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Influence of an Enzymatic Hydrolyzate of *Chlorophytum comosum* (L.) on Morphofunctional Integrity of a Liver of White Rats at Experimental Toxic Damage During Various Periods of Ontogenesis

[1]D.A. Areshidze, [2]L.D. Timchenko, [3]A.I. Klimenko, [4]M.I. Gulyukin and [1]M.A. Kozlova

[1]Researching Laboratory of Experimental Biology and Biotechnology,
Moscow State Regional University, Moscow, Russian federation
[2]Institute of Applied Biotechnology Department of the living systems of the
North Caucasus Federal University, Stavropol, Russian federation
[3]Don State Agrarian University, Rostov-on-Don, Russian federation
[4]Russian Research Institute of Experimental Veterinary Science, Moscow, Russian Federation

Abstract: As a result of the conducted researches it is established that at using an identical dose of toxin the severity of injury in organ and changes of information parameters of a liver of rats at the age of 1.5, 4.5, 11 and 30 months are more expressed, than in 1, 3, 8 and 18 months. Furthermore, application of a enzymatic hydrolyzate of the *Chlorophytum comosum* (L.) is effective at all listed age periods, but protective effect is much higher at the age of 1, 3, 8 and 18 months and at the age of 1.5, 4.5, 11 and 30 months the available hepatoprotective effect is lower and isn't so expressed. Based on the aforesaid, it is possible to claim that severity of toxic damage of a liver is depending on age of animals and, respectively, on information condition of organ. It testifies to existence of dependence of efficiency of application of a biostimulator on the period of ontogenesis. Thus, it is expedient to carry out biostimulation on the most sensitive to it development stages.

Key words: Liver · Hydrolizate · Hepatotoxicity · Hepatocyte · *Chlorophytum comosum* (L.)

INTRODUCTION

The study of developmental changes in mammals, the mechanisms of their implementation at different levels from the molecular to the system, remains one of the most urgent problems of modern biology. Changes in pre- and postnatal development are increasingly seen as a phenomenon caused by the dynamics of adaptation and regeneration capabilities of living systems at different hierarchical levels [1-4]. Several authors do not exclude the existence of a direct link of the system information change with the development of pathological processes in the different periods of ontogeny. It is shown that the frequency of various pathologies manifestation and the tension of physiological processes, including the immunobiological reactivity, are subject to certain developmental cycles [5-7]. There are several reports on the interrelation of aging to age energy-information changes. There is a consideration that entropy of tissue systems is steadily increasing with age [8-10].

We have to assume the changes of that criterion, displaying the state of adaptation and regenerative abilities of the organism and tissue homeostasis, during periods of ontogenesis, marking by the manifestation of a disease process.

Liver disease is one of the most pressing public health problems around the world, because the liver is one of the central organs to ensure homeostasis. Hepatic injury is associated with distortion of various metabolic functions [11-14].

Researches of age-dependent changes of liver functions and their correction with the use of various biologically active substances are an important issue of modern biomedicine. Aging of liver is characterized by alterations of liver biology and by a reduction of many functions which are important for the maintenance of

Corresponding Author: D.A. Areshidze, Moscow State Regional University,
Center of Cell Biology and Applied Biotechnology, Moscow, Russian Federation.

body homeostasis. The main dysfunctions include appearance of enlarged hepatocytes, violation of liver regeneration, development of hepatic steatosis, alterations in the hepatic sinusoid [15-20].

The elderly are predisposed to a variety of diseases, which contribute to a marked increase in morbidity in this subpopulation. The incidence of liver disease increases in the elderly, but the cellular and subcellular perturbations that underlie this suspected predisposition to pathology remain unresolved. Several age-related changes have been documented, including a decline of liver volume, an increase in the hepatic dense body compartment (lipofuscin), moderate declines in the Phase I metabolism of certain drugs, shifts in the expression of a variety of proteins and diminished hepatobiliary functions [21].

