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Research Article

Study the Effects of Sub-chronic Exposure to Meloxicam on Some Hematological and Liver Function Parameters in Rats and the Role of Beetroots Ethanolic Extract

Salma Jameel Askar

Department Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine , University of Baghdad, Iraq.

Abstract | One of the greatest treatment options for preventing and treating postoperative pain is nonsteroidal anti-inflammatory drugs, suppression of cyclooxygenase (COX-1) activity by these drugs has been associated with substantial side effects, beetroots act as a medicinal herb in the treatment of hematological disorders, and act as antioxidant. The aim of this study was to examine the effects of sub-chronic exposure to meloxicam, nonsteroidal anti-inflammatory drug, on hematological alterations and liver functions parameters in albino male rats and to determine the effects of Beetroots ethanolic extract in alleviation these alterations. Eighteen male albino rats were used, and they were divided into three groups of six animals each: G1, which received a dose of distilled water as a negative control; G2, which received a dose of meloxicam at 1.3 mg/kg.BW was a positive control, and G3 received a dose of meloxicam and beetroots ethanolic extract. Each animal received a single oral dosage of (0.1ml/100gm) B.W. for six weeks. Red blood cells count, platelets counts, packed cell volume (PCV) percentages, and hemoglobin (Hb) concentrations, clotting times, levels of uric acid and liver enzymes were analyzed. RBCs, platelets, PCV%, and Hb concentration all decreased significantly at in the G2 compared to G1 while clotting time, serum uric acid, blood urea nitrogen levels, and liver enzyme functions all increased significantly. Rats in G3 had significantly higher RBCs, platelets, PCV%, and Hb concentrations, while clotting time, serum uric acid, and blood urea nitrogen levels, and liver enzyme functions were all significantly reduced in comparison to G2. Liver section of G2 showed increased Kupffer cell proliferation, enlarged and apoptotic hepatocytes. Liver sections of G3 showed less side effect than Meloxicam-treated group. From this study concluded supplementation with beetroots ethanolic extract may attenuate the toxicity of Meloxicam, leading us to deduce that Meloxicam induces hepatotoxicity and creates abnormalities in hematological and biochemical markers.

Keywords | Meloxicam, Hematological, Biochemical, Rats, Beetroots ethanolic extract, Herbal medicine, Histopathology, NSAIDS .

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***Correspondence** | Salma Jameel Askar, Department Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine , University of Baghdad, Iraq;
Email: d.salma@covm.uobaghdad.edu.iq
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INTRODUCTION

A wide range of pharmaceutical and chemical substances are known to cause either short- or long-term alterations in liver function and blood count. Treating inflammation with non-steroidal anti-inflammatory medications (NSAIDs) is commonplace in veterinary and human medicine (Ulrich et al., 1998). One of the greatest treatment options for preventing and treating postoperative pain is nonsteroidal anti-inflammatory drugs (NSAIDs) (Hasan et al., 2014). These drugs work centrally as analgesics and antipyretics and peripherally as analgesics and anti-throm-

bus, the development of NSAIDs with a specific action on COX-2 has been a huge step forward in therapeutic pharmacology in recent years (Lozovoy et al., 2011). One of the most well-known drugs in this class, meloxicam, is a relatively new anti-inflammatory and analgesic, this NSAID belongs to the enolic family at therapeutic levels and blocks prostaglandin formation by inhibiting the COX-2 enzyme (Shekelle et al., 2017) When taken in large dosages, Meloxicam can block the COX-1 pathway, reducing the synthesis of the physiologically significant and protective prostaglandins (Kirchgessner, 2006). Suppression of COX-2 is connected to the expected effects and therapeutic advantages of this category of medications. However, suppression of COX-1 activity by these drugs has been associated with substantial side effects, such as gastrointestinal mucosal damage and renal failure (Lees et al., 2004). Meloxicam's most common side effects are gastrointestinal, while anemia and blood count changes such as differential white cell count, leucopenia, and thrombocytopenia are also very prevalent (Krair et al., 2017; Kim et al., 2022). The aminotransferases, which comprise alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are two of the most extensively utilized and sensitive liver enzymes (Al-Kassie and Al-Qaraghuli, 2013). Liver cells are often the repository for these enzymes. Diseases that cause liver cell death, such as shock or medication toxicity, result in a rise in the blood concentration of these enzymes (Hutchinson et al., 2002; Yahya et al., 2021).

