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REVIEW

Antimicrobial applications of inorganic radiosensitizers and their potential in biofilm control

Nissem Abdeljelil[1,2,3] · Abdelwaheb Chatti[3] · David Gillan[1] · Rob Van Houdt[2]

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Abstract

Biofilms are structured microbial communities embedded in a self-produced extracellular matrix. This lifestyle provides significant protection against environmental stressors such as desiccation, chemical treatments and even ionizing radiation. Radiation, while a well-established antibacterial strategy, can be less effective in biofilms. Biofilm superior resilience is due to several advantages such as the shielding provided by the matrix, the metabolic heterogeneity and adaptive stress responses of biofilm-associated cells. To address this challenge, researchers are increasingly employing combination strategies in antibiofilm treatment. Radiosensitizers, compounds originally developed to enhance the efficacy of radiation therapy in cancer treatment, have also garnered attention for their potential in antimicrobial applications. These compounds act by amplifying the effects of radiation, often through mechanisms such as increased oxidative stress or inhibition of DNA repair pathways. However, research on radiosensitizers in bacterial systems has focused on planktonic cultures, with limited studies exploring their effects on biofilms. Given the complexity and unique characteristics of biofilms, their response to radiosensitization remains poorly understood and requires further investigation. The use of radiosensitizers in conjunction with radiation presents a promising approach to overcome the inherent resilience of biofilms. By enhancing the susceptibility of biofilm-associated bacteria to radiation and simultaneously disrupting their protective structures, such approaches could lead to more effective and comprehensive solutions. Understanding the nuanced responses of biofilms to these combined treatments is essential for advancing both medical and environmental applications and addressing the challenge of biofilm persistence.

✉ Nissem Abdeljelil
Nissem.abdeljelil@student.umons.ac.be

[1] Proteomics and Microbiology Lab, Research Institute for Biosciences, Mons University, Mons, Belgium

[2] Microbiology Unit, Nuclear Medical Applications, Belgian Nuclear Research Centre SCK CEN, Mol, Belgium

[3] Laboratory of Biochemistry and Molecular Biology, Faculty of Sciences of Bizerte, University of Carthage, Jarzouna, Tunisia

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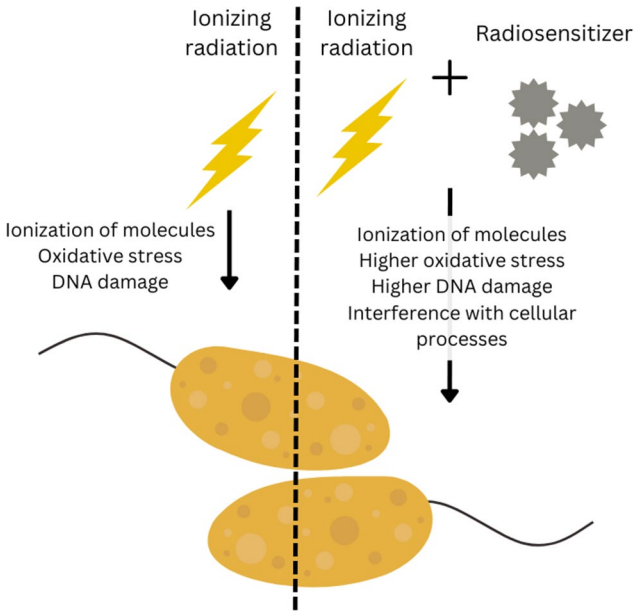
Graphical Abstract



Keywords Bacteria · Microorganisms · Biofilms · Radiosensitizers · Radiation · Nanoparticles

