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RADIOPROTECTIVE PROPERTIES OF PHYTOMEDICINES: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Till today, antiradiation agents have been mainly found among radioprotectors synthesized from sulfur-containing compounds. The search for radioprotectors in other classes of compounds appeared to be less successful.*

The study aimed to *analyze the pharmacodynamics of phytopreparations used to correct disorders of the immune and antioxidant systems and purine metabolism of the body induced by radiation.*

Methods: *The review included publications indexed in PubMed, Medline, E-library, and CyberLeninka databases. The search was made using the Google Scholar scientific search engine. The search filters included: experimental studies performed on mice and rats over the past decade (2012 to 2022).*

Results: *The literary search returned an insufficient number of publications on the qualities of the action of phytopreparations, such as integrity and complexity, the versatility of action, selectivity, and organotropism. The lack of publications on side effects (except for allergic intolerance to any components of plants) requires a profound study of this topic.*

Conclusion: *Radiobiology should search for new non-drug means of treatment and make experiments to study the effect of phytocompositions on biochemical processes in an irradiated organism.*

Keywords: *ionizing radiation, metabolic processes, radioprotectors, phytomedicines, phytocompositions.*

Introduction: The mechanism of action of radioprotectors has still been explained by their direct participation in various radiation and reparation processes. However, a mediated action of radioprotectors has been increasingly confirmed since the 1960s. Nowadays, several concepts explain this indirect effect through biochemical shock, sulfhydryl hypothesis, endogenous reasons for radioresistance, and some other actions [1].

The studies on chemical protection against ionizing radiation have outlined two possible mechanisms of action. First, the initial body resistance level might be increased with the help of radioprotectors and several physical factors. Second, the reasons for extensive resistance of biological objects and systems with different levels of biosystem organization are being studied. The above approaches suggest an endogenous origin of radioresistance. They attribute radioresistance to the radiation protection and sensitization systems available in the body [2].

Numerous radiologists maintain that one of the pressing environmental problems in the world is environmental pollution by waste from the mining and ore processing industries. Mineral production has a comprehensive impact on the environment [3]. Waste and by-products of industries, transport, heavy industry, the nuclear-industrial complex, mechanical engineering, instrument making, heat and power plants, pesticides, wastewater, and gases pollute the environment with heavy metals, causing an acute global environmental problem of our time. The state of human and animal health depends upon solving this problem [4].

This study aimed to analyze the literature on the pharmacodynamics of phytopreparations used to correct disorders of the immune and antioxidant systems and purine metabolism of the body induced by radiation.

Materials and methods: A search for scientific publications on the research topic was conducted in PubMed, Medline, CyberLeninka, e-library, and Cochrane databases using the Google Scholar scientific search engine.

The search included experimental studies performed on mice and rats over the past decade (2012 to 2022), published in English, Russian and Kazakh languages, and full versions of articles with clearly formulated and statistically proven conclusions. The keywords included "ionizing radiation," "metabolic processes," "radioprotectors," "phytopreparations," and "phytocompositions."

Report summaries, newspaper publications, and personal messages were excluded from the analysis.

A total of 547 literary sources were found, from which 50 papers were selected for further analysis. After the automatic search, we performed a manual search for publications to identify other scientific sources to be included in the presented review.

Results: The resistance of biological systems to ionizing radiation depends on the content of endogenous radi-

oprotectors vs. endogenous radiosensitizers. Antiradiation drugs increase endogenous radioresistance by mobilizing the protective resources of the body and suppressing radiosensitizing processes [5]. They launch the cell regulation systems and activate the lipid peroxidation processes' monitoring system. This decreases the severity of lesions from body irradiation and intensifies reparative post-radiation processes [6].

The endogenous background concept can explain the effect of reaching the maximum level of protection against acute radiation. Nature offers certain protective resources; protective drugs can activate these resources. Maximum use of such protective drugs promotes optimal protection for each class of compounds [7]. Speaking about the limited reserve of endogenous protective resources of the body for one class of radioprotectors, we do not assert that this reserve cannot be more capacious for the implementation of the protective effect of any other drugs, as well as multi-component formulations. The concept of the endogenous background of radioresistance also suggests that drugs modulating general resistance, including drugs that have long been used in traditional medicine to normalize the body's homeostasis, can be used for radiation protection [8].

