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Preventive and therapeutic effects of natural antioxidants against damage caused by X-rays

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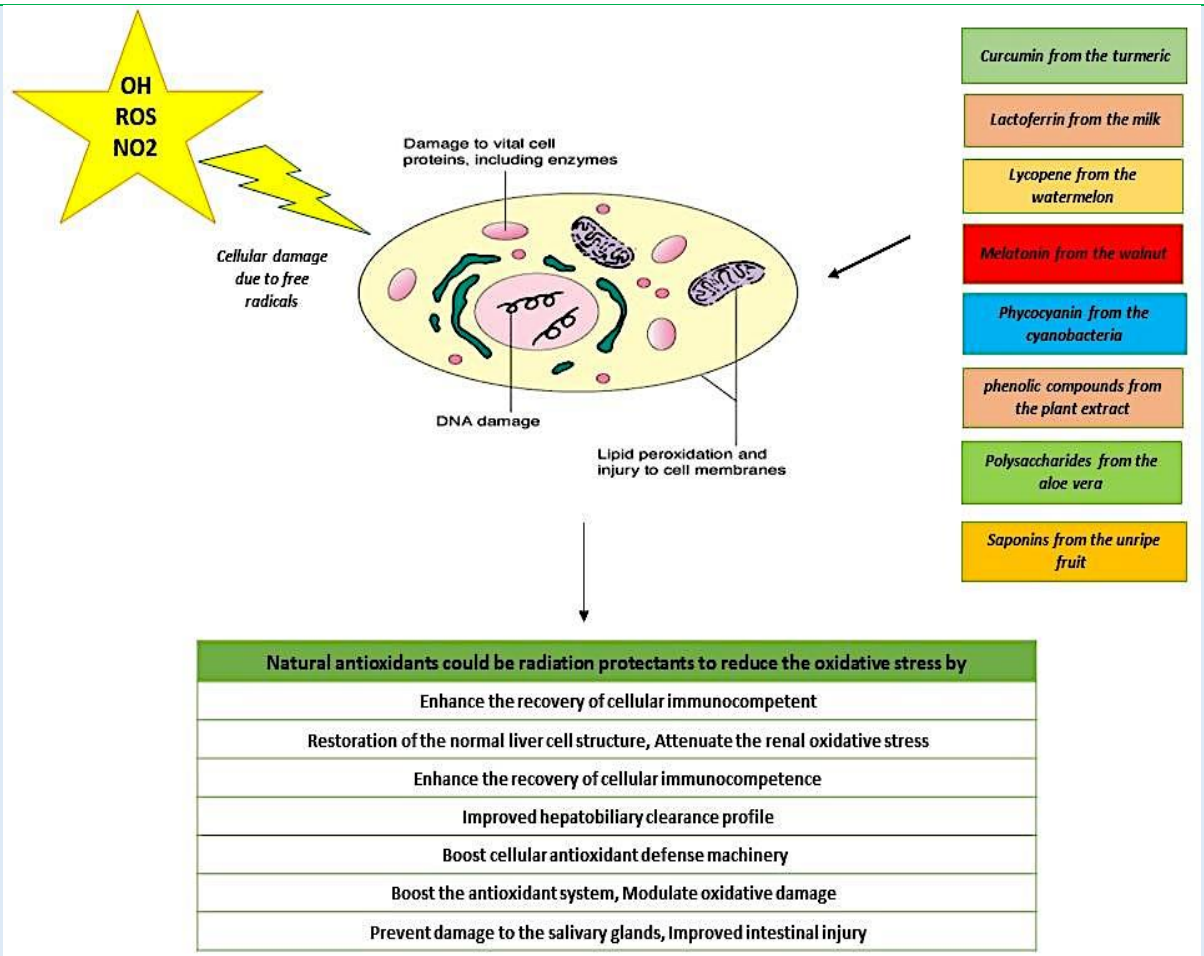
ABSTRACT

Plants and organic foods inherently contain bioactive compounds that combat oxidative stress effectively. A pharmacological overview of the activity and action of the active compounds against X-ray damage is provided, along with a review of the chemistry, functionality, and application aspects of active compounds derived from natural sources that may mitigate the harmful effects of X-ray radiation and shield biological systems from oxidative stress. The findings revealed that natural antioxidants such as natural compounds (lactoferrin, curcumin, melatonin, phycocyanin, and saponin) and phenolic compounds in plant extracts could be preventive and therapeutic agents against X-ray-induced toxicity. Natural antioxidants function as radiation protectants, mitigating oxidative stress induced by X-ray exposure. Given the non-toxic nature of the active compounds examined in this study, we suggest using them to produce a nutraceutical beverage that can be consumed or included in a daily diet to minimize oxidative stress.

Keywords: Active compounds, Antioxidant enzymes, Lactoferrin, Oxidative stress, Saponin, Watermelon juice



Graphical Abstract: Preventive and therapeutic effects of natural antioxidants against damage caused by X-rays

INTRODUCTION

X-rays are high-energy electromagnetic waves extensively utilized in materials science and medical diagnostics [1–2]. Healthcare providers, radiotherapy patients, and workers in sectors such as oil and gas frequently encounter X-ray radiation. [3–4]. Chronic exposure to X-ray radiation generates free radicals in healthy tissues, including the liver and surrounding tissues, within the human body. When X-rays interact with biological tissues, they can ionize atoms and molecules, forming free radicals such as reactive oxygen species (ROS). These free radicals have unpaired electrons, making them highly reactive and capable of causing damage to cellular components, including DNA [4–7]. The interaction of free radicals with cellular constituents, such as water and fat, can lead to the production of various reactive oxygen species, including hydrogen peroxide (H2O2), superoxide radical ($O_2^{\bullet-}$), and hydroxyl radical (•OH) [8–11]. These reactive oxygen species can further react with cellular molecules, including lipids, proteins, and nucleic acids, leading to oxidative damage; in particular, the production of lipid peroxides is a consequence of oxidative stress induced by reactive oxygen species [2–12]. Lipid peroxidation involves the oxidation of polyunsaturated fatty acids in cell membranes, generating lipid hydroperoxides and other reactive lipid species. This process can disrupt cell membrane integrity, impair cellular function, and contribute to tissue damage and inflammation [13]. The liver, a vital organ responsible for detoxification and metabolism, is particularly susceptible to oxidative stress from free radicals generated by X-ray radiation [14]. Oxidative damage to liver tissues can impair hepatic function and contribute to the developing of various liver diseases, including inflammation, fibrosis, and cirrhosis [15]. Overall, the production of free radicals and reactive oxygen species due to X-ray

