Radioprotectors.org: an open database of known and predicted radioprotectors

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ABSTRACT

The search for radioprotectors is an ambitious goal with many practical applications. Particularly, the improvement of human radioresistance for space is an important task, which comes into view with the recent successes in the space industry. Currently, all radioprotective drugs can be divided into two large groups differing in their effectiveness depending on the type of exposure. The first of these is radioprotectors, highly effective for pulsed, and some types of relatively short exposure to irradiation. The second group consists of long-acting radioprotectors. These drugs are effective for prolonged and fractionated irradiation. They also protect against impulse exposure to ionizing radiation, but to a lesser extent than short-acting radioprotectors. Creating a database on radioprotectors is a necessity dictated by the modern development of science and technology. We have created an open database, Radioprotectors.org, containing an up-to-date list of substances with proven radioprotective properties. All radioprotectors are annotated with relevant chemical and biological information, including transcriptomic data, and can be filtered according to their properties. Additionally, the performed transcriptomics analysis has revealed specific transcriptomic profiles of radioprotectors, which should facilitate the search for potent radioprotectors.

INTRODUCTION

Among the tasks of modern radiobiology [1], searching for the agents with radioprotective action is one of the most important. Such activity can be achieved by using gene therapy for increasing radioresistance by exoge-nous engineered DNA repair and radioprotective constructs, replacing organic molecules with strengthened isoforms, slowing down metabolic activity while maintaining cognitive function or strengthening the regulation of endogenous repair and radioprotective machinery by means of chemical compounds. Only two

radioprotective compounds, amifostine, and palifermin, currently have the US FDA approval for use in radiation therapy. However, several agents have been reported that show therapeutic promise [2]. Creating a database on radioprotectors is a necessity dictated by the modern development of science and technology.

The success in the development of radioprotective agents depends on an understanding of the molecular biology of radiation damage [3]. Increasing the radio-resistance of the different tissues can be achieved with procedures that affect the primary radiochemical reactions, the protective mechanisms of the organism itself, or both.

All radiation modificator agents [4] can be divided into two groups: radiation mitigators (or simply mitigators) and radioprotectors (radioprotective agents). Radiation mitigators are substances which are used after irradiation that can reduce the negative effect of radiation. Radiation mitigators include, for example, substances such as TGF-β receptor inhibitors, protease inhibitors, COX2 inhibitors, and others [5]. Thus, radiation mitigators neutralize the negative consequences of mitotic cell death and DNA damage, reduce the activity of cytokine cascades, reducing the level of vascular damage, tissue hypoxia, and fibrosis [6].

In contrast, radioprotectors are drugs or compositions of drugs that are injected into the body before it is irradiated in order to provide a high protective effect. Radioprotectors are chemical compounds obtained synthetically or extracted from natural products. Their protective effect is manifested by a smaller lesion during the irradiation of radiosensitive tissues and their more rapid post-radiation recovery, which generally leads to a decrease in the severity of radiation injury. The use of radioprotectors after irradiation is usually ineffective [7, 8].

In this paper, we describe a manually curated database Radioprotectors.org containing an up-to-date list of substances with proven radioprotective properties at different levels of structural organization of the organisms.

RESULTS AND DISCUSSION

The motivation behind the creation of the Radioprotectors database was to provide a one-stop resource for researchers interested in quick access to the results of experiments and approved drugs. As a result, a platform for cross-species, cross-study comparison of the effects of these compounds was created. The interface was developed to make it visually appealing and intuitive for rapid, effortless overviews of radio-

protective compounds, with links to original studies and other databases for users seeking further detail. The site was not designed as a mere list of radioprotectors; instead, a comprehensive intervention profile was created for each compound, including its biochemistry and bioactivity, possible or known mechanisms of action, MESH indication, and its current drug status. Figure 1 represents a visual overview of the content, data sources, and user-directed exploration of these within Radioprotectors.

Analysis of experiments related to radioprotective compounds

The database contains summaries of more than 150 radioprotective compounds. Each compound was manually selected from the existing biomedical literature by searching the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed), DrugBank database (https://www.drugbank.ca/), and PubChem database (https://pubchem.ncbi.nlm.nih.gov/) using key-words relevant to pharmacological interventions in radioprotection.

All entries in Radioprotectors have links to original publications, making access to raw data fast and convenient. For any given compound, links to relevant study can be accessed directly from the search results or within each compound profile.

Comparison with existing databases of radioprotectors and radiation mitigators

To date, there is only one database on radioprotectors [9], similar to that presented by the Bioinformatics Database of Radiosensitizers and Radioprotectors by the University of Mumbai. (http://bioph.mu.ac.in/Welcome/). DB includes about 100 compounds, a significant part of which is an extract of various plants, in which, as a rule, it is impossible to identify in its pure form a substance that can have a radioprotective effect. Radioprotectors.org includes more than 150 substances of both synthetic and natural origin and contains detailed information on the mechanism of action and pharmacological properties of the substance. Information on experimentation and efficiency is taken from peer-reviewed scientific journals. All substances have a unique identifier that allows one to quickly find the desired compound in leading chemical databases, including PubChem, ZINC, etc.

Analysis of compounds with radioprotective activity

To date, all radioprotective drugs can be divided into two large groups, differing in their effectiveness depending on the type of exposure. The first of these is

radioprotectors, highly effective for pulsed, and some types of relatively short exposure. These are radio-protectors mainly of short duration. Their protective activity, depending on the properties and methods of application, manifests itself within a few minutes or a maximum by the end of the first hour after administration, but is limited to 30 min-5 hours. In radioprotectors of this group, the highest level of the protective effect is usually observed when they are administered in maximum tolerated doses, which cause changes in the metabolism of radiosensitive cells. The second group consists of long-acting radioprotectors. These drugs are effective for prolonged (prolonged) and fractionated (fractional) irradiation. They also protect against impulse exposure to ionizing radiation, but to a lesser extent than short-acting radioprotectors. The duration of the protective action of radioprotectors of prolonged action can be from one up to several days. The radioprotective effect of these drugs is mainly associated with the mechanisms of increasing the general nonspecific resistance of the organism [10].

Short-acting radioprotectors, depending on the initial protective action mechanisms and chemical structure, are divided into the following groups [11, 12]: reducing agents, which include sulfur-containing compounds (cysteine, cystamine, cystaphos, etc.), antioxidants

(ascorbic acid, vitamin E, tocopherols, etc.); and drugs that cause hypoxia of cells and tissues (indo-lealkylamines, methemoglobin formers, cyanides, azides, nitrites, etc.).

Sustained-release radioprotectors include drugs with anabolic properties (primarily with estrogenic activity), polyanionic polymers (heparin, chondroitin sulfate, and other polysaccharides, nucleic acids, polynucleotides and their derivatives, some vaccines, synthetic polymers).

The following mechanisms of radioprotectors action are possible [13, 14]:

