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The importance of nanoparticles for development of radioprotective agents

Abstract

Radiation, ionizing or non-ionizing radiation affects living forms in a variety of ways; it has helped life forms evolve, provided a source of energy and is an invaluable tool in modern medicine while its inadvertent use results in serious radiation induced damages For exploiting the complete beneficial use of radiation, the risks of radiation exposures in a biological system are to be restricted which may be achieved through the use of radioprotectors which are any medicinal agent or device when applied prior to or during radiation exposure prevents or limits radiation injury at the molecular, cellular, tissue or organ system level Recently nanoparticles are gaining interest in the field of radioprotection as nanoparticles of various metal oxides were found to possess antioxidant properties and several of them have the ability to offer protection against radiation damages The present review details on the recent advances in the research on the use of nanoparticles for development of radioprotective agents.

Keywords: radioprotector, platinum nanoparticles, gold nanoparticles, silver nanoparticles, cerium oxide nanoparticles, fullerenes or carbon nanoparticles

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Abbreviations: PLGA, Poly (lactic-co-glycolic) acid; ROS, reactive oxygen species; ER stress: endoplasmic reticulum stress; FDA, food and drug administration; CT scan: computed tomography scan; OH•, hydroxyl free radical; H•, hydrogen free radical; HO2•, hydroperoxyl radical; SN, silver nanoparticle; GLY, glycerrhizic acid; LA, lipoic acid

Introduction

Ionizing radiation and radioactive elements have influenced human life in a variety of ways; apart from helping life forms evolve, they provided a source of energy and are invaluable in modern medicine as diagnotic and therapeutic tools The widespread use of ionosing radiation and radioactivity has generated an increased fear of exposure of living beings to radiation and consequent radiation-induced deleterious effects.[1] Ionizing radiation both electromagnetic and particle radiation produce ions during passage through the matter and when interacting with living cells, causes a variety of changes depending on the exposed and the absorbed doses, duration of exposure and interval after exposure, and the sensitivity or susceptibility of the tissues.[2] and cause immediate chemical alterations in cells damaging DNA and membranes The harmful effects of radiation in biological systems are mediated through ionized or excited atoms and molecules that produce free radicals through radiolysis of water in the cellular milieu The products of radiolysis of water molecules are the highly reactive free radicals, such as hydrogen free radical ($H^{\bullet}$) and hydroxyl free radical ($OH^{\bullet}$) The third type of free radical, hydroperoxyl radical ($HO_2^{\bullet}$), is formed when the hydrogen free radical interacts with molecular oxygen 60%–70% of tissue damage induced by ionizing radiation is believed to be caused by $OH^{\bullet}$ radicals.[3] These free radicals causes single strand breaks, double strand breaks, oxidative damage to sugar and base residues in DNA and many forms of cellular damage, such as reproductive death, interphase death, division delay, chromosome aberrations, mutations and transformations.[4]

Ionizing radiations are encountered in different spheres of human life Human beings are constantly getting exposed to natural background radiation which accounts for approximately 80% of exposure, mostly from indoor radon, followed by radiation from space and Earth's crust while man-made sources of radiation account for the rest 20% exposure.[5] The anthropoigenic radiation sources include, diagnostic X-rays, radiopharmaceuticals for diagnosis and treatment, radiation therapy for cancer, for sterilizing medical equipment and food products, nuclear power reactors for energy generation, etc This widespread use of radiation in diagnosis, therapy, industry, energy sector and inadvertent exposure during air and space travel, nuclear accidents and nuclear terror attacks, etc has increased the exposure of living beings to radiation.[6]

Need for radioprotectors

Recent reports indicate the possibility of cancer induction due to exposure of humans to radiation during therapeutic and diagnostic X rays.[7] and CT scans (computed tomography scan).[8] For exploiting the complete beneficial use of radiation, the risks of radiation exposures are to be restricted Thus, the role of radioprotection is very important in clinical situations of radiation exposure.[6] Radioprotectors can be defined as "any medicinal agent or device applied prior to or during radiation exposure that actively prevents or limits injury, whether that injury be at the molecular, cellular, tissue or organ system level".[9] Radioprotectors have the ability to reduce the biological effects of ionizing radiation on normal tissues, including lethality, mutagenicity and carcinogenicity,[10-11] and have applications in clinical oncology, space travel, radiation site clean-up, radiological terrorism and military scenarios.[12]

