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LIST OF ABBREVIATIONS

AA – antioxidant activity
ALE – average life expectancy
ARS – acute radiation sickness
BC – biological control
DMF – dose modifying factor
FDA – Food and Drug Administration, USA
FRO – free radical oxidation
GIMRO of NAMS of Ukraine – State Organisation "Grigoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine"
GIP – growth inhibition percentage
GIT – gastrointestinal tract
IAEA – International Atomic Energy Agency
$IFI_{(d)}$% – integral frequency index of occurrence of the ARS symptoms in dead rats
$IFI_{(s)}$% – integral frequency index of occurrence of the ARS symptoms in surviving rats
INES – International Nuclear Event Scale
IR – ionizing radiation
ISR – Integral survival rate
$ISR_{(d)}$% – integral survival rate for dead rats
$ISR_{(s)}$% – integral survival rate for surviving rats
IU – international unit
LD_{30} – lethal dose for rats in a 30 days period
LD_{50} – semi-lethal dose
LPO – lipid peroxidation
MA – mitotic activity
MEA – *β*-mercaptoethylamine
MIC – minimum growth inhibiting concentration (the minimum concentration that inhibits the growth of MO)
MO – microorganisms
PASS – Prediction of Activity Spectra for Substances
ROS – reactive oxygen species
SOD – superoxide dismutase
ZNU – Zaporizhzhia National University

INTRODUCTION

One of the most important and relevant problems of practical pharmacology today is human radiation protection. The widespread use of nuclear energy in a number of industries such as medicine, geology, archeology and agriculture, high-altitude passenger aircraft flights (especially during solar flares), space exploration, and the threat of nuclear conflict and radiological terrorism pose potential threats to our and future generations. To date, no safe and effective anti-radiation drug for the most severe injury – acute radiation syndrome (ARS) – has been approved by the US Food and Drug Administration (FDA). Disadvantages of FDA-approved radioprotectors initiate intensive research for the radioprotectors of the new generation. Today, a limited number of radioprotectors are available for use and only some of them can be used for exceptional nuclear/radiological unforeseen circumstances, while some drugs, although showing some positive results, still remain experimental and unauthorized for human use in the case of ARS. The compounds presented in the monograph have the potential to become effective antioxidants or be the basis for new radioprotective agents with prolonged action with less pronounced side effects and toxic properties. In addition, these compounds can be used to protect healthy tissues in radiation therapy of malignant tumors.

The search for new highly efficient and low-toxic bioactive molecules is based on both natural and synthetic compounds [1]. Nitrogen-containing heterocycle quinoline holds a special place among these compounds since its various derivatives are known as synthons in organic synthesis and are effective biologically active compounds. Modification of known radioprotectors with this heterocycle, in particular of endogenous thiols (cysteamine, cysteine) is one of the promising ways that can reduce toxicity and prolong their action by slowing down their metabolism and reducing required doses for the protective effect. In addition, over the last decade, there have been many publications on the antioxidant properties of various quinoline derivatives that can be the basis for the creation of radioprotective drugs with the antioxidant mechanism of action [2; 3; 4; 5; 6; 7].

The most promising derivatives are 4-thio derivatives of quinoline, which are effective "traps" of free radicals [8].

This paper describes one of the approaches used in the development of bioregulators. Thus, the study of radioprotective activity and obtaining statistically reliable data requires a significant number of animals and time to conduct such studies. Therefore, in order to obtain the most effective experiments, it is advisable to conduct a PASS-prediction of antiradical, antioxidant, membrane-protective, radioprotective activities and perform studies of antioxidant, antiradical action (as the criteria for selecting potential radioprotectors) on several *in vitro* models, using the pulse voltammetry and evaluation of adrenaline oxidation inhibition. Pulse voltammetry allows clarifying the mechanism of antioxidant action of the studied compounds and, in addition, to test antioxidant and antiradical activity in a relatively short period of time. Thus an already limited number of compounds (*hit-compounds*) are tested *in vivo* under acute irradiation conditions.

It should also be noted that this work is a continuation of a series of works conducted by scientists of Zaporizhzhya National University that studied derivatives that combine in their structure a nitrogen-containing heterocycle and endogenous thiols or acids (cysteine, cysteamine, etc.). The study results within the recent years (Brazhko O.A., Kornet M.M., Omelyanchik L.O., Labenska I.B.) show that the combination of nitrogen-containing heterocycle and mercaptocarboxylic acids increases biological action or results in the appearance of new effects due to the influence on free radical oxidation (FRO) in tissues.

CHAPTER 1. KNOWN RADIOPROTECTORS AND ANTIOXIDANTS. THEIR MECHANISM OF ACTION

Fig. 1.
Radiation sign

In recent years the ionizing radiation effect has become more used in all life spheres and that constantly increases human contact with radiation sources in particular with medical exposure that has 15–20% of all the radiation exposure [9; 10; 11; 12; 13]. Along with this, there's always a threat of nuclear disasters, radiological accidents, and nuclear war. As an example, searching for radioprotective agents has started since such disasters as the Hiroshima and Nagasaki bombings (Japan, 1945) that happened during World War II. Further on there were a few great nuclear accidents, such as Three Mile Island (USA, 1979), Chernobyl (USSR, 1986), Fukushima (Japan, 2011), and many others [14; 15; 16; 17; 18]. All these cases make the problem of searching for new radioprotectors more relevant for Ukraine, as well as for the whole world.