Introduction

Free-floating active bacteria are a relatively easy target for sanitation products, as these cells are directly accessible to antimicrobials. However, bacteria can switch to alternative lifestyles known to improve their survival chances such as dormancy, sporulation and biofilm formation. Biofilms represent the most common type of microbial lifestyle where cells attach to a surface or to each other and produce a mix of polymeric substances that build up and form a "microbial nest". There is evidence that the capacity of microbes to produce biofilms appeared with early microbial life billions of years ago (Westall et al. 2011) and this feature is shared between archaea, bacteria and fungi. Biofilms are dynamic biological structures with variable interacting parameters (Stewart and Franklin 2008). In addition, natural biofilms are often microcosms where various species from different phylogenetic branches and kingdoms co-exist (Sadiq et al. 2022; Yang et al. 2011). Therefore, attempting to predict a biofilm's behavior is a challenging task. Based on their needs, biofilm-resident microbes can tune and adapt their production of biofilm building blocks (Guo et al. 2021; Zheng et al. 2024). The sum of these components is known as extracellular polymeric substances (EPS) or matrix, and the building blocks are exopolysaccharides, proteins and nucleic acids (Lu et al. 2024). Depending on the environment, these EPS can trap debris or react with minerals and reinforce further the scaffold turning the soft biomass into hard matter such as stromatolites or dental calculus (Jin and Yip 2002; Paerl et al. 2001). In a man-made environment, microbial biomass build-up and enhanced corrosion caused by biofilms represent an expensive technical issue (Coetser and Cloete 2005; Flemming 2002; Xu et al. 2023) Due to all this, in industry and the medical sector serious efforts are in place to limit biofilm formation as much as possible. When such microbial communities form on a surface or inside an equipment, they become a continuous source of contamination, spoilage and infections. Unwanted biofilms have a significant worldwide economical and medical impact, estimated to 3,967 billion dollars (Cámara et al. 2022).

Research in biofilm control strategies is very active and inventive, however, so are microbes. Thanks to their high ability to adapt and evolve, microbes often overcome challenges imposed by antifouling strategies (Cholley et al. 2020; Han et al. 2019; Oliveira et al. 2023). Moreover, it was demonstrated that biofilms promote the emergence of antibiotic-resistant mutants (Driffield et al. 2008; France et al. 2019; Frapwell et al. 2018). The state of the art in antibiofilm strategies in the industry and medical sector has recently been reviewed. Dawan et al. (2025) detailed the latest advancements in biofilm control technologies for the food industry. Thomas and Thomas (2021) reviewed the current strategies in medical settings and identified emerging approaches with clinical relevance. These strategies can be categorized into physical, chemical and biological methods, and included techniques such as heat, ultrasound,

electric current, antimicrobial metals, hydrogels, antiseptic solutions, small molecules and bacteriophages (Dawan and Zhang 2025; Thomas and Thomas 2021).

To tackle biofilm adaptation to antimicrobial treatments, researchers are increasingly investigating combined antimicrobial methods, including the association of chemical and physical methods. In this context, techniques such as ultrasounds, plasma, ionizing and non-ionizing radiation were investigated in combination with antibiotics, disinfectants, oxidants, antimicrobial molecules and nanoparticles (Bang et al. 2017; Barra et al. 2015; Huang et al. 2020; Jung et al. 2018a; Park et al. 2018; Petrini et al. 2022; Shabani et al. 2023; Teirlinck et al. 2018). The association of physical and chemical techniques offers more options and several advantages such as decreasing the concentration of antibiotics or antimicrobials usually required for a single chemical treatment or decreasing the required radiation dose and sterilization time. Combined approaches allow tailoring the anti-microbial strategy to the specificities of the targeted microbial community and adjusting the protocol to the treated environment (patient, sensitive equipment, products under strict regulations).

Combining treatments in order to control unwanted cell proliferation is a common practice in fields such as oncology. In fact, despite their unrelated origins there is a remarkable resemblance between biofilms and solid tumors. Both represent organized multicellular structures dynamically evolving in their microenvironment. They are also characterized by cell heterogeneity and an increased resistance to chemical and radiation treatment. In the case of tumors, to overcome the resistance of some cancerous cells to treatments, radiosensitizing agents are being used to maximize the effects of radiotherapy (Wang et al. 2018). These radiosensitizers enhance the sensitivity of cells to radiation therapy. They have been categorized in detail based on their biological effect or chemical/biochemical class (Rashidzadeh et al. 2022; Wardman 2007). Depending on the compound, mechanisms of action may involve the interference with cell integrity, repair mechanisms and homeostasis, the induction of reactive oxygen species (ROS) or the increase in DNA damage. Hence, it is tempting to suggest that radiosensitizing strategies could also improve the outcomes of antimicrobial irradiation protocols. However, for a broad application such strategies should be based on biocompatible radiosensitizers that are effective against unwanted microbial proliferation as well as safe for large-scale use in industry and for the environment. Several studies investigated plants extracts for their radiosensitizing properties. For example, carvacrol, thymol and trans-cinnamaldehyde radiosensitized *Escherichia coli* O157:H7 and *Salmonella* Typhi in contaminated ground beef (Borsa et al. 2004). Coatings containing carvacrol radiosensitized *E. coli* ATCC 25,922 and *Salmonella* Typhimurium (Severino et al. 2015). Methylcellulose-based coatings containing mixtures of organic acids and citrus extract were found to enhance the sensitivity of *E. coli* to γ-radiation (Takala et al. 2011). Thyme and oregano essential oils increased the radiosensitivity of *Aspergillus niger*, *Bacillus cereus* and *Paenibacillus amylolyticus* inoculated to rice grain (Shankar et al. 2020). It was suggested that disruption of the intracellular ATP concentration and cell wall composition caused the radiosensitizing effect of oregano essential oil (Shareck and Lacroix 2009). In these studies, the impact of such treatments on biofilms was not reported. Only experiments reported by Borsa et al. (2004) and Severino et al. (2015) provided conditions for substantial biofilm development although this was not specifically discussed by the authors. Although organic radiosensitizers show promising results, their broad application is challenged by their reactivity, allergenic risk (Sarkic and Stappen 2018), storage requirements and overall availability.

