IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# Role Of Nanoparticles As Radioprotector

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## Abstract

Radiation therapy uses ionizing radiation to kill cancer cells but it has adverse side effects. Some radioprotective drugs can reduce the damage in healthy tissue caused by radiation. But nowadays, with the great interest in development of nanotechnology in the biological field, the multifunctional nanoparticles not only establish powerful drug delivery systems to improve the molecular radioprotective drugs, but also open a new route to develop radioprotective agents because some nanoparticles possess intrinsic radioprotective abilities. The purpose of this paper is to review the different types of nanoparticles as radioprotectors. In this review paper we also review the metallic and biological nanoparticles, which protect normal tissue from the side effects of radiation.

**Keywords-** Radiation, Harmful effect of radiation, Radioprotectors, Radiosensitizers, Nanoparticle .

## INTRODUCTION

Radiotherapy is the feasible treatment approach for many malignant diseases and cancer. But it also has disadvantages including the possibility of injury to the surrounding normal tissue. The most common approach to reducing the side effects of radiation is radioprotectors (Jimmie Colon MS *et al.,* 2010). The first chemicals that decrease the adverse effects of ionizing radiation on the mammalian body were discovered more than half a century ago. This effect was named protection from radiation sickness, while the chemicals that exert this effect were named radio protective substances (Vasin *et al.,* 2010).

Recently, nanoparticles as radioprotectors have received increasingly greater attention in research. Nanoparticles enhance therapeutic effectiveness and reduce the side effects of the radiation (Che Ming *et al.,* 2010). Nanoparticles are known to be well absorbed into systemic circulations, better permeation into the tumor tissue. Presently, different metallic nanomaterials are being produced using copper, zinc, titanium, magnesium, gold, alginate and silver (Hasan, Saba 2015).

## Radiation and Radiotherapy

Radiation is energy that comes from a source and travels through space and may be able to penetrate various materials. There are two types of radiation ionizing and nonionizing. Ionizing radiation has very high energy, which can separate electrons from atoms and create ions. This radiation is used to kill the cancer cell, generate electric powers and in many other processes (ion and non ionizing radiation). According to ref (Mgada k. *et al.,* 2018, Rad. safety handbook and ion and non ionizing radiation), ionizing radiation have three types Alpha (α), Beta (β) and Gamma (γ). Alpha particles include two protons and two neutrons. They do not travel very far in the air and it can easily stop by a thin layer of sheet. But if they inhaled or ingested, it can be harmful. Beta particles are negatively charged. They can travel in air more than alpha particles but stopped by sheet of plastic. Gamma and X-rays are completely energy photons and have high energy. They can travel great distance through air. They require shielding of concrete and lead plating to stop them. These are very harmful for body. Non ionizing radiation has enough energy to move atoms in a molecule around and vibrate but it cannot remove electrons from atoms for example infrared, microwaves and visible light. Non ionizing radiation has low frequency with a low wavelength (ionizing and nonionizing radiation).

Ionizing radiation is used in medical science in three ways diagnostic, nuclear medicine and radiotherapy. For diagnosis we use radiation such as x-rays, computed tomography and medical devices. Nuclear medicines are used for diagnosis or treatment. Nuclear medicines are radioactive elements which introduced into the patient's body (Steel G. *et al.,* 2002). In treatment of cancer patient is treated by radiotherapy with or without combination with surgery and chemotherapy (institution of medicine (US) committee 1996).

### Harmful Effect of Radiation on Animal

Radiation therapy has many side effects swelling or pain, mild neutropenia etc. Radiation also damage the cancer cell DNA and kill the cell which is removed by body (Xiao L. *et al.,* 2014). Ionizing radiation interacts with cell in two ways direct or indirect. In direct interaction ionizing radiations damage the DNA and kill the complete cell (Nias AHW. 1998). In indirect interaction, radiation does not interact with DNA and macromolecules of the cell. It interacts with cellular water and does hydrolysis of water molecules. Water molecule divided in hydrogen molecule and hydroxyl molecule (free radical) (Dowd SB *et al.,* 1999). These free radicals can damage the cell membrane, cell molecules and DNA that create dysfunction of cell and also cell death (Nair *et al.,* 2001). Exposure of high dose of radiation human being may lead to adverse side effect like Acute Radiation Syndrome (ARS). ARS is an illness caused by irradiation of the whole body or partial body by a high dose of intense radiation in a short period of time (Kamrain *et al.,* 2016). Ionizing radiation also has immediate, measurable harmful effect on cells for example increasing in reactive oxygen species (ROS) (Xiao L *et al.,* 2014). Ionizing radiation also can damage the cell in three ways: cell division delay, reproduction failure, cell death in inter phase. Some cancerous cells also show apoptosis. Any of this type cellular damage can occur by direct or indirect interaction of radiation with cell (Dowd SB *et al.,* 1999).