In modern scientific literature there are few reports about the healing properties of the plant *Chlorophytum comosum* (L.). It is shown that the leaves of this plant have a high sorption characteristics with respect to formaldehyde, carbon monoxide, benzene, trichlorethylene, phenols and other compounds [22, 23]. By chemical analysis of the enzymatic hydrolyzate of *Chlorophytum comosum* in its composition was found DL-ornithine monohydrochloride having desintoxication and hepatoprotective action [24-27].

Previous studies have revealed the hepatoprotective effect of the enzymatic hydrolyzate of *Chlorophytum comosum* (L.) on the liver of rats with experimental toxic damage in young and middle age. Besides, it was shown that in post-natal ontogenesis of white rats the information parameters working as an indicator of level of adaptation and regenerator resources, are exposed to certain natural changes [24-30].

In ontogenesis we identified such periods in which there is a change of energy-information parameters: the period of infantile, juvenile period, the period of youth, adulthood, old age and the period of maximum age.

Thus, we consider currently important an investigation of efficiency of action of a hepatotropic toxin and hepatoprotective substance on a liver of rats during various periods of ontogenesis.

MATERIALS AND METHODS

Animals: Wistar Albino rats at the age of 1, 1.5, 3, 4.5, 8, 11, 18 and 30 months were used in the study. The animals were fed with standard pellet diet and water ad libitum. They were maintained in controlled environment (12:12 h light/dark cycle) and temperature (30±2°C). All the animal experiments were performed according to the compliance with the EC Directive 86/609/EEC and with the Russian law regulating experiments on animals.

Toxicity Studies: Based on previous studies [30] the dose of enzymatic hydrolyzate of *Chlorophytum comosum* (L.) at the concentration of 6 mg/kg.bw was chosen for the experiments.

Treatment Design: Sixty animals (Wistar Albino rats) of each age category were randomized and divided into three groups on 20 animals in each group. Group I was served as intact control. Animals in Group II were inhaled by carbon tetrachloride to 2 min. per day for 6 days. Rats in Group III were inhaled carbon tetrachloride to 2 min a day for 6 days, but at the same time treated with drinking enzymatic hydrolyzate of *Chlorophytum comosum* (L.) at the concentration of 6 mg/kg.bw (experimental group).

Selection of carbon tetrachloride (CCl_4) as an agent acting on the liver is caused by the fact that this substance is a direct liver poison, widely used in experimental medicine and biology. Selecting of the liver-toxic and exposure method is determined by the fact that the use of carbon tetrachloride under this scheme provides the appearance and development of reversible changes in liver at tissue and organ level.

Assessment of Hepatoprotective Activity

Histopathological Analysis: A small portion of liver was taken and fixed in to 10% formaldehyde. After several treatments for dehydration in alcohol, sections having 5µm thickness were cut and stained with hematoxylin and eosin and histopathological analysis was carried.

To detect apoptotic cells semi-thin sections (3µm) were stained with methylene blue-azure II with afterstain by fuchsin. All stained sections were embedded in balsam.

Determination of Mitotic, Apoptotic and Necrotic Index: At hematoxylin and eosin stained sections were determined mitotic and necrotic cells. At sections stained by methylene blue-azure II with after stain by fuchsin were determined apoptotic cells. Visualization was performed using a microscope Nicon 500L at 900 × magnification. Studied was made for 5 fields of view on each section.

Apoptotic Index Was Calculated by the Formula:

$$AI=N_a/N,$$

where N_a - the number of apoptotic cells; N - total number of cells in the test population.

The mitotic index was calculated by the formula:

$$MI=N_m/N,$$

where N_m - number of mitosis; N - total number of cells in the test population.

Necrotizing index calculated by the formula:

$$NI=N_n/N,$$

where N_n-of necrotic cells; N - total number of cells in the test population.

Morphometric Studies: Volume of the nuclei of hepatocytes was measured by image analyzer "Videotest" at hematoxylin and eosin stained sections.

