Acta Nat. Sci. (2021) 2(2): 109-117
DOI: 10.29329/actanatsci.2021.350.04
e-ISSN: 2718-0638

Original Research Paper
info@actanatsci.com
www.actanatsci.com

ACTA NATURA ET SCIENTIA

Effect of *Homalothecium sericeum* (Hedw.) Schimp. Extract on SOD1 Activity in Rat Tissues (Kidney, Adrenal Gland, Ovary)

Özlem Yayıntaş[1] • Latife Ceyda İrkin[2] • Şamil Öztürk[3]✉

[1] Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Medical Biology, 17020 Çanakkale, Turkey, ozlemyayintas@hotmail.com
[2] Çanakkale Onsekiz Mart University, Çanakkale Faculty of Applied Sciences, Department of Fisheries Technology, 17020 Çanakkale, Turkey, latifeirkin@gmail.com
[3] Çanakkale Onsekiz Mart University, Vocational School of Health Services, 17020 Çanakkale, Turkey, samilozturk16@hotmail.com

✉ Corresponding Author: samilozturk16@hotmail.com

Please cite this paper as follows:
Yayıntaş, Ö., İrkin, L. C., & Öztürk, Ş. (2021). Effect of *Homalothecium sericeum* (Hedw.) Schimp. Extract on SOD1 Activity in Rat Tissues (Kidney, Adrenal Gland, Ovary). *Acta Natura et Scientia*, *2*(2), 109-117. https://doi.org/10.29329/actanatsci.2021.350.04

ARTICLE INFO

Article History
Received: 15.08.2021
Revised: 22.09.2021
Accepted: 29.09.2021
Available online: 25.10.2021

Keywords:
Cu/Zn SOD (SOD1)
Kidney
Adrenal gland
Ovary
Moss
Immunohistochemistry

ABSTRACT

Homalothecium sericeum (Hedw.) Schimp. is growing in habitats such as walls and roofs. It is supported by the studies that moss contains antioxidant, antimicrobial and antitumoral compounds. It was aimed to determine the immunoreactivity of Cu / Zn SOD enzyme in the kidney, adrenal gland, and ovarian tissues of rats due to the increase in the dose of moss extract. In this study, 1 mL of distilled water were given control groups (G1), 50 mg/kg (G2), 100 mg/kg (G3), 300 mg/kg (G4) and 500 mg/kg (G5) moss extract were administered by gavage for 30 days another groups. At the end of the experiment period, the tissues taken from the rats were subjected to routine histopathological procedures. Cu /Z n SOD primary antibody was applied using immunohistochemical staining methods to detect immunoreactivity. The study was terminated by using the Kruskal-Wallis test, which is one of the nonparametric tests. To determine the differences between the groups by evaluating the stained tissue samples with the image analysis system in the light microscope. A significant difference was found in the dose-related positivity of the kidney, ovarian and adrenal gland tissues of the groups given moss extract p. It has been determined that *H. sericeum* species increases Cu/Zn SOD enzyme activity in the kidney, adrenal gland and ovarian tissues, and its cytotoxic effects shows a dose-related increase in the histopathological table.

INTRODUCTION

Bryophytes have been widely used as medicinal plants to cure cuts, burns, boils, abscesses, fractures, ringworm, convulsions, pneumonia, tuberculosis, uropathy, and neurasthenia in many countries (Chandra et al., 2016). The bryophytes have been medically used in Chinese traditional medicine for thousands of years and contained compounds with antioxidant, antimicrobial, and antitumoral activity (Sabovljević et al., 2016). There are few in vivo studies to determine the antioxidant and therapeutic activity of bryophytes, these studies led to the research of many biologically active compounds that are likely to be found in bryophytes (Krzaczkowskieta et al., 2009). The liverworts and mosses had the potential to have active compounds that may affect the cell cycle. Pharmacological studies showed that different moss species had cytotoxic, antifungal, antimicrobial, and antioxidant activity. They were secondary metabolites, phenolic compounds, benzyl, mono-di-tri sesquiterpenes, and flavonoids that provide antioxidant activity in mosses (López-Lázaro, 2009).

The first defence in the organism against free radicals occurs with SOD. The Cu/Zn SOD enzyme is in the cytoplasm. An increase in the amount of cellular SOD was observed during stress (Ighodaro & Akinloye, 2018). Many studies have proven that herbs are antioxidant components that help cope with oxidative stress. Another study, they reported that the antioxidant activity of *Nyctanthes arbor tristis* would be beneficial in the development of drugs for the treatment of arthritis (Lad & Bhatnagar, 2017).

Our study aimed to determine the enzyme production of Cu/Zn SOD in the kidney, adrenal gland, and ovarian tissues of rats fed with the extract obtained from *Homalothecium sericeum* species.

MATERIAL AND METHODS

Plant materials were collected from Karabiga and Bayramiç (Çanakkale, Turkey) and identified by Dr. O. TONGUC YAYINTAS and Dr. L. Ceyda İRKİN from Çanakkale Onsekiz Mart University in May 2018.

Ethical Statement

A total of 30 female Wistar albino rats, weighing 290-310 g, were included in the study. The study protocol was approved by the Çanakkale Onsekiz Mart University Ethics Committee for Animal Research (Protocol number: 2018-03).

Preparation of the Extracts

Fresh gametophytic samples of *H. sericeum* were treated with Tween 80 aqueous solution (0.8%) to remove the epiphytic hosts normally found on the surface, extensively washed in tap, and distilled water, and dried on filter paper at room temperature. Extraction procedures were applied as described elsewhere (Yetgin et al., 2017). The flour-form material will be treated with methanol to 10 mL/g in the dark for 24 hours (Yayintas et al., 2019).

Animal Groups

In this study, animal groups were designed in five different groups.

