Faehaa Azher Al-Mashhadane et al /J. Pharm. Sci. & Res. Vol. 11(6), 2019, 2208-2212

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Histopathological effects of chronic use of tramadol on liver and kidney in sheep model.

Faehaa Azher Al-Mashhadane [1], H. Kh. Ismail [2], A. M. Al-Saidya [3],

[1] Department of Dental Basic Sciences, Faculty of Dentistry , Mosul University , Mosul, Iraq. [2,3]Department of Pathology and poultry Diseases, Faculty of Veterinary, Mosul University, Mosul, Iraq.

Abstract

Background: Tramadol " a synthetic analgesic of opioids " is serotonin reuptake blocker. Also it is inhibitor of norepinephrine transporter function.

Objectives: to evaluate the effect of chronic use of tramadol on liver and kidney in sheep model, focusing on histopathological changes.

Material and method: current study was done in the Basic Science Department, Dental College, Mosul University, Iraq. Ten mature healthy male sheep of "10-12 months old" and "body weight of 25±2kg" were incorporated in the study. They were randomly divided into 2 groups, each group consisted of 5 sheep: Group 1: received no any treatment "control group". Group 2: were treated by tramadol hydrochloride in dose of 5 mg/kg/day "treatment group". All animals were sacrificed on day 125. Tissues of liver and kidneys were washed with physiological saline, and fixed with 10% neutral buffered formalin for morphological and histopathological examination. These sections were then examined under a light microscope for histological changes.

Results: Liver sections of treatment group showed several abnormal histological alteration includes congestion and dilatation of central vein and degenerative hepatocytes. Also kidneys demonstrate uneven pathological changes in glomeruli and renal tubules which characterized by swelling of tubular cells , with dilation of inter-tubular blood vessels, degeneration and necrosis in epithelial cells lining the renal tubules, infiltration of inflammatory cells were also observed, with thickening in the blood vessels wall and deposition of collagen fibers in the interstitial tissue around the blood vessels wall.

Conclusion: there are risks of increased hepatic and renal damage due to a long duration use of tramadol. Although its effective in pain management including dental pain, tramadol destructive effects must be considered during the continual treatment.

Key Words: tramadol, sheep, liver, kidney.

INTRODUCTION

Tramadol is analgesic drug with chemical structure of (C16H25NO2). It is action is depend on block of serotonin reuptake and inhibition of norepinephrine transport system. it is weak μ-receptor agonist [1]. It reliefs pain within one hour after intake orally [2]. Tramadol is metabolized in the liver into O- and N-demethylated five different metabolites by cytochrome P450 [3]. The most significant metabolite is O-desmethyltramadol " 200 times the μ- opioid receptors affinity of the parent tramadol molecule " . In the previous few years, tramadol maltreatment is gradually growing. The long term usage of opioids could provoke destruction and apoptosis of tissues like neurons [3].

The major task of liver and kidney in drug kinetics predisposes them to toxic injury. Every drug induced hepatotoxicity almost definitely related to the essential role of the liver in metabolism of that drug which converts it into easily excreted products with lower pharmacologic activity. Although metabolite could have greater activity and/or more toxicity than the parent drug [4]. Also drugs metabolites that are eleminated by kidneys may induce tissue injury causing functional problems in this organ [4]. The work of this study aimed to inspect the sequel of chronic use of tramadol on the liver and kidney in sheep model, focusing on histopathological changes.

MATERIALS AND METHODS

This study was accepted by scientific committee in the Basic Science department , Faculty of Dentistry, Mosul University, Iraq. Fifteen mature male sheep of 10-12 months old and body weight of 25±2kg, were included in the work. Animals were kept in a standard group housing . Clinical examination of animals was done in daily manner by veterinarian until slaughtering. Sheep were divided randomly into 2 groups " 5 animals / group " : Group 1: receive no any treatment " control group ". Group 2: were treated by intramuscular injection of tramadol hydrochloride in dose of 5mg/kg/day " treatment group ". All animals were sacrificed on day 125 and tissues of liver and kidneys were washed with physiological saline, and fixed with 10% neutral buffered formalin for morphological and histopathological examination. They were embedded in paraffin and cut into 5 μm sections, then stained with Masson's Trichrome and hematoxylin-eosin (H&E) stains. These sections were then examined for histological changes by 2 blinded pathologists.

