Texila International Journal of Public Health
ISSN: 2520-3134
DOI: 10.21522/TIJPH.2013.13.02.Art064

Histological Evaluation for the Effect of the Ivermectin Drug on Certain Visceral Tissues of the Albino Mice

Hussain I. Hussain[1], Elham M. Mahmood[1], Saif Kamil[1], Huda A. Hameed[2], Samira A. H. Abdulla[1], Entedhar R. Sarhat[1*], Anas A. Saleh[1]
[1]*College of Medicine, Tikrit University, Tikrit, Iraq*
[2]*College of Veterinary Medicine, Tikrit University, Tikrit, Iraq*

Abstract

Twenty albino mice of both sexes were used in this study. The animals were kept in steel cages of the animal house of the College of Veterinary Medicine of Tikrit University. The animals were distributed into two groups. Group A (10) animals were administered ivermectin subcutaneously (s/c) at a dose of 0.02mg/kg every 48 hours for two weeks. Group B (10), considered as control, received normal saline for two weeks' s/c too. The whole animals were sacrificed by a deep, intensive dose of chloroform in closed glass box. Histological Technique was done to obtain tissues from the kidney, liver and stomach. The results were indicated that the kidney tissue had sloughing of the bowman's capsule, lymphocytic aggregation on glomerular surfaces, widening of capsular space and presence of glomerular filtrate in the lumen of proximal and distal convoluted tubules with hypertrophy of epithelial cells of those tubules and the liver tissue demonstrated the presence of hyperplasia of liver cells, presence of many Kupffer cells in the narrowed blood sinusoids and pyknosis of many nuclei of liver cells. The gastric mucosa was demonstrated the degeneration of epithelial cells of gastric pits and damage to the chief cells and parietal cells of lamina propria with WBCs infiltration in the interstitial c.t of gastric mucosa. In conclusion: the chemical drug ivermectin had many histopathological effects on the visceral organs although consider as anti-parasitic drug used commonly in the world.

Keywords*: Albino Mice, Ivermectin, Visceral Tissues.*

Introduction

In the twentieth century, large amount of drugs and chemical substances used by human as therapy for different diseases [1]. A drug is a substance which do modify certain aspects of living organism after exposure [2], regardless of whether the effects are useful or harmful, regardless of being natural, semisynthetic, and synthetic chemical agents, regardless being protective for the disease's prevention or cure [3].

These drug and chemical substance are used for the benefit of human. But there are many side effects and malformations caused by the using of these substances [1]. Taking the drugs commonly at pre-embryonic development till 17th days after fertilization, in this case defect of implantation and abortion happened. But if the pregnancy continued, the embryonic malformation will be caused [4]. The restricted or the critical dangerous time is the organogenesis period [5]. Which leads to absence of organ or external malformation [6].

Ivermectin, is a commonly used medicament in veterinary applications, it is structurally a macrocyclic sugar derived from soil bacteria *Streptomyces avermitilis.* The mechanism of killing parasites via the opening of GABA-gated chloride channels [7]. The study aimed to show the histological lesions induced by of the ivermectin in some visceral of the body after administration of the drug at alternative days,

Received: 06.02.2025 ***Accepted: 28.03.2025*** ***Published on: 30.06.2025***
****Corresponding Author: entedharr@tu.edu.iq***

and Show the effect of the drug on the behavior activity, clinical and morphological changes of animals.

Materials and Methods

Twenty (20) albino mice *Mus.nusculus* (of both sexes) were used in this study. The mouse were properly treated via handling them in the animal house in wire- meshed stainless-steel cases; in pairs in each cage, under standard conditions [fed commercial pellet diet, free access to water, 20-24^{o}C temperature, 12/12 hours light/dark schedule, and good ventilation [8]. These animals were handled in this way before and during experimentation, with one week left for environmental adaptation before experimentation.

The drug used in the experiment was; ivermectin_anti parasitic agent (it is mixture of 80% 22,23-dihyroavermectin B_{1a} and no more than 20% 22,23-dihydroavermectin B_{1b}), manufactured and distributed by VETANCO S.A. in the form of solution (1% solution injectable, 50ml). It was kept under 25^{o}C, in its original packaging, away from direct and sun light. The dose in adult mice was 0.02 ml/kg body weight, doses given by injection under the skin using a needle (insulin 0.1ml) [9,10].

