IJPSR (2020), Volume 11, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 June 2019; received in revised form, 18 October 2019; accepted, 30 November 2019; published 01 April 2020

# USING OF INFORMATIONAL PARAMETERS AS A CRITERION FOR DETERMINING THE EFFECTIVENESS OF BIOSTIMULATION WITH USE OF TISSUE PREPARATIONS

D. A. Areshidze *, M. A. Kozlova, L. A. Makartseva, A. A. Gritsyunayte, K. A. Sakhnova and E. A. Shmigelskiy

Researching Laboratory of Experimental Biology and Biotechnology, Moscow State Regional University, 10A Radio st., Moscow, Russian Federation.

**Keywords:**

Liver, Tissue preparation, Biological activity, Entropy

**Correspondence to Author:**
**Dr. (Mr.) David A. Areshidze**

Head,
Researching Laboratory of Experimental Biology and Biotechnology, Moscow State Regional University, 10A Radio st., Moscow, Russian Federation.

**E-mail:** notbio@mgou.ru

**ABSTRACT:** Possibility of use of the informational parameters, which characterize adaptational and regenerative opportunities of organ, as potential criteria for the assessment of biological activity of tissue preparations, is investigated in this research. The influence of tissue preparation «STEMB» on the morphofunctional condition of a liver of rats at experimental toxic damage of organs was studied. The assessment of a morphofunctional condition of a liver under the influence of preparation was carried out as with use of traditional morphological, biochemical and histologic parameters, and also by means of informational parameters. A correlation analysis was conducted between the used biochemical, morphological and morphometric parameters and informational criteria. As a result of research it is established that hepatoprotective activity of preparation «STEMB» is confirmed both with results of traditional techniques of an assessment and with informational parameters, that allows drawing a conclusion on possibility of use of informational parameters as criterion of an estimation of biological activity of tissue preparations.

**INTRODUCTION:** Now the increasing number of researches is devoted to the potential biological activity of preparations made of tissues of plants or animals. This fact is due to a very wide range of biological effects of substances contained in the preparations of tissue origin, which ensures their applicability in various fields of biology, medicine and veterinary [1-5]. The high development of modern biotechnological and pharmaceutical technologies improves the process of extracting biologically active agents from natural raw materials, allow to specify the active components of preparations and to definite mechanisms and targets of their actions [6, 7].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(4).1592-01

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(4).1592-01

Particularly, biologically active remedies are now produced from tissues of a wide range of species of eukaryotes. Extractions from different parts of the organism of invertebrates and vertebrates and vegetative and generative organs of plants possess significant biological activity [8-11]. The entire organism, or separately taken organs, like skin, muscles, liver, immunocompetent organs, blood serum, and whole blood, antlers, placenta and chorion, fragments of tissue of an embryo of various species or whole embryo completely can be raw materials for producing of biologically active agents [12-14]. In particular, an embryonic tissue should be highlighted as one of the most promising sources of bio stimulating preparations, and the most convenient for use for this purpose is the chicken embryo [15-18].

The effect of bioactive preparations of natural origin is caused by the contents of the natural composites similar to constructs of living cells or

tissue in them. These composites carry out stimulation in process of functional inquiry of an organism. They may serve as an additional source of the major nutrients, bioactive peptides, growth factors, and the vitamins and mineral nutrition for an organism. Natural bioactive preparations contain so-called biogenous stimulators that have impact on the main parts of metabolism. This impact is expressed in changes of metabolic conversion and energy processes of an organism [19-21]. Biogenous stimulators and adaptogens are one of bases of efficiency of preparations of natural origin [22-23].

Experiments show that remedies made of living tissues demonstrate considerable effectiveness at application at smoldering pathological processes like inflammation, degeneration, atrophy, tumorigenesis, *etc*., as they activate immune and regenerative functions of an organism at diseases and injuries of various genesis. Tissue preparations also show the properties making them applicable as adaptogens at high physical activities at sportsmen and manual workers and at persons having strong cognitive and emotional load [24-29].

Derivatives of living tissues are widely applied also in veterinary science where their application is expedient because of the necessity of large volumes and high efficiency of the using substances and also their potential safety for the end-user of food and other products of farm animal origin [30-33]. In this regard, the matter of criteria of determination of efficiency of action of tissue biological preparations is important now.

For determination of efficiency of use of biologically active substances and biological products (which are in essence the highly active catalyst of biological processes, including their ability for essential change and violation in the existing tissue homeostasis through changing of both adaptive and regenerative specifics of tissue), the wide range of methods and techniques is now applied. Traditionally, tests of stimulators are carried out on laboratory animals [34]. Speaking about the influence of one or another biostimulator on the studied organ or system, we estimate the level of adaptational and regenerative opportunities of this system, but the uniform integrative criteria of an assessment of these opportunities are not present.

At all wide range of approaches to a question of determination of level of adaptational and regenerative processes in norm, at pathologies and as a result of biostimulation [35-48, 50], it isn't possible to mark out an adequate criterion of an assessment of intensity of these processes which wouldn't demand confirmation by any other methods and reflect unity of a structure and functions of the studied systems.

One of the methods applied to an assessment of adaptational and regenerative processes is use of informational parameters. In particular, this method finds application in medicine. So, entropy was used for the definition of violations of cardiac activity at fetuses at the last stages of prenatal ontogenesis [51]. Also, entropy was applied to the description of regularities of secretion of hormones [52]. Very widely informational parameters are used at research of cardiovascular system [53, 54], in neurophysiology [55, 56], and also in various areas of science studying cellular, tissue, and organ structures [57-63].

