Protection in nuclear and radiological emergencies: a novel oral countermeasure

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**Abstract:** Exposure to ionizing radiation (IR) in nuclear and radiological accidents can cause great harm to human health, the environment and the economy. The study and development of effective medical countermeasures (MCM) to protect the population is a neglected need that urgently should be addressed in order to implement a response to an emergency. Potentially protective agents against harmful radiation exposure have been investigated for decades, but at this moment no ideal radioprotector is available. Potential countermeasures according to a specific scenario requires considering basic issues e.g., sort of radiation, people directly affected and first responders, range of doses received regardless the exposure or contamination has affected the total body or it is partial.

Ionizing radiation damages are caused by direct ionization of cellular targets and by indirect effects mainly dependent on reactive oxygen species (ROS) formation. The biological effect of radiation exposure relies on dose/time exposition, cell type, inherent tissue sensitivity and modulating intracellular factors. The biological impact of ionizing radiation can be deterministic (in a period range *a posteriori* of the event and due to tissue/organ harm) or stochastic (irregular, e.g. mutation-related pathologies and heritable infections).We tested the radioprotective potential of natural polyphenols (i.e., resveratrol, gallic acid, curcumin, caffeic acid, epigallocatechin gallate, genistein, ...) in mice exposed to a total LD50/30 -irradiation. The combination of pterostilbene (PT, 3,5-dimethoxy-4’-hydroxystilbene, a natural stilbene present in e.g. blue berries) and silibinin (SIL, (2R,3R)-3,5,7-trihydroxy-2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one, a natural flavanone isolated from the *Silybum marianum*) was the most effective, resulting in 100% survival of mice after exposure to a LD50/30 -irradiation. Moreover, the radioprotective effects of PT were higher than those of aminofostine which is, at this moment, one of the few radioprotector approved by the FDA. Treatment post -irradiation with two potential radiomitigators nicotinamide riboside (NR, a vitamin B3 derivative), and/or fibroblast-stimulating lipopeptide 1 (FSL1, a toll-like receptor 2/6 agonist), did not extend survival. However, the combination of PT, SIL, NR and FSL1 achieved a 90% survival one year post -irradiation. The mechanism involves induction of the Nrf2-dependent cellular antioxidant defense, reduction of NF-B signaling, upregulation of the PGC-1/sirtuins 1 and 3 axis and the PARP1-dependent DNA repair, and stimulation of hematopoietic cell recovery. The pathway linking Nrf2, sirtuin 3 and SOD2 is key to radioprotection. Importantly, this combination did not interfere with X-ray mediated killing of different tumor cells *in vivo*. In conclusion, we have found an effective radioprotective formula, combining 2 radioprotective natural polyphenols (PT and SIL) with 2 radiomitigating agents (NR and FSL1). These results were published in the Journal of Advanced Research (Obrador et al. 2022, doi: 10.1016/j.jare.2022.05.005) and are under patent protection (PCT/EP2022/051038).

**Keywords:** nuclear and radiological emergencies; ionizing radiation countermeasures, radioprotectors; radiomitigators; polyphenols; nicotinamide riboside, fibroblast-stimulating lipopeptide 1.