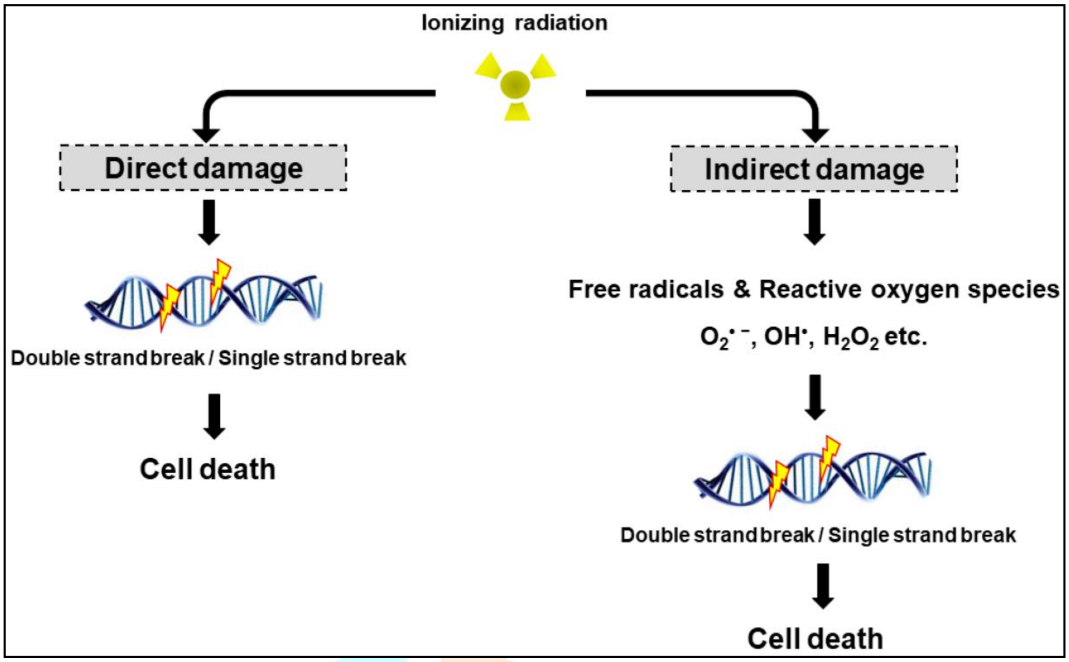


**Figure: 1 Direct or indirect damage by ionizing radiation (Hur *et al.,* 2017)**

## Mechanism of ROS

Reactive oxygen species are generated in the cell by radiation therapy in cancer treatment and alters the cell permeability. This disrupts the transport of molecules across the membrane (Borrego *et al.,* 2015, Srinivas *et al.,* 2019).

By radiation therapy, ROS are generated. They induce Double Strand DNA breaks. Ataxia telangiectasia and Rad3- related (ATR), Ataxia-telangiectasia mutated (ATM) and DNA dependent protein kinase (DNA-PK) like several sensor proteins activated by Double strand break in response to DNA damage repair pathway (Yang J. *et al.,* 2004). These cause phosphorylation of Checkpoint kinase Chk1 and Chk2 (Yang J. et al. 2004, Bartek *et al*., 2003). These activate the $P^{53}$ signaling after radiation exposure. These all cause cell death (Borrego *et al.,* 2015).

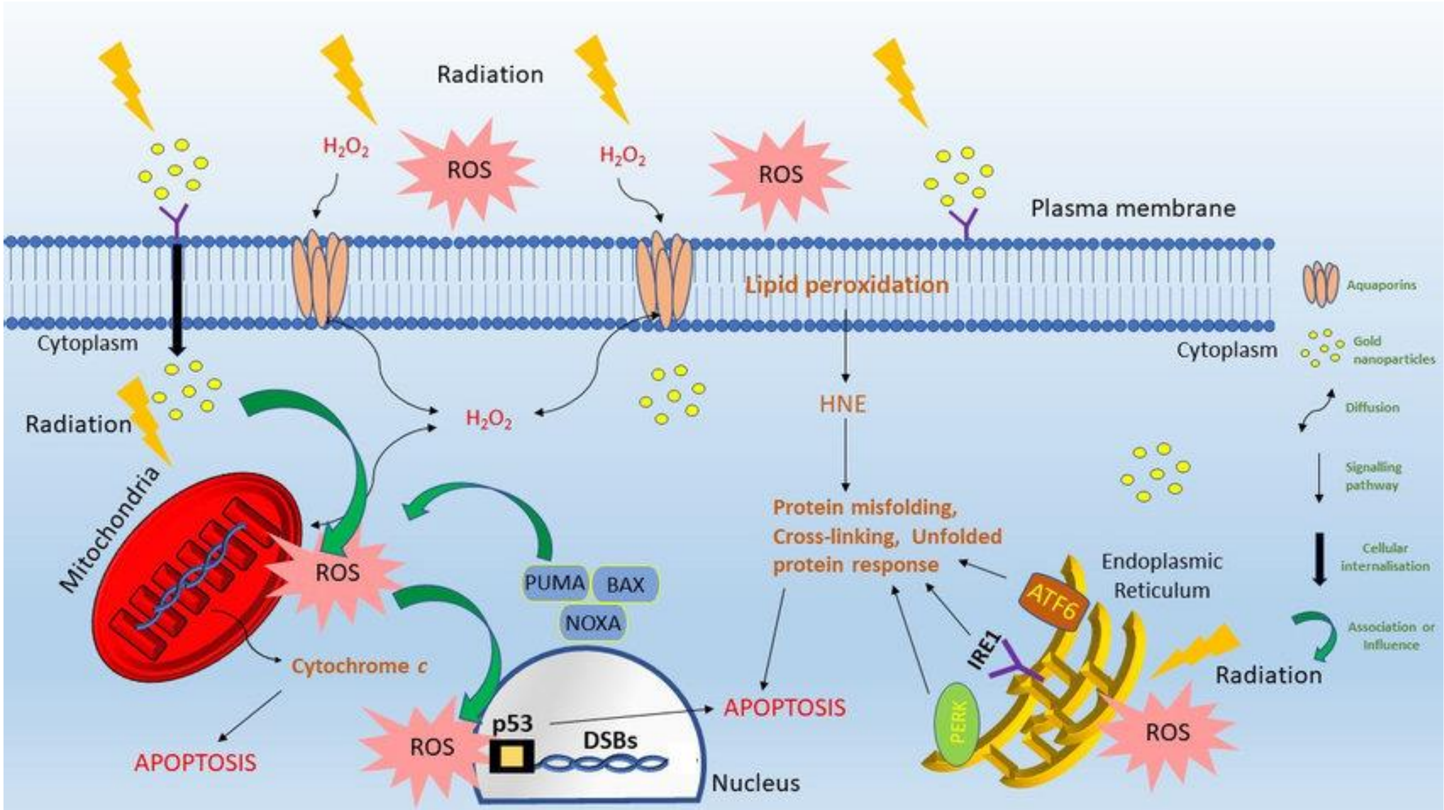


**Figure: 2 mechanisms of ROS, generated during exposure to ionizing radiation, leading to apoptosis (Douglas *et al.,* 2020).**

## What is Free Radical Chain

Free radical has an unpaired electron in an atomic orbital. They behave like oxidant and reductants because they can donate and accept the electron from other molecule (Cheeseman *et al.,* 1993). Free radicals can derived either in human body by metabolic process or from outer sources like ozone, air pollutants, x-rays, industrial chemicals and by cigarette (Bagchi K. *et al.,* 1998). In cancer treatment, after irradiation radiation interacts with DNA and produces free radicals like hydroxyl $OH^•$, hydrogen $H^•$, water $H_2O+$, $H_3O+$, superoxide $O_2$ – and also produces free electrons and ions (Neuman D *et al.,* 2008).

Hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical are oxygen containing free radicals. These are highly reactive and they can damage the cell membrane and cell molecules like DNA, carbohydrate, lipids and proteins (Young *et al.,* 2001).

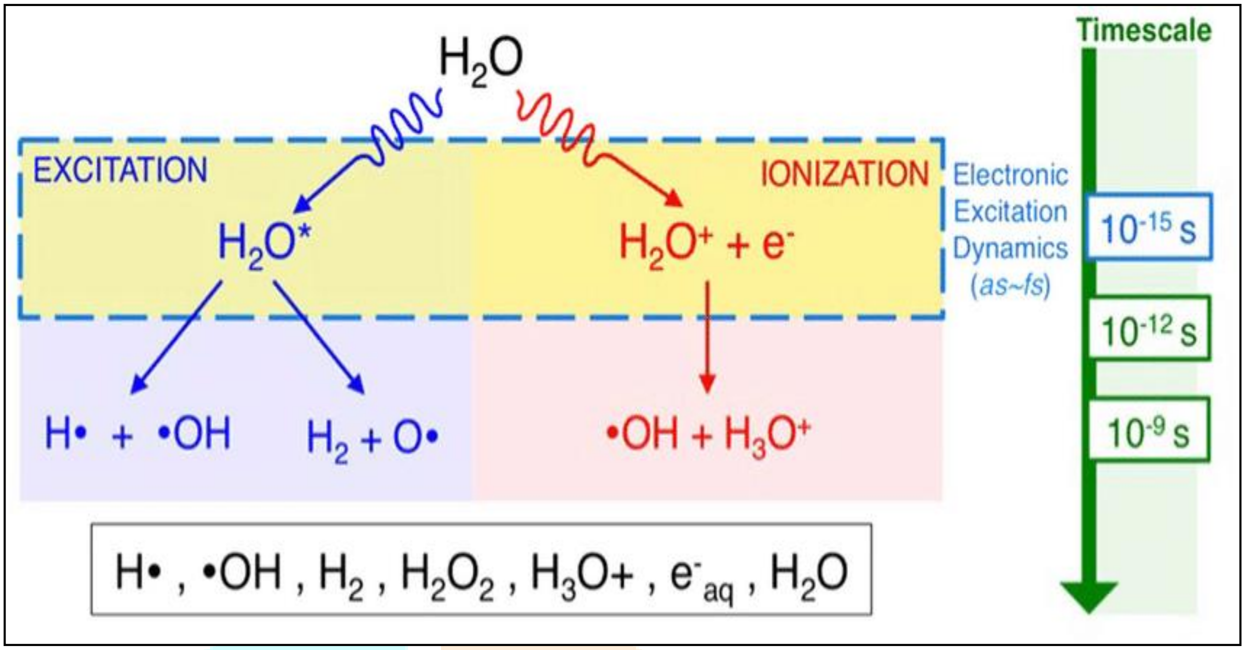


**Figure: 3 mechanisms of radical generation in water radiolysis (Roeves *et al.,* 2017)**

# Radiosensitizers and Radioprotectors

## Radiosensitizers

Radiosensitizers can sensitize the tumor cell from radiation exposure. After radiation exposure radiation damage the tumor cell but also damage the normal cell by producing free radicals. Radiosensitizers promote the fixation of free radical; these are captured by electron affinity of radiosensitizers (Gosselin *et al.,* 2005).

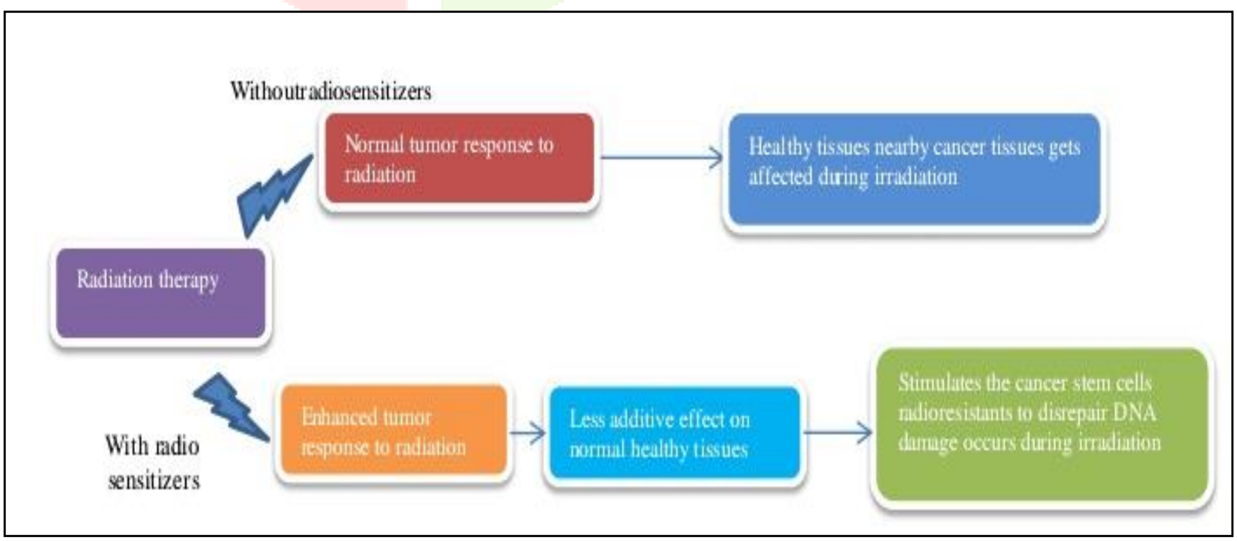


**Figure: 4 Effect of radiation with or without use of radiosensitizers (Ruba T *et al.,* 2018)**

Uterine cervix cancer is common cancer in women worldwide. Trypsin, Chymo trypsin and papain are enzymes, used with radiotherapy. They can reduce the side effect, which are produced by radiation in cervix cancer treatment (Dale *et al.,* 2001).

