Introduction. Formulation of the problem

Nuclear technologies applied in the energy and military areas pose a threat to people and the environment. Nuclear-weapon tests and nuclear power plant (NPP) accidents demonstrate that the adverse effects of using these technologies can cross national borders and affect people’s health for generations [1,2].

Ukraine has a highly developed nuclear energy complex. By the number of nuclear reactors, Ukraine ranks ninth in the world and fifth in Europe. There are 4 active NPP with 15 nuclear power units work in Ukraine. One of them, Zaporizhia NPP, is the most powerful in Europe [3]. In accordance with international treaties, nuclear fuel is transited across the Ukrainian territory for nuclear plants of some European Union countries. Outside Ukraine, there are more than 160 operational nuclear power units in Western and Eastern Europe, where accidents are not impossible. Some Ukrainian NPP are located close to the active combat zones, so can be attacked at any time by unmanned aerial vehicles, and the experience has shown there is no effective protection from them [4]. All the above opens the door for possible deliberate or accidental destruction of nuclear facilities due to military operations or a terrorist attack [5,6].

Because of nuclear proliferation and terrorist activity, there are threats of the ionising radiation (IR) impact on military personnel, civilians, and employees of various rescue services. The main reasons why IR can affect the human body are: accidents at nuclear power plants and in nuclear reactors; accidental or deliberate destruction of nuclear power plants during military activities;
emission of radioactive materials into the environment during their transportation and storage; spraying radioactive materials from aeroplanes; ingress of the materials in drinking-water supplies. Besides, one cannot exclude the possibility of using tactical and strategic nuclear weapon [7-9].

Radionuclides released into the environment can be present in water, air, and soil, and affect foodstuffs of plant and animal origin which also become radioactive. People’s health can be affected by ionising radiation in case of external irradiation, eating radionuclide-contaminated food, inhalation of radionuclides from aerosols in the plume of smoke after an explosion or fire, or from the cloud of radioactive soil particles raised into the air. radionuclides entering the body are toxic due to their physical properties and to the ability to start irradiation of cells resulting from nuclear decay. This irradiation manifests itself in too small amounts, which distinguishes it from the toxicity of chemicals.

The Chernobyl accident shows how necessary it is to find effective medicines to prevent radiation damage to Ukrainian people. This is especially important for those living close to the NPP. Starting from the second half of the twentieth century, ways of preventing radiation damage have been actively searched for to protect the human body from the effects of ionising radiation in space, and to provide radiotherapeutical treatment of cancer which may result from NPP accidents or a nuclear war. However, so far, there are no ideal and absolutely safe synthetic drugs preventing radiation damage (radioprotectors). So, the search for alternative sources of them, including those of plant origin, is still in progress [10].

Searching for them systematically among edible, aromatic, and medicinal plants is a promising direction to discover new sources of safe natural medicines preventing radiation damage. An example is Ayurveda, an Indian system of medicine. It uses medicinal plants to treat diseases caused by free radicals, so it is but logical to expect that herbs like these can be used to prevent radiation damage [10]. One of these promising plants, as evidenced by the recent research, is Podophyllum hexandrum (Royle) of the family Berberidaceae, also known as Indian may apple. In both in vitro and in vivo experiments, it was demonstrated that Podophyllum hexandrum rhizome extract reduced the effect of ionising radiation. It provided over 80% of total-body radioprotection in mice due to its antioxidant properties, free radical absorption, and significant reduction of lipid peroxidation [11]. It was shown that the radioprotective properties of P. hexandrum can be compared to those of modern synthetic radioprotectors [12].

In today’s conditions, it is almost impossible to provide pure food free from radioactive substances to residents of radioactively contaminated territories and NPP observational zones. So, it is necessary to search for foods that can reduce the negative effects of ionising radiation.

The purpose of the research is analysing the scientific information available and summarising the data concerning bioactive substances contained in edible and aromatic plants that grow in Ukraine and can be potential sources of medicines and dietary supplements preventing radiation damage. In these plants, there are bioactive substances with antioxidative, anti-inflammatory, wound-healing, and other properties that can be used to prevent radiation damage and treat its consequences.

