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Radio-protective Effects and Mechanisms of Medicinal Plants against X-ray: A Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

X-ray is used routinely in many medical procedures for the diagnosis and treatment of diseases. But despite many benefits, there are several complications including breakdown of different bio-molecules, lipids, DNA and proteins that cause cytotoxicity in the body tissue by several mechanisms like the generation of free radicals and oxidative stress. This study was conducted to investigate the radio-protective effects and mechanisms of medicinal plants against X-ray damages and X-ray-toxicity in diagnostic radiology. Medicinal plants and their derivatives contain polyphenols which exert potent anti-oxidant activity via up-regulated mRNAs of anti-oxidant enzymes including catalase (CAT), glutathione peroxidase (GPX), glutathione S-transferases (GSTs), superoxide dismutase (SOD) and thus may counteract the oxidative stress induced by ionizing radiations. In addition, they exhibit protective effects against radiation-induced apoptosis by increasing Bcl-2 gene expression, with a significant decrease in BAX gene expression in irradiated cells and tissues and reduction in caspase-3 and caspase-6. Medicinal herbs and their compounds act as anti-inflammatory agents and exert their radio-protective effects against x-ray they exert anti-

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inflammatory effects by inhibiting pro-inflammatory cytokines. Hence the possible protective mechanisms against X-ray are anti-oxidant activity, anti-inflammatory and anti apoptotic properties of medicinal plants.

Keywords: Radio-protective; medicinal plants; X-ray; radiotherapy.

1. INTRODUCTION

Medical diagnostic tools have a frequent use in medical settings and still ionizing radiation plays an important role in these devices. One form of ionizing radiation is X-radiation and it serves as a basic part of function in computed tomography (CT), fluoroscopy, and radiography and is also used to destroy malignant tissue [1,2]. The diagnostic equipment is used to make detailed images of soft tissue and bones in the body, for airport security screening, and in industrial processes. Despite the widespread use of x-rays and other radiation technologies and many applicable benefits, they can also cause potential harm [1]. X-rays are capable of creating ions by waves that contain sufficient energy to overcome the binding energy of electrons in the tissues [3]. So the absorbed energy damages directly or indirectly cellular structures. Directed energy deposition causes damage to macromolecules due to the photolysis of H_2O_2, which leads to the formation of reactive free radicals such as hydroxyl radicals. Indirect attack leads to the production of reactive oxygen species (ROS), which react with different bio-molecules, lipids, DNA, and proteins, culminating in oxidative damage to them. In addition, irradiated cells that escape cell death and direct effects may undergo mutations and create errors in the DNA blueprint [4]. Several studies have shown medicinal plants can be effective, cheap and safe treatments for various disorders and produce protective effects against radiation [5-13]. In this regards, many natural products have been known as a radio-protective agent and inhibited cytotoxicity in normal cells [14]. Considering the importance of X-rays in medical settings and its various complications for staff and patients, this study was done to investigate radio-protective effects and mechanisms of medicinal plants against X-ray damages and X-ray-toxicity in diagnostic radiology.

2. MATERIALS AND METHODS

The key words of interest and the Endnote software were used to conduct this review. The key words Radio-protective or Radio protective with X ray or X-ray in combination with some herbal terms such as *medicinal plant*, *phyto** and *herb** were used to search for relevant publications indexed in the Institute for Scientific Information (ISI) and PubMed with EndNote software. In total 21 articles were found in PubMed and 27 in ISI databases (Table 1).