Studies of the Information Condition of the System of the Liver: We carried out a breakdown of the aggregate of the measured volumes of hepatocytes nuclei into classes.

Based on the concept of information in a tissue system as the displaying of the diversity of morphology and function of the process for assessing the information status of organs and tissues have been proposed and tested the such indicators - information morphological capacity (H_{max}), information morphological entropy (H), information morphological organization (S), the relative morphological entropy (h) and redundancy (R) [13, 26, 29]. In this case, the baseline characteristics, which were used to calculate these parameters, can vary widely (the linear dimensions of the structures, their number, etc.). In our study was defined the volume of the nuclei of hepatocytes.

Information morphological capacity H_{max}, which means the maximum structural diversity, calculated by formula [13, 26, 29]:

$$H_{max}=\log_2 n,$$

where n - number of classes.

Next, we made the calculation of the real structural diversity H. Real structural diversity is the parameter that clearly illustrates the degree of determinism of morphofunctional system in time and space [5]. The calculation was made using the formula:

$$H=-\Sigma P_i \log_2 P_i,$$

where ΣP_i is the sum of probabilities of stay of the measured parameter of cells in a one of existing classes; $\log_2 P_i$ - logarithm of the probability of staying in one of the possible classes. In this case, the value of P_i is defined as the classical probability [13,26,29].

Knowing the maximum and actual structural diversity, we can calculate the organization of the system (S), the difference between the maximum possible and the real structural diversity (implemented structural diversity). This parameter, in our opinion, displays the state of the system adaptability to date. To determine the value of this parameter is used the formula [13,26,29]:

$$S=H_{max}-H.$$

It is necessary to consider that when $H = H_{max}$, the system is deterministic, but such relation to the vast majority of permissible is possible only in theory.

Then we determined the coefficient of relative entropy of the system, or (the coefficient of compression of information) h by formula [13, 26, 29]:

$$h=H/H_{max}.$$

High levels of relative morphological entropy provide evidence of the disorder of the system and significantly reducing of its structural integrity [13, 26, 29].

The coefficient of the relative organization of the system (redundancy factor) R is given by [13, 26, 29]:

$$R=(S/H_{max})\times 100\%.$$

With these data, the researcher has the opportunity to calculate the equivocation of the system (the value of reliability) *e* [13, 26, 29]:

$$e=(H_p-H_n)/H_{max},$$

where H_n - real structural diversity in normal, H_p - real structural diversity in pathology.

Statistical Analysis: Values are expressed as mean (± SD). The statistical analysis was performed using one-way analysis of variance (ANOVA). The statistical difference determined using repeated measures analysis of variance or paired Student t-tests. A p value of < 0.05 was considered statistically significant.

RESULTS

Effects of Enzymatic Hydrolyzate of Chlorophytum Comosum (L.) On Histopathology: The conducted research of influence of carbon tetrachloride and enzymatic hydrolyzate of the *Chlorophytum comosum* (L.) on a liver of rats during various periods of ontogenesis allowed to reveal a number of essential differences in efficiency of influence of substances depending on age of animals. These differences were revealed as in subgroups of the rats, only inhalated by CCl_4 and in subgroups of the animals receiving a hydrolyzate against impact of CCl_4 on an organism.

At pathomorphologic research of a liver of the rats affected by carbon tetrachloride at 1.5, 4.5, 11 and 30 months, we found a similar picture.

The liver of animals at these age periods was red colored, sometimes with a yellowish or gray shade. 20% of rats at these ages had a spotty liver. The organs were friable and easily being torn, bleeding on a cut. The obviously expressed discomplexation of hepatic beams is noted. Hepatocytes were bulked up, with muddy cytoplasm and indistinct borders. Nuclei were also bulked up, light, with the indistinct contours. In the cells are distinctly observed transparent vacuoles. Liver vessels in various sites of a cut are unevenly expanded and filled with blood. In a field of triads and in a perivascular area the signs of weak mesenchymal reaction are observed.

