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Radioprotection by curcumin: A mini review

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Abstract

Ionizing radiations are detrimental to the biological system. Exposure to ionizing radiations results in many chronic diseases including cancer. It may cause dysfunctions to almost all organs of the body depending on the total dose, duration and site of irradiation. Apart from its bad effect, radiotherapy is now extensively used for the treatment of several kinds of cancers. Still, the key disadvantage in the procedure is that normal cell, in the surrounding area of the tumor, also receiving radiation doses similar to the tumor, leads to undesirable side effects and risk to patients. Curcumin has been found to protect harmful effects of ionizing radiation. So, it can be beneficial during radiotherapy of cancer. Curcumin helps to kill tumor cells effectively by enhancing the effect of radiation. It also protects normal cells against the harmful effects of radiation. Pre clinical studies are expected to lead to clinical trials to prove the potential of this age-old golden spice for treating cancer patients. This review summarizes the protective effect of curcumin against harmful radiations.

Keywords: curcumin, radiation, radioprotection, tumor cells

Introduction

Medicinal plants are source of numerous organic compounds with therapeutic values. Turmeric (*Curcuma longa* L.) is typical of the herbaceous plant with thick and fleshy rhizomes that characterize the family Zingiberaceae (Govindarajan 1980). Turmeric contains a wide range of phytochemicals namely, curcuminoids, zingiberene, curcumenol, triethylcurcumin, turmerin, and turmerones (Chattopadhyay *et al*. 2004). Curcumin (70-75%), demethoxycurcumin (15%), bisdemethoxycurcumin (10%) are the curcuminoids of commercially available turmeric (Shehzad *et al*. 2003). The value of the turmeric products is based on their curcuminoids content (Merina 2003). Curcumin content in turmeric is approximately 2–6%. This compound was first isolated in 1815, and the structure defined in 1910 as diferuloylmethane with a molecular formula $C_{21}H_{20}O_6$ (Figure 1) (Aggarwal *et al.* 2007; Balaji & Chempakam 2010).

Curcumin, the wonder compound, has been widely investigated in recent years due to its high medicinal potential. Several studies indicate that curcumin shows anti-inflammatory, anti-angiogenic, antioxidant, wound healing and anti-cancer effects (Maheshwari *et al*. 2006; Naidu *et al*. 2009). Curcumin inhibits cancer cell survival and proliferation and induce apoptosis without promoting the development of side effects (Salem *et al*. 2014). It can scavenge oxygen free radicals, inhibit lipid peroxidation, and protect the cellular macromolecules, including DNA from oxidative damage (Kalpana & Menon 2004; Polasa *et al*. 2007). Evidences from literature prove that curcumin exhibit powerful radioprotective activity. Several studies have suggested that curcumin was able to protect healthy cells during radiotherapy (Jagetia 2007).

Effects of ionizing radiations to the biological system

High energy radiation that has enough energy to remove tightly bound electron, resulting in the formation of ion is named as ionizing radiation. They have adequate energy to remove electrons and ionize atoms of the medium. Major ionizing radiations are X-rays, γ- rays, UV rays, β particles, α particles and Neutrons. Exposure to ionizing radiations can cause adverse effects to human body.

Effects of ionizing radiations are categorized into two: (i) Higher doses of radiation exposure over a short time result in the short term, or acute effects. (ii) Low doses of radiation exposure over a prolonged time results in long term or chronic effects. Radiations of higher doses can kill the cells and damage tissues and organs, where as low doses of radiation may impair or alter cells. Rapid exposure to body results in Acute Radiation Syndrome (ARS) (Zakariya & Kahn 2014). Biological system contains more than 80% water, the predominant effect by which ionizing radiations cause damage to the biomolecules is through radiolysis of water. Peroxide, •OH, •H are the reactive oxygen species (ROS) produced when water molecules interact with ionizing radiation (Jagetia 2007; Grant & Schneider 2000). The hydroxyl radical is a very reactive and oxidizing species. It can react with all cell components (Lin & Lin-Shiau 2001). Macromolecules are the primary target for the attack of free radicals in the cell (Joe *et al*. 2004). Free radicals can react with DNA and RNA & cause structural and functional changes to these biomolecules. If ROS are not effectively scavenged by cellular constituents, they lead to disease conditions (Halliwell & Gutteridge 1990).

