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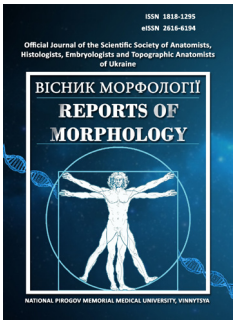


# Studies of changes in rat hepatocytes under conditions of central blockade of luteinizing hormone synthesis with the additional quercetin

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*The nucleus, exchanging information with the cytoplasm of the hepatocyte, controls and coordinates all cell activity: division, growth, intermediate metabolism, protein synthesis and its differentiation. During the cell life cycle the nucleus remains in interphase. The large variation in the size of hepatocyte nuclei is explained by the fact that during postnatal growth, some hepatocytes undergo cytogenetic transformations characterized by gradual polyploidy. Polyploidy, or amplification of the entire genome, refers to cells/organisms containing more than 2 main chromosome sets. The aim of this study is to determine the morphogenesis and dynamics of variability of subtypes of rat hepatocytes, binucleate and with two nucleoli, under conditions of central blockade of luteinizing hormone synthesis with long-term action of triptorelin, with the addition of quercetin to the animal diet. The experiment was conducted on 60 sexually mature white male rats weighing 140-160 g. The animals were divided into 3 groups: group 1 – control, saline solution was administered (10 animals); group 2 was subcutaneously administered triptorelin embonate solution at a dose of 0.3 mg of active ingredient per kg of body weight for 12 months (25 animals); group 3 was administered triptorelin solution at a rate of 0.3 mg of active ingredient per kg of body weight with the addition of quercetin in terms of animal body weight three times a week (25 animals). The animals were removed from the experiment after 1, 3, 6, 9 and 12 months by an overdose of ether anesthesia. A comprehensive study of histological preparations of the liver and quantitative counting of hepatocytes with two nucleoli and binucleate were performed using a light microscope with a digital microfilter and software adapted for these studies. Statistical processing of the study results was performed using Microsoft Office Excel software and the Real Statistics 2019 extension. Pathological processes that occur in liver tissue during experimental oxidative-nitrosative stress caused by the administration of triptorelin lead to both quantitative and qualitative changes. Thus, the number of hepatocytes with two nucleoli significantly increased in group 2 and at the 12th month of observation was 5.291±1.156 cells per field of view at $p<0.05$. The number of binucleated hepatocytes also tended to change with maxima at the 12th month of observation. Thus, in group 2 at the 9th month, the number of binucleated hepatocytes was 7.012±0.527 cells per field of view at $p<0.05$, and with the addition of quercetin only 5.311±1.561 cells per field of view at $p<0.05$. An increased number of mitoses was detected in group 2 at the 6th month of observation, in group 3 it was determined only at the 9th. The study showed that the administration of triptorelin causes oxidative-nitrosative stress, which leads to pathological changes in hepatocytes in the form of quantitative changes in cells with two nucleoli and binucleate cells. Additional administration of quercetin reduces the negative effect on liver hepatocytes, which is confirmed by the indicators in the experimental groups of animals.*

**Keywords:** *liver, hepatocyte, binucleated hepatocytes, mitosis, testosterone, luteinising hormone, quercetin, tryptorelin.*

## Introduction

According to WHO, the incidence of prostate cancer has been increasing worldwide in recent years. Prostate cancer is the most common cancer in men aged 55 years and older. In Western and Eastern Europe, this disease ranks third among oncological pathologies, and in the Americas it already ranks first [16, 28]. In terms of incidence, prostate cancer is in fourth place in Ukraine. Approximately 6.5 thousand new cases are registered each year. Insufficient testosterone can aggravate liver damage, cause obesity, or even lead to hepatosis [20, 22, 24].

Chronic liver diseases are also quite common in clinical practice. As of 2019, approximately 1.69 billion people worldwide suffered from liver diseases. The liver is crucial for the metabolism of many substances, including sex hormones and lipids [26]. Disturbances in sex hormone, glucose, and lipid metabolism are common complications of chronic liver disease and are high-risk factors for endocrine insufficiency. To date, attention to risk factors for endocrine insufficiency has focused on diabetes mellitus, cardiovascular disease, neurological disease, and psychological factors. Several studies have assessed the prevalence and risk factors for endocrine insufficiency in patients with liver disease [1, 19, 29]. The information collected from different literature sources varies to some extent and is often not comparable, due to the different etiology of liver disease, sample size, survey methodologies, and assessment tools used in each study.

Testosterone is known to be a key hormone in the pathology of metabolic diseases such as obesity. Low testosterone levels are associated with increased fat mass (especially central obesity) and decreased lean mass in men. These morphological features are associated with metabolic dysfunction, as testosterone deficiency leads to energy imbalance, impaired glucose control, decreased insulin sensitivity, and dyslipidemia [6, 21]. Androgenic effects on enzymatic pathways of fatty acid metabolism are evident and often tissue-specific, with distinct effects observed in regional adipose tissue, muscle, and liver [11, 15]. Testosterone replacement therapy has been shown to have beneficial effects on obesity indices, partly due to direct metabolic effects on adipose tissue and muscle, and potentially by increasing motivation, vigor, and energy, allowing obese individuals to lead more active lifestyles. The extent of these beneficial changes may depend on the treatment modality, with long-term use often providing greater efficacy.