Research of the possibility of an assessment of informational parameters as the criterion displaying an effect of application of a tissue biostimulator seemed to us actual. For this purpose, the assessment of influence of the tissue preparation «STEMB» on a morphofunctional condition of a liver of rats at experimental toxic hepatitis was carried out. Thus, the assessment was performed with use of traditional morphological, physiological, histochemical and histologic techniques, and also by an assessment of informational condition of organ. The choice of the preparation «STEMB» is caused by that its biostimulating influence on a liver, which is shown by earlier conducted researches. Besides, it is revealed that the informational parameters applied by us reflect the level of adaptational and regenerative resources of organ [64].

## MATERIALS AND METHODS:

**Animals:** Male Wistar Albino rats of body weights ranging from 170 g to 200 g were used in the study. The animals were fed with standard pellet diet and water *ad libitum*. They were maintained in a 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.

Each animal was assigned with an individual number, in accordance with which the animal was marked by coloring with stains according to the developed schemes. On the cage label of a certain color the group, animal number, type of mark and research code were indicated.

**Treatment Design:** 150 animals (Male Wistar Albino rats) were randomized and divided into three groups of fifty animals in each group. One of the groups served as intact control. Animals in Group I was inhaled with carbon tetrachloride for 2 min per day for 6 days (control group). Rats in Group II were inhaled with carbon tetrachloride for 2 min per day for 6 days, but at the same time received hypodermic injections of «STEMB» in a dosage of 3 mg/kg.bw at 1-5$^{th}$ days of research. The use 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 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.

On the 7$^{th}$ day of research, animals were sacrificed in carbon dioxide chamber.

**Weight Measurements:** All rats were weighed in grams. The weighing was made at the beginning and at the end of research in each group. At the end of experiment, it was measured absolute (in grams) and relative mass of a liver of rats.

**Biochemical Analyses:** Levels of uric acid, creatinine, total bilirubin, of an alanine amino-transferase (ALT) and aspartate aminotransferase (AST) in blood serum were investigated by means of the biochemical StatFax3300 analyzer (USA) by means of sets of Spinreact firm (Spain); then the De Ritis ratio was calculated.

**Histochemical Analysis:** Small fragments of liver were taken and fixed in 10% formaldehyde. After several treatments for dehydration in alcohol, sections of 5 mm thickness were cut. Sections were subjected to stain with hematoxylin and eosin, and then the histopathological analysis was carried, including determination of mitotic, apoptotic and necrotic indexes in the liver. A hematoxylin and eosin-stained sections we determined quantity of mitotic and necrotic cells. At sections stained by methylene blue-azure II with after staining by fuchsine we determined a quantity of apoptotic cells. Visualization was performed using a microscope Nikon Eclipse 80i at 900x magnification. All studies were made for 10 fields of view on each section.

Apoptotic index was calculated by the formula:

$$AI = N_a/N \times 100\%$$

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

Mitotic index was calculated by the formula:

$$MI = N_m/N \times 100\%$$

Where $N_m$ - number of mitotic cells; N - total number of cells in the test population.

Necrotic index was calculated by the formula:

$$NI = N_n/N \times 100\%$$

Where $N_n$- number of necrotic cells; N - total number of cells in the test population

**Morphometric Studies:** All measurements were taken with use of image analyzer "Video test" at hematoxylin and eosin-stained sections. The study was made for 10 fields of view on each section.

**Studies of the Informational Condition of the System of the Organs:** To determine the informational status at focal lesions of the liver, pieces of tissue were taken from the least altered areas on the border of macroscopically visible lesions. In case of visual homogeneity of the organ the material for research was taken from random part of it.

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 informational status of organs and tissues such parameters have been proposed and tested: informational morphological capacity ($H_{max}$), informational morphological entropy (H), informational morphological organization (S), the

relative morphological entropy (h) and redundancy (R) [65-68]. The baseline characteristics, which are used to calculate these parameters, can vary widely (the linear dimensions of the structures, their quantity, *etc*). In our study we defined the volume of the nuclei of hepatocytes. Informational morphological capacity $H_{max}$, which means the maximum structural diversity, was calculated by formula:

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

Where n - number of classes.

Next, we made the calculation of the real structural diversity H. Real structural diversity (informational morphological entropy) is the parameter that clearly illustrates the degree of the determinism of morphofunctional system in time and space [65-68]. The calculation was made using the formula:

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

Where ΣPi is the sum of probabilities of staying of the measured parameter of cells in one of the 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.

Knowing the maximum and real 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 we used the formula:

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

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 the formula:

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

High levels of relative morphological entropy provide evidence of the disorder of the system and of significant reduction of its structural integrity.

The coefficient of the relative organization of the system (redundancy factor) R is given by formula:

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

With this data, the researcher has the opportunity to calculate the equivocation of the system(the value of reliability) *e*:

$$e = (H_p-H_n)$$

Where $H_n$ - real structural diversity in the norm, $H_p$ - real structural diversity in pathology.

**Statistical Analysis:** The obtained data, analyzed using Graph Pad Prism 6.0, were expressed as Mean ± SD. The difference between the control and experimental groups was analyzed using Mann-Whitney U test. $P<0.05$ was considered statistically significant. Using the same program, the correlation analysis was performed.

## RESULTS AND DISCUSSION:

**Effect on Body and Liver Mass:** By results of research it is established that at experimental toxic hepatitis (I group) there is a decrease in body weight of animals and also in an absolute and relative mass of a liver. At the same time, similar parameters of animals of the second experimental group are reliably higher, than in the first, and don't differ significantly from control parameters **Table 1**.

**Effect on Blood Serum Parameters:** Results of biochemical researches testify that at experimental toxic hepatitis, there is an essential deviation of all studied parameters of blood serum, except for the total protein, in comparison with norm.

In the second group, there is insignificant change of the studied parameters in comparison with control, except for the level of AST, but also the level of a total protein is constant in **Table 2**.