RESULTS

Histopathological examination of liver section of sheep treated with tramadol (Figure 1) showed several histological alteration includes congestion and dilatation of central vein , diffuse of kupffer cells between the sinusoids and degenerative hepatocytes, on other hand infiltration of mononuclear inflammatory cells were observed , dilatation of sinusoids) . Additionally , there was pre-portal fibrosis , with moderate proliferation of fibroblastic cells. Area of hepatocytes necrosis with pyknotic nuclei and karyolitic in other nuclei. Other section showed proliferation of bile ducts also observed

with thickening of the liver capsule, and thickening in the wall of the interlobular blood vessels. Histopathological examination of kidney taken from sheep treated with tramadol (Figure 2) showed variable pathological changes in glomeruli and renal tubules which characterized by swelling of tubular cells and inter-tubular blood vessels dilatation. The alteration in the glomeruli include glomerular tuft lobulation and atrophy leads to expansion of space, degeneration and necrosis of epithelial lining the renal tubules. Also infiltration of inflammatory cells were observed with lobulation of glomeruli and thickening in the blood vessels wall (Vasculitis) with deposition of collagen fibers in the interstitial tissue around the blood vessels wall.

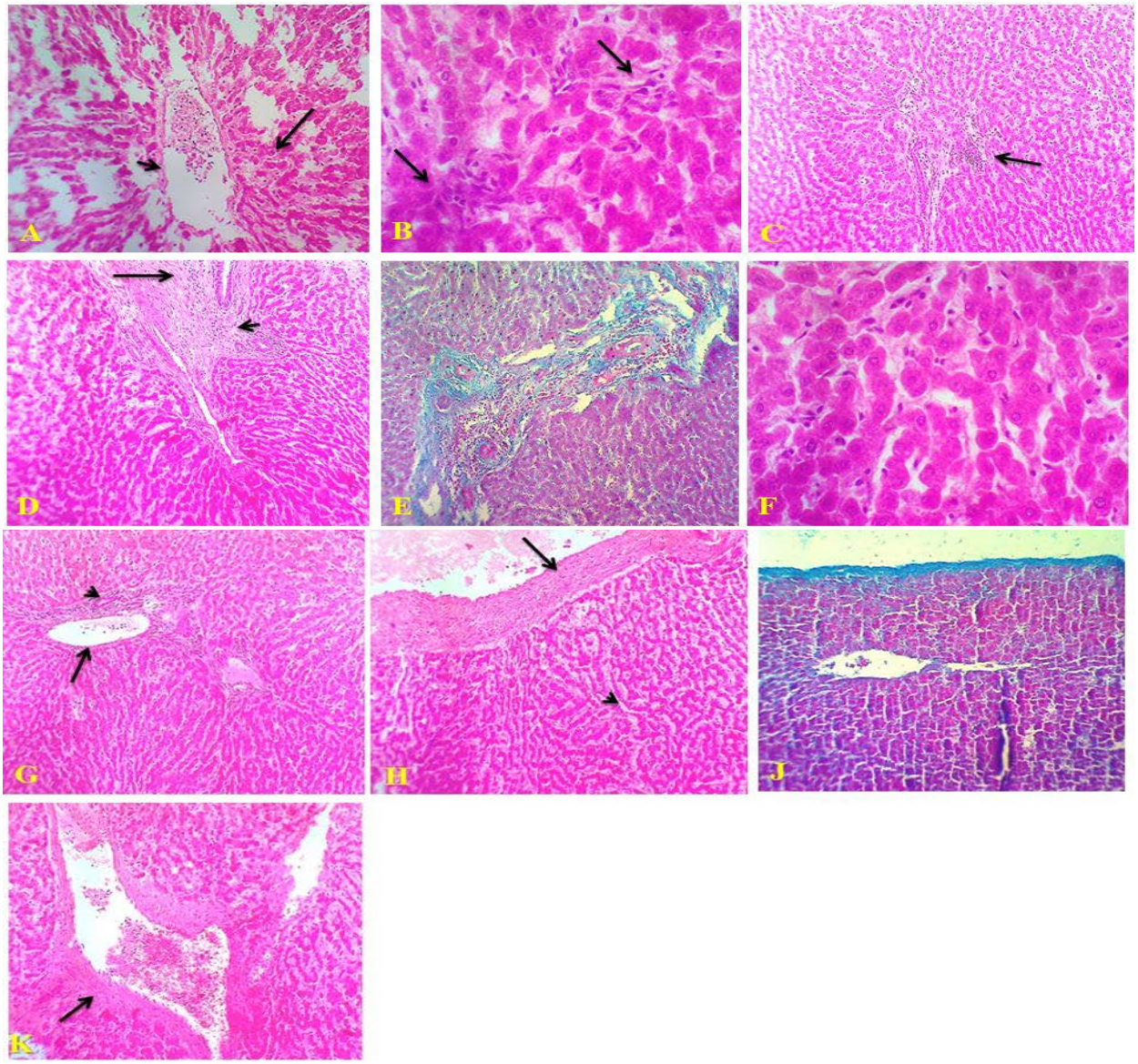

Figure 1: Micrograph of sheep liver , treated with tramadol (A) Dilatation and congestion of central vein (Arrowhead) , Coagulative necrosis of hepatocyte(Arrow) (H&E 10x). (B) Kupffer cells difused between sinosoid (Arrow) (H&E 40x). (C) Infiltration of mononuclear inflammatory cells(Arrow)(H&E10x). (D) Periportal fibrosis (Arrowhead) with infiltration of fibroblast(Arrow) (H&E 10x). (E) Masson's Trichrome stain(10x). (F) Pyknotic and karyolitic of hepatocytes nucleus (H&E 40x) . (G) Proliferation of bile ducts((Arrowhead) and dilatation of portal vein (Arrow) (H&E 10x). (H)Thickening of liver capsule (H&E 10x). (J) Masson's Trichrome stain(10x). (K) Thickening of interlobular blood vessels (Arrow) (H&E 10x).