radiation exposure underscores the importance of mitigating oxidative stress and protecting cellular components from damage [16]. Enhancing antioxidant defenses and mitigating oxidative damage are key strategies for minimizing the harmful effects of prolonged X-ray exposure on human health [17]. There is a linear correlation between X-ray exposure and carcinogenesis (formation of cancer), such as skin cancer, liver cancer, cervical cancer, colon cancer, and lung cancer [18]. Other previous studies have indicated that free radicals generated by X-rays can reduce the levels of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione, thereby compromising immune functions [19–20]. They can also lead to decreased monoamine levels in the stomach and small intestine [21–24]. Therefore, protecting healthy body tissues from genotoxicity caused by free radicals is critical.

Natural antioxidants in plant extracts have been demonstrated to protect human cells against free radicals with no side effects[25 –26]. As we are frequently exposed to X-rays daily, antioxidants from foods are essential for reducing the risk of free radicals caused by X-rays [27]. Compared with synthetic compounds, natural antioxidants in plants and organic foods have received significant attention [28]. Various review articles and studies have emphasized the effectiveness of active compounds in protecting against oxidative stress caused by free radicals and their associated human health risks [29]. However, there is a notable gap in methodological evaluation concerning the efficacy of antioxidants against the harmful effects of X-radiation. While antioxidants have been extensively studied for their potential to mitigate oxidative stress and damage caused by various environmental factors and diseases, research specifically focused on their effectiveness against the harmful effects of ionizing radiation, such as X-rays, is relatively limited, mixed, and often inconclusive. Therefore, this review aims (1) to evaluate the scientific evidence relevant to the chemistry of natural compounds and their potential health-promoting role in human/our diet, (2) to identify gaps in the current literature, and (3) to suggest potential opportunities for future research and development related to the therapeutic and protective functions of the active compounds while addressing their roles in countering the harmful effects of X-radiation.

Oxidative stress induced by X-radiation: The term oxidative stress involves both a disruption of the cell's redox balance and an imbalance in the production of reactive oxygen species (free radicals) and antioxidant defenses [30–32]. Superoxide anion radicals, hydroxyl, alkoxyl, lipid peroxyl radicals, nitric oxide, and peroxynitrite are examples of reactive oxygenated/nitrogenated species [33–34]. Oxidative stress can be described by a decreased ability of endogenous systems to fight oxidative attacks on target biomolecules, which results from either an increased formation of ROS/RNS or a decrease in antioxidant protective ability [35–36]. Free radicals interact with cellular constituents inside cells, such as water and fat. The interaction of free radicals with biological systems produces reactive oxygen species such as hydrogen peroxide, superoxide radicals, and hydroxyl radicals, which produce lipid peroxides [31–32]. These findings clarify how reactive oxygenated/nitrogenated species play a role in disease development. Specific factors that cause oxidative damage in cells, such as the overexpression of oncogene genes, the generation of mutagen compounds, the stimulation of atherogenic activity, the occurrence of senile plaque, or inflammation, can be triggered by an imbalance between oxidant species and the antioxidant defense system, the consequences of which are cancer, neurodegeneration, cardiovascular disease, diabetes, and kidney disease [36–37]. Exposure to X-radiation has caused liver and kidney tissue damage, DNA damage, enzyme dysfunction, enhanced cell apoptosis, lipid peroxidation, and damage to the central nervous system (Figure 1) [25]. There is a linear correlation between X-ray exposure and carcinogenesis (formation

of cancer), such as skin cancer, liver cancer, cervical cancer, colon cancer, and lung cancer [19]. There is a linear correlation between X-ray exposure and DNA impairments, which are caused primarily by indirect impacts comprising crosslinks, base damage, single-strand breaks, and double-strand breaks, resulting in complex DNA impairment. It may cause mutations (noncancerous) and consequent carcinogenesis depending on the dose ratio and time, mode of delivery, intensity, field size, and overall cumulative dose after radiation exposure [38]. The continuous manufacture of free radicals in the human body plays a key role in increased cell apoptosis [39], dysfunction of enzymes [24], and DNA damage [19]. Malondialdehyde and 4-hydroxynonenal, as well as isoprostanes from unsaturated fatty acids, are produced when lipids undergo oxidative collapse [25].

