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Flavonoids and Effective Factors for Protection against Radiations

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Abstract- As the title indicated, this paper studies flavonoids which is a plant composition having the antioxidant characteristics which plays a key role in strengthening the health, decreasing the risk of the diabetes, cancer, and heart diseases. It also focuses on the effective factors for protecting the human beings against the radiations. The data for this study are extracted from different scientific papers published in international journals such as Google Scholar, Scopus, Web of Science, and PubMed. This paper first discusses the damages caused by the ionizing radiations, next, I have talked about the classification of flavonoids. A table containing the data such as the affected animals or cells, the prescribed dosage of the flavonoids, the timing of dosage, the type of radiation, and the result seen on the animals. The result of the study shows that flavonoids truly reduce the adverse effects of the radiations on healthy cells during radio-therapy, accidental radiations, or radiations caused by terrorist attacks on nuclear power plants.

Keywords- flavonoids, ionizing radiation, protection

I. INTRODUCTION

In the recent years, as the technology expands, ionizing radiation is widely used in diagnostic and treatment purposes in medical sciences, agriculture, and industry [61]. Thus, human being are exposed to a bigger quantity of the radiation [57]. Moreover, the increase of the possibility of terroristic attacks on the nuclear power plant and reactors, unintentional events, and accidental leakage of radioactive materials are always a matter of concern [2]. Radio therapy, alone or with chemotherapy, is one of the popular methods of treatment of cancer instead of surgery. Damaging the healthy cells, and the risk of creating new malignant cancer have always been one of the main challenges of radiotherapy which are controllable by using the protective materials against the radiation, or by increasing the resistance of the natural cells [62],[31]. Ionizing radiation causes the production of free radicals in the body, and this radicals have important roles in the pathogens of various diseases. That is because these radicals are able to harm the cells, and DNA, as well as oxidizing the proteins, or induction of lipid peroxidation [48]. These distractive impacts can cause dysfunction of hematopoietic and immune systems, and acceleration of the process of aging [53]. Therefore, much importance is given to the protection of the human being in radio-therapy, and the endangered people such as the military forces [53]. Flavonoids are a group of polyphenolic compounds that more than 9000 types of them have been recognized in different plants so far [24]. Since the beginning of 1920 the biological activities of flavonoid derivatives such as neutralization of free radicals, increase of resistance against the radiations, decrease of inflammation, antitumor effects, and retard of aging of cells have been known [41],[45],[4]. Currently, most of the investigations have targeted the effects of protection against the radiations. Hence, the study of mechanism of protection by flavonoids against

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the radiation, and the implementation of them in prevention of the crisis, and the right ways of dealing with the crisis have got importance.

II. METHODOLOGY

I have reviewed a number of papers in different web pages such as Google Scholar, Scopus, Web of Science, and Pubmed, and retrieved the data from those sources.

III. DAMAGES CAUSED BY IONIZING RADIATIONS

These radiations are naturally found in different types such X-ray, Alfa, Beta, Gama, and Neutron [18]. The effect of these radiations on human body can cause a series of complex bio-chemical changes, and eventually, the damage or necrosis of the targeted organ [12].

The studies have shown that these radiations have caused direct and indirect damages on human body. The direct damages happen when various vital macromolecules in the living organism get in physical touch with the radiations which causes the serious damage [46]. The indirect damages of radiations are mainly caused by free radicals which are coming from the water molecules in the body [3]. Ionizing radiations produce free radicals such as hydroxyl radical and superoxide that overlap with the vital macromolecules of the body, and bring significant changes in the function of them which in turn is the result of serious damage of radiations [50]. The damage in DNA, immune and hematopoietic systems are some of the most drastic damages that these ionizing radiations cause to the living organism. The damage in DNA results in omission of cell information, and disorder in the natural function of the cell which can cause the death of the cell or expulsion of it out of the cell cycle or creation of tumor [71].

The cells of immune and hematopoietic systems are highly sensitive to the ionizing radiations. Ionizing radiations can decrease the number of immune cell or dismiss the specific and nun-specific function of them [44]. In relation with the hematopoietic system too these radiations can harm the bone marrow which result in decrease of erythrocyte [71], [22].