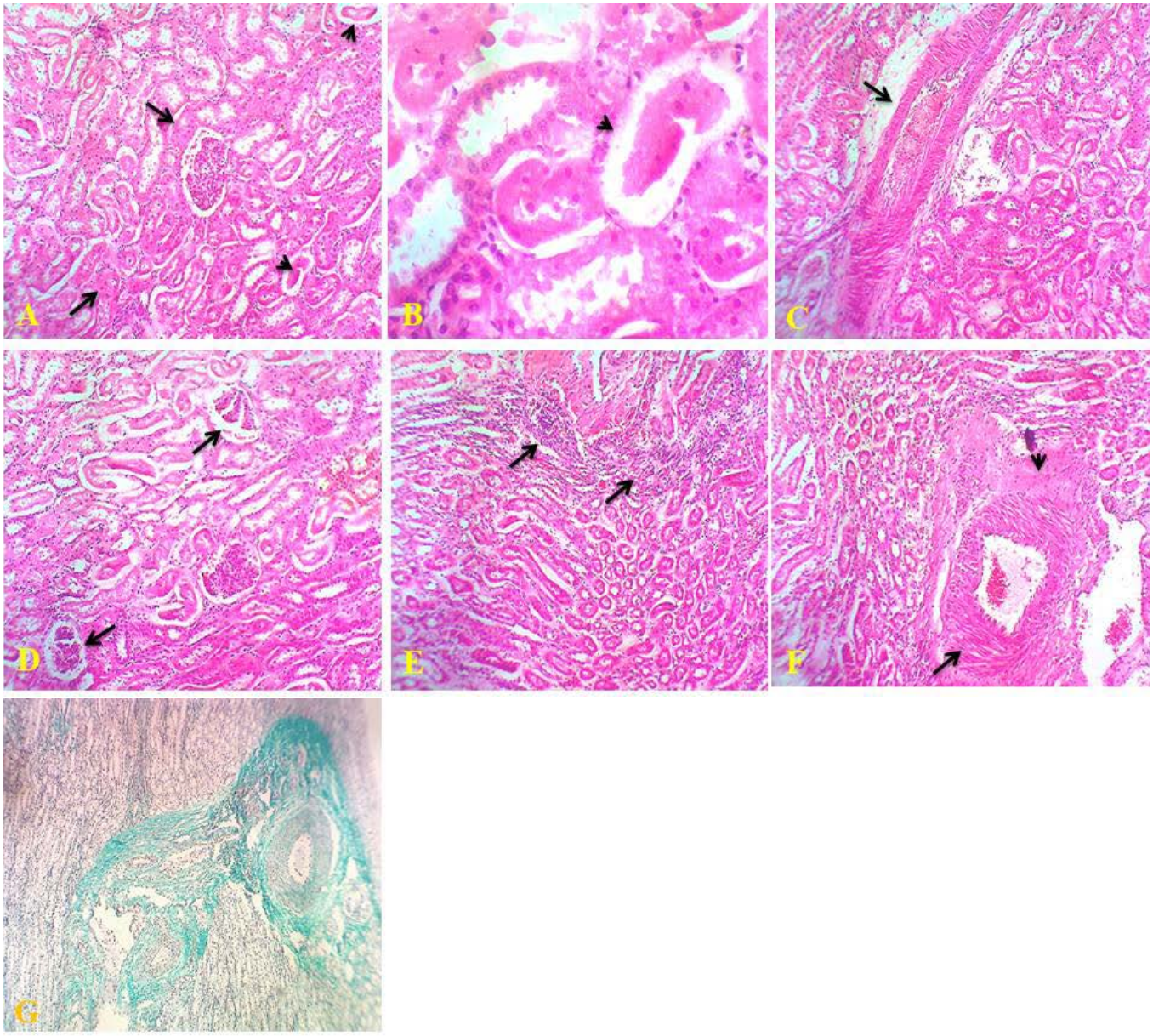

Figure 2: Micrograph of sheep kidney , treated with tramadol (A) Swelling of renal tubules(Arrow) , Necrosis of of renal tubules (Arrowhead) (H&E 10x). (B) , Necrosis of of renal tubules (H&E 40x). (C) Congestion and thickening in the wall of blood vessels (Arrow) (H&E 10x). (D) Lobulation of the glomerular tuff and expansion of Bowman's space(Arrow) (H&E 10x). (E) interstitial infiltration of inflammatory cells (H&E 10x). (F) Vasculitis with thickening of the blood vessels wall (H&E 10x) . (G) Masson's Trichrome stain(10x).

DISCUSSION

Tramadol is synthetic codeine analog with analgesic effect mediated centrally. The antinociceptive effect of tramadol is due to both parent compound and its metabolite (O-desmethylated tramadol) and this metabolite is 4–6 times more potent than the tramadol itself [5,6]. Tramadol is largely prescribed for numerous medical and dental implications for management of moderate to severe pain, but there has been a raising incidence of its misuse, and accordingly in the recorded undesirable reactions and intoxications. however, little is known about its exact mechanisms of toxicity [7] .The present study was performed to assess the effect of choric use of tramadol on both liver and kidney functions in sheep model. Histopathological changes resulted from long term use of tramadol in liver tissues and kidneys were evaluated in sheep model, alterations in central vein and hepatocytesin beside inflammatory cells infiltrate were noticed. Additionally , there was proliferation of fibroblastic cells and areas of hepatocytes necrosis. Other section showed observed thickening of the liver capsule, and thickening in the wall of the interlobular blood vessels. This was in agreement with other studies which revealed severe centrolobular congestion and focal necrosis, disarranged hepatic architecture, hepatic congestion, hemorrhage and necrosis, apoptotic hepatocytes, mononuclear cellular infiltration in the liver after chronic usage of tramadol in rats [8,9].