The average body weight of the mice was 25±2 gram at the beginning of experiment. Animal were divided into two groups as follows:

Group A: includes 10 animals, injected the dose 0.02ml/kg body weight of ivermectin for a period of two weeks (every 2 days).

Group B: (control group) includes 10 animals, received normal saline for a period of two weeks.

Preparation for Histological study: All animals were exposed to intensive chloroform anesthesia and the tissues were obtained and processed according to [11-13], based on several steps, including fixation, followed by sequential steps of dehydration, clearing, and ended by cassette embedding. Following that tissue sectioning, de-waxing, and hydration. Finally, the slides were underwent staining and mounting. Descriptive histology obtained via light Microscope (Motic microscope, China) via supplied camera [14-16].

Results

The images examined under light microscope examination revealed that the cortex of kidney was normal and formed by renal glomeruli (tuft of blood capillaries) bordered by capsular space and bowman's capsule. The proximal convoluted tubules were lining by simple pyramidal cell with narrow lumen and distal convoluted tubules with wide lumen and lined by simple cuboidal cells (Figure 1).

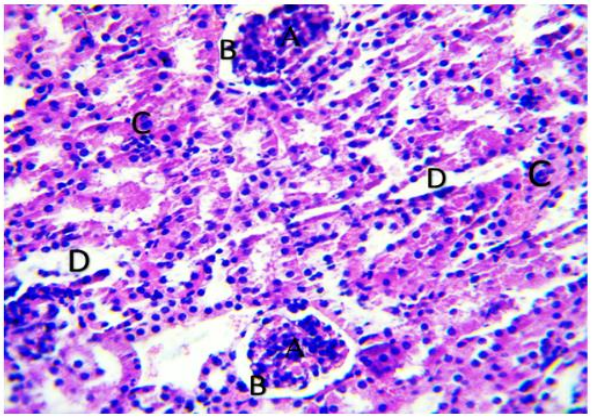

Figure 1. Renal Cortex, Renal Glomeruli (A), Capsular Space (B), Proximal Connective Tissue. (C), Distal Connective Tissue. (D) (H&E X40)

The medulla of the kidney contains the collecting tubules, which are lined by simple cuboidal cells, bordered by WBCs in the interstitial connective tissue. Also, there are segments of the Henle loop which are lined by simple squamous epithelium (Figure 2).

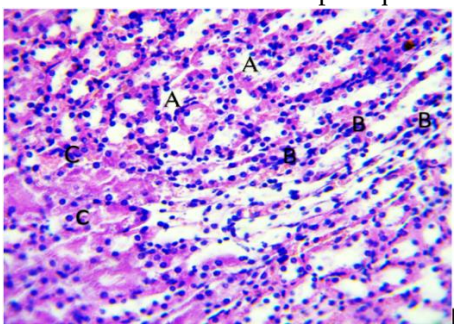

Figure 2. Renal Medulla, Renal Tubules (A), WBCs in the Interstitial Connective Tissue. (B) Thin Segments of Henle Loops (C) (H&E X40)

The architecture of the liver lobule has a middle vein, bordered by layers of hepatocytes. These hepatocytes showed a shape of polyhedral shape with a spherical nucleus. These hepatocytes were bordered by blood sinusoids infiltrated with Kupffer cells (Figure 3).

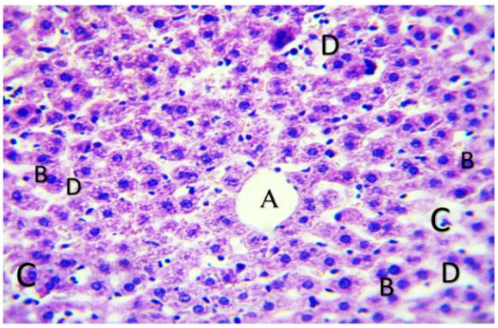

Figure 3. Liver Lobule, Middle Vein (A), Liver Cells with Polyhedral Shape (B), Kupffer Cells (C), in Blood Sinusoid (D) (H&E X40)

The region of portal vein entrance to liver is made up of venous tissue, branches of hepatic artery, and bile ducts; these are bordered by columns of liver cells, blood sinusoids infiltrated by WBCs, especially Kupffer cells

The portal area inside the liver shows the portal vein, the bile duct, and a branch of the hepatic artery. Additionally, the portal region was infiltrated with immune cells and bordered by a layer of hepatocytes and blood sinusoids containing macrophages (Kupffer cells) (Figure 4).