**TABLE 1: SOME MORPHOLOGICAL PARAMETERS OF A LIVER OF RATS AT AN ASSESSMENT OF BIOLOGICAL ACTIVITY OF THE TISSUE PREPARATION «STEMB»**

| Group | Bodyweight, g | Absolute mass of liver, g | Relative mass of liver, % |
|---|---|---|---|
| Control group (n=50) | 209.30±5.61 | 7.60±0.37 | 3.62±0.30 |
| I group (n=50) | 181.40±9.14* | 9.10±0.44* | 5.02±0.37* |
| II group (n=50) | 201.80±12.51▲ | 7.69±0.91▲ | 3.81±0.31▲ |

Hereinafter: control group – intact animals; I group – the animals inhaled by $CCl_4$; II group – the animals inhaled by $CCl_4$ and at the same time treated with tissue preparation «STEMB». *P≤0,0 5 - in comparison with control group, ▲P≤0,05- the II group in comparison with the I group

**TABLE 2: SOME BIOCHEMICAL PARAMETERS OF BLOOD SERUM OFRATSAT AN ASSESSMENT OF BIOLOGICAL ACTIVITY OF THE TISSUE PREPARATION «STEMB»**

| Group | AST, u/l | ALT, u/l | De Ritis ratio | Total bilirubin, g/l | Total protein, g/l | Glucose, µmol/l |
|---|---|---|---|---|---|---|
| Control group (n=50) | 141.5±3.72 | 84.2±2.78 | 1.68 | 9.82±0.38 | 75.24±5.23 | 6.58±0.52 |
| I group (n=50) | 168.8±22.14* | 303.1±33.74* | 0.55 | 23.88±1.42* | 76.52±4.48 | 11.84±1.1* |
| II group (n=50) | 148.51±25.98* | 190.11±37.18▲ | 0.78 | 10.74±1.40▲ | 74.59±4.16 | 7.61±1.14▲ |

**Effect on Mitotic, Apoptotic and Necrotic Activity:** In a liver of animals of Group I there is an essential decrease in mitotic and apoptotic activity at simultaneous increase in number of necroses. Under the influence of «STEMB» the quantity of cells in a condition of mitosis and necrosis reaches control level, but thus the level of apoptotic activity is higher, than in a liver of intact rats and animals of the first group **Table 3**.

**TABLE 3: MITOTIC, APOPTOTIC AND NECROTIC INDEXES OF RAT LIVER AT AN ASSESSMENT OF BIOLOGICAL ACTIVITY OF THE TISSUE PREPARATION «STEMB»**

| Group | Mitotic index, % | Apoptotic index, % | Necrotic index, % |
|---|---|---|---|
| Control group (n=50) | 6.41±0.37 | 1.87±0.22 | 0.70±0.09 |
| I group (n=50) | 2.41±0.36* | 0.71±0.20* | 14.14±2.56* |
| II group (n=50) | 6.91±0.48▲ | 3.12±0.30*▲ | 1.21±0.25▲ |

**Histopathologic Findings:** The histopathologic feature of a liver of intact rats complied with norm **Fig. 1, 2**.

At the pathomorphological examination of the liver of rats exposed to carbon tetrachloride, it was found that the organs had a red color, sometimes with yellow or gray tint. About 20% of rat liver were spotty. The organs were loose and easily tearing, with blood oozing on the cut. The histological study revealed a pronounced attenuation of hepatic beams. Hepatocytes were swollen, with turbid cytoplasm; the edges of the cells were not clearly discernible; the nuclei were also swollen, bright, with blurred edges. In hepatocytes the clear vacuoles were distinctly observed. Detached hepatocytes were in state of granular dystrophy. The vessels of the liver in different parts of the cut were irregularly expanded and filled with blood, in the field of triads the signs of mild perivascular mesenchymal reaction were observed.

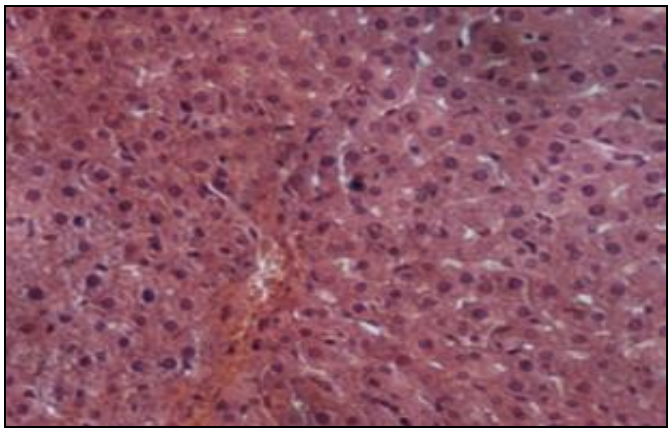

**FIG. 1: LIVER OF INTACT RAT ×400, H & E**

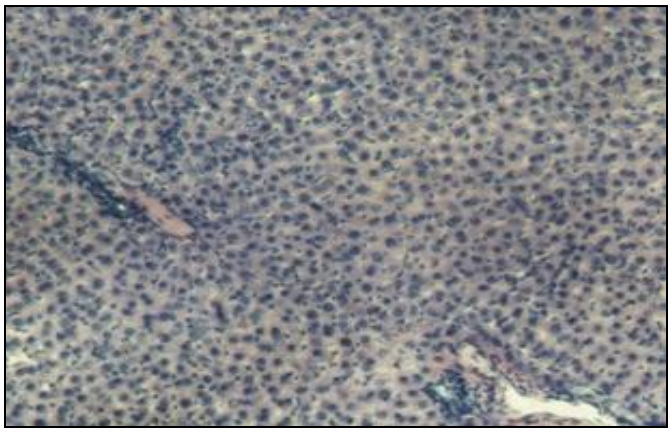

**FIG. 2: LIVER OF INTACT RAT × 200, H & E**

In a number of cases the layers of connective tissue, thickened and infiltrated by small cells, primarily in the fields of triads, are observed. Blood vessels (central vein capillaries) of the liver are dilated (hyperemia of blood vessels), the permeability of the walls of vessels for the blood cells is increased, the focal hemorrhages are observed. Among the cells, a large number of white blood cells, the macrophages, are observed. Some single cells are very large and are in fact a continuous vacuole.