In Hepatocellular carcinoma (liver cancer) Ganetespib works as radiosensitizer. Radiation therapy combined with Ganetespib produces supra-additive tumor growth delay and decrease clonogenic survival. Genetespib also arrest cell in G2-M phase (Chettiar *et al.,* 2016).

Prostate cancer is leading cancer in India among male population. Prostate cancer cells are very sensitive to higher dose of radiation in radiotherapy. They fail to improve the response of therapy. Curcumin is plant derivative chemical compound, which is found in Turmeric also works as radiosensitizer. Curcumin increase the growth inhibitory effects in cancer tumor cells (Chendil D *et al.,* 2004). Super paramagnetic zinc ferrite spinel ($ZnFe_2O_4$) nanoparticles also works as radiosensitizers in lymph node carcinoma in prostate cells (Meidanchi *et al.,* 2015). Many other radiosensitizers Fluoropyrimidines, Thymidine analogs, Hydroxyurea, Gemcitabine, Fludarabine (Raviraj *et al*. 2014 ) Betulinic acid, Ellagic acid (EA) they induce apoptosis in cells and enhance the radiotherapy effects in many cancer cells like lung, colon, head and neck cancer etc. (Ruba T *et al.,* 2018)

## Radioprotectors

Administering, radio protective agents has been proposed as one way to decrease radiation – related harmful effects on cells (Kuefner *et al.,* 2015, Zhou R *et al.,* 2014). Radioprotectors are delivered prior to or at the time of radiation exposure. To protect the harmful effect of radiation various nanoparticles have been tested for their ability to protect normal cell and tissue.

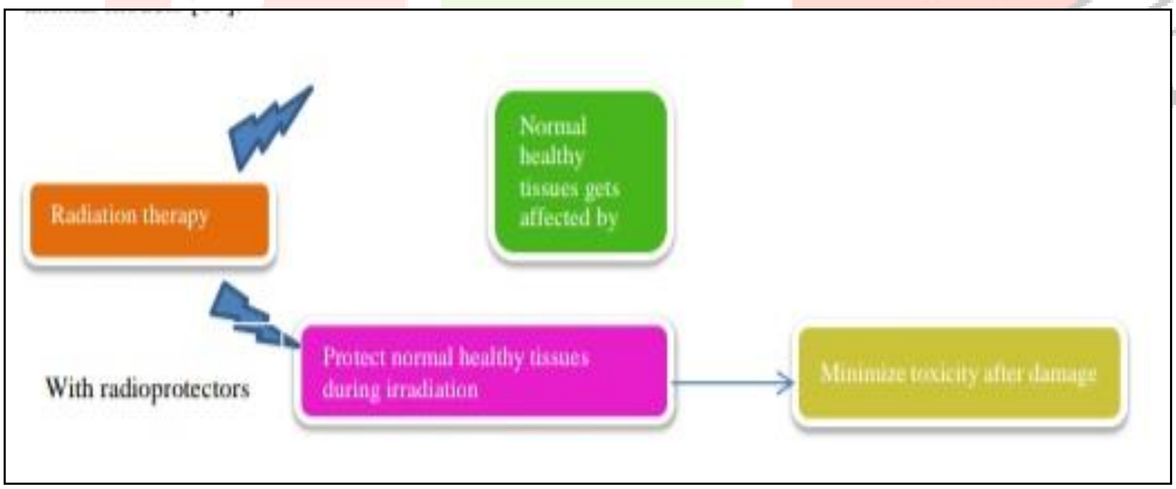


**Figure: 5. Effect of Radiation therapy with and without the use of radioprotectors (Ruba T *et al.,* 2018)**

There are many radioprotectors for example Amifostine. It protects oral mucosa, salivary glands, lungs, bone marrow, heart, intestines, and kidneys tissues from radiation exposure of radiotherapy. Amifostine also reduce xerostomia, mucositis, dysphagia, dermatitis, pneumonitis, proctitis, and cystitis. Amifostine is currently in clinical use (Citrin D *et al.,* 2010).

Nitroxide is also a radioprotector. Nitroxide radioprotector is most promising for future use (Ruba T *et al.,* 2018, Citrin D *et al.,* 2010). Nitroxide protects the cell from exposure of oxidative stress (Soule BP *et al.,* 2007).

## Antioxidants as Radioprotectors

Antioxidants have the potential to enhance DNA repair, reduce the free radical oxidative stress (Bhartiya et al. 2008, Pei H *et al.,* 2014). For example Antioxidants or glutathione-elevating compounds may be able to reduce DNA damage (Brink JA et al. 2012, Xie *et al.,* 2018) and Phenolic glucoside which occurs naturally in plants has excellent anti radical activities (Materska M *et al.,* 2015). Many flavanoids such as quercetin, genistein, rutin and orientin also works as radioprotectors in vivo (Hosseinimehr *et al.,* 2007).

Some radioprotectors are found naturally in body like Melatonin is a hormone of pineal gland. Melatonin reduces the oxidative damage from gamma irradiation in liver tissue (Koc M *et al.,* 2003). Generally vitamin A, C, E and selenium works called as antioxidants. They also work as radioprotector by suppressing the chain reaction of free radicals (Weiss JF *et al.,* 2003). Vitamin E with WR-3689 can increase survival rate after radiation exposure (Srinivasan V *et al.,* 1992). Vitamin E also protects oral mucosa cells from radiation therapy of head and neck cancer (Ferrira PR *et al.,* 2004). Selenium in the form of selenoprotein also protects against oxidative stress initiated by free radicals after radiation exposure (Micke O *et al.,* 2009). Flavanoid such as quercetin, genistein, orientin and rutin also works as radioprotector. Flavanoid obtained ocimum protects against 2 Gy, γ – irradiation (Devi PU *et al.,* 1998). Methylxanthines found in every body tissue and also in medical plants. Methylxanthines families are pentoxifylline, caffeine, theophylline and theobromine. Caffeine also protects mice against 7.5 Gy, γ-irradiation (George KC *et al.,* 1999).

