Republic of Iraq
Ministry of Higher Education and Scientific Research
University of Basrah
College of Pharmacy

Potential Role Of Montalukast On Some Physiological Parameters In Laboratory Rats

A graduated project submitted to the department of pharmacology and toxicology, the committee of projects discussing of the College of Pharmacy, University of Basrah

By:

Khaled Jalal Abdel Qader

Adel Talal Jameel

Muntadher Abdul Amir Kazem

(2021)

Supervised by:

Assist prof.
Dr. Manal Nasser Alhayder

List of Contents

Abstract

Montelukast a selective reversible cys-leukotriene-1 receptor antagonist is used in the treatment of asthma and is reported to reduce airway eosinophilic inflammation in this disease . That play an important role in bronchoconstriction, but can also enhance endothelial cell permeability and myocardial contractility. Twelve animals were randomized and divided into two groups (6 in each group). The control group received vehicle 0.2 ml of (saline solution 0.9%) by intraperitoneal injection. While the other group treated with 10 mg/kg/day of montelukast diluted in saline solution 0.9% administered by intraperitoneal injection (0.2 ml) for five consecutive days, then the hematological, biochemical and histopathological analyses were performed . The present results showed that there is no statistically significant difference was noted in the final body weights relative organs. Moreover ,each of hematological and liver enzymes revealed that there is no statistically significant difference compared control group. The present results showed a significant decreased levels of total cholesterol, triglyceride and high density lipoprotein TG compared control group. Additionally, motelukast caused some histopathological changes in rat liver tissues and kidney compared with control except lung tissue not affected at all. In conclusion, this study suggests that safe effect of montelukast on each of body weight ,blood parameters, liver function also the lipid profile but it has harmful effects on the kidneys. So future studies are needed to replicate this work on asthmatic patients and evaluate the efficacy of montelukast on kidney function.

1.Introduction

Montelukast, pranlukast, zafirlukast and pobilukast were the main leukotriene receptor antagonists (LTRA) and selective inhibitors of CysLT1 receptor that were appropriate for use in asthmatic patients then later on for the treatment of allergic rhinitis and urticaria (Capra et al.,2006). Montelukast is reported to reduce airway eosinophilic inflammation in this disease (Aharony ,1998; O'Byrne ,1998; Wenzel ,1999). $CysLT_1$ receptor antagonists or biosynthesis inhibitors have been described to enhance ethanol-induced gastric mucosal damage and experimental colitis (Carsin et al.,2002) also the gastro protective effect on indomethacin-induced ulcerations and alendronate prompted lesions of the rat gastric mucosa, which is attributed to its modifying effect on oxidative damage and myeloperoxidase (MPO) activity (Amran et al.,2011).

As a chemistry Montelukast (which has the formula $C_{35}H_{36}ClNO_3S$) is a member of quinolines, a monocarboxylic acid and an aliphatic sulfide, has the chemical name {2-[1-[(R)-[3-[2(E)-(7-chloroquinolin-2-yl) vinyl]phenyl]-3-[2-(1- hydroxy-1-methylethyl)phenyl]propyl-sulfanylmethyl] cyclo- propyl] acetic acid sodium salt} . Is a potent and highly selective cysteinyl leukotriene receptor antagonist(CysLTRA) , selectively and competitively blocks the cysteinyl leukotriene 1 ($CysLT_1$) receptor, preventing binding of the inflammatory mediator leukotriene D_4 (LTD_4) (with an affinity two fold greater than the natural ligand), and has been shown to be effective in the treatment of chronic asthma , Montelukast is sensitive toward light and this requires special dealing precautions to avoid it's possible degradation by the light whether it is in solution or solid state (Benninger & Waters,2009; Al Omari et al .,2007).

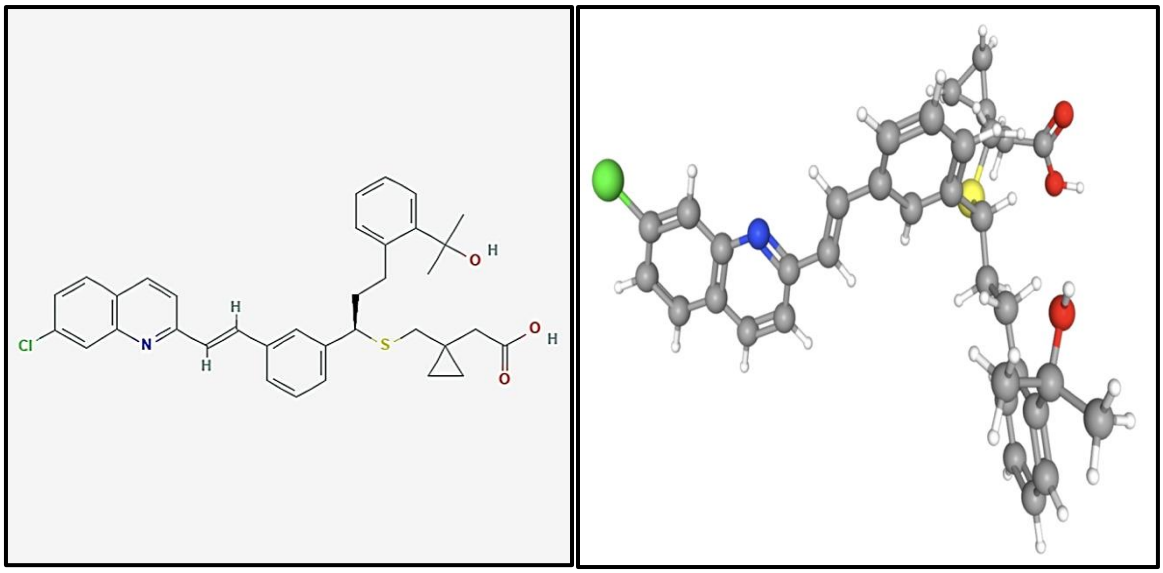

Figure 1.*The chemical structure of montelukast cited by National center for biotechnology information*