1. The first group (n: 6); 1 ml of distilled water for 30 days (gavage)
2. The second group (n: 6); 50 mg/kg moss every day for 30 days (gavage)
3. The third group (n: 6); 100 mg/kg moss every day for 30 days (gavage)
4. The fourth group (n: 6); 300 mg/kg moss every day for 30 days (gavage)
5. The fifth group (n: 6); 500 mg/kg moss every day for 30 days (gavage)

Histopathological Examination

The animal model study of our investigation continued approximately for a month. At the end of one month, the kidney, adrenal gland and ovaries of rats anesthetized with rompun and ketas were removed and trimmed and placed in tissue transport cassettes for 24 hours. Tissue samples taken from each subject and cut to a thickness of 5 µm were treated with Hematoxylin-Eosin (H&E) and staining was performed (Ozturk et al., 2019).

Immunohistochemical Examination

Immunohistochemical reactions were performed according to the ABC technique described. First, the endogenous peroxidase activity was inhibited by exposing the specimens to 3% hydrogen peroxide in distilled water for 30 minutes. After washing the sections in distilled water for 10 minutes, the binding of nonspecific antibodies was diluted by 1:4. Following this step, the sections were incubated with a polyclonal rabbit anti-superoxide dismutase (Cu/Zn SOD1, dilution 1:50, Enzo Life Sciences, Lausen, Switzerland) and following another step (Ozturk et al., 2019).

Evaluation of Tissue Samples and Statistics

The immunoreactivity was evaluated with the H-score method, calculating the ratio of immunopositively cells to all cells in the selected fields. The results obtained with this formula were analysed using SPSS 21 software package program. Kruskal–Wallis test was used to determine the differences between Cu/Zn SOD immunoreactivities between groups. A difference of $p<0.05$ between the groups were considered significant (Numata et al., 2013).

RESULTS

Kidney

There were no histopathologic findings in the renal tissues of rats in the first control group with routine haematoxylin-eosin. Cortex and medulla were normal. Tubular dilatations were increased in some of the mossed groups and renal parenchyma of G_4 and G_5 groups and tubules and the concentration of glomerular shrinkage were observed in some groups. There were remarkable enlargements in the cavities of the Bowman capsule. Swelling and necrotic cells were observed in tubular epithelial cells. Congestion was also observed in the capillaries (Table 1, Figure 1).

The rats receiving moss extract differed between the control group and other dose-dependent groups in immunohistochemical Cu/Zn SOD staining of renal tissue. Immunoreactivity was observed in the distal and proximal tubule epithelial cells in the control group, G_2 and G_3. Groups' immunity was more intense in cortex tubules but also in collecting tubule cells along the medullary beam. The severity of immunoreactivity increased in line with the moss dose. Cu/Zn SOD immunoreactivity was severed especially in the cortex of kidney tissues of G_4 and G_5 groups (Figure 2, Figure 3).

Adrenal Gland

Histological staining with haematoxylin-eosin did not reveal the cortex and medullary structure in the adrenal tissue of rats in the first group (G_1). The zones located under the connective tissue capsule were clear and normal. The boundaries between the zones disappeared in the cortex of the adrenal tissue of the G_4 and G_5 mossed groups, the pyknotic cells increased in the zone glomerulosa, the fat droplets in the zone fasciculata increased with steroid secretions and expanded considerably. Focal haemorrhage and increased necrotic cells were observed (Figure 4).

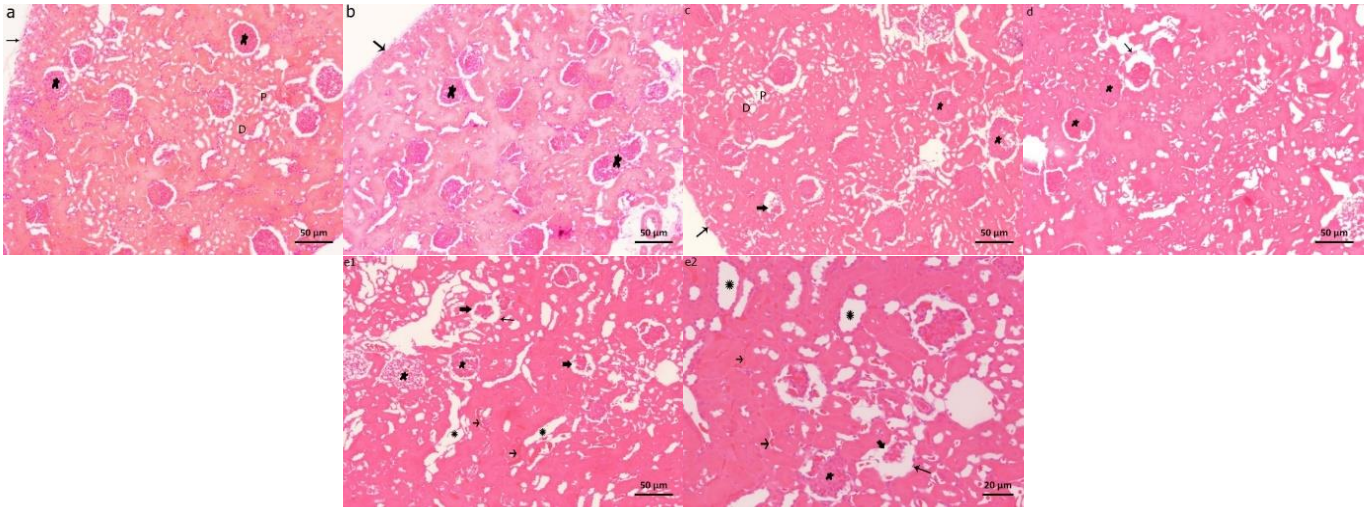

Figure 1. a-) Renal tissue of control group, magnification ×100 (Ok: Cortex capsule, renal corpuscle), b-) Renal tissue of the second group of giving moss, magnification ×100 (Star: glomeruli), c-) Renal tissue of the third group of giving moss, magnification ×100 (Star: renal corpuscle, thin arrow: capsule, thick arrow: shrunk glomeruli, P: proximal tubule, D: distal tubule), d-) Renal tissue of the fourth group of giving moss, magnification ×100 (Star: glomeruli, arrow: Bowman capsule), e-) Renal tissue of the fifth group of giving moss, magnification ×100, ×200 (Thick arrow: shrunk glomeruli, Thin arrow: expanded Bowman capsule, Star: glomeruli, Short arrow: congestion, Multiple stars: dilated collector tubules).