Ionizing radiation includes alpha, beta, gamma rays, X-rays, as well as other high-energy charged particles such as protons and ions obtained in accelerators. While passing through the substance, neutrons don't ionize its atoms, but ionization occurs due to secondary processes in the absorption of neutrons by nuclei, knocking out protons or the decay of neutrons into protons and electrons or antiprotons and positrons [19; 20; 21; 22; 23; 24; 25; 26; 27].

Ionizing radiation comes from radioactive materials, X-ray tubes, particle accelerators and is present in the environment. It is invisible and cannot be directly detected by human sensations and thus such tools as the Geiger counter, ionization detector in various modifications are used quite often (Fig. 2) [28; 29; 30; 31; 32; 33; 34; 35; 36].

Fig. 2. Geiger counters, ionization detectors

Ionizing radiation has many practical applications in medicine, scientific research, construction and other fields, but at the same time, it's dangerous to health when improperly used. Exposure to high doses of radiation leads to living tissue damage that results in burns, radiation sickness, death. And exposure to at low doses leads to cancer, tumors and genetic mutations [37; 38].

In 1988 the International Atomic Energy Agency (IAEA) developed and put to use the International Nuclear Event Scale (INES) that is used to assess emergencies related to accidental radiation releases to the environment at nuclear power plants and is applied to all institutions related to the civilian nuclear industry. According to the INES scale, nuclear and radiological accidents and incidents have 7 levels of classification, as well as the area of impact is also taken into consideration. This data is given in Annex A [39; 40; 41; 42].

Radioprotectors are substances or drugs, mainly of synthetic origin. Their introduction into the environment with biological objects or into the whole organism before irradiation reduces the harmful effect of ionizing radiation by its absorption, increasing radioresistance or decreasing radiosensitivity as well as enabling radioprotective effects at physico-chemical and biochemical levels [9].

There are different classification types of radioprotectors. They are often divided into three groups – short-acting radioprotectors (classic),

long-acting radioprotective agents and radioresistance stimulators (radiomodifiers).

Short-acting radioprotectors (I protectors type) are pharmacological agents from different classes and groups of chemical compounds that show antiradiation action at the cellular level during primary radiation-chemical processes during the absorption of ionizing radiation energy [43].

Characteristics of classic radioprotectors:

- ✓ optimal radioprotective effect is applied only when used immediately before irradiation in high doses;
- ✓ protective action lasts only within the first minutes and hours since the substance enters the tissues and is limited to a few hours;
- ✓ the short duration of action is determined by their high metabolic rate;
- ✓ antiradiation effect is the main pharmacological effect for this group of compounds.

Short-acting radioprotectors can be divided into three specialized groups according to their purpose:

- ➢ **myeloprotectors** – protect the bone marrow and other hematopoietic tissues when irradiated in the "bone marrow" dose range 1–10 Gy. The most numerous group of myeloprotectors consists of sulfur-containing drugs – *β*-mercaptoethylamine (MEA), its disulfide cystamine, WR-638 (cystaphos), WR-2127 (amifostine), gammaphos and other aminothiol derivatives. Sulfur-containing radioprotectors are considered as one of the most effective in terms of dose reduction factor (DRF) (DRF = 1.5–1.7) [44]. The short-term action lasts for 3–4 hours. In some cases, drug redosing might be needed. 5-Methoxytryptamine (mexamine), indralin (B-190), as well as their pharmacological agonists (serotonin, adrenaline, mezaton, clonidine, etc.) and compounds that disrupt oxygen transport (methemoglobin) or its utilization by cells (azides, cyanides, nitrite) have sufficiently high anti-radiation activity among the indolylalkylamines. The most demonstrative protective effect was determined for indralin (B-190), that belongs to the biogenic amines radioprotectors and is a direct-acting α1-adrenomimetic [45];

- **enteroprotectors** – protective means against specific radiation enteritis in case of radiation doses of 10–20 Gy. Currently, there are no nomenclature enteroprotectors, however, experimental data indicate the fundamental possibility of protection against radiation enteritis when using compounds that have a protective effect on intestinal stem cells and support the proliferative pool of enterocytes [46; 47; 48].
- **cerebroprotectors** – protective means against the cerebral form of acute radiation syndrome (ARS) and for prevention of acute radiation death (ARD) within the first 3 days after irradiation above 80 Gy. As of today, metal-containing complexes are used as cerebroprotectors, that reduce lipoperoxidation processes and prevent the consumption of high-energy compounds (NADP and ATP) as well as prevent energy run out and neurons death [49].

Long-acting radioprotective agents (II-type protectors) are pharmacological agents that show radiation protection as a result of secondary reactive changes in biological systems that limit their radiation activity. Unlike "classic" radioprotectors (type I), long-acting radioprotective agents have a wide range of pharmacological properties and the anti-radiation activity is often not the main one.

The main characteristics of II-type radioprotectors:

- ✓ effectiveness in both – preventive (from several hours to 3–4 days before irradiation) and therapeutic use;
- ✓ optimal protective effect is observed in case when irradiation doesn't exceed $LD_{70–80}$ ("bone marrow death") and along with increasing the radiation dose their activity decreases sharply;
- ✓ action against the radiation effect requires several hours or days and lasts for a long time;
- ✓ radiation activity is limited by the physiological capabilities of specific biological systems, through which the radioprotective effect is applied.

Long-acting radioprotective agents include hormonal drugs with estrogenic activity and their synthetic analogs (*β*-estradiol) [50], the human recombinant