ОБЗОР | REVIEW
УДК 623.454.86+615.2
https://doi.org/10.35825/2587-5728-2024-8-4-305-322
https://elibrary.ru/xckbzz



# Radioprotection in the 21st Century

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**Highlights**
In nature, there are bacteria and eukaryotic multicellular organisms (insects, arthropods) that have extraordinary, nevertheless still poorly understood radiation resistance. Knowledge of its mechanisms can significantly increase the effectiveness of radioprotectors and can lead to fundamental discoveries for the radioprotection in humans.
***Relevance.*** The growing threat of nuclear war and nuclear accidents requires updating and deepening the knowledge of the occurrence of radiation resistance in nature and the development of pharmaceutical means for human radiation protection.
***The purpose of the study*** is to summarize the ideas available in the scientific literature about the mechanisms of increased radiation resistance of some living organisms and about modern radioprotectors.
***The source base of the study***. Scientific publications available through the biomedical research database PubMed.
***Research method.*** Analytical.
***Discussion.*** The reasons for the high radioresistance of the bacterium *Deinococcus radiodurans* and scorpions of the genus *Androctonus* are considered. For *D. radiodurans*, the radioresistance is based on the ability to protect its proteome, and not the genome, as previously thought. The resistance of bacterial cells to radiation is regulated by manganese antioxidants. With this ability, *D. radiodurans* can repair up to 500 breaks, while *E. coli* can repair two or three DNA breaks at once. The new bioconcept can be expressed as "Primacy of the proteome over the genome". The principle of the radioresistance of scorpions is less clear. It is known that the main role is played by the hemolymph cells the anulocytes ("hémocytes annelés"), and hemocyanin molecules present freelely in the hemolymph. The paper further describes general therapeutic approaches to the development of new radioprotective agents. Radioprotectors are supposed to prevent/inhibit the formation of free radicals caused by radiation (most of which are formed during radiolysis of water), thereby inhibiting their reactions with biomolecules reducing the frequency of DNA strand breaks and preventing the occurrence of cellular disorders. The classification of radioprotectors is given, their properties are described in detail.
***Conclusions***. For the future development of radioprotectors, it is important to recognize the "new" paradigm of radioresistance – the "primacy of the proteome over the genome". From today's practical point of view, the cytoprotective complexing drug Amifostine can be recommended in radiation protection.

***Key words:*** *Amifostine; anulocytes; Deinococcus radiodurans; DNA; hemocyanin; manganese (Mn); nuclear explosion; protein; proteome; radioprotection; radioresistance; scorpion*

***For citation:*** *Lakota J. Radioprotection in the 21st Century. Journal of NBC Protection Corps. 2024;8(4):305–322. EDN: xckbzz. https://doi.org/10.35825/2587-5728-2024-8-4-305-322*

***Financial disclosure:*** *The author has no financial interests in the submitted materials or methods.*

***Conflict of interest statement:*** *The author is a member of the editorial board of the journal (since 2023). This had no impact on the peer review process and the final decision.*

***Funding:*** *There are no funding sources to declare.*

Received October 28, 2024. Revised December 18, 2024. Accepted December 27, 2024.

# Радиационная защита в 21 веке

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**Основные моменты**
Существуют бактерии и эукариотические многоклеточные организмы (насекомые, членистоногие), имеющие очень высокую устойчивость к радиационному излучению, природа которой до конца не изучена. Знания о механизмах развития данной устойчивости позволили бы значительно повысить эффективность существующих средств радиационной защиты и сделать прорыв в области радиационной защиты человека.
***Актуальность.*** Постоянная угроза ядерной войны, а также чрезвычайные происшествия, связанные с утечкой радиоактивных веществ, вынуждают нас расширять имеющиеся знания о механизмах возникновения сопротивления радиационному излучению в природе, а также о разработке фармацевтических средств радиационной защиты человека.
***Цель работы.*** Обобщение информации о механизмах возникновения повышенной радиационной устойчивости у живых организмов и данных о современных медицинских средствах радиационной защиты, представленных в научных работах.
***Источниковая база исследования.*** Научные работы, представленные в базе данных медицинских и биологических публикаций PubMed.
***Метод исследования.*** Аналитический.
***Обсуждение.*** В статье рассматриваются причины повышенной устойчивости к воздействию радиации, выявленной у бактерии *Deinococcus radiodurans* и скорпионов рода *Androctonus*. Что касается бактерии *D. radiodurans*, ее повышенная радиационная стойкость обусловлена способностью этой бактерии защищать свой протеом, а не геном, как считалось ранее. Способность клеток данной бактерии противостоять воздействию радиации зависит от наличия антиоксидантов марганца. Благодаря указанному свойству *D. radiodurans* может восстанавливать до 500 возможных разрывов молекулы ДНК, в то время как бактерия кишечной палочки способна восстанавливать лишь 2–3 подобных разрыва одновременно. На основании вышеизложенного можно сделать следующий вывод – «протеом важнее генома». Механизмы возникновения повышенной устойчивости к воздействию радиации у скорпионов не так хорошо изучены. Известно, что ключевую роль в этом процессе играют клетки гемолимфы – сфероциты и молекулы гемоцианина, широко представленные в гемолимфе. Также описаны общие терапевтические подходы к разработке новых средств защиты от воздействия радиации. Предполагается, что эти средства должны предотвращать или замедлять процесс образования свободных радикалов, появляющихся в результате воздействия радиации (большинство этих радикалов образуются в результате радиолиза воды). Вследствие этого, замедляются реакции этих радикалов с биомолекулами, что в свою очередь снижает частоту возникновения разрывов молекул ДНК и предотвращает нарушения строения клеток. В работе приведена подробная классификация медицинских средств защиты от радиации с описанием их основных свойств.
***Выводы.*** «Новая» парадигма радиационной устойчивости, которая гласит: «протеом важнее генома» – крайне важна для разработки эффективных средств защиты от воздействия радиации в будущем. С практической точки зрения, комплексное цитопротекторное средство Амифостин может быть рекомендовано как средство защиты от воздействия радиации.

***Ключевые слова:*** *Амифостин; бактерия; белок; Deinococcus radiodurans; ДНК; гемоцианин; марганец (Mn); протеом; радиационная защита; радиационная стойкость; скорпион; сфероцит; ядерный взрыв*

***Для цитирования:*** *Лакота Я. Радиационная защита в 21 веке. Вестник войск РХБ защиты. 2024;8(4):305–322 EDN: xckbzz. https://doi.org/10.35825/2587-5728-2024-8-4-305-322*

***Прозрачность финансовой деятельности:*** *автор не имеет финансовой заинтересованности в представленных материалах или методах.*

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***Финансирование:*** *источников финансирования для декларирования нет.*

Поступила 28.10.2024 г. После доработки 18.12.2024 г. Принята к публикации 27.12.2024 г.

The development of radioprotective agents in the past decades became one of the main challenges of mankind. The reason is obvious – use of nuclear materials in civil, military and possible misuse by terrorists. Here we present approaches which can be helpful in the development of such agents. The research in molecular biology of the bacterium *Deinococcus radiodurans*, one of the most radioresistant organisms on the Earth, can bring rather simple solutions in the development and practical use of radioprotective agents. On the other hand, the radioresistance of eukaryotic multicellular Arthropods – scorpions is known for decades. Nevertheless, the detailed results of this research are not known so far. At last, however not least, we review of the currently searched spectrum of radioprotective agents.

**Introduction**

"Gurkha, flying on a fast and powerful viman, threw a single projectile charged with the power of the Universe at three cities. A glowing column of smoke and flame, as bright as ten thousand suns, rose up with all its splendor. It was an unknown weapon, an iron lightning, a gigantic messenger of death that reduced to ashes an entire race of Krishnas and Andhakas." This is a quote from Book VII of the Mahabharata. A slightly softer and less "radiant" expression "Brighter than a thousand suns" was used by the writer austrian journalist Robert Jungk (1913–1994) as the title of his book. This statement was (supposedly) said by J. Robert Oppenheimer (1904–1967) when the atomic bomb was detonated near the city of Alamogordo, New Mexico in 1945. Oppenheimer is widely known as the "father of the atomic bomb," who infamously summed up his life's work in a 1965 NBC News documentary by reciting a line from the sacred Hindu text Bhagavad Gita: "Now I have become death, the destroyer of worlds." Quite apt, isn't it? Nevertheless, we do not intend to analyze either the "Eastern" books or the mysticism of India. We were interested in another superstition, widespread in India, original Persia, and Arab countries. It claims that a scorpion will not burn in a fire. If you "get" a scorpion and throw it into the fire, the scorpion will burn very quickly and turn into ashes. However, in Sanskrit the word "fire" has plentiful meanings. In the 1960s, France carried out tests of nuclear (atomic) bombs in Reggano and In Ekker (Sahara region) in Algeria. Similar tests were carried out by the U.S. at a nuclear shooting range in Nevada. The first discovery that scorpions have an unusually high resistance to ionizing radiation was known as early as 1960. The only creatures that survived detonations in nuclear weapons testing near the epicenter of the explosion ("ground-zero") were scorpions (genus *Androctonus*) and some beetles of the superorder *Coleopterida* (genus *Pimelia*). The resistance of these animals to radiation was soon (in 1963) confirmed in laboratory tests [1], and repeated in the field (in 1973) at a test site in Nevada in the United States.