Analysis of recent research and publications

Mechanism of the radioprotective effect of plant-derived polyphenolic compounds. There are several theories about mechanisms protecting an organism from radioactive IR by means of radioprotectors. They include absorption of free radicals, blocking the calcium channels, inhibiting lipid peroxidation, stimulating the proliferation of stem cells, etc. [13]. It is believed that the effect of IR on a cell can be direct and indirect. The direct effect of IR results in damaging protein, lipid and DNA macromolecules [14]. The indirect effect results from radiolysis of water and from formation of free radicals that destroy proteins, lipids, and DNA in the membrane and in the cell nucleus [13,15]. Of the free radicals formed during radiolysis of water, the most dangerous is the hydroxyl radical [13,16]. It is established that hydroxyl radicals are responsible for up to 70% of ionisation-induced radiation damage to cells [13,17]. A hydroxyl radical can alter the structure of a protein by oxidation of amino acids [18,19]. Cellular reducing enzyme systems (superoxide dismutase, glutathione peroxidise, and catalase) normally neutralise the effects of free radicals, but with a sharp increase in the number of the latter, cannot perform their functions [20,21].

The main bioactive substances that have a radioprotective effect include compounds with thiol (sulphhydryl) groups, such as thiols, β-aminothiols, thiadiazoles, or benzothiazoles, and compounds with antioxidant or free radical absorbing properties [22,23]. An important tendency in studying the radioprotective properties of plant-derived active substances is prophylactic administration of substances that have strong antioxidant, anti-inflammatory, and immunomodulatory effects [24].

The most common class of bioactive substances of plant origin that exhibit antioxidant, anti-inflammatory, and immunomodulatory properties are phenolic compounds. Phenols comprise a group of compounds in whose molecules aromatic rings are linked to one or more hydroxyl groups. Polyphenols contain several phenolic groups. They can neutralise free radicals, reactive oxygen species, and products of their interaction with organic molecules, and besides, they exhibit antimutagenic activity. Polyphenolic

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compounds are characterised by antioxidant, antitumour, antimutagenic, antiaging, antiallergic, antiatherosclerotic, antithrombotic, antibacterial, antiviral, anti-inflammatory, antiulcer, detoxifying, hepatoprotective, and sedative effects. Polyphenols maintain the oxygen supply of tissues at the optimum level, and prevent the adverse effects of environmental factors [25-33].

Due to the peculiarities of their chemical structure, polyphenolic compounds can neutralise electrons of free radicals and thus terminate radiation-induced chain oxidation in cells [34]. Polyphenols are also capable of trapping and neutralising lipoperoxide radicals, and can chelate metal ions, such as iron and copper, which play an important role in the initiation of free radical reactions [35,36].

**Radiation nephropathy: the present situation in the search of promising renoprotective therapeutic agents of plant origin.** The kidneys are especially radiosensitive among other organs of the abdominal cavity, which limits the total possible dose of radiation therapy for gastrointestinal cancers, gynecologic cancers, lymphomas, and sarcomas of the upper abdomen, and in case of total body irradiation (TBI). Radiotherapy with or without chemotherapy can cause several radiation-induced kidney injuries, including radiation nephropathy (RN) [37-39].

Radiation nephropathy is kidney damage and loss of function caused by ionising radiation. It develops after both kidneys have been irradiated strongly enough [39]. Application of TBI directly before haematopoietic stem cell transplantation (HSCT) and targeted radionuclide therapy have caused an increase in incidence of clinical RN, since it occurs in up to half of patients exposed to threshold or still higher radiation doses [37,39]. Excessive ionising radiation injures most or all parts of the kidney [37]. RN can develop within a year after irradiation with a single 10 Gy dose of TBI, as 14 Gy may be fractionated over 3 days. Lower radiation doses can lead to kidney damage after many years of observation [39]. The radiation-induced kidney damage could progress into chronic kidney disease (CKD), which occurs in more than 20% of TBI-treated patients [40]. CKD after HSCT takes place in 10-30% of HSCT survivors [39].

RN as a chronic radiation injury is characterised by progressive glomerulosclerosis and tubulointerstitial fibrosis, resulting in acquired renal failure. The glomerular and tubular fibrotic changes develop most significantly 24 weeks after irradiation. A slow reduction of renal function, and its clinical symptoms such as azotaemia, hypertension, and anaemia develop after 6 to 12 months after irradiation [40]. The latency is related to the slower cell turnover in kidney tissues in comparison with rapidly proliferating cells [39]. Also, RN usually manifests as proteinuria and disbalanced urine concentration [37].

Chronic oxidative stress (OS) after TBI is related to the inductive effect of radiation on OS in kidneys. It is believed to be the cause of RN in rats, since in the renal tissue of the animals, there is no significant increase in either DNA or protein oxidation products over the first 89 days after irradiation [41].

