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Research Article

Effect of ibuprofen on histological parameters of the liver in male albino rats

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Abstract
The present work was conducted to study the effect of ibuprofen (IBU) on histological parameters of male rats' liver for 30 and 60 days following oral administration. Fifty albino male rats are used in this study and they divided into five treatments each including five rats as control group, group administrated with 10mg/kg/day, group administrated with 20mg/kg/day, group administrated with 30mg/kg/day and group administrated with 40mg/kg/day of ibuprofen. The male rats were randomly divided into two main groups, comprising twenty-five rats for each group. The first main group was treated for 30 days and the second main group for 60 days. The animals were treated for 30 and 60 days following oral administration of 10, 20, 30, and 40mg/kg/day. The histological sections of the liver of the treatments at doses of 10, 20, 30, and 40mg/kg/day for 30 and 60 days showed high histopathological changes and their severity had raised by increasing concentration and exposure time.

Keywords: Drug, Histology, NSAID, Anti-inflammatory.

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Introduction

Ibuprofen is a highly effective nonsteroidal anti-inflammatory medicine (NSAID) that treats various ailments, including rheumatoid arthritis, osteoporosis, dysmenorrhea, and gout (Adebambo & Haji 2021). Severe pain related to local inflammation is ideal for sedative usage. This compatibility can be obtained with a dose of 400mg of ibuprofen at the very least (Hale 2020), which is considered an acceptable dose, especially without consulting a physician by established norms. This model is compatible with the dental extraction model or stimuli-induced acute pain model in which the dose size is time-dependent (Hocevar et al. 2019).

The immune response's evident mediators, such as T and B leukocytes, which are released as a precursor to immunological activity, are proportionate to the key circumstances of acute inflammation, and subsequently, transition to chronic inflammation, such as rheumatoid arthritis (Tu et al. 2021). Ibuprofen was thought to directly affect several cellular mediators and reaction pathways, resulting in soft-tissue inflammation, joint-annihilation enzyme, and osteoarthritis (Rainsford 2013; Mesripour & Gasemi 2021).

This medicine has therapeutic effects as an anti-tumorigenic and neuroprotective agent by inhibiting cyclic anti-oxidant enzymes (e.g. COX-1 and COX-2) (Litchfield 2020) while indicating the hazards associated with the digestive system and other essential organs under the speculative reach of study, such as the liver, to determine the range of potential future damage (Upadhyay et al. 2021). Several researchers found that in rats, the content of propionic acids such as ibuprofen in plasma and tissues was highest in hepatic tissue since it is

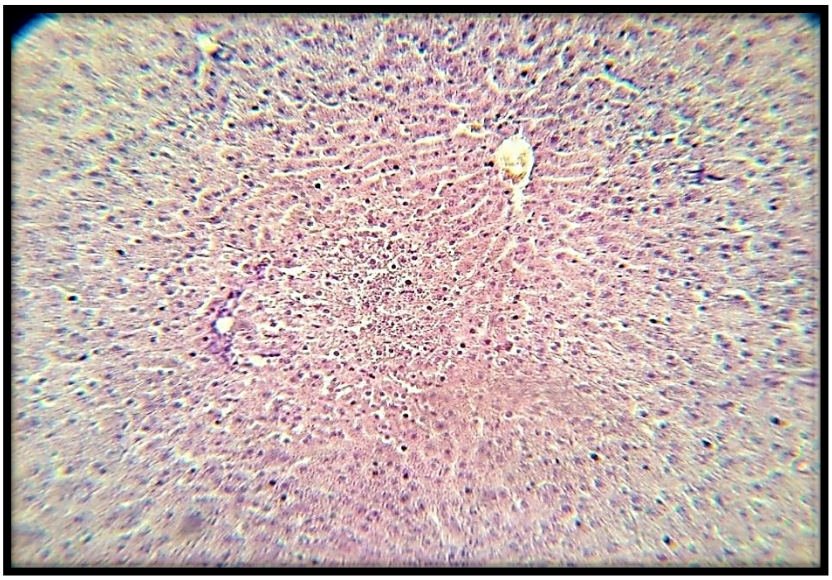

Fig.1. Cross section of the liver in control group showing no significant occupied lesion (SOL) (H&E, 100x).

metabolized there (Pirat et al. 2012; Mulkiewicz et al. 2021). Therefore, this work aimed to study the effect of IBU on histological parameters of male rats' liver for 30 and 60 days following oral administration.