Quercetin is a common naturally occurring flavonoid, a pigment found in many fruits, vegetables, and seeds. It helps to avoid the development of cardiovascular diseases [8, 33], reduces the risk of oncological pathology and degenerative processes in the brain. This substance has antioxidant properties, protecting the body from free radicals, binding and neutralizing unstable molecules [18, 32, 34]. Triptorelin, a synthetic analogue of the neurohormone gonadotropin-releasing hormone, which suppresses the expression of the receptor in the pituitary gland, but does not change the functioning of the pituitary-testicular complex as a whole. Central deprivation of luteinizing hormone synthesis leads to the development of oxidative stress [34] in the connective tissue of the testicles of rats, quercetin was used as a pharmacological agent to correct the pathological effect on the interstitial endocrinocytes of the testicles. The question of the effect on liver tissue of long-term inhibition of testosterone synthesis by triptorelin is insufficiently studied.

Therefore, the study of morphological changes in hepatocytes under conditions of central blockade of luteinizing hormone synthesis with the addition of quercetin can help increase the effectiveness of treatment of chronic liver diseases and improve the prognosis for patients.

*The aim* of this study is to determine the distribution, morphogenesis and dynamics of variability of hepatocyte subtypes, namely binucleolus and binuclear under conditions of central blockade of luteinizing hormone synthesis with long-term action of triptorelin with the addition of quercetin to the animal diet.

### Materials and methods

The experiment was conducted on 60 sexually mature white male rats weighing 140-160 g. The material for the study was liver tissue. The animals were divided into 3 groups. Group 1 was the control group, which was administered saline (10 animals). Group 2 was subcutaneously administered diphereline (triptorelin embonate) [4] at a dose of 0.3 mg of the active substance per kg of body weight with drug activity for 365 days (25 animals). Group 3 was administered a triptorelin solution at the rate of 0.3 mg of the active substance per kg of body weight with the addition of quercetin to the diet using a gastric tube, calculated on the body weight of the animals three times a week (25 animals). The animals were withdrawn from the experiment after 1, 3, 6, 9 and 12 months by overdose of ether anesthesia. The animals were kept in standard conditions of the vivarium of the Poltava State Medical University. The study is a fragment of the scientific project “Experimental and morphological study of the influence of diphereline, cryopreserved placenta transplants on the morphofunctional state of a number of internal organs”, state registration No. 0124U003358.

The Bioethics Committee of Poltava State Medical University (protocol No. 234 dated 01.23.2025) established that all research and euthanasia of experimental animals were carried out in accordance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1986), as well as with the “General Ethical Principles of Animal Experiments” adopted by the First National Congress on Bioethics (Kyiv, 2001).

Small fragments of the liver were fixed according to the generally accepted method and placed in paraffin blocks, from which 4 μm thick sections were made and stained with hematoxylin and eosin [3]. In the complex study of histological preparations, a light microscope BIOREX-3#5605 was used. By visual assessment, using digital microfilters and software adapted for this study, hepatocytes were counted in the

field of view. Photography was performed using a digital microphotographic attachment DCM 900 with appropriate software.

As a result of the morphometric study, the actual diameters of hepatocyte nuclei were established. The area of cells and their nuclei (S) was calculated by the formula: $S=(D_1/2\times D_2\times/2)\times\pi$ where $\pi$ is a constant value equal to 3.14; $D_1$ is the larger diameter of the cell/nucleus; $D_2$ is the smaller diameter of the cell/nucleus.

Statistical processing of the study results was carried out using Microsoft Office Excel software and the Real Statistics 2019 extension to it. To determine the statistical significance of differences between groups, the non-parametric Mann-Whitney test was used. The difference was considered statistically significant at $p<0.05$.

## Results

When we studied the structural organization of the liver of the control and experimental groups of animals using histological preparations stained with hematoxylin-eosin, the following was established. The liver is an organ with a predominance of the parenchymal component over the stromal one, which are clearly separated from each other with the formation of structural components, namely hepatic lobules. The parenchyma consisted of hepatocytes and non-hepatocyte cells (endotheliocytes, Ito cells, Kupffer cells, lymphocytes, neutrophils and other cells (Fig. 1). Our study of hepatocytes themselves established that in the intact liver of white rats they are the dominant cells, significantly outnumbering other cellular elements in quantitative terms (see Fig. 1). All cells had clear contours, a polygonal shape, and their average dimensions were: transverse 18.22±0.91 μm, longitudinal 22.06±2.33 μm. The average area of hepatocytes was 407.5±23.9 $\mu m^2$.

The variability of cells was clearly traced from the central vein to the periphery of the hepatic lobule. When we studied the cytoplasm of hepatocytes, we found a change in the reaction with different dyes, in some cases moderate granularity, which, in our opinion, is associated with the functional state of each individual group of cells (Fig. 2). The perinuclear space contained aggregations of basophilic material, which correspond to the localization of the granular endoplasmic reticulum and stand out well against the background of the relatively palely stained cytoplasm. The nuclei had a regular rounded, somewhat less often elliptical shape, were located in the center of the cells and contained from one to two nucleoli.