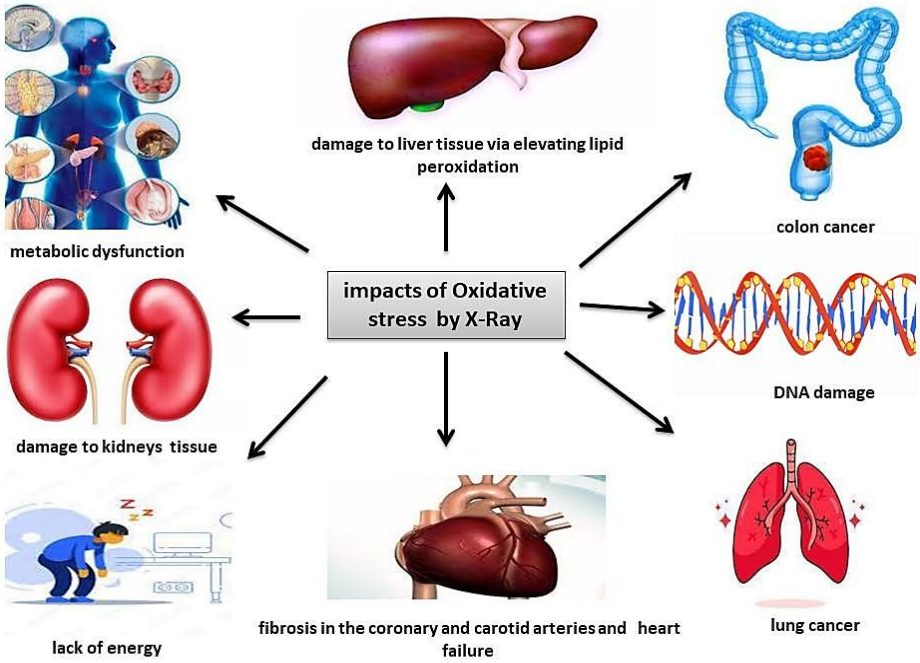


Figure 1: Effects of X-ray irradiation on oxidative stress

Role of natural antioxidants in preventing oxidative stress: Natural antioxidants primarily act as chain breakers, donating hydrogen to neutralize free radicals. Some secondary antioxidants are singlet oxygen quenchers, peroxide decomposers, metal chelators, oxidative enzyme inhibitors, and X-ray absorbers [40– 41]. Antioxidant functions imply a decrease in oxidative stress, DNA mutations, malignant transformation, and other parameters associated with cell damage. Epidemiological studies have shown the ability of antioxidants to affect reactive oxygen species activity [42–43]. Natural antioxidants are found in functional foods and several fruits and vegetables; they can be added as natural food preservatives [45] to prevent and cure various chronic ailments [44]. As we are frequently exposed to X-rays in daily life, we must take antioxidants from food to reduce the risk of free radicals caused by X-rays [46]. Compared with synthetic compounds, natural antioxidants in plants and foods have received significant attention [47–48]. Therefore, they must consume natural antioxidants in plants and foods instead of synthetic antioxidants [39]. Natural antioxidants help improve pathological conditions by slowing disease progression (Figure 2) [49–50]. Frequent X-ray exposure generates free radicals that interact with proteins, lipids, and DNA, leading to cellular dysfunction [51–53]. Endogenous enzymes, such as CAT, SOD, and GSHPx, may inhibit the oxidative damage caused by free radicals in human cells [36]. During oxidative injury, the levels of these enzymes within the cells increase to protect them. The SOD enzyme converts O2– into H2O2, whereas CAT

converts H2O2 into H2O and O2 [51–55]. Catalase transforms H2O2 to H2O and O2 [53], whereas GSHPx converts H2O2 to H2O, preventing the oxidation and interlacement of thiol groups in proteins [56]. Effective defense and repair processes are present in natural antioxidants to safeguard against oxidant species. During the reduction in oxidative stress, energy is shifted from free radicals to antioxidant molecules, resulting in a state of energy-rich triplet. The trapping of other OH, ROS, NO2, or peroxynitrite results in the oxidative decomposition of the molecules of antioxidants. Therefore, antioxidants may safeguard against DNA, protein, and lipid oxidation in vivo [57–59].

Figure 2. Targets of natural antioxidants

Biological activities of active compounds, which are found naturally against X-ray-induced damage in vivo: Choosing active compounds with minimal side effects that are readily available is crucial when considering potential radioprotective agents. Several compounds have been studied for their biological activities against oxidative stress induced by X-radiation, with varying degrees of effectiveness and safety profiles. In this review, these active compounds were selected based on their demonstrated antioxidant, anti-inflammatory, and radioprotective properties and their relatively low risk of side effects and availability.

Effects of lactoferrin against X-ray radiation: Lactoferrin is a crucial component of the mammalian innate immune system. It is an 80 kDa iron-binding multifunctional glycoprotein found in various biological fluids, including milk [60–62]. Lactoferrin is vital in host defense against pathogens and modulating immune responses [63–66].

Table 1 summarizes the antioxidant effects of lactoferrin in vivo and its ability to modify biochemical indicators of oxidative stress. According to a study by Feng *et al.* [64], lactoferrin at a concentration of 15.30 mg/kg was administered to male BALB/c mice for 30 days after radiation exposure at a 7 Gy X-ray dose. This reduced radiation-induced damage to DNA in hepatocytes. Leukocyte, erythrocyte, and platelet counts are the laboratory indicators of rapid recovery. The superoxide dismutase (SOD) level increased significantly, whereas the malondialdehyde (MDA) level significantly decreased. A review published by Sakai *et al.* [65] showed that administering 4 mg/kg

body weight lactoferrin to male mice after they were exposed to 9 Gy of whole-body X-irradiation prevented damage to the salivary glands and regulated submandibular salivary gland branching morphogenesis. It also induced cell proliferation and improved the recovery rate of acinar cells after irradiation, especially regarding the restoration of the salivary gland percentage. In a different study by Wei *et al.* [66], lactoferrin was given to male BALB/c mice at doses of 2, 4, and 6 mg/kg bw before they were exposed to doses of 5 or 8 Gy of radiation, which decreased DNA damage in the mice after X-ray irradiation, increased cell viability, activated SOD and GST enzymes, and reduced cell death.

Regarding intestinal histology, there was a notable improvement in radiation-induced injury. There was also a significant increase in villus length and its ratio to crypt depth, a considerable decrease in the serum levels of IL-6 and TNF-α, a reduction in the radiation-induced expression of IKKα/β and NF-κB, and an improvement in intestinal injury through the downregulation of NF-κB expression and a decrease in inflammatory cytokines. Following a report by Nishimura *et al*. [67], male C3H/He mice were intraperitoneally administered lactoferrin at a dose of 4 mg/kg body weight after 30 consecutive days of 6.8 Gy whole-body X-ray exposure. This resulted in increased hemoglobin and hematocrit values and lactoferrin, demonstrating hydroxyl radical scavenger activity in vivo and decreasing glutathione depletion in the liver, kidney, and intestine. According to a study by Feng *et al*. [67], a high dose of lactoferrin (15.30 mg/kg) significantly decreased DNA damage caused by exposure to 7 Gy of X-rays. These findings indicate that lactoferrin, by scavenging free radicals and enhancing DNA repair processes, can protect cells from damage caused by radiation. Sakai *et al.* [64]. focused on the effects of a moderate lactoferrin dose (4 mg/kg) on radiation-induced damage to the salivary glands of animal models. These findings demonstrated that lactoferrin was an excellent defense against damage caused by 9 Gy of X-rays to the salivary glands. After radiation exposure, lactoferrin affects the structure and function of acinar cells. It also prevents damage to the salivary glands, regulates the morphogenesis of submandibular salivary gland branches, increases the expression of phosphorylated ERK1/2 and AKT proteins, and induces cell proliferation. As reported in a study by Wei *et al*. [65], intestinal damage from 5.8 Gy of radiation exposure decreased after low doses of lactoferrin (2, 4, and 6 mg/kg) were applied. The protective effects of lactoferrin are linked to a decrease in inflammatory cytokine levels, which decreases intestinal inflammation. A low dose of lactoferrin (4 mg/kg) significantly reduced glutathione depletion in the liver, kidney, and intestine caused by oxidative stress induced by 6.8 Gy of radiation, according to an additional research study by Nishimura *et al*. [66]. A crucial antioxidant that is essential for preventing cell damage is glutathione.