## Mechanism of Radioprotectors

Ionizing radiation can cause damage in cells by formation of reactive oxygen species and free radicals such as hydroxyl. DNA repair by radioprotectors might be important mechanism of radiation protection (Roos *et al.,* 2006). Radioprotectors protects cells from radiation by many signaling pathways such as $p^{53}$ signaling, STAT3 Signaling, P13k/Akt signaling and NF-κB Signaling. In NF-κB signaling radioprotectors activates DNA damage sensor proteins, these proteins activates NF-κB and activates the repair of DNA by homologous recombination (Volcis *et al.,* 2012). NF-κB expression is increased during cellular oxidative stress. It is redox sensitive protein. NF-κB directly or indirectly controls expressions of genes. These genes are responsible for many cellular processes like apoptosis, proliferation, growth and survival (Oeckinghous *et al.,* 2009, Levonen *et al.,* 2014).

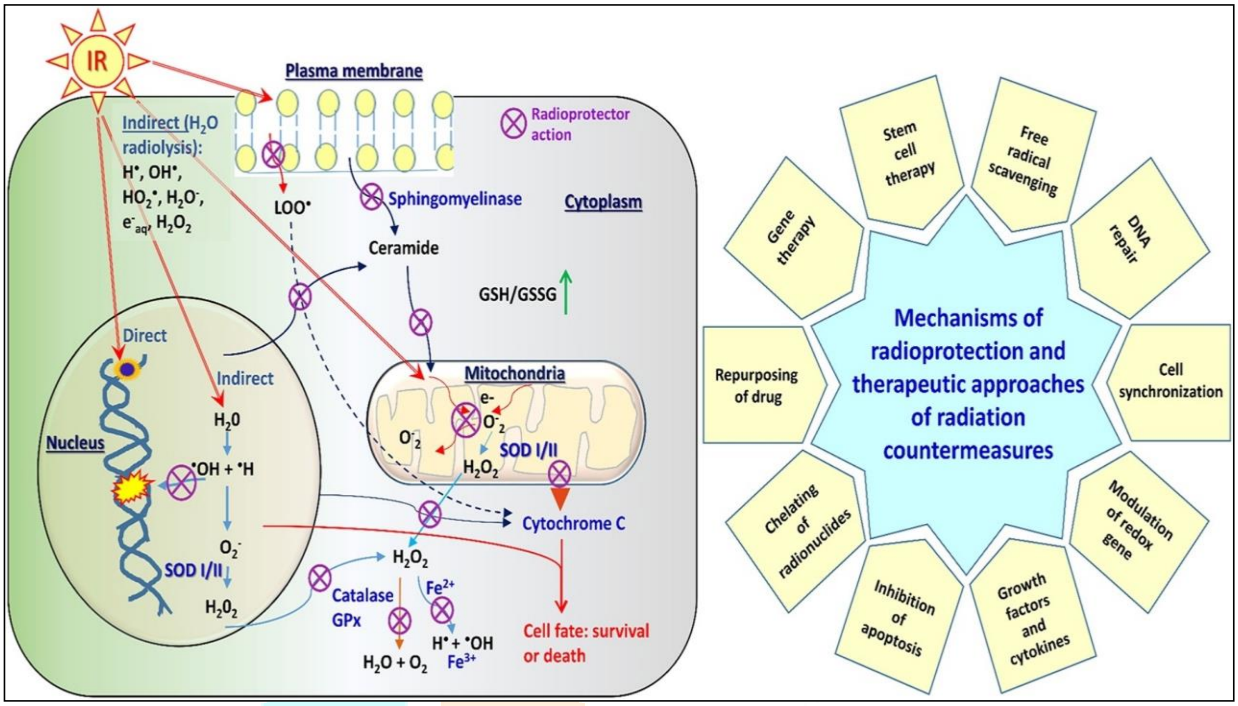


**Figure: 6 showing radioprotection effect and mechanism in cell (Mishra *et al.,* 2018)**

$P^{53}$ pathway also regulates D-type cyclin; it controls G1/S phase transition with CDK4/6 (Hiyama H *et al.,* 1999). ATM and ATR regulate the activity of $P^{53}$ by phosphorylation (Marechal A *et al.,* 2013). DNA damage checkpoints are activated by ATM and ATR, which starts cell cycle arrest, apoptosis or DNA repair (Abraham *et al.,* 2001).

STAT3 activated by cytokines and by many growth factors. It activates the various genes which are involved in cell survival and proliferation (Yu H *et al.,* 2014).

# Nanoparticles evolving as radioprotector

Nanoparticle research has currently intense focus in scientific research. Nanoparticle defined as particle between 1-100nm in size (Praetorious NP *et al.,* 2007). Recently, with the rapid development of nanotechnology in the medical field, the multifunctional nanomaterials not only establish powerful drug delivery system to improve the molecular radioprotective drugs, but also create a new route to develop radioprotective agents because some nanoparticles have intrinsic radioprotective abilities (Xie *et al.,* 2018). Radioprotective agents may be useful as an adjunct to medical imaging to reduce the harmful effect of ionizing exposure.

Nanoparticles synthesize naturally and artificially. Various plants and herbs preparation has been reported deterge free radicals, to provide radioprotection (Jagetia GC *et al.,* 2007). Natural radioprotectors for example green and black tea polyphenols, gingko extract, grape extract, ginger roots have less toxicity and high tolerability. Aromatic herb mint has also been described as radioprotector (Baliga MS *et al.,* 2010, Kma L *et al.,* 2014). Initial studies were focused on development of thiol –containing compounds as radioprotectors (Patt HM *et al.,* 1949). In this paper we provide a review of recent literature about different type of radioprotectors.

## Types of Nanoparticles

# 1 Metallic Nanoparticles:

Metal nanoparticles can enhance the effects of radiotherapy, and can protect from radiation side effect due to their unique physical and chemical properties (Conde J *et al.,* 2012).

## 1.1 Gold Nanoparticles (AuNPs)

In 19th century Michael Farday published the first scientific report on the synthesis of Gold Nanoparticle. Recently, GNPs receiving intensive focus due to unique physicochemical properties including surface Plasmon resonance (SPR) and the ability to bind with amine and thiol groups, allowing surface modification and function (Ruba T *et al.,* 2018). Many groups are studying the benefit of AuNP with radiotherapy. Gold Nanoparticle can enhance the dose of ionizing radiation because of high atomic number and Auger effect. Gold Nanoparticle strongly depends on several parameters for example size, concentration, radiation energy, intracellular location and cellular uptake (Sah *et al.,*), because of having therapeutic potential in treating a variety of diseases (Bhattacharya *et al.,* 2008).