Inorganic compounds are more available on the market than essential oils and plant extracts because of differences in supply chains, production capacity and economic demand. They are also more stable and less sensitive to environmental conditions. In the following sections, we will focus on inorganic radiosensitizers, especially oxidizing agents and elements with high atomic number and their nanoparticles. The current state of the art in inorganic radiosensitization of microbial cells and biofilms will be described, in addition to general mechanisms behind radiosensitization.

Biofilms and ionizing radiations

Biofilms represent a more complex biological structure compared to planktonic bacterial cells. They are significantly richer in extracellular polymeric substances than liquid cultures and have different transcriptomic and proteomic profiles than their planktonic counterparts (Charlebois et al. 2016; Kives et al. 2006; Resch et al. 2005; Svensäter et al. 2001; Zhang et al. 2007). It was shown that EPS such as alginate and secreted enzymes had a protective role against electromagnetic radiation such as UVA (Pezzoni et al. 2014, 2022). Culture density and configuration (aggregates) also interfered with the antimicrobial action of UVC radiation by improving significantly cell survival (Garcés et al. 2021; Labadie et al. 2024). Biofilm resident cells of *Deinococcus geothermalis* had improved cell culturability compared to planktonic cells after a 16-month exposure to space vacuum and radiations (Panitz et al. 2019). Bacterial biofilms could grow in the radioactive water of a spent nuclear fuel pool. These bacteria exposed to 2,030 Bq/cm² could also entrap radionuclides, especially ^{60}Co (Sarró et al. 2007). Mixed biofilms formed on the cladding of nuclear spent fuel rods

and survived for 64 days in high-radiation fields (2.1 Gy/h) (Bruhn et al. 2009). A recent study demonstrated that mixed biofilms developed on the walls of a nuclear reactor pool, in metal-contaminated water and at just 2 m distance from the core. *Bacillus flexus* isolated from these biofilms could tolerate 15 kGy of gamma and neutron radiation (Bratkic et al. 2024).

On the other hand, a series of experiments on pathogens such as *E. coli* O157:H7, *Listeria* spp. and *Salmonella* spp., showed that ionizing radiations doses between 1.5 and 2.5 kGy could significantly reduce the biofilm's cell population and the sessile communities were not necessarily more resistant to gamma rays than free-floating bacteria (Niemira 2007, 2010; Niemira and Solomon 2005). The same team described similar observations in a study on *Pseudomonas fluorescens* exposed to X-rays (Olanya et al. 2015). However, for the moment these are the sole comparative studies on the radiation sensitivity of planktonic bacterial cells and biofilms.

Mechanisms of radiosensitization by oxidants and applications in biofilm mitigation

Oxidants such as hydrogen peroxide H_2O_2, ozone O_3 (Komanapalli and Lau 1996; Ramseier et al. 2011), chlorine dioxide ClO_2 (Han et al. 2001, 2017) or sodium hypochlorite NaOCl (Han et al. 2016; Panasenko et al. 1995) can cause lipid peroxidation and therefore weaken and destabilize biological membranes (Clark et al. 1969; Janero et al. 1991; Linley et al. 2012; Sheridan et al. 1996). They are also involved in the production of ROS that disturb general homeostasis and key cellular components such as proteins and DNA (Andrés Juan et al. 2021). Damage caused by oxidizing agents adds up to the damage caused by ionizing radiation and overwhelm cellular repair mechanisms resulting in cell death. A recent study demonstrated that the use of H_2O_2 preparations as radiosensitizer improved the outcomes of the radiation treatment in cancer patients significantly (Usui and Saito 2024). While the effectiveness of H_2O_2 as a radiosensitizer in cancer treatment has been proved, similar strategies were explored for biofilm control. Researchers have used sodium hypochlorite to improve the antimicrobial effect of an X-ray treatment against *Salmonella enterica* Typhimurium biofilms attached to eggshell (average biofilm cell population was 7.7 ± 0.1 log CFU/egg) and showed that the combined protocol could induce nearly two times more cell reduction than a single treatment of X-rays (2.7 ± 0.06 log CFU/egg) or NaOCl (2.2 ± 0.11 log CFU/egg) (Jung et al. 2018a). In a similar setup using X-rays and ClO_2, the combined approach resulted in enhanced reduction of cell viability (4.7 ± 0.15 log CFU/egg) compared to irradiation or ClO_2 alone (2.5 ± 0.07 log CFU/egg and 1.4 ± 0.08 log CFU/egg respectively) (Park et al. 2018).