Most hepatocytes had one nucleus, the relative number of such cells was 77.33 %. Accordingly, 22.67 % of hepatocytes contained two nuclei. We did not detect a greater number of nuclei in hepatocytes in either the control or experimental

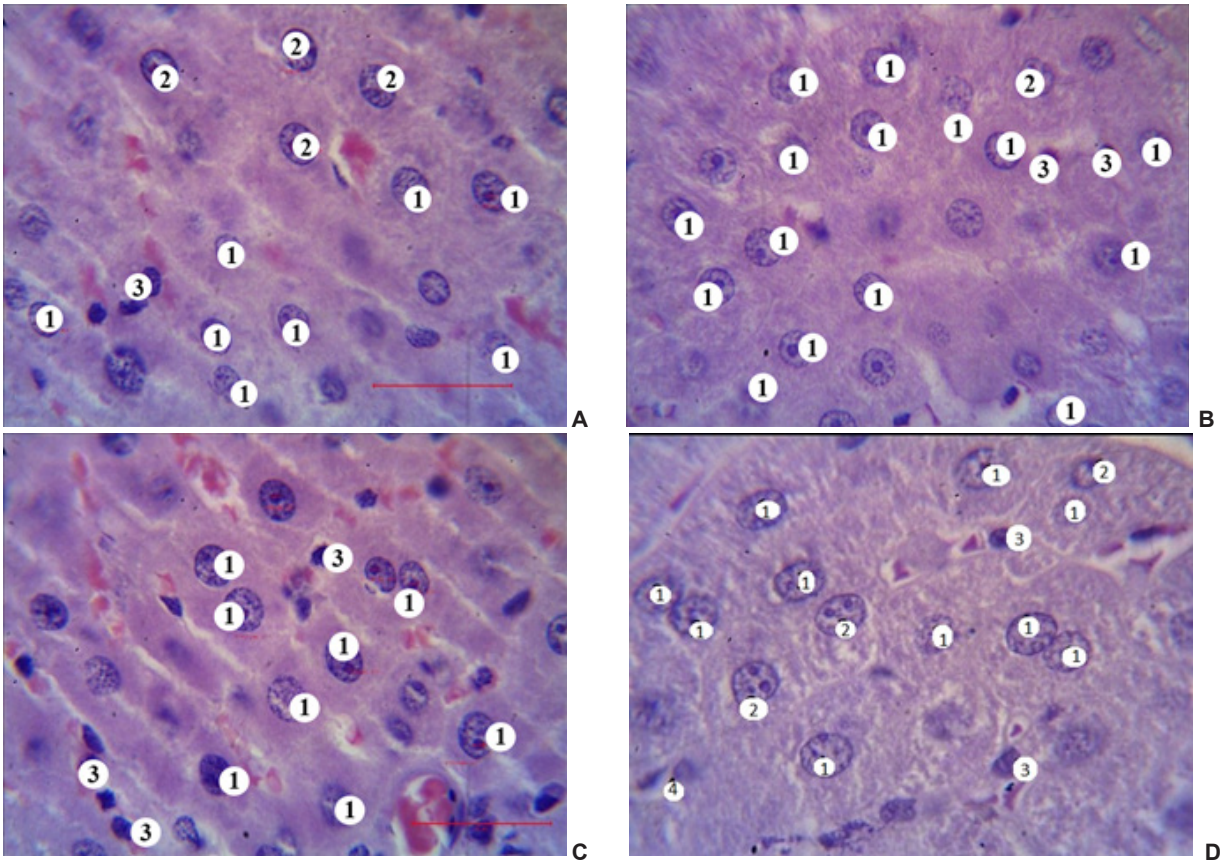


**Fig. 1.** Morphogenesis of hepatocytes with two nucleoli in the group of animals with the administration of triptorelin (T) and the group of animals that were administered quercetin (T+Q) against the background of triptorelin administration at different times of the study. A, C – group with the administration of triptorelin (3rd and 9th months). B, D – group with the administration of quercetin against the background of triptorelin (3rd and 9th months). 1 – mononuclear hepatocytes, 2 – binuclear hepatocytes, 3 – liver macrophages, 4 – Ito cell. Hematoxylin-eosin staining. Lens×40. Eyepiece×15.

