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МЕХАНІЗМИ РАДІОПРОТЕКТОРНОЇ ТА РАДІОКОРИГУЮЧОЇ ДІЇ ДІЄТИЧНОЇ ФІТОДОБАВКИ – ПЛОДІВ РОЗТОРОПШІ ПЛЯМИСТОЇ

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MECHANISMS OF RADIOPROTECTIVE AND RADIOCORRECTIVE EFFECTS OF DIETARY PHYTOADDITIVE OF MILK THISTLE FRUITS

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Keywords: irradiation, radioprotection, radiocorrection, thistle, mechanisms.

Nuclear power plays a leading role in the provision of energy sources to society. But the consequences of the malfunctions in the operation of nuclear power plants are catastrophic. The accidents in Kyshtym (the former USSR, now the RF, 1957), Three Mile Island (the USA, 1979), Chornobyl (the former USSR, now Ukraine, 1986), and Fukushima (Japan, 2011) became the examples of the destructive effect of radiation on living organisms. A large amount of information on the effects of radiation with the high radiation doses and much less on the effects of the low dose radiation, that can be compared with the level of the natural radiation backgound, has been accumulated over the years of the use of nuclear energy. As it turned out, the low doses of radiation cause a destructive effect not only on the irradiated organism, but also on the subsequent generations of its offspring [1-2]. Therefore the search of the radioprotectors does not lose its relevance.

At present there is a significant number of radioprotectors both synthetic and natural ones [3]. However, they can be only effective if they are applied immediately before exposure to radiation, i.e. if irradiation is expected. Though, when it is impossible to predict the time of irradiation, there is a need to use the radiocorrective preparations. In comparison with the synthetic preparations, the plant derivatives have a low toxicity, a wide spectrum of action and are more socially adapted. Therefore, lately, in a search for such preparations, more attention is paid to the natural compounds: from more studied propolis and green tea to more exotic schisandrin [4] and baikalein [5]. In the range of such phytoadditives the fruits of milk thistle (Silybum marianum (G.) attract a considerable attention, due to the flavonoid silumarin in their compositions,

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Низькі дози опромінення справляють руйнівну дію не тільки на сам організм, а й на наступні генерації його нащадків.
***Метою роботи** стало визначення механізмів радіопротекторної та радіокоригуючої дії in vivo дієтичної фітодобавки – мелених плодів розторопші плямистої – на системи гідролізу та транспорту вуглеводів різного ступеня полімерності у тонкій кишці нащадків опромінених самців щурів.*
***Матеріали та методи.** Опромінення проводили одноразово на телегамма-установці «Агат-Р1», потужність дози – 120 рад/хв, поле – 20 х 20 , ВПД = 75 см, доза – 0,5 Гр, час експозиції – 32 с. Акумулюючий препарат слизової оболонки (АПС) виготовляли за методом О.М. Уголєва та співавторів. Інкубували АПС протягом 1 години за температури 37º С в оксигенованому середовищі. Як інкубаційне середовище використовували розчини 10 ммоль/л глюкози або 5 ммоль/л мальтози, які виготовляли на розчині Рінгера рН = 7,4. Для емульгування до середовищ додавали по 3 краплі кролячої жовчі. Концентрацію глюкози визначали колориметрично на КФК-2МП, $\lambda = 625$. Оцінювали активність транспорту вільної та М-глюкози в АПС нащадків опромінених самців за різних умов вживання розторопші батьками.*
***Результати**. Дієтична добавка – мелені плоди розторопші плямистої – стимулює транспорт вільної та М-глюкози (в 1,6 рази відносно інтактних груп в обох випадках) у нащадків опромінених самців, які отримали розторопшу перед опроміненням, та інтактних самиць (радіопротекторний ефект), у 2,7 та 2,8 рази відповідно – у нащадків опромінених натще самців через самиць, які споживали розторопшу протягом лактації (радіокоригуючий ефект).*
***Висновки**. Дієтична фітодобавка мелені плоди розторопші плямистої справляє радіопротекторний і радіокоригуючий ефекти у нащадків першого покоління опромінених самців. Реалізація обох ефектів має гендерні особливості: радіопротекторний ефект реалізується через опромінених ситими самців, які отримали розторопшу перед опроміненням, та інтактних самиць, натомість радіокоригуючий ефект реалізується у нащадків опромінених натще самців через самиць, які вживали розторопшу протягом лактації.*

Ключові слова: опромінення, радіопротекція, радіокорекція, розторопша, механізми.

they are a basis for a number of known hepatoprotectors : from Karsil (Bulgaria) and Legalon (Germany) to Fosfontsiale (the RF) and Levasil (India).

