World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

ASSESSMENT ON THE EFFECT OF SELECTED ERGOT-DERIVED DOPAMINE ON THE LIVER FUNCTIONALITY AND INTEGRITY IN WISTAR RATS

[1]*Odinga T., [2]Enebeli S. K., [3]Austin-Asomeji, I., [3]Ohaka, J. C., [4]Gabriel-Brisibe C. U

[1]Department of Biochemistry, Faculty of Science, Rivers State University, Nigeria.
[2]Department of Pharmacology, Faculty of Basic Medical Sciences, College of Medical Science, Rivers State University, Nigeria.
[3]Department of Community Medicine, Faculty of Clinical Sciences, College of Medical Sciences, Rivers State University, Nigeria.
[4]Department of Medical Biochemistry, Faculty of Basic Medical Sciences, College of Medical Science, Rivers State University, Nigeria.

Corresponding Author: Odinga T.
Department of Biochemistry, Faculty of Science, Rivers State University, Nigeria.
DOI: https://doi.org/10.17605/OSF.IO/32CGZ

Article Received on 03/01/2022 **Article Revised on 23/01/2022** **Article Accepted on 13/02/2022**

ABSTRACT

Abuse of drug has become a norm in the society due to people using drugs in doses not prescribed and time. Ergot derived dopamine drugs has been of great advantage in the treatment of ailments and disorders, however, a possible effect on the liver is envisaged, as the liver is saddled with the responsibility of drug metabolism. This study assessed the effect of Bromocriptine and Cabergoline on the liver functionality and integrity. Twenty-five rats grouped into five groups of five rats in each were used for this study. Group 1 was the control group, the rats were administered Low and high dose of Bromocriptine for group 2 and 3, Low dose and high dose Cabergoline for groups 4 and 5. The drugs were administered at the various doses twenty-four hourly. After a period of 21 days, blood samples were collected and Liver harvested for bioassay. On analysis of Albumin, Total protein, Total Bilirubin, Conjugated bilirubin, AST, ALT and ALP using standard laboratory procedures, results revealed that both low and high dose Bromocriptine and Cabergoline increased the serum concentration of total protein, albumin, conjugated bilirubin and total bilirubin, however albumin level showed no significant increase at P value 0.05. The results also observed that the concentration of ALT, AST and ALP all increased when administered High and Low concentrations of Bromocriptine and Cabergoline. The increased variations in AST concentration were significant at $P \leq 0.05$. The histological examination result revealed that Bromocriptine caused congestion of the central vein, vacuolation and nuclear pyknosis as well as tissue necrosis while those treated with Cabergoline experienced congested central vein, vacuolation nuclear pyknosis and sinusoidal space expansion. The findings of this study therefore suggests that both Cabergoline and Bromocriptine may alter the functionality and integrity of the liver, dose dependent, with the most alteration in Cabergoline.

KEYWORDS: *Bromocriptine, Cabergoline, Liver, Liver functionality, Liver integrity.*

INTRODUCTION

Ergot-derived dopamine agonists are a group of medicines consisting of bromocriptine, cabergoline, dihydroergocryptine, lisuride and pergolide. They are mainly used for the treatment of Parkinson's disease, either on their own or in combination with other medicines. They are also used to treat conditions including hyperprolactinaemia, prolactinoma and to prevent lactation and migraine.[1]

Bromocriptine is an ergot alkaloid and dopamine D2 receptor agonist used in the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and galactorrhoea. The drug is also active against pituitary hormone-dependent tumors.[2] Bromocriptine lowers prolactin levels in the blood, inhibits prolactin- secretion resulting in suppression of lactation and bound to dopamine D2 receptor.[3] Bromocriptine is also used together with proper diet and exercise to lower blood sugar levels in patients with type 2 diabetes.[4] Bromocriptine as reported by[5] is helpful in preventing or reducing milk production when this is needed for medical reasons. Likewise, it is helpful in some types of infertility, breast problems and menstrual problems caused by higher-than-usual levels of prolactin.[6]

Cabergoline is an ergot line derivative with potent, selective and long-lasting inhibitory activity on prolactin

secretion acting on dopamine receptors present in pituitary lactotrophes.[7] It is a dopamine receptor antagonist used to treat a hormone imbalance in which there is too much prolactin in the blood.[8] Cabergoline may be useful as long acting anti diabetic agent in patients with type 2 diabetes mellitus. Carbegoline is long acting agonist of dopamine which has a high affinity to dopamine receptors (Type 2) treatment using a dopaminergic agonist reduces hypothalamic stimulation that increases during liver gluconeogenesis, lipids synthesis and insulin resistance.[9,10]

Recent studies have reported alteration of the normal concentrations of some hepatic Biomarkers on exposure to drugs and substances[11], resulting to adverse effects, which may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods or procedures, such as drug interactions.[12] Drugs are important causes of liver injury, more than 900 drugs, toxins, and synthetic drugs have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure.[13] It has also been reported that derivatives of the ergot alkaloid induced acute hepatitis in Parkinson's disease patients[14], hepatotoxicity and nephrotoxicity in mice.[15]

A recent study categorized derivatives of the ergot alkaloid as a drug-induced liver injury.[16] Toxic effects on the kidneys related to medications are both common and expected. Any drugs having nephrotoxic potential can cause more than one pattern of injury.[17]

The development of the symptoms of fibrosis has also been known as a side effect of ergot-derived dopamine agonists for many years, particularly when the medicines are used for long periods.[1]

Drugs have been reported to be extensively metabolized by the liver, hence, a consistent evaluation of the effect of drugs on the liver is expedient for the normal functioning and maintenance of the integrity of the liver.