Since that time several studies have sought to identify the characteristics of animals that determine susceptibility to ionizing radiations[1] [2, 3].

**Main**

**Bacterium *Deinococcus radiodurans*.** Despite the radioresistance of scorpions mentioned in the part Introduction we will start with another "highly radioresistant" living organism *Deinococcus radiodurans*. Bacteria of *D. radiodurans* were discovered accidentally in 1956 when cans of ground meat were treated with massive doses of ionizing gamma radiation to rid them of dangerous bacteria. This bacterium was found to be capable of surviving radiation doses up to 10000–15000 Gy i.e. one thousand times higher than that which is lethal for a human being [4]. Among biologists and biophysicists, this extremophile is often known jokingly as "Conan the bacterium" [5].

*Deinococcus radiodurans* is also on the list of "the world's toughest bacterium" in the Guinness Book of World Records[2].

It is known that ionizing radiation causes the most deleterious influence on genetic material because it induces Double-Strand Breaks (DSB) in DNA. In most cases, this kind of damage cannot be effectively repaired. In other words, DSB disrupts DNA strands, shattering them into

[1] Max Goyffon: Resistance to ionizing radiation. P. 157–163. In: Stockmann R., Ythier E. Scorpions of the world. N.A.P. Editions, Verrières-le-Buisson; 2010. 565 p. ISBN 978-2913688117. https://1lib.sk/book/2034275/80fdf1/scorpions-of-the-world.html

[2] Most radiation-resistant lifeform. URL: https://www.guinnessworldrecords.com/world-records/most-radiation-resistant-lifeform (date: 30.08.2024).

myriads of small pieces of different sizes. The former process is mainly due to the deleterious activity of Reactive Oxygen Species (ROS) produced by water radiolysis, leading to DSBs. Besides DNA mutilation, ROS inflicts severe damage on the cell's proteome, which plays a vital role in DSB repair; therefore, this mechanism is unfeasible.

In further studies it has been shown that ROS stimulates protective reactions that donate electrons to the free radicals, thus making them nonreactive. As shown by some of the pioneering studies [6, 7], the amazing radioresistance of *D. radiodurans* is attributed to a scavenger that exists in the cytosol (moieties of less than 3 kDa). These small molecules protect *D. radiodurans* proteome from oxidizing radicals by quenching the ROS produced by radiation. The secret behind *D. radiodurans'* incredible radioresistance lies in its ability to protect its proteome. Thanks to this ability, *D. radiodurans* can repair up to 500 breaks, while *E. coli* can fix two or three breaks at once in its DNA only. This peculiarity is generalized by the following concept: A cell dies when its proteome ceases to function, as the most critical biological information comes not from its DNA but from its protein structure.

A new bio-concept, expressed as "The primacy of Proteome over Genome", or "The primacy of biological function over information", was both proposed and demonstrated by Krisko and Radman [8].

In short, they argue that: (1) a cell dies when its vital functions performed by the proteome cease, whereas (2) genome integrity is required (in addition to an active proteome) for the perpetuation of the surviving cell. It is of importance to note that the preservation of vital functions of proteins is fundamental for transmission of information—however, information is effectively useful once transmitted and received.

A small theoretical experimental summary concerning the radioresistance and radiosensitivity of *D. radiodurans* can be found in the reference [9].

A comprehensive description of the astonishing DNA repair ability has been described in a review article [10].

According to the author – soon after the structure of DNA was published, the field of radiobiology coalesced around two ideas: (*i*) cellular damage is indiscriminate in irradiated cells and caused mainly by ROS, and (*ii*) DNA is the critical radiation target. Because individual proteins in a cell typically exist at much higher levels than their corresponding genes, "death by DNA damage" became radiation dogma [11].

Over the next decades, however, the two central tenets of classical radiobiology were repeatedly tested and refuted. It has been shown that:

i) *cellular damage in irradiated cells is not indiscriminate, but instead dependent on a cell's $Mn^{2+}$ antioxidant content,*

ii) *proteins are the critical targets of radiation in sensitive cell-types, not DNA [12–16].*

The three earliest *D. radiodurans* findings that set the stage for overturning the central tenets of DNA-centric radiotoxicity models are: 1) in 1964, A.K. Bruce demonstrated an LMW (<15 kDa) protein-free *D. radiodurans* extract capable of protecting *E. coli* against the lethal effects of ionizing radiation [17]; 2) in 1964, J.K. Setlow and colleagues showed that DNA in *D. radiodurans* is no more protected from UVC radiation than DNA in radiosensitive bacteria [18], and 3) in 1976, A.K. Bruce and colleagues further showed that *D. radiodurans* accumulated 100 times more $Mn^{2+}$ than *E. coli*, and importantly, that lowering the concentration of $Mn^{2+}$ in the culture medium resulted in a marked decrease in the survivability of *D. radiodurans* after UVC irradiation [19].

Evidently, any protein expressed in *D. radiodurans* or *D. geothermalis* is protected from ROS under high-level chronic ionic irradiation [20].

This form of protein protection was shown to be independent of MnSOD, yet dependent on the accumulation of $Mn^{2+}$ ions in the cells. This led M.J. Daly and colleagues to shift their studies from DNA repair to cell-cleaning functions, and in 2004, they reported the identification of a widespread $Mn^{2+}$-dependent, nonenzymatic mechanism required for extreme radiation resistance [12]. Moreover, the *Deinococcus* group further showed that cellular $Mn^{2+}$ does *not* protect DNA, which implied that proteins are the targets of Mn protection in *D. radiodurans* [21].

In 2007, extreme radiation resistance among bacteria was shown to consistently coincide with a greatly diminished susceptibility to radiation-induced protein oxidation but with similar radiation-induced DNA lesion-yields as in other organisms. Thus, a new model of radiation resistance was proposed in 2009 wherein naturally sensitive bacteria are killed by radiation mainly owing to protein oxidation, whereas $Mn^{2+}$-metabolite complexes accumulated in extremely resistant cells protect enzymes needed to repair DNA and allow survival [22].

The new theoretical contribution to the understanding of radiation resistance is a new concept where a cell's proteome, rather than its genome, is the prime target responsible

for radiation-induced cell death, and that cellular radiation resistance is governed by Mn antioxidants [23, 24].

Resistance to acute and chronic forms of ionizing radiation in archaea, bacteria, fungi, and simple animals critically depends on the intracellular accumulation of Mn antioxidants, nonenzymatic $Mn^{2+}$ ions bound to LMW metabolites such as orthophosphate ($P_i$) and peptides. The resulting Mn complexes catalytically quench $O_2^{\bullet-}$ radicals and have been shown to confer greatly enhanced radiation survivability on polyploid cells by enhancing their capacity to mend DSBs. Manganous ions first facilitate radiation survival by preventing $O_2^{\bullet-}$ damage to proteins: by replacing $Fe^{2+}$ with $Mn^{2+}$ as mononuclear cofactors in enzymes, which protects active sites from oxidative damage. More importantly, surplus $Mn^{2+}$ ions (i.e., the portion of a cell's $Mn^{2+}$ budget that is not bound to proteins) spontaneously form Mn antioxidants, which provide global protein protection and thereby preserve the functions of irradiated enzymes.

For completeness we include here the physiological roles of manganese in humans. Adult humans have 15–18 mg of manganese, stored mainly in the liver [25].