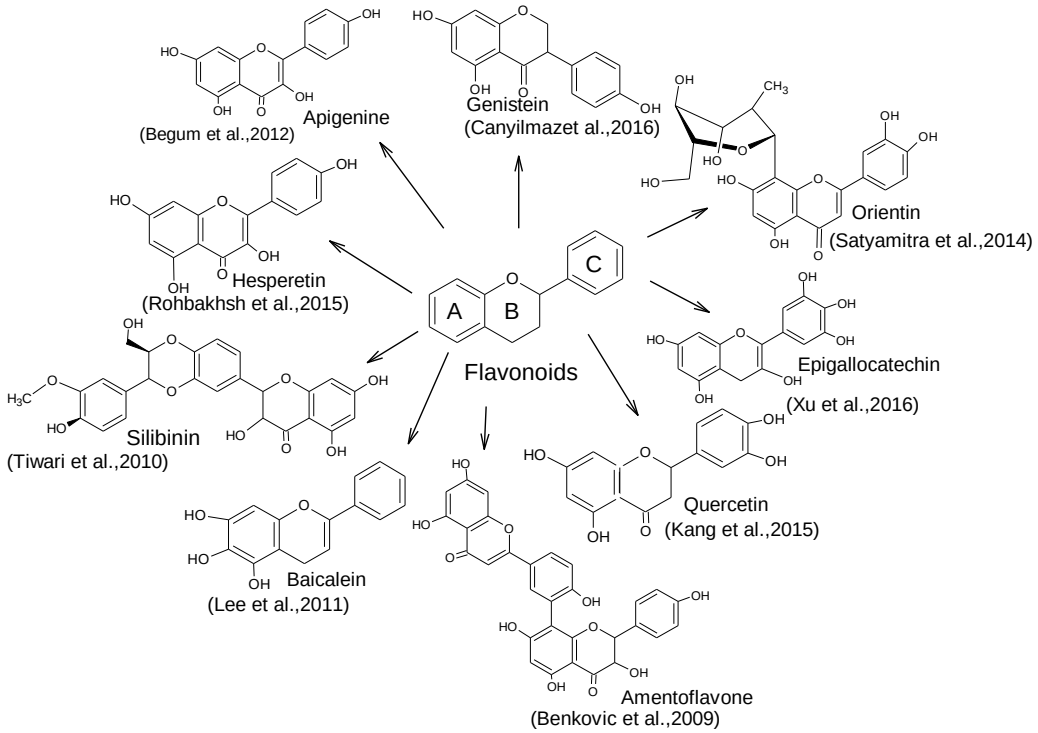

Fig. 1 The nucleus of chemical structure of flavonoids, and the basic mechanisms of molecule in the protection against the radiation by eight key types of flavonoids [58],[32],[49],[65],[34],[52],[9],[7],[14].

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IV. CLASSIFICATION OF FLAVONOIDS

Flavonoids are polyphenolic compounds having the basic nucleus of 2-phenyl chromone. These compounds are in the free form of di-cycle aromatic with phenolic OH (A and B cycles) which are joint to carbon section [60]. Their cyclic formula are $C_6C_3C_6$ which are shown in the figure 1 [21]. These compounds are extensively found in the fruits, and also in the stem and body of the plants, and generally, in the form of secondary metabolite in the plants [64]. On the basis of chemical characteristics of carbonic cycles, the number and the type of distribution of hydroxyl groups flavonoids are classified into 10 different groups among which flavones, flavonons, flavonoles, flavononols, isoflavones, flavanoles (catsines), and antocianydines are more prominent which are being discussed in the followings [13].

V. MOLECULAR MECHANISMS OF FLAVONOIDS IN PROTECTING AGAINST RADIATIONS

The nonpoisonous or less poisonous compounds produced through natural procedures which can be used prior or after being exposed to the ionizing radiation to reduce the damages of radiations are called natural radio protective [16].

The benefits of flavonoids in different purposes such as anti-ionizing radiations, anti-oxidant and anti-free radicals, anti-virus and anti-bacterial effects, anti-tumor traits in prevention or treatment of cancer, and anti-inflammatory effects are proven in cell and animal studies [30],[51].