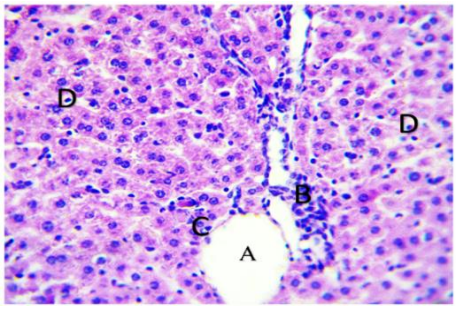

Figure 4. Portal Area, Portal Vein (A), Bile Ductal (B), WBCs Around the Portal Vein (C), Blood Sinusoids with Kupffer Cells (D) (H&E X40)

The architecture of the stomach has revealed that the stomach lining is made up from gastric pits indulged by columnar epithelium layer with underlining lamina propria endorsed by gastric gland. These glands were covered and bordered by mucous secreting cells with scattered parietals cell and chief cells, these layers were also infiltrated by WBCs (Figure 5).

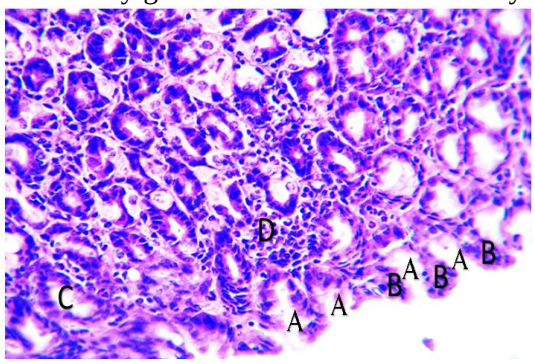

Figure 5. Gastric Pits of Stomach (A), Simple Columnar epi. (B), Gastric Glands (C) WBCs (D) in the Interstitial Connective Tissue (H&E X40)

The lamina propria layer of gastric mucosa were filled with gastric glands indulged with infiltration of WBCs overlapped by interstitial connective tissue (Figure 6).

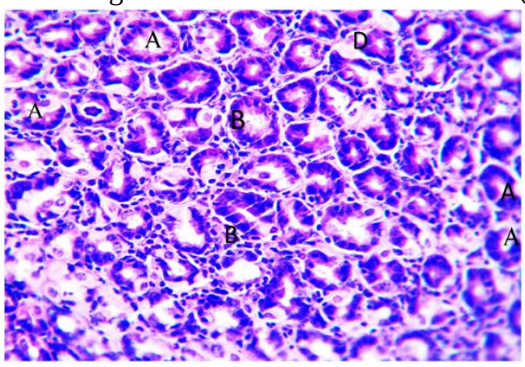

Figure 6. Lamina Propria of Stomach, Gastric Glands (A), WBCs Infiltration (B), in the Interstitial Connective Tissue (H&E X40)

More deep layers of gastric mucosa at lamina propria layers were filled with gastric glands consisting of mucous secreting cells with scattered parietals cell and chief cells at mucosal layer with extension to submucosa in somewhere (Figure 7).

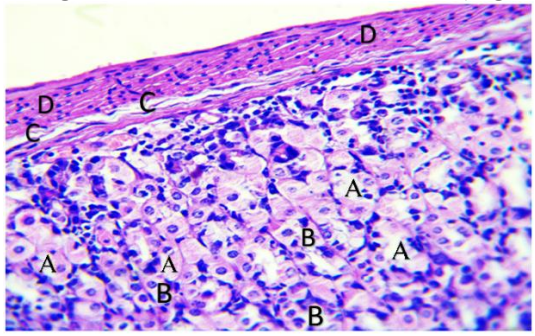

Figure 7. Gastric Glands, Parietal Cells (A), Mucus Cells (B), Submucosa (C), Muscular Coat (D) (H&E X40)

The renal cortex, revealed the sloughing of capsule completely and the glomeruli capillaries had infiltration of lymphocytes on its surface, also widening of capsular space was present, glomerular filtrate was seen in the lumen of distal convoluted tubules which had cellular degeneration for its epithelial cells lining the walls of tubules (Figure 8).

