

# Histomorphological Alterations of Lymph Nodes in Experimental Ulcerative Colitis

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**Abstract Background:** Ulcerative colitis is a chronic inflammatory bowel disease characterized by destructive lesions of the intestinal mucosa and disturbances of immune regulation. Inflammatory processes developing in ulcerative colitis affect not only the intestinal wall but also peripheral immune organs, particularly lymph nodes. However, histomorphological and immunohistochemical alterations occurring in lymphatic tissues during experimental ulcerative colitis remain insufficiently investigated. **Materials and Methods:** The study was carried out on 120 white outbred rats aged 3, 6, and 12 months. Experimental ulcerative colitis was induced by intrarectal administration of 8% acetic acid. Histological, morphometric, and immunohistochemical methods were used to evaluate structural alterations in lymph nodes. Tissue sections were stained with hematoxylin-eosin and examined using CD-3 immunohistochemical markers. Quantitative analysis of immunopositive cells was performed using QuPath 0.5.1 software. Additionally, the biocorrective effect of milk thistle oil was evaluated in experimental animals. **Results:** Experimental ulcerative colitis caused significant structural remodeling of lymph nodes, including widening of medullary sinuses, enlargement of paracortical zones, stromal edema, and reduction of lymphocyte density. Immunohistochemical analysis demonstrated increased CD-3 expression and redistribution of T-lymphocytes in inflammatory conditions. Positive CD-3 expression increased from 9.50% in the control group to 33.39% in experimental animals. Biocorrection with milk thistle oil contributed to partial restoration of lymph node architecture and stabilization of T-cell activity, with positive expression reaching 40.22%. **Conclusion:** Experimental ulcerative colitis induces pronounced morphofunctional and immunohistochemical alterations in lymph nodes. Milk thistle oil demonstrated protective and immunomodulatory effects by improving lymphoid tissue organization and reducing inflammatory changes. The obtained findings expand current understanding of immunopathogenetic mechanisms involved in ulcerative colitis and may contribute to the development of new therapeutic approaches for inflammatory bowel diseases.

**Keywords** Ulcerative colitis, Lymph nodes, Morphology, Morphometry, Immunohistochemistry, CD-3 marker, T-lymphocytes, Experimental study, Milk thistle oil, Biocorrection, Inflammatory bowel disease, White outbred rats

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## 1. Introduction

Ulcerative colitis (UC) is a chronic nonspecific inflammatory disease of the colon characterized by recurrent inflammation of the intestinal mucosa, ulcerative-destructive lesions, and dysregulation of the immune system [1,2]. In recent years, the incidence and prevalence of inflammatory bowel diseases, including ulcerative colitis, have been steadily increasing worldwide, making this pathology one of the most important problems in modern gastroenterology and experimental medicine [3]. The chronic recurrent course of the disease and the development of severe complications significantly reduce patients' quality of life and increase the social and economic burden on healthcare systems [4].

Currently, the etiology and pathogenesis of ulcerative colitis remain incompletely understood. Modern studies indicate that the disease develops as a result of complex interactions between genetic predisposition, environmental factors, intestinal microbiota disturbances, and immune dysregulation [5,6]. Cytokine imbalance, excessive activation of T- and B-lymphocytes, and impaired immune tolerance play a central role in the progression of inflammatory processes in ulcerative colitis [7]. Persistent inflammation causes structural and functional alterations not only in the intestinal wall but also in regional lymphatic tissues. Lymph nodes are among the most important peripheral organs of the immune system and perform filtration, antigen presentation, lymphocyte proliferation, and immune regulatory functions [8]. During inflammatory diseases, lymph nodes undergo significant morphological and functional remodeling associated with activation of

immune responses. Experimental and clinical studies have demonstrated that inflammatory bowel diseases are accompanied by lymphoid follicle hyperplasia, sinus histiocytosis, stromal edema, vascular disturbances, and alterations in immune cell populations within lymphatic tissues [9]. Although numerous investigations have focused on histopathological changes in the intestinal mucosa during ulcerative colitis, morphological alterations occurring in lymph nodes remain insufficiently studied [10,11]. Previous studies reported proliferative and degenerative changes in lymphoid structures, including disruption of normal lymph node architecture and alterations in T- and B-cell activity during experimental colitis [12]. Immunohistochemical markers such as CD-3 and CD-20 are considered informative indicators for evaluating changes in lymphocyte populations and immune activity in lymphatic tissues [13]. At present, studying the immunopathogenetic mechanisms of ulcerative colitis and identifying structural changes in lymphatic organs are among the priority directions of modern morphology and immunology [14]. In this regard, investigation of potential biocorrective agents with anti-inflammatory and antioxidant properties is of particular scientific interest. Milk thistle oil, known for its membrane-protective and antioxidant effects, may have a beneficial influence on morphological alterations developing in lymphatic tissues under inflammatory conditions [15]. Therefore, investigation of morphological, morphometric, and immunohistochemical changes in lymph nodes following experimental ulcerative colitis is important for understanding disease pathogenesis, improving diagnostic approaches, and increasing treatment effectiveness. The scientific novelty of the present study lies in the fact that, for the first time, comparative morphometric characteristics of lymph nodes in normal and experimental ulcerative colitis conditions were identified in white outbred rats, histomorphological and histochemical alterations in lymph nodes after experimental ulcerative colitis were comprehensively analyzed, and immunohistochemical changes using CD-3 and CD-20 markers were determined. In addition, the biocorrective effects of milk thistle oil on lymph node structures after experimental ulcerative colitis were experimentally substantiated, which expanded current understanding of the immunopathogenetic mechanisms of ulcerative colitis and the role of lymphatic tissue remodeling in inflammatory bowel diseases.