Effects of natural pigments against X-ray radiation: Several plant pigments have demonstrated remarkable efficacy in mitigating the harmful effects of X-ray exposure. These include lycopene, which is abundant in watermelons [68]; curcumin, the primary bioactive compound in turmeric [69]; and phycocyanin, which is derived from blue–green algae [70]. Lycopene, curcumin, and phycocyanin might help protect cells from damage (**Figure 3**). Lycopene is a type of organic pigment called a carotenoid; it is related to beta-carotene and gives some fruits, such as watermelon, a color; Lycopene, a potent antioxidant, protects cells from oxidative damage [71–72].

Table 1 summarizes the antioxidant effects of lycopene, found in watermelon juice in vivo, and its ability to modify the biochemical indicators of oxidative stress. Based on a study by Mohammad *et al*. [73], when male ICR mice were given 50 mg/kg bw of lycopene orally for 28 days before exposure to 100 Gy/min X-rays, lycopene in watermelon juice restored their intracellular antioxidant activities by significantly increasing the levels of glutathione and superoxide dismutase (SOD), decreasing malondialdehyde in liver

tissues, helping reduce reactive oxygen species (ROS) and hydrogen peroxide (H2O2) in the serum, decreasing hydroxyl radical activity while increasing the serum levels of superoxide dismutase, glutathione-s-transferase, and catalase enzyme activity, and finally effectively attenuating apoptosis. Curcumin, a yellow-orange pigment, serves as the primary bioactive component of turmeric [73]. The compound is a diarylheptanoid, a family of natural phenols responsible for the yellow color of some plants[75]. Table 1 summarizes the antioxidant effects of curcumin in vivo and its ability to decrease the harmful effects of X-rays by reducing oxidative stress. According to a study by Cervelli *et al*. [76], male Wistar albino rats presented reduced levels of hydrogen peroxide, blood urea nitrogen, and malondialdehyde when given 10 mg/kg body weight curcumin for fourteen days after exposure to radiation at 0.25 Gy/min. In addition, it decreased lipid peroxidation and the expression of apoptotic and inflammatory markers, decreased renal dysfunction, balanced changes in renal morphology, and preserved the tissue structure of the kidneys. It also increased glutathione and total antioxidant levels.

Phycocyanin is a pigment-protein complex from the light-harvesting phycobiliprotein family [77]. Phycocyanin is a characteristic light blue color and is an accessory pigment to chlorophyll [78]. Phycocyanin is often found in cyanobacteria that thrive around hot springs; phycocyanin is used in the food and beverage industry as a natural coloring agent and in sweets and ice cream [79]. Phycocyanin has been shown to have anti-inflammatory and antioxidant properties, inhibit lipid peroxidation, and prevent hepatotoxicity in rats [78–79]. Table 1 summarizes the antioxidant effect of phycocyanin in vivo and its ability to decrease the adverse effects of X-rays by reducing oxidative stress. Based on research by Liu *et al*. [80], in mice given 200 mg/kg phycocyanin before being exposed to 0.47 Gy/min for seven consecutive days, phycocyanin treatment markedly upregulated radiation-induced oxidative stress damage by reducing the levels of malondialdehyde alanine aminotransferase, aspartate aminotransferase, lipid peroxidation, and apoptotic and inflammation markers; preserving the liver tissue structure; decreasing the level of ROS in the liver; and reducing DNA damage. Moreover, it increased glutathione and total antioxidants in the serum and liver. Notably, Mohammad *et al.* [73] reported that a dose (50mg/kg bw) of lycopene given orally to male ICR mice effectively modulates oxidative damage resulting from a 100 Gy/min dose. Lycopene given orally to male ICR mice effectively modulates oxidative activity, restoring intracellular antioxidant activity, reducing malondialdehyde levels in liver tissues, reducing hydroxyl radical activity, and increasing superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in the serum. It was reported that a dose (200 mg/kg) of phycocyanin has strong effectiveness in suppressing the harmful effects caused by a dose of 0.47 Gy/min X-rays through reduced malondialdehyde, alanine aminotransferase, aspartate aminotransferase, lipid peroxidation, and apoptotic and inflammatory markers; preserving the liver tissue structure; decreasing the level of ROS in the liver; and reducing DNA damage. Moreover, it increased glutathione and total antioxidants in the serum and liver tissue.

Effects of melatonin on X-ray radiation: Melatonin is found in many foods, such as walnuts [81]. Melatonin was first reported as a potent antioxidant and free radical scavenger in vivo [82]. Melatonin enhances cytokine production and promotes T-cell expansion, counteracting acquired immunodeficiencies [85] and anti-inflammatory effects [83]. Table 1 summarizes the antioxidant effects of melatonin in vivo and its ability to decrease the adverse effects of oxidative stress. A study by Zhu et al. [84] showed that when melatonin was administered intraperitoneally to mice at a dose of 100 mg/kg before irradiation at 1.5 Gy/min for 30 min, melatonin pretreatment significantly inhibited radiation-induced DNA strand breaks and lipid peroxidation. The inhibition of apoptotic proteins and radiation-induced sperm abnormalities in cauda-epididymes were reduced considerably. Another study by Musa et al. [85] revealed that administering 50,100

mg/kg melatonin to male Wistar rats for 30 min before exposure to 8 Gy X-ray radiation reduced malondialdehyde levels, induced cell proliferation, delayed the onset of mortality; reduced hydroxyl radical activity; increased superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in the liver and kidney tissue; and restored normal liver and kidney cell structure in pretreated animals. The increase in superoxide dismutase activity protected liver tissues.