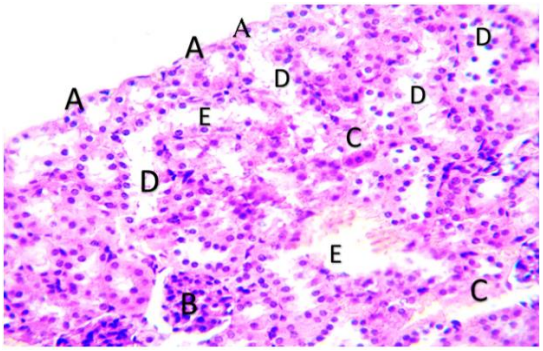

Figure 8. Renal Cortex, Sloughing of Capsule (A), Glomerular Atrophy with Lymphocytic Aggregation on its Surface (B), Glomerular Filtrate (C) Cellular Debris (D) in Lumens of Distal Conv. Tubules (E) (H&E X40)

The renal cortex, revealed the sloughing of capsule completely and the glomeruli capillaries had infiltration of lymphocytes on its surface, also widening of capsular space was present, glomerular filtrate was seen in the lumen of distal convoluted tubules which had cellular degeneration for its epithelial cells lining the walls of tubules (Figure 9).

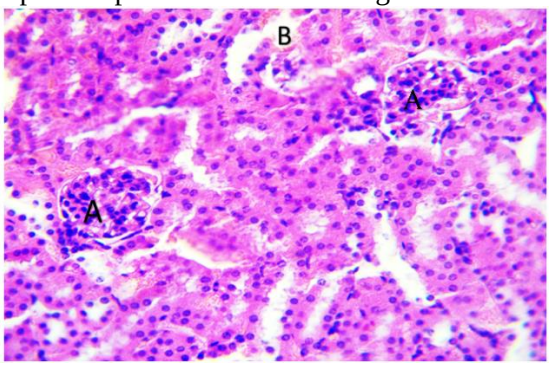

Figure 9. Glomerular Mass with Lymphocytic Diffusion on its Surface (A), Cellular Debris (B) in the Distal Convoluted Tubules (H&E X40)

The proximal convoluted tubules had hypertrophy of its cells which appeared as homogenization of it cytoplasm and present as mass, devoid most of its nuclei, the distal convoluted tubules had cellular debris in its lumens (Figure 10).

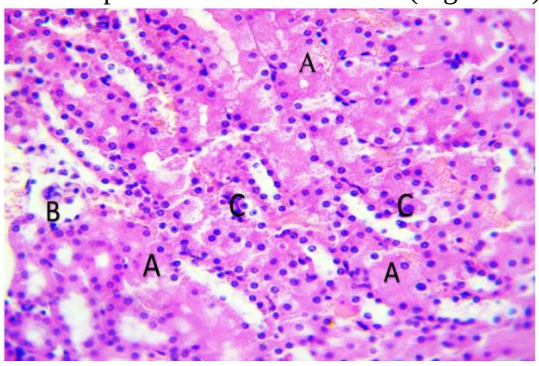

Figure 10. Hypertrophy of the Epithelial Cells lining the Proximal Convolutes Tubules (A), Cellular Debris (B), Macrophages (C) (H&E X40)

The renal medulla was formed by renal tubules which are lined by simple cuboidal cells and the thin segments of Henle loops lined by simple squamous epithelium, the interstitial connective tissue was containing macrophages and lymphocytic diffusion (Figure 11).