Several studies have examined the efficacy of various medicinal plants in preventing drug-induced toxicities (Hasan, 2019). The Amaranthaceae family includes Beta vulgaris, a common garden plant. In addition to sterols, triterpenoids, tannins, flavonoids, alkaloids, glycosides, and saponins in leaves extract (Jain and Singhai, 2012), betaine and betalain are the most prevalent phytochemical components of beetroots (Lee et al., 2014). Beetroots have been studied for their possible use as a medicinal herb in the treatment of cardiovascular problems as well as for their purported anticancer, carminative, hemostatic, and renal-protecting qualities (Vali et al., 2007). Also, the antioxidant properties of beetroot have been well-documented (Lee et al., 2014). In Chinese medicine, beetroot juice is used as a herbal therapy for eliminating and reducing kidney and bladder stones and improving sexual weakness (Sharma et al., 2011). Recent studies have shown that the active ingredients in Beta vulgaris roots have hepatoprotective, anti-inflammatory, anti-inflammatory, and anti-hypertensive properties (Jain and Sharma, 2011). Recent studies in laboratory animals have demonstrated that beetroot extract has a potent tumour-suppressing effect across several organ systems (Kapadia et al., 2011; Sharma et al., 2011) The roots of Beta vulgaris have been used for a long time in traditional Arab medicine to treat a range of disorders, and the leaves are tonic, diuretic, and anti-inflammatory, making them effective in spleen and liver diseases (Ormsbee et al., 2014). Beetroot has emerged as the go-to natural food for giving athletes a surge of energy in recent years. (Chakole et al., 2011; Jain and Sharma, 2011). The aim of this study was to examine the effects of sub-chronic exposure to Meloxicam, nonsteroidal anti-inflammatory drug, on hematological alterations and liver functions parameters in albino male rats and to determine the effects of Beetroots ethanolic extract on these alterations.

MATERIAL AND METHODS

Ethical Approval

Ethical approval was done by the Scientific Committee of the Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Baghdad and the Ethics Committee of the College of Veterinary Medicine, University of Baghdad, Baghdad – Iraq (IACUC#: P.G.-1499).

Experimental Animals

The current investigation utilized adult male Wister albino rats weighing between (200-230 g) and with age two months. For two weeks, rats were acclimated to their new environment by being kept in plastic cages measuring 20 x 50 x 75 cm and put in a dedicated housing area at the University of Baghdad's College of Veterinary Medicine's Department of Physiology, Biochemistry and Pharmacology. Rats have unrestricted access to commercial feed pellets and running water *ad libitum*. The temperature ranged from 20°C to 25°C in air-conditioned rooms, and the light/dark cycle was 12/12.

Plant Material

We bought "the fresh Beta vulgaris roots from a market in Baghdad, Iraq. To remove any remaining dirt or dust, we ran the items under the running water in the kitchen. Abu Ghraib, Baghdad, Iraq's Ministry of Agriculture's State Board for Seed Testing and Certification (S.B.S.T.C.)" recognised and categorised the plant roots.

Preparation of Beetroots Extract

We thoroughly macerated 1 kilogramme of Beta vulgaris by immersing it in 1.5 litres of 90% ethanol for three days. We used a rotatory evaporator to concentrate the resultant alcoholic extract under low pressure until full drying had occurred. (El–Gamal et al., 2014).

Preparation of Beetroots Ethanolic *Extract* Concentration

To create a stock solution, we combined 10,000 milligrams of dried extract with five millilitres of distilled water, yield-

ing a solution of 2,000 milligrammes per millilitre. (El – Gamal et al., 2014).

Preparation of Meloxicam Solution

To dose the animals in the treatment groups, we dissolved a tablet of meloxicam (15 mg) in (11.5 ml) of distilled water, resulting in a 1.3 mg/ ml concentration. The dosage volume was 0.1 ml per 100 g.BW, which done according to Al-Rekabi et al., (2009).

