International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Natural Antioxidants as Promising Radioprotectors: A Mini Review

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Abstract: ***Radiotherapy is widely used in cancer treatment, but its exposure to ionizing radiation leads to severe side effects due to the generation of free radicals. This review explores the potential of natural antioxidants as radioprotectors to mitigate these effects. Natural antioxidants such as chamomile, Ginkgo biloba, green tea, Angelica archangelica, and ginger exhibit radioprotective properties by scavenging free radicals, modulating inflammatory responses, and regulating apoptosis. Their low toxicity and ability to enhance DNA repair mechanisms make them promising agents in radiation protection. This review highlights the biochemical mechanisms of these antioxidants and their potential clinical applications in radiotherapy.***

Keywords: Radiotherapy, ionizing radiation, radioprotectors, natural antioxidants and free radicals

1. Introduction

Reactive oxygen species (ROS) are byproducts of living cells that include ions, atoms, molecules, and radicals including hydroxyl radical ($OH^•$), superoxide anion radical ($O_2^{•\,-}$), singlet oxygen ($_1O_2$), and hydrogen peroxide (H_2O_2). Reactive oxygen species are essential for life, but an imbalance in their concentrations can be harmful [1].

Overproduction of ROS can lead to the destruction of organelles and cell membranes, which have different biological effects such as necrosis and apoptosis, as well as the emergence of diseases including cancer and diabetes. Living cells use a variety of enzymatic antioxidants to counteract free radicals [2]. The main enzymatic antioxidants are superoxide dismutase, which changes superoxide anions into water and molecular oxygen, glutathione peroxidase, which provides two electrons to decrease peroxides, and catalase.
In addition to enzymatic antioxidants, non - enzymatic antioxidants 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 [3]. These non - enzymatic antioxidants help regulate reactive oxygen species, reducing oxidative damage in living cells (Figure 1).

Since water makes up the majority of living cells, ionizing radiation (IR) radiolysis of water molecules produces an increase in the production of reactive oxygen species (ROS), such as OH, H -, HO2, and H3O - [4, 5].

These ROS molecules rapidly interact with macromolecules such as proteins, nucleic acids, and lipids, leading to apoptotic cell death and cellular dysfunction.

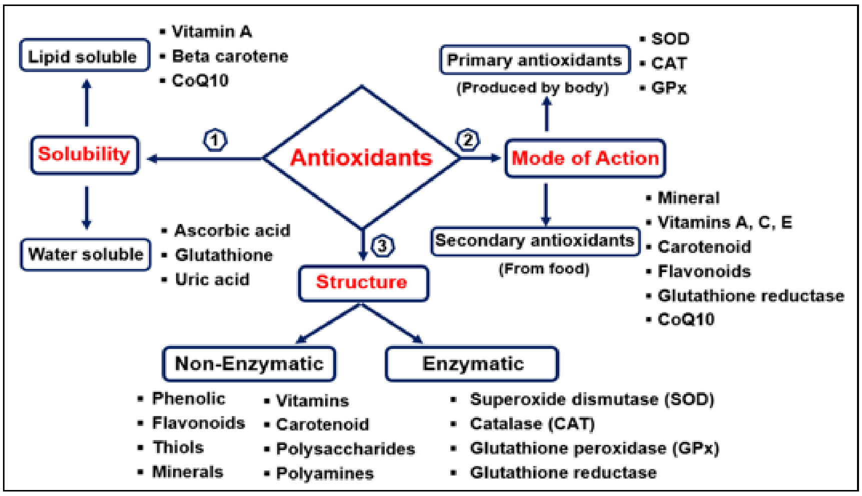

Figure 1: Classification of antioxidants according to their structure, mode of action, and solubility.

The primary requirement for an optimal radioprotector is low toxicity combined with the capacity to scavenge free radicals, immunomodulate, inhibit inflammation, promote DNA repair enzymes, upregulate antioxidant enzymes, and improve the immune and hematopoietic systems' ability to recover (figure 2).

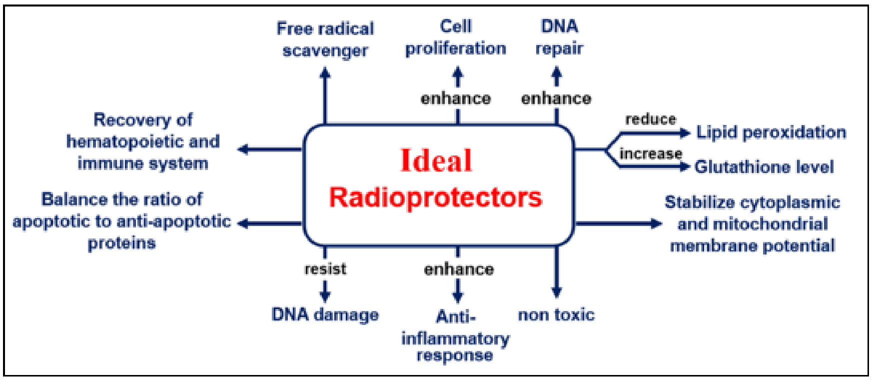

Figure 2: Criteria to become ideal radioprotector

The development of promising radioprotective devices has recently moved its focus to natural antioxidants with minimal toxicities [6].