Gold Nanoparticles are very helpful in tumor targeting with radiation and help to improve various biological molecules stability and drug carrying capacity (Toulany M *et al.,* 2014). Gold Nanoparticles can enhance the radiation effect in radiotherapy of radioresistant mouse squamous cell carcinoma. In this, mouse is irradiated by X-rays with or without Gold nanoparticles. AuNPs were more effective at 42Gy. It represents that radiation dose, energy and hyperthermia influence efficacy and better define the potential utility of gold nanoparticles for cancer x-ray therapy (Hainfeld *et al.,* 2010). Gold Nanoparticles have two types of functional groups Cysteamine (AET) and Thioglucose (Glu). Gold Nanoparticles coated with thioglucose taken up in equal numbers by HeLa cells this result that conjugated particles showed more radiosensitization compare to thioglucose conjugated particles (Song K *et al.,* 2012).Heinfeld *et al.* said that 1.9 diameter having Gold Nanoparticle given by intravenous injection resulted in the better radiotherapy on mammary carcinoma in mice (Hainfeld JF *et al.,* 2004).

Table: 1 types of GNPs (Rehman *et al.,* 2016)

| Cell line | GNP size | Surface coating/ bound | GNP conc. | GNP target/ distribution | Radiation | Study | Year | Experiment |
|---|---|---|---|---|---|---|---|---|
| **MDA-MB-231** | 16nm<br>49nm | Glu-Gnps<br>Glu-Gnps | 20nM | Cytoplasm (endosomes / lysosomes) | 6-MV | Wang C *et al.* | 2015 | In- vitro |
| **HeLa** | 52nm<br>47nm | Folate-GNPs<br>Pegylated-GNPs | 50µM<br>50µM | N/A | X-ray 2 Gy at 180kVp<br>γ rays $C_O$ 60 | Khoshkqard *et al.* | 2014 | In-vitro |
| **SCCVII**<br>**A549**<br>**V79** | GNP 8nm<br>GNG 106±2.68nm | PEGylated Nanogel with Large payloads of GNPs | 20ug/ml<br>15ug/ml<br>50ug/ml | Cytoplasm (endosomes/ lysosomes) induced ER-stress in cells | X-rays 5,10,15,20 Gy at 200kVp | Yasui H *et al.* | 2014 | In-vitro |
| **U251** | N/A | Surface modified with polyethylene glycol | 1mM<br>100ul GNP Concentrated inj. into mice tumor | N/A | 4 Gy(150kVp)<br>20 Gy (175kVp) | Joh DY *et al.* | 2013 | In-vitro<br>In-vivo |
| **EMT-6**<br>**CT26** | 6.1nm | Polyethylene glycol | 400,500 or 1000µM | N/A | 10 Gy<br>6.5 keV<br>8.048 keV<br>73 keV<br>6 MeV<br>3Mev<br>Protons | Liu CJ *et al.* | 2010 | In-vitro |
| **HeLa** | 14.74nm | N/A | 1nM | N/A | 105 kVp<br>220 kVp | Chithrani DB *et al.* | 2010 | In-vitro |
| **SCCVII** | 1.9nm | N/A | 1.9 gkg-1 | N/A | 30 Gy<br>42 Gy (68 keV)<br>40 Gy, 50.6 Gy ( 157 keV) | Hainfeld *et al.* | 2010 | In-vivo |
| **BAEC** | 1.9nm | N/A | 250-1000µM | Cytoplasm | 80 kV , 150 kV , 6 MeV Electrons<br>12MeV electrons | Rahman WA *et al.* | 2009 | In-vitro |
| **B16F10** | 13nm | N/A | 10nM in cells<br>200nM in mice | Cytoplasm (E-R, golgi - apparatus) | 25 Gy<br>(6 MeV) | Chang MY *et al.* | 2008 | In-vitro<br>In-vivo |

## 1.2 Silver Nanoparticle (AgNPs)

Silver nanoparticles were prepared from silver nitrate. According to previous research Silver Nanoparticle has antimicrobial activity, free radical scavenging and has intrinsic therapeutic properties. Silver nanoparticles (SN) were re-dispersed in aqueous solution of Pluronic F127 and make complex with the phytoceutical, glycyrrhizic acid (GLY) to obtain SN-GLY complex. SN-GLY protects from ionizing radiation after irradiation. SN-GLY protects against radiation induced damage on hemopoetic and gastrointestinal system. Oral administration of SN-GLY before 1 hour of 4Gy gamma radiation exposure reduce the depletion of cellular antioxidants and lipid peroxidation various tissue (Dhanya C *et al.,* 2010, Dhnaya K *et al.,* 2012).

Silver nanoparticles also increasing interest in the field of nanomedicine with alpha- lipoic acid, it protects normal tissues from radiation damages and also to enhance the anti-tumor activity of gamma radiation. Alpha – lipoic acid is disulphide derivative of octanoic acid (Ramachandran *et al.*, 2011).

Silver nanoparticle with vitamin C derivative, 6-palmitoyl ascorbic acid-2-glucoside (PAsAG), enhance the rate of repair of cellular DNA damage in blood leucocytes and bone marrow cells (Dhanya K *et al.,* 2011). Silver nanoparticle has power to inhibit HIV-1 virus to bind with host cell. GLY-silver nanoparticle has higher free radical scavenging property than glycyrrhizic acid (GLY). The complex has significant radio protection against 6 Gy gamma irradiation to bone marrow cellularity, total blood count and endogenous spleen colony formation (Dhanya K *et al.,* 2013).Nowadays silver nanoparticle is having great interest in green synthesis.