Table 1. Number of studies divided by database

Radio-protective +medicinal plant+	X ray	PubMed	4
		ISI	3
	X-ray	PubMed	1
		ISI	3
Radio-protective +phyto*+	X ray	PubMed	1
		ISI	4
	X-ray	PubMed	1
		ISI	4
Radio-protective +herb*+	X ray	PubMed	6
		ISI	5
	X-ray	PubMed	4
		ISI	4
Radio-Protective+ medicinal plant+	X ray	PubMed	0
		ISI	0
	X-ray	PubMed	1
		ISI	0
Radio-Protective+phyto*+	X ray	PubMed	0
		ISI	1
	X-ray	PubMed	0
		ISI	1
Radio-Protective+herb*+	X ray	PubMed	0
		ISI	0
	X-ray	PubMed	0
		ISI	0
Radio Protective+ medicinal plant+	X ray	PubMed	1
		ISI	0
	X-ray	PubMed	0
		ISI	0
Radio Protective+phyto*+	X ray	PubMed	1
		ISI	1
	X-ray	PubMed	1
		ISI	1
Radio Protective+herb*+	X ray	PubMed	0
		ISI	0
	X-ray	PubMed	0
		ISI	0
Total		PubMed	21
		ISI	27

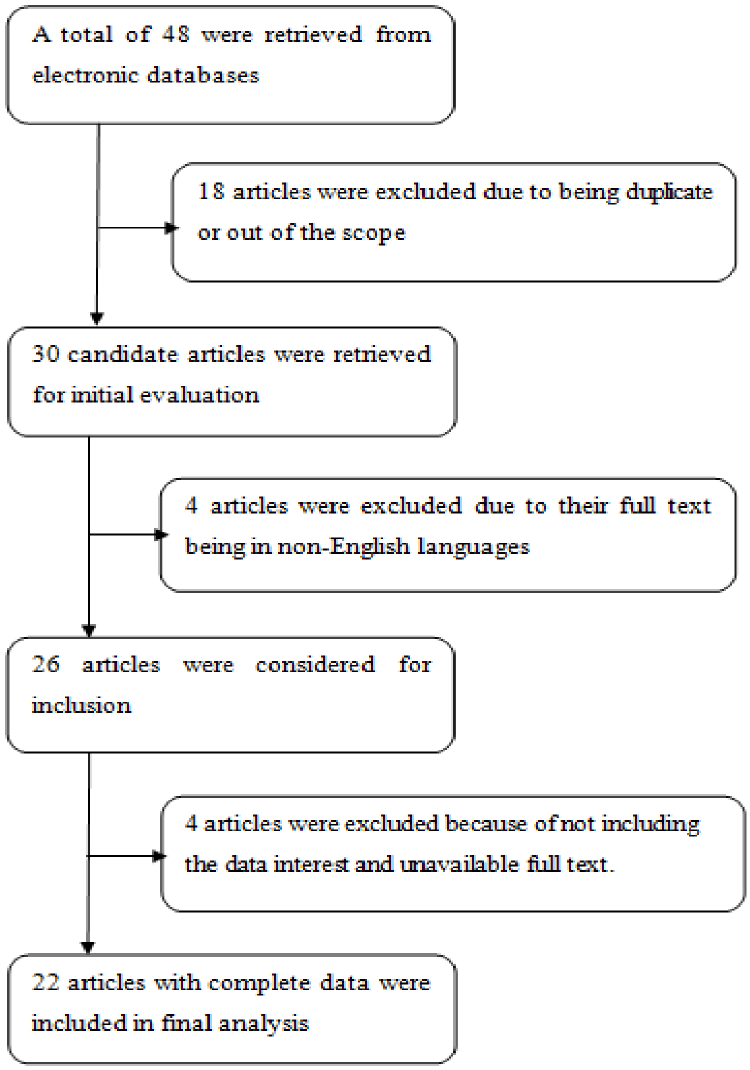

Fig. 1. Flowchart of the process of selecting the articles for final analysis

The articles whose full texts were not accessible, non-English language articles, studies with non-positive effects, review articles, and studies that were not related to the aim of this study and have not enough quality of the reviewed were excluded after all authors' agreement was achieved. Fig. 1 illustrates how the articles were selected for final analysis.

