Efficacy of Some Natural Antioxidants in Targeting Free Radicals Induced by Radiation Exposure: A Mini - Review

Ahmed Saleh

Department of Physical Sciences, College of Science, Jazan University, P. O. Box.114, Jazan 45142, Kingdom of Saudi Arabia
Email: *asalehisa[at]jazanu.edu.sa*

Abstract: ***Radiotherapy is a common treatment approach for millions of patients with cancer each year. As a result, there is a need for effective radiation mitigation strategies. Scientists have investigated agents with reduced toxicity for improving radioprotection and potential mitigation of the harmful effects of ionizing radiation exposure. Natural antioxidants have shown promising results as radioprotectors that can be administered at high doses with low toxicity. The main mechanisms of radiation protection with natural antioxidants involve the scavenging of free radicals, the management of inflammatory responses, and the attenuation of apoptosis signaling pathways in radiosensitive organs. By exploring the potential of various antioxidants, researchers aim to enhance their radioprotective effects and minimize the adverse consequences of ionizing radiation exposure.***

Keywords: radiotherapy, radiation mitigation, natural antioxidants, radioprotection, ionizing radiation

1. Introduction

During metabolism, living cells produce reactive oxygen species (ROS) as byproducts, including ions, atoms, molecules, and radicals, such as hydrogen peroxide (H_2O_2), singlet oxygen ($_1O_2$), superoxide anion radical ($O_2^{\bullet -}$), and hydroxyl radical ($OH^{\bullet}$). These reactive species play important roles in biological processes and are essential for life. However, they can also be harmful if their levels are excessive or if they are present in inappropriate amounts [1].

Overproduction of ROS can lead to the destruction of organelles and cell membranes, resulting in various biological effects including apoptosis, necrosis, autophagy, and the development of conditions such as diabetes and cancer. Hydroxyl radicals pose the greatest risk to tissues because of their high reactivity and ability to oxidize numerous cellular components, including lipids, proteins, carbohydrates, and deoxyribonucleic acids. Living cells employ a range of enzymatic antioxidants to neutralize free radicals [2]. The primary enzymatic antioxidants include three crucial enzymes: glutathione peroxidase, which donates two electrons to reduce peroxides; catalase, which converts hydrogen peroxide into water and molecular oxygen and superoxide dismutase, which converts superoxide anions into hydrogen peroxide [2]. In addition to primary enzymatic antioxidants, secondary enzymatic antioxidants support primary defense mechanisms. These include glutathione reductase, which reduces oxidized glutathione to its reduced form [3], and glucose - 6 - phosphate dehydrogenase, which regenerates NADPH and creates a reducing environment.

In addition to enzymatic antioxidants, there are also non - enzymatic antioxidants that play a role in combating oxidative stress. These include vitamins such as A, E, and C, enzyme cofactors such as Q10, minerals such as zinc and selenium, peptides such as glutathione, phenolic acids, and nitrogen compounds such as uric acid [4]. These non - enzymatic antioxidants contribute to the maintenance of a balance between the production of reactive oxygen species and their neutralization, thereby reducing oxidative damage in living cells.

Ionizing radiation (IR) is a form of energy that causes the ionization of a material medium upon interaction [5]. Each type of radiation differs in terms of energy, penetrating ability, and biological effects of exposure. This energy can be transferred through electromagnetic waves, such as X - rays, gamma rays, and a limited range of high - energy ultraviolet radiation with short wavelengths and it can also be transferred through the emissions of alpha and beta particles. Because living cells have a high - water content, radiolysis of water molecules by IR becomes the predominant process, leading to an increased generation of ROS including OH, H^-, HO_2, and H_3O^- [6, 7]. These ROS molecules swiftly interact with macromolecules such as proteins, nucleic acids, and lipids, resulting in cellular dysfunction and apoptotic cell death. The augmented oxidative stress contributes to the development of ROS - related diseases.

The most important prerequisite in the development of an ideal radioprotector is minimal toxicity at the dose at which it is delivered. In addition, it should have free radical scavenging ability, immunomodulatory capability, anti - inflammatory activity, promotion of DNA repair enzymes, upregulation of antioxidant enzymes, and enhancement of the recovery of the hematopoietic and immune systems.

In recent years, the focus on developing novel radioprotectors has shifted towards natural compounds with reduced toxicities [8]. Consequently, herbs may play a significant role in bolstering antioxidant defense mechanisms and modulating redox signaling processes [9].