Mechanisms of radiosensitization by high atomic number elements and antimicrobial applications

Heavy elements are being intensively investigated as radiosensitizers and they showed promising results against uncontrolled proliferation of eukaryotic cells. When present in a biological environment, elements with high atomic number such as Au (Z = 79), Pt (Z = 78), Gd (Z = 64) or Ag (Z = 47) have numerous possibilities for interactions. They can engage with the biological components (Glišić et al. 2012; Kanellis and dos Remedios 2018), be involved in chemical reactions, or react with photons during radiation exposure (Kobayashi et al. 2010; Leung et al. 2011; Wang et al. 1996). Hence, the introduction of these elements in the proximity of living cells can have biological, chemical and physical consequences. The biological consequences consist for example in protein binding, enzyme inactivation (Che and Siu 2010; Vrèek and Šinko 2013), membrane damage and the induction of oxidative stress (Jiravova et al. 2016; Paesa et al. 2023; Rohde et al. 2021). Moreover, heavy elements have often dense atoms and larger cross-sections than lighter elements, which promotes the probability for interactions with X-rays or gamma (γ) rays photons (Ebel et al. 2003; Seibert and Boone 2005). Depending on the energy of the incoming radiation colliding with matter, three scenarios that can partially overlap are possible: a photoelectric interaction, a Compton scattering or a pair production (Ragheb 2008). In our context, we will focus on the photoelectric effect and the Compton scattering as the pair production phenomenon happens at very high energy ranges rarely relevant for biological applications. To comprehend the mechanism of radiosensitization by high Z elements it is important to understand their interactions with high-energy electromagnetic radiations (Fig. 1). An X-ray or a γ-ray is a shower of photons with a spectrum of energies characteristic of the source, it is known that within certain energy ranges different types of interaction will dominate. For example, at radiation energies in the eV and keV range, the interaction of high Z elements with these photons results mainly in a photoelectric effect. This is a situation where the incoming photon has the required energy to act on an inner shell electron of the dense atom. The photon is then completely absorbed, and its energy transferred to the electron drives this latter out of its orbit, ionizing the atom. The ejected electron is known as a photoelectron. To fill in the vacancy left by the photoelectron, another electron from an outer shell of the atom transits back to the empty spot and is required to lose energy (equal to the difference in energies between the two shells) either in the form of a photon (secondary radiation)