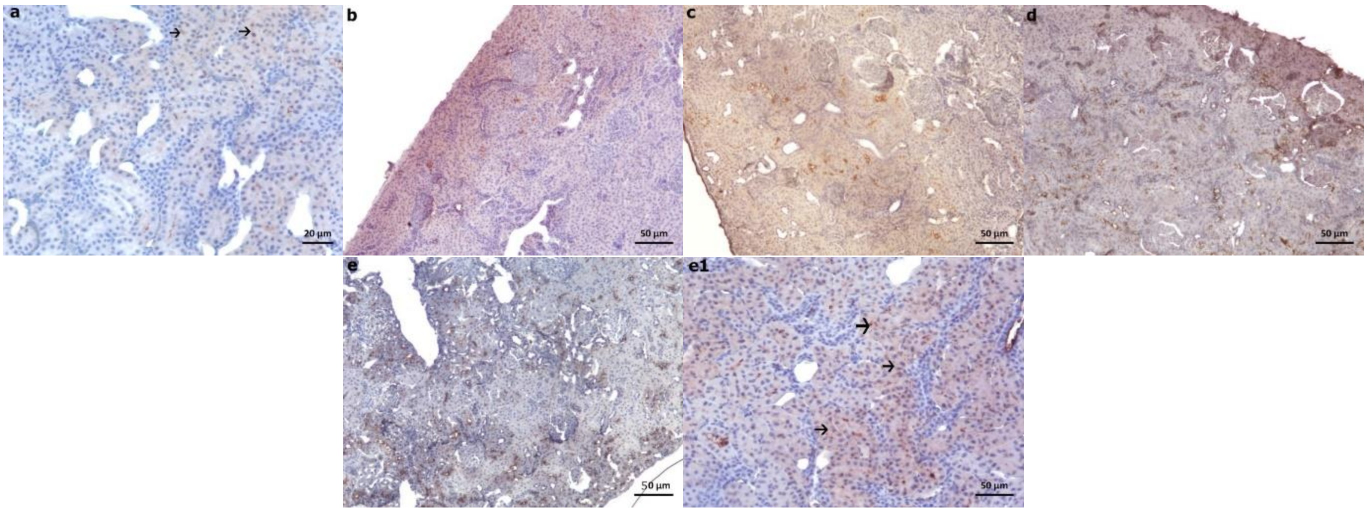

Figure 2. Control and experimental groups of renal tissue. Immunohistochemical staining of Cu/Zn SOD, magnification a, e1 ×200, other samples ×100 (Arrow: immunoreactivity).

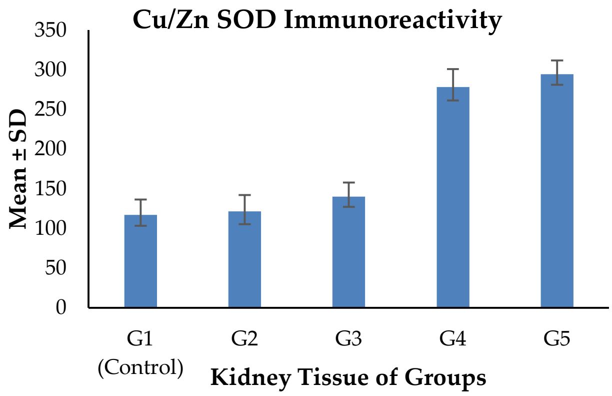

Figure 3. Immunoreactivity distribution of Cu/Zn SOD immunohistochemical staining in renal tissues of groups (Control (G1) vs G2 *p<0.05, G1 vs G3 **p<0.01, G1 vs G4 ***p<0.001, G1 vs G5 ****p<0.0001, G2 vs G3 **p<0.01, G4 vs G5 *p<0.05).

The control group had more positivity in glomerulus cells than G_2 and G_3. Both groups' immunity was increased. The severity of immunoreactivity increased in G_4 and G_5 in line with the moss dose. There was a significant difference between the H-scores of the control group and G_4 and G_5 ($p<0.0001$) (Figure 5, Figure 6).

Ovary

No histopathologic structures were observed in the ovarian tissue of the rats in the first group in the histological staining with Haematoxylin-Eosin. Like the control group, G_2 and G_3 also had a normal histological structure in the ovary. Primordial follicles and developing follicular structures were observed in the cellular connective tissue located on and below the germinal epithelium.

