Renal Disfunction and Histopathological Effects of Bupropion on Kidney of Male Albino Rats

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Abstract

Background: Bupropion is an atypical antidepressant belonging to the aminoketone class and is also used for smoking cessation. However, despite its widespread clinical use at various dosages available information regarding its effects on the kidneys particularly at the histological level remains limited.

Objective: this study aims to evaluate the dose-dependent effects of Bupropion on renal function, and histological changes induced by drug in the kidneys of male albino rats.

Methods and materials: male albino rats (weighing 180-200g) were divided into three groups (control,150mg\kg,300mg\kg) each group have eight of rats and received oral treatment daily for 56 days. Serum urea and creatinine levels were measured to assess renal functions. Additionally, histological examination was performed on kidney tissues stained with hematoxylin and eosin (H&E).

Results: daily administration of Bupropion to rats for 56 days resulted in dose-dependent renal changes characterized by a significant increase in urea levels, a decrease in creatinine levels. microscopic histological examination of kidney sections revealed tubular dilation, inflammatory cell infiltration, congestion, hyaline degeneration, and glomerular hypercellularity in both groups. These lesions were more severe in the 300mg\kg group which was characterized by interstitial hemorrhage alongside congestion. **Conclusion**: Bupropion induced dose-dependent renal injury in rats associated with distinct histological changes and alteration in renal function this indicates that prolonged exposure to high doses may affect the integrity of renal tissue.

Key Words: Bupropion, kidney, urea, congestion.

Introduction

Depression is mood disorder that causes feelings of hopelessness and a persistent loss of interest. Depression can lead to a loss of appetite and desire to work, study and sleep, thus hindering daily life and the enjoyment of life events and hobbies (Selman, et al, 2025). According to the latest World Health Organization (WHO) statistics for 2025 approximately 4% of the population suffers from depression. Around 332 million people worldwide suffer from depression, and it is about and half times more common in women than in men. Antidepressants are available in the form of selective serotonin reuptake inhibitors (SSRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), serotonin- adrenergic reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCA) (Martini, et al, 2023). Bupropion is an atypical aminoketone antidepressant it is highly lipid-soluble and basic and is a trimethyl mono cyclic antidepressant. Structurally, it differs from other antidepressant Bupropion has a different mechanism of action as it doesn't immediately affect serotonin rather it inhibits dopamine and norepinephrine (NDRI) (Costa, et al, 2019 and Khan, et al, 2016). The benefits and side effects of Bupropion are related to its active metabolites and concentration in the active ingredient. Bupropion is metabolized to hydroxy Bupropion (OH-Bup) by enzymes CYP2B6, CYP2CT9, CYP3A4 and metabolized into threhydroxy Bupropion and erthrohydroxy Bupropion by enzymes 11β-hydroxy steroid dehydrogenase-1 and aldo-ketoreductase (Fay, et al, 2021). The most common side effects of this drug are dry mouth, headache, insomnia, constipation, nausea and dizziness. Other important side effects associated with Bupropion include seizures and allergic reactions (Fava, et al, 2005). The kidney performs multiple key functions: the eliminate toxins produced from the metabolism of foreign substances and cells (Levassort, et al, 2024). The kidneys also filter many drugs through metabolism by using glucuronyl UDP(UGT) transferase enzymes (Margaillan, et al, 2015).

Materials and Methods

Laboratory Animals

Twenty- four adult male albino Wistar rats, weighing between 180-200 gram were used in this study. These animals were sourced from the Bio Vet laboratory for veterinary and molecular diagnostics from Basra. The experiment was conducted at the college of Education for pure sciences, department of Biology at University of Thi-Qar, in the animal house, and lasted for sixty- five days. The rats were allowed to acclimatize and ensure their health for 9 days prior to commencement of oral dosing, which continued for 8 consecutive weeks. The rats were distributed in plastic cages covered with metallic wash lids, each equipped with a half- liter water bottle fitted with a metallic nipple. Four rats were distributed per cage. The cages were furnished with wood shavings, which were replaced weekly to maintain cleanliness throughout the experimental period. The animals were maintained at a temperature of 22-26 C and exposed to 12hr light\12hr dark cycle daily. All rats were provided with water and food.

