Republic of Iraq

Ministry of Higher Education

And Scientific Research

University of Babylon

College of Pharmacy

The effect of orlistat on the liver and brain histology in male of albino rats

A Research Project

Submitted to The Council College of Pharmacy, University of Babylon in Practical Fulfillment of The Requirements For The Degree of Bachelor's in Pharmaceutical Sciences

Presentation by

Kawther Hussein Ghani

Rosul Hamza Alawi

Noor Satea Malik

Supervision by

Dr. Rafah Saleem

31 May 2022 29 Shawwal, 1443

إهداء

لمن يكدح أطراف أصابعه ليمنحنا لحظة من السعادة

لمن حصد الأشواك من طريقي ليمهد لي طريق المعرفة

إلى القلب الكبير ... والدي العزيز.

لمن شرب الكأس فارغه ليعطيني قطرة من الحب

لمن غذاني الحب والحنان

إلى رمز الحب وبلسم الشفاء

إلى القلب الأبيض ... أمي العزيزة.

إلى إخواني وأخواتي الذين ساعدوني ودعموني ووفروا لي

الملاذ الآمن في أوقات الشدائد.

وللقلوب الطاهرة والطيبة والنفوس البريئة .... أصدقائي

....

مساندتي في حياتي.

INTRODUCTION

Obesity is a chronic disease that results in the accumulation of excess fat in the body due to an energy imbalance. The obesity may be caused by multifactorial etiology, including lifestyle, environment, genetics, metabolism, and behavioral components[1] .

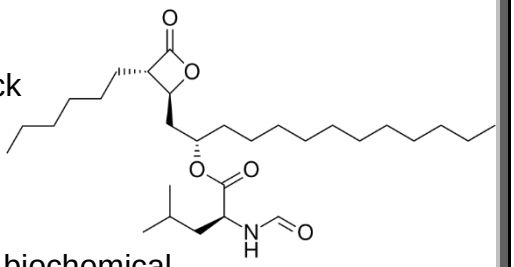
The factors of lifestyle, such as regular physical activity, proper nutrition and changes in eating behaviors play an important role in combating obesity[2] .

Numerous diseases are caused by obesity, including hypertension, hypercholesteremia, sleep apnea, pulmonary hypertension, cardiovascular disease and type 2 diabetes[3] .

Martorell *et al*., reported that Egypt have the highest proportion of obesity (20.1%)[4] .Anti-obesity drugs are all pharmacological agents used to reduce or control weight. These medications alter one of the human body essential processes, either by altering appetite or absorption of calories[5] .

Excessive fat intake is a common cause of the development of hyperlipidemia and obesity, a compound that selectively limits the absorption of ingested fat might be useful in both condition treatments[6] .

Orlistat is a pharmacological agent facilitating the weight loss and the weight maintenance via inhibiting of pancreatic lipase, an enzyme that is necessary for the TG digestion, it reduces the absorption of fat by 30%.



In general there are no side effects of orlistat due to its lack of absorption[7] .

So, we have investigated in the present study the

the ameliorating of orlistat on some hormones and biochemical parameters in a High Fat Diet (HFD) induced animal model of obesity.[8]

Orlistat is a potent, specific, irreversible inhibitor of pancreatic and gastric lipases. Also known as tetrahydrolipstatin, it is a chemically synthesized derivative of lipstatin, which is naturally produced by Streptomyces toxytricini[8] .

AIM OF STUDY

Is to determine the histological changes in liver and brain tissue after chronic administration of orlistat.

MATERIALS AND METHODS:-

In this investigation, twelve rats (about 193-212 mg), during the period from December 2021 to March 2022. It has been achieved in the Animal House of Faculty of Pharmacy Babylon University. All animal experiments comply with the guidelines and should be carried out in accordance with the U.K. Animals.

The animals were maintained under controlled environmental conditions and were provided with a free access to high protein diet and tap water. After one week acclimatization period, the animals were randomly divided into two groups as follows: Group 1 (G1): 5 Healthy control rats. Group 2 (G2): 5 Rats of this group were received orlistat dissolved in DW orally by a gastric tube at a dose of 0.8 mg/kg /day [9].

Chemical and medicine

Orlistat capsule was used in this experiment 'Xenical' , it was dissolve in warm DW and administered to each rat in oral tube (5 ml of DW for dissolving 1.4 mg of orlistat).

Treatment was done once daily for a continuous 70 days.

Histological study

According to Bancroft's idea , histological sections of the liver and brain (5 thick) were generated to evaluate the alterations that may be discovered in the treatment animal groups compared to the control group. [10]

THE RESULTS

The control group (group I) showed normal histological structures (fig.1) .The cells are polygonal and appeared as cords radiating from central veins. The cords were separated from each other by blood sinusoids. The hepatic sinusoids appeared as narrow spaces between the hepatic cords which lined by flat endothelial cells , normal vessels .