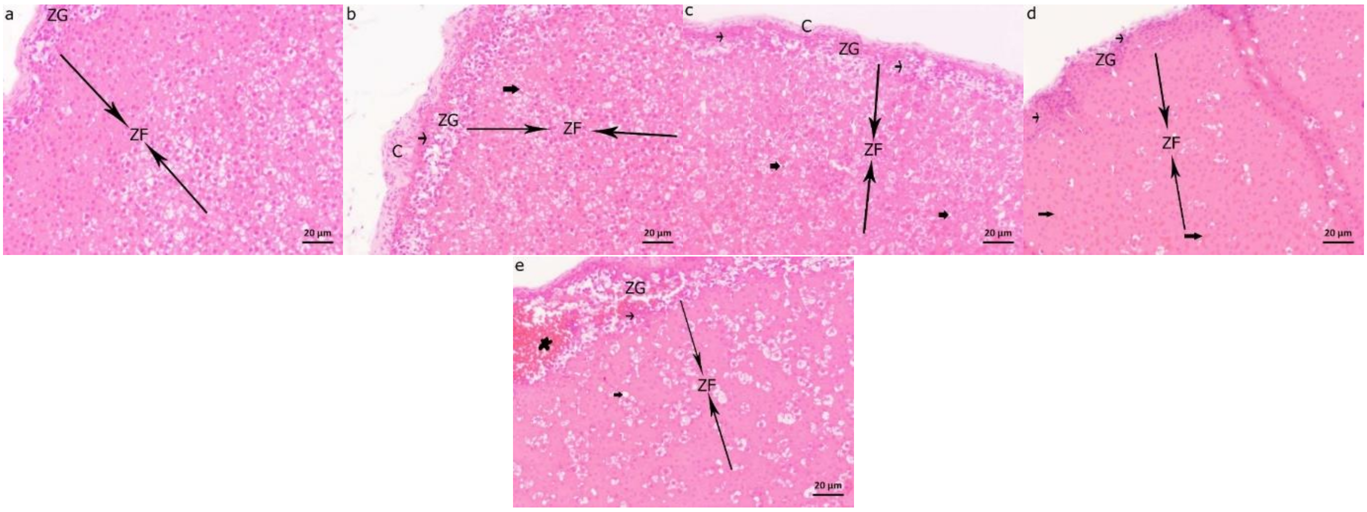

Figure 4. a-) Control group adrenal gland tissue b-) The second group of mossed adrenal gland tissue (Thick arrow: vacuolysis, Thin arrow: cells with pyknotic nuclei), c-) The third group of mossed adrenal gland tissue (Thick arrow: vacuolysis, Thin arrow: cells with picnotic nucleus), d-) Fourth group of mossed adrenal gland tissue (Thick arrow: hemorrhagic areas, Thin arrow: cells with pyknotic nuclei), e-) Fifth group of mossed adrenal gland tissue (ZG: zona glomerulosa, ZF: zona fasciculata, Thick arrow: vacuolysis, Thin arrow: cells with pyknotic nuclei, Star: hemorrhage area), magnification ×200.

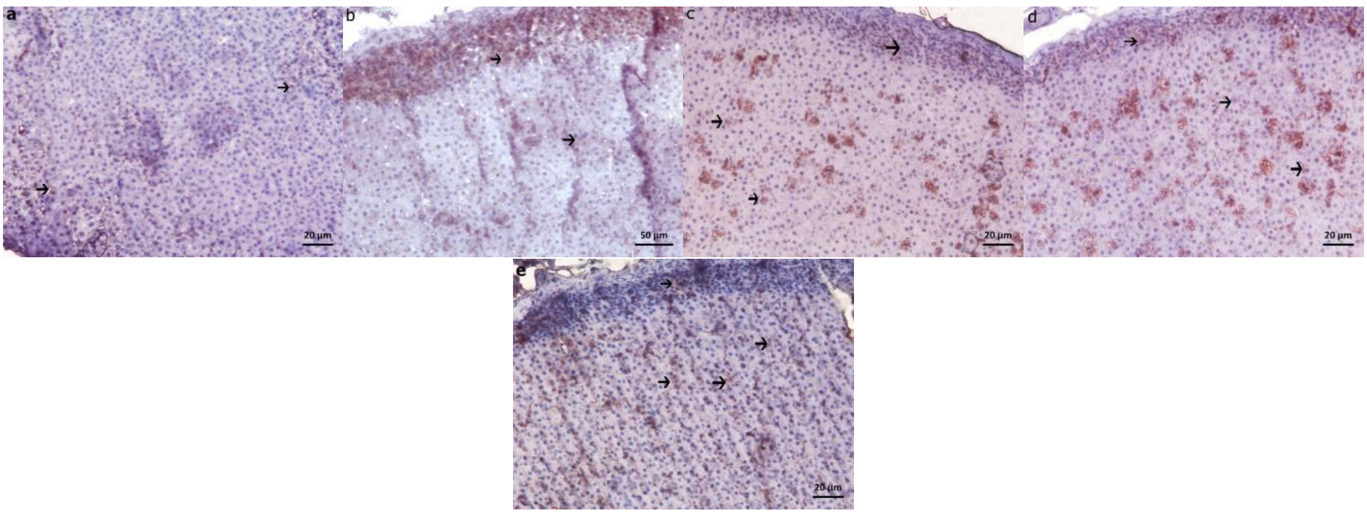

Figure 5. Control and experimental groups of adrenal gland tissue of Cu/Zn SOD immunohistochemical staining, magnification ×200, other samples ×100 (Arrow: immunoreactivity).

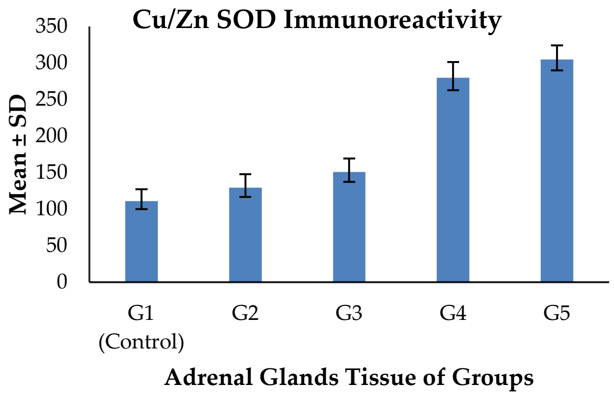

Figure 6. Immunoreactivity distribution of Cu/Zn SOD immunohistochemical staining in adrenal gland tissues of groups (Control (G1) vs G2 *p<0.05, G1 vs G3 **p<0.01, G1 vs G4 ***p<0.001, G1 vs G5 ****p<0.0001, G2 vs G3 *p<0.05, G4 vs G5 *p<0.05).