The hepatoprotective effect of the milk thistle fruits' derivatives is explained primarily by the membranotropic activity of silymarin. So it was thought that this activity can be realized for other tissues and organs except liver. The last barrier between the internal medium of the organism and the environment is a small intestine where the processes of digestion and absorption of nutrients end. It is the most radiosensitive chain of gastrointestinal tract. The small intestine reacts on the irradiation by the desquamation of enterocytes, the stratification of the intestinal wall, the decrease of the viscosity of the lipid bilayer of membranes, etc. [6]. Therefore, in our experiments, the small intestine of rats was chosen to study the effects of irradiation and the effect of phytoadditives of milk thistle on them. The grist, oil or milled fruits of milk thistle are wide-spread as such phytoadditives (first of all, for hepatoprotection). However, milled fruits contain also chlorophyll, ether oil (0.08%), 20~30% fixed oil (approximately 60% is linoleic acid, approximately 30% is oleic acid, and approximately 9% is palmitic acid); 25~30% protein; 0.038% tocopherol; alkaloids, saponins, mucilage, organic acids, 0.63% sterols, (cholesterol, campesterol, stigmasteroll, and sitosterol); vitamins, bitterness, biogenic amines (tyramine and histamine), resins, as well as iodine, zinc, selenium, calcium, phosphorus, chromium, boron, etc. [7]. Obviously, these components also participate in the realization of the membranotropic effect of milk thistle. But grist does not contain fat-, oil-, and watersoluble components. In previous experiments in vitro, we showed the advantage of the effect of total dried water-alcohol extract of milled thistle fruits under effect of their water- and fatsoluble fractions [8]. Therefore, the aim of this work was to determine the mechanisms of radioprotective and radiocorrective effects in vivo of dietary phytoadditive of milled milk thistle fruits on the systems of hydrolysis and transport of carbohydrates of various degrees of polymerisation in the small intestine of the offspring of one-time irradiated male rats.

Materials and methods. The experiments were performed in Vistar's two-month male rats with a mass of 60-70 gram that were held out by the standard ration of vivarium and kept without feed for 18-24 hours before the experiment. 8 groups of the offspring were used: group 1 – intact; group 2 – the offspring of hungry irradiated males and intact females; group 3 – the offspring of fed males and intact female rats; group 4 – the offspring of irradiated fed males which got 3 g of milled milk thistle fruits with a food before irradiation and intact females; group 5 – the offspring of hungry irradiated males which got 3 g of milled milk thistle fruits with a food after irradiation and intact females; group 6 – the offspring of hungry irradiated males and females which got 1.5 g of milled milk thistle fruits with a food every day during all time of lactation (2 months); group 7 – the offspring of hungry irradiated males which got 3 g of milled milk thistle fruits with a food after irradiation and females that got 1.5 g of milled milk thistle fruits with a food every day during all time of lactation (2 months); group 8 – the offspring of hungry irradiated males which got milled milk thistle fruits with a food after irradiation and females which got 1.5 g of milled milk thistle fruits with a food every day during 1 month of lactation, and then their offspring consumed milled milk thistle fruits themselves during 1 month.

A single exposure of male rats was performed with a help of telegammasetting «AGAT-R1», a radiation dose rate was 120 rad/min, a field – 20x20, a distance from the source of irradiation to the field – 75 cm, a dose – 0.5 Gy, exposure time – 32 sec. Accumulating mucosa preparation (AMP) was produced by the Ugolev method [9]. AMP was incubating during 1 hour at t=37° C in oxygenated medium. The solutions of 10 mmol/l of glucose and 5 mmol/l of maltose (equivalent to 10 mmol/l of glucose) were used as an incubation medium made on the Ringer solution with pH 7.4. The bile was added into all incubation media. Concentration of free glucose and M-glucose formed due to the hydrolysis of maltose was determined by the colorimetric method described in ref. [10] with the help of CFC-2MP, λ = 625 nm. Statistical processing of the data was carried out with the help of Primer Biostatistics program.