It is against these contradictions that this study was carried out, to assess the effect of Bromocriptine and cabergoline on the liver biomarkers, as an indication of the functionality and integrity of the liver.

MATERIALS AND METHODS

Experimental animals: Twenty-five adult female albino rats were obtained from the Animal house of Rivers State University, Port Harcourt and taken to the experimental site where they were divided into 5 groups of five albino rats each. They were allowed standard feed and water ad libitum and allowed to acclimatize for 7 days.

Drug of study

Bromocriptine (2.5mg tablet) and Cabergolin (0.5mg) were purchased from a Medical Pharmacy in Port Harcourt, Rivers State, Nigeria for the study.

Experimental grouping/Administration: The female albino rats were divided into five groups

Group 1: Feed + Water only
Group 2: Low dose Bromocriptine (2.5mg/kg BW) + feed + water
Group 3: High dose Bromocriptine (5mg/kg BW) + Feed + Water
Group 4: Low dose Cabergoline (2.5mg/kg BW) + Feed + Water
Group 5: High dose Cabergoline (5mg/kg BW) + Feed + Water

The administration was done 24 hourly using a 2 ml syringe for oral administration via an oro-gastric tube. These doses were determined based on comparative dosage per body weight proportion akin to humans. The administration was done for a period of 21 days.

Sample collection: Twenty-four hours after the last administration, the albino rats were sacrificed, blood samples were collected from each of the rats into sterile sample bottles for analysis of the liver functionality and integrity biomarkers. The liver of each albino rat was harvested for Histological examination.

Sample analysis

Liver functionality was evaluated using the by the serum concentration of total protein, total and conjugated bilirubin and these were assayed as described[18] for total protein and[19] for bilirubin contents.

Serum aspartate amino transferase (AST) and alanine amino transferase (ALT) activities were estimated for liver integrity using Randox reagent kit using 2, 4-dinitrophenylhydrazine substrate.[20]

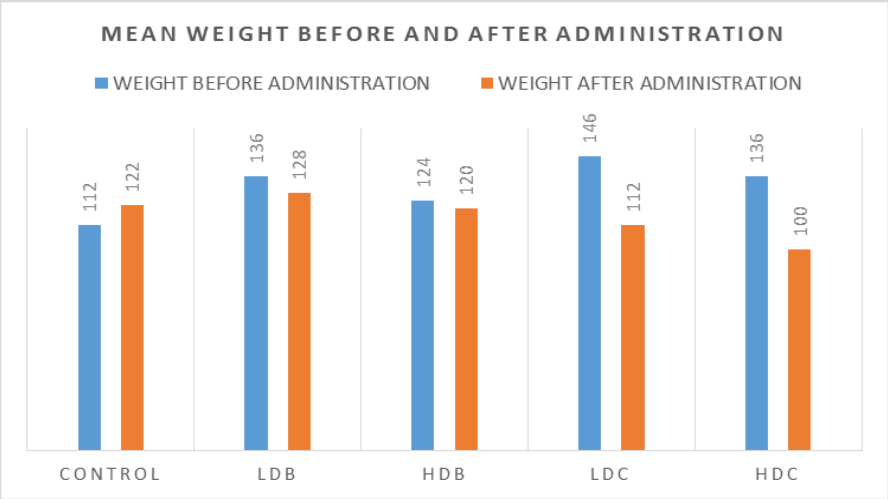
Alkaline phosphatase (ALP) activity was determined with the Randox reagent kit using the p-nitrophenylphosphate substrate as described.[21]

Histology of the liver

Liver organs were washed with saline to remove blood stain and fixed in Bouin's fixative, dehydrated with different grades of alcohol, cleared in chloroform, infiltrated with molten paraffin wax and embedded in paraffin wax. Sections of 5µm thickness were taken and stained with haematoxylin and eosin and evaluated under the light microscope.[22]

Data analysis: The Mean ± Standard deviation was determined and one-way analyses of variance were performed using SPSS version 25 software, thereafter, the Turkey Post Hoc was done for multiple comparison. The significance level was set at $p<0.05$.

RESULTS



- *LDB:Low dose bromocriptine; HDB:High dose bromocriptine; LDC:Low dose cabergoline; HDC:High dose cabergoline*

Figure 1: Mean weight of albino rats before and After administration.