Among the many radioprotective compounds that have been developed over the years, a majority was designed to reduce the levels of radiation-induced free radicals within the cell Thiol compounds like Amifostine (WR-2721), which are efficient free radical scavengers, have been studied extensively Amifostine is the only Food and Drug Administration (FDA) approved radioprotector in use and is currently employed in the clinic for reducing the incidence and severity of xerostomia in head and neck cancer patients undergoing radiation therapy Unfortunately, application of this drug has so far been less than hoped for, owing to toxicity often being evidenced at optimal radioprotective doses.[13-14]

In view of these scenarios, a radioprotector for therapeutic (protects tissues when administered after radiation exposure) or preventive (protects tissues when administered prior to radiation exposure) application, capable of attenuating the deleterious effects of radiation on normal human tissue is needed for use in various planned or unplanned radiation exposure situations especially for cancer patients undergoing radiotherapy and thus, the search to identify or develop less toxic or non-toxic agents to counter the effects of ionizing radiation remains an area of intense focus Recently nanoparticles are gaining interest in the field of radioprotection as nanoparticles of various metal oxides were found to possess antioxidant properties and several of them have the ability to offer protection against radiation damages

Nanoparticles in radiation protection

Nanoparticles constitute a new generation of free radical scavengers Nanoparticles of Carbon, Cerium, Yttrium, silver, gold, platinum, zinc oxide, poly(lactic-co-glycolic) acid (PLGA), etc function as potential biological free-radical scavengers or antioxidants and they may be a used to scavenge ROS (Reactive Oxygen Species) responsible for radiation-induced cell damage The role of nanoparticles as radioprotectants is a cutting edge development regarding the protection of normal cells and tissues from radiation.[15]

Fullerenes or carbon nanoparticles

Fullerenes represent a family of molecules that contain 20, 40, 60, 70, or 84 carbon atoms C-60 fullerene is the most frequently used member of this family.[16] Fullerenes and its derivatives are well known as a new class of antioxidants and they have attracted considerable attention in biologic applications due to their high reactivity toward radicals,[17] especially reactive oxygen species (ROS) such as superoxide,[18-20] hydroxyl radical,[21-24] peroxyl radicals,[25-26] and nitric oxide.[27-28] It has been established that water soluble fullerenes can be used as potential antioxidants and neuroprotective drugs against degenerative diseases related to oxidative stress.[29-33] Thus, water-soluble fullerenes are promising candidates for use as antioxidants.[34] A water-soluble C-60 fullerene derivative (dendrofullerene) containing 18 carboxylic groups was shown to possess radioprotective effects in zebrafish embryos.[35-36] Polyhydroxylated fullerenes. fullerenol or (C60(OH)24 act as exogenous redox balance modulators and exert anti-oxidative effects in both *in vitro* and *in vivo* systems.[37] The antioxidant and radioprotective properties of Fullerene nanoparticles in comparison to other radioprotective agents has been reviewed by Vavrova et al.[38] It possess *in vivo* radioprotective efficacy in irradiated rats, as well as nitric oxide (NO)- quenching activity in both *in vivo* and *in vitro* systems.[28,39-41] Fullerenol was found to prevent the deleterious effects of ROS directly by increasing the cellular antioxidant enzyme activities.[42] Fullerene derivatives are also able to inhibit all three forms of Nitrous Oxide Systems (NOS).[43] Water soluble fullerenes have shown promising results in mitigating neurodegenerative diseases related to oxidative stress.[32,33,44-45] in addition to its promising cardioprotective,[46] hepatoprotective,[47] nephroprotective and radioprotective.[39] ability, because of its virtue as a antioxidant.[34] It has been postulated that C_{60} may be able to scavenge a comparatively higher number of radicals than the currently available antioxidants.[48]

There are more than one hypotheses for explaining the antioxidant abilities of C_{60} As per the 'direct reaction', it is supposed that an extended electron-conjugation system determines the high reactivity of fullerene molecules toward reactive oxygen species and it was considered to be a novel "structural" antioxidant and characterized as a "radical sponge" by Krusic et al.[17] Another experiment showed that.[20] water-soluble fullerene derivates can deactivate ROS through a nonstoichiometric mechanism A more recent report[49-50] suggested that fullerene derivates possess superoxide dismutase (SOD) mimetic properties Bensasson et al,[51] observed that fullerenes quench singlet oxygen in a more accelerated rate in water medium compared to all other solvents which suggested a possible role of water structures conjoined on the fullerene surface in free radical neutralization It has been shown that introduction of pinup oxygen on C_{60}, such as that in the oxidized fullerene (fullerene epoxide) $C_{60}O_n$, induces significant increase in the antioxidant activity as compared to pristine C_{60}.[34]