Acute Toxicity Assessment

Research on the acute toxicity of Beetroot ethanolic extract uses a range-finding approach (Frank et al., 2009). We delivered ethanolic extracts using a gastric gavage needle at 250, 500, 1000, and 2000 mg/Kg dosages.BW to 20 male rats in four groups of identical size. Acute toxicity was defined as causing death within 7 days after dosage. Three more animals received a 2000 mg/Kg dosage of the plant extract and were monitored for the same time frame.

Experimental Design

"The total number of (18) Swiss Albino male rats weighed (200-230 g) were used. The animals were divided equally into three groups (6/each)) as follows":
G1: "Negative control: Dosing Distilled water".
G 2: "Positive control: Dosing Meloxicam 1.3 mg/kg."
G3: The recommended doses are Beetroot ethanolic extract 2000 mg/kg and Meloxicam 1.3 mg/kg. All the animals received their treatments orally once daily at a 0.1 ml/100g for a total of 6 weeks. After being put to sleep with chloroform, the animals' cardiac blood was separated for haematological and biochemical analysis. We checked red blood cells count, platelet count, haemoglobin level, platelet clumping volume, clotting time, uric acid and BUN levels, and the quality of liver's enzymes and histopathology. Using a Hawksley microhematocrit centrifuge and spinning the sample for 5 minutes at 12,000 x g, we calculated the packed cell volume and then determined the hematocrit value using the hematocrit reader.

(Khan et al., 2006). Clotting time was also determined using the microhematocrit method, in which "blood was drawn from the tail and filled into a capillary tube, with timing starting when a fibrin strand appeared and continuing until a piece of the tube broke off once every 60 seconds until the blood had clotted". Hemocytometer analysis of red blood cell count. Haemoglobin measurement:-the drinking reagent and Hb-meter technique measure the amount of methemoglobin produced from Haemoglobin. (Wintrobe, 1998; Al-Rekaby et al., 2009).

The Lucas and Jamroz technique measures the number of platelets in the blood supplied to a tube containing the anticoagulant di-potassium EDTA. "Alanine amino-transferase (ALT) (Randox et al.), aspartate aminotransferase (AST) (Randox, United Kingdom), pyruvate produced by ALT transaminase reacts with 2,4-Dinitrophenyl hydrazine (NAPH) to give coloured hydrazones, oxaloacetate produced by AST decarboxylates to pyruvate and the": spontaneously.

"[T-C / S-B] × 0.4 × 1 / 30 × 1000 / 0.1 (ALT)"
"[T-C / S-B] × 0.4 × 1 / 60 × 1000 / 0.1 (AST)"
"T = test, C = control, S = standard, B = blank, 0.4 = normality of Na OH, 30, 60 = time of pyruvate formation, 1000 = pyruvate formed per litter".

"Blood urea nitrogen by urea – kit (Randox, United Kingdom) enables endpoint enzymatic determination of urea concentration (Conc.) (urease - modified Benhelot reaction) in serum, urease hydrolyzes urea by producing ammonium which is formed green color indophenol in an alkaline medium when reacts with salicylate and hydrochloride, the color intensity is proportional to the urea Conc. in the sample (Wills and Savory, 1981).

Histopathological Examination

liver tissues are gotten after scarifying of the rats after finishing the experiment. Specimens of liver tissues with dimensions 1x1x1 cm were engaged, the Specimens were fixed in 10% buffer formaldehyde solution directly after removal. After seventy two hours of the fixation, the tissues of liver were washed with tap water and then the processing was normally achieved with a set of upgrading alcoholic concentrations from 70% to absolute 100% for 2 hrs in each concentration to remove water from the tissues, then clearance was done by xylol, then the specimens were infiltrated with semi-liquid paraffin wax at 58 ºĊ on two stages, then blocks of specimens were prepared with paraffin wax and sectioned by rotary microtome at 5µm for all tissues. all tissues were stained with Hematoxylin and Eosin (H&E) stain and the histopathological changes were observed under light microscope (Okła et al., 2014).