Morphologic investigations dedicated to RN have found evidence of damage to blood vessels, glomeruli, tubular epithelium, and interstitium [38]. Glomerular damage involves at least its endothelium and mesangium, with the further glomerular scarring due to thrombotic microangiopathy. It is later followed by inhibition of tubular injury; formation of tubulointerstitial scars can be explained by the expression of local mediators, such as TGFβ1, or by activation of the renin-angiotensin system [37].

Iodine-containing contrast agents, known to produce nephrotoxic effects, are widely applied nowadays in radiological diagnostic and interventional procedures. An increase in creatinine in blood serum after exposure to a contrast agent is often applied to diagnose contrast-induced nephrotoxicity (CIN) [42].

RN can result from a nuclear accident or nuclear terrorism: irradiation doses that cause it can be in the range 5 to 10 Gy [37].

In recent years, promising preparations and agents of plant origin, their extracts and individual compounds preventing and alleviating RN have been actively searched for [40,42-47]. The filtration level between the renal tubules and glomeruli is expressed as the creatinine concentration in blood serum [42]. Since the abdominal irradiation increases the levels of blood urea nitrogen (BUN) and creatinine (Cr), known as serum markers of the kidney function [40,43], scientists pay special attention to studying hypoaotaemic activity.

Administration of soya bean oil containing CoQ10 reduced RN in rats. The BUN and creatinine levels were significantly lower after supplementing the diet with CoQ10 compared with the group of animals that underwent 10 Gy abdominal irradiation. Applying CoQ10 essentially decreased glomerular and tubular changes (like glomerulosclerosis and tubulointerstitial fibrosis) in the irradiated tissue [40].

3-O-β-D-galactoside of quercetin, the main active substance of aqueous ethanolic extract of *Podophyllum hexandrum*, had a radioprotective effect in the renal model system against supralethal (0.25 K Gy) gamma radiation, of mice’s kidney homogenate [44]. The flavonoid baikalein (5mg/kg/day) suppresses a radiation-induced (15 Gy) inflammatory process and phosphorylation of the signal pathways MAPK and Akt in mouse kidneys [46], negatively regulating NF-κB and up-regulating FOXO activation. Epigallocatechin-3-gallate (EGCG) administered in the doses 50 and 100mg/kg (per os) alleviated CIN in rats, in the model with no toxin as well as in the glycerol-aggravated one. Both doses of EGCG protected kidneys against dysfunction, as evidenced by a decrease in the high Cr and BUN levels in blood serum and by histopathological analysis [42].
Aqueous extract of powdered coriander seed (Coriandrum sativum L.) (300mg/kg b.w./day for 42 days) demonstrated radioprotective activity against total body γ-irradiation of rats at a dose of 4 Gy. Due to the ability of coriander seed to absorb free radicals, the treatment significantly attenuated the radiation-induced biochemical changes in the blood serum, and decreased the urea and Cr levels, as compared to those in radiation-treated animals [45].

Prolonged oral administration of rhabar extract along with total body γ-irradiation of male rats (100 mg/kg b.w. daily for 21 days prior to irradiation at 7 Gy and for 7 days after the exposure) demonstrated a significant decrease in renal marker enzymes. After the irradiation, the percentage of the change in creatinine was 56% in comparison with the group that had not been exposed to radiation, while in the radiation-treated rats that were given the extract, this value was 14% [47].

Two-week administration of ethanolic extracts from olive and ziziphus leaves (200mg/kg b.w., per os) to γ-irradiated rats (4 and 6 Gy) showed a significant decrease in the Cr and urea levels in comparison with the γ-irradiated group [43].

Dose fractionation does not allow avoiding RN completely [38]. So, it is but an obvious renoprotective strategy to administer radioprotective agents containing polyphenolic compounds prior to radiation treatment, in order to prevent or attenuate damage to the kidneys.

The main polyphenolic compounds of edible and aromatic plants. Some food plants (fruit, berries, vegetables, and cereals) contain a lot of polyphenolic compounds that exhibit radioprotective effects. It is known that 100 g of apples, pears, or cherries contain 200 to 30 0mg of polyphenols [48-50]. A lot of polyphenolic compounds are found in grapes (Vitis vinifera L.). The pulp of the berries contains 10% of the total polyphenolic compounds, the seeds 60-65%, and the skins 20-35%. Polyphenolic compounds are retained in grape-based beverages [51,52]. It has been established that a concentrate of a natural polyphenolic complex obtained from red grape wine containing anthocyanins, flavonoids, and phenolic acids has radioprotective properties [53,54]. It has also been proved that one of the polyphenolic compounds of grape berries, resveratrol (C14H12O3), is radioprotective. Resveratrol (Fig. 1) belongs to phytoestrogens, which, in their action, are similar to animal and human hormones. The richest sources of resveratrol are seeds and skins of grapes, dewberries, mulberries, blueberries, and cranberries [55].