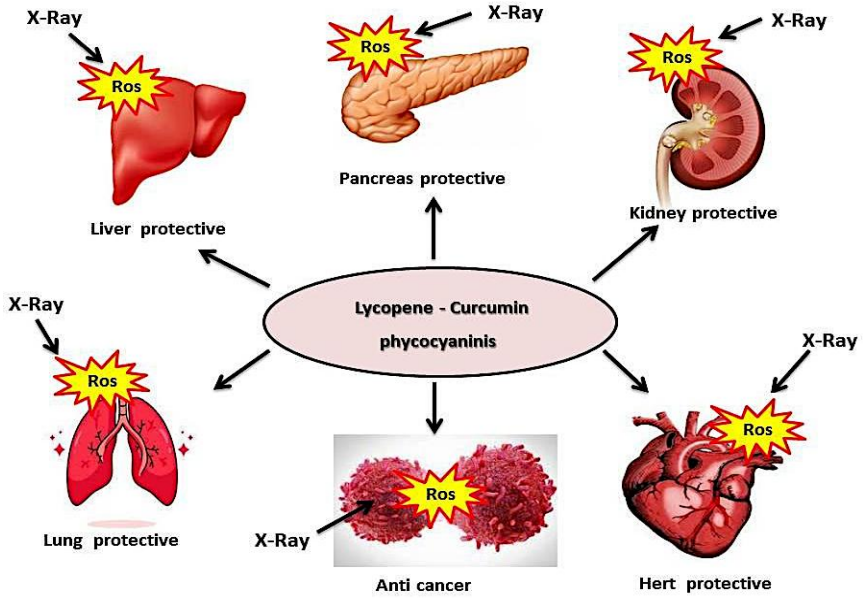


Figure 3. Effects of natural pigments on oxidation

In a different report by Carrillo *et al.* [86], the administration of 200 mg/kg melatonin to female C57BL/6 N mice intraperitoneally daily for 2 weeks before exposure to 3,12 Gy X-rays led to reduced hydroxyl radical activity with increased superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in liver and lung tissue. It restored normal liver and lung cell structure in pretreated animals, with decreased malondialdehyde levels. Zhu *et al.* [84] reported that a dose of melatonin (100 mg/kg) has a positive effect on reducing oxidative stress and increasing antioxidant enzymes via the inhibition of radiation-induced DNA strand breaks and lipid peroxidation, the inhibition of apoptotic proteins, and radiation-induced sperm abnormalities in cauda-epididymes, which are significantly affected by irradiation of the bodies of the animals at a dose of 1 or 5 Gy/min for 30 min (X-rays). The results of the study by Musa *et al.* [85] revealed that a dose (50,100 mg/kg) of melatonin was sufficient to increase the recovery of cellular immunocompetence in experimental animals that were subjected to oxidative stress because 8 Gy X-ray radiation was used for 30 minutes to delay the onset of mortality; reduce hydroxyl radical activity; increase superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in liver and kidney tissue; and restore the normal liver and kidney cell structure in the pretreated animals, improve superoxide dismutase activities, and protect liver tissues. Carrillo *et al.* [86] reported that a dose of melatonin (200 mg/kg) positively reduced the oxidative stress caused by X-ray radiation at a dose of 3.12 Gy through the protected male reproductive system.

Effects of polysaccharides against X-ray radiation: Polysaccharides are natural biomacromolecules found in plants, fungi, algae, animals, and bacteria [87]. Owing to their nontoxicity, stability, biodegradability, biocompatibility, and excellent antioxidant activity, polysaccharides have potential value in treating or preventing disease caused by oxidative stress [88]. Polysaccharides can reduce damage to the cell structure, regulate the signaling pathways related to antioxidation, improve the intracellular antioxidant

enzyme system, reduce the substances that efficiently produce ROS, and protect the body tissue from ROS-induced damage through free radical scavenging activity and immunomodulatory activity [89]. Polysaccharides, found in aloe vera and ganoderma lucidum karst, have potential value in treating or preventing diseases caused by oxidative stress induced by X-rays [90]. Table 1 lists the antioxidant properties of polysaccharides in aloe vera gel tested in male BALB/c mice by Bala *et al.* [91]. A study used 50 mg/kg body weight aloe vera gel extract with X-ray radiation at 2 Gy/min for 30 consecutive days, and aloe vera gel extract helped scavenge hydroxyl free radicals, thereby eliminating chromosomal abnormalities. A minute increase in total antioxidants, thus protecting against hepatic and renal damage, improved hepatic and renal function parameters, which were associated with a reduction in ROS levels compared with those of their irradiated counterparts. Another review by Bala *et al.* [92] reported that administering aloe vera gel 50 mg/kg to male BALB/c mice via gavages after whole-body X-irradiation at 0.258 Gray for 30 days induced cell proliferation, reduced ROS activity, reduced hydroxyl radical activity; increased superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in testicular tissue; and restored standard testicular cell structure in pretreated animals. Another review by Bala *et al.* [93] reported that aloe vera extract (50 mg/kg) can be administered to male BALB/c mice after whole-body X-irradiation with 2 Gray; aloe vera gel extract helps to inhibit lipid peroxides and scavenge ROS, and a minute increase in the glutathione content in the lungs, along with significantly improved bone mineral density and the hepatobiliary clearance profile, was detected. Ganoderma Lucidum Karst is a feathery fungus widely found in China and Japan and has bioactive substances such as polysaccharides [94].