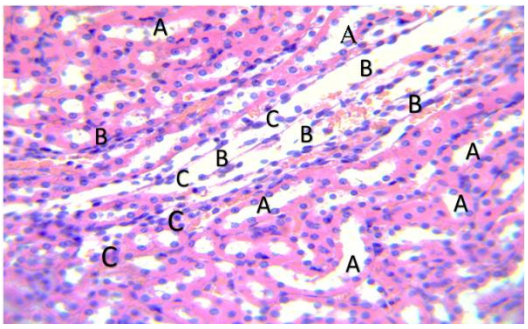

Figure 11. Renal Medulla, Renal Tubules (A), Thin Segments of HENLE Loops (B), Lymphocytes and Macrophages (C) (H&E X40)

The renal medulla also had blood vessels with great number of RBC inside its lumens and the lymphocytic infiltration was present in the interstitial connective tissue there are many cells present inside the lumen of renal tubules due to sloughing of it form the walls of tubules (Figure 12).

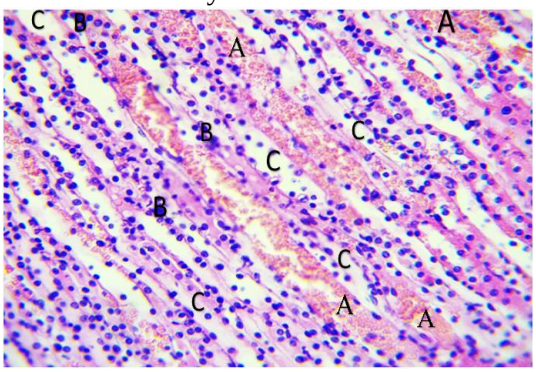

Figure 12. Renal Medulla, Blood Vessels with RBCs (A), WBCs (B) in the Interstitial Connective Tissue. WBCs Inside the Lumens of Tubules (C) (H&E X40)

The parenchyma of liver was seen with presence of hyperplasia of liver cells, associated with great-spherical basophilic nuclei, the blood sinusoids were rarely seen and certain number of Kupffer cells were present (Figure 13).

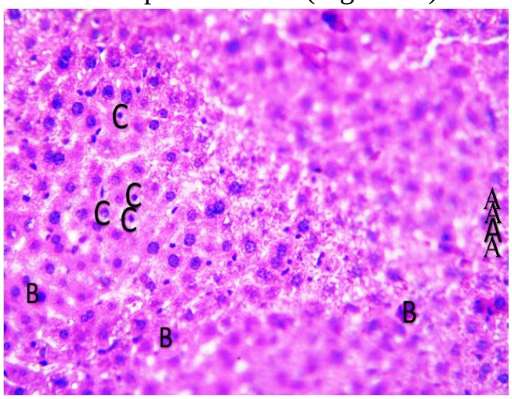

Figure 13. Liver Tissue, Hyperplasia of Liver Cells (A), Great Size of Nuclei (B), Kupffer Cells (C) in the Narrow Blood Sinusoids (H&E X40)

The middle vein of liver lobule was empty from blood and its basement membrane was lost, the vein was bordered by hyperplastic liver cells, which appeared as a mass of cells with spherical basophilic pyknotic nuclei, the Kupffer cells were present in the narrow blood sinusoids (Figure 14).

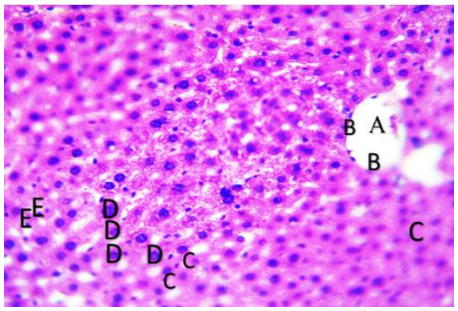

Figure 14. Middle Vein of Liver Lobule (A), with Lost its Basement Membrane (B), Hyperplasia of Liver Cells (C) Pyknotic Nuclei (D) Narrow Blood Sinusoids (E) (H&E X40)

The gastric pits of mucosa of stomach were containing degenerated epithelial cells, the lamina propria was engorged with gastric glands which are mostly had degenerated cells of chief and parietal cells, spaces in between gastric glands were demonstrated and these spaces had cellular debris (Figure 15).