Results and discussion. It was detected in previous investigations that a single consumption of milled milk thistle fruits with a food by males led to a significant radioprotective effect in the small intestine of their offspring (table, group 4). This effect is realized both for the free glucose transport system and for the enzyme-transport conveyor (ETC) for the hydrolysis of maltose and transport of formed M-glucose. Thus, components of milk thistle fruits are able to prevent the injury of main systems of enterocytes of the offspring of irradiated male. Moreover, it is exactly the effect of milk thistle but not the satiate status of male rats at the time of irradiation: there was no high increase of glucose accumulation in the group 3, but not maltose. However, in this group the deviations from the mean parameter of the glucose accumulation (but not maltose) were 3.9-fold less than in the group 1 and 4.9-fold less than in the group 2 (table). So, the satiate status of the male rats before irradiation leads to the stabilization of the free glucose transport system but not maltose, i.e. irradiation injures just a hydrolytic chain of ETC, and the satiate status cannot protect it [11]. Therefore, exactly a presence of milk thistle fruits in the food of the male rats before the irradiation probably protects both transport and hydrolytic chains of maltose assimilation system. Taking into account these radioprotective properties of thistle, its radiocorrective effect should be expected. But in the group 5 (table) the transport parameters of free glucose were the lowest among all studied groups, although they were within the borders of active component of the transport. Instead, the deviations from the mean in this group were higher than in the groups 3 and 4. It indicates a certain imbalance of the system of transport of free glucose but still lower than in the group 2 and even in the intact group. So, the consumption of milk thistle by male rats with a food immediately after irradiation leads to a decrease of the activity

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The low doses of irradiation cause a destructive effect not only on the organism but also on the subsequent generations of its offspring
Objective*: We determined the mechanisms of in vivo radioprotective and radiocorrective effects of dietary phytoadditive of milled milk thistle fruits on the systems of hydrolysis and transport of carbohydrates of various degrees of polymerization in a small intestine of the offspring of one-time irradiated male rats.*
Materials and methods: *A single exposure of male rats was performed with a help of teletherapy gamma-apparatus «AGAT-R1». A dose rate was 120 rad/min, a field – 20x20, a distance from the source of irradiation to the field – 75 cm, a dose - 0.5 Gy, an exposure time – 32 sec. Accumulating mucosa preparation (AMP) was produced by the Ugolev method [9]. AMP was incubated for an hour at $t = 37^{o}$ C in oxygenated medium. The solutions of 10 mmol/l of glucose or 5 mmol/l of maltose, made on the Ringer solution with pH 7.4, were used as an incubation medium. 3 drops of rabbit bile were added for emulsification into all media.*
Concentration of glucose was established by the colorimetric method with the help of photoelectrocolorimeter – CFC-2MP, $\lambda = 625$ nm. We assessed the activity of the transport of free and M-glucose in the AMP of the offspring of irradiated male rats under various conditions of the use of milk thistle by the parents.
Results*: The dietary additive of milled fruits of milk thistle causes a stimulation of the transport both free and M-glucose (1.6-fold in relation to the intact groups in both cases) in the offspring of irradiated male rats that got the thistle before irradiation and intact female rats (radioprotective effect), and respectively 2.7-fold and 2.8-fold in the offspring of irradiated hungry male rats through female rats that were consuming the thistle during lactation (radiocorrective effect).*
Conclusions*: The dietary additive of milled fruits of milk thistle causes the radioprotective and radiocorrective effects in the offspring of the first generation of irradiated males. Realization of both effects has the gender features: radioprotective effect is realized through irradiated fed male rats that got thistle before irradiation and intact female rats but radiocorrective effect is realized in the offspring of irradiated hungry male rats through female rats that were consuming the thistle during lactation.*

Keywords: irradiation, radioprotection, radiocorrection, thistle, mechanisms.

of the system of glucose transport in their offspring – almost twice as compared to the intact group; 1.7-fold – in comparison with the group 2; 2-fold – in the group 3; and 3-fold – in the group 4. The same effect was also noted for maltose ETC : M-glucose transport parameters were the lowest in the group 5 among all studied groups (table) and only the deviations from the mean were also the lowest. It indicates a stabilization of the system. Thus, at the first glance, it seems that the radiocorrective effect of milk thistle is realized only by the increase of the stability of the activity of ETC for maltose and, in any way, doesn't cause the activation of transport of carbohydrates of various degrees of polymerisation. But in our experiments on the study of gender characteristics of the transfer of the injuries from irradiated males and the ways for the correction of those injuries, it was determined that the consumption of 1.5 g of thistle by intact female daily during the period of lactation (2 months) led to a very significant activation of transport systems of both hydrocarbon substrates (group 6, table): the parameters of the accumulation of free glucose exceeded 2.7-fold the parameters for the intact group; 3-fold – the parameters in the group 2; 2.5-fold – in the group 3 ($p<0.001$ in all groups); 1.7-fold the parameters in the group 4 ($p = 0{,}007$); and 5-fold – the parameters of the group 5 ($p<0.0001$). For M-glucose, the parameters of that group exceeded 2.8-fold the parameters of the groups 1 and 2 ($p<0.0001$ in all groups); 1.7-fold – the parameters of the group 3 ($p = 0.006$); and 6.2-fold – the parameters of the group 4 ($p = 0.006$). Thus, the consumption of 1.5 g of milk thistle fruits by intact female every day during the period of lactation caused a bright radiocorrective effect on both carbohydrate substrates and much stronger than the radioprotective effect in the offspring of the males that got milk thistle fruits before irradiation (group 4). This effect persists in the group of the offspring of hungry irradiated male rats that got milk thistle after irradiation and the females consumed the milk thistle during lactation (group 7), but it is reliably lower ($p = 0.013$) than in the group 6 (1.6-fold) by free glucose and almost the same by M-glucose (1.5-fold, $p = 0.017$).