Table: 2 different type of AgNP nanoparticle (Raj *et al.,* 2015)

| S. No. | Types of AgNPs | Shape | Size (nm) | Biomedical application | Reference |
|---|---|---|---|---|---|
| 1 | PVP-stabilized AgNPs | Spherical | 3,11,30 | Anti-leukemia | Guo *et al.* (2013) |
| 2 | AgNPs | Spherical | 5-8 | Inhibition of human breast cancer cell (MCF-7) | Gurunathan *et al.* (2013a) |
| 3 | AgNPs | Spherical | 10-20 | Inhibition of MDA-MB-231 human breast cancer cells | Gurunathan *et al.* (2013b) |
| 4 | Gurunathan et al. (2013b) | Spherical | 8 | Inhibition of malignant melanoma (skin cancer) | Liu *et al.* (2012) |
| 5 | AgNPs | Spherical | 12-40 | Inhibition of human cervical carcinoma cell | Jeyaraj *et al.* (2013a) |
| 6 | AgNPs | Spherical | 22 | Inhibition of human breast cancer cell (MCF-7) | Jeyaraj *et al.* (2013b) |
| 7 | AgNPs | Oval, triangle, pentagon, hexagon | 50 | Inhibition of human breast cancer cell (MCF-7) | Gurunathan *et al.* (2013c) |
| 8 | AgNPs | Spherical | 8-20 | Inhibition of MCF-7 and Ehrlich solid tumor | El-Sanbaty (2013) |
| 9 | AgNPs | Spherical | 15 | Inhibition of lung | Han *et al.* (2014) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | epithelial adenocarcinoma cell line (A549) | |
| **10** | AgNPs | Spherical | 2-6 | Inhibition of SiHa cervical cancer cell line | Jha & Prasad (2014) |
| **11** | AgNPs | Spherical | 27 | Inhibition of breast and lung cancer line | Mfouo-Tynga *et al.* (2014) |
| **12** | AgNPs | Spherical | 120 and 10 | Inhibition of B16F10 melanoma Tumor | Sierra-Rivera *et al.* (2013) |
| **13** | PVP-stabilized AgNPs | Spherical | 30–50 | Inhibition of L5178Y murine lymphoma tumor | Lara-Gonza´lez *et al.* (2013) |
| **14** | Silver nanowires | Wire | 17_0.11 mm | Drug delivery in cancer treatment | Singh *et al.* (2013) |
| **15** | AgNPs conjugated with cancer targeting and nuclear targeting peptide | Spherical | 35 | Imaging of human oral cancer cell | Austin *et al.* (2011) |
| **16** | AgNPs | Spherical | 30 | against E. coli and M. tuberculosis inhibition | Zhou *et al.* (2012) |
| **17** | BSA and PVP-stabilized AgNPs | Spherical | 5–9, 6–45 | MDR M. tuberculosis inhibition | Seth *et al.* (2011) |
| **18** | AgNPs | Spherical | 5–30 | S. aureus, K. pneumoniae, Bacillus spp. Inhibition | Naqvi *et al.* (2013) |
| **19** | AgNPs | ** | 10-30 | Methicillin resistant S. aureus Inhibition | Sharifi-Rad *et al.* (2014) |
| **20** | AgNPs | ** | 100 | E. coli, P. aeruginosa, Streptococcus pyogenes inhibition | Lara *et al.* (2010c) |
| **21** | Ampicillin-functionalized AgNPs | Spherical | 4 | P. aeruginosa, Enterobacter aerogenes, MRSA inhibition | Brown *et al.* (2012) |
| **22** | AgNPs | ** | 120 | Neiserria gonorrhoeae inhibition | Li *et al.* (2013) |
| **23** | AgNPs | Spherical | 1-10 | HIV-1 inhibition | Elechiguerra *et al.* (2005) |
| **24** | PVP-stabilized AgNPs | ** | 30-50 | HIV-1 III B inhibition | Lara *et al.* (2010b) |
| **25** | AgNPs | ** | 30-50 | HIV-1 III B inhibition | Lara *et al.* (2011) |
| **26** | AgNPs | ** | 25 | Pseudo-typed HIV-1-based viruses Inhibition | Tefry *et al.* (2012) |
| **27** | AgNPs | Spherical | 4-13, 5-23 | HSV-1 and -2 and HPIV-3 | Gaikwad *et al.* |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Inhibition | (2013) |
| **28** | AgNPs | Spherical | 11.4 | Adenovirus type 3 inhibition | Chen *et al.* (2013) |
| **29** | PVP-stabilized AgNPs | ** | 30-40 | HSV-2 inhibition | Hu *et al.* (2014) |
| **30** | AgNPs/chitosan Composites | Spherical | 3.5, 6.5, 12.9 | H1N1 influenza A virus inhibition | Mori *et al.* (2013) |
| **31** | AgNPs | Spherical | 5-20 | H1N1 influenza A virus inhibition | Xiang *et al.* (2011) |

## 1.3 Platinum Nanoparticle

Platinum enhance the biological effect of radiation, platinum has higher atomic number as gold and large surface area. Platinum nanoparticle used as antioxidants to scavenge ROS persistently and catalytically in living organisms (Ruba T *et al.,* 2018). Recently, platinum nanoparticle protected by polyacrylic acid (PAA) gain more attention because they may use as an antioxidants to scavenge ROS (Kajita M *et al.,* 2007). Platinum ions from nanoparticles could be used as anticancer therapies as same cisplatin. Some data showed that there was increase in toxicity with decrease in diameter using Human colon carcinoma cell line (HT29) (Porecel E *et al.*, 2010). Platinum and silver nanoparticle received limited research because of their potential toxicity from dissociation of metal ions (Yamata M *et al.,* 2018).

Some researches shows that pre-treatment of platinum nanoparticle inhibit the LPS induced inflammatory response in RAW 264.7 and radiation induced ROS production in human lymphoma U937 cells. Platinum nanoparticles also suppress the superoxide and peroxide in macrophages and also inhibit the radiation induced caspase-3 activation which can cause apoptosis in cell (Rehman MU *et al.*, 2012).