The main incentive in the search for natural antiradiation agents was to eliminate some significant disadvantages of classical synthesized drugs. These disadvantages included toxic side effects, limited duration of use, and a decrease in protective activity at lower radiation dose rates [9]. Indeed, the use of natural drugs made it possible to obtain a therapeutic and prophylactic effect, partially or entirely devoid of the listed disadvantages. A sort of payment for those advantages was the low efficiency of natural remedies used at lethal doses of radiation. There was a danger of their ineffectiveness that could discredit the very idea of using radiation protection equipment. However, unlike classical radioprotectors, natural adaptogens stabilize homeostasis and increase nonspecific body resistance [10]. Adaptogens' varied therapeutic and prophylactic effects make them a preferred choice for pharmacological sanitation [11]. The drugs introduced into the body must have the following qualities: be completely harmless, have a wide range of therapeutic action; cause minimal changes in the normal conditions and normalize altered homeostasis; they should increase resistance to harmful effects of a wide range of factors of chemical, physical and biological nature; their normalizing effect should not depend on the direction of previous deviations of homeostasis [12, 13].

An important feature of the action of phytoadaptogens is their regulation of brain activity, expressed in the normalization of excitation and inhibition reactions, optimization of learning and memorization processes, and restoration of some biochemical disorders, including the exchange of biogenic amines [14]. An increased central nervous system reactivity is accompanied by the activation of neurohormonal regulation of internal organs, mainly the hematopoietic system, and increased dynamic accuracy of homeostasis correction. At the same time, it is known that stimulation of the formation of biogenic amines under the influence of phytoadaptogens can increase the radioresistance of animals [15]. In acute radiation sickness, preparations isolated from some highly radio-resistant plants exhibit antiradiation activity [16]. Despite low efficiency, some qualities of these drugs attract attention: they are non-toxic, can be used as a food substance during chronic irradiation and repeated administration, and increase general nonspecific body resistance [17].

Such compounds are contained in some well-known medicinal plants. These substances, jointly called "adaptogens," increase the body's resistance to extreme factors of varied nature. They can help an individual adapt to extreme conditions and be more effective in these conditions [18]. Regardless of the increased resistance to extreme factors due to adaptogens and their analogs, a comprehensive analysis of this phenomenon has not been carried out despite repeated attempts [19].

Discussion: The literature provides data on the presence of adaptogens with a significant effect on the mediator mechanisms of adaptation. They particularly influence the functioning of catecholaminergic synapses and CNS endorphin receptors. This indicates the multiplicity of potential mediator effects of plant adaptogens [20]. Many adaptogenic compounds, widely represented in the plant world, enter the body in varying amounts with food. They protect the cell membranes from destruction by free radicals caused by extreme factors and thus significantly affect the adaptation process [21]. It was discovered that a mixture of lipid peroxidation inhibitors has a synergic effect on inhibiting free radical oxidation [22]. An interaction with a free radical reduces a more active lipid peroxidation inhibitor due to the abstraction of a hydrogen atom from a less active inhibitor. This process continues until all inactive inhibitors in the mixture are consumed. Polyphenols ingested with food do not inhibit lipid peroxidation in the body but reactivate the natural non-enzymatic antioxidant system [23, 24].

Adaptogens inhibit lipid peroxidation in rat liver against the background of chronic cold stress. They reduce the concentration and accumulation of malondialdehyde and diene conjugates. This coincides with the data of other authors who found that ginseng glycosides protect yeast cells under X-ray irradiation, and Eleutherococcus extract increases the resistance of animals to the action of ionizing radiation [25]. There is evidence that adaptogens enhance anabolic processes, particularly DNA synthesis. However, probably, adaptogens do not stimulate anabolic processes but weaken the damaging effect of free radicals on cellular and subcellular structures, thus optimizing the formation of a systemic structural trace as the final stage of adaptation [26].

Of great interest are the works of radiobiologists who use the most ancient experience of traditional medicine to create therapeutic and prophylactic agents for radiation injury. Many obtained antiradiation drugs act as hemoimmunomodulating agents, hormone stimulants, detoxifiers, antineoplastic drugs, etc. [27]. They are usually low in toxicity and can be successfully combined with other components to prepare antiradiation formulations. The action of natural drugs is due to a group of complementary substances participating in the control system of the physio-

logical processes of a healthy and irradiated organism, i.e., they can be classified as adaptogens that increase the general nonspecific body resistance [28].

Polysaccharides have low toxicity and activate antioxidants. Antiradical biogenic substances are the essential components for endogenous radioresistance. They provide a long-term increase in the body's radioresistance [29]. They stimulate immunity and hemopoiesis [30].

Therapeutic and prophylactic use of the listed food multi-component phytoadaptogens invariably causes an increase in the endogenous background of resistance, normalization of lipid peroxidation processes, and replenishment of the antioxidant system reserves [31].

The antiradiation effect of some extracts and rough extracts from plant and animal tissues may be associated with the effect on the body of several biologically active compounds which complement or enhance each other, balanced by nature itself [32]. Indeed, in many cases, the activity decreases as the coarse hoods are cleaned. Such multi-component mixtures are difficult to identify, and therefore they often remain in the literature without a chemical characterization of the active principle [33]. Some publications do not report the chemical compositions and source of the drugs due to forthcoming patenting. All this complicates the systematization and assessment of antiradiation substances' mechanism of action [34].