- competition for strong oxidizing agents and free active radicals formed during irradiation of tissues and especially during radiolysis of water (peroxide or hydroperoxide radicals);
- increase in the content of endogenous thiol compounds in tissues;
- the formation of mixed disulfides and their temporary reversible bond;
- formation of temporary reversible bonds with radiosensitive groups of vital enzymes or other protein molecules, which ensures their protection at the time of irradiation;
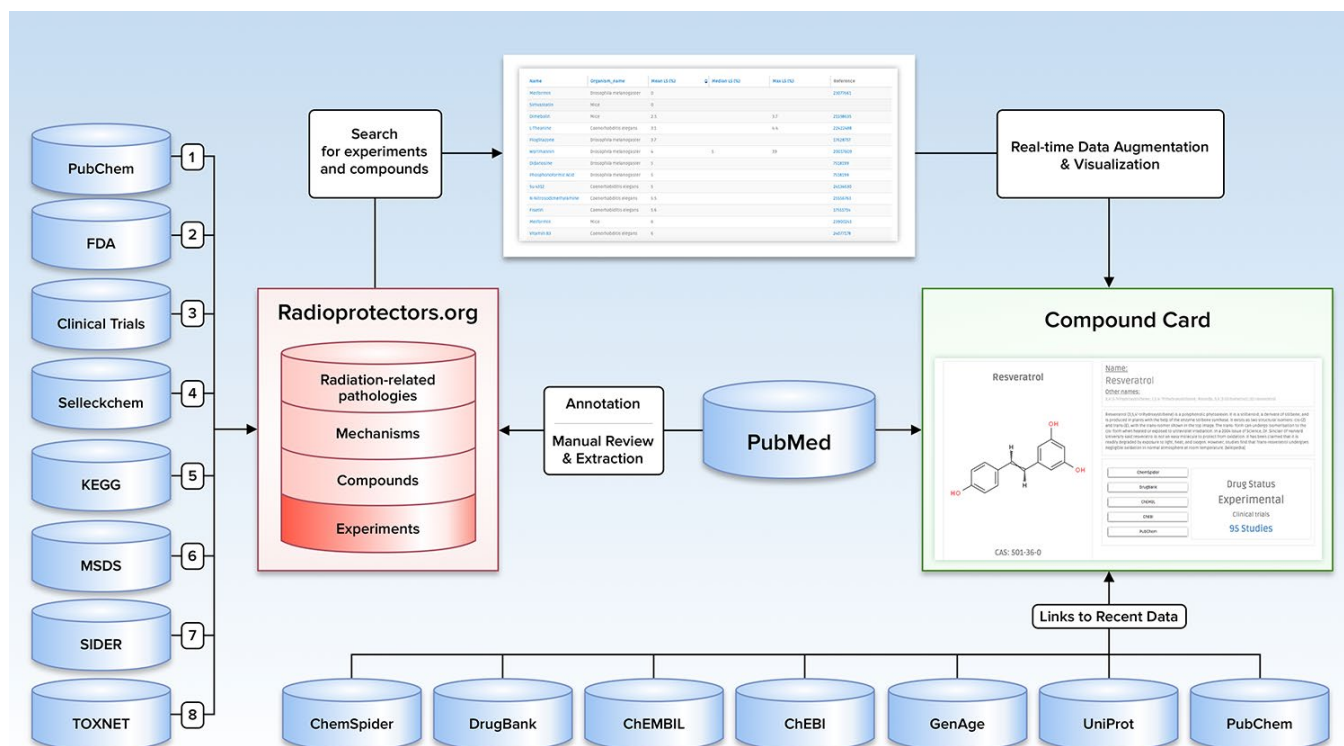

Figure 1. Illustration depicting the content, data sources, and user-directed flow of Radioprotectors.org.

- formation of strong compounds with heavy metals, providing accelerated course of chain oxidation reactions;
- migration of excess energy from the macromolecule to the radioprotector;
- inhibition of oxidation chain reactions;
- absorption of secondary ultraviolet radiation, exciting macromolecules such as nucleic acids;
- increase the stability and mobility of the protective mechanisms of the body, including compounds with the hormetic effect [15–18];
- inhibition of metabolism;
- detoxification or accelerated elimination of toxic products from the irradiated organism.

However, there is no such chemical substance, which would have all the above properties. That is why radioprotectors belong to the most diverse classes of chemical compounds.

Many of these agents are free radical scavengers/ antioxidants. Superoxide dismutase and superoxide dismutase mimetics, nitroxides, and dietary antioxidants are all being investigated. Recently, alternative strategies of drug development have been evolving [19], which focus on targeting the series of cellular insult recognition/repair responses initiated after radiation. These agents, which include cytokines/ growth factors, angiotensin-converting enzyme inhibitors, and apoptotic modulators, show promise of having a significant impact on the mitigation of radiation injury [2].

Antioxidants and free radical scavengers
Ionizing radiation induces damage of cellular structures in two primary ways: direct damage to DNA and generation of free radical-containing reactive molecules. Free radicals are generated through the interactions between ionizing radiation and small oxygen-containing molecules (including water). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the main sources of damage to cell macromolecules. Ionizing radiation leads to the generation of ROS and RNS in the presence of oxygen and nitrogen. ROS include superoxide anion ($O_2\bullet-$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH\bullet$). Reactive forms of nitrogen are nitric oxide ($NO\bullet$) and peroxynitrite ($ONOO-$) [20]. Free radicals that are generated by ionizing radiation can react with DNA, lipid membranes, and proteins causing damage and/or dysfunction to various cellular structures. The cell has mechanisms to mitigate and manage damage from free radicals. Hydroxide ions are reduced by the enzyme glutathione peroxidase and superoxide ions are reduced to hydrogen peroxide by superoxide dismutase. Hydrogen peroxide generated by superoxide dismutase is used by catalase to generate water. Significant damage to cellular structures occurs

when the ionizing radiation-induced generation of radicals out-paces the cell's ability to clear these reactive molecules [13, 21, 22].

Several approaches have been followed in recent decades to scavenge radicals [13, 21]. Sulfhydryl compounds, particularly the aminothiols and phospho-rothioates contain an SH group, make them suitable for free radical scavenging because of their propensity to donate a hydrogen atom for the reduction of radical species [23]. We have included several substances including cysteine, cysteamine, glutathione, AET, amifostine [24]. Currently, amifostine is the only cytoprotective agent that is approved by the US FDA specifically for use as a radioprophylactic. The mechanism underlying amifostine's protective action appears to be multifaceted, involving free radical scavenging, enhanced DNA protection and repair, and induction of hypoxia [25].

Redox homeostasis within a cell is maintained in part by a series of antioxidant enzymes that include glutathione peroxidase, catalase, and superoxide dismutase (SOD). All the SOD isoforms have been reported to have radioprotective potential, reducing acute radiation toxicity through neutralization of radiation-induced ROS and delaying radiation injury through suppression of chronic oxidative stress [26]. SOD mimetics have a metal ion (Cu, Fe, Mn, and Zn) at their active centers, which behave like the metal center of the SOD molecule. Advantages of the SOD-mimetics class of compounds include prolonged half-lives and widened time windows of action compared to native SOD. For example, M40403, manganese (Mn)-containing biscyclohexylpyridine, that has demonstrated equivalent or superior catalytic activity to that of native SOD, has been given FDA approval [27]. Also, this group includes AEOL 10150 [28] and Mn complexes EUK-189 and EUK-207 [29], tempol (4-hydroxy2,2,6,6-tetramethylpiperidine-1-oxyl) [29, 30].

A number of naturally occurring vitamins and dietary antioxidants have been tested for their efficacy as radioprotectors [31]. Both vitamin E and selenium, as well as their combination, have been reported to reduce radiation-induced transformations *in vitro* [32]. Vitamins C and E have been shown to decrease chromosomal damage, mutations and apoptosis in mammalian cells, and vitamin A and N-acetylcysteine have been suggested to be effective against radiation-induced carcinogenesis [33]. *In vivo* studies also report the use of antioxidants as effective radiation protectors. α-Lipoic acid significantly increased the survival rate following lethal total body irradiation in mice, while vitamins A, C, E and β-carotene have been shown to

increase resistance to high doses of radiation, and *in vivo* protection against radiation-induced oxidative stress has been reported for L-selenomethionine and such antioxidants such as vitamins C and E, glutathione, α-lipoic acid, N-acetylcysteine and co-enzyme Q10 [34]. Another naturally occurring antioxidant receiving considerable interest is the hormone melatonin and its analogs, which have been documented to have a radioprotective effect in normal tissues in a number of animal models while, at the same time, exert direct antitumor effects [35].

Cell cycle modulators

Upon the DNA damage induced by ionizing radiation, all eukaryotic cells activate protecting mechanisms associated with cell cycle arrest until the DNA damage is repaired and – in the case of too extensive damage – necrosis or apoptosis [36]. Radioprotectors may affect cell fate acting through both mechanisms: either promoting cell cycle arrest or inhibiting necrosis/ apoptosis.

The apoptosis is largely a p53-dependent process and inhibition of p53-mediated apoptosis by chemicals results in increased radioresistance [37]. This can be achieved by direct inhibitors of p53 activity such as pifithrins [38] or by modulation of other important pro-apoptotic proteins. For instance, kukoamine increases the level of anti-apoptotic mediators (BCL2) and decreases the level of pro-apoptotic mediators (BAX and caspase-3) in a dose-dependent way [39]. Acteoside has been shown to inhibit expression of caspase 3, and thus to decrease apoptosis [40] in human skin fibroblasts. Similarly, atorvastatin down-regulates expression of caspase 3 [41]. Carvacrol is another compound with anti-apoptotic action shown in cultured human peripheral blood lymphocytes but the molecular mechanism of it is not clear [42]. Isofraxidin inhibits apoptosis in a p53-independent way via cytochrome C in addition to caspase 3 [43].