Ganoderma lucidum has antihepatotoxic and free radical scavenging properties, influences the cell cycle and cellular signal transduction, reduces lipid peroxidation, inhibits leukemic cell growth, and induces the differentiation of leukemic cells into mature monocytes. Furthermore, it may inhibit platelet aggregation, impede complex viral interactions with cell plasma membranes, inhibit tumor growth, and reduce other ailments, such as sleeping problems, headaches, glomerulonephritis, and tumors [95]. Table 1 summarizes the effects of polysaccharides in Ganoderma lucidum in vivo and their ability to decrease the harmful effects of oxidative stress. A review of the literature by Kubo *et al.* [94] revealed that when ganoderma lucidum extract was administered orally at doses of 1.25, 2.5, or 5 mg/kg bw to male B6C3F1 (Crj:B6C3FI) mice, for 1 week before irradiation at 2, 4, 7, 8, 10, or 12 Gy/min, animals treated with Ganoderma lucidum extract before irradiation exhibited a significant time-dependent increase in the studied hematological parameters, reduced hydroxyl radical activity, and increased survival rates and recovery of the seminiferous tubules [93]. The concentration (50 mg/kg body weight) of polysaccharides present in aloe vera gel has proven to be enormously effective against the damaging effects that occur when X-rays are used at a dose of 2 Gy/min through the scavenging of hydroxyl free radicals, thereby eliminating chromosomal abnormalities, providing protection against hepatic and renal damage, and improving hepatic and renal function parameters, which are associated with a reduction in reactive oxygen species (ROS) levels in male BALB/c mice [92]. Bala *et al.* [91] reported that a concentration of 50 mg/kg polysaccharide isolated from Aloe vera has a strong positive effect on the harmful damage caused by a dose of 0.258 Gray for 30 days through the induction of cell proliferation, a notable reduction in ROS activity, a reduction in hydroxyl radical activity with increases in superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in testicular tissue, and the restoration of the standard testicular cell structure in male BALB/c mice. A study conducted by Bala *et al.* [92] revealed that a concentration (50 mg/kg) of polysaccharides isolated from aloe vera leaves intensely effectively suppressed the harmful effects caused by a dose of 2 Gray X-rays. By helping to

inhibit lipid peroxides and scavenge ROS, a minute increase in the glutathione content in the lung occurred, along with a significant improvement in the bone mineral density and the hepatobiliary clearance profile in male BALB/c mice. A study conducted by Kubo *et al.* [93] revealed that the concentrations (1.25, 2.5, and 5 mg/kg bw) of polysaccharides isolated from Ganoderma lucidum demonstrated strong effectiveness against the damaging effects resulting from X-ray doses (2, 4, 7, 8, 10, and 12 Gy/min) by increasingincreasing the studied hematological parameters, reducing hydroxyl radical activity, and increasing the survival rate and recovery of the seminiferous tubules in male B6C3F1 (Crj:B6C3FI) mice.

Effects of phenolic compounds against X-ray radiation: Phenolic compounds are important plant constituents with redox properties responsible for antioxidant activity, and the hydroxyl groups in plant extracts facilitate free radical scavenging [95]. Many studies have shown that phenolic compounds, such as those found in Polyalthia longifolia leaf extract, costus afer leaf extract, *Olea europaea* L. leaves, and Pycnanthus angolensis seed extract, have inhibitory effects on damage resulting from X-rays [96–97]. Polyalthia longifolia is a famous medicinal plant grown in India and Pakistan and contains bioactive substances such as phenolic compounds [98]. The literature indicates that polyalthia longifolia reduces lipid peroxidation, antioxidant, anti-inflammatory, and antimicrobial activities; protects DNA and other cellular macromolecules from oxidative stress; and preserves biological processes [99]. Table 1 lists the antioxidant properties of phenolic compounds from Polyalthia longifolia leaf extract tested in male Swiss albino mice by Jothy *et al.* (2016) [100]. A study used 250 or 500 mg/kg BW Polyalthia longifolia leaf extract for 30 consecutive days after exposure to 1.33 Gy/min and 6 MV/min X-ray radiation for one hour. Polyalthia longifolia leaf extract helps scavenge hydroxyl free radicals and has anti-inflammatory and antimicrobial activity; increases superoxide dismutase and catalase activity in both the liver and intestine; reduces hydroxyl radical activity; increases superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in liver tissue; and restores the normal liver cell structure in pretreated animals. Cooper is a famous plant grown in tropical Africa with bioactive substances such as phenols [101]. Many studies have shown that it has antioxidant, anti-inflammatory, and antibacterial properties and is also an antidote against poison [102]. Table 1 summarizes the antioxidant effects of phenolic compounds in Costus after leaf extraction against damage caused by X-rays, A study by Akomolafe. and Chetty. (2021) [103] used 250 mg/kg BW 6 days after exposure to 3,6 Gy/min X-ray radiation. Costus combined with leaf extract helped reduce the elevated levels of ALT and AST, increase superoxide dismutase activity and catalase activity in the liver, restore the normal numbers of red blood cells, platelet counts, and white blood cells; and restore the normal liver cell structure in animals pretreated with leaf extract [104]. Another review by Aguayo Torrez [26] revealed that the administration of costus after leaf extract (250 mg/kg body weight) to male and female Swiss albino mice via gavage after whole-body X-irradiation (3, 4, 6, or 8 Gy/min) for 36 days induced cell proliferation; delayed the onset of mortality; reduced hydroxyl radical activity; increased superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in the liver and kidney tissues; and restored normal liver and kidney cell structure in the animals pretreated with leaf extract. Olea europaea is a famous medicinal plant grown in Australia and southern Africa and contains bioactive substances such as phenolic compounds [105]. The literature indicates that olive leaf extract reduces lipid peroxidation, antioxidant, anti-inflammatory, and antimicrobial activities[106] and reduces other ailments, such as colds, sleeping problems, leprosy, and tumors[107]. Table 1 summarizes the effects of phenolic compounds extracted from Olea europaea L. leaves in vivo and their ability to decrease the negative effects of X-rays by reducing oxidative stress. A review of the literature revealed that administering Olea europaea L. leaves extracted orally at doses of 24.20 and 30.30 mg/kg bw