In 80% of cases, the multiple foci of necrosis of different sizes are observed, in which the structural

elements of the individual cells are not rendered, and the tissue of liver is a homogeneous structureless mass. In 47% of cases the extensive necroses are noted. The observed changes indicate the development of typical toxic damage of liver at animal groups. However, at some rats the characteristic signs of the micro-focal alterative inflammation were established. A significant part of animals had typical signs of acute toxic hepatitis with high intensity of tissue damage (alterative hepatitis). Some animals had severe hepatic steatosis with necrotic component **Fig. 3, 4**.

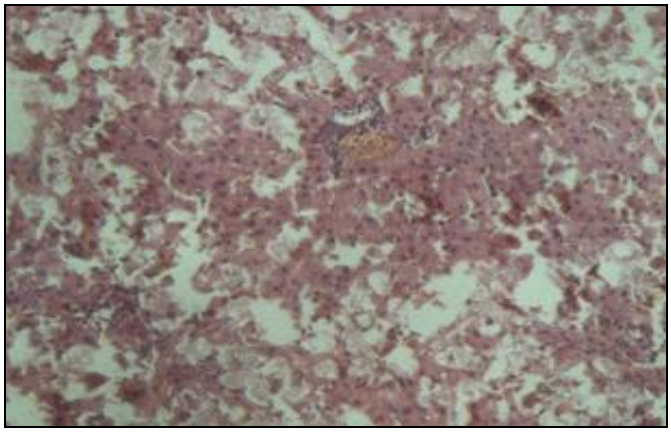

**FIG. 3: LIVER OF RAT FROM GROUP I ×200, H & E**

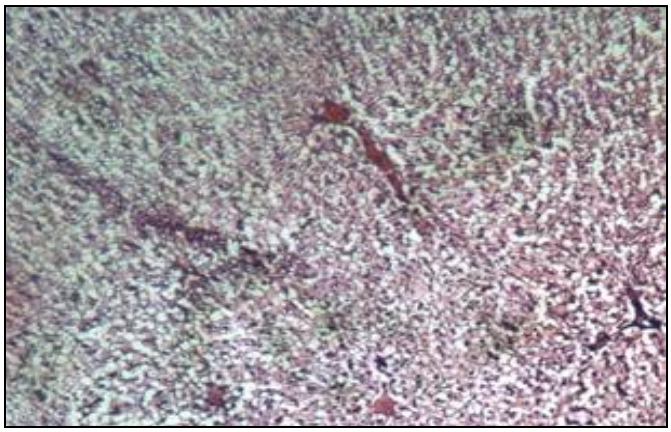

**FIG. 4: LIVER OF RAT FROM GROUP I ×100, H & E**

At inhalation by $CCl_4$ with the simultaneous use of the «STEMB» the pathological changes in the liver are much less severe. In particular, hepatic beams and lobular structure in the liver of all animals stay intact. A few fields of malnutrition alternate with areas represented with binuclear and intact hepatocytes (signs of recovery) or hepato-cytes in a condition of the initial stage of granular dystrophy, fatty degeneration occurs in 21%.

Also, there are substantially less hepatocytes in a state of necrosis. It is noted the absence of focal hemorrhages, capillaries are moderately bloodshot, and there are no signs of swelling.

The permeability of vessels is also considerably less. Vessels in the triads are moderately dilated. Over 29% of hepatocytes have small vacuoles **Fig. 5, 6**.

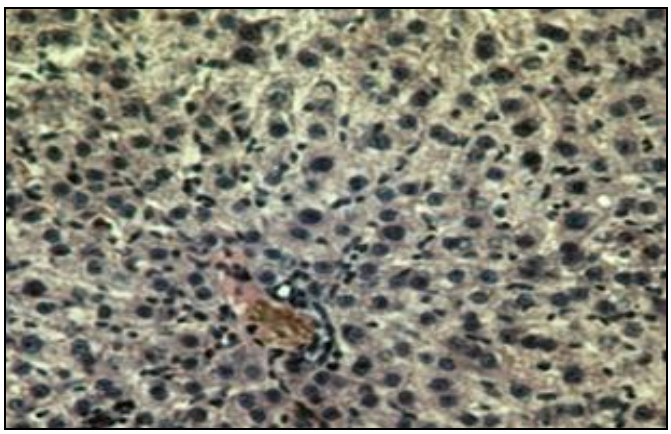

**FIG. 5: LIVER OF RAT FROM GROUP II. ×400, H&E**

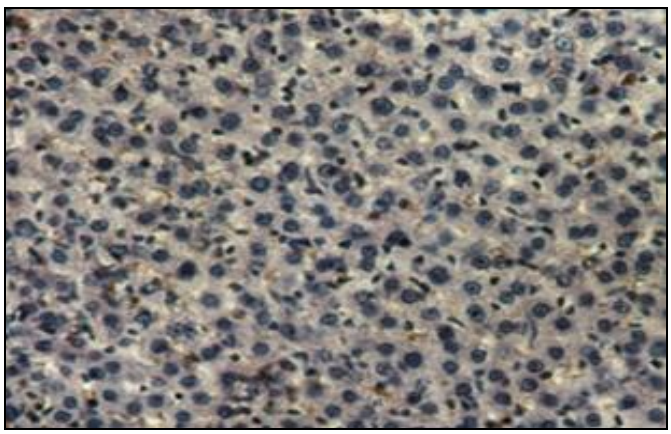

**FIG. 6: LIVER OF RAT FROM GROUP II. ×400, H&E**

**TABLE 4: INFORMATIONAL PARAMETERS OF LIVER OF RATS AT AN ASSESSMENT OF BIOLOGICAL ACTIVITY OF THE TISSUE PREPARATION «STEMB»**