Materials and Methods

A total of 50 male albino rats (*Rattus rattus*) weights 200-250g were obtained from the animal house of the Faculty of Science, University of Kufa. The rats were kept in plastic cages with metal covers (42x25cx15cm). The animals were maintained under suitable laboratory conditions with a temperature of 20-25Cº and light/dark cycle of 10/14, ventilation rate time/hour 10-15, and relative humidity of 30-70%.

The treated groups were administrated with 600mg ibuprofen (Degirmenci et al. 2019) and calculated based on the weight of the rats. An experimental dose of the ibuprofen drug was prepared by dissolving in normal saline (N.S) (Kovačević et al. 2018). The ibuprofen was obtained from Ajanta House (Charkop, Kandivli, Mumbai, 400 067, India) at a dose of 200mg/kg.

The treatments were as follow: (1) group administrated with 1ml of normal saline per day as the control group, (2) Group administrated with 10mg/kg of 1ml from prepared solution per day, (3) group administrated with 20mg/kg of 1ml the prepared solution per day, (4) group administrated 30mg/kg of 1ml the prepared solution per day, and (5) group administrated 40mg/kg of 1ml the prepared solution per day.

Animals were sacrificed at the end of the experiment using ketamine: Xylazine (90mg/kg: 10mg/kg intraperitoneal). The ketamine 0.5ml and xylazine 0.1ml were used as 250g of body weight for anesthesia, and their kidney were fixed into 10% formalin after dissection of the specimens (Al-Tameemi et al. 2014). For histological preparations**,** all fixed samples in 10% formalin were processed and stained according to Obayes (2019).

Results

The histopathological examination of male rats' liver showed mild to severe changes in liver at the doses of 10, 20, 30, and 40mg/kg/day for 30 days (Figs. 2, 3, 4, 5) of ibuprofen compared to control group (Fig. 1). The hepatocytes, hepatic degeneration, bleeding in the hepatic vasculature, and white blood cell (neutrophil) aggregation were observed with increasing drug doses. These alternations were also observed at 60 days, and the hepatic blood vessel congestion and necrosis in some areas were extra

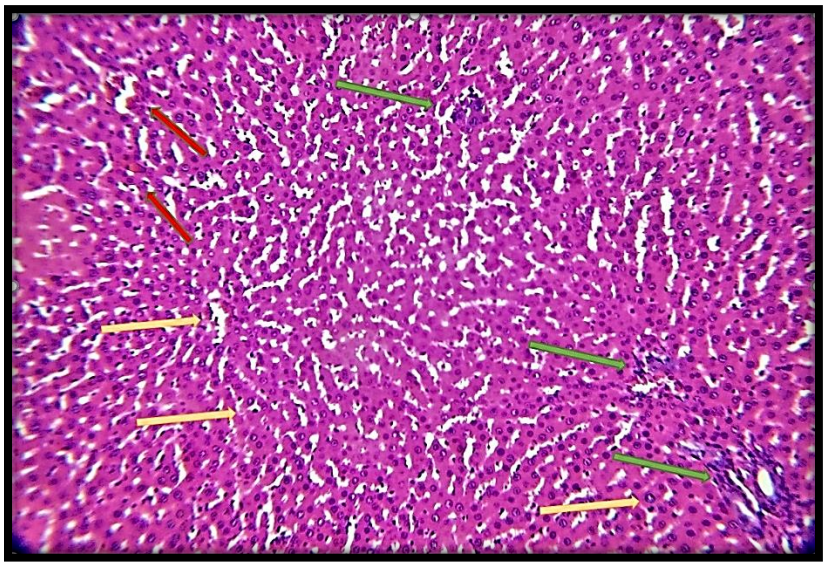

Fig.2. Cross section of the liver treated with 10mg/kg/day for 30 days shows hemorrhage (red arrow) degeneration of hepatocyte necrosis (yellow arrow) inflammation (neutrophil) (green arrow) (H&E, 100x).