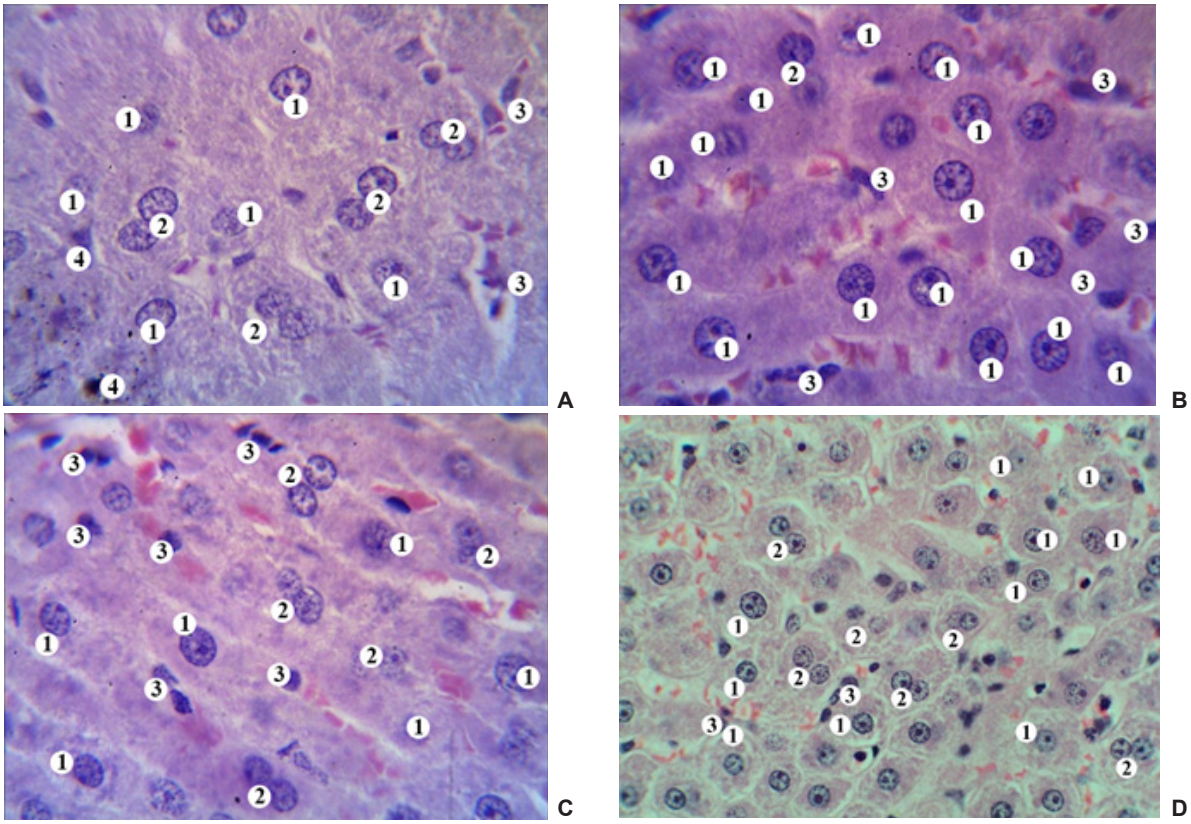


**Fig. 2.** Morphogenesis of binuclear hepatocytes in the group of animals with the administration of triptorelin (T) and the group of animals that were administered quercetin (T+Q) against the background of triptorelin administration at different study periods. A, C – group with the administration of triptorelin (6th and 12th months). B, D – group with the administration of quercetin against the background of triptorelin (6th and 12th months). 1 – mononuclear hepatocytes, 2 – binuclear hepatocytes, 3 – liver macrophages, 4 – Ito cell. Hematoxylin-eosin staining. Lens×40. Eyepiece×15.

groups of animals.

With experimental oxidative-nitrosative stress caused by the administration of triptorelin, quantitative and qualitative changes occur in hepatocytes. The first statistically significant signs are detected from the 3rd month of observation in both experimental groups. Thus, the number of hepatocytes with two nucleoli significantly increased in the group using triptorelin and at the 3rd month was 4.782±1.042, and in the group with the addition of quercetin 3.661±0.798, respectively, at $p<0.05$ in the field of view. The tendency to increase the number of cells with an increased number of nucleoli (two) persists and at the 12th month of observation was 5.701±1.243 at $p<0.05$ in the field of view, which is 3.35 times more than in the control group. And in the group with the addition of quercetin, this indicator was statistically significantly higher compared to the control at $p<0.05$, but less than in the group without quercetin and amounted to 5.291±0.156 cells in the field of view.

In the morphological study of the number of binucleated hepatocytes, we also observed a tendency to changes in the number of such cells with maxima at the 12th month of observation in both experimental groups, but the indicators were significantly different in both experimental groups at the 9th month of observation (Fig. 3). Thus, in the group without the addition of quercetin at the 9th month, the number of binuclear hepatocytes was 7.012±0.527 at $p<0.05$ in the fields of view, and with the addition of quercetin, only 5.311±0.156 cells in the fields of view at $p<0.05$, with a difference of 32.00%.

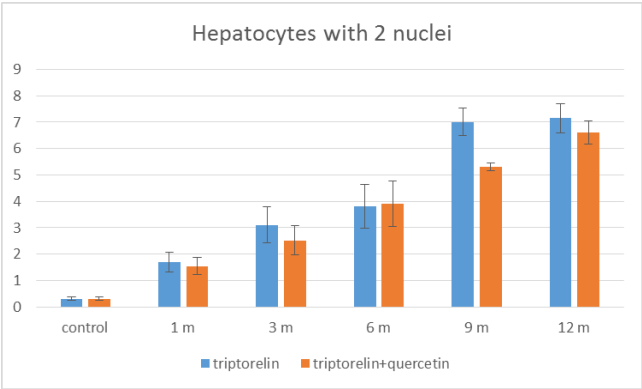


**Fig. 3.** The number of binuclear hepatocytes in the field of view in the group of animals administered triptorelin (T) and the group of animals administered quercetin (T+Q) against the background of triptorelin administration at different study periods.

## Discussion

In this article, we examined the morphofunctional changes in hepatocyte nuclei during long-term (12 months) blocking of the synthesis of releasing hormone caused by the use of the substance triptorelin. The “hypothalamus-pituitary-testis-liver”

system was studied, namely testosterone – hepatocytes of male rats. Testosterone deficiency and its consequences are increasingly being determined in men in clinical conditions, and this is of increased interest in research worldwide [5, 14, 16].