This review aimed to explore the role of natural antioxidants as radioprotectors, analyzing their potential benefits in mitigating the harmful effects of ionizing radiation. Therefore, it is significant in identifying safe, natural alternatives to synthetic radioprotectors, which often pose toxicity concerns. Understanding the mechanisms of natural antioxidants may contribute to developing effective radiation mitigation strategies in clinical settings.

2. Some Major Natural Antioxidants

2.1 Chamomile

Family: Asteraceae; Genus: Matricaria; Species: Matricaria; native: western Asia; part used: flowers

2.1.1 Major bioactive compounds of Chamomile

The main bioactive ingredients in chamomile extract are phenolic compounds, including caffeic acid (phenylpropanoids), herniarin and umbelliferone (coumarins), and chlorogenic acid. The flavonoids luteolin and luteolin - 7 - O - glucoside (flavones), naringenin (flavanone), quercetin and rutin (flavonols), and different acetylated derivatives are other important components of the flowers. The most promising ingredient is apigenin (Table 1). [7].

Table 1: Chemical analysis of Chamomile flower and extracts [7]

Parts	Compound	Chemical constituents		
Flowers	Phenylpropanoids	Coumarin		Herniarin & Umbelliferone
		Phenolic acids		Chlorogenic acids & caffeic acids
		Flavonoids	Flavones	Apigenin, Apigenin - 7 - O - glucoside, luteolin and luteolin-7-O-glucoside
			Flavonols	Quercetin & Rutin
			Flavanone	Naringenin
	Others	Volatile oils		Isopentyl isobutyrate & Isobutyl isobutyrate

2.1.2 Radioprotective effect of Chamomile

In a study by Mohamed T. Khayyal, et. al [8], rats were given chamomile extract to see if it may prevent intestinal mucositis by radiation. Five days before exposure and two days following exposure to gamma irradiation, the rats were given the extract orally. The rats were slaughtered the next day so they could be examined. Sections of the small intestine were examined, and the results showed several negative consequences, such as mucosal shrinkage, inflammatory cell infiltration in the lamina propria, villi shortening and fusion, and activation of mucus - secreting glands. The results of the biochemical study of intestinal homogenates suggested increased oxidative stress and inflammation since they showed decreased glutathione content and higher levels of myeloperoxidase, thiobarbituric acid reactive compounds, and tumor necrosis factor. Furthermore, there was an increase in apoptotic markers such as caspase - 3, cytosolic cytochrome c, and the B - cell lymphoma - 2/Bax ratio depletion. The injection of chamomile extract, significantly reduced the majority of these histological changes and related metabolic abnormalities, suggesting that it may have protective properties against radiation - induced intestinal mucositis.

2.2 Ginkgo Biloba

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

2.2.1 Major bioactive compounds of Ginkgo biloba:

Terpenoids, flavonoids, biflavonoids, organic acids, polyprenols, and other bioactive substances are found in ginkgo (Table 1). EGb 761, a standardized leaf extract of Ginkgo biloba, has 10% organic acids, 6% terpenoids, and 24% flavonoid glycosides. These elements are in charge of the many health advantages that ginkgo biloba provides. [9].

Paper ID: SR25215155646 DOI: https://dx.doi.org/10.21275/SR25215155646

Table 1: Chemical analysis of *Ginkgo biloba* leaves and extracts [9].

part	Compound	Chemical constituents
Leaf - root - bark	Terpenoids	Diterpenes: ginkgolides A, B, C and (a)
Root		Diterpenes: ginkgolides M (a)
Leaf - bark		Sesquiterpene: bilobalide (b)
Leaf – bark		Triterpenes: sterols
Leaf	Flavonoids	Quercetin (c), kaempferol (d), isorhamnetin (e), rutin, lutolin
	Biflavonoids	Sciadopitysin, ginkgetin, amentoflavone, bilobetin
	Organic acid	Benzoic acid derivative
	Polyprenols	Di - trans - poly - cis - octadecaprenol
	Others	Wax, steroids, phenols, aliphatic acids, rhamnose

2.2.2 Radioprotective effect of Ginkgo biloba:

It was shown that supplementing with ginkgo biloba increases the activity of two crucial enzymes: glutathione peroxidase (GSH - Px) and superoxide dismutase (SOD). Furthermore, there was a notable drop in malondialdehyde (MDA) levels, an indicator of oxidative stress. A study by Ertekin MV, et al. [10] found that a single dosage of 5 Gy of total cranial irradiation facilitated the development of cataracts. Ginkgo biloba supplementation, however, guards against cataracts in the lenses. These findings suggest that Ginkgo biloba supplements enhance the body's antioxidant defense system by increasing the activity of SOD and GSH - Px enzymes while reducing MDA levels.