Experimental design

After 9 days of adaptation, rats were assigned into three groups (n=8 in each group) as follows:
1-Control group: all rats were given an equivalent volume of normal saline via oral gavage for 56 days
2-Bupropion 150mg: all rats were given Bupropion 150mg\kg via oral gavage for 56 days
3-Bupropion 300mg: all rats were given Bupropion 300mg\kg via oral gavage for 56 days

Blood sampling

At the end of experiment about fifty-six days animals were anesthetized. Then blood samples were collected directly from cardiac puncture. Withdrawn blood was let to clot in gel tube then centrifuged at a speed 3000rpm for 15min to get serum and then utilizing a micropipette to take rest component and kept in an Eppendorf tube 1.5ml and then samples of serum kept in a freezer at -20C until it was needed.

Kidney function test

Serum level of urea was measured by using commercially diagnostic kit supplied by (Agappe Diagnostics LTD, India) with procedure described by (Kassirer, et al, 1971, and Talk and Schubert,1965). Creatinine was measured by using commercially diagnostic kit supplied by (Agappe Diagnostics LTD, India) with procedure described by (Barits, et al, 2006, and Artiss, et al, 1984). Urea and Creatinine both analyzed by using (Semi-Automatic Biochemical A analyzer, Mindray, China) according to standard procedure.

Histological aspect

After removal of tissue samples from animals after anesthetized and scarified are fixed in 10% formalin solution for 24 hours at room temperature and labeling all tissue samples. After 24 hours the tissues are washed and transferred to 70% ethanol these tissues undergo to several stages to obtain histological sections for diagnosis according to (Bancroft, 2013).

Statical analysis

By using SPSS.26 statical analysis was performed. Differences across groups were examined using analysis of variance (ANOVA) and the LSD post-hoc test. Graphed design by using Microsoft 365 excel.

Result

The result showed significant increase urea a p value≤ 0.05 this indicates difference between treated group and control group. LSD also show a p value≤ 0.05 significant differences between1,2 group and between 3,2 group indicating to different urea levels.
The results show no significant decrease creatinine a p value≥0.05 between treated group and control group. LSD also shows no significant difference.

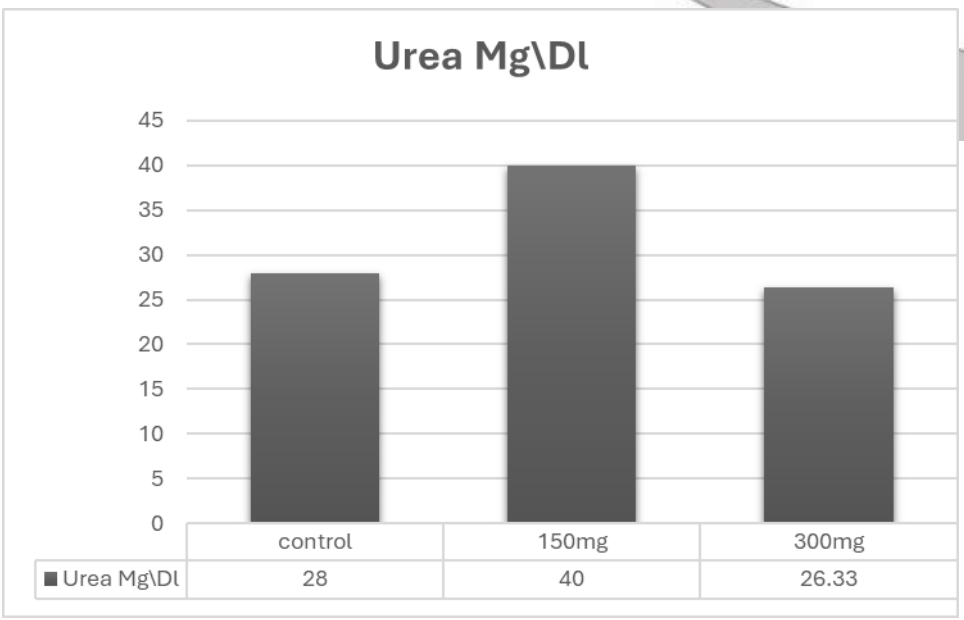

Figure1: the mean serum level urea mg\dL among control and treated groups after 56 days of treatment