As is known, the bulk of DNA is concentrated in the nucleus – the carrier of hereditary information and the regulator of metabolic function. The most important matrix processes – DNA replication, transcription (RNA synthesis) and RNA processing (maturation) take place in it. The nucleus transfers genetic information to the cytoplasm to the site of protein synthesis - ribosomes - using mRNA or messenger RNA. The nucleus, exchanging information with the cytoplasm of the hepatocyte, controls and coordinates all cell activity: division, growth, intermediate metabolism, protein synthesis and its differentiation [20]. During the life cycle, the cell nucleus is in interphase. The large variation in the size of hepatocyte nuclei is explained by the fact that during postnatal development, some cells undergo cytogenetic transformation, characterized by gradual polyploidy. Polyploidy, or amplification of the entire genome, is inherent in cells/organisms containing more than 2 main chromosome sets [10, 31]. The proportion of hepatocyte diferon is 60-70 % of cells and 78 % of the volume. Among them, about 25 % of hepatocytes have two nuclei, 70 % of single-nucleated hepatocytes are tetraploid (4n), about 2 % are octaploids (8n) with 4 or 8-fold chromosome sets. Polyploid hepatocytes appear at an early age, their number increases with age. Adults have about 30-40 % of polyploid hepatocytes with a 4-fold set of chromosomes. The increase in nuclear polyploidy is accompanied by an increase in the size of hepatocytes. The volume of hepatocyte nuclei doubles when the DNA content doubles. No significant difference in the volume of polyploid hepatocytes containing one or two nuclei with the same sets of chromosomes has been found [9]. There are several hypotheses to explain polyploidy. Some authors suggest that liver polyploidy is necessary to improve hepatocyte function [13, 30]. A polyploid cell may allow for a two- or four-fold increase in the expression of some genes and thereby enhance certain metabolic functions. However, comparison of gene expression profiles of isolated diploids, tetraploids and octaploids using microarray analysis revealed that only 50 candidate genes from a wide range of different biological processes were differentially expressed [9, 10, 13]. Polyploidy-activated genes are present in all major liver-specific functions, including nitrogen metabolism, protein synthesis, maintenance of the redox state, xenobiotic metabolism and immunity. It has been established that polyploid hepatocytes have a tendency to increase anaerobic energy production by producing ATP from carbohydrates rather than fatty acids, suggesting that polyploidy is associated with the transition of liver-specific functions into an economy mode [7]. According to other hypotheses, polyploidy provides protection of hepatocytes from oxidative stress and genotoxic damage. Polyploid chromosome sets may serve as a buffer against mutations that inactivate genes by DNA-damaging agents. For example, early tumor lesions in the liver are characterized by an increase in the number of diploid cells, which are less protected from mutations than polyploid ones. Notably, a comparison of diploid and polyploid hepatocytes on a genome-wide scale shows that polyploids induce genes directed against pathogens, DNA damage, and oxidative stress, and repress genes that promote apoptosis. In addition, progressive polyploidization allows the liver to adapt to cell loss during the aging process or may be a protective response to the accumulation of damaged DNA. In pathological conditions accompanied by loss of function, the liver is able to compensate for the loss of volume by increasing the number of genomes [19]. Liver polyploidization mainly indicates the severity of the lesion: the higher the observed rate of polyploidization, the greater the injury. However, an increase in diploid cells is a characteristic feature of hepatocellular carcinoma due to their increased proliferative capacity and susceptibility to further mutations [23, 25].

Both basic and clinical studies have shown that testosterone acts on the liver parenchyma both in health and pathology. It is known that testosterone contributes to a global improvement in energy metabolism, the introduction of its excessive amount can cause an excess of reactive oxygen species along with oxidative damage, which indicates electron leakage from the mitochondrial respiratory chain and metabolic uncoupling.

It is assumed that the vasoprotective effects of quercetin are realized due to its ability to reduce the activity of the inflammatory process in the vascular endothelium, enhance the activity of endothelial NO synthase (eNOS), which, in turn, increases the level of nitric oxide in endothelial cells and leads to improved endothelial function [27].

In our work, we observed a tendency to a gradual increase in the number of nucleoli and hepatocyte nuclei at all times of the experiment in both experimental groups. In our opinion, this may indicate a compensatory effect caused by the addition of quercetin to the diet of experimental animals, which, due to its vasoprotective and antioxidant properties, reduces the inflammatory process in the endothelium and in hepatocytes, contributing to an increase in the level of nitric oxide [34].

Our results are consistent with the data of some other experimental and clinical studies, which draw attention to the fact that the use of quercetin leads to antioxidant, anti-inflammatory, hypolipidemic, antisteatotic and antifibrotic effects. The above indicates the potential benefit of this flavonoid in the treatment of various liver diseases, in particular non-alcoholic fatty liver disease, chronic hepatitis of various etiologies and drug-associated liver diseases [9, 10, 13, 35].