| Group | $H_{max}$(bit) | H (bit) | S (bit) |
|---|---|---|---|
| Control group (n=50) | 3.32±0.002 | 2.518±0.023 | 0.8018±0.023 |
| I group (n=50) | 3.32±0.002 | 2.719±0.024* | 0.6013±0.024* |
| II group (n=50) | 3.32±0.002 | 2.569±0.029*▲ | 0.7508±0.029*▲ |
| **Group** | **h (bit)** | **R (%)** | ***e* (bit)** |
| Control group (n=50) | 0.7585±0.007 | 24.15±0.71 | - |
| I group (n=50) | 0.8189±0.007* | 18.11±0.73* | 0.201±0.010 |
| II group (n=50) | 0.7739±0.009*▲ | 22.61±0.89▲ | 0.051±0.006▲ |

**Effect on Informational Condition:** At comparing with control in a liver of both studied groups it is observed an increase in level of parameters H and h, decrease of level of parameters S and R. At the same time, changes of the studied informational parameters in the group II are reliably differed than parameters of the first group I **Table 4**.

**TABLE 5: CORRELATIONS BETWEEN VALUE OF PARAMETER H AND VALUES OF OTHER STUDIED PARAMETERS**

| | Bodyweight, g | Absolute mass of liver, g | Relative mass of liver, % | AST, u/l | ALT, u/l | De Ritis ratio |
|---|---|---|---|---|---|---|
| H, Control group (n=50) | r=0,77* | r=0,77* | r=0,74* | r=0,81** | r=0,80* | r=-0,81** |
| H, I group (n=50) | r=0,78** | r=0,84* | r=0,73* | r=0,84* | r=0,92* | r=-0,83** |
| H, II group (n=50) | r=0,71* | r=0,88* | r=0,74* | r=0,77** | r=0,90* | r=-0,80** |
| | **Total bilirubin, g/l** | **Total protein, g/l** | **Glucose, µmol/l** | **Mitotic index,%** | **Apoptotic index,%** | **Necrotic index,%** |
| H, Control group (n=50) | r0=0,73* | r=0,69* | r=0,58* | r=-0,92** | r=-0,71* | r=0,80** |
| H, I group (n=50) | r=0,74* | r=0,77* | r=0,64* | r=-0,94* | r=-0,80** | r=0,82 ** |
| H, II group (n=50) | r=0,70* | r=0,78** | r=0,66* | r=-0,84** | r=-0,84** | r=0,80** |

**Results of Correlation Analysis:** The conducted correlation analysis showed significant correlations between informational parameters and all other studied criteria. In particular, in all the studied groups, the negative correlations between the value of H and values of MI and AI were found, while at the same time there was a positive correlation between the values of this parameter and other studied parameters **Table 5**.

**CONCLUSION:** The conducted research shows that the tissue preparation «STEMB» has a hepatoprotective effect on experimental toxic hepatitis at rats. It is shown in the expressed normalization of most of studied biochemical parameters, preservation of morphological integrity of a liver, maintenance of tissue homeostasis of organ. It is remarkable that the leading mechanism of cellular death at toxic hepatitis and simultaneous application of the preparation «STEMB» is not the necrosis, but apoptosis, which intensity increases in a liver of animals of the second experimental group even in comparison with control.

By results of the analysis of informational condition, we noted an increase in parameter H in both groups, which testifies that there is an increase in degree of disorder of tissue system of organ. Also, in both groups the level of structural integrity of system decreases, which is confirmed by increase in value of parameter h. At the same time, the decrease in the values of parameters S and R testifies about decrease of adaptational opportunities of organs and about decrease in quantity of the structural elements capable to provide the necessary level of adaptation and the necessary level of structural and functional integrity of organ. At comparing of values of the studied parameters, the intergroup distinctions are clearly evident.

Values of parameters H and h are increased in the group treated with the preparation to 2.02% and 2.03% respectively (that is no more than for 5% of norm) in comparison with control, but in group without application of preparation these parameters increased for 7.98% and 7.96% respectively. These data testify to success of biostimulation at use the preparation «STEMB». Besides, values of parameters S and R decrease in the range up to 10% from norm, to 6.36% and 6.38% respectively, whereas in group without application of preparation these parameters decreased to 25.0% and 25.01%. The increase of parameter *e* to level of 0.051 bits (which isn't exceeding 0.1 bits), is also revealed in group treated with «STEMB», whereas in group without application of tissue preparation it made up more than 0.2 bits.

Correlation analysis testifies about a close interrelation of the dynamics of the values of informational parameters with the dynamics of other studied parameters. Thus, the decrease in morphological and functional integrity of a liver, as it is shown by results of the analysis of informational condition of organ, is more expressed at animals of the first group. At the same time, the studied informational parameters characterizing the liver of rats of the second experimental group, despite the identification of certain changes in structure and function of organ, confirm the hepatoprotective effect of preparation «STEMB» to

the same extent as the earlier described results of biochemical, morphological and histologic researches. These facts allow claiming that the informational investigations used in research can be applied as the criteria characterizing biological activity of tissue preparations.