## 2. Materials and Methods

This experimental investigation was performed at the scientific laboratory of the Bukhara State Medical Institute named after Abu Ali ibn Sino during 2024–2026. The study protocol was developed according to modern biomedical research standards, and all procedures involving laboratory animals were conducted in accordance with internationally accepted ethical principles.

The study included 120 white outbred rats of both sexes aged 3, 6, and 12 months. Before inclusion in the experiment, all animals were kept under quarantine conditions and examined

to exclude infectious and somatic diseases. Subsequently, the rats were housed in standard vivarium conditions with a controlled environment, standard nutrition, and free access to water.

Experimental animals were divided into three groups. The first group consisted of intact rats and served as the control group. The second group included animals with experimentally induced ulcerative colitis. Experimental colitis was modeled by daily intrarectal administration of 1 ml of 8% acetic acid through a special probe for 20 days. The third group consisted of rats with induced ulcerative colitis that received milk thistle oil for biocorrection. During the experimental period, several animals died due to complications associated with severe inflammatory changes.

Throughout the experiment, the animals' body weight, physiological status, and behavioral activity were regularly monitored. At the end of the observation period, the rats were euthanized under ether anesthesia by decapitation according to international recommendations for biomedical studies using laboratory animals.

Lymph node tissues collected from experimental and control animals served as the main material for morphological analysis. Tissue samples were fixed in 10% neutral buffered formalin, followed by washing and dehydration in ascending ethanol concentrations. After dehydration, the specimens were cleared in xylene and embedded in paraffin using standard histological techniques.

Paraffin blocks were sectioned into 4–7  $\mu\text{m}$  slices using a microtome. Histological preparations were stained with hematoxylin-eosin, Van Gieson, and Alcian blue methods for evaluation of tissue architecture and connective tissue alterations. Morphological observations and morphometric measurements were carried out using trinocular light microscopes equipped with digital imaging systems.

Immunohistochemical analysis was performed to determine the expression of T- and B-lymphocyte markers within lymph node tissues. CD-3 and CD-20 antibodies were used for immunophenotypic evaluation. Tissue sections placed on adhesive-coated slides underwent deparaffinization, rehydration, antigen retrieval, and blocking of endogenous peroxidase activity before incubation with primary antibodies. Immunoreactivity was visualized using DAB chromogen staining.

The immunohistochemical reaction was evaluated in several microscopic fields at  $\times 200$ – $\times 400$  magnification. Quantitative analysis of positively stained cells was performed using QuPath 4.4.0 software. Depending on the proportion of immunopositive cells, expression intensity was categorized as low, moderate, or high.

Statistical analysis of the obtained data was carried out using Microsoft Excel and STATGRAPH software packages. Arithmetic means, standard deviations, and standard errors were calculated for all quantitative variables. Student's t-test was applied for normally distributed data, while the Mann–Whitney U-test was used for nonparametric analysis. Differences between groups were considered statistically significant at  $p < 0.05$ .