Harmful Effects of Ionizing Radiation

Harmful effects of radiation exposure vary from simple irritation to deadly diseases including cancer depending upon types, doses

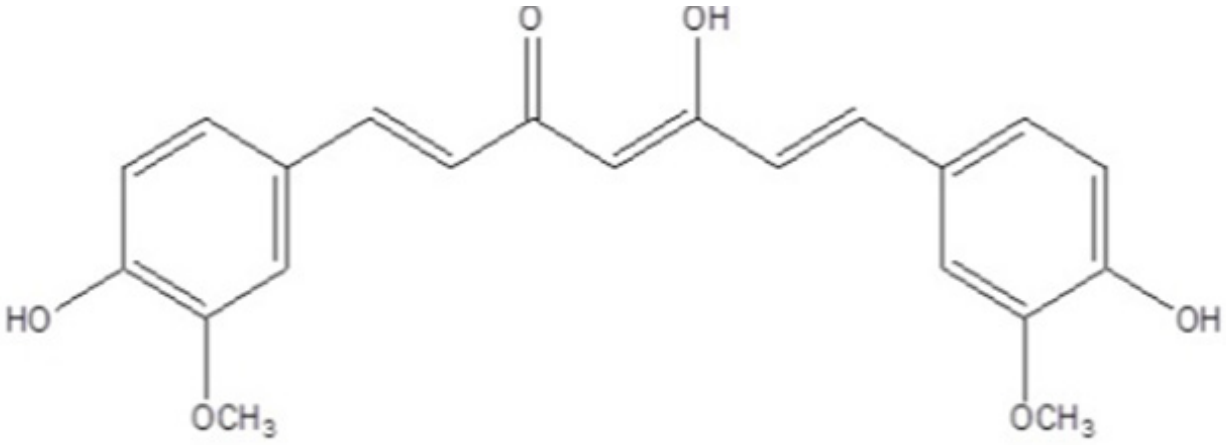

Figure 1: Curcumin structure.

and duration of radiation. Different factors are responsible for the effects of ionizing radiation. It includes radiation types, doses, time and age of the person. Effects of radiations can be classified into somatic or hereditary effects (Zakariya & Kahn 2014). Entire body irradiation causes radiation sickness and other syndromes. Radiation syndromes depend upon the doses and duration. More than 50 Gy radiations are considered as very high dose. Death within minutes to two days is the outcome of exposure of these high doses of radiation and is called central nerve system syndrome. Whole body irradiation to doses between 5 and 10 Gy cause death of the person within 10 days due to failure of the gastrointestinal tract. If the exposure dose is between 2 to10 Gy, the death of exposed individual takes up to thirty days. The major reason for this is the damage of bone marrow, resulting in symptoms like fatigue and ulcer of mouth and pharynx. Radiation burns affect soft tissues of skin. Skin injuries vary depending upon duration and doses of radiation. Severe injuries may affect bone and muscles also (Barabanova 2002). Harmful effects of radiation exposure vary from simple irritation to deadly diseases including cancer depending upon types, doses and duration of radiation. Birth anomalies are also an important effect of radiation exposure. Damages to organs are also seen as a result of local body irradiation depending upon radiation doses. In our body, some of the organs are considered as radio resistant and some are radiosensitive. Brain, thyroid, bone, pituitary, adrenals, muscles, and liver are radio resistant. Bone marrow, lymphoid organs, and reproductive organs are radiosensitive (Jagetia 2007). Radiation exposures have the potential to cause genetic effects. But radiation-induced genetic changes are comparatively less in human population than other species.

Therapeutic Uses of Ionizing Radiation

Ionizing radiations are now used as a powerful tool in the medical field. Mainly used for cancer treatment, radiation therapy is used before surgery to "reduce" the size of the tumor to enable surgical removal. After surgery, radiation helps to destroy any cancer cells that were not removed by surgery. Radiotherapy and chemotherapy can also be used together to efficiently treat the cancer. Radiation therapy is a valuable remedial method in the treatment of different types of tumors. But the effectiveness of this therapy is restricted by its instant and delayed side effects (Grdina *et al*. 2002). Major disadvantage of radiotherapy is normal cell, near to the tumor receiving radiation doses may result in adverse side effects, increasing the risk of secondary cancers.

Protective effect of curcumin against radiation-induced damage

Radio protective dietary molecules can be effectively and safely used in patients undertake radiotherapy. Patients might tolerate dietary agents better than other synthetic radio protective drugs (Holt *et al*. 2005). It is better to use natural agents with low cytotoxicity and high antioxidant and anti-inflammatory activities for preventing radiation-induced side effects (Riley 1994). Hence, studies on natural agents provide another important tag to curcumin as an effective radioprotectant. Curcumin administration in cancer patients is claimed to destroy the tumor cells efficiently by improving the benefits of radiation.