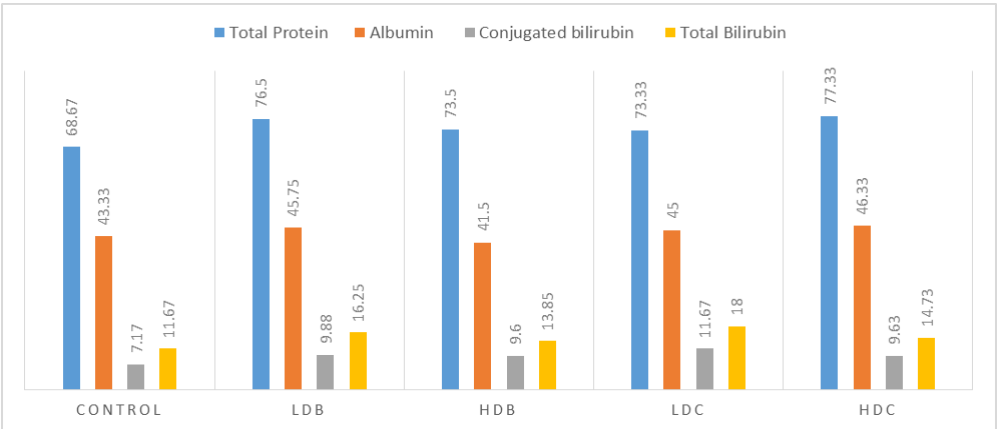
The chart of the mean weight of albino rats before and after administration revealed that the rats administered the different doses of Bromocriptine and Cabergoline had a reduced body weight.

Table 1: Effect of Bromocriptine and Cabergoline on the non-enzymatic biomarkers of the Liver in female albino rats.

Parameter	Total Protein(g/dl)	Albumin (mg/dl)	Conjugated bilirubin (mg/dl)	Total Bilirubin (mg/dl)
Group 1 (control)	$68.67^{a} \pm 4.16$	$43.33^{a} \pm 3.51$	$7.17^{a} \pm 1.17$	$11.67^{a} \pm 1.11$
Group 2 (LDB)	$76.50^{b} \pm 3.42$	$45.75^{a} \pm 2.22$	$9.88^{a} \pm 3.09$	$16.25^{a} \pm 3.66$
Group 3 (HDB)	$73.50^{a} \pm 2.12$	$41.50^{a} \pm 2.12$	$9.60^{a} \pm 1.98^{a}$	$13.85^{a} \pm 1.20$
Group 4 (LDC)	$73.33^{a} \pm 1.53$	$45.00^{a} \pm 2.00$	$11.67^{a} \pm 0.85$	$18.00^{b} \pm 0.70$
Group 5 (HDC)	$77.33^{c} \pm 2.52$	$46.33^{a} \pm 2.08$	$9.63^{a} \pm 1.21$	$14.73^{a} \pm 1.72$

- *Values are Mean ± Standard deviation, Values with the same superscript are not significant at 0.05 level, Values with different superscript are significant at 0.05level. LDB: Low dose Bromocriptine, HDB: High dose Bromocriptine, LDC: Low dose Cabergoline, HDC:High dose Cabergoline.*

The results on table 1 for the effect of bromocriptine and cabergoline on the liver functionality revealed that; Bromocriptine and Cabergoline at both low and high doses significantly increased the Total protein concentration of the serum at P value 0.05 level. However, the most increase in comparison to the control group was highest with the administration of Bromocriptine than Cabergoline.



- *LDB: Low dose Bromocriptine, HDB: High dose Bromocriptine, LDC: Low dose Cabergoline, HDC:High dose Cabergoline.*

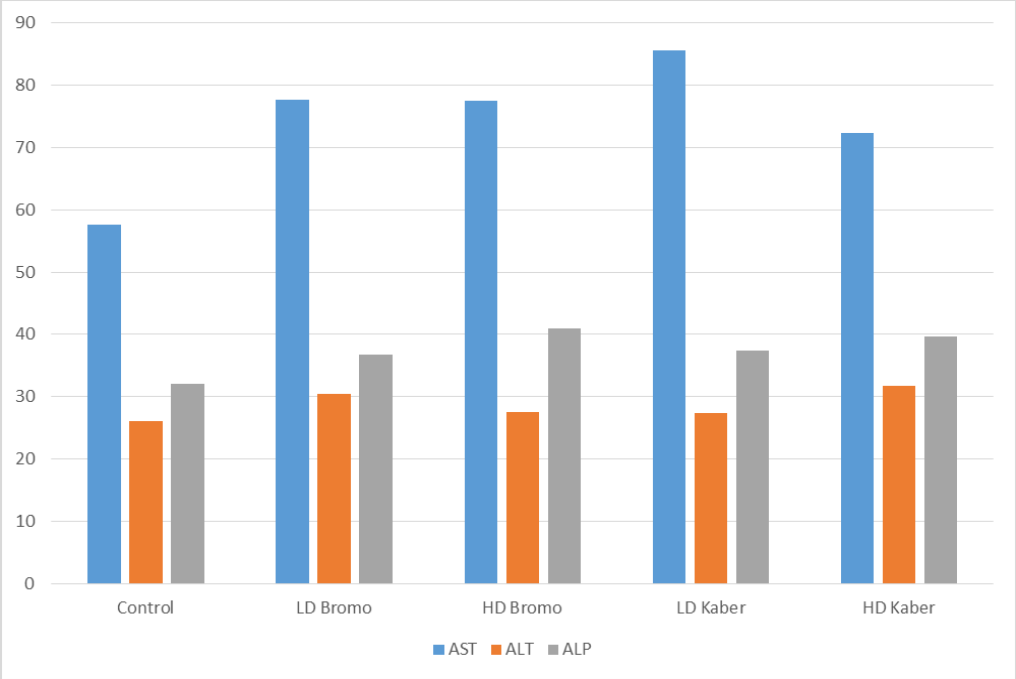
Figure 2: Effect of Bromocriptine and Cabergoline on the non-enzymatic liver biomarkers.