Apart from the down-regulating apoptotic answers, some radioprotective substances lead to cell cycle arrest. Resveratrol is one of the most well-studied examples of this group of compounds. It has effects on cyclin expression and induces S-phase arrest [44].

DNA protectors

The radioprotectors can elicit their action by various mechanisms and DNA protection via decreasing DNA damage is among them. Moreover, the late effects of ionizing radiation are associated with DNA damage that can be visualized by persistent DNA Damage Response (DDR) foci and might be prevented by radioprotectors [45, 46]. Reduction of DNA damage might be reached by suppressing the formation of reactive species,

detoxification of radiation-induced species, target stabilization, and enhancing the repair and recovery processes [22]. The chemical or biochemical consumption of oxygen can lead to hypoxia in cells and tissues. This may be one of the mechanisms by which sulphydryl compounds (RSH), which can undergo an oxidation reaction with molecular oxygen, result in radioprotection. Also, some interest has been drawn to the thiol-induced hypoxia caused by amifostine and cystaphos, which offer selectivity in protecting normal cells vs. tumor cells [47, 48].

Radioprotectors can also interact with cellular targets, like DNA, by forming mixed disulfides and prevent radiation damage by stabilizing the target. Several amino thiol radioprotectors, such as cysteamine and WR 1065, bind to DNA and their DNA binding is coupled with their radioprotective potency [47–50]. Since one of the most important molecular targets damaged by radiation is the genomic DNA of a cell, cells must repair these lessons. Thiols, such as glutathione and adeturon, may be involved in the repair of DNA single-strand breaks. Cells genetically deficient in GSH synthesis or cells in which GSH deficiency is produced by dl- Buthionine-sulfoximine or by hypoxia or misonidazole show a lack of DNA single-strand break repair [51–53].

The cellular defense mechanisms against radiation and chemical stresses elicit an early SOS response to damage and subsequent adaptation. The SOS response is required for eliminating lesions in DNA while the adaptation response is needed for restoring cellular metabolism and return to normal functioning. SOS repair plays a very important role in protecting the key molecular targets, which comprise the activation or synthesis of several proteins, DNA precursor synthesizing enzymes, and DNA precursors [54]. Drugs and chemicals, which stimulate or increase the activity of DNA precursor-synthesizing enzymes, such as ribonucleotide reductase, could function as radio-protectors. The administration of the drug indomethacin prior to radiation exposure to animals (mice and dogs) resulted in higher survival of animals from lethal doses of gamma-radiation [54]. All of these radioprotectors are listed in https://radioprotectors.org/home.

Sunscreening agents

UV radiation has a broad spectrum, ranging from 40 to 400 nm, which is divided into Vacuum UV (40–190 nm), Far UV (190–220 nm), UVC (220–290 nm), UVB (290–320 nm), and UVA (320–400 nm), of which the latter two are medically important. UVA radiation is divided into two distinct subtypes: short-wave UVA (320–340 nm) and long-wave UVA (340–400 nm) [55].

Both UVA and UVB radiation can cause sunburn, photoaging reactions, erythema, and inflammation. Mechanisms that modulate UV-induced damage involve nuclear and mitochondrial DNA damage, generation of reactive oxygen species (ROS), immune suppression, lipid peroxidation (membrane damage), activation of matrix metalloproteinases [56].

Radioprotectors.org includes a set of compounds that exert protective effects against UV-spectrum irradiation and thus form a group termed "sunscreening agents". This group can further be divided into two subgroups with different mechanisms: physical (inorganic) and chemical (organic) sunscreens. For organic compounds, the mechanism of action is based on their chemical structure involving an aromatic compound conjugated with a carbonyl group. This structure allows the absorption of high energy UV rays and the molecule switches to an excited state. As the molecule returns to the ground state, it releases the lower energy of longer wavelengths. [57] Such compounds as Avobenzone, Oxybenzone, Ecamsule, Octinoxate are FDA-approved components of topical sunscreens with different spectrums of absorption and various photostability. Octinoxate is identified as one of the potent UVB-absorbers [58], but is not photostable and degrades in the presence of sunlight after a short period of time, while Ecamsule, a very photostable product, acts as UVA-blocker. In animal studies, it prevented UVA-induced photoaging [59].

The mechanism of action of physical sunscreens, such as Zinc oxide, Titanium dioxide is based on the reflection and scattering of UV light. The reflective properties - reflective index, the size of the particles, the film thickness, and the dispersion of base determine the effectiveness of inorganic sunscreens [57]. Microfine zinc oxide has shown to be efficient against a wide range of UVA including UVA 1 (340 to 400 nm), but less efficient in blocking UVB, compared to Titanium oxide. Microfine titanium dioxide protects against UVA 2 (315-340 nm) and UVB but does not protect against UVA 1 [59]. Notably, both of these compounds have shown remarkable shielding properties against ionizing radiation and can also be classified as potential radioprotectors [60].

Inductors of autophagy

Autophagy is the essential, regulated cellular mechanism that disassembles and degrades unnecessary or dysfunctional components. Further recycling of those components serves as an additional energy source under various stress conditions [61]. In recent years, autophagy became one of the crucial cellular events in the context of aging research. Pharmacological or genetic inhibition of autophagy promotes degenerative

tissue changes, resembling those that occur during aging and also reduces the longevity-promoting effects of caloric restriction. Contrariwise, interventions that stimulate autophagy, increase lifespan in model organisms - notably, among all pharmacological manipulations MTORC1 inhibition is known to have the most dramatic effect [62, 63]. Activation of AMPK, another key autophagy regulator, triggers a number of cellular-protective mechanisms and prevents the hydrogen peroxide-induced dysregulation of the autophagic flux in senescent cells [64].

Autophagy is a generally cytoprotective (rather than a self-destructive) process. However, under certain conditions autophagy machinery is likely to be required for essential cell death [65]. In some cases, autophagy shares rather pro-senescent than anti-senescent features - once the cell comes into a senescent state, autophagy is likely to sustain its viability by reducing the level of overall metabolic stress. Under normal conditions, autophagy exerts anti-senescence effects. [66] Such dual nature of the autophagic process opens a perspective to use destructive autophagy properties to combat cancer and it's a progression in some cases, by triggering autophagic cell death or senescence of malignant cells [67].

A number of compounds that share both gero- and radioprotective properties have an ability to promote autophagy - understanding of how this feature contributes to radioresistance is important for further radioprotectors research and development. In a short-term period after irradiation, autophagy plays a positive role due to its cytoprotective properties. Autophagy protects the hematopoietic system from nuclear injury through modulation of DDR (DNA damage response) [68]. However, in the long-term perspective, the role of autophagy remains controversial. Malignant trans-formation of irradiated cells remains one of the most serious long-term consequences of radiation-induced damage. A number of studies have revealed that cancer cells rely on autophagy to gain radioresistance [69, 70]. On the other hand, irradiation has an ability to trigger autophagic cell death that involves Becklin, LC3, ATG1, ATG5, and ATG7 proteins (Figure 2) [71].

Remarkably, some radioprotective compounds such as Buthionine sulfoximine, Hoechst 33342, exert dual activity - enhance radioresistance in normal and radiosensitized transformed cells.

Due to the ability of some autophagy inductors to promote cancer cell apoptosis and display negative effects on cancer cell metabolism, natural compounds that can synergically work with chemotherapy agents

have received certain attention in the field of cancer research. [72]. Such plant-derived components as Luteolin [73], Naringin [74], Caffeine [75] showed an inhibitory effect on tumor cell growth and enhanced apoptosis.

We have performed an analysis to identify how various natural compounds, including those with gero- and radioprotective activities, modify the activity of the common autophagy-associated pathways (Figure 3). In a vast majority, the upregulation of AMPK signaling pathway and downregulation of mTOR signaling pathway was observed. Notable upregulation of pathways that are involved in lysosome vesicle biogenesis was also shown for most of the compounds. MAPK signaling pathway activation may be related to the mTORC1-MAPK feedback loop, which was observed both in cancer and normal cells [76]. In common,

signaling pathway landscape induced by most of the compounds, identifies them as potent autophagy inductors.