As all medicines, montelukast has number of adverse effects and the most common of them include upper respiratory infection, fever, headache, sore throat, cough, stomach pain, diarrhoea, earache or ear infection, flu, runny nose, and sinus infection (Paul et al.,2010).

Montelukast improves burn- and sepsis induced multiorgan damage by a neutrophil-dependent mechanism (Sener et al.,2005). Furthermore, it has been shown reduce I/R-induced oxidative damage in the liver, intestine, kidneys, testes and bladder, because of its anti-inflammatory and antioxidant properties (Daglar et al.,2009). Also, leukotriene biosynthesis diminishes lung injury after hemorrhagic shock (Amran et al.,2011).On the other hand, human experimental studies have also been showed to examine the role of LRA in CV diseases. Ingelsson et al. informed that montelukast might have a possible role for secondary anticipation of CV disease. The results established a decline in the risk for frequent myocardial infarction in male subjects , as well as recurrent stroke in patients taking montelukast (Ingelsson and Bäc,2012).Accordingly, LTRAs might have a protective role in the CV and cerebrovascular events through their antiapoptotic and anti-inflammatory functions (Hoxha et al.,2017). However , the present study aims to investigate the influences of

potential role of montelukast on body weight , blood parameters, lipid profile , some of liver enzymes of rats. also, histopathological features of all samples were analyzed under the light microscopic.

2. Materials And Methods

2.1. Animals care

A total of twelve albino male Wistar Kyoto rats of nine weeks of age and weighing between 100g to 120g were obtained from animal center of Veterinary College / Basrah University, (Basrah, Iraq). Animals were housed in animal center at College of Pharmacy, University of Basrah and they were kept in a 12 h light–dark cycles and a temperature of 25 ± 2°C in polypropylene cages using disposable absorbent cloths under sterile paddy husks to avoid contamination from radioactive urine. The animals were fed with standard chow and water throughout the experiment.

2.2. Experimental Design

Twelve animals were randomized and divided into two groups (six in each group). The control group received vehicle 0.2 ml of (saline solution 0.9%) by intraperitoneal injection. While the other group treated with 10 mg/kg/day of montelukast (Pioneer Co. for pharmaceutical industries-Iraq) diluted in saline solution 0.9% administered by intraperitoneal injection (0.2 ml) for five consecutive days (Hegab et al.,2018).

2.3. Analysis of body weight and relative organs weight

The body weights of rats were measured before the onset of the experiment and prior to the sacrifice of the animals. After euthanasia, the whole livers, lungs, kidneys, hearts, thymus glands and ovaries were carefully removed and weighed on analytical balance for relative weight analysis, using the formula:

organ weight (g)/animal weight (g) X 100. The data were tabulated and statistically analyzed.

2.4. Hematological analysis

At the end of experiment , animals were weighed and anesthetized using chloroform. Blood samples were collected from the rats by cardiac puncture then they were transferred into a lavender top collection tube containing the anticoagulant ethylenediaminetetraacetic acid (EDTA) and used for hematological analysis. Analysis of complete blood count (CBC) was performed through automated blood cell analyzer(Count 60 , Genex, USA).

The parameters analyzed were total white blood cell (WBC) count, lymphocyte and monocyte counts, red blood cells (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets (PLT), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW). The automated blood cell analyzer was used for evaluation the blood parameters.

2.5. Biochemical analysis

Blood was collected from the rats by cardiac puncture and transferred into tubes without anticoagulant and left at room temperature for 30 min for clot retraction. Serum was obtained from the blood samples by centrifugation for 20 min (Genex, Florida, USA). After centrifugation, the serum was collected for further biochemical analysis such as : alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol were investigated to determine liver function using commercial kits (JOURILABS, Ethiopia). following the manufacturer's instructions. Low-density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) were measured using formula given by friedewald (Friedewald et al., 1972).

2.6. Histopathological Evaluation

After euthanasia, the whole kidney and lung and liver were carefully removed and they were fixed with 10% neutral formalin. The organs of rats were dissected, embedded in paraffin and 5µm sections were cut by using a rotary microtome and the samples were then stained with haematoxylin and eosin (H&E) for microscopic examination (Mescher, 2015).

2.7. Statistical analysis

All results such as changes in animal body weight, hematology and biochemistry studies were analyzed with the software Graph Pad Prism 5 for windows (San Diego, CA, USA). Findings were reported as Mean ± Standard Error of Mean (SEM). One-way analysis of variance (ANOVA) was performed followed by Bonferroni's multiple comparison tests (MCT). The results were considered significant when P-values< 0.05.