Table 1 exhibits a description of studies on evaluation of the effects of flavonoids in protection against the radiations

Flavonoid name	Animal or cell category studied	Prescribed dose	Time of prescription	Dose or type of radiation	The proposed mechanism	Test	Observed biological effect	References
Apigenin	Human lymphocytes	3.2 µM	One hour before the encounter	3Gy of gamma rays from ^{60}Co	Reducing damage to chromosomes	(CBMN) Cytokinesis-block micronucleus	Reduction of damage to chromosomes caused by ionizing radiation in human lymphocytes/reduction of micronucleus formation	[7]
Amentoflavone	Guinea pig lung fibroblast cells	30 to 120 mg/kg	24 hours before radiation	8Gy gamma rays from ^{60}Co	Inhibition of oxidative stress	Measurement of cell viability, apoptosis and ROS levels	Inhibition of apoptosis and reduction of ROS	[67]
Baicalein	Mouse blood cells	5 grams per kilogram	Flavonoids before exposure to radiation	15Gy	Decreased expression of pro-inflammatory factors such as NF-KB and Akt	Alkaline comet assay and Micronucleus assay	Reducing DNA and bone marrow damage	[34]
Genistein	mouse	200 mg/kg	One hour before the encounter	X-Ray	Reduction of apoptosis inhibitory factors such as phosphoinositide-3-kinase along with protein kinase (PI3K-Akt) B, mitogen-activated protein kinase (MAPK) and metalloproteinases 2 and 9 (MMPs)	RT-PCR	Improving bone marrow function increases the thirty-day life expectancy index in mice by 44 percent index in mice	[15]

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Hesperidin	mouse	50 and 100 mg/kg	2 weeks ago	7 Gy	Decreased levels of TNF α and increased IL-10	Biochemical analysis	Reduce inflammation	[25]
Orientin	mouse	200 µM	30 minutes before exposure	4 Gy	scavenging induced hydroxyl free radicals	DPPH	Effectively reduce radiation-induced genotoxicity and protect DNA from radiation damage	[52]
Quercetin	HaCaT keratinocyte cell category	20 µM	8 hours before exposure	UVB	Increasing SOD activity and reducing ROS, TNFα and MDA levels	MTT assay and ROS assessment	Significant reduction in cell death	[72]
Silibinin	mouse	3 days before exposure	7.5 gray	Reduction of micronuclei	DNA damage assay	Dramatic reduction of deaths caused by these rays and protection of DNA damage of blood cells		[59]

Prescribing different flavonoids on the mouse caused the significant increase of 30 days of survival, and the decrease of apoptosis and necrosis induced by ionizing radiations [47], [67]. In general, the main mechanisms of protection against the radiation by flavonoids include the protection of DNA, anti-oxidant effect, protection of immune system, protection of hematopoietic system, and the decrease of inflammation which are discussed in the following.

VI. PROTECTING DNA AGAINST THE DAMAGES AND SEXUAL TOXICITY

The damage of DNA is the initial and the main impact of ionizing radiations. When DNA is exposed to ionizing radiations, and got damaged, it affects the human body as the secondary impact. Hence, lowering the effect of ionizing radiation on DNA is one of the most important issues in research on protecting the human body against the ionizing radiations [27].

The method of alkaline comet assay for examining the effect of protecting Baicalein radiation on DNA when exposed to radiation showed that prescribing flavonoids before exposing the body to the radiation had a remarkable result in preventing the damages [19]. Micronucleus assay in mice blood cells being exposed to radiation indicates a reduction of damage in bone marrow. It has been shown that the treatment of mice lymphocyte exposed to 3 Gary ionizing radiation by silibinin reduces the damages of DNA, and the production of micronucleus. Similarly, prescribing edible silibinin to the mice exposed to 7.5 Gray ionizing radiation resulted in reduction of death caused by these radiation. It also resulted in protection of DNA of blood cells [58].

The results of Cytokinesis block-micronucleus (CBMN) assay in evaluation of effects of protection against apigenin in human lymphocytes indicate that the damages due to the ionizing radiation on the chromosome have been reduced [7]. This flavonoid reduces the speed of formation of dosage-related micronucleus significantly.
[67]. studied the effect of protection against the radiation by guipipill flavonoids on the mice, and showed that the prescription of these flavonoids six days prior to exposure to 8 Gary ionizing radiation increases the chance of 30 day- survival in these animals [66]. It has been proved that these flavonoids cause the increase of number of leucocyte and the content of DNA of bone marrow [35].