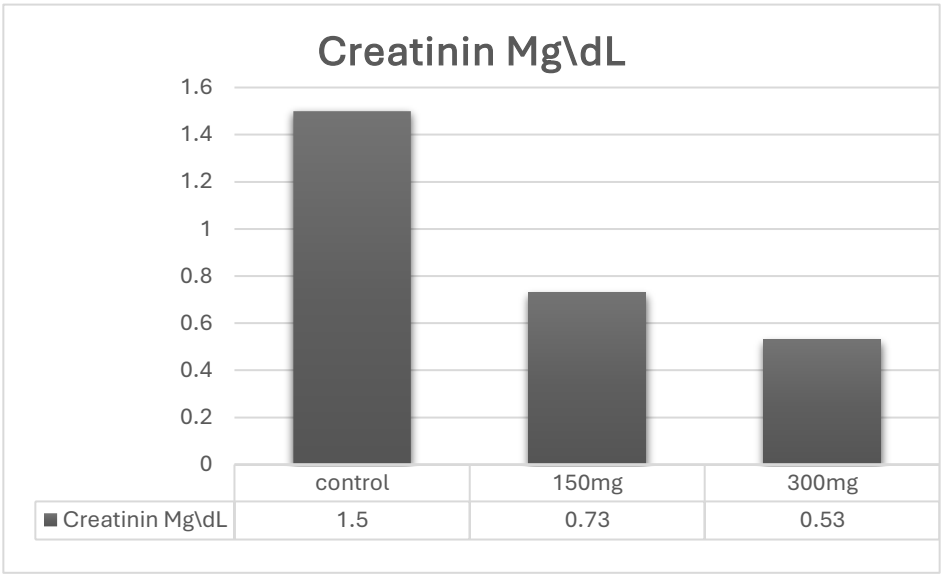

Figure2: the mean serum level creatinine mg\dL among control and treated groups after 56 days of treatment

Table: change in the Urea and Creatinine between treated group with Bupropion 150mg,300mg and control group (mean ±SD)

Groups	Urea	Creatinine
Control	**28.0±4.97mg\dL**	**1.5±2.20mg\dL**
150mg\kg	**40.0±5.32mg\dL**	**0.73±0.12mg\dL**
300mg\kg	**26.3±4.04mg\dL**	**0.53±0.20mg\dL**

Histological study:

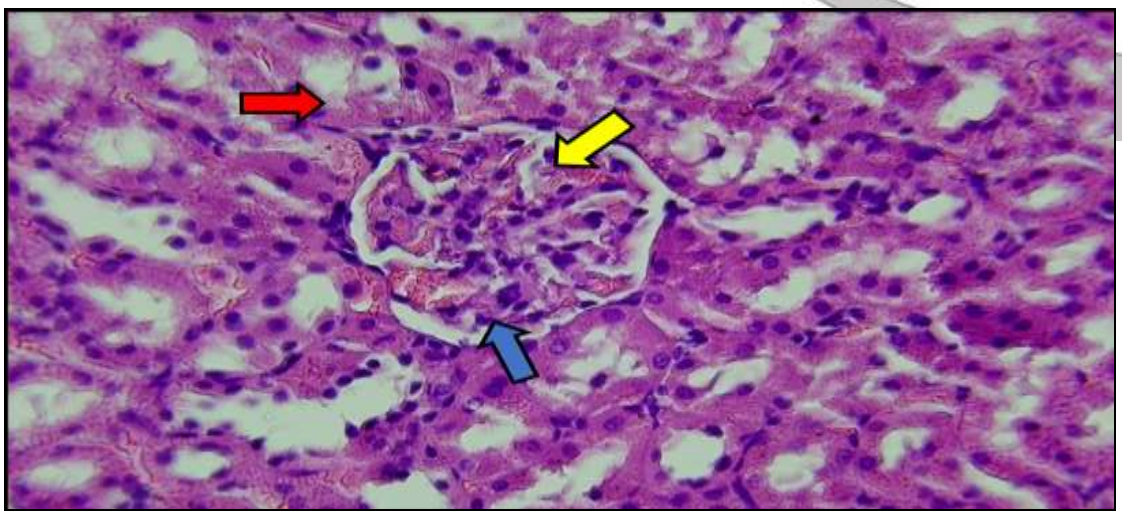

Figure 3: Histopathological section of the kidney control group after 56 days experimental period showing normal glomerulus (yellow arrow), normal Bowman space (blue arrow), and normal renal tubules (red arrow) (H&E stain,40X).