Using the open database LINCS1000, we have collected gene expression profiles for each compound on the heatmap. In order to obtain the list of differentially expressed genes, data were processed using the R 'limma' package [77] Benjamini-Hochberg FDR adjustment was applied to the p-values [78]. The pathway-level analysis was performed using the iPANDA software suite [79]. Positive and negative iPANDA scores indicated up- and down-regulation of the pathway, respectively. The pathway database used for the analysis included 1856 annotated and manually curated signalling pathway maps from KEGG, Reactome, and NCI-PID and SA Biosciences collections [80–82].
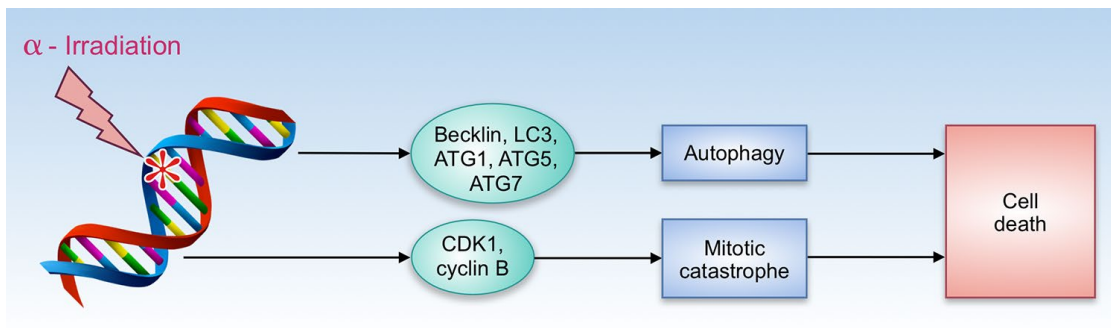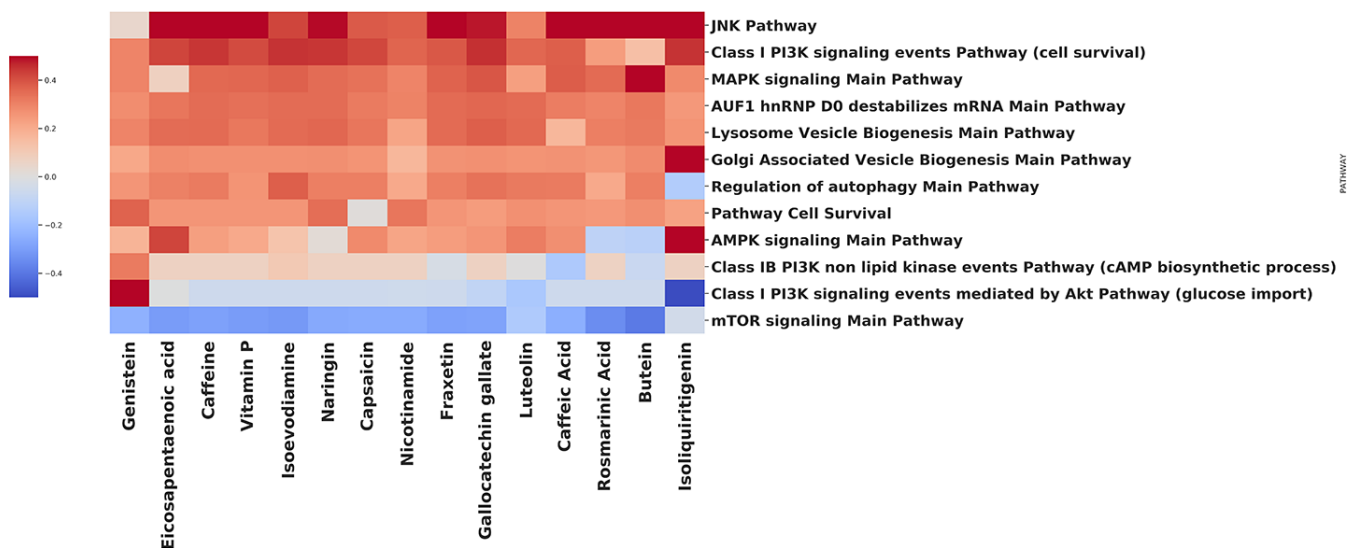

Figure 2. Autophagy and cell death by α-radiation.

Figure 3. Effect of compounds on autophagy-related pathways.

Table 1. Chemical compounds with combined gero- (according to Geroprotectors.org) and radio-protective activity.

Compound name	
Amifostine, Lithium chloride, Vitamin D3, Kanamycin, 2,4-dinitrophenol, Ellagic acid, Catechin, Carbonyl, Cyanide M-Chlorophenyl Hydrazone (CCCP), Glycerol, Deprenyl, Trichostatin A, Cysteamine, Quercetin, Fisetin, 4'-o-methyl epicatechin, Cyclosporin A, Valproic acid, Metformin, Rosmarinic acid, Rapamycin, Ibuprofen, Resveratrol, Simvastatin, Caffeine, Nitrendipine, Euk-134, Caffeic acid, Indirubin, 1,2,3,4,6-Penta-O-Galloyl-B-D-Glucose (PGG), Carnosine, Dimethyl Sulfoxide (DMSO), Ly294002, 4- phenylbutyrate, Beta- estradiol, Epigallocatechin Gallate, Minocycline, 10-Hydroxy-2-decenoic acid, Baicalein, Gallic acid, N-acetyl-L-cysteine, Genistein, Aspirin (Acetylsalicylic acid, ASA), Quercetin-3-O-Glucoside, Enalapril, A-Lipoic Acid, Celecoxib, Ursolic acid, Curcumin, Kaempferol, Melatonin, Ascorbic acid, Polydatin, Sodium Butyrate, Spermidine, 2-mercaptoethanol, Maltose, Trehalose, Cyproterone acetate, Fenofibrate	
Glutatione	The effect is ambiguous [107]
Pioglitazone	Effect was shown for a derivative [108]
Butylated hydroxytoluene (BHT)	The effect was shown for S. cerevisiae but not for cell cultures [109]
Fullerene C60	Effect was shown for a derivative [110]
Doxycycline	In combination with valproic acid [111]
Fumarate	Effect was shown for a derivative [112]
Nitroflurbiprofen	Effect was shown for a derivative [113]

Comparison of radio- and geroprotectors databases

There is a substantial intersection between aging and radiation-induced damage [83]. Multiple radiation-induced conditions are classified as diseases [84], and aging and radiation-accelerated aging may be classified as diseases [85]. Significant crosstalk between the mechanisms underlying the radiation protection and geroprotection is also notable [19, 86]. Many of the compounds that can be found in https://radioprotectors.org/home can be also found in the known databases of geroprotectors [87, 88]. In total, 66 substances included in the present database of radio-protectors also show geroprotective activity being listed in the Geroprotectors.org database [88]. These compounds are shown in Table 1. The functional similarity between geroprotectors and radioprotectors is partially due to the similar nature of negative effects on DNA imposed by radiation and developed during aging. Damages of the genetic material gradually accumulate throughout life, as the effectiveness of the repair systems and the ability of cells to neutralize genotoxic factors decrease. The death and senescence of cells, leading to fibrosis and chronic inflammatory processes, as well as a decrease of the stem cell pool and their malignant transformation under conditions of genotoxic stress, are key events in the aging process [89–91].

Ultraviolet radiation is considered one of the key factors in skin aging as well as an inducer of the above-mentioned processes. At the same time, ionizing radiation rapidly causes numerous and often un-repairable lesions (i.e., double-strand DNA breaks), leading to a vast cell death, primarily of the cells with a high proliferative index. A critical event is the almost complete inhibition of hematopoiesis and depletion of the bone marrow stem cells. Radiation causes the development of a senescent phenotype as a protective mechanism against a possible malignant transformation. Thus, the processes of aging and irradiation-induced changes are closely related at molecular and cellular levels [19]. Substances possessing gero- and radio-protective properties can exhibit similar protective effects (for example, act as antioxidants and reduce the number of free radicals formed both naturally in the processes of cell metabolism and those resulting from radiolysis), as well as affect the same signaling pathways leading to positive effects [92, 93].

Development of new effective drugs against aging and radiation-induced aging is an ambitious but at the same time pleading task. Several approaches can be applied to solve the problem including pathway analysis and searching for new targets [19, 93–95], searching for possible biomarkers for both aging and radiation exposure [96–104] and even generation of new chemical compounds [105, 106]. However, all of them rely on the availability of profoundly annotated data about chemical compounds with radioprotective effects and their molecular modes of action. The present curated database of radioprotectors will become a convenient onset for the development of medicines against radiation-induced damage and aging following both the structure-based and ligand-based approaches.