to male Swiss mice before irradiation at 2 cGy/min reduced DNA damage; reduced hydroxyl radical activity; increased superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in liver and kidney tissues; and restored normal liver and kidney cell structure in pretreated animals, facilitating DNA repair and restoring the lymphocyte percentage[108]. Pycnanthus angolensis is a plant that is widely grown in West Central Africa and contains bioactive substances [109]. Many studies have shown that it has anti-inflammatory, anti-inflammatory, and antibacterial properties and is also an antidote against poison [110]. Several studies have reported that Pycnanthus angolensis seed extract has various health benefits, such as antihyperlipidemic, antiobesity, antibacterial, and fat deposition-inhibiting effects, and that the water extract of Pycnanthus angolensis has in vivo antioxidant activity [111]. Table 1 lists the antioxidant properties of phenolic compounds in pycnanthus angolensis warb seed extract tested in human blood samples by Achel *et al.* [112]. A study used 0.2 mg/kg BW pycnanthus angolensis warb seed extract to prevent the structural and molecular transformation of human serum albumin irradiated with X-ray radiation at 4, 6, 8, and 10 Gy per hour, which protects human serum albumin against damage to its secondary structure after exposure to 4, 6, 8, and 10 Gy per hour X-ray radiation. Pycnanthus angolensis warb seed extract helped scavenge hydroxyl free radicals, thereby eliminating an increase in bityrosine; there was a minute increase in the protein configuration rate. The concentration (250, 500 mg/kg body weight) of the phenolic compounds present in the Polyalthia longifolia leaf extract has proven to be strongly effective against the negative effects that occur at doses of 1.33 Gy/min and 6 MV/min from X-ray radiation for one hour. By increasing superoxide dismutase and catalase activity in both the liver and intestine, hydroxyl radical activity is reduced, superoxide dismutase, glutathione-s-transferase, and catalase enzyme activity are increased in liver tissue, and the normal liver cell structure is restored in male Swiss albino mice [100]. The concentration (250 mg/kg BW) of phenolic compounds present (costs after leaf extract) effectively suppressed the harmful effects resulting from an X-ray dose of 3.6 Gy/min through increasing superoxide dismutase and catalase activity in the liver, restoring normal numbers of red blood cells, platelet counts, and white blood cells; and restoring the normal liver cell structure in male BALB/c mice [103]. On the other hand, [16] reported that the concentration (250 mg/kg of body weight) of phenolic compounds found in (costus after leaf extract) effectively curbed the harmful effects resulting from a dose of (3, 4, 6, 8 Gy/min) radiation. x reduces hydroxyl radical activity; increases superoxide dismutase, glutathione-s-transferase, and catalase enzyme activity in liver and kidney tissue; and restores normal liver and kidney cell structure in male and female Swiss albino mice. Benavente-García *et al.* [104] reported that the concentration (24.20, 30.30 mg/kg bw) of phenolic compounds isolated from Olea europaea L. leaf extract has a new effect on inhibiting damage caused by a dose of 2 cGy/min, which is accomplished by reducing hydroxyl radical activity; increasing superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in liver and kidney tissue; and restoring the normal liver and kidney cell structure in male Swiss mice. For the phenolic compounds isolated from Pycnanthus angolensis warb seed extract, 0.2 mg/kg BW had a high efficiency in suppressing the negative effects of the dose (4, 6, 8, and 10 Gy per hour). X-rays protect human serum albumin from damage to its secondary structure and help scavenge hydroxyl free radicals, eliminating increased bityrosine [108].

Effects of saponins against X-ray radiation: Saponins are organic chemical compounds with a bitter taste because they contain various triterpenoidal and steroidal aglycons. Saponins are widely distributed in many plants, unripe fruits, and marine organisms and are used in medicines, dietary supplements, and soft and alcoholic beverages[113]. The consumer demand for natural products coupled with their physicochemical (surfactant) properties and increasing evidence of their biological activity (such as anticancer

and anti-cholesterol activity) has led to the emergence of saponins as commercially significant compounds with expanding applications in the food, cosmetics, and pharmaceutical sectors[114]. Saponins are used as natural stabilizers, foaming agents, and emulsifiers in food applications. They have possible health benefits, such as decreasing cholesterol and having anticancer effects, and they help give food products their texture and solidity. In the pharmaceutical sector, saponins are valued for their extra bioactivities, which include anti-inflammatory, antibacterial, antiviral, and antiparasitic properties. In addition to their ability to act as adjuvants and exhibit cytotoxic activity against cancer cell lines, saponins can also increase the immune system's response to vaccinations. The promise of these materials in drug delivery systems is further enhanced by their ability to form stable complexes with medicines. However, for saponins to be effectively used in foods and related applications, issues such as bitterness, cytotoxicity, and instability under specific conditions must be resolved [115]. Table 1 summarizes the antioxidant*oxidant effects of saponins* in vivo and their ability to decrease the negative effects of X-rays by reducing oxidative stress. A previous study demonstrated that the oral administration of saponins at 25.50 mg/kg body weight over 14 days before irradiation and 7 days after the exposure of male Wistar albino rats to 5 or 10 Gy/min increased the survival rate, protected the hematopoietic system by decreasing reactive oxygen species levels; elevated the activities of superoxide dismutase, catalase, and glutathione peroxidase in the liver; and decreased DNA damage [116]. Drymaria cordata is a famous plant grown in India and contains bioactive substances such as saponins and tannins [117]. The literature indicates that dry milk reduces lipid peroxidation, antioxidant, anti-inflammatory, and antimicrobial activities, in addition to reducing other ailments, such as colds, sleeping problems, headache, glomerulonephritis, coryza, bronchitis, leprosy, and tumors[118]. Table 1 summarizes the effects of saponins isolated from drymaria Cordata extract in vivo and their ability to reduce the negative effects of X-rays. A review of the literature by Akomolafe. Chetty [9] reported that administering saponins orally at doses of 250 mg/kg to female BALB/c mice for thirteen consecutive days before exposure to X-ray radiation to the whole body at rates of 4 and 8 Gy/min increased superoxide dismutase and catalase activity in the liver, increased mouse survival, and restored normal red blood cell and platelet counts [119]. Another review by Aguayo Torrez[120] revealed that administering saponins isolated from drymaria cordata extract at 250 mg/kg body weight to male and female Swiss albino mice through gavages after whole-body X-irradiation (3, 4, 6, or 8 Gy/min) for 36 days induced cell proliferation; delayed the onset of mortality; reduced hydroxyl radical activity; increased superoxide dismutase, glutathione-s-transferase and catalase enzyme activity in liver and kidney tissue; and restored normal liver and kidney cell structure in pretreated animals. In a study by Yalinkilic, O., & Enginar, H. [116], the concentration (25, 50 mg/kg body weight) of saponin found in many unripe fruits has proven its strong effectiveness against the negative effects that occur due to a dose of 5 and 10 Gy/min from X-ray radiation) through the protection of the hematopoietic system by decreasing the reactive oxygen species levels, increasing the activities of superoxide dismutase, catalase, and glutathione peroxidase in the liver, and decreasing DNA damage in male Wistar albino rats [120]. A review of the literature revealed by Akomolafe. and Chetty [119] that the concentration (250 mg/kg body weight) of saponin found in (drymaria Cordata extract) had strong effectiveness against the negative effects that occur due to a dose of 4 and 8 Gy/min from X-ray radiation) through increasing superoxide dismutase and catalase activity in the liver, increasing mouse survival, and restoring normal red blood cell and platelet counts in female BALB/c mice[120]. A study conducted by Aguayo Torrez [116] revealed that a concentration (250 mg/kg body weight of saponin isolated from drymaria cordata extract) has strong effectiveness against the negative effects that occur at doses of 3, 4, 6, and 8 Gy/min of -ray radiation) and reduces hydroxyl radical activity; increases