Table 2: Effect of bromocriptine and cabergoline in some enzymatic hepatic bio-makers of the liver in albino rats.

Group	AST(U/L)	ALT(U/L)	ALP(U/L)
Group 1(Control)	57.67^{a} ±2.52	26.00^{a} ± 2.00	32.00^{a} ± 9.85
Group 2 (LDB)	77.75^{a} ±14.90	30.5^{a} ± 5.00	36.75^{a} ± 11.87
Group 3 (HDB)	77.50^{a} ±6.36	27.50^{a} ± 6.36	41.00^{a} ± 24.04
Group 4 (LDC)	85.67^{b} ±4.04	27.33^{a} ±3.51	37.33^{a} ± 8.02
Group 5 (HDC)	72.33^{a} ± 10.20	31.67^{a} ± 8.73	39.67^{a} ± 11.50

- *Values are Mean ± Standard deviation, Values with the same superscript are not significant at 0.05 level, Values with different superscript are significant at 0.05level. LDB: Low dose Bromocriptine, HDB: High dose Bromocriptine, LDC: Low dose Cabergoline, HDC:High dose Cabergoline, AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase.*

The result on table 2 for the effect of bromocriptine and cabergoline on the enzymatic biomarkers of liver function shows an increase in AST, ALT and ALT in all groups when compared to the control group. For AST, a statistical significance at p value 0.05 was observed for Low dose cabergoline in comparison to the control. The most increase was observed in the Cabergoline groups for AST and ALT.



- *Control – Normal control; LD Bromo : low dose bromocriptine; HD Bromo : high dose bromocriptine; HD Caber : high dose Cabergoline; LD Cabergoline low dose Cabergoline, AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase.*

Figure 3: Effect of Bromocriptine and Cabergoline on the enzymatic liver biomarkers.

HISTOTOLIGAL EXAMINATION OF THE LIVER

The histological examination of the liver of the albino rats of study were as follows:

Group 1 (Control) reveealed the liver tissue with normal hepatocytes, Sinusoidsa and Central vein, LD Bromocriptine group liver tissues showed congested central vein, vacoulations, and nuclear pyknosis. Liver tissues of the HD Bromocriptine group showed congested central vein, vacoulations, nuclear pyknosis and tissue necrosis. The liver tissues of LD Cabergoline rats also revealed congested central vein, vacoulations, and nuclear pyknosis while HD Cabergoline rats had congested central vein, vacoulations, as well as sinusoidal space expansion.

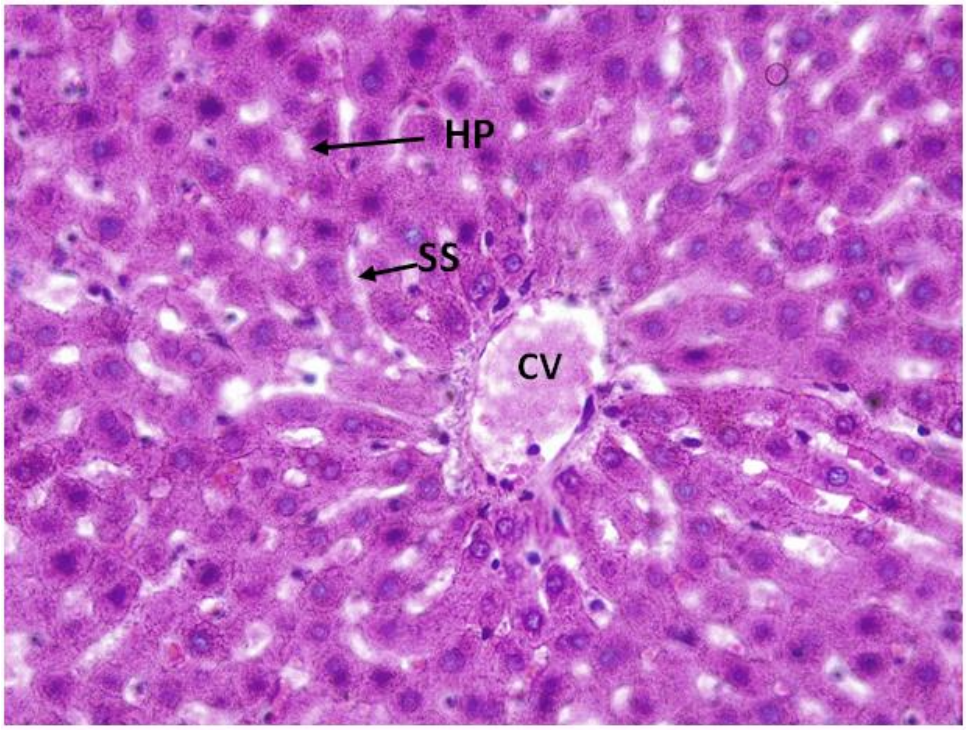


Figure 4: Photomicrograph section of Liver tissue from rats in normal control group showing Liver hepatocytes (HP), sinusoids (SS), and central vein (CV). (H&E X400).