$Mn^{2+}$ functions include: 1. Cofactor or an activator of enzymes such as arginase, glutamine synthase, isocitrate dehydrogenase, pyruvate carboxylase, glycosyltransferases, cholinesterase, lipoprotein lipase, phosphotransferases, hydrolases, acetyl-CoA carboxylase, squalene synthase, ALA synthase, mitochondrial superoxide dismutase, and all three enzymes of the oxidative phase of pentose phosphate pathway (glucose 6-phosphate dehydrogenase, gluconolactone hydrolase, 6-phosphogluconate dehydrogenase). 2. Role in carbohydrate metabolism – as a cofactor of isocitrate dehydrogenase, pyruvate carboxylase, and the enzymes of oxidative phase of pentose phosphate pathway, $Mn^{2+}$ plays important roles in the TCA cycle, gluconeogenesis, and pentose metabolism. 3. Role in mucopolysaccharide and proteoglycan synthesis – participating in glycosyltransferase activity, $Mn^{2+}$ plays a role in the synthesis of heteroglycan mucopolysaccharides such as chondroitin sulfates, which are than incorporated into proteoglycan aggregates of extracellular matrices of connective tissues, tendons, and bones. 4. Porphyrin synthesis – $Mn^{2+}$ may help in heme synthesis as a cofactor of ALA synthase. 5. Antioxidant action – as a constituent of mitochondrial superoxide dismutase, $Mn^{2+}$ helps in the conversion of superoxide free radical to $H_2O_2$ ($2O_2^{\bullet-} + 2H^+ = O_2 + H_2O_2$)).

Manganous ions are unique among redox-active transition metals that accumulate in cells in that they are innocuous under conditions where other biologically active transition metals (in particular, $Fe^{2+}$) tend to promote the formation of ROS. Electron-dense cytoplasmic granules in *D. radiodurans* cells are depots of Mn antioxidant precursors (*Figure 1A*), and contain the highest intracellular Mn (3 mmol/L) and $P_i$ (25 mmol/L) concentrations in the cells [10] cells can accumulate up to millimolar concentrations of $Mn^{2+}$ ions in the form of cytoplasmic Mn antioxidants, in addition to the MnSOD [23]. Both MnSOD and Mn antioxidants catalytically scavenge $O_2^{\bullet-}$ formed through metabolic processes or by radiation exposure, converting these ions to $H_2O_2$ (*Figure 1B*). $H_2O_2$ is membrane-permeable and can escape the cell, whereas $O_2^{\bullet-}$ is not membrane-permeable and would become trapped and accumulate inside irradiated cells [26].

It should be noted that the Mn ions are radioprotective against acute radiation syndrome if administered in the form of $MnCl_2$ in mice [27].

Early tests of the "death by protein damage" radiation model gave rise to a novel irradiated vaccine technology [28].

The tests revealed that while proteins in *D. radiodurans* are highly resistant to ROS during irradiation, they are as sensitive to ROS as *E. coli* proteins when purified from the cells. However, when purified *E. coli* proteins are mixed with *Deinococcus* Mn antioxidants, they can survive undamaged after exposures greater than 30 kGy of gamma-rays, a dose that obliterates similarly treated DNA. Mn antioxidants have been found to protect the activity of a range of irradiated enzymes in vitro, including the DNA repair enzyme T4 DNA ligase [29].

Ionizing radiation is a commonly used method for sterilizing laboratory and medical supplies, and it has been reported as a vaccine production strategy since the early days of vaccinology. However, decades ago, irradiation was largely abandoned as a vaccine development approach because of the coincident oxidative destruction of critical surface epitopes during pathogen inactivation. In aqueous conditions, nucleic acids and proteins are severely damaged by the indirect action of ROS generated from the radiolysis of water. In vaccine production, radiation-induced destruction of the nucleic acids in a pathogen is desired while damage to the structural proteins on the surface of a pathogen is not because it reduces antigenic potency. *Deinococcus* Mn antioxidants thus can be used to selectively protect surface proteins of cells and viruses from the indirect effects

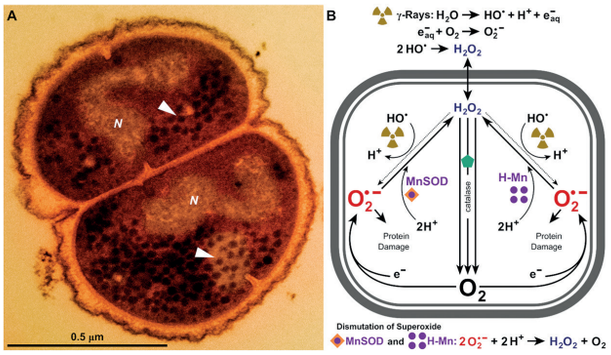


**Figure 1:** *Deinococcus radiodurans antioxidant defenses. (A) Electron-dense granules are highly enriched in $Mn^{2+}$ and phosphate precursors of Mn antioxidants, visualized by transmission electron microscopy (TEM), identified by arrows inside a dividing. The 4–8 identical genomes per cell in D. radiodurans are condensed into nucleoids (N) wherein the chromosomes and plasmids are highly recombinogenic. Scale bar 0.5 µm. (B) Ionizing radiation-driven reactions that generate reactive oxygen species (ROS) and cellular mechanisms related to dismutation of superoxide ($O_2^{\bullet-}$) by Mn-dependent superoxide dismutase (MnSOD) and Mn antioxidants, illustrating the two complementary catalysts of superoxide defense, MnSOD and Mn antioxidants (H-Mn). Importantly, $O_2^{\bullet-}$ damages proteins, but not DNA. (the figure is adapted from [10])*
**Рисунок 1** – *Антиоксидантные защитные свойства бактерии Deinococcus radiodurans. А – Электронно-плотные гранулы обогащены $Mn^{2+}$ и фосфатными прототипами антиоксидантов марганца Mn, которые можно разглядеть через просвечивающий электронный микроскоп. Они выглядят как стрелы внутри разреза 4–8 идентичных геномов на клетку D. radiodurans спрессованы в нуклеоиды (N), хромосомы и плазмиды, в которых обладают высокой рекомбинантностью. Шкала деления 0,5мкм. В – Воздействие радиации вызывает реакции, в результате которых образуются частицы активного кислорода, а также запускаются клеточные механизмы, отвечающие за дисмутацию супероксида ($O_2^{\bullet-}$) посредством марганец-зависимой супероксиддисмутазы (MnSOD) и антиоксидантов марганца, что позволяет нам увидеть два дополнительных катализатора защиты супероксида, MnSOD и антиоксиданты марганца (H-Mn). Важно отметить, что $O_2^{\bullet-}$ повреждает протеины, но не наносит никакого вреда ДНК (рисунок подготовлен по [10])*

of gamma radiation, while leaving DNA and RNA inside cells and viruses unprotected. This approach gave rise to a rapid and highly effective means of producing inactivated vaccines with preserved antigenic epitopes at supralethal doses of irradiation [30].

Mn antioxidants constitute about 70% of the cytosolic $Mn^{2+}$ in *D radiodurans*, where they form complexes with Pi and peptides [7]. Through the analysis of naturally occurring *Deinococcus* Mn complexes, the peptide components of Mn antioxidants were rationally designed to yield a synthetic complex called MDP (manganese–decapeptide–phosphate). The MDP complex forms spontaneously when the decapeptide DEHGTAVMLK, Pi, and $Mn^{2+}$ are combined (*Figure 2*). The ability of MDP to preserve neutralizing epitopes during supralethal irradiation has been critical to the commercial development of irradiated vaccines[3].

Over the past 50 years, radioprotection approaches have firmly focused on compounds that protect DNA and those that modulate cellular radiation responses, but they have yielded few radioprotectors. MDP, which is innocuous in mice and rats, has been tested as an in vivo radioprotector in a murine model at the Armed Forces Radiobiology Research Institute (AFRRI) [29].

Notably, MDP has been shown to completely protect mice from a typically lethal gamma radiation dose of 9.5 Gy when administered both pre- and post-irradiation [29] (*Figure 3*).

Manganese antioxidants based on peptides are also accumulated in eukaryotes, including vertebrates. However, whereas peptides in Mn antioxidants of bacteria are derived mainly by proteolysis, $Mn^{2+}$-binding peptides in eukaryotes are synthesized mainly from amino acid precursors (e.g., glutathione). A second example of Mn antioxidants shown to act as in vivo radioprotectors is glutathione (l-γ-glutamyl-l-cysteinyl-glycine), the most abundant LMW thiol in animals, ranging from 0.5 to 10 mmol/L. Mn-glutathione-like complexes act as in vivo radioprotectors when administered to mice [31].

MDP provides exceptional hematopoietic protection as reported in the AFRRI study where MDP significantly protected against hematopoietic acute radiation syndrome

[3] Phelan M. Bacteria Found in Nuclear Reactors Could Be the Secret to Faster, Cheaper Vaccines. URL: https://gizmodo.com/bacteria-found-in-nuclear-reactors-could-be-the-secret-1843965129 (date: 30.08.2024).