Therefore, the possibility of the correction of the functional activity of the small intestine in the offspring of irradiated male rats with the milk thistle fruits depends on the females.The results of the group 8 (table) are very informative for the determination of the mechanisms of radioprotective and radiocorrective effects of milk thistle on the functional activity of the small intestine of the offspring of irradiated rats (table): if the parameters of glucose transport were still within the active component, the transport of M-glucose was almost absent. It is an evidence of a significant inhibition of the hydrolytic chain of the maltose ETC. Analyzing the transport parameters of both carbohydrate substrates, it can be concluded that the consumption of thistle by males after irradiation (group 5) reduces significantly the activity of the transport system both for free glucose and the activity of ETC for maltose in their offspring, but the consumption of thistle by females during lactation (group 7) increases the transport of both carbohydrate substrates in the offspring of such males to one level (75 ± 4) mmol/l), and transport rates are practically the same as those in the group 4 (table).

So, firstly, there is, obviously, a gender-specific feature of the realization of radiocorrective thistle effect: in this case, it is realized exclusively through a female, it is confirmed by the results obtained in the group 6 (table). Secondly, the radiocorrective effect, realized through the female, is comparable to the radioprotective effect that is realized through a male (ibid.).

Taking into account a role of the females in the realization of the radiocorrective effect of thistle, one would expect the higher rates of carbohydrates' transport in the group 8 (table). Instead, in this group, the parameters of transport activity were the lowest among all studied ones. It should be noted that the consumption of thistle was distributed between the female and the offspring in this group (table). So, the results, obtained in this group, give a possibility to make a conclusion that such a scheme of thistle use is not effective. At the same time, the questions arise: why its bright radioprotective and radiocorrective effects were leveled at the given scheme of the use of milk thistle and why the effect of the inhibition of the transport of both carbohydrate substrates appeared instead of it? The first thing that comes to mind: the reason is a toxic effect of thistle, perhaps due to the excessive dose. But, firstly, the toxic effect of thistle is manifested in doses that are many times greater than the doses used in our study [14]. Secondly, in the group 8, the rats consumed the milk thistle with pleasure themselves, having an opportunity to refuse. Their weight and appearance were quite normal that also excluded the possibility of intoxication with milk thistle. Thirdly, a stimulation of transport of both carbohydrate substrates was determined in the groups 6 and 7 that excluded the possibility of toxic effect. Proceeding from the above and analyzing the composition of milk thistle fruits which main components have the antioxidant effect [7], a reason of such an inhibition of the functional activity of the small intestine of the offspring may be the prooxidant effect of antioxidants. It is also possible that such an inhibition are caused with the cellulose of thistle and mixed fodder which irritates the mucous membrane of the small intestine sensitive after irradiation of the male-predecessors that contributed to its increased desquamation and thus affected the parameters of the functional activity of their offspring. It is also probably that a division of the total term of the use of thistle in the group 8 between female and the offspring (table) is not appropriate, taking into account that a daily use of thistle by the female during lactation has contributed to a significant radiocorrective effect in the offspring and even to a significant stimulation of the transport systems of both carbohydrates which were inhibited by the use of milk thistle by irradiated males after irradiation, exactly the use of milk thistle by female in lactation is the most appropriate.