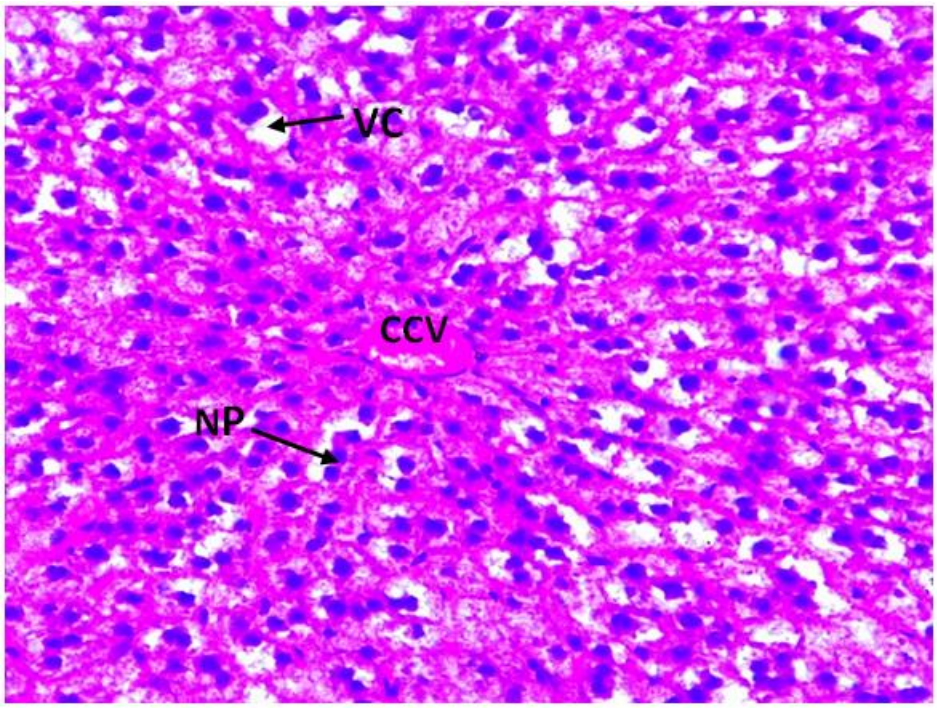


Figure 5: Photomicrograph section from liver of rats treated with LD Bromocriptine showing congested central vein (CV), vacoulations (VC), and nuclear pyknosis (NP). H&E X400.

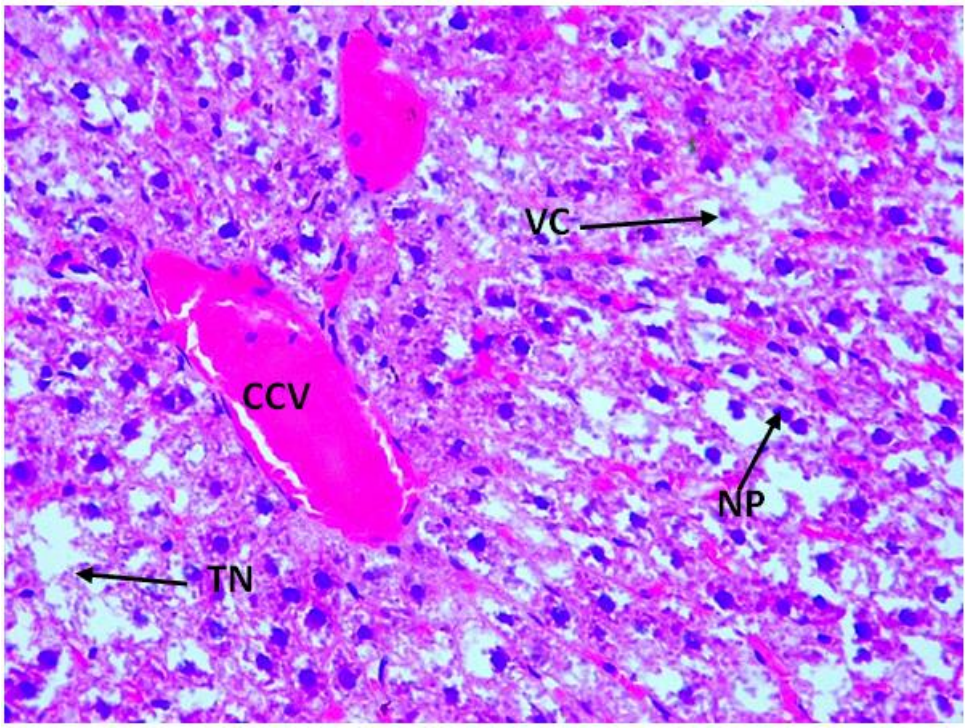


Figure 6: Photomicrograph section from liver of rats treated with HD Bromocriptine showing congested central vein (CCV), vacoulations (VC), nuclear pyknosis (NP) and tissue necrosis (TN). H&E X400.