3. Results

3.1. Effect of montelukast on body weight and relative organs weight

The body weight was measured before the experiment and prior to sacrifice. The present results showed that there is no statistically significant difference was noted in the final body weights relative liver, lung, kidney and thymus gland also in ovary weight of montelukast group as compared to control group ($P < 0.05$) as in (Figure. 2).

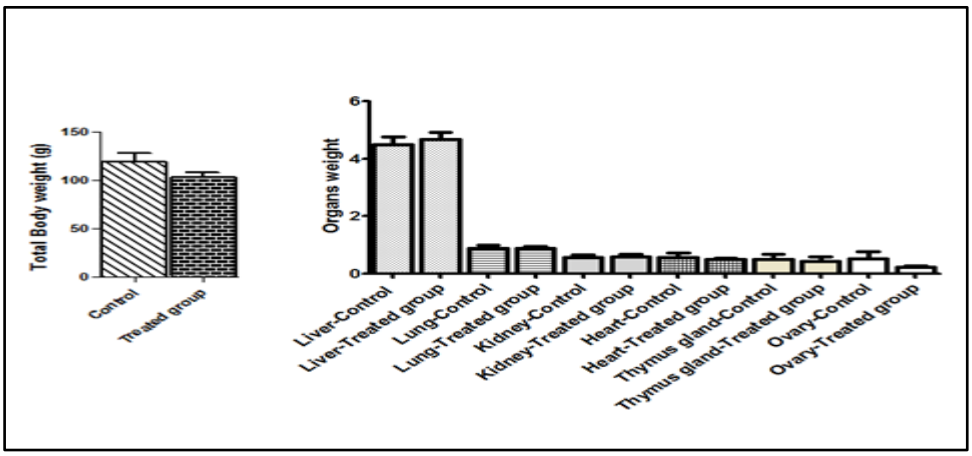

Figure 2. Effect of montelukast on body weight and relative organs weight.

3.2. Hematological evaluation

Hematological investigation was performed to study the effects of montelukat on hematological parameters in rats. The findings of the CBC evaluation showed not observed significant differences in all parameters of montelukat group compared with the control group as in (figure.3A,B &C).