CONFLICTS OF INTEREST

These authors declare no conflicts of interest.

REFERENCES

1. Cortese F, Klokov D, Osipov A, Stefaniak J, Moskalev A, Schastnaya J, Cantor C, Aliper A, Mamoshina P,

Ushakov I, Sapetsky A, Vanhaelen Q, Alchinova I, et al. Vive la radiorésistance!: converging research in radiobiology and biogerontology to enhance human radioresistance for deep space exploration and colonization. Oncotarget. 2018; 9:14692–722. https://doi.org/10.18632/oncotarget.24461 PMID:29581875

2. Johnke RM, Sattler JA, Allison RR. Radioprotective agents for radiation therapy: future trends. Future Oncol. 2014; 10:2345–57. https://doi.org/10.2217/fon.14.175 PMID:25525844

3. Greenberger JS. Radioprotection. In Vivo. 2009; 23:323–36. PMID:19414422

4. Iarmonenko SP. [Radiomodifiers and the progress of radiation oncology]. Vopr Onkol. 1995; 41:93–94. PMID:7483456

5. Citrin D, Cotrim AP, Hyodo F, Baum BJ, Krishna MC, Mitchell JB. Radioprotectors and mitigators of radiation-induced normal tissue injury. Oncologist. 2010; 15:360–71. https://doi.org/10.1634/theoncologist.2009-S104 PMID:20413641

6. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer. 2006; 6:702–13. https://doi.org/10.1038/nrc1950 PMID:16929324

7. Spotheim-Maurizot M. Radioprotectors [Internet]. Encyclopedia of Cancer. 2016. p. 3884–7. https://doi.org/10.1007/978-3-662-46875-3_7082

8. Schwab M, editor. Encyclopedia of Cancer. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017.

9. Dongre PM, Joshi A. A systematic organization of bioinformatics database of radiosensitizers and radioprotectors. Journal of Radiation and Cancer Research. 2018; 9:102. https://doi.org/10.4103/jrcr.jrcr_5_18

10. Domina EA. Anty radiation means: classification and mechanisms. Probl Radiac Med Radiobiol. 2015; 20:42–54. PMID:26695893

11. Livesey JC, Reed DJ, Adamson LF. Radiation-Protective Drugs and Their Reaction Mechanisms [Internet]. American Journal of Clinical Oncology. 1987. p. 89. https://doi.org/10.1097/00000421-198702000-00020

12. Sweeney TR, Musallam HA. Radiation-Protective Drugs and their Reaction Mechanisms [Internet]. Journal of Pharmaceutical Sciences. 1986. p. 728–9. https://doi.org/10.1002/jps.2600750734

13. Smith TA, Kirkpatrick DR, Smith S, Smith TK, Pearson T, Kailasam A, Herrmann KZ, Schubert J, Agrawal DK. Radioprotective agents to prevent cellular damage due to ionizing radiation. J Transl Med. 2017; 15:232. https://doi.org/10.1186/s12967-017-1338-x PMID:29121966

14. Livesey JC, Reed DJ, Adamson LF. Chemical protection against ionizing radiation. Final report [Internet]. 1984. https://doi.org/10.2172/6215269

15. Pilipenko V, Narbute K, Amara I, Trovato A, Scuto M, Pupure J, Jansone B, Poikans J, Bisenieks E, Klusa V, Calabrese V. GABA-containing compound gammapyrone protects against brain impairments in Alzheimer's disease model male rats and prevents mitochondrial dysfunction in cell culture. J Neurosci Res. 2019; 97:708–26. https://doi.org/10.1002/jnr.24396 PMID:30742328

16. Trovato Salinaro A, Pennisi M, Di Paola R, Scuto M, Crupi R, Cambria MT, Ontario ML, Tomasello M, Uva M, Maiolino L, Calabrese EJ, Cuzzocrea S, Calabrese V. Neuroinflammation and neurohormesis in the pathogenesis of Alzheimer's disease and Alzheimer-linked pathologies: modulation by nutritional mushrooms. Immun Ageing. 2018; 15:8. https://doi.org/10.1186/s12979-017-0108-1 PMID:29456585

17. Calabrese V, Santoro A, Trovato Salinaro A, Modafferi S, Scuto M, Albouchi F, Monti D, Giordano J, Zappia M, Franceschi C, Calabrese EJ. Hormetic approaches to the treatment of Parkinson's disease: perspectives and possibilities. J Neurosci Res. 2018; 96:1641–62. https://doi.org/10.1002/jnr.24244 PMID:30098077

18. Miquel S, Champ C, Day J, Aarts E, Bahr BA, Bakker M, Bánáti D, Calabrese V, Cederholm T, Cryan J, Dye L, Farrimond JA, Korosi A, et al. Poor cognitive ageing: vulnerabilities, mechanisms and the impact of nutritional interventions. Ageing Res Rev. 2018; 42:40–55. https://doi.org/10.1016/j.arr.2017.12.004 PMID:29248758

19. Aliper AM, Bozdaganyan ME, Orekhov PS, Zhavoronkov A, Osipov AN. Replicative and radiation-induced aging: a comparison of gene expression profiles. Aging (Albany NY). 2019; 11:2378–87. https://doi.org/10.18632/aging.101921 PMID:31002655

20. Beckman KB, Ames BN. Oxidative decay of DNA. J Biol Chem. 1997; 272:19633–36. https://doi.org/10.1074/jbc.272.32.19633 PMID:9289489

21. Maier P, Wenz F, Herskind C. Radioprotection of normal tissue cells. Strahlenther Onkol. 2014; 190:745–52.

https://doi.org/10.1007/s00066-014-0637-x
PMID:24638269

22. Nair CK, Parida DK, Nomura T. Radioprotectors in radiotherapy. J Radiat Res. 2001; 42:21–37.
https://doi.org/10.1269/jrr.42.21
PMID:11393887

23. Movsas B, Scott C, Langer C, Werner-Wasik M, Nicolaou N, Komaki R, Machtay M, Smith C, Axelrod R, Sarna L, Wasserman T, Byhardt R. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01. J Clin Oncol. 2005; 23:2145–54.
https://doi.org/10.1200/JCO.2005.07.167
PMID:15800308

24. Koukourakis MI, Maltezos E. Amifostine administration during radiotherapy for cancer patients with genetic, autoimmune, metabolic and other diseases. Anticancer Drugs. 2006; 17:133–38.
https://doi.org/10.1097/00001813-200602000-00003
PMID:16428930

25. Kouvaris JR, Kouloulias VE, Vlahos LJ. Amifostine: the first selective-target and broad-spectrum radioprotector. Oncologist. 2007; 12:738–47.
https://doi.org/10.1634/theoncologist.12-6-738
PMID:17602063

26. Case AJ. On the origin of superoxide dismutase: an evolutionary perspective of superoxide-mediated redox signaling. Antioxidants (Basel). 2017; 6:82.
https://doi.org/10.3390/antiox6040082
PMID:29084153

27. Louie KG, Behrens BC, Kinsella TJ, Hamilton TC, Grotzinger KR, McKoy WM, Winker MA, Ozols RF. Radiation survival parameters of antineoplastic drug-sensitive and -resistant human ovarian cancer cell lines and their modification by buthionine sulfoximine. Cancer Res. 1985; 45:2110–15.
PMID:3986765

28. Zhang XR, Zhou WX, Zhang YX. Improvements in SOD mimic AEOL-10150, a potent broad-spectrum antioxidant. Mil Med Res. 2018; 5:30.
https://doi.org/10.1186/s40779-018-0176-3
PMID:30185231

29. Limoli CL, Giedzinski E, Baure J, Doctrow SR, Rola R, Fike JR. Using superoxide dismutase/catalase mimetics to manipulate the redox environment of neural precursor cells. Radiat Prot Dosimetry. 2006; 122:228–36.
https://doi.org/10.1093/rpd/ncl458 PMID:17166877

30. Hahn SM, Sullivan FJ, DeLuca AM, Krishna CM, Wersto N, Venzon D, Russo A, Mitchell JB. Evaluation of tempol radioprotection in a murine tumor model. Free Radic Biol Med. 1997; 22:1211–16.
https://doi.org/10.1016/s0891-5849(96)00556-4
PMID:9098095