The found changes testify to development of typical toxic dystrophy of a liver in listed age subgroups of animals. However at some rats at the age of 11 and 30 months the established micropicture is characteristic for development of a focal alterative inflammation.

The picture of changes in a liver of rats at the age of 1 month, 3, 8 and 18 months as a result of effect of carbon tetrachloride, significantly differs from that in other age subgroups. Color of organ at these animals is various: liver is henna-red or light brown, with multiple hemorrhages, at 30% of animals light gray sites alternate with the dark red. Liver structure in most cases is friable, in some cases with the condensed sites. At the majority of rats liver cut is dry, without bleeding, in some cases the cut moderately bleeds. Violation of structure of a hepatic parenchyma is observed, the lobular structure of a parenchyma is absent. Layers of connective tissue are noted. In the hepatocytes is noted a large number a vacuoles, including lipidic vacuoles. Some cells are very large and actually constitute continuous vacuoles. In 70% of cases the multiple centers of necroses of the different sizes are found. Structural elements of separate cages in these sites aren't visualized and tissue of a liver represents homogeneous unstructured mass. In 30% of cases extensive necroses are noted.

Blood vessels (the central veins, capillaries) in a liver of these animals are expanded (a hyperemia of blood vessels), permeability of vascular walls for blood cells is increased, focal hemorrhages are noted.

As a whole, at the vast majority of rats at these ages histologic pattern of acute toxic hepatitis with rather high intensity of damage of tissues (alteration hepatitis) is observed.

Application of a hydrolyzate of Chlorophytum comosum at simultaneous inhalation of CCl_4 at animals at the age of 1.5, 4.5, 11 and 30 months leads to considerably smaller expressiveness of pathological changes in a liver. So, in a liver of all animals the hepatic beams and lobular structure are traceable. Thus not numerous centers of dystrophy alternate with the sites expressed by intact and two-nuclear hepatocytes (regeneration signs) or hepatocytes in a condition of the initial (reversible) stage of granular dystrophy. Fatty dystrophy meets only in 20% of cases. Also there are significantly less hepatocytes in a condition of necroses. Absence of focal hemorrhages is noted, interframe capillaries are moderately hyperemic, there are no puffiness signs. Vessels in the field of triads are moderately expanded. Thus in 28% of hepatocytes are noted small vacuoles.

In a liver of rats at the age of 1, 3, 8 and 18 months application of an enzymatic hydrolyzate of *Chlorophytum comosum* also leads to improvement of a morphological condition of organ, but thus the tendency to improvement is expressed to a lesser extent. It is shown in bigger, than in other age subgroups, quantity of the necrotic cells, quantity of the centers of necroses, hepatocytes in a state of fatty and granular dystrophy.

Effects of Enzymatic Hydrolyzate of Chlorophytum Comosum (L.) On MI, AI and NI: In the analysis of mitotic, apoptotic and necrotic activity in a liver of rats we revealed that at toxic injury of a liver the greatest

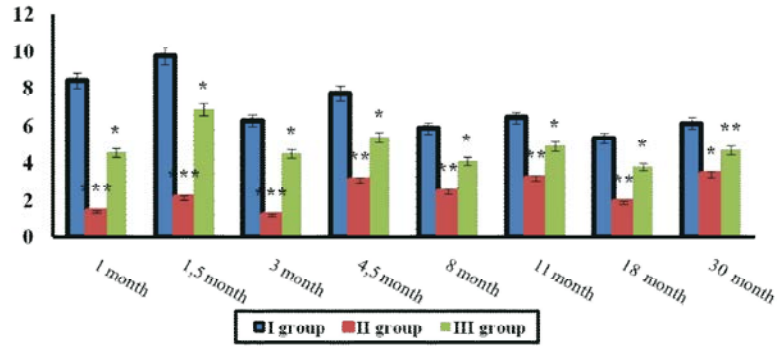

Fig. 1: The value of MI, in the liver of rats. Values are significantly different from intact group, (*** indicates P<0.001, ** indicates P <0.01, * indicates P <0.05).