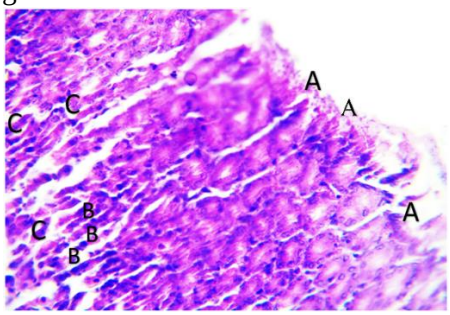

Figure 15. Gastric Tissue, Degeneration of Epithelial Cells of Gastric Pits (A), Degenerated Gastric Glands (B), Cellular Debris (C) (H&E X40)

The lamina propria of gastric mucosa had degeneration cells of gastric glandes with presence of many great vacuolations in between the glands which are also infiltrated with WBCs in the interstitial connective tissue (Figure 16).

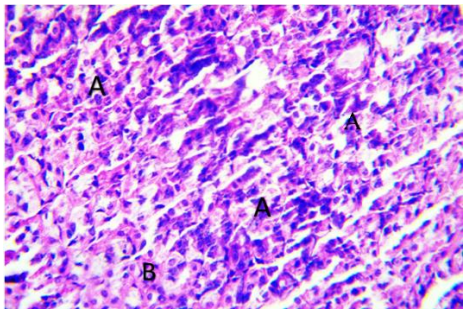

Figure 16. Lamina Propria of Gastric Mucosa, Extensive Degeneration of Gastric Glands (A), WBCs Infiltration (B), in between Gastric Glands (C) (H&E X40)

Discussion

The result of present study was indicated that the ivermectin possess powerful effect on the parasitic invasion which are ecto or endoparasite, whoever its side effect was investigated by this study which effect on the tissues of certain visceral organs, such as kidney, liver and stomach. The extensive damage on the tissue of cortex and medulla of kidney was in agreement with [17] when mentioned that administration of ivermectin to the rabbit's lead to induce nephrotoxicity reflected by dilated of bowman's spaces, dilation of convoluted tubules and those lesions

were present even given to rabbit's vitamin C to reduce the effect of ivermectin.

Hepatotoxicity, also found in Wistar rat given ivermectin with albendazol this result was demonstrated by [18], degeneration changes of liver cells, blood congestion and necrosis of certain liver cells, so this result is in agreement of the present study which indicated the presence of hepatocellular necrosis and Kupffer cell hyperplasia, also vacuolations of certain liver cells and blood sinusoids congestions [19], attributed that administration of ivermectin in human lead to induction of gastro intestinal cramping, so these symptoms indicate that this drug have side effect on stomach and intestine and these events are not away from the results present in this study.

The Veit et al [20] revealed that single dose therapy with ivermectin associated with liver injury, where the onset damage was occurred after one month of injection of ivermectin and characterized by hepatocellular necrosis and Jaundice, but not associated with acute liver failure or chronic liver damage or injury so these results are in agreement with the result of present study. Otherwise in kidney, the histopathological lesions were present after administration of ivermectin in Rabbits subcutaneously at dose 0.2mg/kg, the dose lead to induction of atrophy of the sub capsular vacuolations of proximal and distal convoluted tubules with presence of atrophy of glomeruli [21], these results are same in our study in mice which are comparable when glomerular atrophy, hypertrophy and degeneration of the epithelial lining the convoluted tubules, the interpretation for these events are due to oxidative stress of ivermectin and this concept was indicated by [22] in albino rats, the liver and kidney damage after administration of ivermectin also come from the cumulative effect of this drug and lead to injury of cell membrane in vital organs and subsequent end result is hepatic and renal failure [23].

Concerning the effect of ivermectin administration on gastric mucosa, although literatures are scanty, but investigation for the effect of Abamectin (3mg/kg) s/c was given to rats lead to gastric ulcer and other gastric lesions were observed and this injury could be due activation of vagus nerve which involved in the abamectin-associated gastric protection against the effects of drug in rats in contrast to the present study, the common effect of ivermectin administration in mice was mostly on damage of gastric epithelium and effect the gastric glands which had the chief cells and parietal cells, those events also associated with gastric injury like in rat for study of [24-26].