### 3. Results

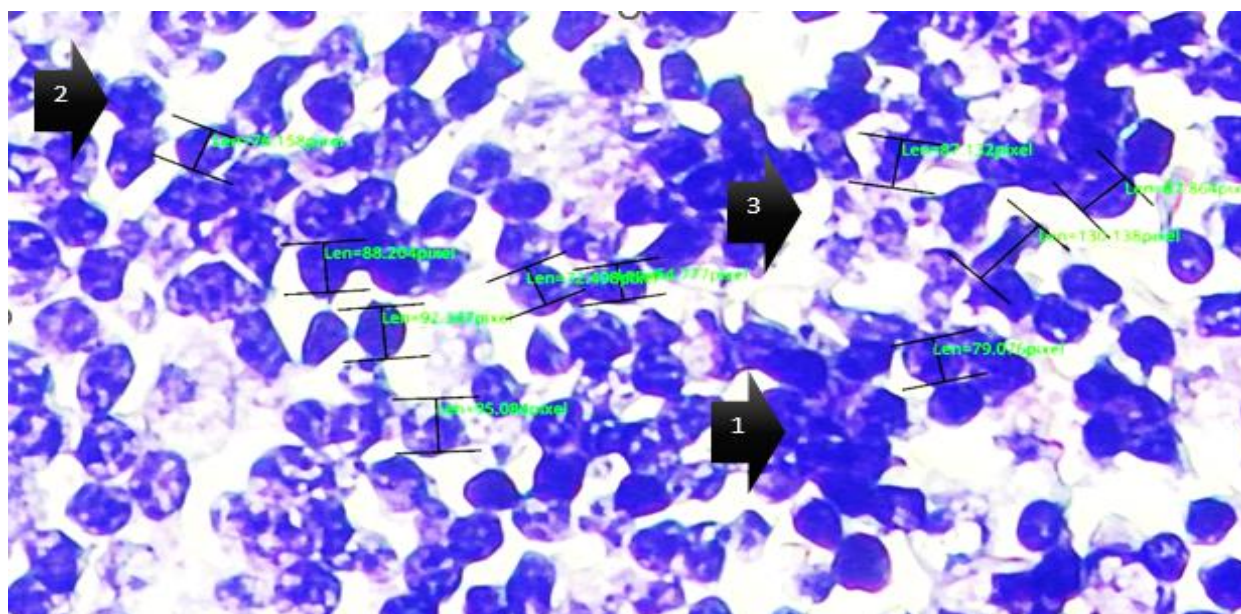
The morphometric analysis of lymph nodes in the control group of white outbred rats demonstrated that their histological structure corresponded to normal physiological parameters. The capsule, cortical, and medullary regions of the lymph nodes were clearly differentiated from each other. The number, shape, and size of lymphoid follicles remained within normal limits, indicating preservation of the overall structural organization of the lymph nodes. Morphometric examination revealed stable values of the total lymph node area, the ratio between cortical and medullary zones, and the diameter of germinal centers. A balanced relationship between stromal and parenchymal components was maintained, while no inflammatory, degenerative, or reactive alterations were detected. These findings confirmed the normal immunomorphological condition of lymph nodes in the control group and served as a reliable basis for comparative evaluation with experimental groups.

Histological examination of lymph nodes in 3-month-old white outbred rats from the control group also demonstrated age-related normal structural organization. Microscopic observations showed clear differentiation of the lymph node capsule, trabeculae, cortical and medullary regions, as well as lymphoid follicles. The capsule exhibited uniform thickness and consisted mainly of dense fibrous connective tissue. Lymphoid follicles located within the cortical zone were observed in normal numbers and sizes, while the proportion between primary and secondary follicles remained preserved. Germinal centers were well developed and distinctly expressed, indicating physiologically active lymphocyte proliferation. In the paracortical zone, the distribution of T-lymphocytes was arranged in a regular and organized manner. Structural integrity of the medullary sinuses and medullary cords was

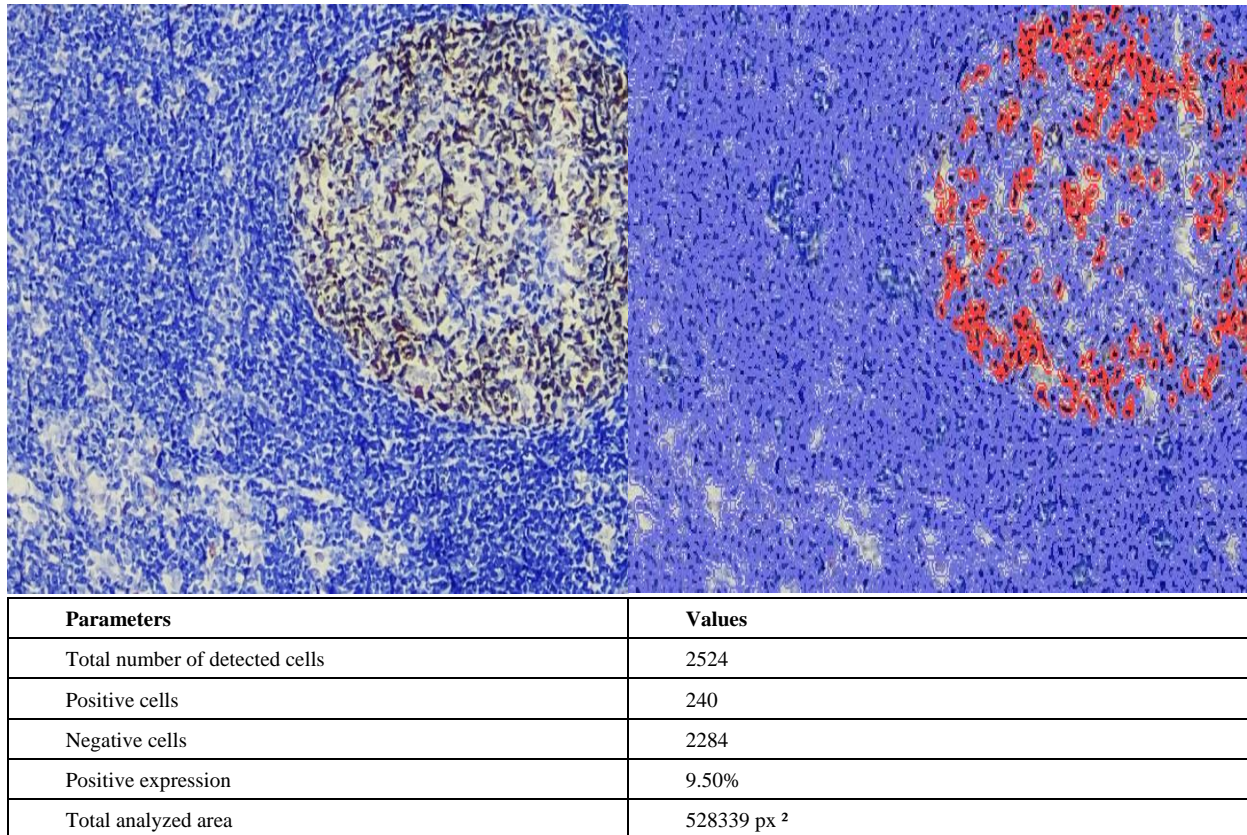
preserved, and cellular density remained within physiological limits. The obtained morphometric results confirmed that lymph nodes of 3-month-old white outbred rats possessed anatomically and histologically normal age-related features. No signs of inflammation, tissue destruction, or other pathological alterations were identified during the examination (Figure 1).