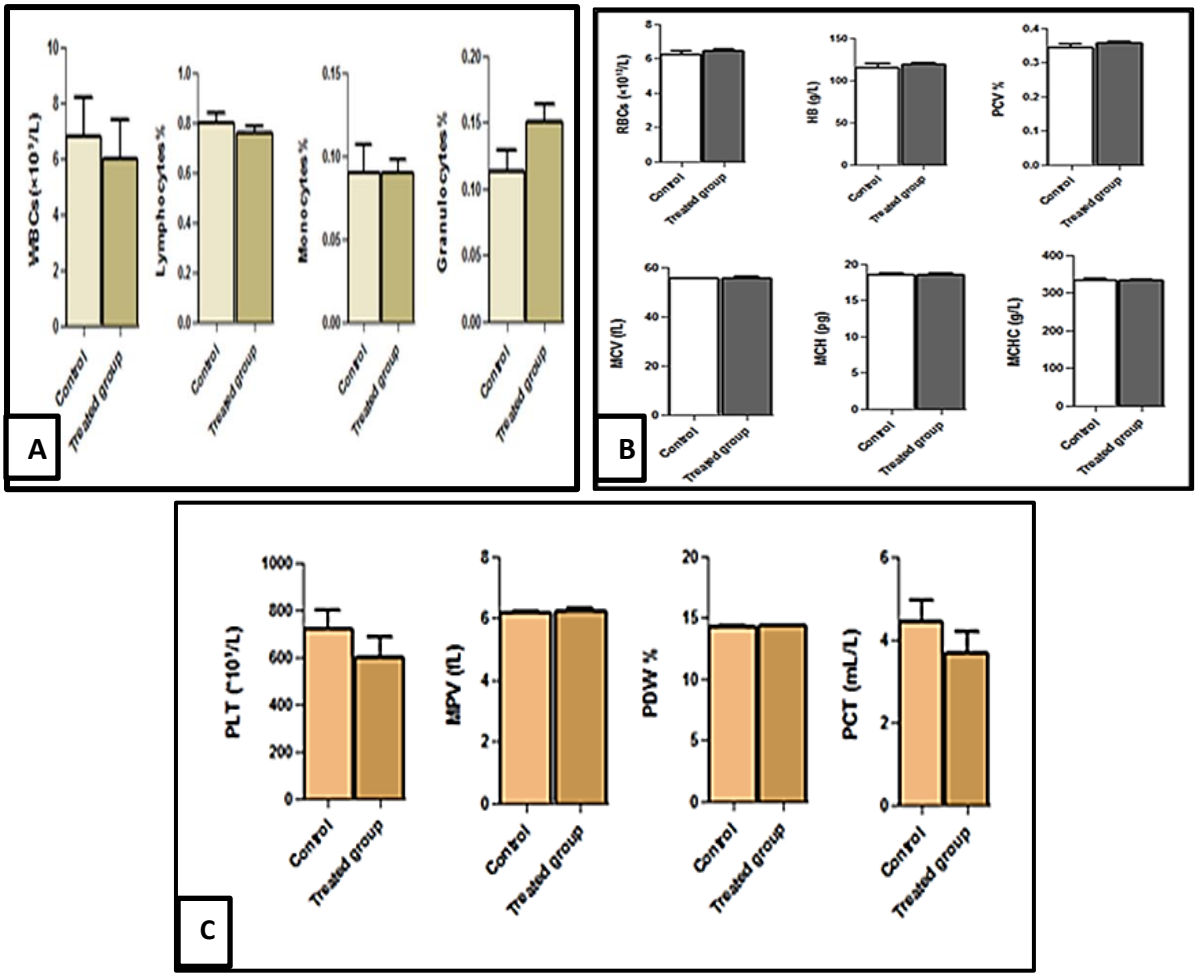

Figure 3. Effect of montelukast on hematological parameters. The picture (A) represent the white blood cells parameters (WBCs, lymphocytes, Monocytes & Granulocytes percent) , picture (B) represent red blood cells parameters (RBCs, HGB, PCV,MCV,MCH & MCHC),picture (C) represent platelets parameters(PLT ,MPV,PDW & PCT).

3.3. Biochemical evaluation

3.3.1. Effect of montelukast on plasma biomarkers of liver injury

The precise liver enzymes including ALT and AST that increase in hepatic diseases and toxic damage of liver cells were assessed in this study. The present results found no significant differences in each serum levels of AST and ALT in montelukast group compared with control (Figure.4).

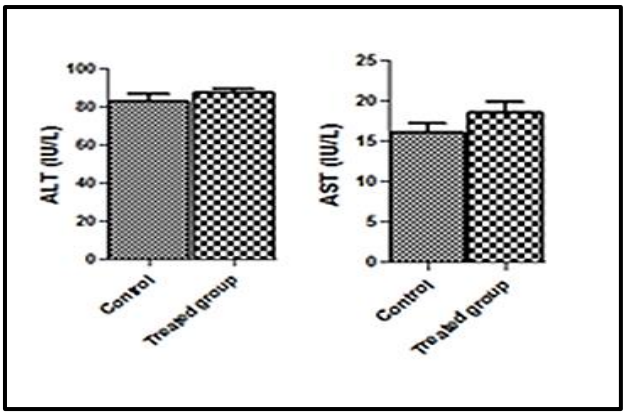

Figure 4. Effect of montelukast on plasma biomarkers of liver injury

3.3.2. Effect of montelukast on serum lipid profiles

Serum lipid concentrations including TC, TG, LDL cholesterol, HD cholesterol and VLDL were investigated to determine the effects of montelukast in experimental rats. The present results showed a significant increased($P < 0.01$) levels of TC and TG in montelukast group compared control group. However, the level of HDL cholesterol was significantly decreased ($P < 0.05$) in rats treated with montelukast compared with control. While the levels of LDL cholesterol and in VLDL not detected significant differences between two groups (Figure. 5).

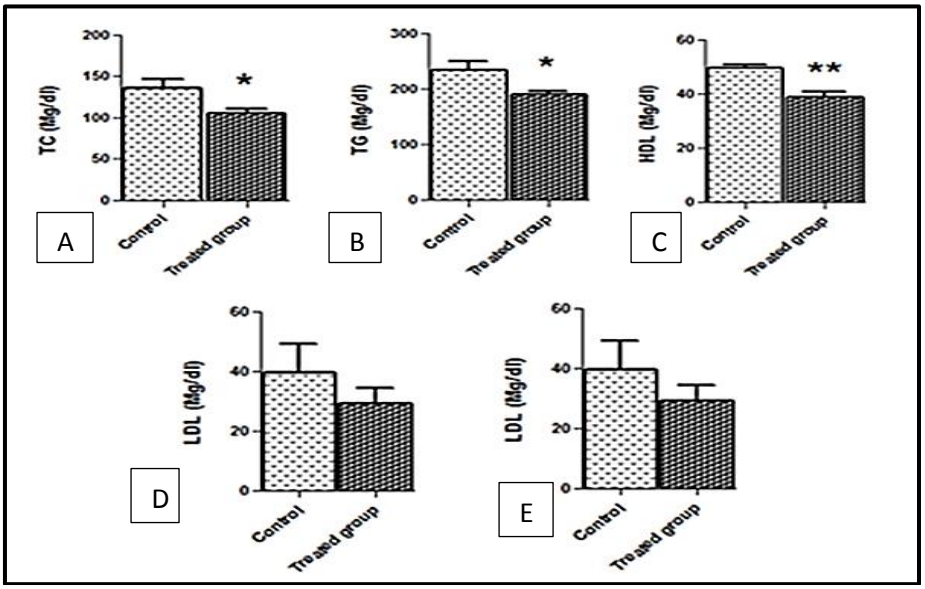

Figure 5. Effect of montelukast on serum lipid profiles. The graphs show the, (A) the total cholesterol (TC), (B) triglycerides (TG), (C) high-density lipoprotein (HDL) cholesterol, (D) low-density lipoprotein (LDL) cholesterol and (E) very low-density lipoprotein (VLDL). One-way ANOVA, Bonferroni's post-test with error bars representing SEM, *$P < 0.05$, **$P < 0.01$ versus control group.