Some pharmaceutical companies in Ukraine, France, and the United States of America produce dietary supplements with antioxidant properties based on red wine extract and grape seed extract. These supplements can be used to prevent radiation damage to residents of the NPP observational zones in Ukraine. One of these supplements, manufactured by Equilibre Attitude (France), contains grapefruit polyphenols, zinc, selenium, extracts of echinacea, ginkgo, eleutherooccus, pine buds, willow bark, and a vitamin and mineral complex with amino acids [56].

Chicory (Cichorium intybus L.) is one of widely used food plants in Ukraine. Chicory improves digestion and has anti-inflammatory, sedative, choleretic, diuretic, and general strengthening properties. Its roots are used to prepare coffee substitutes. It was investigated how methanol extract from chicory seeds protected human lymphocytes against radiation damage caused by ionising radiation. It was found that the extract exhibited free radical absorbing activity depending on its concentration, and was protective against γ-radiation. The methanolic extract of chicory seeds completely protected the DNA from damage caused by ionising radiation. The studies [57,58] showed that the radioprotective effect of methanolic extract from chicory seeds could be explained by the antioxidant effects of chlorogenic acid (Fig. 2).
Betanin, in its powdered form, is widely used in the food industry as the food additive Beet Red (E 162). When dissolved in water, it is immediately restored to natural beet juice. Beet Red is applied to colour meat, sausages, beverages, ice cream, to produce desserts and other sweets. It is permitted to use betanin in food in most countries, including Ukraine.

Drugs preventing radiation damage can be obtained from milk thistle (Silybum marianum (L.) Gaertn.), a nutritious edible plant. All parts of it are consumed in various forms as food. Its peeled roots are consumed raw, boiled, or fried. The young shoots and leaves after steeping are added to salads or boiled. The flowers of milk thistle are dried, crushed, and added to the food as seasoning.

Fig. 4. Silibinin: (2R,3R)-3,5,7-trihydroxy-2-[[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo]|1,4|dioxin-6-yl|chroman-4-one

Beta vulgaris roots contain: 0.652mg of glycosides, 11.64mg of β-carotene, 2.6mcg of vitamin A, 3.2mcg of vitamin K, 0.18mg of vitamin E, 4.36mg of vitamin C, 0.03mg of vitamin B₃, 90mg of vitamin B₂, 0.034mg of vitamin B₁₂, 0.151mg of pantothenic acid, 128.8mg of alkaloids, 16.4mg of steroids, 115.5mg of terpenoids, 3.789mg of saponins, 6.15mg of flavonoids, 20mg of potassium, and 0.76mg of iron [62]. The most important functional phytochemicals of the Beta vulgaris root are betalains, water-soluble pigments, consisting of nitrogenous structures of betalamic acid, which are dissolved in vacuole sap. The main betalain of Beta vulgaris, which has antioxidant properties, is betanin C₂₄H₂₅N₂O₃ (betanidine-5-O-β-glucoside) [63-65]. It was found that at pH=4, betanine (Fig. 3) as a free radical absorber was approximately by 1.5-2.0 times more active than other anthocyanins [66]. Oral administration of aqueous extract from the Beta vulgaris root increased the survival of lethally γ-irradiated mice, stimulated cell proliferation, minimised damage to DNA, and increased the haematocrit and haemoglobin levels [23].

Fig. 3. Betanin (betanidine-5-O-β-glucoside)

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The antioxidant properties of silymarin decrease the level of lipid peroxidation due to reducing the amount of the toxic product malondialdehyde. Silymarin increases the activity of antioxidant protection enzymes, in particular, superoxide dismutase, catalase, glutathione reductase. It inhibits increased oxygen absorption and, when necessary, is able to increase generation of reactive oxygen species by blood cells to ensure the functional activity of phagocytes. silymarin reveals its antioxidant activity at low concentrations, with highly reversible chemical transformations. This is one of the reasons why silymarin is low-toxic [69].

According to the findings of recent studies [67], oral intake of 70 mg/kg of silymarin resulted in the survival of 67% of experimental mice after lethal γ-irradiation at 9 Gy. The following values were increased: red blood cell count from 1.76±0.41·10¹⁰ to 9.25±0.24·10¹⁰, haematocrit from 4.55±0.24% to 37.22±0.21%, and total leukocyte count from 1.4±0.15·10⁶ to 8.31±0.47·10⁶ compared to the control group on the 15th day. Silymarin protects the enzymatic, haematologic, and immune systems from γ-induced toxicity, and may be a useful source of medicines preventing radiation damage [67].