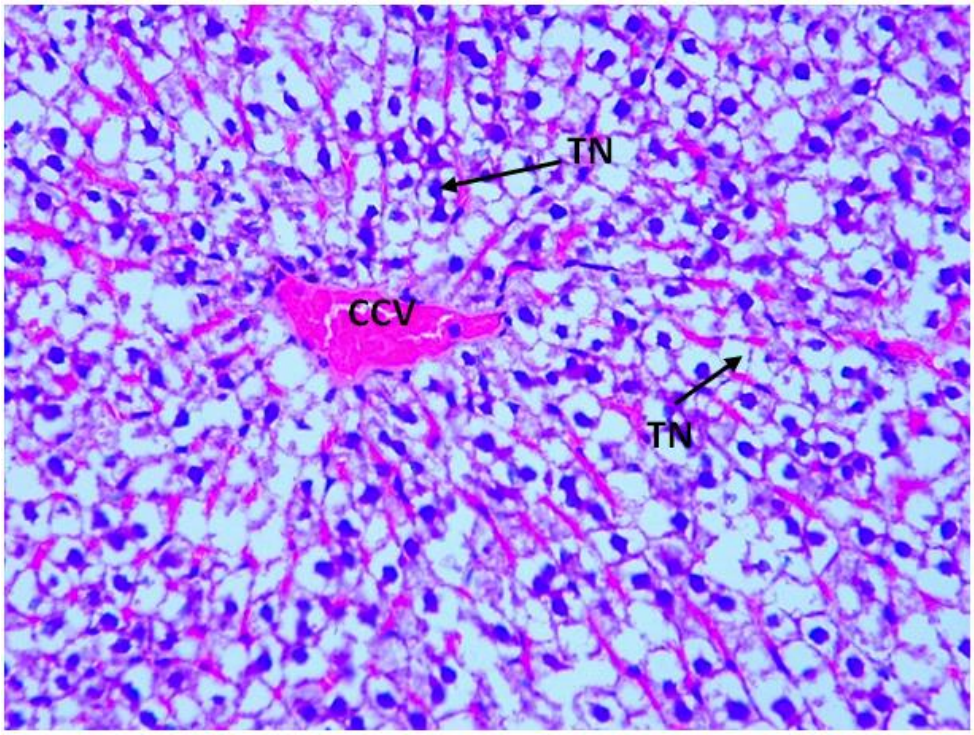


Figure 7: Photomicrograph section from liver of rats treated with LD Cabergoline showing congested central vein (CV), vacoulations (VC), and nuclear pyknosis (NP). H&E X400.

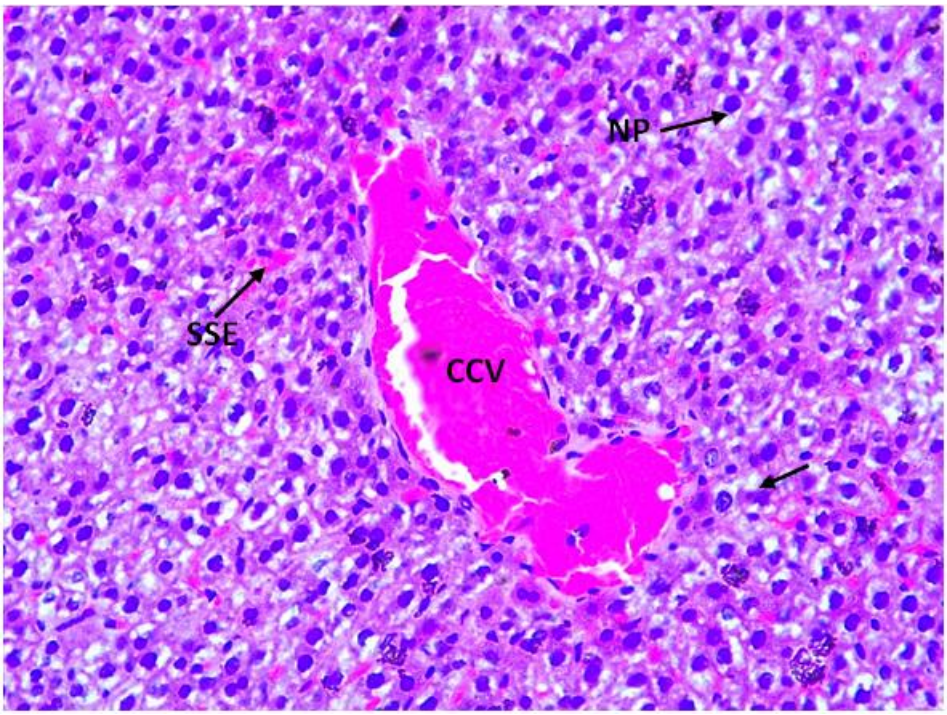


Figure 8: Photomicrograph section from liver of rats treated with HD Cabergoline showing congested central vein (CCV), vacoulations (VC), and sinusoidal space expansion (SSE). H&E X400.