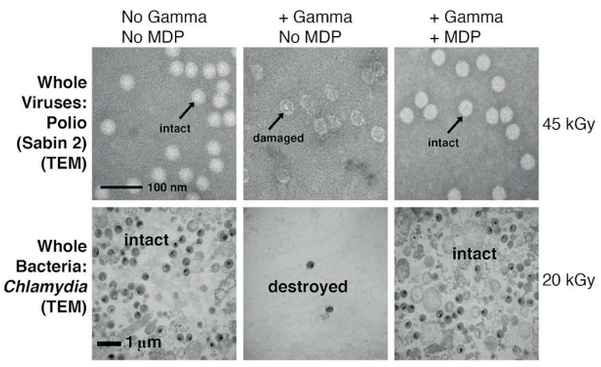


**Figure 2:** *Radioprotection by the rationally designed Mn antioxidant manganese–decapeptide–phosphate (MDP). MDP: 3 mmol/L decapeptide [DEHGTAVMLK], 25 mmol/L phosphate buffer (pH 7.4), and 1 mmol/L MnCl2, added in that order. The previously published material reused without changes; representative Chlamydia transmission electron microscopy (TEM), Uniformed Services University of the Health Sciences (USUHS)). Irradiations: $^{60}$Co (kGy) (the figure is adapted from [10])*

**Рисунок 2** – *Защита от воздействия радиации посредством искусственно созданного антиоксиданта марганца – декапетид фосфат марганца (ДФМ). ДФМ: 3 ммоль/л ддекапептид [DEHGTAVMLK], 25 ммоль/л фосфатного буфера (pH 7,4), и 1 ммоль/л $MnCl_2$, смешаны именно в таком порядке. Повторно использованный ранее опубликованный материал без изменений; образец хламидии, рассмотренный через просвечивающий электронный микроскоп(TEM), Военно-медицинский университет США (USUHS)). Излучения: $^{60}$Co (кГр) (рисунок подготовлен по [10])*

(H-ARS) in mice exposed to 9.5 Gy. MDP pretreatment improved hematopoietic recovery, suppressed radiation-induced erythropoietin and thrombopoietin levels in the serum, and attenuated radiation-induced splenomegaly and hemorrhage in the brain. Moreover, MDP also protected bone marrow against radiation-induced injury, preserving bone marrow cellularity and preventing adipogenesis, compared to untreated controls where bone marrow was largely occupied by fat cells by the end of the study. These results support a possible role of MDP in late mitigation of radiation-induced anemia, a major contributor to mortality after irradiation [29].

In the context of enhancing proteostasis, it will be interesting to consider the substitution of the levorotatory (L) decapeptide component of MDP with the dextrorotatory (D) isomer to harness a fundamental characteristic of all organisms: enzymes cannot degrade D-peptides (nor D-amino acids), but D-peptides retain the same chemical properties as the L-forms, and with indistinguishable ROS-scavenging capacities. D-MDP is thus expected to provide a metabolically more durable form of in vivo proteome protection than L-MDP [29].

**Scorpions.** As mentioned in the part Introduction the only creatures that survived detonations in nuclear weapons testing (French, U.S.) near the epicenter of the explosion ("ground-zero") were scorpions (genus *Androctonus*). Experimental irradiation trials with cobalt-60 in three species of *Androctonus* demonstrated radioresistance, with an $LD_{50}$ of 400–820 grays (Gy) over a period of 30 days, which is much higher than that for many other animals (640 Gy for adult *Drosophila*, 15 Gy for tortoise, 9 Gy for mice a dose of 40 Gy is sufficient to cause instant death in humans and a dose of 2–6 Gy may cause serious blood and digestive problems. (The $LD_{50}$ in humans according to other sources is 3.5–4 Gy). Irradiation of *A. mauritanicus* at a dose of 100–200 Gy causes the reversible arrest of gonad cell mitosis, this arrest becoming irreversible at higher doses. There may be multiple reasons for this exceptional resistance. DNA is highly sensitive to irradiation, but mitosis is rare in scorpion tissues other than during molts and other than in the gonads; scorpions have high circulating taurine (a radioprotective amino acid) concentrations that do not increase following irradiation, low levels of metabolic exchange, low levels of oxygen consumption, and hemocyanin, which has antioxidant enzymatic properties, neutralizing the effects of the radiolysis of water. Desert scorpions from arid areas (*Buthidae*) seem to be the most resistant [32, 33].

It has been shown that hemocyanin plays a role in the radioresistance ot the scorpions [34].

This blue pigment of hemolymph is undoubtedly an important factor in radioresistance because of its copper content and oxyphoric properties, and of its catalytic activity. This molecule possesses a triple antioxidant effect, having enzymatic activities for catalase, peroxidase, and superoxide dismutase [35, 36].

It should be noted that in contrast to hemoglobin the enormous molecules of

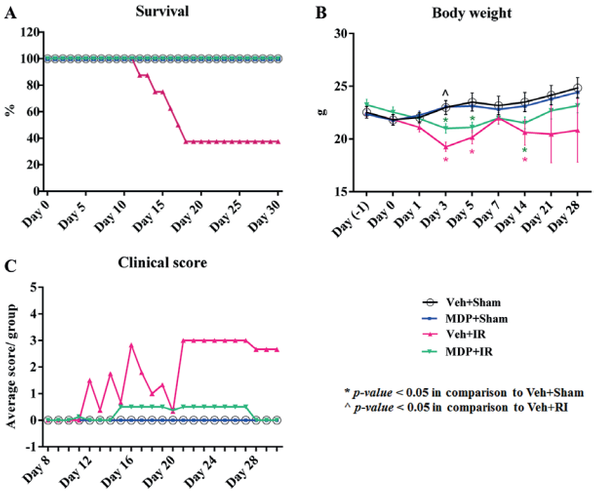


**Figure 3:** *MDP confers radioprotection in vivo and results in improved clinical scores in animals post-irradiation. (A) 100% 30-day survival in MDP-treated irradiated mice. (B) Reduced body weight loss in MDP-treated irradiated mice. (C) Lower average clinical scores in MDP-treated irradiated mice. All the animals were monitored daily for any clinical signs of morbidity or mortality associated with IR exposure and scored accordingly. IR exposure dose was 9.5 Gy. *p < 0.05 vs. Veh+Sham; ^p < 0.05 vs. Veh+IR. Veh, vehicle (the figure is adapted from [29])*

**Рисунок 3** – *ДФМ позволяет получить защиту от радиации in vivo, а также улучшает клинические показатели животных, подвергшихся облучению. А – 100 % 30-дневная выживаемость у животных, которые подверглись воздействию радиации и прошли курс лечения ДФМ. В – Меньшая потеря веса у мышей, которые подверглись воздействию радиации и прошли курс лечения ДФМ. С – Более низкие клинические показатели у мышей, которые подверглись воздействию радиации и прошли курс лечения ДФМ. Состояние всех животных ежедневно контролировали на предмет наличия клинических признаков болезни или летального исхода вследствие воздействия радиоактивного излучения. По результатам проверок выставлялись баллы. Доза радиации, которую получали животные составляла 9,5 Гр. *p <0.05 vs. Veh+Sham; ^p<0,05 vs. Veh+IR. Veh, транспортное средство (рисунок подготовлен по [29])*

hemocyanin are freely circulating in the hemolymph and are not found in any of the cells. These characteristics, found in crude or purified hemocyanin and in its heavy dissociated products (i.e. dodecamers and hexamers) showed that hemocyanin may neutralize the effects of irradiation by disproportionation of the toxic $H_2O_2$ product. The finding that catalase is a component of this complex oxyphoric metalloprotein is an interesting discovery that warrants further study since catalase activity is considered essential to cell protection against all types of irradiation. However, the situation about the scorpion radioresistance is much dimmer as the author of this article expected. Strangely enough the research data are extremely difficult to find. They are simply inaccessible. From the rare amount of data which is accessible we will present PrintScrn figures which are mainly in French. The author apologizes for any inconvenience. As an example of the above-mentioned status, we are providing the following example:

*On April 3, 2023, author M. Allen published a popular article "Résistance aux radiations des scorpions: une explication scientifique" ("Radiation resistance of scorpions: a scientific explanation") which was available on the web until the author asked for details. After that the link disappeared. At the end of the article the author published three references ("Références et lectures complémentaires"):*

*1. Gantenbein B, Fet V, Gromov AV. Scorpions du monde. les éditeurs Pensoft; 2013.*

*2. Khan SA, Jabeen S, Khan SA, et al. Résistance aux radiations chez les scorpions : mécanismes et applications. Mutat Res. 2016;770(Pt B):236-243. doi:10.1016/j.mrfmmm.2015.05.009*

*3. Moustafa IM, Foster RA. Résistance aux radiations chez les scorpions. J Arachnol. 2014;42(3):226-232. doi:10.1636/P13-16.1*

*By careful search one concludes that all three references are "false".*

Scorpion hemolymph contains variable amounts of cells (16000 +/- 7900 cells/µl), three to four different cell types were described [37].