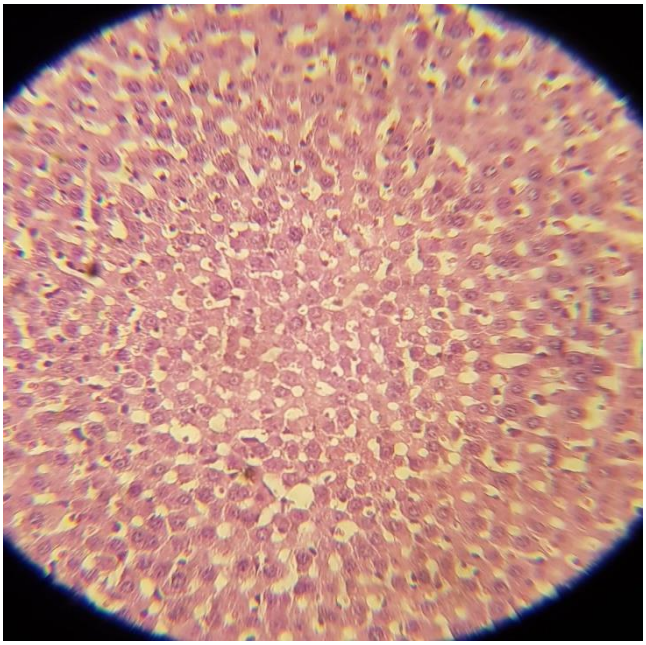


Figure 1 : A photomicrograph of a cross-section of the liver of a rat of group I showing the normal architecture of liver tissue.

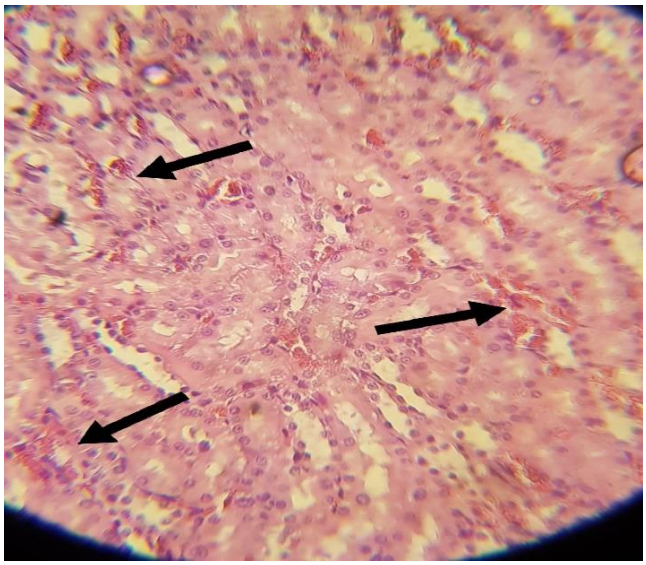


Figure 2 : section of the liver tissue of a rat of group II showing dilated , congested of vessels (black arrow).

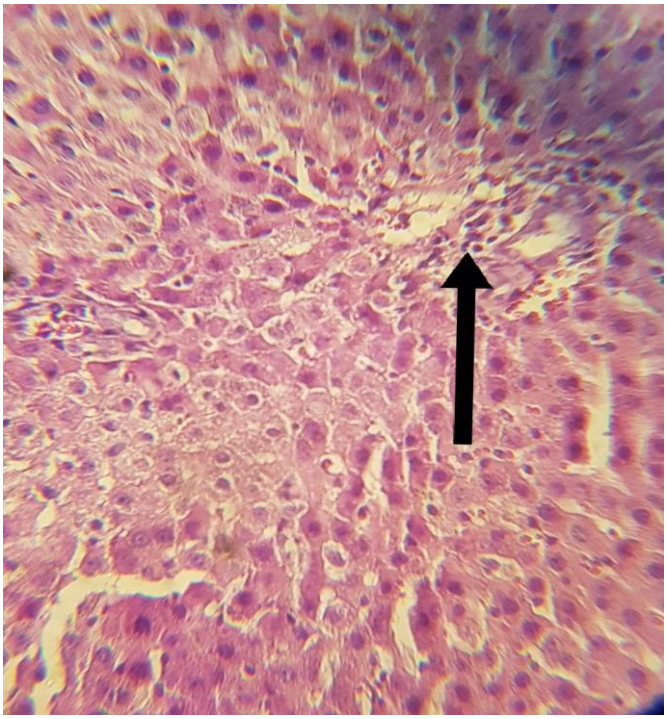


Figure 3 : The orlistat treated group (group II) also showed lymphocyte infiltration.