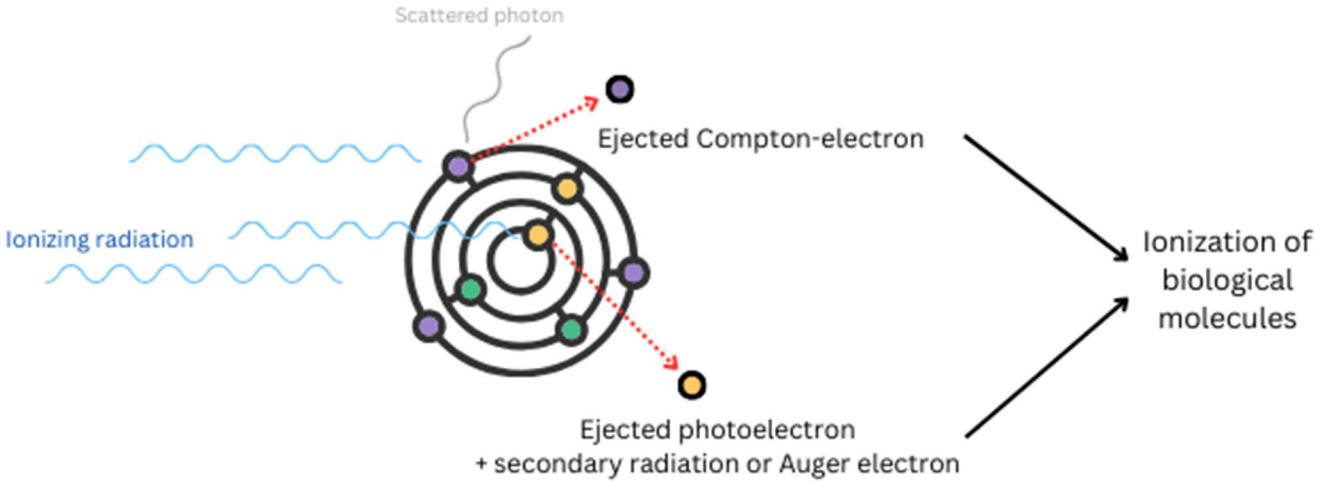


Fig. 1 Schematic illustration of the effect of ionizing radiation on the electrons of an atom. The outcomes of the Compton scattering and photoelectric effect are shown

or the release of a highly reactive Auger electron. The probability of a photoelectric effect happening is directly related to the atomic number (Z) of the irradiated material and the energy level (E). On the other hand, the Compton Effect or Compton scattering happens in all energy ranges in all materials, dominating from keV to MeV. Although Compton scattering is also reported to possibly affect inner-shell electrons in certain conditions (Stutz 2014), it is commonly accepted that Compton effect interactions with loosely bound outer shell electrons and free electrons are more probable due to their availability and low binding energies. In this situation, a photon collides with a weakly bound electron and the latter is ejected. However, the photon is not absorbed but scattered as only a portion of its energy is transferred to the electron. Compton scattering also results in an ionized atom and the ejected electron and scattered photon will cause further interactions in their surroundings. Although the Compton scattering is independent of the element's atomic number, it is affected by the electron density of the matter and a Compton effect will be more important in metals than in biological material (Ragheb 2008; Seibert and Boone 2005). Together, photoelectrons, secondary radiations and Auger electrons from the photoelectric interactions, and scattered electrons from the Compton Effect are responsible for the dose enhancement and related biological damages. In both cases, the presence of high Z elements in biological media allows for a higher energy deposition. These physical phenomena play a crucial role in the medical field, especially in radiology and radiotherapy (Kobayashi et al. 2010; Lusic and Grinstaff 2013; Seibert and Boone 2005; Thariat et al. 2013). In microbiology, radiosensitization by high Z elements has been investigated in bacterial cells and spores. In early experiments, researchers observed that iodine (Z = 53) containing compounds had a significant radiosensitizing effect on bacterial cells exposed to γ-rays. Iodine being the common factor between these compounds, it was suggested that this element may be responsible for the increased efficacy of the radiation treatment (Kada 1970; Kada et al. 1970; Lewis and Kumta 1975). Later on, the radiosensitizing properties of safer forms of iodine-based compounds were demonstrated in vitro and in vivo (Tamura et al. 2017). Ionic forms of copper, zinc and silver also improved the antimicrobial effect of radiation exposure for *E. coli* K12, and *Bacillus megaterium* cells and spores (Kiortsis 1977; Richmond and Powers 1974; Selvaraj et al. 2007).

Next, research on high Z elements as radiosensitizing agents transitioned from soluble complexes to microspheres (Herold et al. 2000), to nanoparticles (NPs) (Hainfeld et al. 2010; Simon-Deckers et al. 2008). Thanks to their nanometric dimensions, NPs have greater surface area than microspheres and crystals. This implies that a larger proportion of their atoms are exposed on the surface and available for physical and chemical interactions. The capacity of nanomaterials in improving the antimicrobial action of X-rays has already been explored. For instance, gold NPs (≈37.5 nm; 3 mg/mL) increased the reduction of *E. coli* K-12 cell viability by 40% compared with X-rays (312 Gy) alone (Simon-Deckers et al. 2008). Flynn et al. (2021) showed that addition of of AuNPs (1.8 nm; 10 µL/mL) to liquid cultures of *E. coli* slightly improved cell reduction compared to only radiation (10 Gy of X-rays). However, surviving bacteria gradually recovered and by 9 h after irradiation the culture resumed normal growth (Flynn et al. 2021). *Microcystis aeruginosa* incubated with gold-titanium oxide nanocomposites (Au/TiO2; 0.2 mg/mL) prior to irradiation (6 kGy of X-rays) showed morphological deformation, loss of cellular content and a decrease in chlorophyll production (Molina Higgins