**ACKNOWLEDGEMENT:** Financial support of research was carried out by Moscow State Regional University.

**CONFLICTS OF INTEREST:** The authors declared that there is no conflict of interest.

## REFERENCES:

1. de Queiroz Dias D, Sales DL, Ferreira FS, Santiago Lemos IC, de Araújo Delmondes G, Rodrigues da Silva RE, Martins da Costa JG, Kerntopf MR, Melo Coutinho HD, Alves RRN and de Oliveira Almeida W: Evaluation of the antibacterial and modulatory activities of Zootherapeutics. Methods and Techniques in Ethnobiology and Ethnoecology. Humana Press, New York 2019: 285-92.
2. da Silva Policarpo I, Barboza RRD, Borges AKM and Alves RRN: Mammalian fauna used in folk medicine among hunters in a semiarid region of Brazil. Environment, Development and Sustainability 2019; 21(3): 1533-42.
3. Meyer-Rochow VB: Therapeutic arthropods and other, largely terrestrial, folk-medicinally important invertebrates: a comparative survey and review. Journal of Ethnobiology and Ethnomedicine 2017; 13(9): 31.
4. El-Seedi HR, Khalifa SA, Yosri N, Khatib A, Chen L, Saeed A, Efferth T and Verpoorte R: Plants mentioned in the Islamic Scriptures (Holy Qur'ân and Ahadith): Traditional uses and medicinal importance in contemporary times. Journal of Ethnopharmacology 2019; 243: 18.
5. Vallejo JR and Gonzales A: Fish-based remedies in Spanish ethnomedicine: a review from a historical perspective. J Ethnobiol Ethnomed 2014; 10(37): 1-31.
6. Noori SMA, Khanzadi S, Fazlara A, Najafzadehvarzi H and Azizzadeh M: Effect of lactic acid and ajwain (*Carum copticum*) on the biogenic amines and quality of refrigerated common carp (*Cyprinus carpio*). LWT 2018; 97: 434-39.
7. Yagi A: Bioactive constituents of a human placenta hydrolysate – from bio-genic stimulants reported by Filatow to biological markers of collagen generation. Nat Med 2004; 58(4): 121-31.
8. Lai CH, Han CK, Shibu MA, Pai PY, Ho TJ, Day CH, Tsai FJ, Tsai CH, Yao CH and Huang CY: Lumbrokinase from earthworm extract ameliorates second- hand smoke- induced cardiac fibrosis. Environmental Toxicology 2015; 30(10): 1216-25.
9. Dharmawati IGAA, Mahadewa TGB and Widyadharma IPE: Antibacterial activity of *Lumbricus rubellus* earthworm extract against *Porphyromonas gingivalis* as the bacterial cause of periodontitis. Open access Macedonian Journal of Medical Sciences 2019; 7(6): 1032.
10. Rivera D, Verde A, Fajardo J, Obón C, Consuegra V, García-Botía J, Ríos S, Alcaraz F, Valdés A, Del Moral A and Laguna E: Ethnopharmacology in the Upper Guadiana River area (Castile-La Mancha, Spain). Journal of Ethnopharmacology 2019; 241: 111968.
11. Sarkic N, López JH, López-Costas O and Grandal-d'Anglade A: Eating in silence: isotopic approaches to nuns' diet at the convent of Santa Catalina de Siena (Belmonte, Spain) from the sixteenth to the twentieth century. Archaeological and Anthropological Sciences 2019; 11(8): 3895-11.
12. Yang, F, Ding F, Chen H, He M, Zhu S, Ma X, Jiang L, and Li H: DNA Barcoding for the identification and authentication of animal species in traditional medicine. Evidence-Based Complementary and Alternative Medicine 2018; 1-18.
13. Mobley CB, Toedebusch RG, Lockwood CM, Heese AJ, Zhu C, Krieger AE Cruthirds CL, Hofheins JC, Company JM, Wiedmeyer CE, Kim DY, Booth FW and Roberts MD: Herbal adaptogens combined with protein fractions from bovine colostrum and hen egg yolk reduce liver TNF-α expression and protein carbonylation in Western diet feeding in rats. Nutr Metab 2014; 11(19): 1-12.
14. Oh TH and Markelson GJ: Dependence of *in-vitro* myogenesis on a trophic protein present in chicken embryo extract. Proc Natl Acad Sci 1980; 77 (11): 6922-25.
15. Alibardi L, Mlitz V and Eckhart L: Immunolocalization of scaffoldin, a trichohyalin-like protein, in the epidermis of the chicken embryo. Anat Rec 2015; 298(2): 279-87.
16. Wakame K, Nakata A, Sato K, Komatsu KI and Maruta T: Application of horse-derived placental peptides in cosmetics. Adv Mater 2019; 4: 1-6.
17. Tseng SH, Sung CH, Chen LG, Lai YJ, Chang WS, Sung HC and Wang CC: Comparison of chemical compositions and osteoprotective effects of different sections of velvet antler. Journal of Ethnopharmacology 2014; 151(1): 352-60.
18. Yadgary L, Wong EA and Uni Z: Temporal transcriptome analysis of the chicken embryo yolk sac. BMC Genomics 2014; 15(1): 690.
19. Chandika P, Ko SC and Jung WK: Marine-derived biological macromolecule-based biomaterials for wound healing and skin tissue regeneration. Int J Biol Macromol 2015; 77: 24-35.
20. Malak HWA and Amin MA: Protective Role of L-arginine on the Suprarenal Gland of Adult Male Albino Rats Subjected to Recurrent Acute Restraint Stress: A Histological and Immunohistochemical Study. Egyptian Journal of Anatomy 2018; 41(1): 156-71.
21. Panossian A, Wilkman G, Kaur P and Asea A: Adaptogens stimulate neuropeptide Y and Hsp72 expression and release in neuroglia cells. Front Neurosci 2012; 6(6): 1-12.
22. Kashiwagi S, Brauns T, Gelfand J and Poznansky MC: Laser vaccine adjuvants: History, progress, and potential. Hum Vaccin Immunother 2014; 10(7): 1892-07.
23. Thakur AK, Chatterjee SS and Kumar V: Adaptogenic potential of andrographolide: An active principle of the king of bitters (*Andrographis paniculata*). Journal of Traditional and Complementary Medicine 2015; 5(1): 42-50.
24. Dumic-Cule I, Pecina M, Jelic M, Jankolija M, Popek I, Grgurevic L and Vukicevic S: Biological aspects of segmental bone defects management. International Orthopaedics 2015; 39(5): 1005-11.
25. Di Nicola V: Omentum a powerful biological source in regenerative surgery. Regenerative Therapy 2019; 11: 182-91.
26. Jiang N, Zhang S, Zhu J and Gao X: Hypoglycemic, hypolipidemic and antioxidant effects of peptides from red