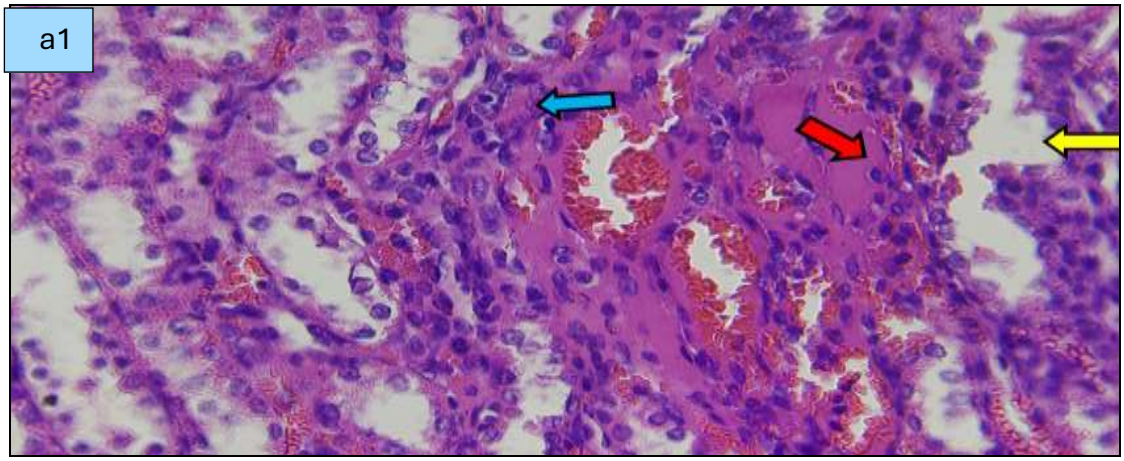

Figure 4: Histopathological section of the kidney rat that treated with 150mg\kg Bupropion at 56 days shows Hyaline degeneration (red arrow), tubular dilation (yellow arrow), and blood vessels congestion with Interstitial Mononuclear cell Infiltration (blue arrow) (H&E stain, 40X).