The corpus luteum was formed because of follicles excreted by ovulation. There was no inflammatory reaction in the ovaries of G_4 and G_5. The primordial follicles in the cellular connective tissue, which were observed in the secondary follicles, were present in the general histological structure (Figure 7).

The Cu/Zn SOD immunohistochemical staining of ovarian tissue was detected in the control group, G_2 and G_3, it was increased immunity in groups. The severity of immunoreactivity was moderated in G4 and G5 as the moss dose increased (Figure 8, Figure 9).

DISCUSSION

Active compounds responsible for existing antimicrobial effects were identified in many bryophyte species. For instance, some extract of liverwort such as Polygodial from Porella and *Conocephalum conicum*, Lunularin from *Lunularia cruciata* were proposed to have not only effective fungicide and bacteriocidic, but also a weak biocide (stomach poison) effect against pests (Saxena & Harinder, 2004).

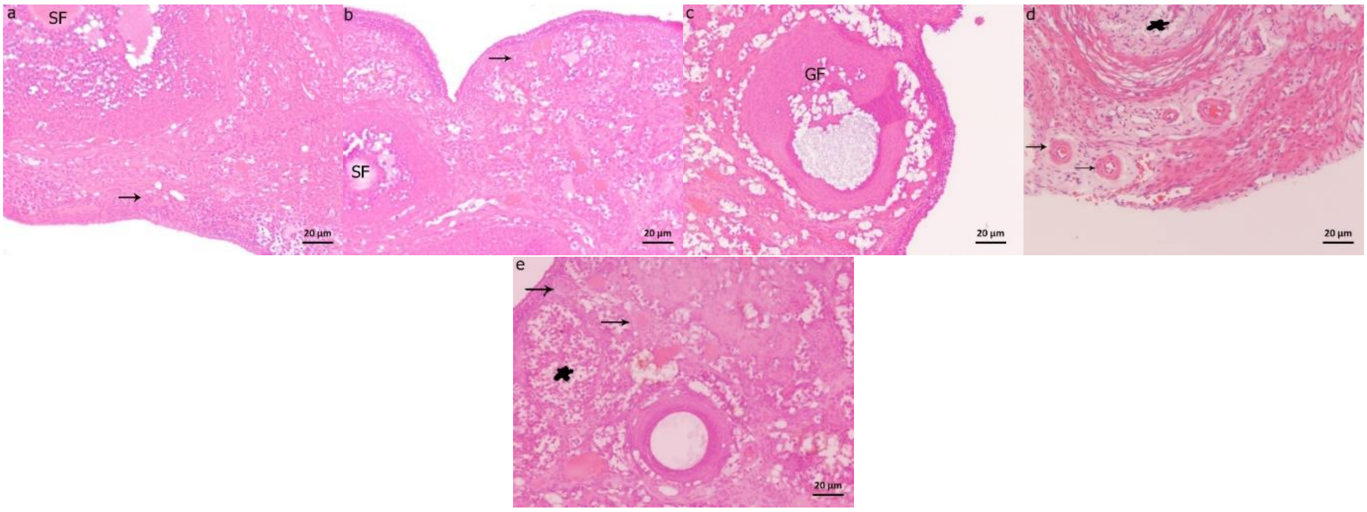

Figure 7. Control and experimental groups of ovarian tissue, magnification ×200 (Long arrow: primordial follicle, Star: corpus luteum, GF: graafian follicles).

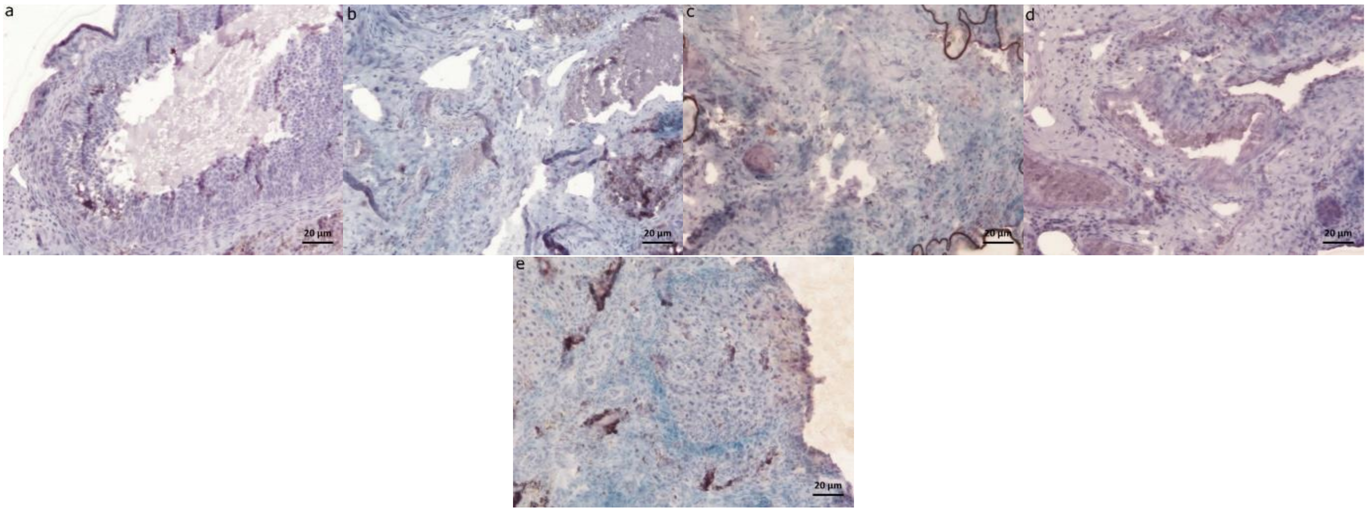

Figure 8. Control and experimental groups of adrenal gland tissue Cu/Zn SOD immunohistochemical staining ×200.