Promising sources of remedies for radiation damage prevention include aromatic plants. They significantly improve the taste of dishes, and are widely used as medicines. In recent years, a number of studies have been carried out on the radioprotective properties of some aromatic herbs and spices. This makes it possible to use these natural agents as potential drugs to prevent radiation damage [70].

Aromatic plants and spices contain significant amounts of essential oils. They are complex mixtures of secondary metabolites and consist of hundreds of
low molecular weight terpenoids [71,72]. They are widely used in cooking, aromatherapy, and cosmetics. As a result of the studies [70,73], it was established that aromatic plants could exhibit antioxidant and antimicrobial activity and be used to prevent cardiovascular diseases, atherosclerosis, and cancer.

Besides essential oils, extracts of aromatic plants contain polyphenols (flavonoids, lignans, stilbenes, tannins), terpenes, and vitamins. Essential oils contain monoterpentenes and diterpenes that have antioxidant properties. The activity of cyclic monoterpene hydrocarbons with two double bonds can be compared with the activity of polyphenols. It was shown that the antioxidant capacity correlated with the total phenolic content in extracts of aromatic plants [70, 74].

Extracts of about thirty aromatic plants and spices were found to have radioprotective properties. These extracts proved able to reduce γ-irradiation-induced lipid peroxidation and the absorption of free radicals both in in vitro and in vivo experiments. The results of most studies show that extracts of aromatic plants can increase significantly the survival of irradiated animals. This suggests that they are a promising source of preparations for prevention and treatment of radiation damage [70].

The examples include peppermint (Mentha piperita L.) and sage (Salvia officinalis L.), which are widely used as medicinal plant materials, aromatic plants, and spice. Peppermint extracts have an antioxidant effect due to the presence of eugenol, caffeic acid, rosmarinic acid, and α-tocopherol. Eriocitrin, luteolin-7-O-glucoside, flavonoids, and s-carvone were identified as free radical scavengers [70,75,76]. Peppermint extract given to mice before γ-irradiating them showed a significant increase in the activity of glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase, and provided protection to bone marrow cells. It significantly reduces the number of aberrant cells and chromosomal aberrations in irradiated mice [77]. Sage as a medicinal and aromatic plant is popular in many countries. It contains volatile oils consisting of a mixture of terpenes, triterpenoids, urosoic acid, and oleanolic acid [78]. Also, sage extracts, contain carnosol, rosemary acid, rosmanol, isorosmanol, and epirosmanol, which have antioxidant properties [79,80]. The presence of active polyphenolic compounds containing aromatic rings with hydroxyl groups allows the aqueous extract of Salvia officinalis to protect brain cells from being damaged by γ-irradiation, and to decrease lipid peroxidation significantly [81].

**Conclusions**

1. The extensive use of nuclear technologies is fraught with risks of the adverse effect of ionising radiation on the human body. So, new effective means of preventing radiation damage should be searched for. So far, there are no absolutely safe synthetic agents preventing radiation damage. Searching for them systematically among edible and aromatic plants is a promising direction to discover new sources of safe natural medicines preventing radiation damage.

2. Polyphenolic compounds in aromatic and food plants, due to their antioxidant properties, can neutralise free radicals (thus inhibiting radiation-induced chain reactions of oxidation in cells), scavenge and neutralise lipoperoxyl radicals, and chelate metal ions. Besides, these compounds are antimutagenic. Polyphenolic compounds are characterised by antioxidant, antitumour, antimutagenic, antiaging, antiaggressive, antithrombosis, antibacterial, antiviral, anti-inflammatory, antiallergic, antiatherosclerotic, antithrombotic, and sedative effects.

3. Radiotherapy can cause various radiation-induced kidney disorders, including radiation nephropathy. Nowadays, scientists are actively searching for promising plant-derived substances that could prevent and alleviate radiation nephropathy. It is an obvious renoprotective strategy to administer radioprotective agents containing polyphenolic compounds preventively, prior to radiation treatment.

4. Literature sources, including experimental studies of domestic and foreign scientists, have been analysed. It has been shown how promising it is to continue phytochemical, pharmacodynamic, and toxicological studies of the properties of polyphenolic compounds in edible and aromatic plants, as these studies aim at creating new plant-derived substances with antioxidant, anti-inflammatory, and antimutagenic action, which prevent and treat radiation damage.

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Ключові слова: радіація, нефропатія, радіопротектори, поліфеноли.
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