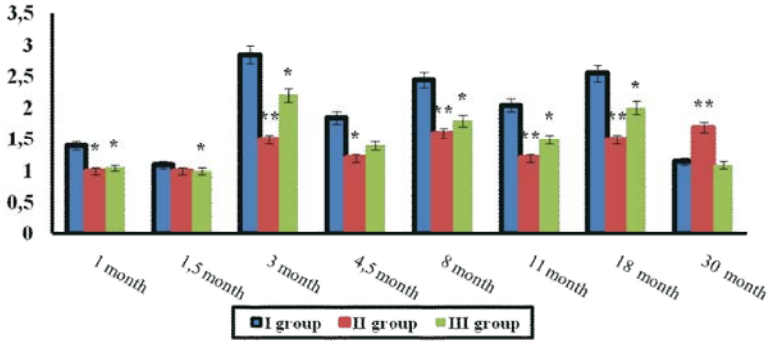

Fig. 2: The value of AI in the liver of rats. Values are significantly different from intact group, (*** indicates P <0.001, ** indicates P <0.01, * indicates P <0.05).

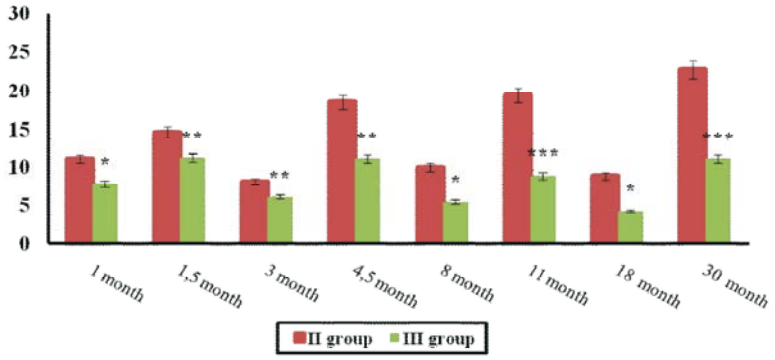

Fig. 3: The value of NI in the liver of rats.

deviations of the studied parameters are noted in 1,5, 4,5, 11 and 30 months and the hepatotropic effect of *Chlorophytum comosum* hydrolizate during these periods is less expressed. (Figs. 1,2,3).

Effects of Enzymatic Hydrolyzate of Chlorophytum Comosum (L.) On Informational Condition of Liver: At research of information condition of a liver of rats at the age of 1 month it is revealed that for a liver of rats of control group H max is equal 3.32±0.003 bits, the H is equal 2.394±0.033 bits, S makes up 0.9310±0.033 bits, h is equal 0.7198±0.04 bits, R makes up 28.01±0.95%. For a liver of animals with model toxic injury of a liver by CCl4, at the invariable value of H_{max}, we revealed an increase in comparison with control of the value of H which was equal to 2.734±0.032 bits, h to 0.8236±0.03 bits, S and R values goes down to 0.5856±0.032 bits and 17.64±0.95% respectively. Value of E makes up 0.332±0.017 bits. In a liver of the rats receiving an enzymatic hydrolyzate in parallel with inhalation of Ccl_4, H is equal to

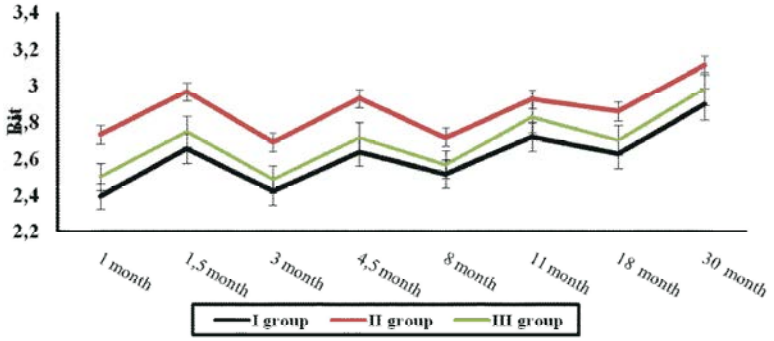

Fig. 4: The value of H in the liver of rats.