Antiradiation natural substances have little or no toxicity. Many of them are effective even after irradiation, and some can maintain their activity for a long time after oral administration [35]. Some drugs are already being used in clinical practice. At the same time, classical synthetic radioprotectors are usually toxic and have a predominantly prophylactic rather than therapeutic effect. However, classical radioprotectors are useless in chronic irradiation of the body, especially in difficult radioecological conditions [36].

Due to an extensive experience in phytochemical research and their high applied significance, obtaining new substances of plant origin with a pronounced biological activity is among the priorities of scientific development. The domain is the "Creation of materials with specified properties by chemical methods from hydrocarbon and plant raw materials; creation of materials using nanotechnologies; obtaining pure materials and alloys with desired properties" [37]. More than 150 plant species are used in official and traditional medicine in Kazakhstan. However, many can be considered substitutes and vicarious species for generally recognized pharmacopeial plants. Their use in recent years has been expanding due to their low cost, complex therapeutic effect on the body, low toxicity, and the possibility of long-term use without side effects [38]. Among the directions being developed to search for new drugs, triterpene compounds of birch occupy a prominent place. In our country, the raw material base for obtaining triterpenoids from birch bark is practically unlimited [39].

Non-drug treatment methods are increasingly being introduced into healthcare practice. However, the level of their use does not correspond to the possibilities and significance of these therapies. Their use in practical medicine will help manage many diseases successfully and reduce the incidence of drug complications. Further phytotherapy research might be of great value for patients living in ecologically unfavorable regions [40]. Under the influence of various non-drug methods of therapy, the body mobilizes specific mechanisms that combine into a functional system and ensure optimal functioning of the body with the lowest energy costs under these conditions. Phytotherapy is a variant of metabolic therapy. Phytotherapy fully meets the requirements for pathogenetic therapy since it directly influences tissue metabolism [41]. Significant depletion of cell bioenergetics by radiation urges to correct metabolic bioenergetic processes and restore altered functions of cells and organs. Adaptation processes can be stimulated by correcting purine and energy metabolism by non-drug means [42].

Lead belongs to the substances of the first hazard class, and it is included in the list of priority pollutants by several international organizations. In many countries of the world, national programs have been developed to reduce environmental pollution with lead and limit its negative impact on the health of the child population. Even in low concentrations, lead can cause many health disorders: immune, neuropsychiatric, hematological, etc. Scientists believe that the human body receives 40 to 70% of lead from food [43]. Also, a significant increase in urban transport pollutes the environment with fuel combustion products. So, when one liter of fuel is burned, up to 40 grams of lead gets into the air. Lead, which enters the lungs, is 10-100 times more toxic than that which enters through the stomach. Despite the developments of domestic and foreign scientists, not all aspects of the problem have been sufficiently investigated [44].

These studies were conducted using high and medium doses of heavy metals in experiments. The effect of low and ultra-low doses of metals and the simultaneous action of various physical and chemical environmental factors on the body, including the combined action of various doses of radiation, are understudied [45]. Radiation injury to the body results in immunodeficiency. The development mechanism of this condition is complex and insufficiently studied. The least studied are the effects of relatively weak ionizing radiation on the immune system. Low radiation does not produce clinical symptoms in the early stages to initiate a study of its consequences [46].

The maximum likelihood of synergism and potentiation of effects and other unfavorable environmental factors exists under the action of small doses of radiation, which contributes to a decrease in the general reactivity of the body, an increase in sensitivity to infections, and the ability to chronicle the process [47]. A combined or predominant effect of various factors depends on the radiation situation characteristics, the time of residence in the radiation risk zone, and age at testing. Studying the combined effect of low doses of gamma-radiation and heavy metal compounds is promising for Kazakhstan's and global medical science. The environment contamination with heavy metals remains a relevant issue in the settings of anthropogenic progress and increased human activity [39]. Analysis of the literature showed that the interest of many scientists attracts the immune system as an object of toxic effects of unfavorable environmental factors, which may result in the development of secondary immunodeficiency [24].

There has been an intensive search for new means of protection and therapy for radiation injuries that do not cause toxic or side effects in animals and humans in recent years. These studies focus on the use in medicine of phytomedicines with radioprotective properties [48]. Due to the annual increase in anthropogenic impact and the deterioration of the ecological environment, it is necessary to develop a national medical, ecological and environmental program to reduce environmental pollution with heavy metals and limit its negative impact, especially on the health of the child population [49]. It is necessary to develop new innovative methods of correction and practical measures to remove heavy metals and their toxic compounds from the body to minimize the risk of adverse consequences for the health of the population of Kazakhstan. The effect of potassium dichromate and lead oxide on altered body reactivity under small doses of radiation requires further study. New pathogenetic ways shall be discovered to correct these disorders using phytocompositions [50].