In the historical paper "Modifications comparées des éléments figurés de l'hémolymphe du Scorpion saharien *Androctonus australis* (L.) Hector C.L. Koch soumis soit à des agressions d'ambiance soit à une irradiation expérimentale"[4] published in 1967 the authors analyzed the hemolymph of scorpions after irradiation. They introduced a new type of cell "hémocytes annelés" (anulocytes) (shown in *Figure 4*).

These cells are present under "normal" conditions in the hemolymph and their content is less than 2%. Their number increases after trauma, chemical, thermal injury (up to 16%) and reaches more than 50% after an irradiation (*Figure 5*).

The "kinetics" of the percentage of the anulocytes 1, 2 and 3 days respectively after irradiation (500, 750 and 1000 Gy, respectively) is shown in *Figure 6* as a histogram.

[4] Modifications comparées des éléments figurés de l'hémolymphe du Scorpion saharien *Androctonus australis* (L.). URL: https://www.biodiversitylibrary.org/part/267677 (date: 10.09.2024).

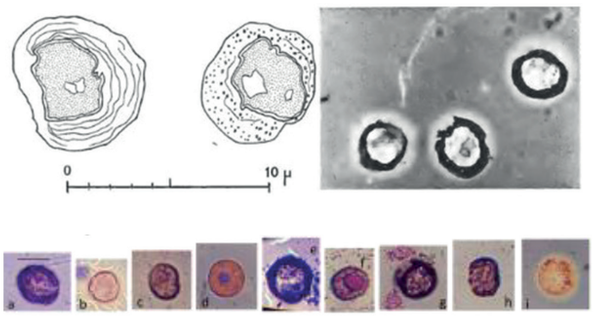


**Figure 4:** *Anulocytes ("hémocytes annelés") (the figure is adapted by author from the web-page URL: https://bsam.biopharm.dz/public/uploads/posters/poster-11.pdf; date: 10.09.2024)*
**Рисунок 4** – *Сфероциты ("hémocytes annelés") (рисунок подготовлен автором по материалам сайта: URL: https://bsam.biopharm.dz/public/uploads/posters/poster-11.pdf; дата обращения: 10.09.2024)*

Here, the anulocytes are cells which appear in the scorpion's hemolymph after irradiation and are "probably" responsible for the radiation resistance. In the year 2024, almost 60 years after the "anulocyte paper" a poster[5]. "La cellule immune de la radio-résistance: de l'analyse morpho-fonctionnelle aux perspectives pharmaceutiques" ("The immune cell of radio-resistance: from the morpho-functional analysis to pharmaceutical perspectives")[6], appeared. The authors without any doubt claim that the anulocytes are responsible for the radioresistance of scorpions. In the conclusion the authors claim: "The cytological belt of the anulocytes is the main actor of the radio-resistance and survival to extreme physical attacks identified in the (scorpion's) immune system. Further analyses of large highly basophilous granulations resulting from the fragmentation of the ringed formation (of the anulocytes) are open for the development of pharmaceutical products of radiation protection". We add that careful biochemical and molecular-biological analysis of the whole process can bring not only new radioprotectors but new deep discoveries in the field of biology.

| Traitement expérimental | Pourcentage d'Hémocytes observés (m ± δ et Sm). | | | |
|---|---|---|---|---|
| | Hémocytes hyalins 1er et 2e stade | Hémocytes granulo-acidophiles | Cellules sphéruleuses | Hémocytes annelés |
| A — Scorpions témoins. n = 9 | 78,89 ± 3,5 Sm = 1,2 | 16,78 ± 2,5 Sm = 0,80 | 2,66 ± 0,8 Sm = 0,20 | 1,44 ± 1 Sm = 0,30 |
| B — Scorpions en élevage sévère (> 4 mois). n = 7 | 42,57 ± 5,5 Sm = 2,2 | 25 ± 8,7 Sm = 3,60 | 27,86 ± 2,2 Sm = 0,90 | 8,28 ± 3,7 Sm = 1,50 |
| C — Scorpions intoxiqués (H.C.H.). n = 5 | 12,8 ± 1,6 Sm = 0,80 | 45,2 ± 4,6 Sm = 2,3 | 30,2 ± 3,8 Sm = 1,90 | 13,8 ± 2,7 Sm = 1,3 |
| D — Scorpions « alternances thermiques ». n = 5 | 10,05 ± 1,3 Sm = 0,60 | 37,20 ± 5,3 Sm = 2,6 | 34,2 ± 4,9 Sm = 2,4 | 16,4 ± 2,0 Sm = 1 |
| E — Scorpions irradiés : 1° 100.000 r. n = 3 | 5,6 | 28 | 9 | 57,3 |
| 2° 75.000 r. J + 1 n = 3 | 3 | 21,7 | 22,3 | 53 |
| J + 2 n = 4 | 3,25 | 27,7 | 13,5 | 55,5 |
| J + 3 n = 4 | 7 | 12 | 57 | 21,5 |
| 3° 50.000 r. J + 1 n = 5 | 5,8 ± 1,3 Sm = 0,6 | 32,4 ± 4,4 Sm = 2,2 | 18,6 ± 9,4 Sm = 4,7 | 53,6 ± 5,1 Sm = 2,5 |
| J + 2 n = 5 | 40,8 ± 1,9 Sm = 0,9 | 30,4 ± 2,07 Sm = 1,30 | 8,4 ± 1,14 Sm = 0,5 | 20,4 ± 1,9 Sm = 0,9 |
| J + 3 n = 5 | 22,2 ± 2,8 Sm ± 1,4 | 56,6 ± 2,4 Sm = 1,2 | 3 ± 1 Sm = 0,5 | 18,2 ± 1,3 Sm = 0,6 |

**Figure 5:** *Anulocytes in the scorpion's hemolymph after different types of injury (right column). 100 r = 1 Gy, J – day (the figure is adapted by author from the web-page URL: https://www.biodiversitylibrary.org/part/267677; date: 10.09.2024)*
**Рисунок 5** – *Сфероциты в гемолимфе скорпиона после получения им различных травм (правый столбик). 100 рад = 1 грей, J – сутки (рисунок подготовлен автором по материалам сайта: URL: https://www.biodiversitylibrary.org/part/267677; дата обращения: 10.09.2024)*

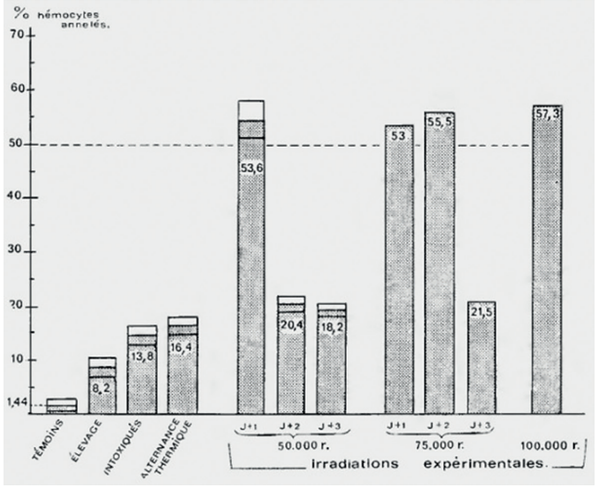


**Figure 6:** *Histogram of the "kinetics" of anulocyte percentage after irradiation (100 r = 1 Gy, J – day) (the figure is adapted by author from the web-page URL: https://www.biodiversitylibrary.org/part/267677; date: 10.09.2024)*
**Рисунок 6** – *Сводная таблица динамики изменения процентного соотношения сфероцитов после облучения (100 рад = грей, J – сутки) (рисунок подготовлен автором по материалам сайта: URL: https://www.biodiversitylibrary.org/part/267677; дата обращения: 10.09.2024)*

[5] Modifications comparées des éléments figurés de l'hémolymphe du Scorpion saharien Androctonus australis (L.). URL: https://www.biodiversitylibrary.org/part/267677 (date: 10.09.2024).