3.4. Organs histopathological evaluation

Histopathological examination of the liver in control group (Fig. 6A) showed intact hepatocytes architecture. While several morphological alterations were observed in rats treated with montelukast. These alterations were manifested by marked empty space or fat vacillation, the hepatic vein was markedly dilated and congested with blood. Also, the hepatic lobe depicted irregular localization of liver (Fig. 6B). Moreover, the photomicrographs of the lung tissue also revealed no evident pathological changes in both treated groups comparing to the control , both showed normal architecture of lung tissue as normal bronchioles and alveoli structure with thin inter-alveolar walls (Figure 7). Histological examination of the kidney tissue in the control group exhibited normal glomeruli, proximal and distal tubules as well as normal thickness of the capillary walls. In contrast, the kidneys' sections of montelukast group illustrated harmful changes including bleeding and congestion in the blood vessels, dilation of the glomerular capillaries, necrosis in the epithelial tissue of tubules, shrinkage of the glomeruli, and enlargement of the Bowman's space (Figure 8).

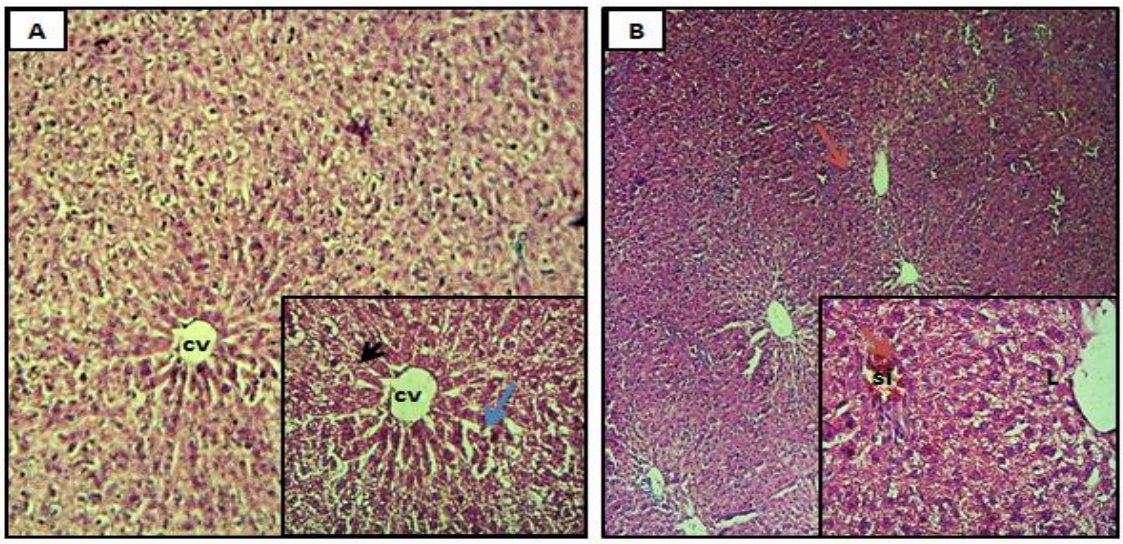

Figure 6. Photomicrographs of the liver tissue in albino rats. *(A) Control group displayed normal liver histology: normal structure of hepatocytes (black arrow) , and normal central vein (cv) also normal sinusoid (blue arrow) (B) montelukast treated group elucidated dilated in central vein and sinusoid infiltration (red arrow) and loss normal structure of hepatocytes (L).Using H&E stain and magnifications 100x and 400x for main and inset images respectively.*