A standard form, which included items such as purpose or the title of the study, intervention, outcome, variables, journal name, intervention period, and article number, was designed. The full text articles that were in accordance with the purpose of the study were recorded in the form and entered to the study with agreement of the researchers. Then, the plants and its products that have protective effects against X-radiations were selected for the study.

3. RESULTS

3.1 Medicinal Plants, Formula and Compounds with Radio-protective Effects and Mechanisms of Action against X-radiation

Medicinal plants and their compounds can be effective against X-radiation toxicity through various mechanisms of action (Table 2).

Table 2. Medicinal plants, formula and compounds with radio-protective effects against X-radiation

Medicinal plants					
References	**Plants scientific name**	**Study Design**	**Type of administration**	**Target tissue or cell**	**Main radio-protective and mechanisms**
Takeda et al. [15]	*Panax ginseng*	Experimental (*In vivo*)	Aqueous extract	Blood cell	Recovering blood cell counts including thrombocyte, erythrocyte and leukocyte.
Hsu et al. [16]	*Ganoderma lucidum*	Experimental (*In vivo*)	Aqueous extract	General	Recovering the body weights and increased the recovery of hemograms of radio-irradiation
Benavente et al. [17]	*Olea europaea L.*	Experimental (*In vitro+in vivo*)	Phenolics extract	Micronucleated polychromatic erythrocytes	Free oxygen radicals and lipoperoxy radicals scavenging capacity and anti clastogenic activity
Wang et al. [18]	*Dioscoreaalata L*	Experimental (*In vitro*)	Aqueous extract and ethanolic extract	Plasmid pGL3 DNA	Inhibiting X-ray induced strand breaks in plasmid pGL3 DNA and act as a copper chelating and radical scavenging.
Malakyan et al. [19]	*Humulus lupulus L.*	Experimental (*In vitro+in vivo*)	Aqueous extract and methanolic extract	Erythrocyte and general	Acting as membrane-stabilizing activity, which protected membranes from the hemolysis and increased survival rate
Menkovic et al. [20]	*Gentiana lutea*	Experimental (*In vitro*+ex vivo)	Aqueous-ethanol extract	Malignant cells and human immunocompetent cells	Inhibiting cytotoxic action of ionizing irradiation and didn't any changes in changing the susceptibility of malignant cells
Christofidou-Solomidou et al. [21]	*Linumusitatissimum*	Experimental (*In vivo*)	Supplement	Lungs	Enhancing mouse survival and decreased pulmonary fibrosis, inflammationcytokine secretion and lung damage
Das et al. [22]	*Saracaindica*	Experimental (*In vitro*)	Hydroalcoholic extract	Hamster fibroblast (V79) cells	Inhibiting of radiation induced Glutathione (GSH), Glutathione S-transferase (GST), Superoxidedismutase (SOD), catalase (CAT) levels and lipid peroxidation, consequent decrease in DNA damage, apoptotic and necrotic cell death
Duan et al. [23]	*Lyciumruthenicum*Murr.	Experimental (*In vivo*)	Aqueous extract	General	Increaseing the DNA contents, total red blood cell count, hemoglobin count and reduced in caspase-3 and caspase-6 of serum and down-regulation expression of P53
Shahani et al. [24]	*Achillea millefolium* L	Experimental (*In vitro*)	Methanolicextract	Lymphocyte	Protecting genotoxicityand exhibited radical-scavenging activity and protecting normal tissues against genetic damage
Yang et al. [25]	*Quercus lusitanic var. infectoria galls*	Experimental (*In vitro*)	Ethanolic extract	Human AHH-1 cell	Down-regulating BAX and up-regulation Bcl-2, enhancing the scavenging activity ofROS, and the down-regulating the activity of procaspase-3, besides modulating themitogen-activated protein kinase (MAPK) signaling pathways
Jothy et al. [26]	*Polyalthialongifolia*	Experimental (*In vitro+in vivo*)	Methanolicextract	General	Decreasing in lipid peroxidation levels, increase in superoxide dismutaseand catalase activity, regenerated of the mucosal crypts, restoration of the normal liver cell structure and decreased the elevated levels of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and bilirubin.
Bala et al. [27]	*Aloe barbadensis Miller*	Experimental (*In vitro+in vivo*)	Aqueous extract	Testis tissue	Increasing in anti-oxidant status, inhibition of lipid peroxidation, apoptotic cell formation and enhanced testicular parameters via free radical scavenging properties and can boost cellular anti-oxidant
Freitas et al. [28]	*Vitislabrusca*	Experimental (*In vivo*)	Juice	Brain	Inhibiting loss of body weight via reverse mandibular changes that interfere with normal feeding, attenuating the severity of