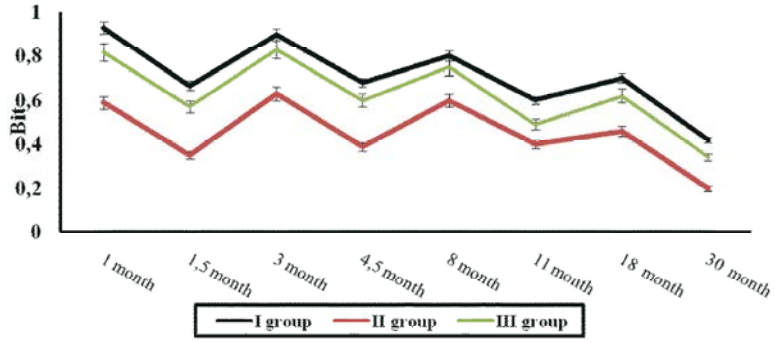

Fig. 5: The value of S in the liver of rats.

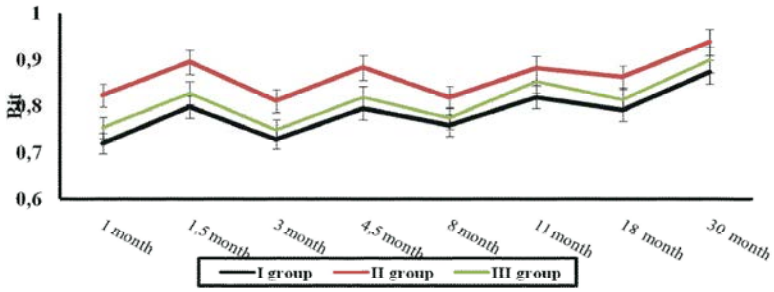

Fig. 6: The value of h in the liver of rats.

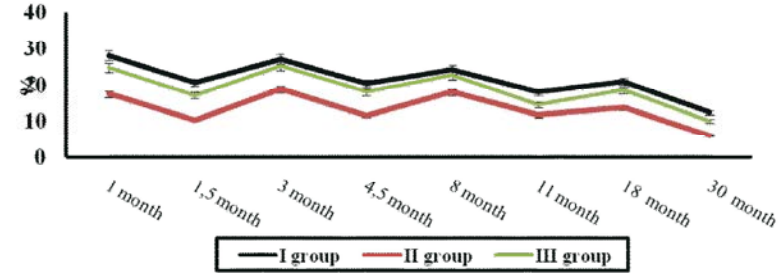

Fig. 7: The value of R in the liver of rats.

2.501±0.034 bits. Value of parameter h makes up 0.7535±0.010 bits, S and R are equal to 0.8185±0.034 bits and 24.65±1.03% respectively and *e* is equal to 0.089±0.06 bits. Information parameters of the group III are differ from indicators of the group II, but their differences from control group are invalid. In a liver of rats of control group at 1.5 months H is equal to 2.655±0.026 bits, S makes up 0.6660±0.026 bits, h is equal to 0.7993±0.008 bits, R makes up 20.06±0.79% (Figs. 4,5,6,7,8).