Statistical analysis

"Analysis of variance (ANOVA) by using of SPSS program (Version 19) one way and least significant differences (LSD) at a significant level of ($P<0.05$) to compare the data of different groups throughout the experiment (Taher Abdulrazzaq and Hasan, 2019). .

RESULTS

Table (1) displays the findings of study that evaluated the acute toxicity of Beetroots ethanolic extract in male rats, which found that none of the rats in any of the four groups given the extract showed any signs of toxicity or mortality throughout the 7-day experiment.

Table 1: The range finding study of Beetroots ethanolic extract in rats orally.

Dose mg/Kg.BW	Number of mice	Number of dead mice After 7 days of treatment with Beetroots extract	Number of alive mice After 7 days of treatment with Beetroots extract
250	5	0	5
500	5	0	5
1000	5	0	5
2000	5	0	5

Table 2: The effects of sub chronic exposure to Meloxicam on Red Blood Cells count (RBCs count), Platelets Counts and Hemoglobin concentration in male rats.

Groups	RBC 10^3/mm M ± SE	Platelets Cu/mm M ± SE	Hb (kg) M ± SE
G1:Negative control	4.43 ± 0.25 A	124.50x10^3 ± 10.76x10^3 A	13.40 ± 0.28 B
G2: Positive control	2.40 ± 1.20 B	41.33x10^3 ± 2.231x10^3 B	8.00 ± 1.28 C
G3:Meloxicam along with Beetroots extract	5.00 ± 0.12 A	126.00x10^3 ± 9.33x10^3 A	18.10 ± 0.04 A

Table 3: The effects of sub chronic exposure to Meloxicam on Packed Cells Volume (PCV%) and Clotting time in male rats.

Groups	PCV% M ± SE	Clotting time/minute M ± SE
G1: Negative control	38.70 ± 1.87 A	3.36 ± 0.33 B
G2: Positive control	30.40 ± 3.10 B	6.52 ± 0.22 A
G3: Meloxicam along with Betroots ethanolic extract	40.00 ± 0.94 A	3.25 ± 0.31 B

Table 4: The effects of sub chronic exposure to Meloxicam on serum Uric acid , BUN , enzymes of liver functions (ALT and AST) in male rats.

Groups	Uric acid (mg/dl) M ± SE	BUN (mg/dl) M ± SE	A L T. U/ L M ± SE	A S T. U/ L M ± SE
G1: Negative control	4.24 ± 0.39 B	41.40 ± 1.49 B	21.71 ± 6.33 B	66.50 ± 5.50 B
G2: Positive control	14.00 ± 1.37 A	55.40 ± 0.74 A	115.55 ± 3.76 A	151.33 ± 1.43 A
G3: Meloxicam along with Betroots ethanolic extract	5.16 ± 0.31 B	40.61 ± 1.55 B	22.40 ± 5.12 B	67.60 ± 4.32 B

And then, we added three more rats at a 2000mg/Kg dosage. The results showed that the RBC count, platelet count, and Hb concentration were all significantly lower in the Meloxicam-treated group (G2) compared to the untreated group (G1) (Table 2). In contrast, the RBC count, platelet count, and Hb concentration were significantly higher in the Meloxicam-plus-Beta vulgaris extract-treated group (G3).

Table 3 shows that when comparing animals in the G1 group to those in the G2 group, the G2 group's packed cell volume (PCV%) and clotting time increased statistically significantly ($P< 0.05$). In contrast, the G3 group's PCV% and clotting time decreased statistically significant.

The serum levels of uric acid and blood urea nitrogen of the Meloxicam-treated group were significantly higher than those of the animals in the negative control group (Table 4). In contrast, those in the G3 group, which received Meloxicam and ethanolic extract of Beetroots, were significantly lower than those in the G2 positive control group (Table 4).

The serum levels of Aspartateaminotransferase (AST) and Alanineaminotransferase (ALT) were significantly higher in the G2 group compared to the animals in the G1 negative control group. However, they decreased and returned to normal in the G3 group compared to the G2 group (Table 4).

Liver histopathology sections from animals in the Meloxicam-treated Group 2 (G2) showed clear lesions, including increased Kupffer cell proliferation, enlarged and apoptotic hepatocytes, and narrowed sinusoids (Figures 1 and 2, respectively). In contrast, liver histopathology sections from animals in the Meloxicam-free Group 3 (Figures 3 and 4) showed no such changes.