31. Mortazavi SM, Rahimi S, Mosleh-Shirazi MA, Arjomandi M, Soleimani A, Koohi Hossein-Abadi O, Haghani M, Alavi M. A comparative study on the life-saving radioprotective effects of vitamins A, E, C and over-the-counter multivitamins. J Biomed Phys Eng. 2015; 5:59–66.
PMID:26157731

32. Cervelli T, Panetta D, Navarra T, Gadhiri S, Salvadori P, Galli A, Caramella D, Basta G, Picano E, Del Turco S. A new natural antioxidant mixture protects against oxidative and DNA damage in endothelial cell exposed to low-dose irradiation. Oxid Med Cell Longev. 2017; 2017:9085947.
https://doi.org/10.1155/2017/9085947
PMID:28852434

33. Giardi MT, Touloupakis E, Bertolotto D, Mascetti G. Preventive or potential therapeutic value of nutraceuticals against ionizing radiation-induced oxidative stress in exposed subjects and frequent fliers. Int J Mol Sci. 2013; 14:17168–92.
https://doi.org/10.3390/ijms140817168
PMID:23965979

34. Elbaky NA, El-Orabi NF, Fadda LM, Abd-Elkader OH, Ali HM. Role of n-acetylcysteine and coenzyme Q10 in the amelioration of myocardial energy expenditure and oxidative stress, induced by carbon tetrachloride intoxication in rats. Dose Response. 2018; 16:1559325818790158.
https://doi.org/10.1177/1559325818790158
PMID:30116167

35. Farhood B, Goradel NH, Mortezaee K, Khanlarkhani N, Salehi E, Nashtaei MS, Mirtavoos-Mahyari H, Motevaseli E, Shabeeb D, Musa AE, Najafi M. Melatonin as an adjuvant in radiotherapy for radioprotection and radiosensitization. Clin Transl Oncol. 2019; 21:268–79.
https://doi.org/10.1007/s12094-018-1934-0
PMID:30136132

36. Vávrová J, Rezáčová M. Importance of proapoptotic protein PUMA in cell radioresistance. Folia Biol (Praha). 2014; 60:53–56.
PMID:24785107

37. Gudkov AV, Komarova EA. Radioprotection: smart games with death. J Clin Invest. 2010; 120:2270–73.
https://doi.org/10.1172/JCI43794
PMID:20577043

38. Strom E, Sathe S, Komarov PG, Chernova OB, Pavlovska I, Shyshynova I, Bosykh DA, Burdelya LG, Macklis RM,

Skaliter R, Komarova EA, Gudkov AV. Small-molecule inhibitor of p53 binding to mitochondria protects mice from gamma radiation. Nat Chem Biol. 2006; 2:474–79. https://doi.org/10.1038/nchembio809 PMID:16862141

39. Zhang Y, Cheng Z, Wang C, Ma H, Meng W, Zhao Q. Neuroprotective effects of kukoamine a against radiation-induced rat brain injury through inhibition of oxidative stress and neuronal apoptosis. Neurochem Res. 2016; 41:2549–58. https://doi.org/10.1007/s11064-016-1967-0 PMID:27241194

40. Yang J, Yan Y, Liu H, Wang J, Hu J. Protective effects of acteoside against x-ray-induced damage in human skin fibroblasts. Mol Med Rep. 2015; 12:2301–06. https://doi.org/10.3892/mmr.2015.3630 PMID:25892089

41. Naeimi RA, Talebpour Amiri F, Khalatbary AR, Ghasemi A, Zargari M, Ghesemi M, Hosseinimehr SJ. Atorvastatin mitigates testicular injuries induced by ionizing radiation in mice. Reprod Toxicol. 2017; 72:115–21. https://doi.org/10.1016/j.reprotox.2017.06.052 PMID:28668617

42. Arivalagan S, Thomas NS, Kuppusamy T, Namashivayam N. Radioprotective Effect of Carvacrol Against X-Radiation-Induced Cellular Damage in Cultured Human Peripheral Blood Lymphocytes. J Environ Pathol Toxicol Oncol. 2015; 34:263–75. https://doi.org/10.1615/jenvironpatholtoxicoloncol.2015013548 PMID:26349608

43. Li P, Zhao QL, Wu LH, Jawaid P, Jiao YF, Kadowaki M, Kondo T. Isofraxidin, a potent reactive oxygen species (ROS) scavenger, protects human leukemia cells from radiation-induced apoptosis via ROS/mitochondria pathway in p53-independent manner. Apoptosis. 2014; 19:1043–53. https://doi.org/10.1007/s10495-014-0984-1 PMID:24692054

44. Joe AK, Liu H, Suzui M, Vural ME, Xiao D, Weinstein IB. Resveratrol induces growth inhibition, s-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. Clin Cancer Res. 2002; 8:893–903. PMID:11895924

45. Pustovalova M, Grekhova A, Astrelina T, Nikitina V, Dobrovolskaya E, Suchkova Y, Kobzeva I, Usupzhanova D, Vorobyeva N, Samoylov A, Bushmanov A, Ozerov IV, Zhavoronkov A, et al. Accumulation of spontaneous γH2AX foci in long-term cultured mesenchymal stromal cells. Aging (Albany NY). 2016; 8:3498–506. https://doi.org/10.18632/aging.101142 PMID:27959319

46. Pustovalova M, Astrelina TA, Grekhova A, Vorobyeva N, Tsvetkova A, Blokhina T, Nikitina V, Suchkova Y, Usupzhanova D, Brunchukov V, Kobzeva I, Karaseva T, Ozerov IV, et al. Residual γH2AX foci induced by low dose x-ray radiation in bone marrow mesenchymal stem cells do not cause accelerated senescence in the progeny of irradiated cells. Aging (Albany NY). 2017; 9:2397–410. https://doi.org/10.18632/aging.101327 PMID:29165316

47. Yuhas JM. Protective drugs in cancer therapy: optimal clinical testing and future directions. Int J Radiat Oncol Biol Phys. 1982; 8:513–17. https://doi.org/10.1016/0360-3016(82)90673-3 PMID:6286544

48. Pomerantseva MD, Ramaija LK. Chemical protection against genetic effect of radiation in male mice. Mutat Res. 1984; 140:131–35. https://doi.org/10.1016/0165-7992(84)90057-5 PMID:6749172

49. Leon SA, Kollmann G, Shapiro B. Properties of DNA irradiated in the presence of the protective agent bis(2-guanidoethyl)disulphide (GED). Int J Radiat Biol Relat Stud Phys Chem Med. 1973; 23:325–32. https://doi.org/10.1080/09553007314550401 PMID:4540846

50. Ramakrishnan N, Catravas GN. Protection of Thymocytes from Radiation-Induced Interphase Death by Dihydrolipoic Acid and WR-1065. Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Radiation Injury. Springer, Boston, MA; 1993. p. 349–52. https://doi.org/10.1007/978-1-4615-3520-1_69

51. Révész L, Palcic B. Radiation dose dependence of the sensitization by oxygen and oxygen mimic sensitizers. Acta Radiol Oncol. 1985; 24:209–17. https://doi.org/10.3109/02841868509134389 PMID:2994369

52. Sonntag C. Free-Radical-Induced DNA Damage and Its Repair: A Chemical Perspective. Springer Science & Business Media; 2006. 523 p.