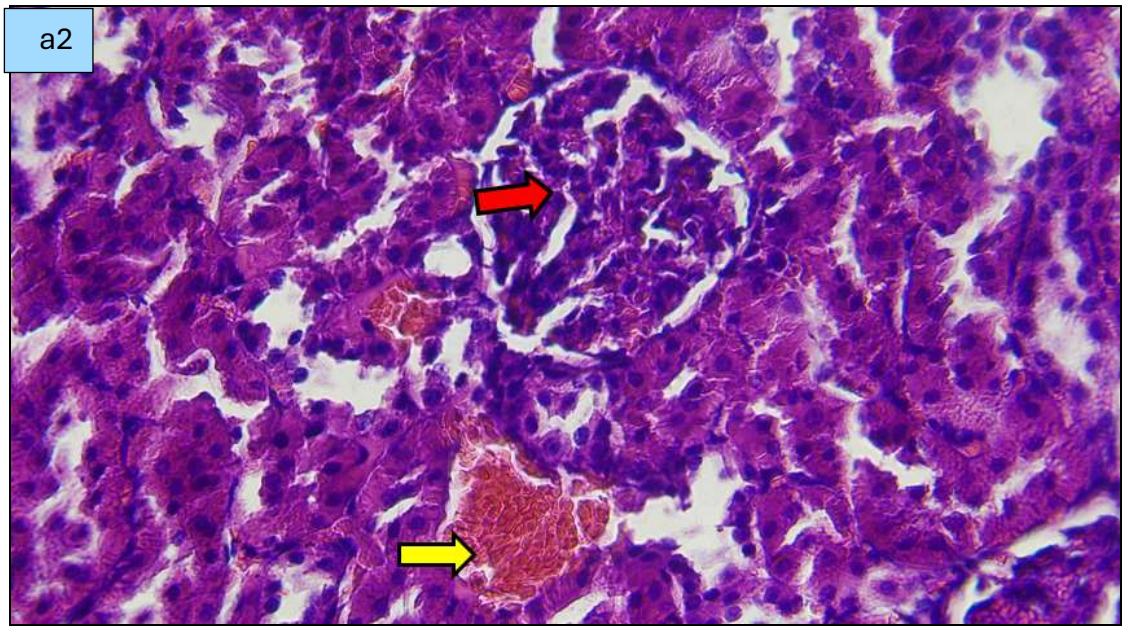

Figure 5: Histopathological section of the kidney rat that treated with 150mg\kg Bupropion at 56 days shows Glomerular Hypercellularity with Narrowing of Bowman space (red arrow) and sever vascular congestion (yellow arrow) (H&E stain, 40X).

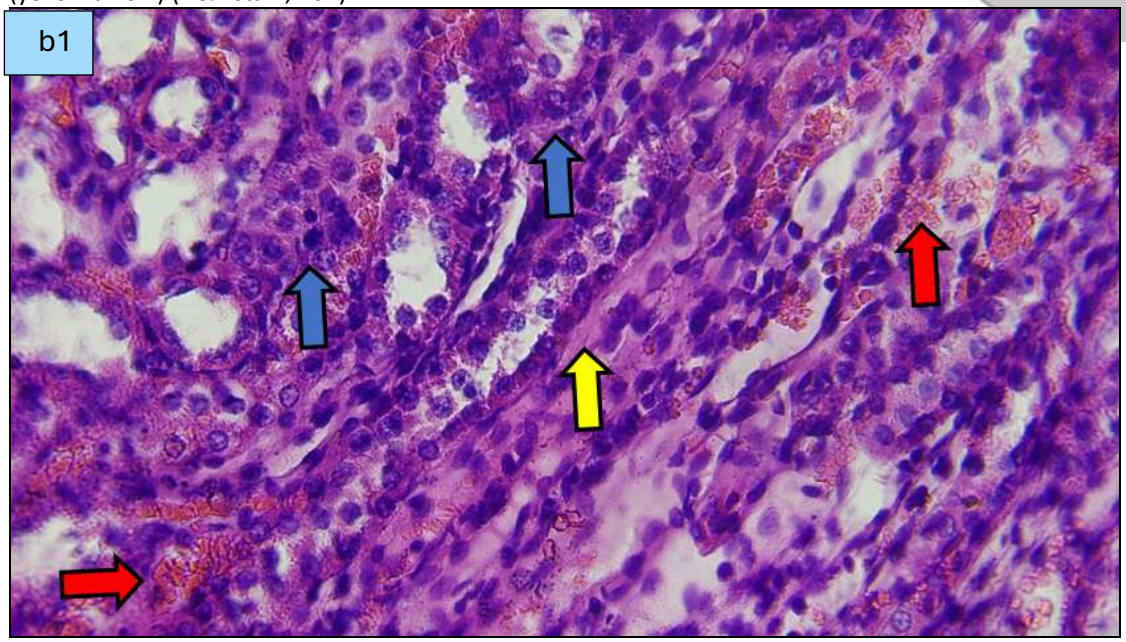

Figure 6: Histopathological section of the kidney rat that treated with 300mg\kg Bupropion at 56 days showing extensive tubular injury, Hyaline degeneration (yellow arrow), sever Mononuclear Inflammatory cell Infiltration (blue arrow), and congestion with Interstitial Hemorrhage (red arrow) (H&E stain,40X).

