supplements—vitamins, nucleotides, oligo-peptides, amino acids, and other compounds. However, in this case system reactions affecting the neuro-immuno-endocrine regulation in the organism are inevitable.

Table 1. The mechanisms and conditions of realization of radiation protective effect of flavonoids.

<table>
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<th>The mechanisms of anti-radiation action</th>
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<td>Pro-oxidant</td>
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<td>Anti-carcinogenic</td>
<td>Inhibition the NF-κB pathway, and the mutation or hyper-expression of the Nrf2/Keap1 signaling pathway in tumor genesis, and angiogenesis</td>
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<td>Anti-inflammatory</td>
<td>Inhibition the NF-κB pathway, pro-inflammatory cytokine decrease → mitigation of post-radiation fibrosis of tissues</td>
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and other natural antioxidants are considered as impacting redox reactions [55,56]. Those with high oxidant potential can directly interact with radiation-induced radicals; this has been recently considered as a basic mechanism of their radioprotective action [57-59].

However, natural antioxidants, in all probability, participate in the gene regulation of the antioxidant system of the organism. Their indirect involvement as antioxidants can be achieved by means of inhibition of the redox-sensitive transcription factors (NF-κB, activator protein-1) and pro-oxidant enzymes (iNOS, cyclooxygenase, xanthine oxidase) through the induction of antioxidant enzymes (glutathione peroxidases, superoxide dismutase), and phase II of cellular respiration. Experiments in vitro revealed that genistein and quercetin are able to significantly increase the gene promoter activity of glutathione peroxidase and superoxide dismutase in the absence of the effect on the activity of catalase [60]. Genistein also increased the expression of metallothionein genes [61]. Quercetin inhibits the synthesis of iNOS through the inhibition of NF-κB and STAT1 [49] and suppresses the growth of xenograft A2780S ovarian tumors by causing cancer cell apoptosis and inhibition of angiogenesis in
vivo [62]. Genistein induces antiangiogenesis and anti-metastatic effects, and cell cycle arrest [63]. The mechanism of anti-carcinogenic action of flavonoids closely is connected with inhibition of the mutation or hyper-expression of the NF-κB, and the Nrf2-Keap1 signaling pathway in tumor genesis [64]. Anti-inflammatory properties of flavonoids are caused by selectively block of nuclear NF-κB transactivation of specific target genes (in particular IL-6) via attenuation of mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase (MEK) and ERK activity [65]. Drugs with NF-κB pathway suppressive and anti-inflammatory actions, such as angiotensin-converting enzyme and prostaglandin biosynthesis inhibitors, and melatonin, and isoflavone genistein can mitigate post-radiation fibrosis of kidney, lungs, skin, and post-radiation myelosuppression of ARS [66-72].

As any antioxidants, flavonoids can show pro-oxidant action under certain condition (for example, high dose of drugs and the exhaustion of antioxidant enzyme network) [73]. This effect may induce NF-κB activation with following increase pro-inflammatory cytokines which have radiation protective and mitigable action [74].

4. Conclusion

The favorable action of natural antioxidants in the presence of the chronic oxidative stress is the reduction in the intensity and time needed to implement the remote impact of radiation damage to particular tissues and systems, primarily associated with their important role in the functioning of the vascular system. This prevents the development of atherosclerosis, disorders of the microcirculation in tissues and their fibrosis, and the manifestation of chronic inflammatory processes in the patients with the immune system disorders; in other words, pre-morbid states leading to, as noted above, cardiovascular and endocrine diseases and the progression of carcinogenesis [75]. It is also known that the bioflavonoids epigallakatehin-3-gallate, luteolin, quercetin, kaempferol, apigenin, and taxifolin are able to block the fatty acid synthase, which is the basis for the anti-carcinogenic action of these compounds [76]. Antioxidants (quercetin, vitamins A and C, beta-carotene, selenium, melatonin, and glutathione) are used in clinical practice as radio-modulators during the radio-chemotherapy of cancer patients [77]. New advances in the area of deciphering the mechanism for a possible modification of the biological effects of radiation exposure at the genetic level make it possible to distinguish the group of radiation protective agents having their own specific features in the implementation of their beneficial effects. The mechanism of the radioprotective action of bioflavonoids is worthy of a detailed analysis in view of their great biological importance [78].

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Declaration of Interest

The author reports no conflicts of interest and is alone responsible for the content and writing of this paper.

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Abbreviations and Acronyms

Nrf2/Keap1 pathway—Signaling pathway involving the repressor protein Keap1 and the transcription factor nuclear factor-erythroid 2-related factor (Nrd2), which binds to the antioxidant response elements in the promoters of antioxidant enzymes and detoxifying enzymes, the global regulator of oxidative stress
Sirtuin/FoxO pathway—Signaling pathway in which sirtuin, nuclear family proteins, key regulators of cell defenses and survival in response to stress, deacetylates and represses FoxO (transcription factor Forkhead box O) dependent apoptosis
NF-κB—Transcription nuclear factor kappaB

ERK—Extracellular signal-regulated kinase
MEK—Extracellular signal-regulated kinase (ERK) kinase
ARS—Acute radiation syndrome
STAT1—A member of the Signal Transducers and Activators of Transcription family of transcription factors
iNOS—Inducible isoform of nitric oxide synthases
G-CSF—Granulocyte-colony stimulating factor
IL-6—Interleukin-6
DNA—Deoxyribonucleic acid
UV-radiation—Ultraviolet radiation
CA—Chromosome aberrations