[6] Kerboua KE, Lasla S, Kaddouri FZ. La cellule immune de la radio-résistance: De l'analyse morpho-fonctionnelle aux perspectives pharmaceutiques. URL: https://bsam.biopharm.dz/public/uploads/posters/poster-11.pdf (date: 30.08.2024).

**Radioprotectors.** In their paper [38] the authors suggested the classification of radioprotective agents as shown in the *Figure 7*.

*Asterisks* indicate agents approved or under considerations for clinical use as follows: Amifostine (Ethyol) is specifically approved by FDA as a radioprotector that prevents cumulative normal tissues toxicity associated with cancer treatments and offers significant reduction of radiation-induced xerostomia in head and neck radiotherapy patients. Genistein (BIO300) has currently an investigational new drug (IND) status as radioprotector of normal tissues to prevent acute radiation syndromes. While FDA has approved Neupogen (filgrastim), Neulasta (pegfilgrastim) and Leukine (sargramostim) to ameliorate neutropenia induced by cancer treatment, these compounds are currently under investigation as radiation countermeasure agents. Palifermin (Kepivance) is an FDA-approved recombinant derivative of human keratinocyte growth factor (KGF) that is used to treat oral mucositis in patients undergoing hematopoietic stem cell transplantation. Recombinant salmonella flagellin CBLB502 (Entolimod) is FDA approved as off-label drug that can be used during nuclear or radiological accidents to protect against acute radiation syndromes. Prussian *blue* (Radiogardase) and potassium iodide (KI) are FDA-approved decorporating agents to increase the rate of elimination of radionuclides in internal contamination[7] [38].

Here the authors describe general therapeutic approaches to develop novel radioprotective agents. Radioprotectors should prevent/suppress the formation of radiation-induced free radicals (most of them are produced during radiolysis with water), thereby inhibiting their reactions with biomolecules, reducing the incidence of DNA strand breaks, and preventing the occurrence of cellular malfunction. Since free radicals are short-lived (approximately 10–10 s) and interact rapidly with biomolecules, it is necessary that radioprotectors are present in sufficient concentration in the cellular milieu, at the time of radiation exposure. Molecules or compounds which increase the activity or expression of antioxidant enzymes are also considered radioprotectors. Many antioxidants have the potential to act as radioprotectors; however, not all antioxidants offer radioprotection, and this paradox may be explained by the relative activity of a compound when reacting with radiation-induced reactive species compared with those generated under $H_2O_2$ induced oxidative stress. Conventional antioxidants may not be able to scavenge this less reactive secondary species because either they do not accumulate in proximity to the secondary radicals, or they may not have enough kinetic reactivity to scavenge them effectively. Thiols (e.g., amifostine), hydrophilic antioxidants (e.g., GSH), and newly developed cyclic nitroxides have adequate reactivity to effectively scavenge •OH and secondary radicals as well. Molecules or events that play a role late in signaling and IR-induced apoptotic pathways may act as potential targets for post-irradiation interventions (*Figure 8*).

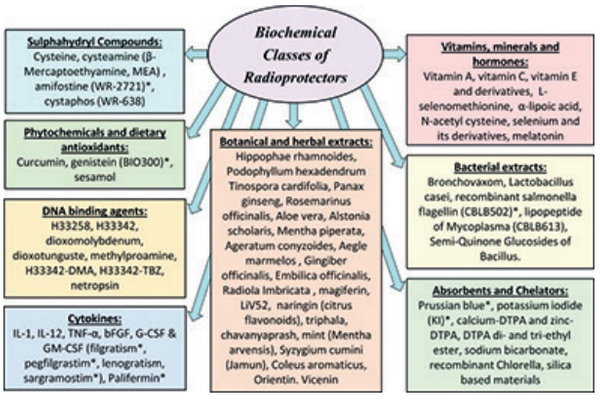


**Figure 7:** *Schematic representation of various classes of radioprotectors citing most studied compounds (the figure is adapted from [38])*

**Рисунок 7** – *Схематическая классификации различных средств защиты от радиации со ссылками на наиболее изученные компоненты (рисунок подготовлен по [38])*

i) ATM/ATR is activated by DNA damage and DNA replication stress; however, they often work together to signal DNA damage and trigger apoptotic cell death by upregulating proapoptotic proteins such as apoptotic protease-activating factor-1 (Apaf-1), phorbol-12-my-ristate-13-acetate-induced protein 1 (Noxa), and Bcl2-associated X (Bax) after IR.

ii) Pifithrin (PFT)-μ (2-phenylethynesulfonamide) directly inhibits p53 binding to mitochondria as well as inactivates the antiapoptotic proteins Bcl-xL and Bcl-2 on the mitochondrial surface, thereby suppressing subsequent release of cytochrome c and apoptosis, whereas PFT-μ reversibly inhibits transcriptionally mediated p53-dependent apoptosis.

iii) Signal transducer and activator of transcription 3 (STAT3) can be activated by various growth factors and protects against IR

[7] The interested reader can find the list of current (FDA approved and not approved) radioprotectors at: Curated database of radioprotectors. URL: https://radioprotectors.org/home (date: 30.08.2024) and in a more recent publication [39].

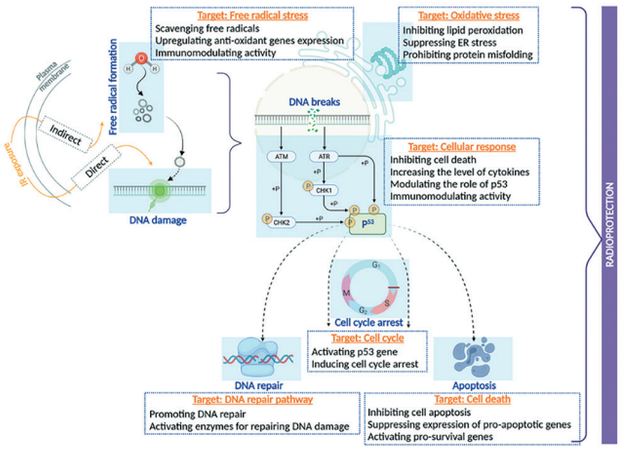


**Figure 8:** *General therapeutic approaches to develop novel radioprotective agents. Ionic radiation, directly or indirectly, causes damage to macromolecules such as DNA, lipids, and proteins. As a result, oxidative stress is generated, which either triggers DNA damage repair or induces p53-mediated cell disorders, such as cell cycle arrest and cell apoptosis. When the damage exceeds the cell's ability to repair itself, the cell appears to follow the death program. The protective activities of potential radioprotectors should target such phases/mechanisms with the aim to shield the normal cells from harmful insults of irradiation (the figure is adapted from [39])*

**Рисунок 8** – *Общие терапевтические подходы к разработке инновационных средств радиационной защиты. Ионизирующее излучение прямо или косвенно повреждает макромолекулы, такие как ДНК, липиды и белки. В результате происходит окислительный стресс, который либо запускает процесс восстановления ДНК, либо вызывает p53-опосредованные клеточные нарушения, например, остановку клеточного цикла или утрату клеток. Если повреждение клетки настолько сильное, что она не может регенерироваться, запускается процесс отмирания клетки. Свойства потенциально новых средств защиты от радиации должны позволять им отслеживать указанные процессы в клетках с целью защиты здоровых клеток от губительного воздействия радиоактивного излучения (рисунок подготовлен по [39])*

damage. The protection mediated by STAT3 is attributed to its genomic actions as a transcription factor (such as upregulating genes that are antioxidative, antiapoptotic, and proangiogenic, but suppressing anti-inflammatory and antifibrotic genes) and other nongenomic roles targeting mitochondrial function andautophagy.

iv) Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a well-characterized ubiquitous master transcription factor, whose activity is tightly controlled by cytoplasmic association along with its redox-sensitive transcriptional inhibitor Kelch-like ECH-associated protein 1 (Keap1). A well-known mechanism of activation of Nrf2 signaling protects cells against radiation-induced oxidative stress and also maintains cellular reduction-oxidation homeostasis. Upon oxidative stress, Nrf2 dissociates from Keap1 and translocates into the nucleus to activate a series of antioxidant response elements, such as GPx, SOD, CAT, and oxygenase-1 (HO-1), increasing total cellular antioxidant capacity (TAC), accompanied by suppressed expression of inflammatory-related genes, avoiding oxidative stress and excessive inflammatory response, which is particularly important in radioprotection.

v) Heat-shock proteins (HSPs), molecular chaperones, are induced in cells during stress conditions. Importantly, HSPs are cytoprotective and can mediate cell and tissue repair after IR-induced deleterious effects. Higher cytosolic levels of HSPs have been shown to induce radioprotective effects by interfering with apoptotic pathways.

vi) Peroxisome proliferator-activated receptor-γ (PPAR-γ), ligand-activated transcription factors, is a part of the nuclear hormone receptor family. It suppresses IR induced survival signals and DNA damage responses and enhances IR-induced apoptosis signaling in human cells.