53. Révész L, Edgren M. Glutathione-dependent yield and repair of single-strand DNA breaks in irradiated cells. Br J Cancer Suppl. 1984; 6:55–60. PMID:6421303

54. Pulatova MK, Sharygin VL, Todorov IN. The activation of ribonucleotide reductase in animal organs as the cellular response against the treatment with DNA-damaging factors and the influence of radioprotectors on this effect. Biochim Biophys Acta. 1999; 1453:321–29. https://doi.org/10.1016/s0925-4439(99)00002-2 PMID:10101250

55. Latha MS, Martis J, Shobha V, Sham Shinde R, Bangera S, Krishnankutty B, Bellary S, Varughese S, Rao P, Naveen Kumar BR. Sunscreening agents: a review. J Clin Aesthet Dermatol. 2013; 6:16–26. PMID:23320122

56. DeBuys HV, Levy SB, Murray JC, Madey DL, Pinnell SR. Modern approaches to photoprotection. Dermatol Clin. 2000; 18:577–90. https://doi.org/10.1016/s0733-8635(05)70208-4 PMID:11059365

57. Heurung AR, Raju SI, Warshaw EM. Adverse reactions to sunscreen agents: epidemiology, responsible irritants and allergens, clinical characteristics, and management. Dermatitis. 2014; 25:289–326. https://doi.org/10.1097/DER.0000000000000079 PMID:25384223

58. Rai R, Shanmuga SC, Srinivas C. Update on photoprotection. Indian J Dermatol. 2012; 57:335–42. https://doi.org/10.4103/0019-5154.100472 PMID:23112351

59. Kullavanijaya P, Lim HW. Photoprotection. J Am Acad Dermatol. 2005; 52:937–58. https://doi.org/10.1016/j.jaad.2004.07.063 PMID:15928611

60. Issa SAM, Mostafa AMA, Auda SH. Radio-protective properties of some sunblock agents against ionizing radiation. Prog Nuclear Energy. 2018; 107:184–92. https://doi.org/10.1016/j.pnucene.2018.04.027

61. Mizushima N. Autophagy: process and function. Genes Dev. 2007; 21:2861–73. https://doi.org/10.1101/gad.1599207 PMID:18006683

62. Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. Cell. 2011; 146:682–95. https://doi.org/10.1016/j.cell.2011.07.030 PMID:21884931

63. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. Gerontology. 2018; 64:127–34. https://doi.org/10.1159/000484629 PMID:29190625

64. Han X, Tai H, Wang X, Wang Z, Zhou J, Wei X, Ding Y, Gong H, Mo C, Zhang J, Qin J, Ma Y, Huang N, et al. AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD $^+$ elevation. Aging Cell. 2016; 15:416–27. https://doi.org/10.1111/acel.12446 PMID:26890602

65. Liu Y, Levine B. Autosis and autophagic cell death: the dark side of autophagy. Cell Death Differ. 2015; 22:367–76. https://doi.org/10.1038/cdd.2014.143 PMID:25257169

66. Kwon Y, Kim JW, Jeoung JA, Kim MS, Kang C. Autophagy is pro-senescence when seen in close-up, but anti-senescence in long-shot. Mol Cells. 2017; 40:607–12. https://doi.org/10.14348/molcells.2017.0151 PMID:28927262

67. Byun S, Lee E, Lee KW. Therapeutic implications of autophagy inducers in immunological disorders, infection, and cancer. Int J Mol Sci. 2017; 18:1959. https://doi.org/10.3390/ijms18091959 PMID:28895911

68. Lin W, Yuan N, Wang Z, Cao Y, Fang Y, Li X, Xu F, Song L, Wang J, Zhang H, Yan L, Xu L, Zhang X, et al. Autophagy confers DNA damage repair pathways to protect the hematopoietic system from nuclear radiation injury. Sci Rep. 2015; 5:12362. https://doi.org/10.1038/srep12362 PMID:26197097

69. Chen X, Wang P, Guo F, Wang X, Wang J, Xu J, Yuan D, Zhang J, Shao C. Autophagy enhanced the radioresistance of non-small cell lung cancer by regulating ROS level under hypoxia condition. Int J Radiat Biol. 2017; 93:764–70. https://doi.org/10.1080/09553002.2017.1325025 PMID:28463025

70. Chaachouay H, Ohneseit P, Toulany M, Kehlbach R, Multhoff G, Rodemann HP. Autophagy contributes to resistance of tumor cells to ionizing radiation. Radiother Oncol. 2011; 99:287–92. https://doi.org/10.1016/j.radonc.2011.06.002 PMID:21722986

71. Baidoo KE, Yong K, Brechbiel MW. Molecular pathways: targeted α-particle radiation therapy. Clin Cancer Res. 2013; 19:530–37. https://doi.org/10.1158/1078-0432.CCR-12-0298 PMID:23230321

72. Pietrocola F, Pol J, Vacchelli E, Baracco EE, Levesque S, Castoldi F, Maiuri MC, Madeo F, Kroemer G. Autophagy induction for the treatment of cancer. Autophagy. 2016; 12:1962–64. https://doi.org/10.1080/15548627.2016.1214778 PMID:27532519

73. Cao Z, Zhang H, Cai X, Fang W, Chai D, Wen Y, Chen H, Chu F, Zhang Y. Luteolin promotes cell apoptosis by inducing autophagy in hepatocellular carcinoma. Cell Physiol Biochem. 2017; 43:1803–12. https://doi.org/10.1159/000484066 PMID:29049999

74. Raha S, Yumnam S, Hong GE, Lee HJ, Saralamma VV, Park HS, Heo JD, Lee SJ, Kim EH, Kim JA, Kim GS. Naringin induces autophagy-mediated growth inhibition by downregulating the PI3K/Akt/mTOR cascade via activation of MAPK pathways in AGS cancer cells. Int J Oncol. 2015; 47:1061–69.

https://doi.org/10.3892/ijo.2015.3095
PMID:26201693

75. Saiki S, Sasazawa Y, Imamichi Y, Kawajiri S, Fujimaki T, Tanida I, Kobayashi H, Sato F, Sato S, Ishikawa K, Imoto M, Hattori N. Caffeine induces apoptosis by enhancement of autophagy via PI3K/Akt/mTOR/p70S6K inhibition. Autophagy. 2011; 7:176–87.
https://doi.org/10.4161/auto.7.2.14074
PMID:21081844

76. Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, Egia A, Sasaki AT, Thomas G, Kozma SC, Papa A, Nardella C, Cantley LC, et al. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest. 2008; 118:3065–74.
https://doi.org/10.1172/JCI34739 PMID:18725988

77. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, Smyth GK. Limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015; 43:e47.
https://doi.org/10.1093/nar/gkv007 PMID:25605792

78. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Series B Stat Methodol. [Royal Statistical Society, Wiley]; 1995; 57:289–300.
https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

79. Ozerov IV, Lezhnina KV, Izumchenko E, Artemov AV, Medintsev S, Vanhaelen Q, Aliper A, Vijg J, Osipov AN, Labat I, West MD, Buzdin A, Cantor CR, et al. In silico pathway activation network decomposition analysis (iPANDA) as a method for biomarker development. Nat Commun. 2016; 7:13427.
https://doi.org/10.1038/ncomms13427
PMID:27848968

80. Croft D, Mundo AF, Haw R, Milacic M, Weiser J, Wu G, Caudy M, Garapati P, Gillespie M, Kamdar MR, Jassal B, Jupe S, Matthews L, et al. The reactome pathway knowledgebase. Nucleic Acids Res. 2014; 42:D472–77.
https://doi.org/10.1093/nar/gkt1102
PMID:24243840

81. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res. 2000; 28:27–30.
https://doi.org/10.1093/nar/28.1.27 PMID:10592173

82. Schaefer CF, Anthony K, Krupa S, Buchoff J, Day M, Hannay T, Buetow KH. PID: the pathway interaction database. Nucleic Acids Res. 2009; 37:D674–79.
https://doi.org/10.1093/nar/gkn653 PMID:18832364

83. Zhavoronkov A, Cantor CR. Methods for structuring scientific knowledge from many areas related to aging research. PLoS One. 2011; 6:e22597.

https://doi.org/10.1371/journal.pone.0022597
PMID:21799912

84. Gofman JW, Morgan KZ. Radiation and Human Health [Internet]. Physics Today. 1983. p. 68–70.
https://doi.org/10.1063/1.2915713

85. Zhavoronkov A, Bhullar B. Classifying aging as a disease in the context of ICD-11. Front Genet. 2015; 6:326.
https://doi.org/10.3389/fgene.2015.00326
PMID:26583032

86. Moskalev A, Anisimov V, Aliper A, Artemov A, Asadullah K, Belsky D, Baranova A, de Grey A, Dixit VD, Debonneuil E, Dobrovolskaya E, Fedichev P, Fedintsev A, et al. A review of the biomedical innovations for healthy longevity. Aging Impact Journals, LLC; 2017; 9:7.
https://doi.org/10.18632/aging.101163

87. Aliper A, Belikov AV, Garazha A, Jellen L, Artemov A, Suntsova M, Ivanova A, Venkova L, Borisov N, Buzdin A, Mamoshina P, Putin E, Swick AG, et al. In search for geroprotectors: in silico screening and in vitro validation of signalome-level mimetics of young healthy state. Aging (Albany NY). 2016; 8:2127–52.
https://doi.org/10.18632/aging.101047
PMID:27677171