The obtained findings may serve as reliable morphological and morphometric criteria for subsequent comparative analysis with experimental groups. The lymph node capsule demonstrated uniform thickness and consisted predominantly of dense fibrous connective tissue. The average capsule thickness remained within physiological limits and measured  $20.1 \pm 0.54 \mu\text{m}$ . The cortical region occupied approximately  $57.3 \pm 0.64\%$  of the total lymph node area. The number and size of lymphoid follicles located within the cortical zone corresponded to normal physiological values. The average follicular diameter was  $198.6 \pm 3.29 \mu\text{m}$ . Germinal centers were clearly distinguished and measured approximately  $105.4 \pm 2.23 \mu\text{m}$  in diameter, indicating physiologically active lymphocyte proliferation.

The paracortical region accounted for  $22.1 \pm 0.62\%$  of the total lymph node area. The zonal distribution of T-lymphocytes remained well preserved, while the average cellular density reached  $8.1 \pm 0.19$  thousand cells/ $\text{mm}^2$ . The medullary region, including medullary sinuses and medullary cords, occupied  $18.4 \pm 0.47\%$  of the total lymph node area. The average width of the medullary sinuses was  $42.3 \pm 3.5 \mu\text{m}$ , and the cellular density within these structures remained within physiological limits, averaging  $5.8 \pm 0.21$  thousand cells/ $\text{mm}^2$ . Overall, morphometric parameters of lymph nodes in the control group remained within normal physiological ranges, indicating preservation of structural and functional stability.



**Figure 1.** Morphometric characteristics of lymph nodes in 3-month-old white outbred rats of the control group. Hematoxylin-eosin staining. Objective lens  $\times 10$ , ocular lens  $\times 100$ . (1) Germinal center of the lymph node; (2) lymphocyte; (3) sinusoidal space



**Figure 2.** Immunohistochemical evaluation of CD-3 marker expression in lymph nodes of 3-month-old white outbred rats from the control group. Stained using the DAB chromogen method. Magnification  $\times 200$ . The image was scanned and analyzed using QuPath 0.5.1 software to determine the level of expression. Expressed cells are highlighted in red

Immunohistochemical examination of lymph nodes in 3-month-old white outbred rats from the control group demonstrated CD-3 marker expression predominantly in T-lymphocytes localized within the paracortical region (Figure 2). In sections stained using the DAB chromogen method, CD-3 positive cells were clearly visualized by brown coloration, while the physiological organization of lymph node structures remained preserved. CD-3 expression was relatively less pronounced in the germinal centers, whereas a dense distribution of T-lymphocytes was observed in the paracortical areas.

Digital image analysis performed using QuPath 0.5.1 software demonstrated immunopositive cells highlighted in red, showing a relatively uniform distribution throughout the lymph node tissue (Figure 2). The number of positive cells remained within physiological limits, indicating normal immunological activity within the lymphatic tissue. These findings confirmed preservation of T-cell mediated immune structures in the lymph nodes of the control group, without evidence of pathological or destructive alterations.

The immunohistochemical analysis demonstrated moderate expression of the CD-3 marker in lymph node tissues of 3-month-old white outbred rats from the control group. CD-3 positive cells were predominantly localized within the paracortical region of the lymph node, corresponding to the normal distribution of T-lymphocytes. The majority of immunopositive cells showed distinct brown cytoplasmic

staining, while digital analysis performed using QuPath 0.5.1 software highlighted positive cells in red.