Natural radioprotectors:

Radioprotective herbs are those that have been studied for their potential to protect against radiation - induced damage. The effectiveness of these herbs in providing radioprotection varies according to their antioxidant properties. Here are some major herbs that have been investigated for their radioprotective and antioxidant properties:

1) Ginkgo biloba l:

Family	Genus	Species	native	part used
Ginkgoaceae	Ginkgo	biloba	East Asia	leaves

The common name "Ginkgo" is derived from a Japanese term that phonetically represents a tree. On the other hand, the species name "biloba" refers to the characteristic presence of two distinct lobes, which are typical of the leaves of this tree. Ginkgo holds a special place in the plant kingdom due to its unique classification as one of the oldest seed plants. It is often referred to as a "living fossil" because of its ancient lineage and remarkable survival over time. [10].

a) Major bioactive compounds of Ginkgo biloba:
Ginkgo is known to contain several bioactive compounds, including terpenoids, flavonoids, biflavonoids, organic acids, polyprenols, and others. A standardized leaf extract of Ginkgo biloba, known as EGb 761, contains approximately 24% flavonoid glycosides, 6% terpenoids, 5% - 10% organic acids, and other constituents. These components are responsible for various health benefits associated with Ginkgo biloba.

b) Radioprotective effect of Ginkgo biloba:
It has been found that Ginkgo biloba supplementation leads to increased activities of two important enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GSH - Px). Additionally, it has been observed that the supplementation results in a significant decrease in the level of malondialdehyde (MDA), which is a marker of oxidative stress.

In a study conducted by [11], it was observed that the total cranium irradiation of 5 Gy in a single dose promoted cataract formation. However, supplementation with Ginkgo biloba protects the lens cataracts. These findings suggest that Ginkgo biloba supplementation plays a beneficial role in enhancing the antioxidant defense system of the body by increasing the activities of SOD and GSH - Px enzymes. Moreover, it helps in reducing oxidative stress, as evidenced by the decrease in MDA levels. Furthermore, Ginkgo biloba supplementation has the potential to protect against the harmful effects of radiation, specifically in preventing the formation of cataracts.

Bassem M. Rafat et al. [12], conducted a study to investigate the impact of ionizing radiation on the concentrations of apoptosis - related proteins and the potential radio - protective role of Ginkgo biloba. The results indicated that the ratio of apoptotic to anti - apoptotic proteins significantly returned to its normal ratio ($p < 0.05$) when the radio - isotopic injection (1 mCi of ^{99m}Tc, based on the animals' body weight) was administered after a week of protection with Ginkgo biloba. The study concluded that Ginkgo biloba can be utilized as a radio - protective agent in cases of exposure to ionizing radiation. In 2021 Bassem M. Rafat et al. [13], observed that the oral administration of Ginkgo biloba, based on body weight, effectively restored functional hemoglobin derivatives and antioxidant activity. This restoration was achieved by inhibiting the rapid formation of free radicals induced by Gallium - 68 injections, a form of ionizing radiation.

2) *Angelica Archangelica*

Family	Genus	Species	native	part used
Apiaceae	Angelica	archangelica	Europe	root

In 1753, Carl Linnaeus, known as Linne, introduced the scientific name Angelica for a plant species in his work Species Plantarum. It is believed that the name Angelica had already been in use since the Middle Ages, as mentioned by [14]. Angelica archangelica is a medicinal and aromatic plant native to Europe, with a long history of use both for medicinal purposes and as a vegetable.

a) Major bioactive compounds of Angelica archangelica:
Angelica archangelica seed was rich in β - phellandrene (33–63%) and α - pinene (4–12%). The roots essential oil carried α - pinene (21%), δ - 3 - carene (16%), limonene (16%), and α - phellandrene (8%) as its main components [15].

b) Radioprotective effect of Anglica archangelica:
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3) Green *tea:*

Family	Genus	Species	native	part used
Theaceae	Camellia	Camellia sinensis	East Asia	leaves

The tea plant grows in a farm of an evergreen shrub in areas with suitable cultivation conditions (optimal temperature in the range of 15 - 20°C. Green tea is an infusion of Camellia sinensis leaves, regarded to possess anti - cancer, anti - obesity, anti - atherosclerotic, antidiabetic, and antimicrobial effects. it contains various bioactive components, including polysaccharides, flavonoids, B vitamins, catechin compounds, and fluoride. Catechin compounds are known as antioxidants. [16].

a) Major bioactive compounds of green tea:
The key components in green tea include polyphenols, which have highly antioxidative, antimutagenic, anticarcinogenic, and radioprotective effects. In addition to polyphenols, other compounds in green tea are of interest for human health as alkaloids, amino acids, glucides, proteins, volatile compounds, and minerals. Polyphenols are powerful