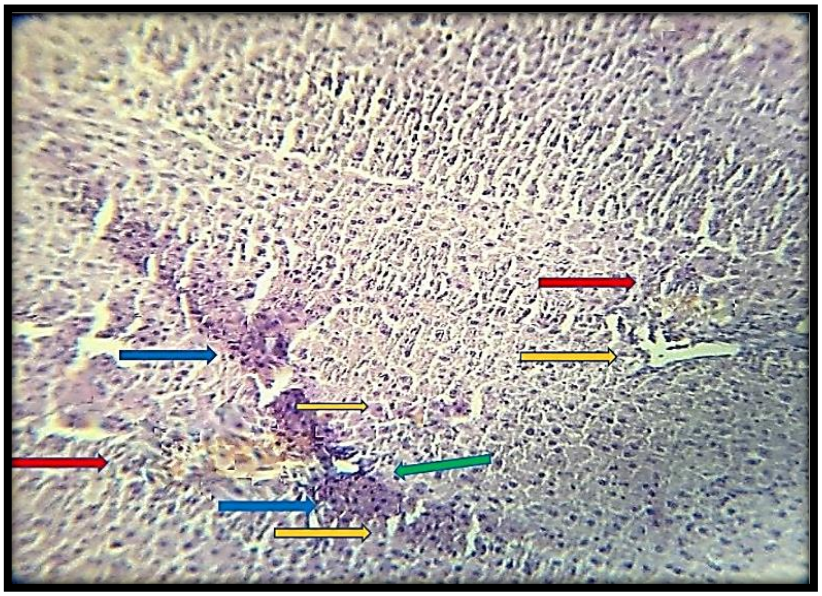

Fig.3. Cross section of the liver treated with 20mg/kg/day for 30 days shows degeneration of hepatocytes (necrosis) (yellow arrow), fibrosis (blue arrow), inflammation (green arrow), hemorrhage (red arrow) (H&E, 100x).

histopathological changes at 60 days (Figs. 6, 7, 8, 9).

The rats administrated with 30mg/kg/day for 30days showed similar alternations but more severe compared to lower doses. They had congestion of the blood vessels and vacuolar degeneration in hepatocytes (Fig. 4). In 60 days, the same doses showed severe congestion of blood vessels and perivascular leukocytes cuffing in size and number in addition to enlargement nuclei of hepatocytes (Fig. 8). The rats administrated with 40mg/kg/day for 30 days displayed an extensive inflammatory reaction of mononuclear cells (macrophages, lymphocytes, and neutrophils) and necrosis (Fig. 5), while in 60 days, all histopathological changes were observed as well as hepatic hemorrhage (Fig. 9), in comparison with the control group that had no histopathological issue in their livers (Fig. 1).