Table: 3 different types of PtNPs (Raj *et al.,* 2015)

| S. no. | Types of PtNPs | Shape | Size (nm) | Biomedical application | Reference |
|---|---|---|---|---|---|
| 1 | PtNPs | ** | 5-8 | Detection of cancer cells | Asharani *et al.,* (2010) |
| 2 | PtNPs | ** | >100 | Prevention of bone loss | Kim *et al.,* (2012) |
| 3 | Apoferritin-encapsulated PtNPs | ** | 2 | Reduction of cellular oxidative stress | Zhang *et al.,* (2010) |
| 4 | PtNPs | ** | ** | Bond Strength between tooth Structure | Hoshika *et al.,* (2010) |
| 5 | PtNPs | Spherical, cuboidal, floral in shape | 1-18 | Bacterio-toxic effect | Gopal *et al.,* (2013) |
| 6 | PtNPs | Spherical | 34 | Cytotoxic effect on cancer cells | Mohammadi *et al.,* (2013) |
| 7 | PtNPs | Spherical | 5-20 | Treatment of Parkinson's Disease | Nellore *et al.,* (2013) |

| | | | | | |
|---|---|---|---|---|---|
| 8 | Calcium phosphate scaffold PtNPs | ** | 100-400µm pore size | Bone allograft | Eid *et al.,* (2013) |
| 9 | Amine-coated super paramagnetic iron-PtNPs | ** | ** | Detection of cancer cells | Taylor *et al.,* (2014) |
| 10 | PtNPs on graphene oxide (PtNPs/GO) | ** | 50 | Detection of cancer cells | Zhang *et al.,* (2014) |

## 1.4 Cerium oxide Nanoparticle

Cerium oxide nanoparticle also has activity as radioprotector in human lymphocyte cell. Cerium oxides exhibit anti-inflammatory property. DNA damage and apoptosis induced by IR is suppressed by cerium oxide nanoparticle (Zal *et al.,* 2018). Cerium oxide nanoparticles also have the ability as radioprotection against gastrointestinal epithelium cells. Pre treatment of normal human colon cells with cerium oxide nanoparticle 24 hours before radiation exposure can reduce the amount of reactive oxygen species and enhance the amount of superoxide dismutase 2 (SOD2) (Jimmie Colon MS *et al.,* 2010).

Cerium oxide nanoparticle has antioxidant properties. Before radiation exposure of rats in lung injury the cerium oxide nanoparticle are given that shows that having cerium oxide nanoparticle significantly decreased in tissue collapse and neutrophile aggregation in comparison with only radiation group (Kadivar *et al.,* 2020).

Cerium oxide nanoparticle in cancer cells also shows radio-sensitization property, anti invasive properties and radioprotection properties. Radiation exposures of breast cancer MDA MB231 cells, cerium oxide nanoparticle are given that suppress the reactive oxygen species level without any adverse side effect (Do *et al.,* 2020). In some studies MRC-5 and MCF-6 cell lines treated with cerium oxide nanoparticle were exposed to 6Mmv photon beams that shows the reduction in DNA damage. It also reduces the probability of secondary cancer after DNA damage (Goushbola *et al.,* 2018).

Nanocrystalline cerium oxide nanoparticle considered as future radioprotector. Some research shows that cerium oxide nanoparticle can also improve immune function. In research, the whole body of mice exposed to 4Gy of X-rays, treated with cerium oxide nanoparticles shows that enhances the immune cell distribution and induce the production of GSH-Px and activity of Superoxide Dismutase (Si *et al.,* 2019). Human lymphocytes cells are highly radiosensitive cells. Some human lymphocyte cells produce IL-1β after radiation exposure. Cerium oxide nanoparticle also reduces the production of IL-1β and prevents the DNA damage and apoptosis in human lymphocyte cells (Zal *et al.,* 2018).

Cerium oxide nanoparticles are excellent agent for biological applications. Some researches show that cerium oxide nanoparticle has a good scavenging activity for 2, 2-diphenyl-1-picryl-hydrazyl-hydrate free radicals. Cerium oxide nanoparticles are very effective as radio protection of skin cells during radiation exposure (Asia H *et al.,* 2017).

# 2 Biological Nanoparticles

Biological nanoparticles are naturally occurring nanoparticles. They may be intra cellular or extra cellular. Herbal plants also show activity as radioprotector because of low toxicity effect and high tolerability. In the last two decades natural compounds extracted from plants gain very attention.

Curcumin is the natural plant product which is non toxic, edible and easily available. Curcumin works as radioprotector and reduces the harmful effect of radiation exposure and reduce the mortality rate (Sadeghi *et al.,* 2019).

Tea poly phenols nanoparticles reduce the radiation induced damage it reduces the Bax expression and restore the redox status of Nrf2-ERK pathway (Kumar *et al.,* 2016). Aloevera also protects against radiation induced mortality in mice. Medical herb *Inula racemosa* is a trans-Himalayan plant. Its roots have radioprotective agents. Aqueous roots extract enhance the survival of NKE cells against 7.5Gy of gamma irradiation (Shikha Mohan *et al.,* 2019). Ginger rhizome also protects from radiation and also protects gastrointestinal syndrome and bone marrow syndrome (Baliga MS *et al.,* 2012, Haniakda R *et al.,* 2013). Arbutin works as strong radioprotector it reduces the damage of hematopoietic cells of liver caused by X-rays irradiation (S Nadi *et al.,* 2020).

Ginger has many therapeutic effects for example anti-cancer, anti-apoptotic and anti-inflammatory activities. Nanoparticle of ginger gives geed therapeutic results compared to ginger extract. These nanoparticle can spread in various organs and being stable for long time within the cell without coagulating (Bakr *et al.,* 2020).

# Conclusion

In this literature we try to explain the radioprotective agents are growing rapidly. Many metallic nanoparticles have radioprotection as well as radiosensitization properties. Nowadays, cerium oxide is having a great interest in radioprotection activities. Many researchers are doing their research on cerium oxide nanoparticle. Platinum nanoparticles are suggested as anti-inflammatory agent. Silver nanoparticles are more effective in anti microbial activity as well as radioprotection. Vitamins also protects against cancer.

Recently many herbal plants extract come forward as radioprotector because of their low toxicity and high tolerability. Many researches are going on plant extract nanoparticles as radioprotector. These herbal plants improve the efficacy of radiation therapy in cancer. They protect against radiation induced harmful effect to different organs and reduce the harmful and side effects of the radiation. By this literature, we can say that providing radioprotecting agents before exposure of radiation can lead to little harmful effects.

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