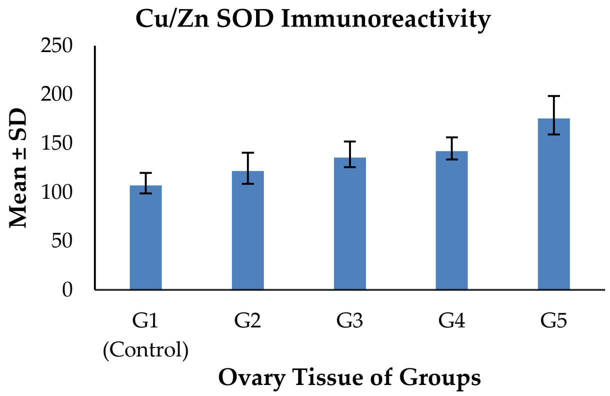

Figure 9. Immunoreactivity distribution of Cu/Zn SOD immunohistochemical staining in ovarian tissues of groups (Control (G1) vs G2 **p<0.01, G1 vs G3 *p<0.05, G1 vs G4 ***p<0.001, G1 vs G5 ***p<0.001, G2 vs G3 p>0.05, G4 vs G5 *p<0.05).

Alcoholic or acidic extracts of *Polytrichum juniperinum* were injected into muscle cells of CAF1 mice and showed antitumor activity against carcinoma (Cheng et al., 2012). In other cases, bryophyte extracts showed a tumour-promoting activity. Molecules such as Marchantin A, cyclopentanol fatty acids and their precursors had antimicrobial activity (Huang et al., 2010). Sanionin A and B were isolated from *Sanionia georgicouncinata* collected from Antarctic Livingston Island. These compounds showed inhibitory activity against multiple resistant staphylococci, gram-positive pathogens, and vancomycin-resistant enterococci. Inflammatory activity and low cytotoxicity were also observed (Ivanova et al., 2007). In a different study, lipophilic extracts of several types of liverworts showed antifungal and antibacterial effects. Bryophytes showed antibiotic activity against fungi and prokaryotic cells (Subhisha & Subramoniam, 2005). Saigusa et al. (2009) investigated CD133, SOX2, and OCT4 gene expression in two colon cancer cell lines, SW480 and LoVo. Following these results, they concentrated on the most active species and carried out antitumoral tests. Again, a fractioned polar isolate of *M. polymorpha* (T1) was the only antiproliferative species against HeLa and A549 lung cancer cells (Yetgin et al., 2017). Oztopcu et al. (2011) investigated the antimicrobial and antiproliferative properties of *Homalothecium sericeum* (Hedw.) Schimp. extract C from this moss was effective on C6 cells. A concentration of 85 µg/mL reduced the survival of cancer cells by 39% and a concentration of 170 µg/mL by 86% after 24 hours (Oztopcu et al., 2011). The results of bryophyte studies showed that they had quite high antibacterial and anticancer properties due to the flavonoid content they contain. There were a very limited number of experimental in vivo studies. The species we studied in the literature was never used in experimental animal models. Therefore, the findings of the present study will contribute to the literature. In subsequent studies, findings that are more specific will contribute to the use of moss extracts in medical treatments by using molecular techniques. Considering the anticancer properties, it can be provided to develop prophylactic drugs that will cost less and have a shorter duration for cancer treatments that increase day by day.

Superoxide dismutase (SODs) constitutes a very important antioxidant defence against oxidative stress in the body. The enzyme acts as a good therapeutic agent against diseases associated with reactive oxygen species. SOD has therapeutic effects in various physiological and pathological conditions such as cancer, inflammatory diseases, cystic fibrosis, ischemia, aging, rheumatoid arthritis, neurodegenerative diseases, and diabetes. However, the enzyme has some limitations in clinical applications. The most abundant copper-zinc (Cu/Zn) SOD in the body is found in the cytoplasm. Superoxide has an important role in cell structure and life such as the bactericidal activity of neutrophils, apoptosis, inflammation, and regulation of vascular functions (Younus, 2018; Rosa et al., 2021). In our study, *H. sericeum* was provided in different doses in immunohistochemical staining with Cu/Zn SOD, and antioxidant activity was tried to be determined in different tissues of rats that were given different doses. Immunoreactivity differed in the cases when *H. sericeum* was taken.

The protective effect of lavender oil was investigated in mice that produced hepato and nephrotoxic effects with the Malathion application. It increased the oxidative stress, which was assessed by the depletion of sulfhydryl group content (-SH) and antioxidant enzyme activity, as well as MDA and hydrogen peroxide levels. Cu/Zn-SOD, Mn-SOD and Fe-SOD increased in kidney and liver. In conclusion, lavender had potential hepato- and nephroprotective effects against oxidative stress caused by malathion in mice. This beneficial effect may be partially related to its antioxidant properties (Selmi et al., 2015). It has been observed that the moss extract we use in vivo increases the antioxidant enzyme activity (SOD) at low doses due to its compounds such as flavonoids and alcohols. Similar effects to the results of lavender and other similar plant-based applications were observed in our study. However, it has been observed that high doses may cause toxic effects. Therefore, we think that it would be beneficial to try it in anticancer studies with its high dose content.