and Rojas 2019). Luo et al. (2013) studied bismuth (Z = 83) NPs grafted with polyclonal antibodies to specifically sensitize *Pseudomonas aeruginosa* to X-rays. Furthermore, they mimicked deep wounds infections by evaluating the efficacy behind a 2-cm thick polymeric material. They demonstrated that although the polymeric surface absorbed X-rays at a significant dose rate (14.9 mSv/min), bacteria still received 5.1 mSv/min. After 10 min of exposure, bacteria accumulated 51 mSv, the equivalent of 0.051 Gy. This dose was sufficient to demonstrate the radiosensitizing potential of bismuth NPs (0.2 mg/mL) as it caused a similar cell reduction as 600 min of radiation exposure (≈3.06 Gy) (Luo et al. 2013). Bismuth for the radiosensitization of *P. aeruginosa* was also used as nanofilms (10 nm) deposited through evaporation on the surface of petri dishes. After inoculation, samples were exposed to 2.5 Gy of X-rays and an enhanced cell killing for the combined treatment (87%) compared to the radiation treatment alone (42%) was observed (An et al. 2015). Crystals of lanthanum (Z = 57) orthophosphate doped with praseodymium (Z = 59) ($LaPO_4$:Pr^{3+}) were used to coat borosilicate glass petri dishes (unreported thickness) and inoculation with 3 mL of *E. coli* suspension and subsequent exposure to ≈75 Gy of X-rays resulted in at least 1.5 more log cell reduction than X-rays alone (Johnson et al. 2016). Finally, nanoparticles based on zinc (Z = 30) and iron (Z = 26) in the form of $ZnFe_2O_4$ (11.85 to 22.63 nm; 1 mg/mL) enhanced *E. coli* cell reduction by radiation (2 Gy of X-rays) by about 6.3% (Hidayatullah et al. 2016).

Knowledge gaps

Based on the state of the art, several knowledge gaps regarding the inorganic radiosensitization of bacteria were identified. Despite their low cost, studies on the radiosensitizing properties of inorganic oxidants against bacteria is still scarce. This is potentially due to their corrosive nature that may discourage industrial applications. Sterilization procedures with ionizing radiation are expensive and energy consuming, oxidants used as radiosensitizers can help decrease costs by reducing the required dose and treatment time. More research could help enhancing their efficiency while minimizing corrosive effects and enabling safer and more cost-effective sterilization methods. On the other hand, high Z elements are currently a hot topic in radiotherapy research, however, the exploration of their potential in a microbiological context is limited and optimal radiosensitizing conditions have not been determined. Based on the reviewed studies, radiosensitizing agents were generally tested on one bacterial species with most experiments performed on *E.coli* and *P. aeruginosa*. Yet, it is known that bacterial sensitivity to metals (Sazykin et al. 2023) and to radiation (Munir and Federighi 2020) differs from species to species, and even strain to strain. Expanding research to cover a wider array of bacteria is critical for understanding the broader applicability of high-Z radiosensitizers in antimicrobial treatments. Au-derived nanomaterials were the most investigated. Silver and silver nanomaterials are used as antimicrobial agents, oxidative stress inducers (Domínguez et al. 2020) and radiosensitizers (Liu et al. 2016), yet they were not explored for the sensitization of bacteria except for Ag_2SO_4 in the study by Richmond and Powers (1974).

Silver is an expensive metal (≈$1000/kg), still its remarkable antimicrobial properties have led to its widespread use. Gold, however, costs nearly ten times more, which may limit its application as a radiosensitizer in large-scale settings. Other radiosensitizing elements like manganese, iron and zinc are much more affordable and accessible, making them good candidates for a broad range of applications, including medical therapies, environmental remediation and industrial processes, where cost-effectiveness is essential.

In the reviewed studies (summarized in Table 1), inorganic radiosensitizers were used either pre- (Lewis and Kumta 1975; Richmond and Powers 1974; Simon-Deckers et al. 2008), during- (An et al. 2015; Flynn et al. 2021; Hidayatullah et al. 2016; Johnson et al. 2016; Kada 1970; Kiortsis 1977; Luo et al. 2013; Molina Higgins and Rojas 2019; Selvaraj et al. 2007) or post-irradiation (Jung et al. 2018b; Park et al. 2018). This implies that bacterial cells experience the cumulative stress differently in each of these scenarios. Pre-treatment could give the radiosensitizer time to act on cell membranes and DNA, however, considering the rapid multiplication of many microorganisms this may give them the opportunity to adapt or activate repair mechanisms. During irradiation, bacteria experience both stressors in parallel. The latter has been shown to be more effective than pretreatment in the case of the radiosensitization of *Bacillus megaterium* by zinc (Kiortsis 1977). For post-irradiation, the successive stress exposure is supposed to overwhelm the bacterial repair mechanisms in cells surviving the first treatment leading to improved antimicrobial outcomes. Thus, depending on the radiosensitization protocol, the sequence of events that follow at the cellular level can vary significantly.