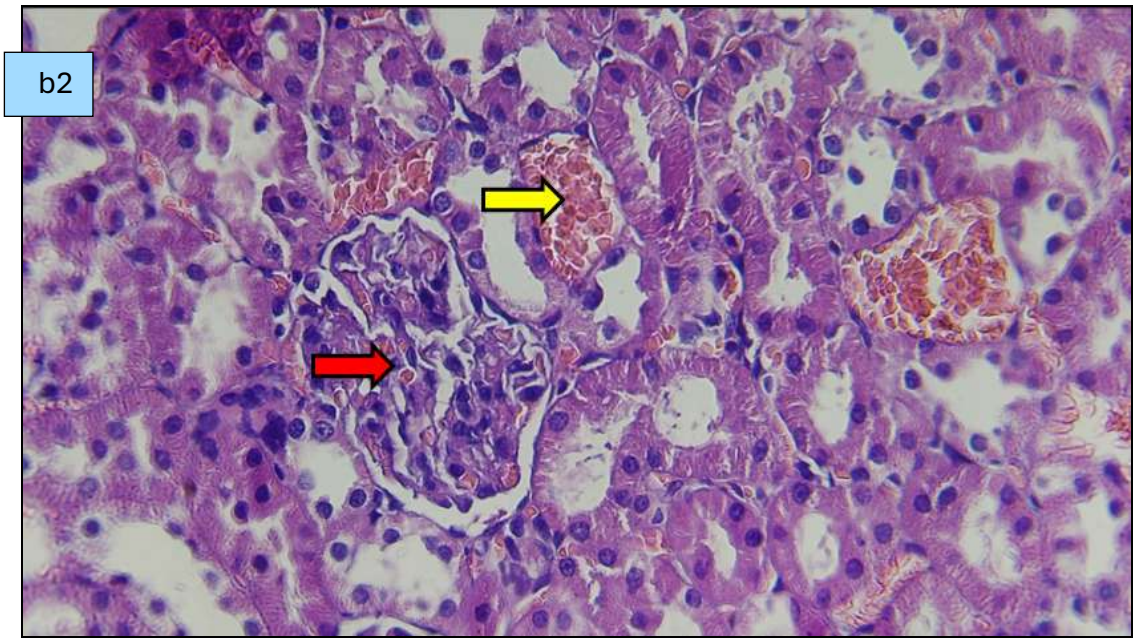

Figure 7: Histopathological section of the kidney rat treated with 300mg\kg Bupropion at 56 days showing Glomerular Hypercellularity with narrowing of Bowman space (red arrow) and sever congestion with Interstitial Hemorrhage (yellow arrow) (H&E stain, 40X).

Discussion

The current study showed significant increase (p value ≤0.05) in urea levels between groups (control,150mg, 300mg) the current study does not agree with (Huang, et al,2025) study where they stated that Bupropion administration to rats induced kidney failure by adenine led to a decrease in the urea level. While creatinine levels showed no significant decrease (p value ≥0.05) between groups (control,150mg.300mg). Urea and Creatinine are produced by the body metabolic process (Abo-Ghanim, et al, 2024). However, decrease does not