Thus, we can assume that changes in the number of nuclei and nucleoli of hepatocytes in the processes of dishormonal disorder protect against oxidative stress and hepatotoxic damage to the cell and increase transcriptional moments in the process of division, growth, intermediate metabolism, protein synthesis and its differentiation. The results obtained by us are a theoretical justification for the development of methods for correcting disorders in the liver during the pathological impact on the body of a dishormonal state of central genesis: “hypothalamus–pituitary–testis–liver”. Data on the functional morphology of hepatocyte nuclei at the stages of adaptation to changes in the endocrine

system expand the existing ideas about the causes that cause liver homeostasis disorders.

## Conclusion

1. Central blocking of the synthesis of releasing hormone and subsequent activation of pituitary gonadotropocytes leads to oxidative-nitrosative stress, which causes pathological processes in hepatocytes, primarily in the form of quantitative changes in binucleolus and binuclear cells in the population.

2. Additional administration of quercetin reduces the negative effect on hepatocytes, which is confirmed by changes in parameters in experimental groups of animals.

## References


[1] Almomani, A., Hitawala, A. A., Kumar, P., Alqaisi, S., Alshaikh, D., Alkhayyat, M., & Asaad, I. (2022). Prevalence of hypothyroidism and effect of thyroid hormone replacement therapy in patients with non-alcoholic fatty liver disease: A population-based study. *World journal of hepatology*, 14(3), 551-558. doi: 10.4254/wjh.v14.i3.551

[2] Alamri, Z. Z. (2019). Effect of luteolin and quercetin on thioacetamide induced hepatic fibrosis in rats. *International Journal of Pharmacology*, 15(7), 863-871. doi: 10.3923/ijp.2019.863.871

[3] Bahriy, M. M., Dibrova, V. A., Popadynets, O. H., & Hryshchuk, M. I. (2016). *Методики морфологічних досліджень: монографія [Methods of morphological research: monograph].* Вінниця: Нова книга – Vinnytsya: Nova knyha.

[4] Botté, M. C., Lerrant, Y., Lozach, A., Bérault, A., Counis, R., & Kottler, M. L. (1999). LH down-regulates gonadotropin-releasing hormone (GnRH) receptor, but not GnRH, mRNA levels in the rat testis. *J Endocrinol*, *162*(3), 409-415. doi: 10.1677/joe.0.1620409

[5] Bou-Nader, M., Caruso, S., Donne, R., Celton-Morizur, S., Calderaro, J., Gentric, G., … & Desdouets, C. (2020). Polyploidy spectrum: a new marker in HCC classification. *Gut*, *69*(2), 355-364. doi: 10.1136/gutjnl-2018-318021

[6] Carteri, R. B., Kopczynski, A., Rodolphi, M. S., Strogulski, N. R., Wannmacher, C. M., Franceschi, I. D., ... & Portela, L. V. (2021). Anabolic-androgenic steroids impair mitochondrial function and redox status in the heart and liver of mice. *Steroids*, *172*, 108861. doi: 10.1016/j.steroids.2021.108861

[7] Chao, H. W., Doi, M., Fustin, J. M., Chen, H., Murase, K., Maeda, Y., … & Okamura, H. (2017). Circadian clock regulates hepatic polyploidy by modulating Mkp1-Erk1/2 signaling pathway. *Nature communications*, *8*(1), 2238. doi: 10.1038/s41467-017-02207-7

[8] Chekalina, N. I., Shut, S. V., Trybrat, T. A., Burmak, Y. H., Petrov, Y. Y., Manusha, Y. I., & Kazakov, Y. M. (2017). Effect of quercetin on parameters of central hemodynamics and myocardial ischemia in patients with stable coronary heart disease. *Wiad Lek*, *70*(4), 707-711. PMID: 29064791

[9] Donne, R., Sangouard, F., Celton-Morizur, S., & Desdouets, C. (2021). Hepatocyte Polyploidy: Driver or Gatekeeper of Chronic Liver Diseases. *Cancers (Basel)*, *13*(20), 5151. doi: 10.3390/cancers13205151

[10] Donne, R., Saroul-Aïnama, M., Cordier, P., Celton-Morizur, S., & Desdouets, C. (2020). Polyploidy in liver development, homeostasis and disease. *Nat Rev Gastroenterol Hepatol*, 17(7), 391-405. doi: 10.1038/s41575-020-0284-x

[11] do Val Lima, P. R., Ronconi, K. S., Morra, E. A., Rodrigues, P. L., Ávila, R. A., Merlo, E., ... & Ribeiro Júnior, R. F. (2023). Testosterone deficiency impairs cardiac interfibrillar mitochondrial function and myocardial contractility while inducing oxidative stress. *Frontiers in Endocrinology*, *14*, 1206387. doi: 10.3389/fendo.2023.1206387

[12] Guo, X., Li, Y., Wang, W., Wang, L., Hu, S., Xiao, X., … & Zeng, J. (2022). The construction of preclinical evidence for the treatment of liver fibrosis with quercetin: A systematic review and meta-analysis. *Phytotherapy research: PTR*, *36*(10), 3774-3791. doi: 10.1002/ptr.7569

[13] Gupta, S. (2000). Hepatic polyploidy and liver growth control. *Semin Cancer Biol*, *10*(3), 161-171. doi: 10.1006/scbi.2000.0317

[14] Hajam, Y. A., Rani, R., Ganie, S. Y., Sheikh, T. A., Javaid, D., Qadri, S. S., ... & Reshi, M. S. (2022). Oxidative stress in human pathology and aging: molecular mechanisms and perspectives. *Cells*, *11*(3), 552. doi: 10.3390/cells11030552