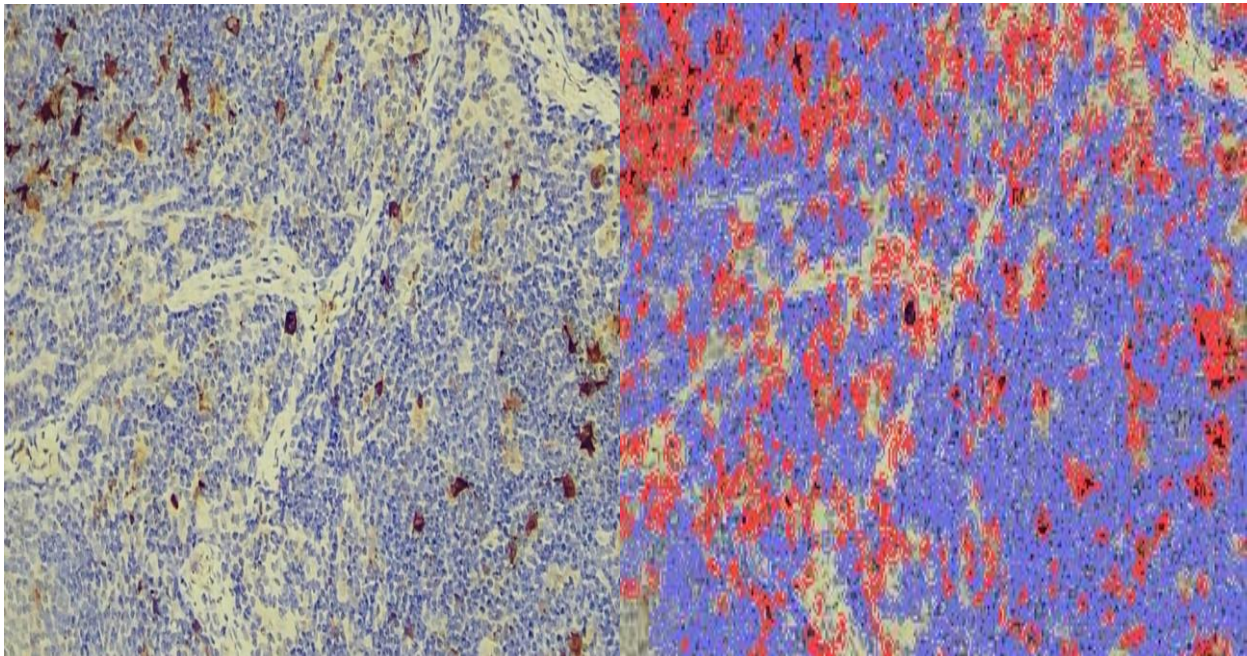
Quantitative assessment revealed a total of 2524 detected cells, including 240 positive and 2284 negative cells. The overall level of positive CD-3 expression reached 9.50%, indicating physiologically normal T-cell immunoreactivity in the control group. The total analyzed area comprised 528339 px<sup>2</sup>. No signs of excessive immune activation, inflammatory infiltration, or pathological structural alterations were identified in the examined lymph node tissue.

Immunohistochemical examination of lymph nodes in experimental animals demonstrated pronounced expression of the CD-3 marker in T-lymphocyte populations localized mainly within the paracortical and interfollicular regions (Figure 3). In sections stained using the DAB chromogen method, CD-3 positive cells appeared as intensely brown-stained immunoreactive elements distributed throughout the lymphoid tissue. Compared with the control group, an increased number of immunopositive cells and a more diffuse distribution pattern were observed.

Digital image analysis performed using QuPath 0.5.1 software identified CD-3 positive cells highlighted in red, confirming enhanced T-cell immunoreactivity within the lymph node structures (Figure 3). Positive cells were detected around lymphoid follicles, medullary cords, and stromal regions, indicating activation of cellular immune responses. The increased density of immunopositive lymphocytes suggests intensified