Additionally, flavonoids of the ocimum, procyanidin, narigin (orientin) family, the collection of propolis flavonoids, and gentianella flavonoids also can reduce the genetic toxicity caused by radiation, and can protect the DNA from the damages of radiation [8], [43].

VII. Cleaning Free Radicals and Antioxidant Effects

Ionizing radiations can affect the liquid environment of living organisms, and eventually produce many types of free radicals. These radical can reduce the activities of Superoxide dismutase (SOD), Glutathione peroxidase,(GSH-Px), and Catalase (CAT), cause peroxidation of lipids, and increase the indication of malondialdehyde (MDA) which have a high potential to harm the cell membrane and DNA materials [48],[38]. Flavonoids can effectively clean the free radical of oxygen, and eliminate the indirect effects of ionizing radiation on human body [52]. Most of the studies on the animals show that these effect can reduce the rate of death caused by radiation [26].

It has been shown that the flavonoids of humulus lupulus family can increase the activities of SOD, GSH-PX, and CAT, and decrease the content of MDA in a mouse exposed to the radiation. These flavonoids also can increase the number of leukocytes of blood, and exhibit the protective effect on the immune system of mouse exposed to the radiation [27].

A comparative study on the category of keratinocytes HaCaT shows that quercetin is the number one, and genistein in the second position are the most effective factors in clearing the hydroxyl free radicals induced by the radiation of UVB. In addition, treatment of cells by the above mentioned flavonoids before contact with radiation can increase the activity of SOD, and decrease the levels of TNFα, ROS, and MDA [73].

In a similar study, an effective increase in total antioxidant capacity and SOD activity in 12PC rat pheochromocytoma cells treated with Quercetin compared to control cells was noticeable [6]. It has been determined that the group of flavonoids (breviscapine) obtained from the plant (Erigeron breviscapus) effectively neutralizes free radicals produced by radiation, and subsequently increases the total antioxidant capacity of cells by reducing lipid peroxidation. It acts as a radiation protector [29].

Ping et al that was cited in [68]. Evaluated the radioprotective effects of Amentoflavone by measuring cell viability, apoptosis and ROS levels after exposure to 8Gy of gamma radiation from ^{60}Co in guinea pig lung fibroblast cells. This study showed that treatment of cells with this flavonoid within 24 hours before irradiation significantly inhibited apoptosis and reduced ROS levels. Another similar study showed that the prescription of Genistein at the rate of 200 mg/kg one hour before exposure to X-rays improves bone marrow function and increases the 30-day life expectancy index in rats by 44% [23].

VIII. Protection of the Immune System

The immune system is very sensitive to harmful rays. Exposure to ionizing radiation can lead to functional problems of the immune system and even death due to the reduction of the number of immune cells. Also, ionizing rays are capable of causing problems in antibody production and disrupting the regulation of the cytokine network.

Among flavonoids, isoflavones, which are mostly found in leguminous plants, have played a stronger role in protecting the immune system against ionizing radiation [36]. It has been shown that treating mice with only 4 Gy of ionizing radiation is enough to reduce the function of the immune system in the thymus and spleen. Mice receiving soy isoflavones had improvement in lymphocyte performance index, reduction of apoptosis, reduction of cells in 0G or 1G phase and increased presence of cells in 2G and mitosis phases after receiving radiation. In addition to this, a noticeable increase in the phagocytosis ability of macrophages and the levels of serum hemolysin, IgA, IgG and IgM was also seen [38]. Tartary buckwheat flavonoids have also had a similar effect in protecting immune system cells, especially T lymphocytes [36].

Other studies show that Quercetin, Apigenin, Hesperidin and Rutin can strengthen the immune system by increasing the proliferation of lymphocytes and the secretion of key cytokines and significantly reduce the

damage to peripheral blood lymphocytes [30], [70]. It has been shown that the prescription of Resveratrol in workers who work in an environment with a high potential of electromagnetic hazards can help to restore the expression and function of nuclear factor (kB-NF) κB and 6-IL and finally prevent the deterioration of the immune system function [71].