Table

Accumulation of glucose from its 10 mmol/l solution and maltose from its 5 mmol/l solution with the preparations of mucosa of the small intestine of the offspring of irradiated male rats under the different conditions of the effects on the parents, M±m, mmol/(l mg) of wet mass of preparation, n=5 in each group

Group	Substrate	
	Glucose	Maltose
1. Intact	47.85±5.59* 11.7%	42.71±2.31* 5.4%
2. The offspring of irradiated hungry males and intact females	42.25±6.22* 14.7%	42.67±1.95* 4.6%
3. The offspring of irradiated fed males and intact females	51.97±1.50* 3% $P3_{3-2} = 0.013$	42.62±1.94* 4.5%
4. The offspring of irradiated fed males that got 3 g of milled milk thistle fruits with a food before irradiation and intact females	75.66±3.89* 5% $P_{4-1} = 0.004$ $P_{4-2} = 0.002$ $P_{4-3} < 0.001$	70.59±3.88* 5.5% $P_{4-1} < 0.0001$ $P_{4-2} < 0.0001$ $P_{4-3} < 0.0001$
5. The offspring of hungry irradiated males that got 3 g of milled milk t histle fruits with a food after irradiation and intact females	24.97±2.45* 9.8% $P_{5-1} = 0.008$ $P_{5-2} = 0.032$ $P_{5-3} < 0.0001$ $P_{5-4} < 0.0001$	19.26±0.68* 3.5% $P_{5-1} = 0.006$ $P_{5-2} < 0.0001$ $P_{5-3} < 0.0001$ $P_{5-4} < 0.0001$
6. The offspring of hungry irradiated males and females that got 1.5 g of milled milk thistle fruits with a food every day during all time of lactation (2 months)	127.64±14.04^ 11% $P_{6-1} < 0.0001$ $P_{6-2} < 0.0001$ $P_{6-3} < 0.0001$ $P_{6-4} = 0.007$ $P_{6-5} < 0.0001$	119.21±12.52^ 10.5% $P_{6-1} < 0.0001$ $P_{6-2} < 0.0001$ $P_{6-3} < 0.0001$ $P_{6-4} = 0.006$ $P_{6-5} < 0.0001$
7. The offspring of hungry irradiated males that got 3 g of milled milk thistle fruits with a food after irradiation and females that got 1.5 g of milled milk thistle fruits with a food every day during all period of lactation (2 months)	78.40±6.72^ 8.6% $P_{7-1} = 0.008$ $P_{7-2} = 0.004$ $P_{7-3} = 0.005$ $P_{7-5} < 0.0001$ $P_{7-6} = 0.013$	76.77±6.37^ 8.3% $P_{7-1} = 0.001$ $P_{7-2} < 0.0001$ $P_{7-3} < 0.0001$ $P_{7-5} < 0.0001$ $P_{7-6} = 0.017$
8. The offspring of hungry irradiated males that got 3 g of milled milk thistle fruits with a food after irradiation and females that got 1.5 g of milled milk thistle fruits with a food every day during 1 month of lactation, and then the offspring got it with a food themselves during 1 month	16.47±3.16^ 19.2% $P_{8-1} = 0.001$ $P_{8-2} = 0.006$ $P_{8-3} < 0.0001$ $P_{8-4} < 0.0001$ $P_{8-6} < 0.0001$ $P_{8-7} < 0.0001$	6.60±2.05^ 31% $P_{8-1} = 0.0001$ $P_{8-2} = 0.0001$ $P_{8-3} < 0.0001$ $P_{8-4} < 0.0001$ $P_{8-6} < 0.0001$ $P_{8-7} < 0.0001$

Notes:
*Data obtained earlier were used for comparison: * – [12], ^ – [13].*
The bile was added into all incubative media.
Under the parameters of accumulation, the percentages of distributions from the mean are given.

Thus, a dietary phytoadditive of milled milk thistle fruits makes a radioprotective effect which is realized in the offspring of irradiated males that got the thistle before exposure and intact females and radiocorrective effect which is realized in the offspring of irradiated males through the females that got the thistle during lactation. Taking into account a presence of water- and fat-soluble components in the fruits of milk thistle that have antioxidant and membranotropic effects, it is likely that such effects are due to the impact not only of silymarin but also other biologically active components of milk thistle fruits. Based on this, and taking into account a low toxicity, the dietary phytoadditive of milled milk thistle fruits can be used to prevent the disturbances of assimilation of carbohydrates of different degrees of polymerization in the offspring of irradiated parents, as well as for the correction of the disturbances already obtained as a result of their irradiation.

Conclusions

1. Dietary phytoadditive of milled fruits of milk thistle causes radioprotective and radiocorrective effects in the offspring of the first generation of irradiated males.

2. Realization of both effects has gender distinctions: the radioprotective effect is realized through irradiated fed males that got a milk thistle before irradiation and intact females, where as the radiocorrective effect is realized in the offspring of hungry irradiated males through females that got milk thistle during lactation.

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