Histopathological examination of kidney taken from sheep treated with tramadol chronicaal revealed pathological changes in glomeruli and renal tubules with dilatation of inter-tubular blood vessels. Moreover, degeneration and necrosis in epithelial cells lining the renal tubules, With infiltration of inflammatory cells were observed also thickening in the blood vessels wall (Vasculitis) with deposition of collagen fibers in the interstitial tissue around the blood vessels wall .all these finding was in agreement with other study that describe vacuolization in tubular cells and kidney damage after long term use of opioids [8]. These histopathological changs in both liver and kidney could be related to mitogen activated protein kinase pathway (MAPK) protein expression in tissues, oxidative stress, and apoptosis signaling pathways [7,10,11]. On other hand, the dose of tramadol should be adjusted in the existence of liver and kidney diseases to allow normal metabolism and excretion of this drug [12,13]. In disagreement with these results, Mahmoud MF et al [2016] evaluate the hepatoprotective effects of tramadol on hepatic I/R, they suggest that tramadol has a beneficial role in the protection of liver from I/R injury during liver transplantation and hepatic resection after short term (single dose) use [6]. Many researchers have referred to the relation between the intake of opioids and greater synthesis of reactive oxygen species " ROS " [14-18]. Oxidative stress is defined as an discrepancy between ROS synthesis and the capacity of antioxidant to counteract them. High concentrations of reactive intermediates initiate cellular destructions with formation of secondary toxic compound. Nuclear factor-kappa B " NF-κB " can be activated by ROS; which then activates inflammatory genes transcription and consequent formation of numerous inflammatory mediators [19]. In accordance, a recent study conducted by H.M. Mohamed et al demonstrate the pro-oxidant effect of continual tramadol intake demonstrated by the significant increase in the levels of MDA and NO in the cerebrum of rats [20]. Also opioid pro-oxidant effect has been reported in the tissues of liver and kidney in mouse model [14,15]. Bameri et al offered a proof that dopaminergic system is implicated in oxidative damage induced by tramadol [21]. A single injection of tramadol intravenously " 25 mg/kg " result in considerable increase in mitochondrial ROS production, peroxidation of protein and lipid and mitochondria GSH reduction in the brain tissue of mice model. These results recommended that tramadol-induced oxidative stress is connected with dysfunction of mitochondria [21]. Also, the dopamine D2 receptors inhibition caused reduction in mitochondrial dysfunction and oxidative stress of tramadol. On other hand, their stimulation cause reduction in GSH contents, indicating the function of dopaminergic system in mediating the role of tramadol in mice brains [21]. Both oxidative stress and inflammation can take action in the induction of cell death through apoptosis [22,23,24,25]. Accordingly, oxidative stress and inflammation induced by tramadol were connected with considerable, dose dependent up-regulation of gene and protein expression of the pro-apoptotic markers [26,27, 28]. Tramadol can act by inhibition the reuptake of Norepinephrine and improve the release of 5-HT [29], and this lead to significant increase in NE and 5-HT levels. Panadanabiona has newly reported elevated levels of E, NE, DA and 5-HT in the cerebral cortex of rats 72 h after acute SC injection of tramadol [30]. Although opioids are being widely used since very long time, their chronic effects particularly at molecular and cellular levels are not obviously explained. The impacts of tramadol on the liver and kidney need to be demonstrated [31,32]. So, the present study intended to examine the effects of chronic use of tramadol on the these tissues.

CONCLUSION

This study referred to the increased risk of liver and kidney damage due to the use of tramadol over long period. Opioids are reported to be effective in management of medical and dental pain, but their adverse toxic reactions must be taken into consideration. Focused attention by the dental and medical communities is required.