deer antlers in streptozotocin-induced diabetic mice. Tohoku J Exp Med 2015; 236(1): 71-79.
27. Kumju Y, Eun-Young Y, Jinhyuk L, Ji-Young K, Jae-Sam H and Woo-Sik J: Oleic acid and linoleic acid from Tenebrio molitor larvae inhibit BACE1 activity in vitro: molecular docking studies. J Med Food 2014; 17(2): 284-89.
28. Kang Y, Lee B, Bucci L and Stohs S: Effect of a Fibroin Enzymatic Hydrolysate on memory improvement: a placebo-controlled, double-blind study. Nutrients 2018; 10(2): 233.
29. Bałan BJ, Demkow U, Skopiński P, Bychawska M, Skopińska-Różewska E, Lewicki S and Zdanowski R: The effect of pentoxifylline on L-1 sarcoma tumor growth and angiogenesis in Balb/c mice. Central-European Journal of Immunology 2017; 42(2): 131.
30. Kim H, Mohanta TK, Park YH, Park SC, Shanmugam G, Park JS, Shanmugam G, Park JS, Jeon J and Bae H: Complete genome sequence of the mountain-cultivated ginseng endophyte *Burkholderia stabilis* and its antimicrobial compounds against ginseng root rot disease. Biological Control 2019. doi: https://doi.org/10.1016/j.biocontrol.2019.104126
31. Csongová M, Gurecká R, Koborová I, Celec P, Domonkos E, Uličná O and Šebeková K: The effects of a maternal advanced glycation end product-rich diet on somatic features, reflex ontogeny and metabolic parameters of offspring mice. Food & Function 2018; 9(6): 3432-46.
32. Mazzei R, De Marco EV, Gallo O and Tagarelli G: Italian folk plant-based remedies to heal headache (XIX-XX century). Journal of Ethnopharmacology 2018; 210: 417-33.
33. Tantamacharik T, Carne A, Agyei D, Birch J and Bekhit AEDA: Use of plant proteolytic enzymes for meat processing. Biotechnological applications of plant proteolytic enzymes. Springer Cham 2018: 43-67.
34. Yao B, Gao H, Liu J, Zhang M, Leng X and Zhao D: Identification of potential therapeutic targets of deer antler extract on bone regulation based on serum proteomic analysis. Molecular Biology Report 2019; 46(5): 4861-72.
35. Hou F, Wen L, Peng C and Guo J: Identification of marine traditional Chinese medicine dried seahorses in the traditional Chinese medicine market using DNA barcoding. Mitochondrial DNA Part A 2018; 29(1): 107-12.
36. Chakraborty M, Karmakar, I, Haldar S, Nepal A and Haldar P: Anticancer and antioxidant activity of methanol extract of *Hippophae salicifolia* in EAC induced Swiss albino mice. Int J Pharm Pharmaceut Sci 2015; 7(8): 24-32.
37. Salzet M: Anticoagulants and inhibitors of platelet aggregation derived from leeches. FEBS letters 2001; 492(3): 187-92.
38. Fumiere M, Fumiere M, Poltronieri H and Endringe R: Seasonality modifies rosemary's composition and biological activity. Ind Crop Prod 2015; 70: 106-18.
39. Guan S, Peng C, Li H, Xu S and Yuan Z: Determination of biological activity of extract from hirudo by N-benzoyl-L-arginine ethyl ester. Zhongguo Zhong Yao Za Zhi 2016; 35(15): 1990-92.
40. Halboos MHN: Spectrophotometric method for determination and biological activity of trace amount of Cd(II) by bis(2-((pyridin-2-ylimino)methyl)phenyl)-4,4'-(diazene-1,2-diyl)dibenzoate. Int J Sci Res 2015; 4(3): 2222-26.
41. Dobolyi A, Irwin S, Makara G, Usdin TB and Palkovits M: Calcitonin gene- related peptide- containing pathways in the rat forebrain. Journal of Comparative Neurology 2005; 489(1): 92-19.
42. Demay J, Bernard C, Reinhardt A and Marie B: Natural products from Cyanobacteria: Focus on beneficial activities. Marine Drugs 2019; 17(6): 320.
43. Molnar J, Thornton B, Molnar A, Gaal D, Luo L and Bergmann-Leitner E: Thermodynamic aspects of cancer: possible role of negative entropy in tumor growth, its relation to kinetic and genetic resistance. Lett Drug Des Discov 2005; 2: 429-38.
44. Moreta C, Tena MT and Kannan K: Analytical method for the determination and a survey of parabens and their derivatives in pharmaceuticals. Environ Res 2015; 142: 452-60.
45. Penkov D, Dimitrova S, Andronova V, Milieva E, Murdjeva M, Stanimirova I, Draganov M and Kassarova M: Biological activity of bulgarian Folia Betulae dry extract. Int J Pharm Pharmaceut Sci 2015; 7(7): 124-36.
46. Preuett B, Leeder S and Abdel-Rahman S: Development and application of a high-throughput screening method to evaluate antifungal activity against *Trichophyton tonsurans*. J Biomol Screen 2015; 20(9): 1171-77.
47. Choi H, Charnsangavej C, de Castro Faria S, Tamm EP, Benjamin RS, Johnson MM, Macapinlac HA and Podoloff DA: CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. American J of Roentgenology 2004; 183(6): 1619-28.
48. Singh A and Srivastava V: Multi-functional chimeric peptides: the more the merrier. Protein and peptide letters 2018; 25(12): 1090-00.
49. Sasaki Y, Hamedpour V, Kubota R, He Y, Torii Y and Minami T: Facile indicator displacement assay-based supramolecular chemosensor: quantitative colorimetric determination of xylose and glucose in the presence of ascorbic acid. Chemistry Letters 2019; 48(10): 3.
50. Zou Y, Ding Y, Feng W, Wang W, Li Q, Chen Y., Wu H, Wang X, Yang L and Wu X: Enzymolysis kinetics, thermodynamics and model of porcine cerebral protein with single-frequency countercurrent and pulsed ultrasound-assisted processing. Ultrasonics sonochemistry 2016; 28: 294-01.
51. Pincus SM and Keefe DL: Quantification of hormone pulsatility *via* approximate entropy algorithm. Am J Physiol 1992; 262: 741-54.
52. Pincus SM and Viscarello RR: Approximate entropy: a regularity measure for fetal heart rate analysis. Obstet Gynecol 1992; 79 (2): 249-55.
53. Safara F, Doraisamy S, Azman A, Jantan A and Ranga S: Wavelet Packet Entropy for Heart Murmurs Classification. Adv Bioinformatics 2012; 6.
54. Hasan ES and Caceres DJLH: Heart Rate Variability Analysis Based on Photoplethysmographic Signals. Revista Cubana de Informática Médica 2015; 7(2): 113-21.
55. Darbin O, Jin X, Von Wrangel C, Schwabe K, Nambu A, Naritoku DK, Krauss JK and Alam M: Neuronal entropy-rate feature of entopeduncular nucleus in rat model of Parkinson's disease. International Journal of Neural Systems 2016; 26(02): 11.
56. Wu HT, Lee CY and Liu AB: Multiscale cross-approximate entropy analysis as a measurement of complexity between ecg r-r interval and ppg pulse amplitude series among the normal and diabetic subjects. Comput Math Methods Med 2013; 7.
57. Copstein RN, Abichequer V, Andrade MC, Machado LA, Rodrigues E, Soares LP and Pinho MS: Image processing strategies for automatic detection of common