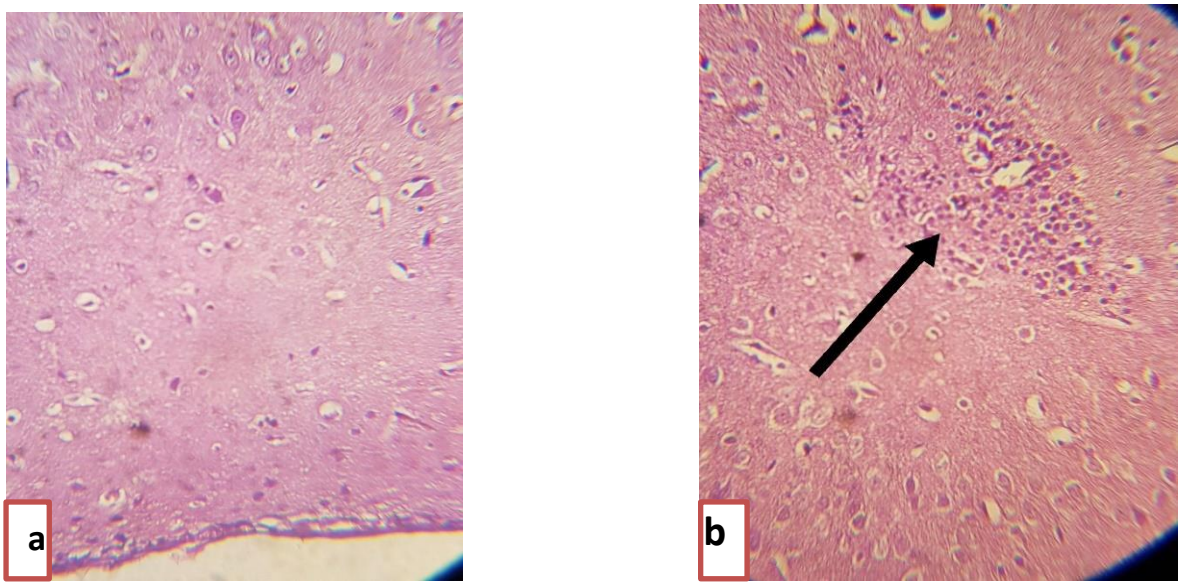


Figure 4: Cross section of the brain tissue of a rat showing normal brain tissue (a) vs encephalitis (b), dominated by neutrophils or mononuclear leukocytes.

DISCUSSION

In the present study, the administration of orlistat induced histological changes in liver and brain tissues of male albino rats. The lymphocytes infiltration that observed in this study were also detected by some research Sahar (2018)[11] and Atiq *et al*. [9]. The cellular infiltration was observed by Filippato *et al.* (2008)[12] who explained the mononuclear cellular infiltration induced the inflammatory mediators (such as TNF-α) which are most expected to act in a paracrine manner to induce liver injury (Bu *et al*. ,2005)[13].

In our experiment ,the orlistat treated group (group II) showed severely dilated and congested vessels, in previous experiences has show inflammatory cells infiltration in preportal area, presence of degenerated cells and widening of blood sinusoids.

In previous study, orlistat group showed some mild changes in liver tissue as enlargement of the hepatocytes, cytoplasmic vacuolations and shrunken nuclei and this were in agreement with Hu *et al.* (2018) [14] . The results of this study also were in agreement with Sahar (2018) [11] .

This agreed with Filippatos *et al.* (2008) who showed that orlistat adminstration was associated with hepatic adversative effects such as cholelithiasis, cholostatic hepatitis, and subacute liver failures. Mitochondrial swelling was observed by Lu *et al.* (2006) [15] who showed that the swollen mitochondria are the major morphological changes in the mitochondrial injury, and this was explained as swelling mitochondria can be a result from reduced mitochondrial ATP production and membranes injures by hydroxyl radicals.

Through this experiment we noticed some changes to the mind, namely "Encephalitis" .

Encephalitis: This condition occurs as a result of a defective response of the immune system to infections elsewhere in the body. Instead of attacking only cells that cause infection, the immune system mistakenly attacks healthy cells in the brain as well. Encephalitis, also known as postinfective encephalitis, usually occurs two to three weeks after the initial infection.[17]

Sanaa *et. al*. the histological sections of the cerebellar cortex of rats treated with high fat diet plus Orlistat showing Molecular layer and Granular cell layer showed many vacuoles. Other immage of histological sections of the cerebellar cortex of rats treated with high fat diet plus Orlistat showing Granular cell layer showed haemorrhage (Hy) and pyknosis of urkinje cells.[18]

Al-Safo *et. al* orlistat treated group shows vacuolation of neurons and myelin. Sheaths, congestion and dilatation of blood vessel and vasogenic edema , perineuronal edema , gliosis , and periaxonal edema.[19]

CONCLUSION

It was concluded that orlistat-induced pathological changes in liver like lymphocyte infiltration and congestion of blood vessels, while in brain it was induced encephalitis in cerebral cortex. Thus, clinicians should be carefully observe their patients for any abnormal signs.