Effects of curcumin against gamma radiation

Gamma rays have much higher energy and are very penetrating. Studies show that γ-radiation cause many detrimental effects on living systems. Several studies are conducted to understand the radioprotection by curcumin against the harmful impact of γ-radiation. Radio protective value of curcumin was tested using yeast cells. The result showed that γ-radiation induced damage in normal yeast cells can be protected by curcumin intake of 1-, 10-, or 100-mM concentration. A study involving rad 52 mutants also showed that curcumin helps to reduce radiation induced DNA damage (Nemavarkar *et al*. 2004). A study in mice

shows that Protein kinase C (PKC) activity is increased in mice liver cytosol subsequent to 5 Gy irradiation. In contrast, treatment of liver cytosol with curcumin reduced the radiation-induced PKC activity (Varadkar *et al*. 2001). Radiation-induced lipid peroxidation in rat liver microsomes was found to be inhibited by curcumin and tetrahydrocurcumin (THC). Increase in radiation doses also increases lipid peroxidation. But curcumin help to decrease this lipid peroxidation (Jagetia 2007; Khopde *et al*. 2000).

Another study in mice showed that, intake of 5, 10, and 20 mg/kg body weight curcumin remarkably decrease the frequencies of micro-nucleated polychromatic erythrocytes (MPCEs) exposed to 1.15 Gy or 0.05 Gy/s γ-radiation at 24, 30, and 48 h post-irradiation (Abraham *et al*. 2003). Treatment with 400 μmol of curcumin decreased the radiation induced chromosomal aberrations and micronuclei in polychromatic erythrocytes of mice exposed to 1.5-3 Gy γ-radiation. Curcumin helps to protect rat from radiation-induced mammary tumorigenesis without any side effects, indicating that it can be used as an efficient chemoprevention agent (Inano *et al*. 1999). Another study showed that 200 mg/kg body weight of curcumin administration reduced the radiation-induced mucositis in rats (Rezvani & Ross 2004). Curcumin also shows a defensive action on γ-radiation induced DNA damage and lipid peroxidation in cultured human lymphocytes, and it displays a modulatory effect on γ-radiation induced cellular damage in primary culture of isolated rat hepatocytes. This study proved that curcumin can be used as an effective radio protector during radiation therapy (Hooper *et al*. 1987).

Glyoxalase enzyme system has an important role that regulates cell division and differentiation and glyoxalase I is radiosensitive (Sharma & Kale 1993). In a study, 0-6 Gy radiation exposure to mice liver elevated the activity of glyoxalase I. In contrast, glyoxalase II activity was inhibited after irradiation. 5, 25 and 50 mg/kg body weight of curcumin intake before exposure to radiation and also resulted in the restoration of glyoxalase I activity to a control level (Kale 1996). Other studies showed that curcumin decreased acute and chronic skin toxicity in mice indicating that curcumin has a defensive effect on radiation-induced cutaneous injury in mice. It reduces the inflammatory and fibrogenic cytokines in irradiated tissues mainly in the early phase after radiation (Okunieff & Ding 2006). Kapoor *et al.* (2001) studied protective effect of curcumin against radiation induced protein damages. Low doses of radiation induced chromosomal damage can be protected by different combination of dietary antioxidant including β-carotene, α-tocopherol, ascorbic acid and curcumin (Sharma *et al*. 1994). Curcumin shows radio-sensitizing effect in prostate cancer cell line-3. Treatment with curcumin helps to defend against radiation-induced micronuclei in rat bone marrow erythrocytes (Bagheri *et al*. 2018). A study on lung cancer in mice revealed that antioxidant effect in the lung can be increased by curcumin. In vitro studies showed that curcumin increases heme oxygenase 1 (HO-1) in primary lung endothelial and fibroblast cells and prevent reactive oxygen species (ROS) by radiation exposure. This leads to the increase in antioxidant defense (Lee *et al*. 2010).

In another study, radiation-induced lipid peroxidation was inhibited by curcumin. Curcumin was incorporated into microsomes during ultracentrifugation. During post-irradiation incubation, lipid peroxidation can be effectively inhibited by curcumin in a concentration-dependent manner (Sreejayan *et al*. 1992). Pre-treatment with curcumin protects the cell from γ- radiation induced damage by inhibiting peroxidation of membrane lipids and free radicals induced DNA strand break formation (Srinivasan *et al.* 2006).