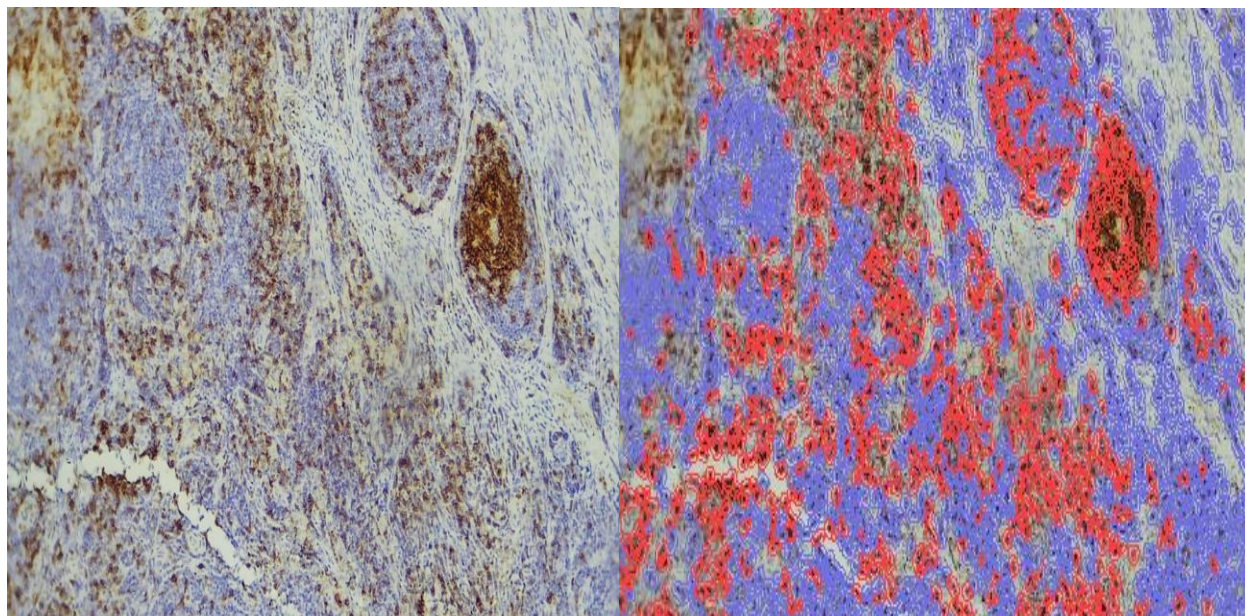
immune-inflammatory activity associated with experimental ulcerative colitis. Structural organization of the lymph node

remained partially preserved; however, focal cellular infiltration and moderate stromal alterations were also noted.



Parameters	Values
Total number of detected cells	3687
Positive cells	2213
Negative cells	1474
Positive expression	33.39%
Total analyzed area	523260 px <sup>2</sup>

**Figure 3.** Immunohistochemical evaluation of CD-3 marker expression in lymph nodes of 12-month-old white outbred rats under experimental conditions. Stained using the DAB chromogen method. Magnification  $\times 200$ . The image was scanned and analyzed using QuPath 0.5.1 software to determine the level of expression. Expressed cells are highlighted in red



Parameters	Values
Total number of detected cells	1775
Positive cells	710
Negative cells	1065
Positive expression	40.22%
Total analyzed area	529496 px <sup>2</sup>

**Figure 4.** Comparative evaluation of immunohistochemical alterations in lymph nodes of 3-month-old white outbred rats and biocorrected groups treated with milk thistle oil, with assessment of CD-3 marker expression. Stained using the DAB chromogen method. Magnification  $\times 200$ . The image was scanned and analyzed using QuPath 0.5.1 software to determine the level of expression. Expressed cells are highlighted in red

Immunohistochemical expression of the CD-3 marker was analyzed in lymph nodes of 12-month-old white outbred rats under experimental conditions. The study made it possible to evaluate the activity of T-lymphocytic components, their zonal distribution, and age-related morphofunctional alterations within lymph node tissues.

Immunohistochemical analysis demonstrated that CD-3 positive cells were predominantly localized in the paracortical region of the lymph nodes. In the cortical zone, CD-3 expression within lymphoid follicles was relatively weak and appeared diffusely distributed in the interfollicular areas. In the medullary sinuses and medullary cords, CD-3 positive cells were detected in small numbers and showed a scattered distribution pattern.

The immunohistochemical condition of lymph nodes in 3-month-old white outbred rats from the experimental group was compared with the biocorrected group treated with milk thistle oil, and the expression levels of the CD-3 marker were analyzed (Figure 4). The study made it possible to evaluate the activity of T-lymphocytic components, their zonal distribution, and the effects of milk thistle extract on lymph node tissues.

Figure 4 demonstrates immunohistochemical expression of the CD-3 marker in lymph nodes of 3-month-old white outbred rats after biocorrection with milk thistle oil. CD-3 positive T-lymphocytes were mainly localized within the paracortical and interfollicular regions of the lymph node. Immunopositive cells showed distinct brown staining after DAB chromogen application, while digital analysis using QuPath 0.5.1 software highlighted positive cells in red. Compared with the untreated experimental group, the lymph node architecture appeared relatively preserved, with a more regular distribution of T-lymphocytes and reduced signs of diffuse inflammatory infiltration. These findings suggest that milk thistle oil contributed to partial restoration of immune cell organization and stabilization of T-cell activity in lymphatic tissue under experimental ulcerative colitis conditions.