Medicinal plants					
References	**Plants scientific name**	**Study Design**	**Type of administration**	**Target tissue or cell**	**Main radio-protective and mechanisms**
					osteoradionecrosis (ORN) as well as improving white and red blood cell counts
Haghparast et al. [29]	*Lens culinaris)*	Experimental (*In vitro+in vivo*)	Freeze-dried extract	Lymphocyte	Reducing cytotoxicity, increased resistant to Radiation and protected lymphocyte cells from death and DNA double-strand break formation induced by radiation.
Medicinal plants compounds					
References	**Plants scientific name**	**Study Design**	**Type of administration**	**Target tissue or cell**	**Main radio-protective and mechanisms**
Amer et al. [30]	Sugar cane extract derived from *Saccharum officinarum L.*	Experimental (*In vitro*)	Aqueous extract	Jejunum	Increasing the number of crypt/circumference effects and growth promoting activity
Chang et al. [31]	Alk(en)yl Thiosulfates derived from *Allium*Vegetables	Experimental (*In vitro*)	Extract	Hepatoma H4IIE Cell and lymphoma L5178Y cell	Decreasing DNA damage with their anti-oxidant activity
Cinkilic et al. [32]	Chlorogenic and quinic acid derived from Coffee beans	Experimental (*In vitro*)	Extract	Blood lymphocytes	Decreasing DNA damage inhuman lymphocytes due to anti-oxidant activity
Pietrofesa et al. [33]	Lignan component derived from*Linumusitatissimum*	Experimental (*In vivo*)	Supplemente	General and lung	Reducing radiation-related animal death and lung fibrosis, increased survival rate, decreasing bronchoalveolar lavage protein and inflammatory cytokine/chemokine release and reducing in inflammatory cell infiltrate in airways and levels of nitrotyrosine and malondialdehyde (MDA)
Cinkilic et al. [34]	Cinnamic acid	Experimental (*In vitro*)	Solution	Blood lymphocyte	Reducing the DNA damage reducing the intracellular ROS level through its free-radical scavenging properties
Medicinal plants formula					
References	**Plants scientific name**	**Study Design**	**Type of administration**	**Target tissue or cell**	**Main radio-protective and mechanisms**
Cheeramakara et al. [35]	Thai medicinal plant composed of *Bridelia ovata Decne, Curcuma zedoaria (Berg) Roscoe, Derris scandens (Roxb.) Benth., Dioscoreamembranacea Pierre, Drynariaquercifolia Linn., Erythrophleumteysmannii Craib, Moringa oleifera Lamk., Nardostachysjatamansi DC., Rhinacanthusnasutus (L.) Kurz, Sapindusrarak DC., Smilax corbulariaKunth and Strychnosnux-vomica L.*	Experimental (*In vitro*)	Capsule	Macrophage cell line RAW264	Could prevented cell damage and prevented DNA fraction.
Takauji et al. [36]	Triphala composed of *Terminalia chebula, Terminalia bellirica, and Emblicaofficinalis*	Experimental (*In vitro*)	Ethanolic extract	HeLa cells	Eliminating ROS in HeLa cells and consequently prevented DNA damage. Besides protective effect against bleomycin (which causes DNA strand breaks in cells)