Dynamic expressions of Cu/Zn SOD and Mn-SOD increased in liver, gill, kidney, and spleen after difficulties encountered with *Aeromonas hydrophila* or lipopolysaccharide in a study conducted with fish to determine the level of Cu/Zn SOD in tissues. mRNA expressions are downregulated after a time point in the kidney. In this study, the molecular structures and functional motifs of Cu/Zn SOD and Mn-SOD were determined, and a very important finding was presented for us to understand the biological functions of SODs (Sai et al., 2017). As a mammal, we tried to determine the SOD activity of moss in different tissues of rats. Our findings show that SOD activity increased in kidney and adrenal gland tissues of rats exposed to high-dose moss, while it is stable in the ovary. The reason is thought to be caused by the blood follicle barrier in the ovarian tissue. Cu/Zn SOD enzyme is localized in the cytoplasm of eosinophilic cells in the reticular zone or the internal fascicular region of the cortex. Studies were shown that Cu/Zn SOD and Mn-SOD are stained in the normal adrenal gland and the inner areas of the fascicular zone and the medulla, but the Mn-SOD is weakly stained with the medulla. SOD reflects the origin of the tumour cell and is stained in different cells in different adrenal tumours. Thus, only part of the Mn-SOD is stained in a pheochromocytoma. Medullary tumour tissues were reported to have lower SOD expression than the normal adrenal gland and adrenocortical adenoma. Cushing syndrome adenoma was higher in tumour tissue with Cu/Zn concentration and Mn-SOD is lower in normal adrenal gland concentration (Iwase et al., 2006). The findings obtained in the adrenal gland were in line with the findings in tumorigenic studies. While Cu/Zn SOD activity was characterized by the remuneration showing severe immune reactivity in shingles fascicule, the immune reactivity was milder in the medulla. As a protective mechanism of action in acidophilic cells, SOD reactivity was increased in cytoplasm's of cells against damage in the reticular zone.

In PCOS (polycystic ovary syndrome) patients, serum SOD activity has been reported with mixed results. Follicular fluid is easily available during oocyte pick-up and provides a very important microenvironment for the development of oocytes (Seleem et al., 2014). The immunohistochemical findings of ovarian tissue in our study showed that Cu/Zn SOD immunoreactivity was quite weak. This showed us that ovarian tissue was well protected by the blood follicle barrier and was affected later by metabolic effects. It also suggested in case of damage, the first SOD is not activated as a defence. Lee et al. (2019) investigated the effects of *Populus tomentiglandulosa* extract (PTE) on histopathology and antioxidant enzymes in rat liver and kidneys. PTE examined immunohistochemistry for antioxidant enzymes such as superoxide dismutase (SOD1 and SOD2), catalase (CAT) and glutathione peroxidase (GPx) in the rat liver and kidneys. There were no significant histopathological changes in the liver and kidneys of the diet fed rats with the PTE group. According to these results, PTE treatment significantly increased antioxidant enzymes in rat liver and kidneys (Lee et al., 2019).

CONCLUSION

Cu/Zn SOD activity, which is like our findings in our study, was detected in tissues such as kidney, adrenal gland and ovarian in studies with various plant extracts. The increase in histological damage due to the dose increase in our study contradicted the findings of these and similar studies. It should be said that with the increase of dose, *H. sericeum* species caused histopathology in much important tissue, especially in the liver and kidney, however, it was stronger in antioxidant activity by providing defence. These results showed that the effect of anti-cancer and antitumoral studies will be more effective. Generally, studies carried out with mosses (*H. sericeum*) are in vitro and our study was the first study in vivo.

ACKNOWLEDGEMENTS

This study was funded by Çanakkale Onsekiz Mart University, Scientific Research Project (BAP 2018/2534).

Compliance With Ethical Standards

Authors' Contribution

Author ŞÖ and ÖY designed the study, LCİ and ÖY wrote the first draft of the manuscript, ŞÖ performed and managed statistical analyses. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical Approval

A total of 30 female Wistar albino rats, weighing 290–310 g, were included in the study. The study protocol was approved by the Çanakkale Onsekiz Mart University Ethics Committee for Animal Research (Protocol number: 2018-03).

REFERENCES

Chandra, S., Chandra, D., Barh, A., Pandey, R. K., & Sharma, I. P. (2016). Bryophytes: Hoard of remedies, an ethno-medicinal review. *Journal of Traditional and Complementary Medicine*, *7*(1), 94-98. http://doi.org/10.1016/j.jtcme.2016.01.007

Cheng, X., Xiao, Y., Wang, X., Wang, P., Li, H., Yan, H., & Liu, Q. (2012). Anti-tumor and pro-apoptotic activity of ethanolic extract and its various fractions from *Polytrichum commune* L.ex Hedw in L1210 cells. *Journal of Ethnopharmacology*, *143*(1), 49-56. http://doi.org/10.1016/j.jep.2012.05.054

Huang, W. J., Wu, C. L., Lin, C. W., Chi, L. L., Chen, P. Y., Chiu, C. J., Huang, C. Y., & Chen, C. N. (2010). Marchantin A, a cyclic bis (bibenzyl ether), isolated from the liverwort *Marchantia emarginata* subsp. tosana induces apoptosis in human MCF-7 breast cancer cells. *Cancer Letter*, *291*(1), 108-19. http://doi.org/10.1016/j.canlet.2009.10.006

Ighodaro, O. M., & Akinloye, O. A. (2018). First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine*, *54*(4), 287-293. https://doi.org/10.1016/j.ajme.2017.09.001

Ivanova, V., Kolarova, M., Aleksieva, K., Dornberger, K. J., Haertl, A., Moellmann, U., Dahse, H. M., & Chipev, N. (2007). Sanionins: Anti-inflammatory and antibacterial agents with Weak cytotoxicity from the Antarctic Moss *Sanionia georgico-uncinata*. *Preparative Biochemistry and Biotechnology*, *37*, 343-352. https://doi.org/10.1080/10826060701593241

Iwase, K., Nagasaka, A., Kato, K., Itoh, A., Jimbo, S., Hibi, Y., Kobayashi, N., Yamamoto, H., Seko, T., & Miura, K. (2006). Cu/Zn- and Mn-superoxide dismutase distribution and concentration in adrenal tumors. *Journal of Surgical Research*, *135*(1), 150-5. https://doi.org/10.1016/j.jss.2006.03.027