Discussion

The present study showed that administration of

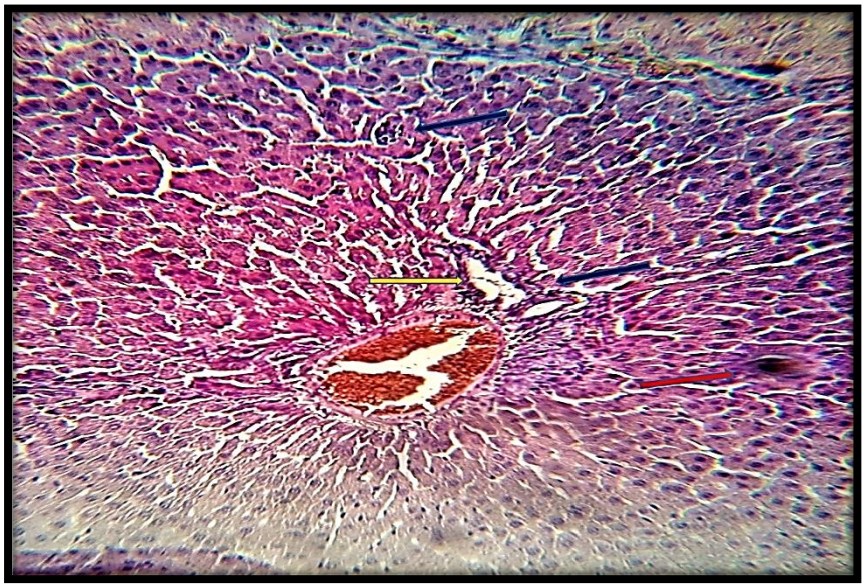

Fig.4. Cross section of the liver treated with 30mg/kg/day for 30 days shows degeneration of hepatocytes (yellow arrow) hepatic blood vessels congestion (red arrow) inflammation (blue arrow) (H&E, 100x).

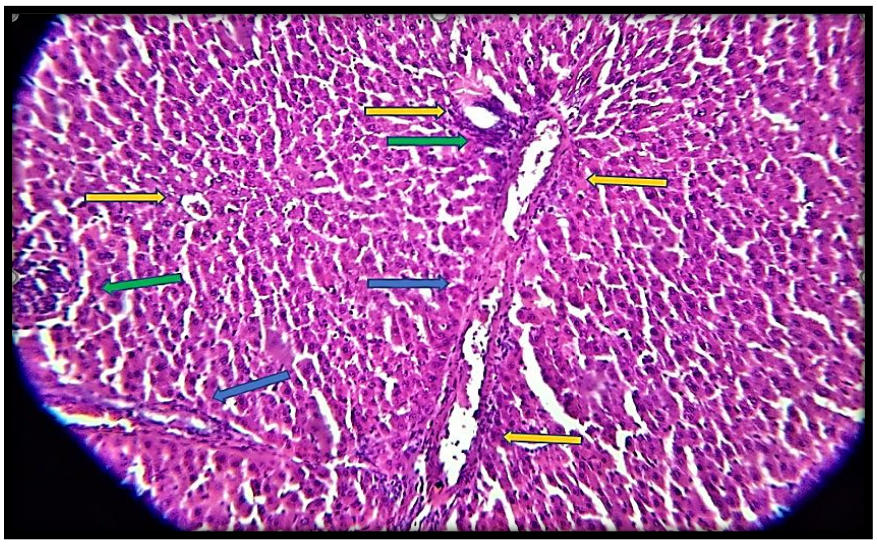

Fig.5. Cross section of the liver treated with 40mg/kg/day for 30 days shows hepatic blood vessels congestion (red arrow) necrosis (yellow arrow) (H&E, 100x).

ibuprofen as 10, 20, 30, and 40mg/kg/day for 30 and 60 days was caused histopathological changes in the liver whose severity was proportional to the concentration of ibuprofen and time of administration. The congestions and hemorrhages in the central vein, degeneration of hepatocytes, extensive inflammatory reaction composed of mononuclear cells, necrosis, and vacuolar degeneration of hepatocytes were observed in the treated animals.

These histopathological changes were to previous studies (Xie et al. 2018; Mohammed et al. 2019). Changes in the liver cell are caused by toxic hypoxia by ibuprofen and other anti-inflammatory non-steroid drugs (Zoubek et al. 2019; Ogunwole et al. 2021). These histological changes showed the severity of the high ibuprofen concentrations as 40 mg/kg/day for 30 and 60 days i.e. ibuprofen has the potential to cause progressive liver cell damages because it is the first organ in the ibuprofen metabolism including hydroxylation of the eco-toxicant molecule (compound 1) to form 9-