necessarily indicate kidney improvement a decrease in the weight of the drug- treated animals was also observed which may have led to a decrease muscle mass and consequently a decrease in Creatinine this consistent with (De Rose, et al, 2023) explanation that decrease in serum Creatinine concentration is affected by muscle mass and nutritional status, which may explain the decrease recorded in this study and also consistent with (Hanies, et al, 2019) explanation that high Urea and low Creatinine levels are indicators of skeletal muscle wasting as the Urea- to- Creatinine ratio is marker of muscle break down. Tubular damage may result from the blood leakage from micro vessels and blood related toxicity where blood components seep into the tubulointerstitial tissue due to the trapping of red blood cells medullary capillaries this led to toxic tubular injury regardless of the duration of ischemia as aggregated red blood cells accumulate within the renal medullary circulation causing congestion such red blood cell trapping is a common feature of acute kidney injury (Maclarnon, et al, 2023). Hemorrhage can occur for various reasons including injury to blood vessels and inflammation. In most cases it arises from acute injury or manifests as a primary lesion associated with nephrotoxic the presence blood within the renal tubule lumen indicates either glomerular damage or disruption of interstitial blood supply as intact red blood cells cannot otherwise pass through effective glomerular filtration barriers (Frazier, et al,2012) the result of the current study agrees with that description of congestion and hemorrhage vascular observation in 150mg\kg group and sever vascular congestion and interstitial hemorrhage in 300mg\kg group. Acute renal tubular injury in kidney tissue is characterized by localized or diffuse dilation of the tubular lumen (Gaut, et al, 2020) this description is consistent with what we found in current study. Glomeruli are the structures responsible for blood filtration located in the renal cortex the consist of networks of interwind capillaries glomerular lesion such as glomerular hypercellularity which is characterized by an increased number of cell nuclei across various regions of the glomerulus impair the kidney filtration capacity leading to tissues such as protein loss and the accumulation of metabolic was products (Chage, et al, 2020) according to (Frazier, et al, 2012) increased glomerular cellularity is characterized by increased cell density leading to hypertrophy this may also explain the narrowing of Bowman space and this observed in histological sections of current study. According to (Raghavan, et al, 2017) drug induce interstitial infiltration of inflammatory cells results from hypersensitivity reaction. Drugs and their metabolites bind to cellular proteins acting as antigens that are subsequently captured by dendritic cells and presented to (T-Cell) this processes triggers T-Cell activation and the release of inflammatory cells into the interstitial tissue. These findings agree with histological observation in the current study. According to (Read,1991) numerous drugs can induce the accumulation of hyalin material with approximal renal tubules of male rats. This phenomenon arises from induced lysosomal degradation of α2µ- globulin and the inhibition of protease activity leading to intracellular protein accumulation and the appearance of hyalin changes. The hyalin degeneration observed in the current study may stem from the same mechanisms given that all animals used were male this explanation for the hyalin changes is plausible though further studies are warranted.

Conclusion

The current study demonstrated that prolonged oral administration Bupropion for 56 days trigger changes in the kidneys' function and histological in albino rats. A significant increase in serum urea was observed, while serum creatinine showed a decrease in the groups treated with Bupropion. Histopathological examination shows renal lesions characterized by congestion, hemorrhage, inflammatory cell infiltration, tubular dilation and hyalin degeneration. These findings suggest that the long time exposure to Bupropion may induce renal injury.

References

- Abo-Ghneim, F.D., Mohammed, H.J., & Al-Koofee, D.A. (2024). Biochemical variations in patients with renal failure: A comparative study. World Academy of Sciences Journal, 6, 66. https://doi.org/10.3892/wasj.2024.281
- Artiss, J. D., McEnroe, R. J., & Zak, B. (1984). Bilirubin interference in a peroxidase-coupled procedure for creatinine eliminated by bilirubin oxidase. Clinical chemistry, 30(8), 1389-1392.
- Bancroft, J. D. (2013). Histochemical techniques. Butterworth-heinemann. cc.v07n0305
- Chagas, P., Souza, L., Araújo, I., Aldeman, N., Duarte, A., Angelo, M., Dos-Santos, W. L. C., & Oliveira, L. (2020). Classification of glomerular hypercellularity using convolutional features and support vector machine. Artificial intelligence in medicine, 103, 101808. https://doi.org/10.1016/j.artmed.2020.101808