In the following text we will include the most important (in our opinion) groups of radioprotective agents:

*Thiol-Containing Molecules*

In the search for an effective radioprotective agent, the Walter Reed Army Research Institute (USA) screened approximately 4500 compounds from the late 1950s. Cysteine was the first agent to confer radiation protection in mice after total body irradiation (TBI) in 1949. Later, various synthetic compounds with the aminothiol group were developed and proved to be highly effective in preclinical models [40].

Among them, the most effective was WR-2721 or amifostine, a prodrug activated by alkaline phosphatase to an active sulfhydryl compound WR-1065, and at this moment, it is the *only cytoprotective agent specifically approved by the FDA* as a radioprotector. The efficacy of amifostine is attributed to the free radical scavenging, along with DNA protection and repair, all of which are coupled with the initial induction of cellular hypoxia. At the cellular level, amifostine has significant effects on cell cycle progression and has antimutagenic and anticarcinogenic properties [41].

In fact, amifostine indirectly induces the expression of proteins involved in DNA repair and triggers antiapoptotic pathways [42] and expression of antioxidant enzymes. Some authors have also proposed that it may enhance protective effects by increasing nuclear accumulation and inducing transcription factors related to p53 expression [43].

It should be noted, that WR-1065 accumulates more rapidly in normal tissues than in malignant cells, because the concentration of membrane-bound alkaline phosphatase tends to be higher on normal cells. Moreover, the lower vascular supply and the acidic environment of many tumors reduce the rate of dephosphorylation of WR-2721 and its uptake. It thus seems to be a unique molecule that might potentiate radiotherapy (RT) efficacy in two opposite ways at the same time [44].

The US FDA has approved the use of amifostine in pre enting/reducing xerostomia (dry mouth) in head and neck cancer patients undergoing RT [41]. It has also been assayed in clinical trials to reduce mucositis, dysphagia, dermatitis, and pneumonitis during radiotherapy of head and neck cancers [45].

However, like other radioprotective aminothiols, the safety profile of amifostine has considerable limitations. Although the side effects such as nausea, vomiting, and hypotension are not life threatening, they can further aggravate the gastrointestinal syndrome. As it will be exposed latter, amifostine has been assessed in combination with other FDA-approved drugs (growth factors, cytokines, vitamin E, metformin, etc,) looking for additive or synergistic radioprotective effects to prevent Acute Radiation Syndrome (ARS). Nevertheless, in most of cases none of these novel strategies completely counteracts amifostine's toxic side effects at the doses needed to be efficacious as radioprotector [44]. The mechanism of amifostine protection is shown in *Figure 9*.

*Cyclic Nitroxides (NRs)*

NRs, like Tempol, JP4-039, XJB-5-131, TK649.030, or JRS527.084, are stable free

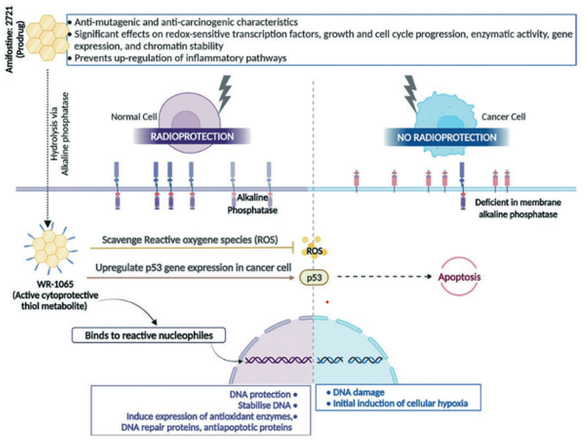


**Figure 9:** *Mechanisms of radioprotection by amifostine (the figure is adapted from [39])*

**Рисунок 9** – *Схема действия Амифостина в качестве средства защиты от радиации (рисунок подготовлен по [39])*

radicals containing a nitroxylgroup (-NO.) with an unpaired electron. The action of nitroxides to metabolize ROS is ascribed primarily to cyclic one or two-electron transfer among three oxidation states: the oxoammonium cation, the nitroxide, and the hydroxylamine. Nitroxides undergo a very rapid, one-electron reaction to the corresponding hydroxylamine, which has antioxidant activity. In addition to their ability to neutralize free radicals, NR can easily diffuse through the cell membranes (and have SOD-like activity), prevent Fenton and Haber-Weiss reactions by oxidation of transition metal ions to a higher oxidation state, confer catalase-like activity on heme proteins, and inhibit lipid peroxidation. NRs are able to mitigate TBI-induced hematopoietic syndrome, when are administered before or as late as 72 h after radiation exposition [46].

*Phytochemicals*

Over the last decades, plant-derived polyphenols have been screened for their potential ability to confer radioprotection. The free radical scavenger potential and antioxidant activity of polyphenols depends, in part, on their ability to delocalize electron distribution, resulting in a more stable phenoxy group. Moreover, intercalation in DNA double helices induces stabilization and condensation of DNA structures making them less susceptible to free radicals' attack, reducing genotoxic damage induced by IR [47].

They are capable of trapping and neutralizing lipoperoxide radicals and can chelate metal ions (i.e., iron and copper), which play an important role in the initiation of oxidative stress reactions [48, 49].

Polyphenols radioprotective efficacy is mainly attributed to its antioxidant and anti-inflammatory properties, to their capacity to detoxify free radicals, eliciting DNA repair pathways, stimulating the recovery of hematopoietic and immune functions [48, 49]. In addition to the biochemical scavenger theory, there is also evidence of another potential mechanism by which polyphenols activate Nrf2, exhibiting cellular protection against excessive ROS production, oxidative stress, and inflammation as well. Since the chemical features of these natural organic compounds are analogous to phenolic substances, their antioxidant and antiradical/scavenging radical (such as $H_2O_2$, 2,2-diphenyl-1-picrylhydrazyl) properties may be correlated positively with the number of hydroxyl groups bonded to the aromatic ring. They can exert their protection against environmental stimuli with the aid of remarkable antioxidant power by balancing the organic oxidoreductase enzyme system, regulating antioxidant-responsive signaling pathways, and restoring mitochondrial function.

*Oligoelements*

Many antioxidant/defense enzymes, like SOD and metalloproteins, require trace elements as cofactors. The main oligoelements showing protective effects against radiation-induced DNA damage are zinc (Zn), manganese (Mn), and selenium (Se) [50].

The principle how these elements are involved in radioprotection is shown in the *Figure 10*.

*Superoxide Dismutase (SOD) Mimetics and Nanoparticles*

SODs are a group of metalloenzymes that catalyze the dismutation of superoxide radicals ($O_2^{\bullet -}$) to $H_2O_2$ and $O_2$, thus are first line of defense to prevent IR damages. In the event of a radio-nuclear attack or nuclear accident, the skin damage used to be severe. A synthetic SOD/CAT mimetic (EUK-207) administered 48 h after irradiation significatively mitigated radiation dermatitis, suppressed indicators of tissue oxidative stress, and enhanced wound healing [51] Mn porphyrin-based SOD mimics (MnPs) are reactive with superoxide and with other reactive oxygen, nitrogen, and sulfur species. MnPs have CAT and GPx-like activities and peroxynitrite-reducing activity [52].

MnPs administered before and continued after radiation exposure protect from γ-ray, X-ray, and proton beam irradiation damages in different animal models, and a few studies indicate that beginning treatment with MnPs after radiation exposure is also effective. In normal tissues, MnPs treatment reduces oxidative stress, NF-κB, and TGF-β signaling pathways and activates Nrf2-dependent pathways. Strange enough MnPs administration in combination with cancer therapy results in more oxidative stress in cancer cells, which leads to the reduction of NF-κB and HIF-1α and their downstream signaling pathways. These changes are associated with increasing apoptosis and reducing overall cancer growth [53].

*Hormonal and Hormonal Mimetic Radioprotectors*

Several hormones are known to exhibit radioprotective characteristics, and melatonin, N-acetyl-5-methoxytryptamine, one of the "most protective", is one of them. It is the main secretory product of the pineal gland. Its radioprotective properties are outlined in *Figure 11*.