REFERENCES

1. Fayhaa AM Al – Mashhadane, Ghada Abdul-Rhman Taqa, Tahani A. AL-Sandook.(2013). Effects of tramadol on serum alkaline phosphatase, bone morphogenetic protein 2 and healing of dental implants in sheep model. International Journal of Pharmaceutical, Biological and Chemical Sciences (IJPBCS), 2 (4):13-19.
2. Katz, W.A.(1996). Pharmacology and clinical experience with tramadol in osteoarthritis. Drugs, 52 (3) : 39–47.
3. Leppert, W.(2011).CYP2D6 in the metabolism of opioids for mild to moderate pain, Pharmacology, 87 (5-6): 274–285.
4. Atici S, Cinel I, Cinel L, Doruk N, Eskandari G and Oral U.(2005). Liver and kidney toxicity in chronic use of opioids: An experimental long term treatment model; J. Biosci, 30: 245–252.
5. 5- Elmanama , AA. Abu Tayyem , Noor E. S. Essawaf , Hend N. Hmaid , Ikram M..(2015). Tramadol-Induced Liver and Kidney Toxicity among Abusers in Gaza Strip , Palestine. Jordan Journal of Biological Sciences, 8(2): 133-137.
6. Mona F. Mahmoud, Samar Gamal, Mohamed A. Shaheen, and Hassan M. El-Fayoumi.(2016).The effects of tramadol on hepatic ischemia/reperfusion injury in rats; Indian J Pharmacol, 48(3): 275–280. doi: [10.4103/0253-7613.182882].
7. Barbosa J, Faria J, Leal S, Afonso LP, Lobo J, Queirós O, Moreira R, Carvalho F, Dinis-Oliveira RJ. (2017).Acute administration of tramadol and tapentadol at effective analgesic and maximum tolerated doses causes hepato- and nephrotoxic effects in Wistar rats. Toxicology, 15(3)89:118-129. doi: 10.1016/j.tox.
8. Atici, S., Cinel, I., Cinel, L.(2005). Liver and kidney toxicity in chronic use of opioids: An experimental long term treatment model. J Biosci, 30(2):245-52. https://doi.org/10.1007/BF02703705.
9. Omar NM, Mohammed MA. (2017).The impact of black seed oil on tramadol-induced hepatotoxicity: Immunohistochemical and ultrastructural study. Acta Histochem, 119(5):543-554.doi: 10.1016/j.acthis.2017.05.008.
10. Sadek KM, Lebda MA, Abouzed TK, Nasr SM, El-Sayed Y. (2018).The molecular and biochemical insight view of lycopene in ameliorating tramadol-induced livertoxicity in a rat model: implication of oxidative stress, apoptosis, and MAPK signaling pathways.Environ Sci Pollut Res Int, 25(33):33119-33130. doi: 10.1007/s11356-018-3265-7.
11. Arafa MH, Atteia HH. (2018).Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6) are associated with long term tramadol treatment-induced oxidative damage and hepatotoxicity. Toxicol Appl Pharmacol, 1(346): 37-44. doi: 10.1016/j.taap.