Kong, X., Qiao, D., Zhao, X., Wang, L., Zhang, J., Liu, D., & Zhang, H. (2017). The molecular characterizations of Cu/Zn-SOD and Mn-SOD and its responses of mRNA expression and enzyme activity to *Aeromonas hydrophila* or lipopolysaccharide challenge in Qihe crucian carp *Carassius auratus*. *Fish Shellfish Immunology*, *67*, 429-440. http://doi.org/10.1016/j.fsi.2017.06.031

Krzaczkowski, L., Wright, M., Reberioux, D., Massiot, G., Etiévant, C., & Gairin, J. E. (2009). Pharmacological screening of bryophyte extracts that inhibit growth and induce abnormal phenotypes in human Hela cancer cells. *Societe Francaise de Pharmacologie et de Therapeutique Fundamental and Clinical Pharmacology*, *23*, 473-482.

Lad, H., & Bhatnagar, D. (2017). Modulation of oxidative stress mediators in the liver of adjuvant induced arthritic rats by *Nyctanthes arbor tristis*. *Clinical Phytoscience*, 3(1), 1-8. https://doi.org/10.1186/s40816-016-0041-4

Lee, C. H., Park, J. H., Ahn, J. H., Kim, J. D., Cho, J. H., Lee, T. K., & Won, M. H. (2019). Stronger antioxidant enzyme immunoreactivity of *Populus tomentiglandulosa* extract than ascorbic acid in rat liver and kidney. *Iranian Journal of Basic Medical Sciences*, *22*(8), 963-967. http://doi.org/10.22038/ijbms.2019.34926.8296

López-Lázaro, M. (2009). Distribution and biological activities of the flavonoid luteolin. *Mini Reviews in Medicinal Chemistry*, *9*, 31-59. http://doi.org/10.2174/138955709787001712

Numata, M., Morinaga, S., Watanabe, T., Tamagawa, H., Yamamoto, N., Shiozawa, M., Nakamura, Y., Kameda, Y., Okawa, S., Rino, Y., Akaike, M., Masuda, M., & Miyagi, Y. (2013). The clinical significance of SWI/SNF complex in pancreatic cancer. *International Journal of Oncology*, *42*(2), 403-410. http://doi.org/10.3892/ijo.2012.1723

Oztopcu, V. P., Savaroglu, F., Iscen, C. F., & Kabadere, S. (2011). Antimicrobial and antiproliferative activities of *Homalothecium sericeum* (hedw.) schimp. extracts. *Fresenius Environmental Bulletin*, *20*(2), 461-466.

Ozturk, S., Sonmez, P. K., Ozdemir, I., Topdagi, Y., & Tuglu, M. (2019). Antiapoptotic and proliferative effect of bone marrow-derived mesenchymal stem cells on experimental asherman model. *Cukurova Medical Journal*, *44*, 434-446. https://doi.org/10.17826/cumj.573200

Rosa, A. C., Corsi, D., Cavi, N., Bruni, N., & Dosio, F. (2021). Superoxide dismutase administration: a review of proposed human uses. *Molecules*, *26*(7), 1844. https://doi.org/10.3390/molecules26071844

Sabovljević, M., Sabovljević, A., Ikram, N., Peramuna, A., Bae, H., & Simonsen, H. (2016). Bryophytes – an emerging source for herbal remedies and chemical production. *Plant Genetic Resources*, *14*(4), 314-327. https://doi.org/10.1017/S1479262116000320

Saigusa, S., Tanaka, K., Toiyama, Y., Yokoe, T., Okugawa, Y., Ioue, Y., Miki, C., & Kusunoki, M. (2009). Correlation of CD133, OCT4, and SOX2 in rectal cancer and their association with distant recurrence after chemoradiotherapy. *Annals of Surgical Oncology*, *16*, 3488-3498. http://doi.org/10.1245/s10434-009-0617-z

Saxena, D. K., & Harinder, K. (2004). Uses of Bryophytes. *Resonance*, *9*(6), 56-65. https://doi.org/10.1007/BF02839221

Seleem, A. K., El Refaeey, A. A., Shaalan, D., Sherbiny, Y., & Badawy, A. (2014). Superoxide dismutase in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection. *Journal of Assisted Reproduction and Genetics,* **31**(4), 499-504, 2014. http://doi.org/10.1007/s10815-014-0190-7

Selmi, S., Jallouli, M., Gharbi, N., & Marzouki, L. (2015). Hepatoprotective and renoprotective effects of Lavender (*Lavandula stoechas* L.) essential oils against malathion-induced oxidative stress in young male mice. *Journal of Medicinal Food, 18*(10): 1103-1111. http://doi.org/10.1089/jmf.2014.0130

Subhisha, S., & Subramoniam, A. (2005). Antifungal activities of a steroid from *Pallavicinia lyellii*, a liverwort. *Indian Journal of Pharmacology, 37*, 304-308. http://doi.org/0.4103/0253-7613.16854

Yayintas, T. O., Yilmaz, S., & Sökmen, M. (2019). Determination of antioxidant, antimicrobial, and antitumor activity of bryophytes from Mount Ida (Canakkale, Turkey). *Indian Journal of Traditional Knowledge, 18*(2), 395-401.

Yetgin, A., Senturan, M., Benek, A., Efe, E. ,& Canlı, K. (2017). *Pterigynandrum filiform* Hedw. tütünün antimikrobiyal aktivitesinin belirlenmesi. *Anatolian Bryology*, *3*(1), 43-47. https://doi.org/10.26672/anatolianbryology.310856

Younus, H. (2018). Therapeutic potentials of superoxide dismutase. *International Journal of Health Sciences (Qassim)*, *12*(3), 88-93.