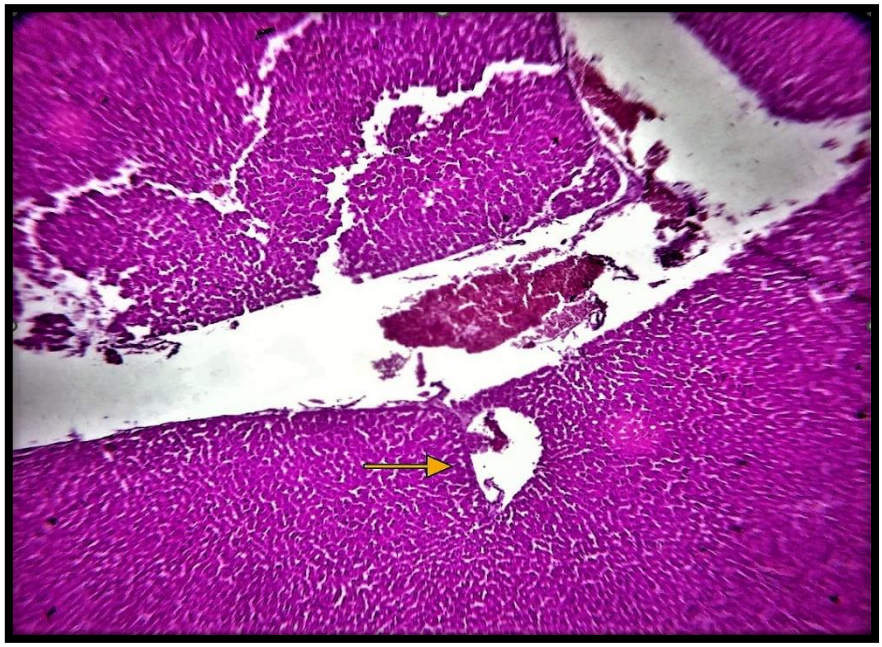

Fig.6. Cross section of the liver treated with 10mg/kg/day for 60 days shows vacuolar degeneration of hepatocytes (yellow arrow) with pre- vascular leukocytes cuffing (H&E, 100x).

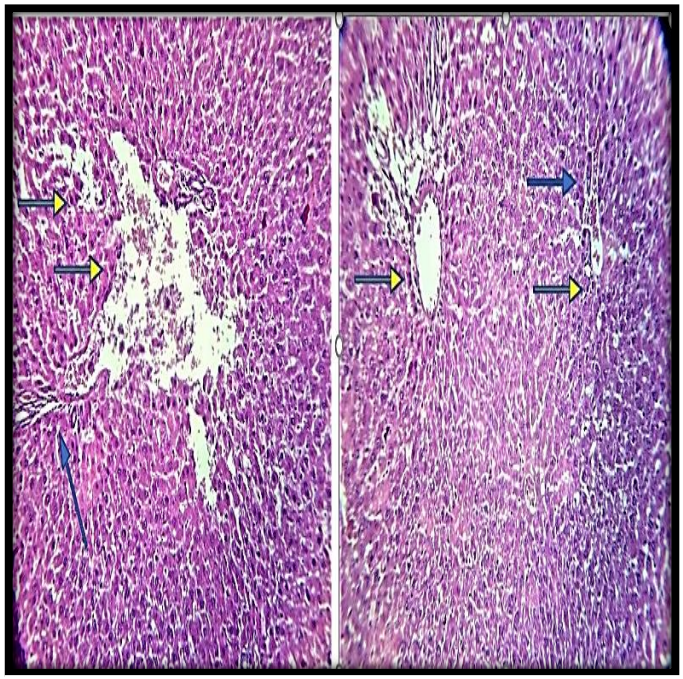

Fig.7. Cross section of the liver treated with 20mg/kg/day for 60 days shows an extensive inflammatory reaction composed of mononuclear cells (macrophages, lymphocytes and neutrophils) (blue arrow) also there was extensive necrosis extending from central zone to midzone or further to portal triad and vacuolar degeneration of hepatocytes (yellow arrow) (H&E, 100x).