[15] Kasarinaite, A., Sinton, M., Saunders, P. T. K., Hay, D. C. (2023). The Influence of Sex Hormones in Liver Function and Disease. *Cells*, *12*(12), 1604. doi: 10.3390/cells12121604

[16] Klaunig, J. E. (2018). Oxidative stress and cancer. *Curr Pharm*, *24*(40), 4771-4778. doi: 10.2174/1381612825666190215121712

[17] Kostenko, V., Akimov, O., Gutnik, O., Kostenko, H., Kostenko, V., Romantseva, T., ... & Taran, O. (2023). Modulation of redox-sensitive transcription factors with polyphenols as pathogenetically grounded approach in therapy of systemic inflammatory response. *Heliyon*, *9*(5), e15551. doi: 10.1016/j.heliyon.2023.e15551

[18] Kozaeva, R., Klymenko, M. O., Katrushov, O. V., & Kostenko, V. O. (2022). Bioflavonoids as agents for correcting nitro-oxidative stress and salivary gland functions in rats exposed to alcohol during modeled lipopolysaccharide-induced systemic inflammatory response. *Wiadomosci Lekarskie (Warsaw, Poland: 1960)*, *75*(3), 685-690. doi: 10.36740/wlek202203121

[19] Kur, P., Kolasa-Wołosiuk, A., Misiakiewicz-Has, K., & Wiszniewska, B. (2020). Sex Hormone-Dependent Physiology and Diseases of Liver. *International journal of environmental research and public health*, *17*(8), 2620. doi: 10.3390/ijerph17082620

[20] Lin, Y. H., Zhang, S., Zhu, M., Lu, T., Chen, K., Wen, Z., … & Zhu, H. (2020). Mice With Increased Numbers of Polyploid Hepatocytes Maintain Regenerative Capacity But Develop Fewer Hepatocellular Carcinomas Following Chronic Liver Injury. *Gastroenterology*, *158*(6), 1698-1712. doi: 10.1053/j.gastro.2020.01.026

[21] Lin, H. Y., Yu, I. C., Wang, R. S., Chen, Y. T., Liu, N. C., Altuwaijri, S., … & Chang, C. (2008). Increased hepatic steatosis and insulin resistance in mice lacking hepatic androgen receptor. *Hepatology (Baltimore, Md)*, *47*(6), 1924-1935. doi: 10.1002/hep.22252

[22] Matsumoto, T. (2022). Implications of Polyploidy and Ploidy Alterations in Hepatocytes in Liver Injuries and Cancers. *Int J Mol Sci*, *23*(16), 9409. doi: 10.3390/ijms23169409

[23] Mavromati, M., & Jornayvaz, F. R. (2021). Hypothyroidism-Associated Dyslipidemia: Potential Molecular Mechanisms Leading to NAFLD. *International journal of molecular sciences*, *22*(23), 12797. doi: 10.3390/ijms222312797

[24] Miyaoka, Y., Ebato, K., Kato, H., Arakawa, S., Shimizu, S., & Miyajima, A. (2012). Hypertrophy and unconventional cell division of hepatocytes underlie liver regeneration. *Current biology: CB*, *22*(13), 1166-1175. doi: 10.1016/j.cub.2012.05.016

[25] Neshat, S. Y., Quiroz, V. M., Wang, Y., Tamayo, S., & Doloff, J. C. (2021). Liver Disease: Induction, Progression, Immunological Mechanisms, and Therapeutic *Interventions. Int J Mol Sci*, *22*(13), 6777. doi: 10.3390/ijms22136777

[26] Raja, T., Sud, R., Addla, S., Sarkar, K. K., Sridhar, P. S.,

Talreja, V., … & Patil, K. (2022). Gonadotropin-releasing hormone agonists in prostate cancer: A comparative review of efficacy and safety. *Indian journal of cancer*, *59*(Supplement), S142-S159. doi: 10.4103/ijc.IJC_65_21

[27] Sharifi-Rad, M., Anil Kumar, N. V., Zucca, P., Varoni, E. M., Dini, L., Panzarini, E., ... & Sharifi-Rad, J. (2020). Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. *Frontiers in physiology*, *11*, 552535. doi: 10.3389/fphys.2020.00694

[28] Song, M. J., & Choi, J. Y. (2022). Androgen dysfunction in non-alcoholic fatty liver disease: Role of sex hormone binding globulin. *Frontiers in endocrinology*, *13*, 1053709. doi: 10.3389/fendo.2022.1053709

[29] Waxman, D. J., & Kineman, R. D. (2022). Sex matters in liver fat regulation. *Science (New York, N.Y.)*, *378*(6617), 252-253. doi: 10.1126/science.ade7614

[30] Wilkinson, P. D., Alencastro, F., Delgado, E. R., Leek, M. P., Weirich, M. P., Otero, P. A., … & Duncan, A. W. (2019). Polyploid Hepatocytes Facilitate Adaptation and Regeneration to Chronic Liver Injury. *The American journal of pathology*, *189*(6), 1241-1255. doi: 10.1016/j.ajpath.2019.02.008