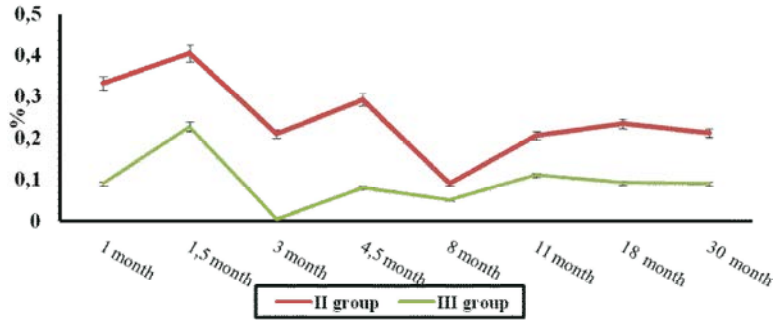

Fig. 8: The value of e in the liver of rats.

The studied indicators of a liver of rats at the age of 1.5 months inhalated by carbon tetrachloride, except for AI, authentically differ from indicators of control group of the same age. In particular, H makes up 2.971±0.029 bits, S is equal to 0.3492±0.029 bits, h - 0.8948±0.009 bits, R is equal to 10.52±0.88% and *e* makes up 0.405±0.003 bits.

The liver of the rats receiving an enzymatic hydrolyzate in parallel with inhalation by CCl4 at the age of 1.5 months is characterized by the information parameters different both from indicators of control and from indicators of a liver of the rats inhalated by carbon tetrachloride. The H of a liver of this group makes up 2.749±0.018 bits, S is equal to 0.5713±0.018 bits, h makes up 0.8279±0.006 bits, R is equal to17.21±0.56%, *e* makes up 0.228±0.05 bits. The liver of rats of control group at the age of three months is characterized by H equal to 2.442±0.018 bits, S makes up 0.899±0.018 bits, h is equal to 0.7292±0.0054 bits, R makes up 27.09±0.55%.

Information indicators of a liver of the rats under influence of CCl_4 are significantly differ from indicators of age norm. So, the H makes up 2.694±0.033 bits, S is equal to 0.6257±0.033 bits, h - 0.8115±0.009 bits, R - 18.85±0.98%, *e* makes up 0.211±0.0011 bits. The liver of the rats receiving an enzymatic hydrolyzate in parallel with inhalation by CCl_4 at the age of 3 months is characterized by the information parameters different from indicators of a liver of rats, only inhalated by carbon tetrachloride. Thus differences from indicators of a liver of control rats are invalid. The H makes up 2.487±0.022 bits, S makes up 0.8333±0.022 bits, h - 0.7490±0.007 bits, R is equal to 25.01±0.68%, a *e* makes up 0,004±0,0002 bits.

At 4.5 months for a liver of rats of control group H makes up 2.639±0.025 bits, S makes up 0.389±0.026 bits, h - 0.8828±0.008 bits, R - 11.72±0.78%. After CCl4 inhalation the H value of a liver of rats of this age makes up 2.931±0.025 bits, S decreases to 0.2996±0.028 bits, h increases to 0.9073±0.008 bits, R decreases to 9.275±0.87% and *E* makes up 0.292±0.015 bits.

At a liver of the rats receiving an enzymatic hydrolyzate in parallel with inhalation by CCl_4 information parameters differ authentically from indicators of two other groups. The H is equal to 2.783±0.02 bits, S - 0.6013±0.02 bits, h is 0.8189±0.048 bits, R - 18.11±0.48%, *E* is equal to 0.08±0.005 bits. The liver of intact rats in 8 months is characterized by H equal to 2.518±0.023 bits, S - 0.8018±0.023 bits, h is equal to 0.7585±0.007 bits, R is equal to 24.15±0.71%. Under the influence of carbon tetrachloride parameter H of a liver is equal to 2.719±0.024 bits, S - 0.6013±0.024 bits, h is equal to 0.8189±0.007 bits, R makes up 18.11±0.73%, E - 0.089±0.01 bits. Application of an enzymatic hydrolyzate at the same time with carbon tetrachloride causes change of H of a liver to 2.569±0.029 bits that doesn't differ authentically from indicators of control animals. The same is right for S equal to 0.7508±0.029 bits, h making 0.7739±0.009 bits, R - 22.60±0.89%. The indicator *E* is equal to 0.051±0.003 bits, that is below, than the I group.