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antioxidants and free radical scavengers. They are strong scavengers of superoxide, hydrogen peroxide, hydroxy radicals, and Nitric Oxide (NO) produced by various chemicals. Flavonoids are polyphenolic compounds that include the subclasses of flavanones, flavones, isoflavones, flavanols (flavans), flavonols, and anthocyanins [17]. Green tea contains several groups of polyphenols that include flavonols (quercetin, kaempferol, and rutin, phenolic acids, theanine, flavor compounds, and leucoanthocyanins, accounting for up to 40% of the dry leaf weight [18]. The pharmaceutical activities of the components have been studied [19, 20]. Chemically, the beverage is characterized by the major polyphenolic catechins such as (–) – epigallocatechin - 3 - gallate (EGCG), (–) – epigallocatechin (EGC), (–) epicatechin - 3 - gallate (ECG), and (–) – epicatechin (EC); these are the most abundant water - soluble components of tea [18]. Polyphenols are present at 10% to 15% in green tea and 5% in black tea. The polyphenols constitute about 42% of the dry weight of green tea extract, of which 26.7% comprise catechin gallate components such as EGCG (11.16%), ECG (2.25%), EGC (10.32%), epicatechin (2.45%), and catechin (0.53%). An infusion of green tea contains up to 200 mg of catechins [21].

b) Radioprotective effect of green tea:

It was found that gamma irradiation (5 and 10 Gy) induces hematological, immunological, and biochemical effects in rats. Treated rats with a mixture of green tea extraction (100 mg/kg BW) and grape seed extraction (200 mg/kg BW) show increasing in concentrations of immune cells (CD4 and CD8). The level of pro - inflammatory cytokines Tumor necrosis factor - α and C - reactive protein elevated after γ - irradiation and significantly decreased by mixture administration. Moreover, groups treated with an antioxidant mixture showed a significant increase in all hematological parameters and a significant decrease in cholesterol and triglyceride levels [22].

EGCG exerts protection against radiation through a variety of mechanisms, including scavenging free radicals, inhibiting lipid peroxidation, reducing DNA damage, and inhibiting ionizing radiation - induced ROS generation and apoptosis [23]. It can increase the antioxidant enzymes such as SOD, glutamate cysteine ligase, and heme oxygenase - 1 (HO - 1) and is, therefore, recognized as an effective free - radical scavenger. In addition, EGCG can enhance DNA repair activity after ionizing radiation damage [24]. Pretreatment with EGCG significantly decreases ionizing radiation - induced apoptosis and ROS production [25]. Recently, it was observed that EGCG could significantly reduce ionizing radiation - induced damage to mice by modulating immunomodulatory activity [26]. EGCG can also reduce intestinal injury caused by total body irradiation in mice by modulating Nrf_2 signaling and inhibiting ionizing radiation - induced apoptosis and ferroptosis. However, EGCG is not only protective against radiation - induced damage at the animal or cellular level; it has also been demonstrated to reduce radiation - induced esophagitis, oral mucositis, dermatitis, and acute skin damage [27].

4) *Ginger*:

Family	Genus	Species	native	parts used
Zingiberaceae	Zingiber	Zingiber officinale	Southeast Asia	roots or underground stem

Ginger is a plant belonging to the Zingiberaceae family. It has a long history of use as a spice in culinary applications and as a traditional medicine for treating various diseases involving inflammation caused by oxidative stress [28]. The antioxidant properties of ginger can help reduce oxidative stress in the body, which is linked to many diseases such as cardiovascular disease, diabetes, cancer, and even Alzheimer [29, 30]. Ascorbic acid present in ginger inhibits peroxidation in both aqueous and lipid regions of cells. It traps peroxyl radicals before they can initiate lipid peroxidation and aids in the regeneration of vitamin E. Additionally, previous studies have shown that ginger extract enhances the activity of SOD and catalase, increases the content of reduced glutathione (GSH), and decreases the level of MDA, thereby protecting against oxidative stress [31].

a) Major bioactive compounds of Ginger:

The key components of ginger are antioxidant phenolic compounds. More than 100 compounds are identified, most of them terpenoids mainly sesquiterpenoids (α - zingiberene, β - sesquiphellandrene, β - bisabolene, α - farnesene, ar - curcumene (zingiberol) and smaller amounts of monoterpenoids (camphene, β - phellandrene, cineole, geraniol, curcumene, citral, terpineol, borneol) [32].

b) Radioprotective effect of Ginger:

Exposure of rats to whole - body gamma radiation (6 Gy) resulted in a significant increase in serum 8 - OHdG levels, which are a biomarker of DNA oxidation. The level of 8 - OHdG in the radiation - exposed group was five times higher than that in the control group, indicating the induction of DNA oxidative damage by radiation. However, when rats were pretreated with ginger extract, 8 - OHdG levels were significantly reduced to twice as high as those in the control group. These results suggest that ginger possesses effective antioxidant activity and exhibits a radioprotective effect against the harmful effects of whole - body gamma irradiation. However, when rats were treated with ginger extract before radiation exposure, the detrimental effects of gamma radiation on cellular DNA were prevented. This finding aligns with the results reported by Jeena [32], who reported that ginger essential oil exhibited strong antioxidant activity and protected against the DNA - damaging effects of gamma radiation. Antioxidants play a crucial role in neutralizing metal ions and scavenging harmful free radicals such as hydroxyl (OH) and hydrogen peroxide (H_2O_2) [33]. Ginger contains various constituents, including 6 - gingerol (the primary bioactive compound in fresh ginger) as well as antioxidants such as vitamin C, vitamin E, beta - carotene, lutein, lycopene, quercetin, genistein, and tannin which contribute to its antioxidant properties [30].

5) *Mentha piperita:*

Family	Genus	Species	native	parts used
Lamiaceae	Mentha L.	M. piperita	Europe and the Middle East	Whole plant

Many Mentha plants have been described as official drugs in several pharmacopoeias. Mentha plants are primarily utilized for addressing gastrointestinal tract disorders. Additionally, they have been reported to possess antioxidant, anti - inflammatory, antimicrobial, analgesic, and anticarcinogenic properties [34]. The pharmacological effects of Mentha plants are primarily attributed to the presence of two key compound groups: phenolic compounds and essential oils.

a) Major bioactive compounds of Mentha Piperita:

Several studies have demonstrated that Mentha plants are rich in phenolic compounds, particularly in phenolic acids and flavonoids. Mentha is enriched in caffeic acid (60-80% of their total phenolic compounds) and its derivatives [35]. Also, seven salvianolic acids have been detected in Mentha plants [36]. In addition to caffeic acid and its derivatives, various other organic acids have been documented in Mentha plants. For instance, caftaric acid, p - coumaric acid, cinnamic acid, ferulic acid, oleanolic acid, and vanillic acid have been identified in these plants [37]. Mentha plants are rich in flavonoids, particularly in flavones and flavanones, the latter being 10-70% of their total phenolics [35]. Luteolin and its derivatives are the main flavones described in Mentha plants. Moreover, glycosidic derivatives like luteoline-O - glucoside and luteoline-O-rutinoside are often described as major phenolic compounds [38]. Apigenin and its derivatives like glucosides and rutinosides can also be found in Mentha. Other flavones described in mints include for example acacetin and its glycosides, diosmin, salvigenin, and thymonin [39]. Mentha plants are rich in flavanones and compounds of this class include mainly derivatives of eriodictyol, naringenin, and hesperetin. Frequently these compounds appear as glucoside derivatives [35].

b) Radioprotective effect of Mentha Piperita:

A study was conducted on mice to investigate the protective effects of Mentha piperita against radiation - induced intestinal injury. The study spanned from day 1 to day 20 after subjecting the mice to whole - body gamma irradiation at a dosage of 8 Gy. The results showed that pretreatment with Mentha effectively safeguarded the intestinal mucosa of Swiss albino mice against radiation - induced damage [40]. Samarth and Kumar [41] showed that the administration of Mentha extract demonstrates a protective and stimulating effect on the hematopoietic system in mice can be attributed to the antioxidant properties of Mentha piperita, which is attributed to the presence of eugenol, caffeic acid, rosmarinic acid, and α - tocopherol. Exposure to gamma radiation led to a notable decrease in the bone marrow cells. However, when mice were pretreated with a leaf extract of Mentha piperita before radiation exposure, there were significant increases in various types of cells in the bone marrow compared to the control group. These included leucoblasts, myelocytes, metamyelocytes, band/stab forms, polymorphs, pro - normoblasts, normoblasts, lymphocytes, and megakaryocytes. Additionally, pretreatment with M. piperita leaf extract followed by radiation exposure resulted in a significant reduction in the frequency of micronuclei in the bone marrow of the mice.

2. Conclusion

The development of a radioprotector is a crucial requirement in the current context. While many synthetic drugs demonstrate effective radioprotection, their practical application is limited due to their high toxicity. Ginkgo biloba, Angelica Archangelica, Ginger, Green tea, and Mentha Piperita possess antioxidant constituents that enable them to show a prophylactic effect against irradiation by scavenging the free radicals induced by radiation exposure.

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