Cerium oxide (CeO2) nanoparticles

Various studies have revealed the prospective biological application of CeO_2 nanoparticles as antioxidant and radioprotector.[52] These nanoparticles have oxygen vacancies due to the dual oxidation state (Ce^{4+} to Ce^{3+}) which is responsible for the interesting redox chemistry exhibited by CeO_2 nanoparticles and makes them attractive for the radical scavenging properties [53-54] CeO_2 nanoparticles protect cells from oxidative stress or radiation induced cell death,[52,55] attenuate myocardial oxidative and/or ER stress (endoplasmic reticulum stress) and inflammatory processes.[56] Cerium oxide nanoparticles have been shown to protect gastrointestinal epithelium cells and human lymphocytes against ionizing radiation These nanoparticles reduce ionizing radiation-induced cellular DNA damage, apoptosis and inflammation.[57,58] Prior administration of cerium oxide nanoparticles before radiation exposure of rats results decrease in lung injury and neutrophile aggregation.[59]

Cerium oxide nanoparticles serve as free-radical scavengers.[52,55,60-64] to provide protection against chemical, biological, and radiological insults and could have a role as effective radioprotectants for normal tissues as well as show a differential protection in normal cells as compared to tumor cells.[65]

Yttrium oxide nanoparticles are also able to rescue cells from oxidative stress-induced cell death There are three alternative explanations for the observation that the cerium oxide and yttrium oxide particles protect from oxidative stress They may act as direct antioxidants, they may block ROS production in cells by inhibiting a step in the programmed cell death pathway, or they may directly cause a low level of ROS production that rapidly induces a ROS defense system.[52,54,55] Nanoparticles of aluminum oxide (Al_2O_3) also behave as potential free radical scavenger.[53]

Silver nanoparticles

Silver nanoparticle complexes of several antioxidant compounds such as sesamol, glycerrhyzic acid, lipoic acid and the vitamin derivative palmitoyl ascorbic acid glucoside showed high radioprotecting acivity under in vitro conditions with DNA, membrane and cellular systems and in vivo conditions in animal models[66-71] These complexes of silvernanoparticles were also found to enhance the cellular DNA repair process.[66-70] Many of the silver nanoparticle complexes had excellent free radical scavenging and anti-inflammatory activities.[71-74]

The potential of silver nanoparticles and its complexes with glyzyrrhizic acid to offer protection to cellular DNA against ionizing radiation induced damages has been demonstrated[64-66] Glycerrhyzic acid complexes of silver naoparticles offered protection against gamma radiation induced cellular DNA damage as shown by the results of comet assay performed in bone marrow cells and blood leucocytes of mice exposed to various doses of whole body gamma radiation under *in vivo* conditions These complexes were also effective in protecting against radiation-induced genotoxic effects of radiation as revealed

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by the results of micronucleus assay and chromosomal aberration analysis in whole body gamma irradiated mice The studies on bone marrow cellularity, total blood count and endogenous spleen colony formation in mice whole body exposed to sublethal doses gamma-radiation revealed thast the complexes offered significant protection to the hemopoeitic system from radiation injury The results on survival of mice following a lethal dose of gamma radiation, further confirmed the potential of GLY-Ag as a radioprotector.[65,66]

Silver nanoparticles complexed with gallic acid were found to have radioprotective and anti-tumor activity under *in vitro, ex vivo* and *in vivo* conditions.[63] Analysis of the extent of cellular DNA damage *in vivo* in tumour and normal cells of tumour bearing animals following radiotherapy by Comet assay showed considerable protection to normal cells while sparing the tumor cells Biochemical analysis of cellular antioxidant levels in various tissues excised from irradiated tumor bearing animals confirmed the radioprotective property of the complexes in normal tissues Thus, the nanoparticle complexes of gallic acid offered radiation protection to normal cells by maintaining the cellular antioxidant levels in the tissues and protecting cellular DNA from radiation induced damage.[63]