Radiation dermatitis has been exhibited by more than 95% of breast cancer patients. Clinical trial of thirty breast cancer patients revealed that oral intake of 6 g curcumin decreased the complications of radiation dermatitis in breast cancer patients (Ryan *et*

al. 2013). Human serum albumin (HAS) is an important transport protein of the circulatory system. γ- radiation cause degradation of secondary structure of HAS. Presence of curcumin offered protection to retain the structural properties of this protein. The protective effect of curcumin was significantly higher in low γ-radiation doses (Kar *et al.* 2017). Shabeeb *et al.* (2020) reported that curcumin administration prevented γ-radiation induced injury to the skin by elevation of activities of anti-oxidant enzymes. Curcumin also shows protective effect on ionizing radiation-induced cataractogenesis in rats (Ozgen *et al.* 2012). Oral administration of curcumin shows protective effect on γ- irradiation induced hepatic toxicity in rats through regulation of the therapeutic targets CYP2E1, Nrf2, and NF-κB, through organizing the miR-122 and miR-802 gene expression (Essawy *et al.* 2020). Curcumin protects radiation-induced liver damages in rats by reducing oxidative stress and inflammation through the modulation of NF-κB pathway. Hence, curcumin treatment before radiotherapy can be helpful to prevent hepatocytic damage (Li *et al.* 2021).

Curcumin and UV- radiation

Exposure of excessive sunlight is the primary way to enter ultraviolet radiation in the human body. UV A, B and C are the common types of ultraviolet radiation. UV-B cause acute inflammation and nonmelanoma skin cancer in the epidermis (Grossman & Leffell 1997). Excessive sunlight exposure leads to increase of acute inflammation along with erythema, edema, and immunosuppression. This leads to skin cancer (Granstein & Matsui 2004). UV irradiation causes p53 mutation, which leads to the formation of precancers, and precancerous lesions converted in to carcinoma *in situ* and squamous cell carcinoma (SCC) (Jagetia 2007; Ziegler *et al*. 1994). UV-B causes harmful effect through the formation of reactive oxygen species (ROS) and direct DNA damages (Gruijl 2002). Direct DNA damage or ROS frequently triggers mitogen-activated protein kinases (MAPKs) that are involved in proliferation and survival of the cells (Rhee 1999; Torres & Forman 2003).

UV radiation is one of the major physical stress factors that affect human skin. UV-A radiation induces photoaging. Liu *et al*. (2018) reported that curcumin shows protective effect against UV-A irradiation induced photoaging in human dermal fibroblasts. Curcumin inhibits UV radiation-induced skin cancer in SKH-1mice, and this antioxidant help to reduce skin cancer formation and prolong time to tumor onset (Phillips *et al*. 2013). The treatment of rats with curcumin in a dose of 5 mg/kg body weight prior to ultra violet C irradiation resulted in protection against harmful effect of radiation, while higher doses of curcumin (25 & 50 mg kg^{-1} body weight) had less protecting effect (Sharaf *et al*. 2012).

Mechanism of radioprotection

Radiation leads to the formation of harmful reactive oxygen species. That involves a chain of events causing DNA damages including strand breakage, base damages and cross link formation. Double strand breaks are very harmful and it may kill the cells. Several mechanisms are involved in the radioprotective effect of curcumin (Jagetia 2007). The assumed mechanisms of radioprotection by curcumin are shown in (Table 1).

Table 1. Curcumin action during radioprotection

Up regulation	Down regulation
DNA repair	Cell cycle
Antioxidant activity	DNA damage
GSH, GST, SOD, CAT	PKC, MAPK, NO
Free radical scavenging	Lipid peroxidation
GSH, GST, mRNA	

The main leading mechanisms of radioprotection involve free radical scavenging and the upgradation of cellular antioxidants by curcumin in irradiated systems. Glutathione

transferase (GST), catalase, glutathione peroxidase, superoxide dismutase (SOD), and their mRNAs are increased by curcumin. Increase in glutathione (GSH) and sulfhydryl groups and reduction in lipid peroxidation can also help in radioprotective activity (Jagetia 2007). Curcumin also inhibits the activation of protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and nitric oxide (NO). It also helps to protect against radiation-induced damage (Subramanian *et al.* 1994; Joe & Lokesh 1994).