- Costa, R., Oliveira, N. G., & Dinis-Oliveira, R. J. (2019). Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects. Drug metabolism reviews, 51(3), 293–313. https://doi.org/10.1080/03602532.2019.1620763
- De Rosa, S., Greco, M., Rauseo, M., & Annetta, M. G. (2023). The Good, the Bad, and the Serum Creatinine: Exploring the Effect of Muscle Mass and Nutrition. Blood purification, 52(9-10), 775–785. https://doi.org/10.1159/000533173
- Fava M, Rush AJ, Thase ME, et al. 15 Years of Clinical Experience With Bupropion HCl: From Bupropion to Bupropion SR to Bupropion XL. Prim Care Companion CNS Disord. 2005;7(3). doi:10.4088/p
- Frazier, K. S., Seely, J. C., Hard, G. C., Betton, G., Burnett, R., Nakatsuji, S., Nishikawa, A., Durchfeld-Meyer, B., & Bube, A. (2012). Proliferative and nonproliferative lesions of the rat and mouse urinary system. Toxicologic pathology, 40(4 Suppl), 14S–86S. https://doi.org/10.1177/0192623312438736
- Gaut, J. P., & Liapis, H. (2020). Acute kidney injury pathology and pathophysiology: a retrospective review. Clinical kidney journal, 14(2), 526–536. https://doi.org/10.1093/ckj/sfaa142
- Haines, R. W., Zolfaghari, P., Wan, Y., Pearse, R. M., Puthucheary, Z., & Prowle, J. R. (2019). Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma. Intensive care medicine, 45(12), 1718–1731. https://doi.org/10.1007/s00134-019-05760-5
- Huang, L., Xiao, Y., Han, X., Yu, Y., Zheng, C., Fang, X., Li, Q., Liu, F., Xia, C., Zhang, Y., & He, J. (2025). Bupropion decreases plasma levels of asymmetric dimethylarginine and ameliorates renal injury by modulation of Ddah1, Oatp4c1, Oct2, and Mate1 in rats with adenine-induced chronic renal injury. Frontiers in pharmacology, 16, 1565713. https://doi.org/10.3389/fphar.2025.1565713
- Kassirer, J. P. (1971). Clinical evaluation of kidney function: Glomerular function. New England Journal of Medicine, 285(7), 385-389.
- Khan, S. R., Berendt, R. T., Ellison, C. D., Ciavarella, A. B., Asafu-Adjaye, E., Khan, M. A., & Faustino, P. J. (2016). Bupropion Hydrochloride. Profiles of drug substances, excipients, and related methodology, 41, 1–30. https://doi.org/10.1016/bs.podrm.2015.12.001
- Levassort, H., & Essig, M. (2024). Le rein, son anatomie et ses grandes fonctions [The kidney, its anatomy and main functions]. Soins. Gerontologie, 29(165), 10–20. https://doi.org/10.1016/j.sger.2023.12.003
- Margaillan, G., Rouleau, M., Fallon, J. K., Caron, P., Villeneuve, L., Turcotte, V., Smith, P. C., Joy, M. S., & Guillemette, C. (2015). Quantitative profiling of human renal UDP-glucuronosyltransferases and glucuronidation activity: a comparison of normal and tumoral kidney tissues. Drug metabolism and disposition: the biological fate of chemicals, 43(4), 611–619. https://doi.org/10.1124/dmd.114.062877
- Martini, M. D., Gregalio, F. A., Vázquez, F. J., Posadas, M. L., Grande Ratti, M. F., & Pollán, J. A. (2023). Prevalencia del uso de antidepresivos en pacientes con enfermedad tromboembólica venosa [Prevalence of the use of antidepressants in patients with venous thromboembolism]. Vertex (Buenos Aires, Argentina), 34(160, abr.-jun.), 20–24. https://doi.org/10.53680/vertex.v34i160.458
- McLarnon, S. R., Johnson, C., Sun, J., Wei, Q., Csanyi, G., O'Herron, P., Marshall, B., Giddens, P., Sullivan, J. C., Barrett, A., & O'Connor, P. M. (2023). Extravasation of Blood and Blood Toxicity Drives Tubular Injury from RBC Trapping in Ischemic AKI. Function (Oxford, England), 4(6), zqad050. https://doi.org/10.1093/function/zqad050
- Raghavan, R., & Shawar, S. (2017). Mechanisms of Drug-Induced Interstitial Nephritis. Advances in chronic kidney disease, 24(2), 64–71. https://doi.org/10.1053/j.ackd.2016.11.004
- Read N. G. (1991). The role of lysosomes in hyaline droplet nephropathy induced by a variety of pharmacological agents in the male rat. The Histochemical journal, 23(10), 436–443. https://doi.org/10.1007/BF01041373
- Selman, A., Dai, J., Driskill, J., Reddy, A. P., & Reddy, P. H. (2025). Depression and obesity: Focus on factors and mechanistic links. Biochimica et biophysica acta. Molecular basis of disease, 1871(1), 167561. https://doi.org/10.1016/j.bbadis.2024.167561
- Talke, H. S. G. E., & Schubert, G. E. (1965). Enzymatische harnstoffbestimmung in blut und serum im optischen test nachwarburg. Klinische Wochenschrift, 43(3), 174-175.