4. DISCUSSION

The results of this study can provide clues to prospective new plant sources of drugs for the alleviation of radiation injuries of patients and radiology staff. Medicinal herbs and their derivatives have radio-protective effects via multiple ways and may be able to minimize the life-threatening effects of irradiation. The studies have shown oxidation is one of the most damage-inducing mechanisms due to ionization. DNA oxidation can result in strand break, deoxyribose oxidation, elimination of nucleotides, and a lot of modifications in the bases of thenucleotides [37-39]. The formation of free radicals such as singlet oxygen, ·OH, ·H and peroxyl radicals causes damage to DNA such as base damage, DNA-DNA or DNA-protein cross-links, single or double-strand breaks (DSBs) that cluster as complex local multiply damaged sites. These mechanisms are the most dangerous consequences of ionizing radiation and have been found to be the primary cause of cell necrosis by radiation [40]. Medicinal herbs and their polyphenolic compounds decreased the formation of ROS and 8-hydroxy-2-deoxyguanosine, a damaged DNA product caused by free radicals, several times more effectively than some classic anti-oxidants. So, they act as a direct scavenger of ROS and can act as an indirect stimulator of the activity of the anti-oxidative defense systems [41,42]. Phytochemicals up-regulated mRNAs of anti-oxidantenzymes including CAT, Glutathione Peroxidase (GPx), Glutathione S-transferases (GSTs), SOD and thus may counteract the oxidative stress induced by ionizing radiations. The up-regulation of DNA repair genes possibly protects against radiation damage as well by bringing error free repair of DNA damage [40,43]. Overall, the inhibition of lipid peroxidation and protein oxidation is one of these protective mechanisms [26]. Medicinal herbs and their derivatives have protective effects against radiation-induced apoptosis. A main observation is that they can increase Bcl-2 gene expression by significantly decreasing the BAX gene expression in irradiated cells and tissues and reducing caspase-3 and caspase-6 [25,44]. Thus they prevented radiation-induced apoptosis and necrosis. Besides, X-irradiation induces the activation of NF-κBwhich leads to theactivation of pro-inflammatory cytokines [45]. Medicinal herbs act as anti-inflammatory agents and exert their radio-protective effects against x-ray. They have been observed to exert anti-inflammatory effects by inhibiting pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNF-α and PGE2 in both *in vitro* and *in vivo* studies [21,33,46-48]. Simplified mechanisms of plants' protective effects are shown in Fig. 2.

Despite the mentioned benefits, there is always the concern that the potency of these compounds/formulations could protect the cancer cells from radiotherapy which would interfere with radiotherapy. But they can facilitate the therapeutic process and even protect normal cells against genetic damage due to radiotherapy [24]. Based on previous studies, dietary intake and supplementation may be expected to reduce the harmful side effects of cancer standard treatments and increase selective toxicity towards malignant cells (by increasing the susceptibility of malignant cells) and consequently improve the overall effectiveness of anticancer therapy [20,49,50]. In fact many phytochemical compounds, such as genistein, curcumin and resveratrol, show radio-sensitizing effects towards malignant cells but have radio-protective effects for normal cells [51].

Protective effects of medicinal herbs and their compounds against x-ray radiation are depending on the taken dose and their effective dosage but also on the injury rate, depending on the severity of the damage caused by X-ray [27,36]. In addition, certain factors such as environmental ones, including water, soil content, season and acidity may be different; different species of the same plant family have different amounts of the bioactive ingredients, resulting in different outcomes due to the same biological activities.