A study by Bassem M. Rafat et al. [11] found that ionizing radiation affected the amounts of proteins linked to apoptosis and whether Ginkgo biloba might have a radioprotective effect. After a week of protection with Ginkgo biloba, the results showed that the ratio of apoptotic to anti - apoptotic proteins considerably recovered to its normal ratio ($p < 0.05$) when the radio - isotopic injection (1 mCi of 99mTc, based on the animals' body weight) was given. In 2021 Bassem M. Rafat et al reported that oral administration of Ginkgo biloba was beneficial in restoring functional hemoglobin derivatives and antioxidant activity by preventing the quick production of free radicals produced by injections of gallium - 68 [12].

2.3 Angelica Archangelica

Family: Apiaceae; Genus: Angelica, Species: archangelic; tree native: Europe; part used: root

2.3.1 Major bioactive compounds of Angelica Archangelica:

The seeds of Angelica Archangelica were abundant in β - pinene (4–12%) and β - phellandrene (33–63%). The essential oil of the root contains major constituents such as α - pinene (21%), δ - 3 - carene (16%), limonene (16%), and α - phellandrene (8%) [13] (Table 2).

Table 2: Chemical analysis of Angelica Archangelica roots, seeds (fruits), and extracts

Parts	Compound	Chemical constituents
Root	Coumarins	Angelicin, osthol, bergapten. imperatorin, oreoselone, oxypeucedanin, umbelliferone, xanthotoxin, xanthotoxol, Diterpenes: ginkgolides M (a)
	Essential oils	α - pinene, camphene, β - pinene, sabiene, 3 - carene, myrcene, α - terpinene, limonene, β - phellandrene, cis - β - ocimene, γ - terpinene, trans - β - ocimene, p - cymene, terpinolene, α - copaene, bornyl acetate, 4 - terpineol, pentadecanolide
	others	Archangelenone (a flavonoid), palmitic acid, sugar
Seeds (fruits)	Essential oils	β - phellandrene (33.6 - 63.4%) and α - pinene (4.2 - 12.8%)

2.3.2 Radioprotective effect of Anglica archangelica:

An oral dosage of Angelica archangelica successfully restores functional hemoglobin derivatives and antioxidant activity, subject to body weight, according to Bassem M. Rafat et al. [12]. This repair was achieved by inhibiting the rapid generation of free radicals caused by ionizing radiation injections of gallium - 68.

An investigation into the effects of ionizing radiation on the levels of proteins linked to apoptosis and the possible radioprotective function of Angelica archangelica was carried out by Bassem M. Rafat et al. [11]. Based on the animal's body weight, the results showed that when the radio - isotopic injection was given after a week of protection with Angelica archangelica, the ratio of apoptotic to anti - apoptotic proteins considerably reverted to its normal ratio ($p < 0.05$). This study concluded that Angelica archangelica can be used as a radio - protective agent against ionizing radiation exposure.

2.4 Green tea

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

2.4.1 Major bioactive compounds of green tea:

Polyphenols (Table 3) are the main ingredient in green tea and have potent antioxidative, antimutagenic, anticarcinogenic, and radioprotective properties. polyphenols are strong free radical scavengers and antioxidants they are potent scavengers of hydroxy radicals, superoxide, hydrogen peroxide, and nitric oxide (NO), which are formed by different substances. The subclasses of flavanones, flavones, isoflavones, flavanols (flavans), flavonols, and anthocyanins are referred as flavonoids [14]. Up to 40% of the dry leaf weight of green tea is made up of various categories of polyphenols, including taste compounds, leucoanthocyanins, phenolic acids, and flavonols (quercetin, kaempferol, and rutin) [15]. Research has been done on the components' pharmacological properties [16, 17]. Chemically speaking, the most prevalent water - soluble components of tea are the main polyphenolic catechins, which include (–) epicatechin - 3 - gallate (ECG), (–) epigallocatechin (EGC), (–) epicatechin - 3 - gallate (EGCG), and (–) epicatechin (EC) [17]. Black tea has five percent polyphenols, whereas green tea has ten to fifteen percent.