Conclusion: The plurality of registered changes in all parts of the immune system during radiation damage to the body is a sign of immune dysfunctions. In this regard, the approaches to preventing and correcting immune dysfunction should be different. The study of phytomedicines and their use for radiation injury seems relevant to the above. Therefore, radiobiologists are still tasked to search for new non-drug means of treatment in an experiment and study the effect of phytocompositions on biochemical processes in an irradiated organism.

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ФИТОПРЕПАРАТТАРДЫҢ РАДИОПРОТЕКЦИЯЛЫҚ ҚАСИЕТТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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ТҰЖЫРЫМ

Өзектілігі: *Күні бүгінге дейін радиацияға қарсы агенттерді іздеудегі сәтсіздіктер негізінен құрамында күкірт бар қосылыстар жүзіндегі радиопротекторлардың синтезімен байланысты болғаны әдебиеттерден мәлім. Қосылыстардың басқа түрлері негізіндегі радиопротекторларды іздеудің де сәтсіз екенін айтып кеткеніміз абзал.*

Зерттеу мақсаты *– сәулеленген организмдегі зат алмасу бұзылыстарын коррекциялауға арналған фитопрепараттардың фармакодинамикасын зерттеу бойынша әдебиеттерге шолуды талдау.*

Әдістер: *Әдеби шолуды іске қосуға ұсынылған барлық жұмыстар «Google Scholar» ғылыми іздеу жүйесі арқылы PubMed, Medline, E–library, Cyberleninka базаларында индекстелген. Таңдау алдында келесі шарттар ескерілген: ағылшын, жапон және орыс тілдерінде жарияланған соңғы 10 жыл ішіндегі тышқандар мен егеуқұйрықтарға жасалған эксперименттік зерттеулер.*

Нәтижелер: *Әдеби мәліметтерге сай тұтастық пен күрделілік, әрекеттің жан-жақтылығы, селективтілігі, ағзалық тропты-лығы сияқты дәрілік шөптердің әрекеті жеткілікті зерттелмеген; өсімдіктердің кез-келген компоненттеріне аллергиялық төзбеушілікті қоспағанда, іс жүзінде ешқандай жанама әсерлері болмайтын препараттарды тереңірек зерттеу қажет.*

Қорытынды: *Радиобиологтар міндеттерінің бірі фитокомпозицияның сәулеленген организмнің биохимиялық үдерістеріне әсерін зерттеу мақсатында тәжірибе жүзінде жаңа дәрілік емес емдеу жолдарын іздестіру болып табылады.*

Түйінді сөздер: *иондаушы сәулелеу, алмасу үдерістері, радиопротекторлар, фитопрепараттар, фитокомпозициялар.*

РАДИОПРОТЕКТОРНЫЕ СВОЙСТВА ФИТОПРЕПАРАТОВ: ОБЗОР ЛИТЕРАТУРЫ

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АННОТАЦИЯ

Актуальность: *До недавнего времени успехи и неудачи в поисках противолучевых средств были связаны главным образом с синтезом радиопротекторов, относящихся в большинстве своем к серосодержащим соединениям. В других классах соединений поиски радиопротекторов велись менее успешно.*

Цель исследования *– анализ опубликованных данных в отношении фармакодинамики субстанций фитопрепаратов для коррекции вызванных облучением нарушений обмена веществ в организме.*

Методы: *В обзор были включены публикации, проиндексированные в базах данных PubMed, Medline, E–library, Cyberleninka. Поиск проводили при помощи научной поисковой системы «Google Scholar». Перед началом поиска были выставлены следующие поисковые фильтры: экспериментальные исследования, выполненные на мышах и крысах, за последние 10 лет (2012-2020 гг.).*

Результаты: *В ходе поиска выявлено недостаточное количество публикаций, посвящённых изучению качеств действия фитопрепаратов, таких как цельность и комплексность, многосторонность действия, селективность, органотропность. Недостаточное количество публикаций относительно побочных эффектов, за исключением аллергической непереносимости к каким-либо компонентам растений, требует более глубокого изучения данной темы.*

Заключение: *Одной из задач радиобиолога продолжает оставаться экспериментальный поиск новых немедикаментозных средств лечения с изучением влияния фитокомпозиций на биохимические процессы облученного организма.*

Ключевые слова: *ионизирующее излучение, обменные процессы, радиопротекторы, фитопрепараты, фитокомпозиции.*

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