Most of the studies concluded in this review, were conducted on animals and were lab trial studies. Most of the reviewed studies were done on plants extract and because the plants have a lot of active compounds, their specific properties have not been studied. Except in Amer et al. [30], Chang et al. [31], Cinkilic et al. [32], Pietrofesa et al. [33], Cinkilic et al. [34] studies the active ingredients were studied. Another limitation of the reviewed studies was mainly done on animal specimens. So it is recommended that clinical trials must be done on the radio-protective effects of medicinal plants on human population, which may explain possible mechanisms of damage in more details and fruitfully yields a potential medicament for the treatment of radiation.

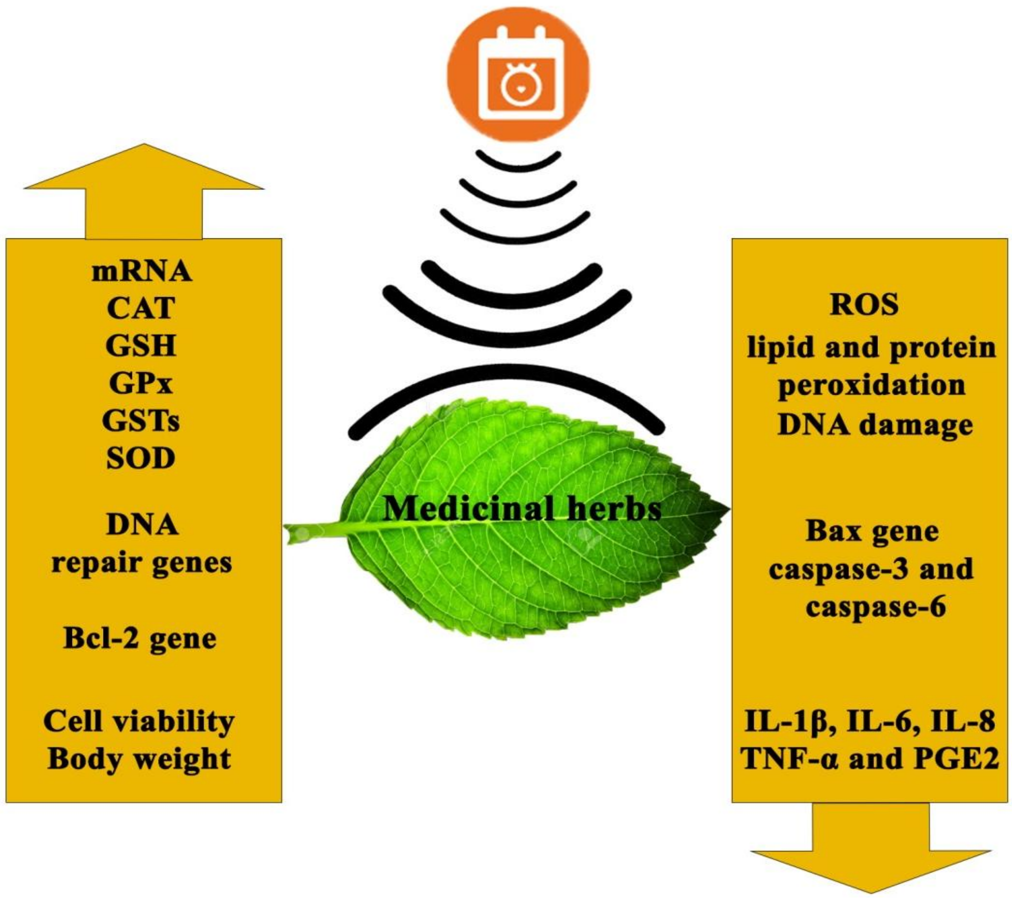

Fig. 2. Possible radioprotective mechanisms of various plants and phytochemicals against X-ray

5. CONCLUSION

Medicinal plants and their derivatives exert radio-protective effects by 3 main ways. Anti-oxidant activity, anti-inflammatory and anti apoptotic activity are the main possible mechanisms of action against X-ray. Hence the possible protective mechanisms against X-ray are anti-oxidant activity, anti-inflammatory and anti apoptotic properties of medicinal plants.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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