REFERENCES

1- S. O. Lee, A. L. P.A. Simons, P. A. Murphy and S. Hendrich, (2005). "Soyasaponins

lowered plasma cholesterol and increased fecal bile acids in female golden Syrian hamsters". Exp. Biol. Med., 230, 472-478 .

2- R. M. P. Rao, Y. Jyothi and S.I. Rabban, (2015). "Anti-obesity activity of Taraxacum

officinale in high fat diet induced obese rats", J. Chem. Pharm. Res., 7 (4), 244-

248.

3- K. M. Gadde, C. K. Martin, H-R. Berthoud and S. B. Heymsfield, (2018). "Obesity: Pathophysiology and management", J. Am. Coll. Cardiol., 71 (1), 69-84 .

4- R. Martorell, L. K. Khan, M. L. Hughes and L. M. Grummer-Straw, (2000). "Obesity in

women from developing countries", Eur. J. Clin. Nutr., 54 (3), 247-52 .

5- H. M. Amin, N. S. Tawfek, B. K. Abo-El Hussein and M. S. Abd El-Ghany, (2015). "Antiobesity potential of orlistat and amphetamine in rats fed on high fat diet",

Middle East J. Appl. Sci., 5 (2), 453-461 .

6- C. A. Williams, F. Goldstone and J. Greenham, (1996)."Flavonoids, cinnamic acids

and coumarins from the different tissues and medicinal preparations of Taraxacum officinale", Phytochemistry, 42 (1), 121-127 .

7- D. S. WEIGLE, "Pharmacological therapy of obesity: Past, present, and future (2003).", J. Clin. Endocr. Metab., 88 (6), 2462-2469 .

8- - B. Borgstrom, (1988)."Mode of action of tetrahydrolipstatin, a derivative of the naturally occurring lipase inhibitor lipstatin", Biochim. Biophys. Acta., 962 (3), 308-316 .

9- Atiq, M., Davis, J.C., Lamps, L.W., Beland, S.S. and Rose, J.E. (2009). Amiodarone Induced Liver Cirrhosis. Report of Two Cases. J. Gastrointestin Liver Dis.18(2):233-235.

10- Bancroft J , Gamble M. 2008: Theory and practice of histological techniques:400-421.

11- Sahar Y.2018. Effect of orlistate on liver of adult male albino rate and positive protective role of B-caroten. Foer.Med.Ant.R. J. 6(2):26-30.

12-Filippatos, T.D., Derdemezis, C.S, Gazi, I.F., Nakou, E.S., Mikhailidis, D.P. ,Elisaf, M.S. 2008. OrlistatAssociated Adverse Effects and Drug Interaction.Drug Saf.31:53-65.

13- Bu, D.X., Erl, W., De M., R., Hansson G.K.,Yan, Z.Q.2005. IKK β-Dependent NF-κB Pathway Controls Vascular Inflammation and Intimal Hyperplasia. FASEB J.19(10) : 1293-1295.

14- Hu W., Li W., Yujia C., Zhiqing X., Yifeng L., Jiang C. (2018). Efficacy of orlistat in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Biomed Rep. l: 9(1): 90–96.

15- Lu X., Hamilton J.A., Shen J., Pang T., Jones D.L. , Potter R.F.2006. Role of Tumor Necrosis Factor-Alpha in Myocardial Dysfunction and Apoptosis during Hind Limb Ischemia and Reperfusion. Crit. Care Med.34(2):484-491.

16- Johar D., Roth J.C., Bay G.H., Walker J.N., Kroczak T.J. and Los M.2004. Inflammatory Response, Reactive Oxygen Species, Programmed (Necrotic-Like and Apoptotic) Cell Death and Cancer. Rocz Akad Med Bialymst.49:31-39.

17- Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57(8):1114–28. 10.1093/cid/cit458

18- Galaly, Sanaa R., et al. (2014). "Effects of Orlistat and herbal mixture extract on brain, testes functions and oxidative stress biomarkers in a rat model of high fat diet." Beni-Suef University Journal of Basic and Applied Sciences 3.2: 93-105.

19- Al-Safo, Alyaa A., and Liqaa H. Al-Duliami. (2022). "Histopathological Study of Orlistat and Rosemary Aqueous Extract in the Brain and Liver of Obese Male Rats." Journal of Applied Veterinary Sciences 7.2: 34-40.

20- Bancroft J , Gamble M. 2008: Theory and practice of histological techniques:400-421.