Conclusion

Continuing use of ivermectin in therapeutic dose caused the appearance of histopathological lesion on some tissues of visceral organs for mice. Administration of drugs for mice lead to abnormal activity and behavior, like aggressive effect and excitation. Optical microscopic observation indicated histopathological effect on the tissues of liver, kidney and stomach, like necrosis, degeneration of cell, congestion of blood vessels and lymphocytic infiltration.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

The authors are thankful for Tikrit University for their provided facilities to accomplish this study.

References

[1]. Saleh, S. S., Sarhat, E. R., 2019, Effects of ethanolic Moringa oleifera extract on melatonin, liver and kidney function tests in alloxan-induced diabetic rats. *Indian Journal of Forensic Medicine & Toxicology,* 13(4), 1015-1019. doi:10.5958/0973-9130.2019.00431.6.

[2]. Sarhat, E. R., Abbas, M. Q., Ali, N. H., Wadi, S. A., Sarhat, T. R., 2022, Evalution of

ceruloplasmin, sialic acid and liver function for women with breast cancer. In AIP Conference Proceedings (Vol. 2394, No. 1). *AIP Publishing*. doi:10.1063/5.0122900.

[3]. Aziz, Z., Sarhat, E., Zaidan, Z., 2023, Estimation of serum ferroportin and liver enzymes in breast cancer patients. *Georgian medical news*, (339), 37-41.

[4]. Mohammed, I. J., Sarha, E. R., Wadee, S. A., Al-Shiakhani, S. M., 2021, Histological and biochemical evaluation of the effect of desloratadine drug in parotid gland tissues. *Al-Anbar Medical Journal*, 17(2), 72-77. doi:10.33091/amj.2021.171074.

[5]. Mahmood, D. A., Sarhat, E. R., Sulaiman, Y. A., Abass, K. S., 2022, Evalution of liver function tests in patients with psoriasis. *Revista Latinoamericana de Hipertension*, 17(6). doi:10.5281/zenodo.7406087.

[6]. Sarhat, E. R., Wadi, S. A., Sedeeq, B. I., Sarhat, T. R., Jasim, N. A., 2019, Study of histopathological and biochemical effect of Punica granatum L. extract on streptozotocin-induced diabetes in rabbits. *Iraqi Journal of Veterinary Sciences*, 33(2), 189-194. doi:10.33899/ijvs.2019.125523.1045

[7]. Sarhat, E. R., Abid, I. M., Kamel, N. A., Sarhat, T. R., Abass, K. S., 2021, Changes of serum Interleukin and Chemerin levels in patients with Polycystic Ovary syndrome. *Journal of Advanced Pharmacy Education and Research*, 11(4-2021), 11-14. doi:10.51847/XP8rpqX3Jx.

[8]. Aziz, Z., Sarhat, E., Zaidan, Z., 2023, Estimation of serum ferroportin and liver enzymes in breast cancer patients. *Georgian medical news*, (339), 37-41.

[9]. Campbell, W. C., Fisher, M. H., Stapley, E. O., Albers-Schönberg, G., Jacob, T. A., 1983, Ivermectin: a potent new antiparasitic agent. *Science*, 221(4613), 823-828. doi:10.1126/science.6308762.

[10]. Roder, J. D., Stair, E. L., 1998, An overview of ivermectin toxicosis. *Veterinary and Human Toxicology*, 1998; 40(6): 369-370.

[11]. Althanoon, Z. A., Merkhan, M. M., 2023, CoQ10 dampens the deleterious impact of doxorubicin-induced liver and spleen injury in white Albino rats. *Pharmacology*, 27.

[12]. Abdullah, S. I., Al-Bayti, A. A., Salih, M. J., Merkhan, M. M., 2022, Histological and Biochemical Changes Associated with Blocking of Serotonin Receptor. *TropJ Nat Prod Res*. 2022; 6(8):1189-1192. doi:10.26538/tjnpr/v1i4.5

[13]. Hamed, Z. S., Abed, R. R., Almashhadany, M. S., Merkhan, M. M., 2022, Effects of Hypericum perforatum on serum lipid vascular systems in mice. *Iraqi Journal of Veterinary Sciences*, 36(2), 525-530. doi:10.33899/ijvs.2021.130708.1868.