In a liver of intact animals at the age of 11 months H makes up 2.721±0.026 bits, S is equal to 0.5991±0.026 bits, h reaches 0.8196±0.008 bits, R is equal to 18.04±0.8%. In a liver of rats of 11 monthly age after influence of CCl4 H makes up 2.928±0.025 bits, S is equal to 0.3915±0.025 bits, h is equal to 0.8821±0.008 bits, R is equal to 11.79±0.76% and *e* makes up 0.207±0.012 bits. At simultaneous impact on a liver of CCl_4 and a enzymatic hydrolyzate of the Chlorophytum comosum H is equal to 2.831±0.02 bits, S is equal to 0.4885±0.02 bits, h makes up 0.8529±0.006, R is equal to 14.71±0,63%, *e* makes up 0.11±0,006 bits.

For intact animals at the age of 18 months H makes up 2.627±0.027 bits, S is equal to 0.6926±0.027 bits, h is equal to 0.7914±0.008 bits, R makes up 20.86±0.83%. After influence of carbon tetrachloride H in a liver of 18-month-old rats makes up 2.862±0.023 bits, S is equal to 0.458±0.023 bits, h - 0.8620±0.007 bits, R - 13.81±0.71%, *E* is equal to 0.235±0.012. Thus, in a liver of rats of the III group at this age H is equal to 2.704±0.026 bits,

S-0.6165±0.026 bits, h - 0.8146±0.008 bits, R - 18.54±0.79%, value of parameter *E* makes up 0.091±0.004 bits. Information parameters of body don't differ from indicators of control group at the same age.

At 30 months the liver of intact animals is characterized by the H value equal to 2.901±0.056 bits, S - 0.4186±0.056 bits, h makes up 0.8739±0.017 bits, R is equal to 12.61±1.69%. After CCl_4 influence at a liver of rats of this age group H makes up 3.11±0.007 bits, S is equal to 0.2057±0.007 bits, h - 0.9381±0.002, R - 6.19±0.2%, *E* is equal to 0.213±0.013. For a liver of the rats receiving an enzymatic hydrolyzate in parallel to inhalation by CCl_4 information parameters differ authentically from control indicators. The H is equal to 3.093±0.03 bits, S - 0.3355±0.03 bits, h is equal to 0.899±0.009 bits, R - 10.10±0.93%, *E* is equal to 0.89±0.006 bits.

DISCUSSION AND CONCLUSIONS

Thus, as a result of the conducted researches it is established that, despite an identical dose of an applied pathogen, the degree of pathological changes in organ and also nature of changes of information parameters of a liver of rats at the age of 1,5, 4,5, 11 and 30 months has more severe character, than at 1, 3, 8 and 18 months. On the basis of the aforesaid it is possible to claim that the severity of damage of a liver by toxin is depending on age of animals and, respectively, on information condition of body.

At the same time, application of an enzymatic hydrolyzate of the Chlorophytum comosum is effective in all considered age periods, but protective effect is much higher at the age of 1, 3, 8 and 18 months and at the age of 1,5, 4,5, 11 and 30 months the available hepatoprotective effect is lower and isn't so expressed. It testifies to existence of dependence of efficiency of application of a biostimulator on the period of ontogenesis. Thus, it is possible to say about expediency of carrying out biostimulation just in sensitive for it development stages. It is shown that the studied age periods are characterized by change of an orientation of information parameters. Various efficiency of pathological influence of carbon tetrachloride and hepatoprotective influence of Chlorophytum comosum hydrolizate during the different age periods is confirmation of such thesis: the ontogenetic periods in which there is a change of an orientation of information parameters are critical and at these age stages there is a change of regenerative and adaptation capacity of organs.

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Conflict of Interest: There are no conflicts of interest.

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