12. Mohammadi S, Nezami A, Esmaeili Z, Rouini MR, Ardakani YH, Lavasani H, Ghazi-Khansari M. (2018).A Disposition Kinetic Study of Tramadol in Intoxicated Rats Induced by Ethanol and Acetaminophen in Perfused Rat Liver Model. , 21. pii: S0741-8329(18)30107-1. doi: 10.1016/j.alcohol.2018.09.006.
13. Esmaeili Z, Mohammadi S, Nezami A, Rouini MR, Ardakani YH, Lavasani H, Ghazi-Khansari M. (2017). A disposition kinetic study of Tramadol in bile duct ligated rats in perfused rat liver model. Biomed Pharmacother, 91:251-256. doi: 10.1016/j.biopha.
14. Bameri B., Shaki F., Ahangar N., Ataee R., Samadi M., Mohammadi H. (2018). Evidence for the involvement of the dopaminergic system in seizure and oxidative damage induced by tramadol, Int. J. Toxicol, 37 (2):164–170.
15. Abdel-Zaher AO., Abdel-Rahman MS. , Elwasei FM. (2011).Protective effect of Nigella sativa oil against tramadol-induced tolerance and dependence in mice: role of nitric oxide and oxidative stress, NeuroToxicology, 32 (6): 725–733.
16. Mohamed TM., Ghaffar HM., El Husseiny RM.(2015). Effects of tramadol, clonazepam, and their combination on brain mitochondrial complexes. Toxicol. Ind. Health, 31(12):1325–1333.
17. 1S. Atici, I. Cinel, L. Cinel, N. Doruk, G. Eskandari, U. (2005).Oral, Liver and kidney toxicity in chronic use of opioids: an experimental long term treatment model. J. Biosci, 30(2):245–252.
18. Zhang YT., Zheng QS., Pan J., Zheng RL.(2004). Oxidative damage of biomolecules in mouse liver induced by morphine and protected by antioxidants. Basic Clin. Pharmacol. Toxicol, 95 (2): 53–58.
19. Bonizzi G., Karin M. (2004).The two NF-kappaB activation pathways and their role in innate and adaptive immunity, Trends Immunol, 25(6) : 280–288.
20. Mohameda HM., Mahmoud AM. (2019).Chronic exposure to the opioid tramadol induces oxidative damage, inflammation and apoptosis, and alters cerebral monoamine neurotransmitters in rats. Biomedicine & Pharmacotherapy, 110: 239–247.
21. Bameri B., Shaki F., Ahangar N., Ataee R., Samadi M., Mohammadi H. (2018). Evidence for the involvement of the dopaminergic system in seizure and oxidative damage induced by tramadol. Int. J. Toxicol, 37 (2):164–170.
22. Mahmoud AM., Hussein OE., Hozayen WG., Abd El-Twab SM.. (2017). Methotrexate hepatotoxicity is associated with oxidative stress, and down-regulation of PPARgamma and Nrf2: protective effect of 18beta-glycyrrhetinic acid, Chem. Biol. Interact, 270: 59–72.
23. Mahmoud AM., Abd El-Twab SM., Abdel-Reheim ES. (2017). Consumption of polyphenol-rich Morus alba leaves extract attenuates early diabetic retinopathy: the underlying mechanism. Eur. J. Nutr, 56 (4) :1671–1684.
24. Mahmoud AM., Hozayen WG., Ramadan SM.. (2017).Berberine ameliorates methotrexate- induced liver injury by activating Nrf2/HO-1 pathway and PPARgamma, and suppressing oxidative stress and apoptosis in rats, Biomed. Pharmacother, 94 :280–291.
25. Juliana Faria , Joana Barbosa , Sandra Leal , Luís Pedro Afonso , João Lobo , Roxana Moreira , Odília Queirós , Félix Carvalho , Ricardo Jorge Dinis-Oliveira. (2017). Effective analgesic doses of tramadol or tapentadol induce brain, lung and heart toxicity in Wistar rats. Toxicology, 385(15) :38-47.
26. Ibrahim MA, Salah-Eldin AE. (2019).Chronic Addiction to Tramadol and Withdrawal Effect on the Spermatogenesis and Testicular Tissues in Adult Male Albino Rats. Pharmacology, 103(3-4):202-211. doi: 10.1159/000496424.
27. Aboulhoda BE, Hassan SS. (2018).Effect of prenatal tramadol on postnatal cerebellar development: Role of oxidative stress. Chem J. Neuroanat. Dec;94:102-118. doi: 10.1016/j.jchemneu 10.002.
28. Manar Hamed Arafa , Hebatallah Husseini Atteia. (2018).Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6) are associated with long term tramadol treatment-induced oxidative damage and hepatotoxicity. Toxicology and Applied Pharmacology, 3(46):37-44.
29. Hoyer D., Clarke DE., Fozard JR., Hartig PR., Martin GR., Mylecharane EJ., Saxena PR., Humphrey PP. (1994).International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin), Pharmacol. Rev. 46 (2):157–203.
30. Panadanabiona SC. (2017).Alterations in aminergic system of rat brain by the opioid analgesic tramadol in the absence of pain-induction, Int. J. Basic Clin. Pharmacol, 6 (12) : 2774.
31. Sadek KM., Lebda MA., Abouzed TK., Nasr SM., Yasser EL-Sayed. (2018).The molecular and biochemical insight view of lycopene in ameliorating tramadol-induced liver toxicity in a rat model: implication of oxidative stress, apoptosis, and MAPK signaling pathways Environmental Science and Pollution Research. 25(33): 33119–33130.
32. Sheweita SA, Almasmari AA, El-Banna SG. (2018). Tramadol-induced hepato- and nephrotoxicity in rats: Role of Curcumin and Gallic acid as antioxidants. PLoS ONE,13(8): e0202110.