superoxide dismutase, glutathione-s-transferase, and catalase enzyme activity in liver and kidney tissue; and restores the normal liver and kidney cell structure in female Swiss albino mice[119].

Table 1. Applications of active compounds in clinical trials

Active compounds	Dose of X-ray	Dose of active compounds	Outcome	In vivo test models	R.F
Lactoferrin	7 Gy/min	15,30 mg/kg bw	Reduced radiation-induced DNA injury	male BALB/c mice	[64]
	9 Gy/min	4 mg/kg bw	Prevent damage to the salivary glands	male C3H/He mice	[65]
	5,8 Gy/min	2,4,6 mg/kg bw	Improved intestinal injury	male BALB/c mice	[66]
	6.8 Gy/min	4 mg/kg bw	Inhibit radiation damage	male C3H/He mice	[67]
Lycopene	100 μGy\min	50 mg/kg bw	Modulate oxidative damage	male ICR mice	[73]
Curcumin	0.25 Gy/min	10 mg/kg bw	Attenuate the renal oxidative stress	male wistar albino rats	[76]
Phycocyanin	0.47 Gy/min	200 mg/kg bw	Reduced liver damage	male C57BL/6 mice	[80]
Melatonin	8 Gy/min	50,100 mg/kg bw	Decreasing oxidative stress and increasing antioxidant enzymes.	male wistar rats	[84]
	3,12 Gy/min	200 mg/kg bw	Enhance the recovery of cellular immunocompetence	Female C57BL/6 N mice	[85]
	1,5 Gy/min	100 mg/kg bw	Protected male reproductive system	male C57BL/6 mice	[86]
Polysaccharides in aloe vera gel	2 Gy/min	50 mg/kg bw	Boost the antioxidant system	male BALB/c mice	[91]
	0.258 Gy/min	50 mg/kg bw	Boost cellular antioxidant defense machinery.	male BALB/c mice	[92]
	2 Gy/min	50 mg/kg bw	Improved hepatobiliary clearance profile	male BALB/c mice	[93]
Polysaccharides in Ganoderma Lucidum Spore	2, 4, 7, 8, 10, 12 Gy/min	1.25, 2.5, 5 mg/kg bw	Enhance the recovery of cellular immunocompetence	male B6C3F1 (Crj:B6C3FI) mice	[94]
Phenolic compounds in Polyalthia *longifolia* leaf extract	1.33 Gy/min; 6MV/min	250,500 mg/kg bw	Restoration of the normal liver cell structure	male Swiss albino mice	[100]
Phenolic compounds in Costus afer leaf extract	3,6 Gy/min	250 mg/kg bw	Protection hematological alterations	male BALB/c mice	[103]
	3,4,6,8 Gy/min	250 mg/kg bw	Increasing the mice's survival rate	male and female Swiss albino mice	[104]
Phenolic compounds in Olea europaea L. Leaves	2 cGy/min	24.20, 30.30 mg/kg bw	Inhibiting the pro-inflammatory cytokines	male Swiss mice	[108]
Phenolic compounds in PycnanthusangolensisWarb Seed Extract	4, 6, 8, and 10 Gy/min	0.2 mg/kg bw	Stabilization of molecular structure of human serum albumin	human blood samples	[112]
Saponins in many unripe fruit	5,10 Gy/min	25.0, 50.0 mg/kg bw	Reinforce the antioxidant systems	male wistar albino rats	[116]
Saponins in Drymaria Cordata extract	4,8 Gy/min	250 mg/kg bw	Reduce radiation-induced damage and increase the survival rate	female BALB/c mice	[119]
	3,4,6,8 Gy/min	250 mg/kg bw	Increasing the mice's survival rate	male and female Swiss albino mice	[120]

CONCLUSION

The main focus of the current study was the therapeutic use of organically active chemicals from plants and other organic foods against oxidative stress caused by X-rays. According to the experimental findings, the materials under consideration offer X-ray protection. As a result, those operating in radiation therapy needs to be given antioxidants from organic food sources to reduce the harm caused by X-rays. This will decrease the need for more medication and enhance quality of life. We examined the associations between the oxidative stress caused by X-rays and the active chemicals found in plants and other organic foods. It has been demonstrated that natural materials can increase the quality of life. In addition to being used in food, it has been proposed that natural antioxidants

could be applied as radiation protectants to reduce the oxidative stress generated by X-rays. Since the active compounds in the study had no toxic effects, we suggest the use of these active compounds to produce a nutraceutical beverage that can be consumed or included in a daily diet to minimize oxidative stress.

ABBREVIATIONS

ROS: Reactive oxygen species, H2O2: Hydrogen peroxide, O2•−: Superoxide radical, OH: hydroxyl radical, RNS: Reactive Nitrogen species, CAT: Catalase, SOD: Superoxide dismutase, GSHPx: Glutathione, MDA: Malondialdehyde, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IL-6: Interleukin 6, TNF-α: Tumor necrosis factor alpha, Gy/min: Gray/min, z BW: Body weight

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