About 42% of the dry weight of the green tea extract is made up of polyphenols, of which 26.7% are components of the catechin gallate class, which include epicatechin (2.45%), EGCG (11.16%), ECG (2.25%), EGC (10.32%), and catechin (0.53%). Up to 200 mg of catechins can be found in a green tea infusion [18].

Table 3: Chemical analysis of green tea compound

Parts	Compound	Types of polyphenols
Leaf	Polyphenols (GTPs)	Flavanolscatechin, epicatechin, Gallocatechin, Epigallocatechin, Catechin 3 - O - Gallate, Gallocatechin 3 - O - Gallate, Epicatechin 3 - O - Gallate

2.4.2 Radioprotective effect of green tea

Rats exposed to 5 and 10 Gy of gamma radiation experience hematological, immunological, and metabolic abnormalities. Immune cell (CD4 and CD8) concentrations increase in the combination of green tea extraction (100 mg/kg BW) and grape seed extraction (200 mg/kg BW). Tumor necrosis factor - α and C - reactive protein, two pro - inflammatory cytokines, increased during γ - irradiation and were considerably reduced upon administration of the mixture. Additionally, all hematological parameters significantly increased while cholesterol and triglyceride levels were decreased in groups treated with an antioxidant mixture [19].

Through many methods, including scavenging free radicals, preventing lipid peroxidation, minimizing DNA damage, and preventing ionizing radiation - induced ROS production and apoptosis, epigallocatechin - 3 - gallate (EGCG) green tea reportedly protects against radiation [20]. Because of its ability to raise antioxidant enzymes such as glutamate cysteine ligase, heme oxygenase - 1 (HO - 1), and SOD, it is acknowledged as a potent free - radical scavenger. Additionally, following ionizing radiation damage, EGCG can increase DNA repair activity [21]. ROS generation and apoptosis generated by ionizing radiation are dramatically reduced by pretreatment with EGCG [22].

Recently, it was observed that EGCG could significantly reduce ionizing radiation - induced damage to mice by modulating immunomodulatory activity [23]. Because it inhibits ionizing radiation - induced apoptosis and ferroptosis and modifies Nrf2 (protein) signaling, EGCG can also lessen intestinal damage in mice that results from total body irradiation. On the other hand, EGCG has been shown to lessen radiation - induced dermatitis, esophagitis, oral mucositis, and acute skin damage [24]. It also protects against radiation - induced damage at the animal or cellular level.

2.5 Ginger

Family: Zingiberaceae; Genus: Zingiber, Species: officinale; native: Southeast Asia; part used: roots and underground stem Ginger's antioxidant properties can aid in lowering oxidative stress in the body, which has been connected to many illnesses, including diabetes, Alzheimer's, cancer, and cardiovascular disease [25, 26]. Ginger's ascorbic acid prevents lipids from peroxiding.

2.5.1 Major bioactive compounds of Ginger

Phenolic compounds, which are antioxidants, are the main ingredients of ginger. Over a hundred compounds have been identified, with the majority being terpenoids, primarily 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) [27]. The principal bioactive component of fresh ginger is 6 - gingerol. Antioxidants such as beta - carotene, lutein, lycopene, quercetin, genistein, and vitamins C and E are among the other components that enhance ginger's antioxidant potential [28]. Previous studies have shown that ginger extract can prevent oxidative stress by raising catalase and SOD activity, lowering MDA levels, and raising reduced glutathione (GSH) levels [27].

2.5.2 Radioprotective effect of Ginger

The production of DNA oxidative damage by radiation was indicated by the considerably increased blood 8 - OHdG levels in rats exposed to whole - body gamma radiation (6 Gy). However, 8 - OHdG levels were dramatically lowered to twice as high as those in the control group when rats were pretreated with ginger extract, preventing the effects of gamma radiation on cellular DNA. These findings imply that ginger has radioprotective properties against the negative effects of whole - body gamma irradiation and has strong antioxidant activity. According to Jeena et al. [28], ginger essential oil has potent antioxidant properties and guards against gamma radiation's ability to damage DNA.

3. Conclusion

Although synthetic radioprotectors have shown efficacy, their high toxicity limits their use. This review highlights the potential of natural antioxidants such as chamomile, Ginkgo biloba, green tea, Angelica archangelica, and ginger as effective radioprotectors. These antioxidants exhibit free radical scavenging, inflammation modulation, and DNA repair enhancement properties, making them viable alternatives for mitigating radiation - induced damage. Further studies and clinical trials are necessary to validate their therapeutic applications in radiotherapy.

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