IX. Protection of the Hematopoietic System

The hematopoietic system is highly sensitive to radiation due to the high volume of cell proliferation and division. Ionizing rays target all stem cell categories of the bone marrow [56]. Therefore, protecting the hematopoietic system is an important factor in preventing radiation damage. Experimental research shows that flavonoids can protect hematopoietic organs from radiation damage and improve its regeneration to increase the body's resistance to radiation damage [69].

Synthetic derivatives of tetrahydroxyisoflavone have more effective biological effects compared to their natural source, and it has been shown that treatment of mice exposed to cobalt-60 gamma rays with these flavonoids greatly restores the hematopoietic system and improves performance [37]. Previous studies have also shown a similar effect of Genistein, Quercetin and water-soluble derivatives of propolis in preventing the decrease in the number of white and red cells, blood platelets and hemoglobin, as well as damage to the DNA of leukocytes caused by ionizing radiation [9], [57]. It seems that a significant part of these effects is due to the increase in the production of granulocyte colony stimulating factors (G-CSFs) as a key factor in stem cell regeneration [36].

It has been shown that the sustained prescription of Genistein nanoparticles in mice reduced the death of hematopoietic tissue stem cells caused by exposure to radiation from 77% to 46% and increased pro-inflammatory factors such as IL-6 and COX-2 in the bone marrow, and the mouse spleen [36].

X. Reduction of Inflammation

Exposure to a large amount of ionizing radiation can cause severe inflammatory reactions. Inflammatory cytokines can cause damage or necrosis in the tissues and organs of any part of the body. Such injuries are more common in lungs and kidneys [34].

Soy isoflavones have shown promising protective effects both before exposure and after exposure to radiation in the lung tissue by reducing the infiltration of macrophages and neutrophils at the alveolar and bronchial levels and ultimately reducing fibrosis [1]. The prescription of Astragalus complanatus flavonoids after exposing the mice to 10 Gy radiation significantly reduced the serum levels of TGF-β, TNF-α and IL-6 and subsequently reduced the damage caused by inflammation in the irradiated mice [64].

Baicalein, as the most active flavonoid of Paeonia lactiflora, can suppress radiation-induced inflammatory responses by negatively modulating NF-κB and increasing activation of FOXOs, catalase, and SOD in mouse kidney. In addition, this compound also inhibits radiation-induced phosphorylation of MAPKs and Akt, which are NFkB-enhancing kinases [35]. It has recently been shown that the prescription of Quercetin and Hesperidin in mice can significantly prevent intestinal damage by reducing TNF-α levels and increasing IL-10 [25].

XI. Flavonoids and Apoptosis

In most of the cellular and molecular studies conducted on various tumor cell categories, flavonoids induce apoptosis with different mechanisms [20]. Pro-apoptotic pathways such as Bax, BID, caspases 3, 8, and 9, tumor suppressors including p53, cell cycle inhibitory factors such as some cyclin-dependent kinases, and ceramide activation cascade and its messengers in tumor cells by flavonoids have been strengthened [42], [11], [41], [5]. In contrast to apoptosis inhibitory factors such as phosphoinositide-3-kinase coupled to protein kinase (PI3K-Akt) B, mitogen-activated protein kinase (MAPK), metalloproteinases 2 and 9 (MMPs) and many growth factors that promote proliferation and differentiation of tumor cells are suppressed by flavonoids [17], [15].

However, the effects of flavonoids in healthy and non-tumor cells have been largely opposite to tumor cells. The protective effects of flavonoids on nerve cells, liver, kidney, heart, skin, immune and hematopoietic systems have been discussed in various studies [41], [43]. Differentiating flavonoids between these two groups of cells has created great hopes for their use for radiation protection and other beneficial effects.

XII. CONCLUSION

According to the studies conducted, it can be said that flavonoids as natural radiation protection in radiation therapy applications to protect healthy cells, accidental radiation accidents and also in terrorist incidents can effectively help to reduce the harmful effects of these rays. The protective effects of DNA, protection of the immune system and hematopoietic system, cleaning of free radicals, strengthening of the immune system and antioxidant properties of flavonoids are proof of this ability. Although these compounds are not toxic to healthy cells in most cases and in mild doses, they have significant toxicity on cancer cells through the induction of programmed cell death. If future clinical studies confirm the radiation sensitizing properties of these materials on healthy tissues, they can also be used as radiation shielding materials in radiation therapy.

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