We also noticed that the scientific approach was generally focused on the behavior of the radiosensitizer and the growth kinetics of the exposed microorganisms. Several studies also used microscopic methods to observe the direct effects on cells such as the impact of bismuth coating and nanoparticles coupled to X-rays on *P. aeruginosa*. The red fluorescence from the LIVE/DEAD staining observed by fluorescence microscopy provided evidence for membrane damage or dysfunction in cells exposed to the combined treatment while cells exposed to a single treatment were

Table 1 Summary of published experiments on the radiosensitization of bacteria using high Z elements sorted by chronological order

Source	Radiosensitizer	Microorganism	Dose	Result of the combined treatment	Reference
^{137}Cs (γ)	Iodoacetic acid (1 mM)	*E. coli* K12	≈153.6 Gy	No cell survival	(Kada 1970)
^{137}Cs (γ)	Potassium iodide, Potassium iodate or iodoacetic zcid (1mM)	*Bacillus subtilis* Marbourg	6.7 Gy	Less than 2.5% cell survival	(Kada et al. 1970)
Gamma cell 220	Iodoacetamide (1 mM)	*Micrococcus radiophilu*	8 µGy	5-log cell reduction	(Lewis and Kumta 1975)
X-rays	Ag_2SO_4 (0.01 mM)	Spores of *Bacillus megaterium* (ATCC 8245)	0.5 Gy	>3-log cell reduction	(Richmond and Powers 1974)
^{60}Co (γ)	$ZnCl_2$ (0.069 mM)	*Bacillus megaterium* Elstre	225 Gy	2-log cell reduction	(Kiortsis 1977)
^{60}Co (γ)	$CuSO_4$ (0.03 mM)	*E. coli* K12 strain AB 4401	29 Gy	Five times more cell killing than radiation alone.	(Selvaraj et al. 2007)
X-rays	Gold nanoparticles (AuNPs) (3 mg/mL)	*E. coli* K-12	321 Gy	Nearly 40% of reduction in viability compared to X-rays alone	(Simon-Deckers et al. 2008)
X-rays	Polyclonal antibody modified bismuth nanoparticles (0.2 mg/mL)	*P. aeruginosa*	≈0.051 Gy	90% reduction in cell survival	(Luo et al. 2013)
X-rays	10 nm thick bismuth film	*P. aeruginosa*	2.5 Gy	45% more cell killing than X-rays alone	(An et al. 2015)
X-rays	$ZnFe_2O_4$ (1 mg/mL) nanoparticles	*E. coli*	2 Gy	Increased absorbed dose in the presence of the NPs	(Hidayatullah et al. 2016)
X-rays	Thin layer of LaPO4:$Pr3^+$ coating	*E. coli* (ATCC 8739)	≈75 Gy	2 log reduction by the double treatment compared to 0.5 log reduction by X-rays alone	(Johnson et al. 2016)
X-rays	Au/TiO2 nanocomposite (0.2 mg/mL)	*Microcystis aeruginosa*	6 kGy	Morphological deformation, loss of cellular content and decrease in chlorophyll production	(Molina Higgins and Rojas 2019)
X-rays	AuNPs (0.01 mg/mL)	*E. coli*	10 Gy	Slightly higher inhibition of growth compared to radiation alone, followed by the recovery of the culture after 4 h.	(Flynn et al. 2021)

mainly green implying unaltered membranes (An et al. 2015; Luo et al. 2013). Thus, a dual treatment with radiosensitizers and ionizing radiation seems to interfere more efficiently with the stability of the bacterial membrane. Still, it is not clear if this is due to a direct damage of the membrane components (lipid bilayer, membrane proteins) or to a cascade of events leading to the disruption of its function. Although two studies (Kada et al. 1970; Selvaraj et al. 2007) examined the impact of dual treatments on DNA, the molecular pathways underlying bacterial death or survival were not explored. Molecular data that could uncover how such simultaneous chemical and physical stress affect gene and protein expression in microorganisms are currently lacking.