gastroenterological diseases. 2018 IEEE 42nd Annual Computer Software and Applications Conference (COMPSAC) 2018; 1: 593-98.
58. Kayser K, Borkenfeld S, Goldman T and Kayser G: How to measure diagnosis-associated information in virtual slides. Diagn Pathol 2010; 6(11): 9.
59. Kayser K, Borkenfeld S, Goldman T and Kayser G: To be at the right place at the right time. Diagn Pathol 2011; 6(68): 9.
60. Kayser K and Gabius HJ: The application of thermodynamic principles to histochemical and morp-hometric tissue research: principles and practical outline with focus on the glycosciences. Cell Tissue Res 1999; 3: 443-55.
61. Kayser K: Qantitive pathology in virtual microscopy: History, applications, perspectives. Acta Histochem 2013; 12: 179-88.
62. Luo LF, Molnar J, Dong H, Lu XG and Spengler G: Attempts to introduce thermodynamics in anticancer therapy. Acta Sci Nat Univ Intramongol 2006; 36: 295-03.
63. Luo LF, Molnar J, Dong H, Lu XG and Spengler G: Physicochemical attack against solid tumors based on the reversal of direction of entropy flow: an attempt to introduce thermodynamics in anticancer therapy. Diagn Pathol 2006; 43(1): 7.
64. Metze K, Adam R and Florindo JB: The fractal dimension of chromatin-a potential molecular marker for carcinogenesis, tumor progression and prognosis. Expert Review of Molecular Diagnostics 2019; 19(4): 299-12.
65. Areshidze DA, Timchenko LD, Kozlova MA, Syomin IA, Rzhepakovsky IV, Piskov SI and Vakulin VN: Influence of Biologically Active Substance "STEMB" on a Morphofunctional Condition of a Liver and Kidneys of Rats at an Experimental Hepatorenal Syndrome. J Pharm Nutr Sci 2015; 5: 186-93.
66. Areshidze D, Timchenko L and Kozlova M: Information Condition of the liver of Dogs at Pathologies at the Reproductive Period of Ontogenesis. Acad J Canc Res 2013; 6(2): 79-83.
67. Areshidze D, Timchenko L and Kozlova M: Informational condition of Dogs liver at Pathologies. Global Vet 2013; 11(3): 357-61.
68. Avtandilov G and Barsukov V: Informational analysis of immune and endocrine organs. Morphological changes in the course of infection. Zentralbl Pathol 1992; 138(5): 345-49.

**How to cite this article:**
Areshidze DA, Kozlova MA, Makartseva LA, Gritsyunayte AA, Sakhnova KA and Shmigelskiy EA: Using of informational parameters as a criterion for determining the effectiveness of biostimulation with use of tissue preparations. Int J Pharm Sci & Res 2020; 11(4): 1592-01. doi: 10.13040/IJPSR.0975-8232.11(4).1592-01.