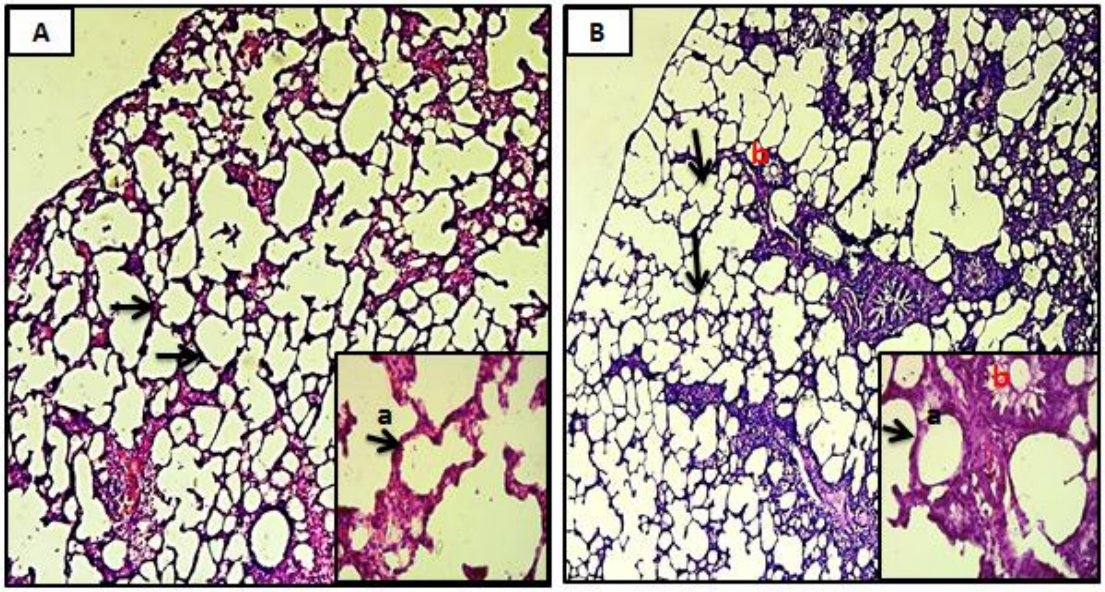

Figure 7. Photomicrographs of the lung tissue in albino rats. *(A) Control group displayed normal lung histology: normal structure of the alveoli enclosed by thin septa (a and black arrow), and normal bronchiole (b). (B) montelukast - treated group elucidated normal structure lung histology as in control group. Using H&E stain and magnifications 100x and 400x for main and inset images respectively.*

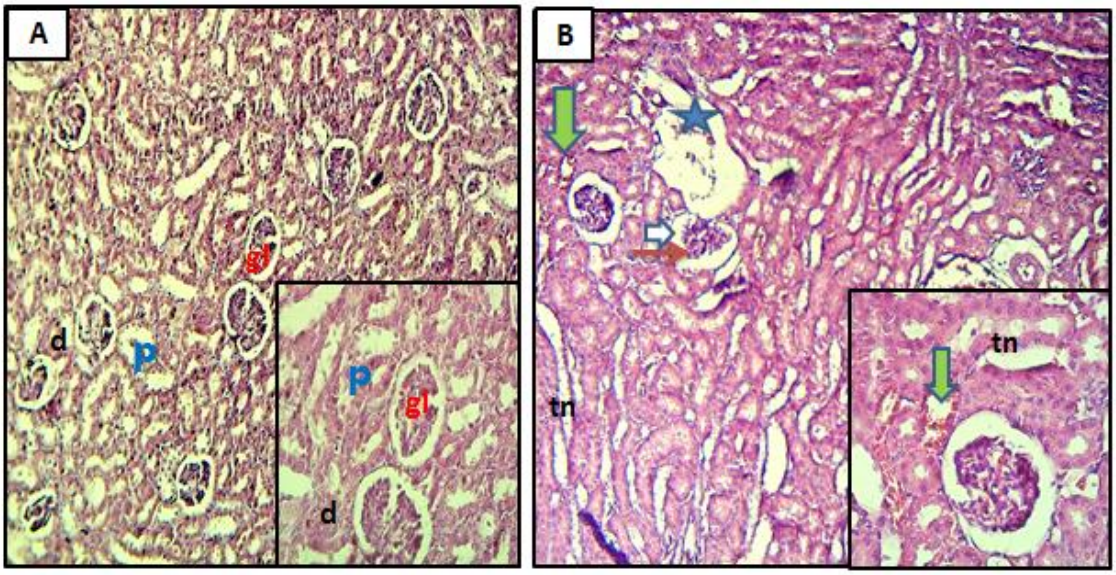

Figure 8. Photomicrographs of the kidney tissue in albino rats. *(A) Control group showed normal kidney histology: normal glomerulus (gl), proximal (p) and distal tubules (d). (B) Montelukast- treated group revealed glomerular shrinkage (red arrow), Bowman's space enlargement (white arrow), and tubular necrosis (tn) , in addition to dilation and congestion in the blood vessels (blue star). Using H&E stain and magnifications 100x and 400x for main and inset images respectively.*

4. Discussion

Montelukast is a prototype, selective, pharmacological antagonist of type 1 cysteinyl-leukotriene receptors (CysLT1Rs). It effectively antagonizes the proasthmatic, proinflammatory, and priming activities of cysteinyl leukotrienes (CysLTs) and forms part of numerous international guidelines

for asthma therapy. Interestingly, recent evidence suggests that montelukast possesses a range of secondary anti-inflammatory activities, apparently unrelated to the antagonism of CysLT1Rs, and also shows antioxidant activity (Tintinger et al.,2010). In the present study, the body weight and organs (liver, kidney, lung, heart, thymus gland and ovary) relative weight did not show any significant changes in rats treated with montelukast . Similar findings were observed in previous studies (Adel et al.,2018).

Also, the hematological analysis showed non-significant differences in whole blood parameter the reason may be due to the short processing time. The results of our current study do not agree with Muslim et al.,2011. The free radicals and reactive oxygen molecules are generated by activated neutrophils, monocytes and other cells during inflammatory processes. In acute inflammation, activated polymorphonuclear leukocytes release lysosomal hydrolytic enzymes, lipid mediators, and reactive oxygen species that may damage the surrounding viable tissues (Noiri et al., 2000). Tugtepe et al. (2007) demonstrated that montelukast attenuated neutrophil recruitment and promoted the resolution of inflammation by antagonizing the effects of leukotrienes, which are potent stimuli for leukocyte infiltration. It has been shown that montelukast acts through the inhibition of neutrophils in several organs targeted by various inflammatory challenges (Sener et al., 2006). The effect of the montelukast on reactive oxygen species (ROS) production in the whole blood (WB) and isolated PMNs,. Biber et al. (2009). The high levels of liver enzymes ALP, ALT and AST are major factors for the development of liver disease (Nanji et al., 1986). The present study showed non-significant increase in the ALT and AST levels in rats treated with montelukast as compared control group, this result agree with et al .,2018. Human studies have shown that CysLTs are involved in the pathogenesis of alcohol intoxication, bile duct obstruction, hepatitis B, hepatorenal syndrome, liver cirrhosis, and other diseases.