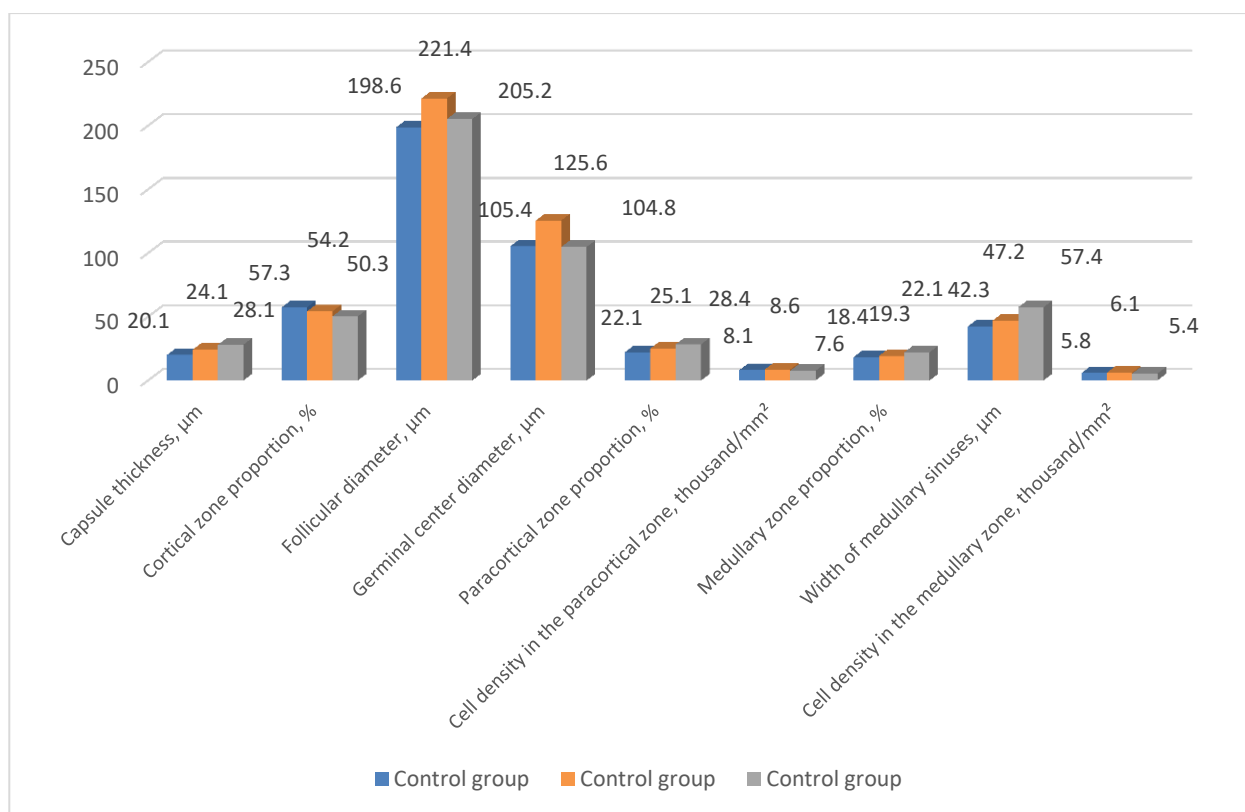
The follicular diameter in the 12-month-old group measured  $205.2 \pm 13.1 \mu\text{m}$ , which was increased by  $6.6 \mu\text{m}$  or 3.3% compared with the 3-month-old rats; however, it decreased by  $16.2 \mu\text{m}$  or 7.3% compared with the 6-month-old group. These findings indicate that follicular activity was more pronounced during the 6-month period, whereas a tendency toward decline began to develop by 12 months of age.

The diameter of the germinal centers measured  $104.8 \pm 8.9 \mu\text{m}$ , which represented a decrease of  $0.6 \mu\text{m}$  or 0.6% compared with the 3-month-old group and a decrease of  $20.8 \mu\text{m}$  or 16.6% compared with the 6-month-old group. This parameter confirms a reduction in lymphocyte proliferative activity in the 12-month-old animals.

The proportion of the paracortical zone in 12-month-old rats reached  $28.4 \pm 2.1\%$ , increasing by 6.3% compared with the 3-month-old group and by 3.3% compared with the 6-month-old group. However, cellular density within the paracortical region measured  $7.6 \pm 0.6$  thousand/ $\text{mm}^2$ , which was reduced by 0.5 thousand/ $\text{mm}^2$  or 6.2% relative to the 3-month-old group and by 1.0 thousand/ $\text{mm}^2$  or 11.6% compared with the 6-month-old group. These findings suggest that although the relative area of the paracortical zone increased, the density of lymphoid cells progressively decreased, indicating age-related attenuation of the T-lymphocytic component.

The medullary zone proportion in the 12-month-old group was  $22.1 \pm 1.9\%$ , showing an increase of 3.7% compared with the 3-month-old rats and 2.8% compared with the 6-month-old animals. The width of medullary sinuses measured  $57.4 \pm 4.2 \mu\text{m}$ , which exceeded the values of the 3-month-old group by  $15.1 \mu\text{m}$  or 35.7% and the 6-month-old group by  $10.2 \mu\text{m}$  or 21.6%. These findings indicate age-related expansion of medullary sinuses and a relative increase in stromal components. In contrast, cellular density within the medullary zone measured  $5.4 \pm 0.4$  thousand/ $\text{mm}^2$ , decreasing by 0.4 thousand/ $\text{mm}^2$  or 6.9% compared with the 3-month-old group and by 0.7 thousand/ $\text{mm}^2$  or 11.5% compared with the 6-month-old group (Figure 5).