We additionally note that the increasing accessibility of X-ray equipment had an impact on the choice of radiation sources used for research. In fact, X-ray irradiators are getting compact and convenient. Today's models are portable and can fit on a bench. They do not produce radioactive waste and are subject to fewer regulations compared to gamma ray sources.

Finally, the investigations cited in Table 1 focused mainly on the radiosensitization of bacterial suspensions. However, in medical and industrial settings bacteria are often encountered as biofilms. Despite the proven potential of high Z elements for the radiosensitization of bacterial suspensions, to date no studies specifically addressed the application of such radiosensitizers in conjunction with X-rays or gamma rays to combat biofilms. Here, we aimed to expose this research gap. If heavy-element radiosensitization remains consistent in biofilms and a significant fraction of these

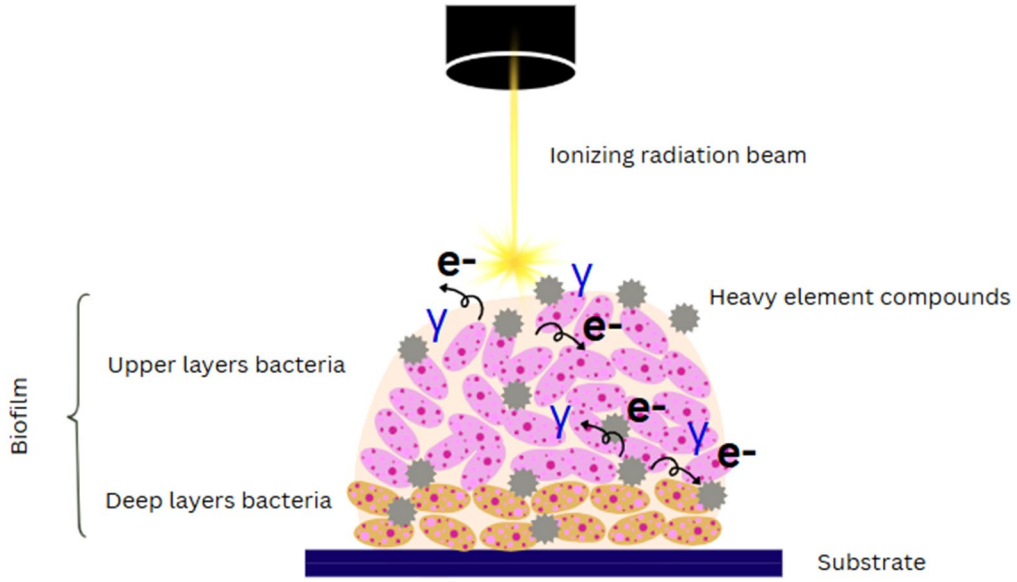


Fig. 2 Expected interactions between ionizing radiation and heavy elements in a biofilm: the release of reactive electrons (e-) and secondary radiations (y)

elements or derived materials diffuses within biofilms, ionization of bacterial molecules via Compton scattering and the photoelectric effect should induce significant damage, even in bacteria embedded in deep biofilm layers (Fig. 2). Additionally, beyond their interaction with radiation, high Z elements such as silver and copper may independently interfere with microbial processes enhancing their antibiofilm potential. Therefore, further exploration is recommended to develop new effective disinfection options in medical and industrial settings.

Concluding remarks

Although the exploration of inorganic radiosensitizers in cancer research has gained significant traction, the application of these radiosensitizers to bacterial cells poses intriguing questions about the fundamental differences in cellular responses between prokaryotic and eukaryotic organisms. Bacterial membranes, primarily composed of phospholipids, lack the sterols found in eukaryotic cells, which may influence how these organisms interact with radiosensitizers. Additionally, the absence of organelles in bacteria results in a more straightforward biochemical landscape, possibly leading to distinct pathways for radiation-induced damage and repair. Molecular biology techniques, such as transcriptomics and proteomics, can help to elucidate the specific genes and proteins that mediate bacterial responses to these agents. Additionally, studying bacterial response to radiation and radiosensitizers is central for optimizing treatment strategies and combating antibiotic resistance. Lastly, despite the prevalence of biofilms in medical and industrial settings, inorganic radiosensitization methods have rarely been explored for biofilm control. Investigating the potential of such procedures against biofilms could answer fundamental questions about microbial resilience and adaptation while improving disinfection methods.

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Declarations

Competing interests The authors declare no competing interests.

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