DISCUSSION

The liver biomarkers are used in assessing liver damage, drug-induced injury, to confirm drug causality or determine the type of drug-induced liver injury.[23] This research evaluated the effect of bromocriptine and cabergoline on some liver biomarkers; Total protein, Albumin, Total bilirubin and Conjugated bilirubin, AST, ALT and ALP. The result obtained as showed in Figure 1 showed a reduction in the weight of the wistar rats during the period of administration of various doses of the drugs when compared to the control group. This agrees with the study[24], the reduction may be due to the action of the drugs as a dopamine agonist which is necessary for regulating body's energy expenditure and also its actions on hepatic triglycerides.[25] Table 1 revealed the effect of Bromocriptine and Cabergoline on the Non enzymatic biomarkers of liver function. Total protein and Albumin are proteins needed by the body to fight infections and carry out other metabolic functions, a lower than normal levels of total protein and albumin may indicate liver damage.[26] The findings of this study revealed an increase in the level of total protein and albumin on administration of various doses of bromocriptine and cabergoline, with the most increase in cabergoline. An increase in total protein serum concentration has been reported to be associated with inflammation or infections, such as viral hepatitis B or C, or HIV, bone marrow disorders, such as multiple myeloma or Waldenstrom's disease[26], but not liver disease. This study agrees with the findings which opined an increase in the concentration of serum Total protein on exposure to sudan 111 dye[27], evidenced by the observed increase in the concentration of serum total protein, however, it is not an indication of a possible liver dysfunction.[26]

The Bilirubin concentration of the serum increased in comparison to the control group in this present study, an increase in bilirubin concentration of the serum may be associated with liver damage, diseases or various types of anaemia.[28] Bilirubin is produces during the degradation of the red blood cells and passes through the liver. This study is in consonance with the report that the ergot derivative drugs may induce hepatotoxicity as evidenced with the increase in bilirubin concentration of the serum.[15] The concentration of the enzymatic liver biomarkers AST, ALT and ALP in this study all had an increase in the serum of the albino rats when administered bromocriptine and cabergoline at various doses. An increase in ALP on administration of bromocriptine at various concentrations, suggests liver injury.[24] Elevations in ALT and AST in out of proportion to ALP and bilirubin denotes a hepatocellular disease, whereas an elevation in ALP and bilirubin in disproportion to ALT and AST would denote a cholestatic pattern.[29, 30, 31] The actual function of the liver can be graded based on its ability to produce albumin as well as vitamin K dependent clotting factors. The present study therefore suggests a possible alteration in the function and integrity of the liver evidenced by the increase in the levels of AST, ALT, ALP and Bilirubin. However, this negates the findings of Mahmood *et al.*,[31] The histological examination of the liver also showed congested central vein, vacoulations, nuclear pyknosis and tissue necrosis for the albino rats administered the various doses of bromocriptine and cabergoline.

CONCLUSION

At the end of the study, it was discovered that both Cabergoline and Bromocriptine had an adverse effect on both the enzymatic and non-enzymatic liver biomarkers, hence suggesting an alteration on the intergrity and functionality of the Liver. However, Cabergoline had more significant effect on the liver biomarkers compared to Bromocriptine. The use of these drugs requires precaution since usage over a long period of time may adversely affect the normal functionality and integrity of the liver.

ACKNOWLEDGEMENT

The Authors wishes to acknowledge Miss Nwanyanwu, Goodluck, Miss Sharon Mgbere and Mr. Barine Rogers for their efforts and contributions towards the success of this research.