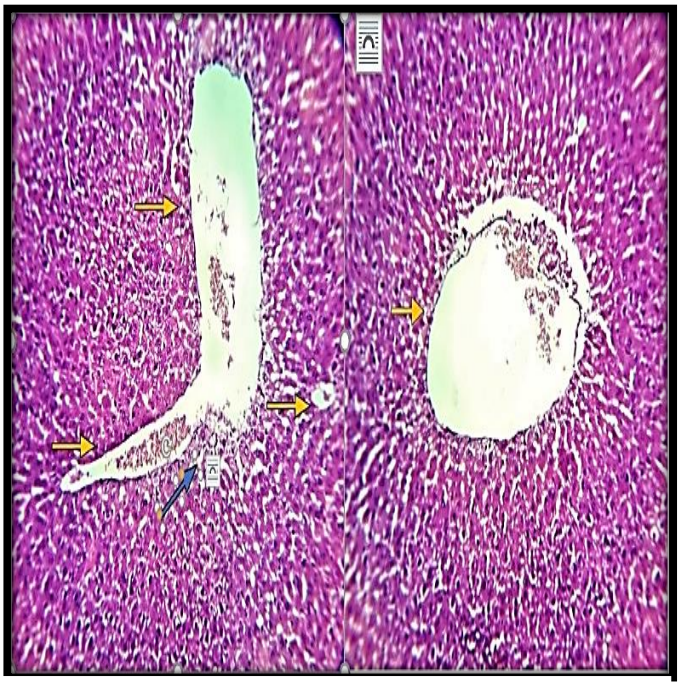

Fig.8. Cross section of the liver treated with 30mg/kg/day for 60 days shows the extensive necrosis extending from central zone to midzone or further to portal triad and vacuolar degeneration of hepatocytes (yellow arrow) also inflammatory reaction (blue arrow) (H&E, 100x).

hydroxyibuprofen (compound 3), 2,6-dihydroxy ibuprofen (compound 4), and 6-hydroxy ibuprofen (compound 5) and by their subsequent decarboxylation (González-Ponce et al. 2018; Ivshina et al. 2021).

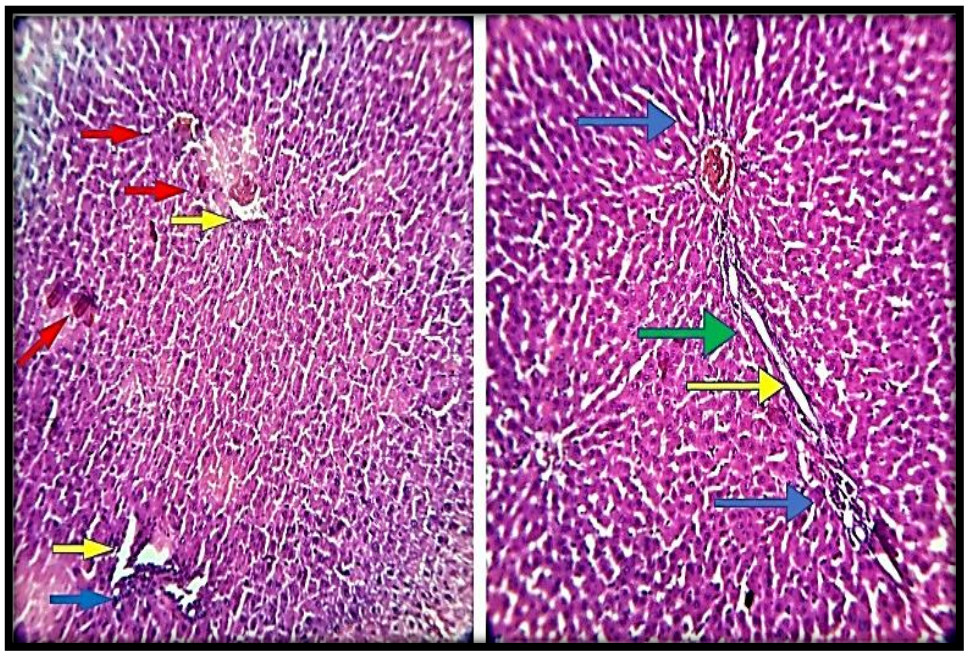

Fig.9. Cross section of the liver treated with 40 mg/kg/day for 60 days shows the periportal fibrosis vacuoles inside the hepatocytes (green arrow) also inflammatory reaction (blue arrow) and necrosis (yellow arrow) hemorrhage in many sites (red arrow) (H&E, 100x).

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