[14]. Hassan, A., Safuan, S., Abdullah, Z., Tan, N. J., 2024, Cholic acid enhanced hypercholesterol parameters in high cholesterol diet fed Sprague-Dawley rats. *Physiology and Pharmacology*, 28(4), 400-408. doi:10.61186/phypha.28.4.400.

[15]. Salem, H. R., Hanna, G., Hassan, M., El-kotb, S., Rashad, S., Yassien, R. I., Amer, G. S., 2024, Combined metformin and insulin therapy improves neurocognitive dysfunction in type 2 diabetic rat model via anti-inflammatory and antioxidant mechanisms. *Physiology and Pharmacology*, 28(2), 141-156. doi:10.61186/phypha.28.2.141.

[16]. Parsaei, H., Nobakht, M., Dadseresht, A., Seidkhani, E., Eftekharzadeh, M., 2024, Intranasal administration of human adipose-derived stem cell-conditioned media ameliorates cognitive performance in a rat model of Alzheimer's disease. *Physiology and Pharmacology*, 28(1), 43-55. doi:10.61186/phypha.28.1.43

[17]. Chahrazed, M., Hassina, K. O., Soumya, B., Yasmine, O., Houda, Z., Nacira, D. Z., 2021, Protective Effects of Vitamin C on Ivermectin Induced Toxicity on Kidney Functions and Brain Tissue in Rabbits (Oryctolagus cuniculus. *Egyptian Academic Journal of Biological Sciences, D. Histology & Histochemistry*, 13(1), 63-77. doi:10.21608/eajbsd.2021.164581.

[18]. Idowu, E. T., Alimba, C. G., Olowu, E. A., Otubanjo, A. O., 2015, Artemether-Lumefantrine treatment combined with albendazole and ivermectin induced genotoxicity and hepatotoxicity through oxidative stress in Wistar rats. *Egyptian Journal of Basic and Applied Sciences*, 2(2), 110-119. doi: 10.1016/j.ejbas.2015.03.001.

[19]. Sarhat, E. R., Wadi, S. A., Mahmood, A. R., 2018, Effect of ethanolic extraction of moringa oleifera on paraoxonase and arylesterase enzyme activity in high fat diet-induced obesity in rats. *Research Journal of Pharmacy and Technology*, 11(10), 4601-4604. doi:10.5958/0974-360X.2018.00842.9.

[20]. Veit, O., Beck, B., Steuerwald, M., Hatz, C., 2006, First case of ivermectin-induced severe hepatitis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 100(8), 795-797. doi: 10.1016/j.trstmh.2006.02.003.

[21]. Khalaf, S. J., Aljader, G. H., Sarhat, E. R., Sarhat, T. R., ABASS, K. S., 2021, Antidiabetic effect of Aqueous Extract of Medicago Sativa with Enhanced Histopathology of Pancreas in Alloxan Induced Diabetic Rats. *PJMH S*, 15(2), 492-496.

[22]. Albarzanji, Z. N., Sarhat, E. R., Mahmood, M. N., 2019, Evaluation of humoral immunity in Amoebiasis. *Eco Env Cons*, 25:186-189.

[23]. Hussain, H. I., Mahmood, E. M., Kamil, S., Hameed, H. A., Abdulla, S. A., Sarhat, E. R., 2024, Chloroquine Induced Lesions in the Visceral Tissues of Albino Mice. *Bahrain Medical Bulletin*, 46(3):*1-5.*

[24]. Hussain, H., Ebraheem, A., Abdulla, S., Sarhat, E., Mahmood, E., 2024, Chloroquine induced lesions in liver of albino mice. *Georgian medical news*, (349), 93-97.

[25]. Nichat, P., 2024, Myofibroblasts and tumor micro-environment in oral squamous cell carcinomas–a histochemical and immunohistochemical analysis. *Texila International Journal of Public Health*, 12(3): 1-14. doi: 10.21522/TIJPH.2013.12.03.Art053**.**

[26]. Preethi, M., Sree, L., Ajitha, R., Anbukkarasi, K., 2024, A Histomorphological Study of Urinary Bladder Lesions in a Tertiary Care Hospital. *Texila International Journal of Public Health*, 12(3): 1-15. doi: 10.21522/TIJPH.2013.12.03.Art048