Radiation and wound-healing

Radiation exposures are continuously increasing, primarily in the use of radiation against cancer therapeutics and other medical treatments (Shore 1990). When wound tissue exposed to ionizing radiation results in disturbance to the normal healing process. It also leads to longer recovery and other detrimental effects. Wounds exposed to radiation, resulting in slow maturation of granulation tissue, severe inhibition of inflammatory response, reduced collagen and hexosamine synthesis and delayed re-epithelialization (Rudolph *et al*. 1988). Fibroblasts play a major role in granulation tissue formation and maturation. Fibroblast isolated from the irradiated wound and the wound after total-body irradiation has significantly reduced attachment, adhesion, and colony formation ability and have longer doubling time compared to non-irradiated fibroblasts (Song *et al*. 1997). Studies indicate that topically applied curcumin on wounds has positive effects. Curcumin enhances cutaneous wound healing by granulation tissue formation and synthesis of matrix proteins. Curcumin application has been found to promote re-epithelialization and improves neovascularization. Curcumin intake before irradiation improved the synthesis of collagen, hexosamine, DNA, and nitrate (Jagetia & Rajanikant 2004a).

Curcumin pretreatment results in decreased wound healing time, improved collagen deposition, increase in fibroblast and vascular density (Jagetia & Rajanikant 2005). So, curcumin treatment shows profound effect on improving the delayed wound healing. Protective effect of curcumin in wound-healing is due to the increased synthesis of DNA, collagen, hexosamine and nitrite during the healing process in the granulation tissue, which allowed early wound modelling. Wound biopsies examination showed increased fibroblasts, angiogenesis, and collagen deposition. Curcumin treatment has a conductive effect on the irradiated wound and could be a solid healing strategy in tissue repair processes of irradiated wounds (Jagetia & Rajanikant 2004b).

Challenges of curcumin and its bioavailability

Although, numerous studies have proved the beneficiary effects of curcumin, there are studies suggesting its ineffectiveness. Curcumin act as a prooxidant by activating molecular oxygen through the reduction of transition metals. Treatment of pBR322 plasmid DNA with curcumin and copper ion resulted in strand break, DNA damage and induction of apoptosis (Yoshino *et al.* 2004). Banerjee *et al*. (2008) studied antioxidant and prooxidant activities of curcumin in RBCs hemolysis model. Results showed that curcumin exhibits both antioxidant and prooxidant activity in a concentration dependent manner. Curcumin at higher concentration (>10 μM) shows prooxidant behavior (Ahsan *et al.* 1999).

Despite their potential therapeutic properties, widespread utilization of curcumin is limited by its low bioavailability, low solubility, rapid degradation, high hepatic metabolism and instability in physiological environment (Baek *et al.* 2017). Poor oral bioavailability is one of the major limitations in clinical application of curcumin. In recent years, efforts have been made to enhance the bioavailability of curcumin by different strategies. Different types of nano formulations including nanoparticles, micelles, liposomes, nanogels and conjugates have been developed to overcome the *in vivo* delivery of curcumin (Yallapu *et al.* 2015; Li *et al.* 2020).

Nanocurcumin exhibits better therapeutic efficiency due to improved bioavailability and tissue distribution. Lipid nanocarriers and polymer nanocarriers can enhance the bioavailability and solubility of curcumin (Yallapu *et al.* 2015). Solid lipid nanoparticle can be used as an efficient oral delivery system for curcumin (Ban *et al.* 2020). Beak *et al.* (2017) reported that N-carboxymethyl chitosan (NCC) coated curcumin-loaded solid liquid nanoparticle inhibit the rapid release of curcumin in acidic environment and enhance the bioavailability. Bioavailability of curcumin can be increased by encapsulation in sophorolipid coated nanoparticles. Both i*n vitro* and *in vivo* studies showed that curcumin nanoparticle had higher bioavailability than that of curcumin crystals (Peng *et al.* 2018).

Nosrati *et al.* (2020) evaluated the radioprotective effect of curcumin conjugated albumin nanoparticles. These nanoparticles have a high loading capacity and showed sustained release behaviour. Loading of curcumin to BSA not only could increase the chemical stability of curcumin, but also could improve radioprotection efficacy of it against X-ray irradiation. *In vitro* and *in vivo* studies proved that BSA-curcumin nanoparticles can be used as a proficient vehicle for improving the potential radioprotective effect of curcumin. Studies state that curcumin can be used as a radioprotective agent and is non-toxic up to 12 g day^{-1} in humans.

Conclusion

Curcumin can be used as a natural radioprotective agent. It protects radiation-induced damage at low doses. Curcumin shows radioprotection against the harmful impact of UV and γ-radiation in various study systems. Radioprotective effect of this natural agent is due to its free radicals scavenging activity and the elevation of antioxidants, upregulation of mRNAs for GSH, GST, SOD and catalase enzyme. Curcumin also shows radiation-induced wound-healing effect, and it can also be used for the treatment of irradiated wound for quick healing. Pretreatment with curcumin leads to decrease in wound healing time, improved collagen deposition, increase in fibroblast and vascular density.

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