[31] Wilkinson, P. D., & Duncan, A. W. (2021). Differential Roles for Diploid and Polyploid Hepatocytes in Acute and Chronic Liver Injury. *Seminars in liver disease*, *41*(1), 42-49. doi: 10.1055/s-0040-1719175

[32] Xiao, J., & Bai, W. (2019). Bioactive phytochemicals. *Critical reviews in food science and nutrition*, *59*(6), 827-829. doi: 10.1080/10408398.2019.1601848

[33] Xu, M. X., Wang, M., & Yang, W. W. (2017). Gold-quercetin nanoparticles prevent metabolic endotoxemia-induced kidney injury by regulating TLR4/NF-κB signaling and Nrf2 pathway in high fat diet fed mice. *International journal of nanomedicine*, *5*(12), 327-345. doi: 10.2147/IJN.S212318

[34] Yelins'ka, A. M., Akimov, O. Y., & Kostenko, V. O. (2019). Role of AP-1 transcriptional factor in development of oxidative and nitrosative stress in periodontal tissues during systemic inflammatory response. *Український біохімічний журнал=Ukrainian biochemical journal*, *91*(1), 80-85. doi: 10.15407/ubj91.01.080

[35] Zhang, S., Lin, Y. H., Tarlow, B., & Zhu, H. (2019). The origins and functions of hepatic polyploidy. *Cell Cycle*, *18*(12), 1302-1315. doi: 10.1080/15384101.2019.1618123

**ЗМІНИ В ГЕПАТОЦИТАХ ЩУРІВ ЗА УМОВ ЦЕНТРАЛЬНОЇ БЛОКАДИ СИНТЕЗУ ЛЮТЕЇНІЗУЮЧОГО ГОРМОНУ З ДОДАВАННЯМ КВЕРЦЕТИНУ**

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*Ядро, обмінюючись інформацією з цитоплазмою гепатоцита, контролює і координує всю активність клітини: поділ, ріст, проміжний обмін речовин, синтез білка і його диференціювання. Протягом життєвого циклу клітини ядро зберігається в інтерфазі. Велика варіація розмірів ядер гепатоцитів пояснюється тим, що при постнатальному зростанні деякі гепатоцити піддаються цитогенетичним перетворенням, що характеризуються поступовою поліплоїдією. Поліплоїдія, або посилення цілого геному, стосується клітин/організмів, що містять більше 2 основних хромосомних наборів. Мета даного дослідження – визначити морфогенез та динаміку мінливості підтипів гепатоцитів щурів, двоядерних та з двома ядерцями, за умов центральної блокади синтезу лютеїнізуючого гормону при довготривалій дії трипторелін, з додаванням в раціон харчування тварин кверцетину. Експеримент проведено на 60 статевозрілих білих щурах самцях масою 140-160 г. Тварин розділили на 3 групи: 1 групі – контрольній, вводився фізіологічний розчин (10 тварин); 2 групі підшкірно вводили розчин трипторелін ембонат у дозі 0,3 мг діючої речовини на кг маси тіла протягом 12 місяців (25 тварин); 3 групі вводили розчин трипторелін із розрахунку 0,3 мг діючої речовини на кг маси тіла з додаванням кверцетину в перерахунку на масу тіла тварин тричі на тиждень (25 тварин). Тварин виводили з експерименту через 1, 3, 6, 9 та 12 місяців шляхом передозування ефірного наркозу. Комплексне дослідження гістологічних препаратів печінки та кількісний підрахунок гепатоцитів з двома ядерцями та двоядерних проводили за допомогою світлового мікроскопа з цифровим мікрофільтром та адаптованого для цих досліджень програмного забезпечення. Статистичну обробку результатів дослідження виконували з використанням програмного забезпечення Microsoft Office Excel та розширення Real Statistics 2019. Патологічні процеси, що виникають у тканині печінки при експериментальному оксидативно-нітрозативному стресі, викликаному введенням трипторелін, призводять як до кількісних, так і якісних змін. Так кількість гепатоцитів з двома ядерцями достовірно збільшувалась в 2 групі і на 12-й місяць спостереження становила 5,291±1,156 клітин в полі зору при p<0,05. Кількість двоядерних гепатоцитів також мала тенденцію до змін з максимумами на 12-й місяць спостереження. Так у 2 групі на 9-й місяць кількість двоядерних гепатоцитів склала 7,012±0,527 клітин в полі зору при p<0,05, а при додаванні кверцетину лише 5,311±1,561 клітин в полі зору при p<0,05. Збільшена кількість мітозів виявлялась у 2 групі на 6-й місяць спостереження, у 3 групі визначалася лише на 9-й. Проведене дослідження показало, що при введенні трипторелін виникає оксидативно-нітрозативний стрес, який призводить до патологічних змін гепатоцитів у вигляді кількісних змін клітин з двома ядерцями та двоядерних. Додаткове введення кверцетину зменшує негативний вплив на гепатоцити печінки, що підтверджується показниками в експериментальних групах тварин.*

**Ключові слова:** *печінка, гепатоцит, двоядерні гепатоцити, мітоз, тестостерон, лютеїнізуючий гормон, кверцетин, трипторелін.*

**Author's contribution**

*Polyviana O. A.* – data collection and analysis.
*Stetsuk Ye. V.* – work concept and design.
*Shepitko V. I.* – final approval of the article.
*Vilkhova O. V.* − methodology of the original draft.
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