88. Moskalev A, Chernyagina E, de Magalhães JP, Barardo D, Thoppil H, Shaposhnikov M, Budovsky A, Fraifeld VE, Garazha A, Tsvetkov V, Bronovitsky E, Bogomolov V, Scerbacov A, et al. Geroprotectors.org: a new, structured and curated database of current therapeutic interventions in aging and age-related disease. Aging (Albany NY). 2015; 7:616–28.
https://doi.org/10.18632/aging.100799
PMID:26342919

89. Moskalev AA, Aliper AM, Smit-McBride Z, Buzdin A, Zhavoronkov A. Genetics and epigenetics of aging and longevity. Cell Cycle. 2014; 13:1063–77.
https://doi.org/10.4161/cc.28433
PMID:24603410

90. Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H, Fraifeld VE. The role of DNA damage and repair in aging through the prism of koch-like criteria. Ageing Res Rev. 2013; 12:661–84.
https://doi.org/10.1016/j.arr.2012.02.001
PMID:22353384

91. MacRae SL, Croken MM, Calder RB, Aliper A, Milholland B, White RR, Zhavoronkov A, Gladyshev VN, Seluanov A, Gorbunova V, Zhang ZD, Vijg J. DNA repair in species with extreme lifespan differences. Aging (Albany NY). 2015; 7:1171–84.
https://doi.org/10.18632/aging.100866
PMID:26729707

92. Prasanna PG, Narayanan D, Hallett K, Bernhard EJ, Ahmed MM, Evans G, Vikram B, Weingarten M, Coleman CN. Radioprotectors and radiomitigators for improving radiation therapy: the small business innovation research (SBIR) gateway for accelerating clinical translation. Radiat Res. 2015; 184:235–48. https://doi.org/10.1667/RR14186.1 PMID:26284423

93. Makarev E, Cantor C, Zhavoronkov A, Buzdin A, Aliper A, Csoka AB. Pathway activation profiling reveals new insights into age-related macular degeneration and provides avenues for therapeutic interventions. Aging (Albany NY). 2014; 6:1064–75. https://doi.org/10.18632/aging.100711 PMID:25543336

94. Yentrapalli R, Azimzadeh O, Sriharshan A, Malinowsky K, Merl J, Wojcik A, Harms-Ringdahl M, Atkinson MJ, Becker KF, Haghdoost S, Tapio S. The PI3K/Akt/mTOR pathway is implicated in the premature senescence of primary human endothelial cells exposed to chronic radiation. PLoS One. 2013; 8:e70024. https://doi.org/10.1371/journal.pone.0070024 PMID:23936371

95. Lee SJ, Dimtchev A, Lavin MF, Dritschilo A, Jung M. A novel ionizing radiation-induced signaling pathway that activates the transcription factor NF-kappaB. Oncogene. 1998; 17:1821–26. https://doi.org/10.1038/sj.onc.1202088 PMID:9778048

96. Mamoshina P, Kochetov K, Putin E, Cortese F, Aliper A, Lee WS, Ahn SM, Uhn L, Skjodt N, Kovalchuk O, Scheibye-Knudsen M, Zhavoronkov A. Population specific biomarkers of human aging: a big data study using South Korean, Canadian, and Eastern European patient populations. J Gerontol A Biol Sci Med Sci. 2018; 73:1482–90. https://doi.org/10.1093/gerona/gly005 PMID:29340580

97. Putin E, Mamoshina P, Aliper A, Korzinkin M, Moskalev A, Kolosov A, Ostrovskiy A, Cantor C, Vijg J, Zhavoronkov A. Deep biomarkers of human aging: application of deep neural networks to biomarker development. Aging (Albany NY). 2016; 8:1021–33. https://doi.org/10.18632/aging.100968 PMID:27191382

98. Zhavoronkov A, Mamoshina P. Deep aging clocks: the emergence of AI-based biomarkers of aging and longevity. Trends Pharmacol Sci. 2019; 40:546–49. https://doi.org/10.1016/j.tips.2019.05.004 PMID:31279569

99. Mamoshina P, Zhavoronkov A. Deep Integrated Biomarkers of Aging [Internet]. Healthy Ageing and Longevity. 2019. p. 281–91. https://doi.org/10.1007/978-3-030-24970-0_18

100. Zhavoronkov A, Mamoshina P, Vanhaelen Q, Scheibye-Knudsen M, Moskalev A, Aliper A. Artificial intelligence for aging and longevity research: recent advances and perspectives. Ageing Res Rev. 2019; 49:49–66. https://doi.org/10.1016/j.arr.2018.11.003 PMID:30472217

101. McClellan RO. Biomarkers of Exposure and Responses to Ionizing Radiation [Internet]. Biomarkers in Toxicology. 2019. p. 757–86. https://doi.org/10.1016/B978-0-12-814655-2.00042-6

102. Horn S, Rothkamm K. Candidate protein biomarkers as rapid indicators of radiation exposure [Internet]. Radiation Measurements. 2011. p. 903–6. https://doi.org/10.1016/j.radmeas.2011.02.001

103. Kirsch DG. Biomarkers for Predicting Radiation Response. Semin Radiat Oncol. 2015; 25:225–6. https://doi.org/10.1016/j.semradonc.2015.05.011 PMID:26384270

104. Mamoshina P, Kochetov K, Cortese F, Kovalchuk A, Aliper A, Putin E, Scheibye-Knudsen M, Cantor CR, Skjodt NM, Kovalchuk O, Zhavoronkov A. Blood biochemistry analysis to detect smoking status and quantify accelerated aging in smokers. Sci Rep. 2019; 9:142. https://doi.org/10.1038/s41598-018-35704-w PMID:30644411

105. Zhavoronkov A. Artificial intelligence for drug discovery, biomarker development, and generation of novel chemistry. Mol Pharm. 2018; 15:4311–13. https://doi.org/10.1021/acs.molpharmaceut.8b00930 PMID:30269508

106. Zhavoronkov A, Ivanenkov YA, Aliper A, Veselov MS, Aladinskiy VA, Aladinskaya AV, Terentiev VA, Polykovskiy DA, Kuznetsov MD, Asadulaev A, Volkov Y, Zholus A, Shayakhmetov RR, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nat Biotechnol. 2019; 37:1038–40. https://doi.org/10.1038/s41587-019-0224-x PMID:31477924

107. Chatterjee A. Reduced glutathione: a radioprotector or a modulator of DNA-repair activity? Nutrients. 2013; 5:525–42. https://doi.org/10.3390/nu5020525 PMID:23434907

108. Mangoni M, Sottili M, Gerini C, Desideri I, Bastida C, Pallotta S, Castiglione F, Bonomo P, Meattini I, Greto D, Cappelli S, Di Brina L, Loi M, et al. A PPAR-gamma agonist protects from radiation-induced intestinal toxicity. United European Gastroenterol J. 2017; 5:218–26. https://doi.org/10.1177/2050640616640443 PMID:28344789

109. Grillo CA, Dulout FN. Butylated hydroxytoluene does not protect Chinese hamster ovary cells from chromosomal damage induced by high-dose rate 192Ir irradiation. Mutagenesis. 2006; 21:405–10.
https://doi.org/10.1093/mutage/gel046
PMID:17065160

110. Theriot CA, Casey RC, Moore VC, Mitchell L, Reynolds JO, Burgoyne M, Partha R, Huff JL, Conyers JL, Jeevarajan A, Wu H. dendro[C(60)]fullerene DF-1 provides radioprotection to radiosensitive mammalian cells. Radiat Environ Biophys. 2010; 49:437–45.
https://doi.org/10.1007/s00411-010-0310-4
PMID:20582595

111. Hoşgörler F, Keleş D, Tanrıverdi-Akhisaroğlu S, İnanç Ş, Akhisaroğlu M, Cankurt Ü, Aydoğdu Z, Uçar AD, Çetinayak O, Oktay G, Arda SG. Anti-inflammatory and anti-apoptotic effect of valproic acid and doxycycline independent from MMP inhibition in early radiation damage. Balkan Med J. 2016; 33:488–95.
https://doi.org/10.5152/balkanmedj.2016.151304
PMID:27761275

112. Held KD, Hopcia KL. Role of protein thiols in intrinsic radiation protection of DNA and cells. Mutat Res. 1993; 299:261–69.
https://doi.org/10.1016/0165-1218(93)90102-j
PMID:7683093

113. Juchelková L, Hofer M, Pospísil M, Pipalová I. Radioprotective effects of flurbiprofen and its nitroderivative. Physiol Res. 1998; 47:73–80.
PMID:9708705