The silver nanoparticle complexes of lipoic acid exhibited DPPH radical scavenging activity *in vitro* and anti- inflammatory activity against acute and chronic paw models of edema in mice and protected mice from whole body gamma-radiation induced body weight losses and mortality revealing its radioprotecting capacity Administration of the complexes to tumour-bearing mice prior to whole body gamma-radiation exposure, aided in better tumour growth delay The results thus suggested the feasibility in using SN-LA as a therapeutic adjuvant during cancer radiotherapy.[67,72]

Ascorbic acid and its glucoside derivatives are reported to have good antioxidant and radioprotective properties[75,76] Silver nanoparticle complexes of palmitoyl ascorbic acid glucoside shoed good radioprotecting ability under *in vitro*, *ex vivo* and *in vivo* models in murine system and it was found that the complexes possess increased protecting ability compared to the corresponding antioxidant compound, palmitoyl ascorbic acid glucoside The enhanced protection might be due to the additive free radical scavenging property of the constituent components,[74,75]

The post-irradiation DNA repair enhancement by the silver nanoparticle omplexes of these antioxidant componds revealed that they could bestow radioprotection in post radiation scenarios and suggest their therapeutic potential as radioprotectors The results of several studies suggest that nanocrystalline silver play a role in altering or compressing the inflammatory events in wounds and facilitating the early phases of wound healing.[67] The flexibility of silver nanoparticle have made it possible to bind antioxidant molecules on its surface,[68-69] thereby making the conjugate much more radioprotective than its individual components.[66-70]

Gold nanoparticles

It has been shown that Gold nanoparticles could act as an anti-oxidative agent, by inhibiting the formation of ROS, scavenging free radicals and increasing the levels of anti-oxidant defense enzymes.[77-78] It has also been shown that functionalizaton of the vitamin E-derived antioxidant with gold nanoparticles could efficiently enhance the antioxidant activity.[79] Preliminary investigation on gold nanoparticles conjugated with antioxidant compounds has presented promising results as a worthy radioprotector.[77-79]

Platinum nanoparticles

Platinum nanoparticle has been shown to scavenge superoxide anion and hydrogen peroxide thereby inhibiting lipid peroxidation under in vitro conditions,[80,81] prevent cell damage and reduce cell death due to oxidant exposure.[82,83] The anti-oxidant capacity of platinum nanoparticles has been used to influence pulmonary inflammation in mice and extend the lifetime of *C elegans*.[84-87] The antioxidant activity can be explained by quenching of superoxide anion radical and hydrogen peroxideby a catalytic redox reaction coupled with an electron transfer.[88]

Other nanoparticles

Functional surfactants with antioxidant properties can be used to form nanostructures of inherent antioxidant activity.[89] Poly (lactic-co-glycolic) acid (PLGA) nanoparticles with entrapped alpha-tocopherol and ascorbic acid showed a promising design for the effective delivery of antioxidants necessary to combat oxidative stress.[90] Recently it has been shown that Melanin coated silica nanoparticles can be used for protection of bone marrow during radiation therapy.[91] This provides an advantage since melanin, a naturally occurring pigment which possesses radioprotective properties, is insoluble and the problem in administration could be solved by complexing with nanoparticles.[91,92-93]

Conclusion

The role of reactive oxygen species in ionizing radiation injury and the potential of antioxidants to reduce these deleterious effects are well established As mentioned, ionizing radiation generates free radicals that in turn lead to DNA damage Most of the radiation induced biological damage arises from the interaction of the radiation-induced free radicals with the biomolecules The chemicals that can scavenge free radicals may also reduce the occurrence of the DNA strand breaks and membrane damages Thus agents that can prevent the formation of free radicals or destroy free radicals by reacting with them, thereby inhibiting their reaction with biomolecules, can function as radio-protectors Nanoparticles of carbon, silver, gold, cerium oxide, etc are reported to possess radiation protection and since the other nanoparticles discussed above are shown to possess free radical scavenging activities, they must also be screened for their possible radiation protection efficiency As envisaged by Rzigalinski in 2011, nanoparticle antioxidants of gold, platinum, fullerene derivatives, and cerium oxide are potent free radical scavengers that have potential in treatment of disorders associated with oxidative stress including neurodegenerative disorders, cardiovascular disease, inflammatory disorders, and cancer.[94]

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None.

Conflicts of interest

Authors declare that there is no conflicts of interest.

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