Figure 5 demonstrates age-related morphometric alterations in lymph nodes of white outbred rats from the control group. Comparative analysis revealed progressive thickening of the lymph node capsule and enlargement of medullary sinus width with increasing age. The cortical zone proportion and follicular diameter reached maximal values in the 6-month-old group, indicating higher follicular and proliferative activity during this developmental period. In contrast, 12-month-old rats demonstrated a tendency toward reduction of germinal center diameter and cellular density within paracortical and medullary regions, reflecting gradual attenuation of lymphoid and T-cell activity associated with aging.



**Figure 5.** Morphometric parameters of lymph nodes in white outbred rats of the control group

Additionally, the increase in the relative proportion of medullary and paracortical zones in older animals was accompanied by widening of stromal components and reduction in lymphocyte density. These findings suggest age-dependent remodeling of lymph node architecture characterized by decreased proliferative activity and moderate involutional changes in lymphoid tissue structures.

#### 4. Discussion

The results of the present study demonstrated that experimental ulcerative colitis leads to significant morphofunctional and immunohistochemical alterations in lymph nodes of white outbred rats. Comparative analysis between control and experimental groups revealed that inflammatory processes induced structural remodeling of lymphoid tissue, disturbances in zonal organization, and changes in immune cell distribution. These findings confirm that ulcerative colitis affects not only the intestinal wall but also peripheral immune organs involved in inflammatory regulation [1,2].

Morphometric investigations showed that lymph nodes of control animals preserved normal histological architecture characterized by clear differentiation of cortical, paracortical, and medullary regions, stable follicular structure, and physiologically balanced cellular density. In contrast, experimental groups demonstrated enlargement of paracortical and medullary zones, widening of medullary sinuses, and

reduction of lymphocyte density. Such changes indicate activation of immune-inflammatory reactions accompanied by stromal edema and progressive disorganization of lymph node architecture.

Immunohistochemical analysis using CD-3 markers demonstrated alterations in T-lymphocyte distribution within lymph node tissues. In control animals, CD-3 positive cells were mainly localized within paracortical regions and exhibited physiologically normal expression levels. Under experimental conditions, increased expression and redistribution of CD-3 positive lymphocytes were observed, reflecting activation of cellular immune responses associated with ulcerative colitis [3]. The decrease in cellular density in older experimental animals may indicate gradual weakening of proliferative and adaptive immune activity.

An important finding of the study was the positive effect of milk thistle oil on lymph node structures. Animals receiving biocorrection demonstrated partial restoration of lymph node architecture, reduction of inflammatory infiltration, and more organized distribution of immunopositive cells. Normalization of CD-3 expression patterns suggests stabilization of T-lymphocyte activity and improvement of immune regulation under inflammatory conditions. These findings may be associated with the antioxidant and anti-inflammatory properties of milk thistle components [4].

Overall, the obtained results indicate that experimental ulcerative colitis causes pronounced structural and immunological alterations in lymph nodes, whereas

biocorrection with milk thistle oil contributes to partial restoration of lymphoid tissue organization and cellular immune balance. The findings expand current understanding of immunopathogenetic mechanisms involved in ulcerative colitis and confirm the important role of lymphatic tissue remodeling in chronic inflammatory bowel diseases [5].

## 5. Conclusions

1. In experimental ulcerative colitis, significant morphometric alterations were identified in lymph nodes of white outbred rats. In 12-month-old animals, capsule thickness increased from  $20.1 \pm 0.54 \mu\text{m}$  to  $28.1 \pm 1.7 \mu\text{m}$ , while the cortical zone proportion decreased from  $57.3 \pm 0.64\%$  to  $50.3 \pm 2.4\%$ . At the same time, the medullary zone proportion increased to  $22.1 \pm 1.9\%$ , indicating age-related structural remodeling of lymphoid tissue.
2. Experimental ulcerative colitis caused pronounced histomorphological disturbances in lymph nodes characterized by widening of medullary sinuses, stromal edema, disorganization of lymphoid follicles, and reduction of cellular density. The width of medullary sinuses increased from  $42.3 \pm 3.5 \mu\text{m}$  in 3-month-old control animals to  $57.4 \pm 4.2 \mu\text{m}$  in 12-month-old experimental rats, reflecting progressive inflammatory and degenerative alterations in lymphoid structures.
3. Immunohistochemical analysis using CD-3 markers demonstrated activation of T-lymphocytic immune responses in experimental ulcerative colitis. Positive CD-3 expression increased from 9.50% in the control group to 33.39% in experimental animals, while redistribution of immunopositive cells within paracortical and interfollicular zones confirmed disturbances in cellular immune regulation.
4. Biocorrection with milk thistle oil exerted a protective effect on lymph node tissues by improving structural organization and stabilizing T-lymphocyte activity. In the biocorrected group, CD-3 positive expression reached 40.22%, accompanied by reduction of inflammatory infiltration and partial restoration of physiological lymphoid architecture, indicating immunomodulatory and anti-inflammatory properties of milk thistle oil.

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