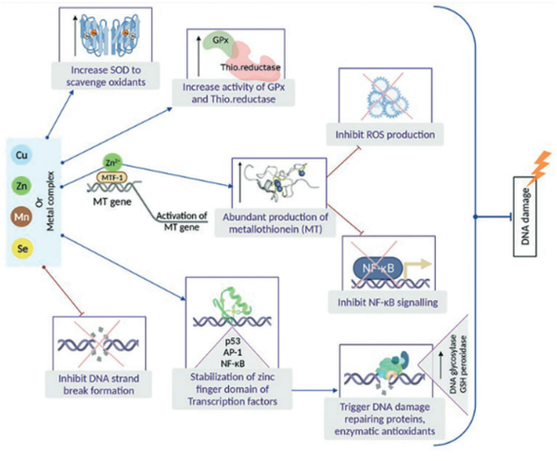


**Figure 10:** *Radioprotection by oligoelements (the figure is adapted from [39])*
**Рисунок 10** – *Защита от радиации посредством олигоэлементов (рисунок подготовлен по [39])*

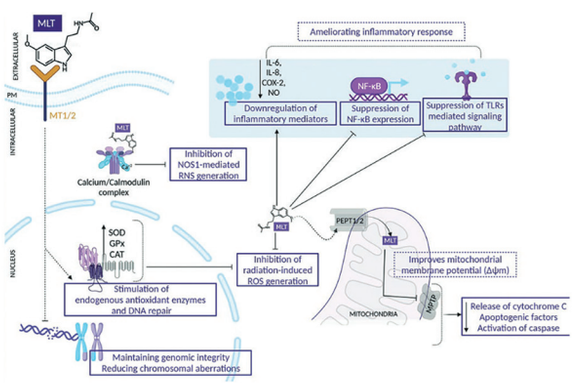


**Figure 11:** *Melatonin and its radioprotective and radiomitigative effects (the figure is adapted from [39])*
**Рисунок 11** – *Мелатонин и его свойства, позволяющие уменьшить негативные последствия от воздействия радиации (рисунок подготовлен по [39])*

| MOPP Level: | Available for Immediate Donning | Available | When used: |
|---|---|---|---|
| MOPP 0 | • IPE<br>• Field Gear | • IPE issued and serviceable<br>• Protective mask filter/hood installed | • CB threat<br>• Preattack |
| *MOPP0 is used during periods of increased alert when the enemy has CB employment capability but there is no indication of use in the immediate future.* | | | |
| **MOPP Level:** | **Worn:** | **Carried:** | **When used:** |
| MOPP 1 | • Overgarment<br>• Field gear | • Footwear covers<br>• Mask<br>• Gloves | • CB threat<br>• Preattack |
| *MOPP1 is generally used when a chemical, and/or biological attack in theater is possible.* | | | |
| MOPP 2 | • Overgarment<br>• Field gear<br>• Footwear covers | • Mask<br>• Gloves | • CB threat<br>• Preattack |
| *MOPP2 is generally used when a chemical, and/or biological attack in theater is likely.* | | | |
| MOPP 3 | • Overgarment<br>• Mask and hood<br>• Field gear<br>• Overboots | • Gloves | • CB threat<br>• Postattack |
| *MOPP3 is generally used in areas with no contact hazard or operationally significant percutaneous vapor hazard.* | | | |
| MOPP 4 | • Overgarment<br>• Mask and hood<br>• Field Gear<br>• Footwear covers<br>• Gloves | | • CB threat<br>• During-attack<br>• During and postattack |
| *MOPP4 is used when the highest degree of CB protection is required, or when CB agents are present; but the actual hazard has not been determined.* | | | |

**Figure 12:** *The five levels of Mission Oriented Protective Posture (the figure is adapted from Chemical, Biological, Radiological, Nuclear. URL: https://web.archive.org/web/20190628220046/https://www.armystudyguide.com/content/army_board_study_guide_topics/cbrn/cbrn-study-guide.shtml; date: 25.08.2024)*

**Рисунок 12** – *Пять уровней мер защиты от ОМП с учетом характера выполняемых задач (рисунок подготовлен по публикации Chemical, Biological, Radiological, Nuclear.*
*URL: https://web.archive.org/web/20190628220046/https://www.armystudyguide.com/content/army_board_study_guide_topics/cbrn/cbrn-study-guide.shtml; date: 25.08.2024)*

**U.S. Military Guidelines.** At the site of the U.S. Department of Health & Human Services Radiation Emergency Medical Management some "guidelines" for the military are present: https://web.archive.org/web/20190628220040/https://www.remm.nlm.gov/MOPP.htm

Mission Oriented Protective Posture (MOPP) Gear: Military PPE

- MOPP Gear: personal protective equipment (PPE) ensemble worn by troops in CBRN-contaminated environments
  - ◦ Protects against:
    - ▪ Chemical agents;
    - ▪ Biological agents;
    - ▪ Radioactive material: external contamination and internal contamination.
  - ◦ Cannot protect against exposure to high energy, highly penetrating ionizing radiation:
    - ▪ Neutrons and gamma radiation pass through all forms of PPE.
  - ◦ Reduces spread of contamination.
  - ◦ Not intended for hot zone entry.

It should be noted that a crucial warning is included: "Cannot protect against exposure to high energy, highly penetrating ionizing radiation. Neutrons and gamma radiation pass through all forms of PPE". On the site[8] the MOPP levels are more specified (*Figure 12*).

**Conclusion**

In the present paper we have described two "highly" radioresistant organisms *Deinococcus radiodurans* and the scorpion. This feature is widely recognized and has been analyzed from different points. For future development it is important to recognize the "new" paradigm of radioresistance – a new bio-concept, expressed as "The primacy of Proteome over Genome", or "The primacy of biological function over information". As mentioned above, the preservation of vital functions of proteins is fundamental for transmission of information—however, information is effectively useful only after it has been transmitted and received. We believe that this research will bring new effective radioprotective agents. Some of them (described in this paper such as MDP: 3 mmol/L decapeptide [DEHGTAVMLK], 25 mmol/L phosphate buffer (pH 7.4), and 1 mmol/L $MnCl_2$,) showed a strong radioprotective activity in the lethal irradiated mice. Such kinds of radioprotectants will presumably in the future be used in men too. On the other hand, in our opinion, the scorpion's analysis from the point of view of a multicellular organism (Arthropods) can bring new fundamental discoveries not only in radioprotection but in molecular biology. Here, the hemolymph' anulocytes are presumably the "key" to explain the incredible radioresistance of scorpions. This could further shift our understanding of radioresistance in the nuclear era of mankind. From today's practical point of view, in radiation protection we can recommend the only FDA approved drug Amifostine. We believe that further research will bring new agents with a high radioprotective index.

[8] Chemical, Biological, Radiological, Nuclear. URL: https://web.archive.org/web/20190628220046/https://www.armystudyguide.com/content/army_board_study_guide_topics/cbrn/cbrn-study-guide.shtml (date: 25.08.2024).

***Limitations of the study / Ограничения исследования***

В данном аналитическом обзоре основным ограничением является отсутствие некоторых данных, которые по неизвестным причинам не были опубликованы в официальных источниках – в основном это касается информации об исследованиях по радиационной устойчивости скорпионов / Lack of some data which are for unknown reasons not publicly available – mainly on research into the radiation resistance of scorpions.

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***Acknowledgement / Благодарность***

I would like to thank Dr. M.V. Supotnitskiy for his helpful suggestions and scientific advice / Выражаю благодарность доктору М.В. Супотницкому за полезные советы и научные рекомендации.

***Author' Contribution / Вклад автора***

Elaboration of the concept of the paper; collection, analysis, and systematization of scientific literature; writing and edition of paper / Разработка концепции статьи; сбор, анализ и систематизация научной литературы; написание статьи.

***Author's Statement / Заявление автора***

I am declaring that I prepared the article from sources freely available on the Internet and free available publications, figures, and other possible legal sources. I, as a sole author declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interests / Я заявляю, что подготовил статью из источников, находящихся в свободном доступе в Интернете, а также свободно доступных публикаций, рисунков и других возможных легальных источников. Я, как единственный автор, заявляю, что исследование проводилось при отсутствии каких-либо коммерческих или финансовых отношений, которые могли бы быть истолкованы как потенциальный конфликт интересов.

***Peer review information / Сведения о рецензировании***

The article has been doubleblind peer reviewed by two experts in the respective field. Peer reviews are available from the Editorial Board and from Russian Science Citation Index database / Статья прошла двустороннее анонимное «слепое» рецензирование двумя рецензентами, специалистами в данной области. Рецензии находятся в редакции журнала и в РИНЦе.

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