Furthermore, experimental data indicate that CysLTs production is increased in CCl4-induced hepatopathy, alcoholic hepatopathy, lipopolysaccharide-induced liver injury, hepatic ischemia/reperfusion (I/R) injury, liver cirrhosis, and liver allograft rejection (Cuciureanu et al.,2009).Hepatic inflammation is an important feature of cholestatic liver disease in both humans and experimental animals. The inflammatory features of obstructive cholestasis include portal tract edema, neutrophil infiltration in the portal tracts, proliferation of the biliary epithelial cells, and portal tract fibrosis (Aller et al.,2008). Moreover, biliary obstruction in rats has been reported to result in a significant depression of the phagocytic function of the reticuloendothelial system (Lechner et al.,1998 and Ding et al.,1994).

Also, the present findings found that the serum lipid concentrations of total cholesterol and triglyceride were decreased in rats treated with montelukast compared with control group. Our result agreed with (Hooman et al .,2007).But differed with (Saibal et al.,2013). Previous study suggesting that montelukast exerts its anti-atherogenic effect through the MCP-1 down regulation (Ge et al.,2009). Becher et al. found that the inhibition of LTC4 activity in mice by montelukast reduces oxidative stress and apoptosis in cardiomyocytes having a beneficial effect on myocardium remodeling after left ventricular injury (2011). Mohamadin et al. (2011) demonstrated that the administration of montelukast protects the liver from lipopolysaccharide-induced oxidative damage, as evidenced by decreased liver marker enzymes, LPO, protein oxidation, and neutrophilic infiltration markers as well as an increased antioxidant cascade.

These results confirmed the protective effect of the lung histopathological changes in montelukast group. While in liver organ, there are some changes, but the most affected organs was the kidney. The present findings suggested

that the continuous treatment with this drug may be caused several health problems such as kidney and hepatic diseases.

5. Conclusions

In conclusion, to the best of our knowledge, this is the first study that highlighted the safe effect of montelukast on each of body weight ,blood parameters, liver function also the lipid profile .However, it has harmful effects on the kidneys. So future studies are needed to replicate this work on asthmatic patients and evaluate the efficacy of montelukast on kidney function.

6. References

- Adel ES, Rania AM, Amany E, Noha Z, Rana E. Protective effect of melatonin versus montelukast in cisplatin-induced seminiferous tubule damage in rats. Andrologia, 2018; Volume50, Issue9: e13077
  https://doi.org/10.1111/and.13077
- Aharony D. Pharmacology of leukotriene receptor antagonists . Am J Respir Crit Care Med. 1998;157:S214-9.
- Al-Amran FG, Hadi NR, Hashim AM. Leukotriene biosynthesis inhibition ameliorates acute lung injury following hemorrhagic shock in rats. J Cardiothorac Surg 2011;6:81.
- Aller MA, Arias JL, Garcia-Dominguez J, Arias JI, Duran M, Arias J. Experimental obstructive cholestasis: the wound-like inflammatory liver response. Fibrogenesis Tissue Repair .2008; 1: 6.
- Al Omari MM, Zoubi RM, Hasan EI, Khader TZ, & Badwan AA. Effect of light and heat on the stability of montelukast in solution and in its solid state: Introduction. Jordan: The Jordanian Pharmaceutical Manufacturing Company,2007.
- Becher UM, Ghanem A, Tiyerili V, Furst DO, Nickenig G, Mueller CF .Inhibition of leukotriene C4 action reduces oxidative stress and apoptosis in cardiomyocytes and impedes remodeling after myocardial injury. J Mol Cell Cardiol . 2011; 50(3): 570–577.
- Benninger MS, & Waters H. Montelukast pharmacology, safety, tolerability and efficacy: cysteinyl leukotrienes.Cleveland, OH, USA:Head and Neck Institute,2009.
- Biber N, Toklu HZ, Solakoglu S, Gultomruk M, Hakan T, Berkman Z, Dulger FG. Cysteinyl-leukotriene receptor antagonist montelukast decreases blood-brain barrier permeability but does not prevent oedema formation in traumatic brain injury. Brain Inj. 2009; 23 (6), 577–584.
- Capra V, Ambrosio M, Riccioni G, Rovati GE. Cysteinyl-leukotriene receptor antagonists: present situation and future opportunities, Curr. Med. Chem. 2006; 13 (26): 3213–3226.
- Carsin H, Bargues L, Stéphanazzi J, Paris A, Aubert P, Le Béver H. Inflammatory reaction and infection in severe burns. Pathol Biol (Paris). 2002;50:93-101.
- Cuciureanu M, Căruntu ID, Păduraru O, et al: The protective effect of montelukast sodium on carbon tetrachloride induced hepatopathy in rat. Prostaglan Other Lipid Mediat 2009; 88: 82–88.
- Daglar G, Karaca T, Yuksek YN, Gozalan U, Akbiyik F, Sokmensuer C. Effect of montelukast and MK-886 on hepatic ischemia-reperfusion injury in rats. J Surg Res 2009;153:31–8.
- Ding JW, Andersson R, Soltesz V, et al: Obstructive jaundice impairs reticuloendothelial function and promotes bacterial translocation in the rat. J Surg Res 1994; 57: 238–245.
- Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 1972; 18:499–502.