REFERENCES

1. European Medicines Agency, (2008). Article 31 of Directive 2001/83/EC as amended, referral under Community interest, http://www.emea.europa.eu
2. Ean- Jeong, S., Yoshikazu, S., Henry. J., Greten, Thomas, E. (2018). Repurposing of bromocriptine for cancer therapy; *Frontiers in pharmacology*, 9: 1030.
3. Radad, K., Gille, G., and Rausch, W.D. (2005). Short review on dopamine agonists: insight into clinical and research studies relevant to parkinson's disease. *Pharmacology Report*, 57(6): 701-712.
4. Cincotta, A. H., Meier, A. H. and Cincotta, M. Jr. (1999). Bromocriptine improves glycaemic control and serum lipid profile in obese Type 2 diabetic subjects: a new approach in the treatment of diabetes. Expert Opin Investig Drugs, 8(10): 1683-1707.
5. Prathibha, D., Govardhani, M. and Krishna, P. T. (1994). Prolactin levels in infertility and bromocriptine therapy in hyperprolactinaemia. *Journal of the Indian Medical Association*, *92*(12): 397–399.
6. Stewart, M. (2020). Hormonal imbalance treatment, https://patient.info/medicine/bromocriptine-parlodel
7. Annamaria, C., Gaetano, L., Lucio, A.(2000). Cabergoline. *Expert Opinion on pharmacotherapy*, 1(3): 555-574.
8. Rains, C. P., Bryson, H. M. and Fitton, A. (1995). Cabergoline. A review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation. *Drugs*, *49*(2): 255–279.
9. Adele, B., Zahra, k., E, D., Ozra, A., Shahram, A. (2016). Effect of cabergolin on blood glucose levels in type 2 diabetic patients: A double blind controlled clinical trial. *Medicine*, 95(40).
10. Bahar, A., Kashi, Z., Daneshpour, E., Akha, O. and Ala, S. (2016). Effects of cabergoline on blood glucose levels in type 2 diabetic patients: A double-blind controlled clinical trial. *Medicine*, *95*(40): e4818.
11. Odinga, T., Gabriel-Brisibe, C. U., Opusunju, B. H., Okwakpam, F. N., Azonwu, O. and Orji, K. O. (2020). Synergistic Ingestion of Tramadol, Calabash Chalk (Nzu), Cigarette, Alcohol and Codeine: It's Impact on the Renal and Hepat-ic Function of Male Humans. Journal of Medicinal Chemistry and Toxicology, 4(1): 1-5.
12. Green, H., Spencer, J., (1966). Drugs with possible ocular side effects. Publisher, London, Hatton.
13. Mehta, N., Ozick, L.A., Gbadehan, E., 2014. Drug-induced hepatotoxicity. http://emedicine.medscape.com/article/169814. Accessed 24 December 2019
14. Liberto, N.L., Poli, M., Bollati, P., Chiofalo, F., Filipponi, M. (1992). Bromocriptine-induced acute hepatitis. *Lancet*, 340(8825): 96970.
15. Adejoke, Y.O., Olakunle, J.O., Adewale, Fi., Ojo, T., Asolo, S., Aisida, O., (2014). Evidence of Liver and Kidney Injuries Attributable To Oral BromocriptineMethanesulfonate in Mice. IOSR-*Journal of Pharmacology in Biology Science*., 9(2): 55-61.
16. Bjornsson, E.S., Hoofnagle, J.H., 2016. Categorization of drugs implicated in causing liver injury: critical assessment based on published case report. *Hepatology.*, 63(2): 590-603.
17. Zager, R.A., 1997. Pathogenetic mechanisms in nephrotoxic acute renal failure. SeminNephrol., 17: 3-14.
18. Tietz, N.W., 1994. Specimen Collection and Processing: Sources of Biological Variation in Textbook of Clinical Chemistry. 2nd Edn., W.B. Saunders, Philadelphia.
19. Tietz, N.W., 1995. Clinical Guide to Laboratory Tests. 3rd Edn., W.B. Sauders, Philadelphia, USA.
20. Reitman, S. and S. Frankel, 1957. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am. J. Clin. Pathol., 28: 56-63.
21. Bessey, O.A., O.H. Lowry and M.J. Brock, 1946. A method for the rapid determination of alkaline phosphates with five cubic millimeters of serum. J. Biol. Chem., 164: 321-329.
22. Bancroft, J.D., Gamble, M., 2008. Theory and Practice of Histological Techniques. 6th Edition, Churchill Livingstone, Elsevier, China.
23. Lucy, M. & Dominique, L. (2019). Drug-induced liver injury: biomarkers, requirements, candidates, and validation. *Frontiers in pharmacology and Gastrointestinal and Hepatic Pharmacology*.https://doi.org/10.3389/fphar.2019.01482.
24. Al-Hamdani, N. M. H., Ali, A. M. H., Al-Khatib, B. Y. H. and Al-Shaibani, E.S. (2020). The Effect of Bromocriptine on the Liver of Immature Female Rats. PSM Biol. Res., 5(1): 30-39.
25. Ingram, D. K., Roth, G. S., Umegaki, H. and Ikari, H. (2000). Development of an adenoviral vector for

intracerebral delivery of the dopamine D 2 receptor. Mech. Ageing Dev., 116: 77-93.
26. Ingram, D. K., Roth, G. S., Umegaki, H. and Ikari, H. (2000). Development of an adenoviral vector for intracerebral delivery of the dopamine D 2 receptor. Mech. Ageing Dev., 116: 77-93.
27. Nwachoko, N., Odinga, T., Akuru, U. B. and Ibanibo T. E. (2020). Toxicological Effects of Sudan III Azo Dye in Palm Oil on Liver Enzyme and Non Enzyme Markers of Albino Rat. International Journal of Nutrition and Food Sciences, 9(4): 104-111.
28. Guyton, A.C. and J.C. Hall, 2006. Text Book of Medical Physiology. W.B. Sanders Company, Philadelphia, 966-971.
29. Ribeiro, A. J. S., Yang, X., Patel, V., Madabushi, R. and Strauss, D. G. (2019). Liver Microphysiological Systems for Predicting and Evaluating Drug Effects. Clin Pharmacol Ther., 106(1): 139-147.
30. Vagvala, S. H. and O'Connor, S. D. (2018). Imaging of abnormal liver function tests. Clin Liver Dis (Hoboken), 11(5): 128-134.
31. Wilkerson, R. G. and Ogunbodede, A. C. (2019). Hypertensive Disorders of Pregnancy. Emerg Med Clin North Am., 37(2): 301-316.
32. Mahmood, I.H., Al-Husaynei, A.J. and Mohamad., S.H. (2010). Comparative effects of bromocriptine and cabergoline on serum prolactin levels, liver and kidney function tests in hyperprolactinemic women. Middle East Fertility Society Journal, 13(1): 33-38.