- Ge S, Zhou G, Cheng S, Liu D, Xu J, Xu G, Liu X. Antiatherogenic effects of montelukast associated with reduced MCP1 expression in a rabbit carotid balloon injury model. Atherosclerosis. 2009; 205(1):74–79.
- Hoxha M, Rovati GE, Cavanillas AB. The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field, Eur. J. Clin. Pharmacol. 2017;1–11.
- Hegab II , El-Horany HE, Elbatsh MM and Helal DS. Montelukast abrogates prednisolone-induced hepatic injury in rats: Modulation of mitochondrial dysfunction, oxidative/nitrosative stress, and apoptosis. J BiochemMol Toxicol. 2018;e22231:1-7. https://doi.org/10.1002/jbt.22231.
- Hooman A, Jaana H, Won L, Margarete M, Charles GI, David V, Conti and John J L.The Effect of Montelukast and Low-Dose Theophylline on Cardiovascular Disease Risk Factors in Asthmatics. CHEST / 132 / 3 / SEPTEMBER, 2007:868-874.
- Ingelsson E, Yin L, Bäck M, Nationwide cohort study of the leukotriene receptor antagonist montelukast and incident or recurrent cardiovascular disease, J. Allergy Clin. Immun. 2012; 129 (3) : 702–707.
- Lechner AJ, Velasquez A, Knudsen KR, et al: Cholestatic liver injury increases circulating TNF-α and IL-6 and mortality after Escherichia coli endotoxemia. Am J Respir Crit Care Med .1998; 157: 1550–1558.
- Mohamadin AM, Elberry AA, Elkablawy MA, Gawad HS, Al-Abbasi FA. Montelukast, a leukotriene receptor antagonist abrogates lipopolysaccharide-induced toxicity and oxidative stress in rat liver. Pathophysiology.2011; 18: 235–242.
- Muslim MA, Sultan AM, Ali M , Ahmed S, Ali S. Al Tuwajri B. Effects of Montelukast on free radical production in whole blood and isolated human polymorphonuclear neutrophils (PMNs) in asthmatic children . Saudi Pharmaceutical Journal Volume 19, Issue 4, October 2011, Pages 215-220 https://doi.org/10.1016/j.jsps.2011.06.002.
- Mescher, A. L. (2015). Jonquiere's Basic Histology Text and Atlas (14th ed.).
- Nanji AA, French SW, Freeman JB. Serum alanine aminotransferase to aspartate aminotransferase ratio and degree of fatty liver in morbidly obese patients. Enzyme. 1986;36, 266–269. https://doi.org/10.1159/000469304.
- Noiri E, Yokomizo T, Nakao A, Izumi T, Fujita T, Kimura S, Shimizu T. An *in vivo* approach showing the chemotactic activity of leukotriene B(4) in acute renal ischemic–reperfusion injury. Proc. Natl. Acad. Sci. 2000; 97, 823–828.
- National Central For Biotechnology Information. Montelukast, PubChem compound summary for CID 5281040.2012.
- O'Byrne PM. Asthma treatment: antileukotriene drugs. Can Respir J. 1998;5 Suppl A:64A-70A.
- Paul W, Flint B & Haughey K. Cummings Otolaryngology - Head and Neck Surgery E-Book: Head and Neck Thomas Robbins, Niparko, Mark A. Richardson, Marci M. Lesperance:333.
- Saibal D, Somnath M, Jayanta K , Sanjib B , Indranil S, Santanu K. A case of montelukast induced hypercholesterolemia, severe hypertriglyceridemia and

pancreatitis. Journal of Young Pharmacists . 2013;5 :64e66. http://dx.doi.org/10.1016/j.jyp.2013.06.002.

- Sener G, Sehirli O, Velioglu-Ogunc A, Cetinel S, Gedik N, Caner M, Sakarcan A, Yegen BC. Montelukast protects against renal ischemia/reperfusion injury in rats. Pharmacol. Res. 2006; 54, 65–71.
- Sener G, Sehirli Ö, Çetinel S, Ercan F, Yüksel M, Gedik N. Amelioration of sepsis-induced hepatic and ileal injury in rats by the leukotriene receptor blocker montelukast. Prostaglandins Leukot Essent Fatty Acids .2005; 73:453.
- Tintinger GR, Feldman C, Theron AJ, Anderson R. Montelukast: more than a cysteinyl leukotriene receptor antagonist? Sci World J 2010; 10: 2403–2413.
- Tugtepe H, Sener G, Cetinel S, Veliog˘lu-Og˘u¨nc, A, Yeg˘en, BC. Oxidative renal damage in pyelonephritic rats is ameliorated by montelukast, a selective leukotriene CysLT1 receptor antagonist. Eur. J. Pharmacol. 2007; 557 (1), 69–75.
- Wenzel SE. Leukotriene receptor antagonists and related compounds. Can Respir J. 1999;6:189-93.