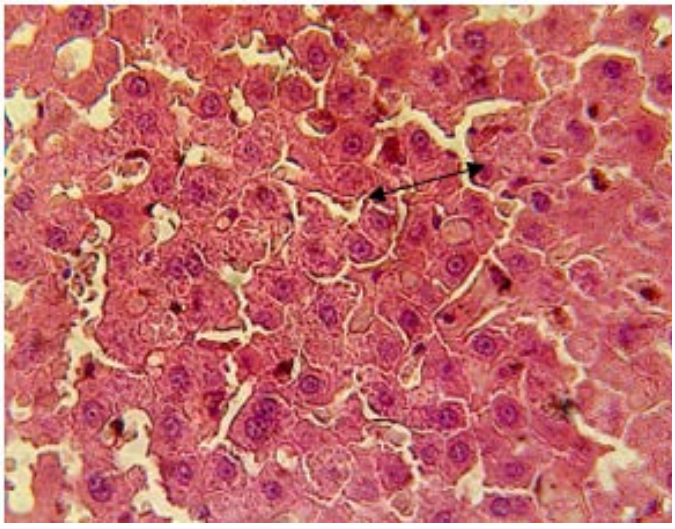

Figure 1: Section in the liver of G2 shows proliferation of Kupffer cells with enlarge - ment and apoptotic of hepatocytes that lead to narrow of sinusoids (H ' & E stain 400X

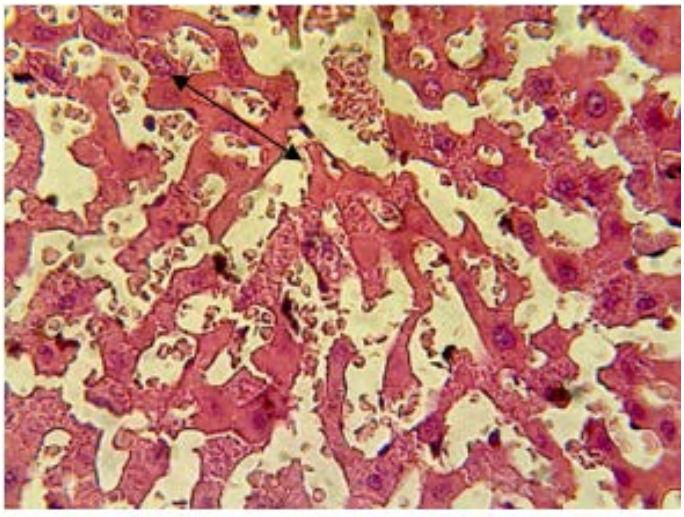

Figure 2: Section in the liver of G2 shows inflammatory cells in dilated congested sinusoids with necrosis of hepatocytes and atrophy of hepatic cords (H ' & E stain 400X)

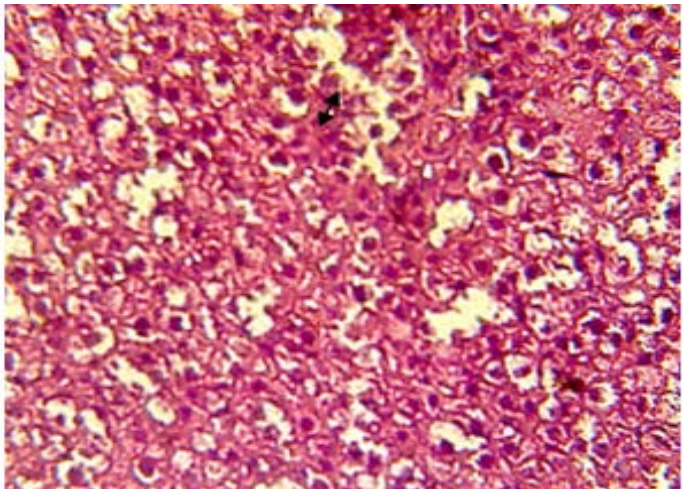

Figure 3: Section in the liver of G3 shows no clear lesions (H ' & E stain 400X)

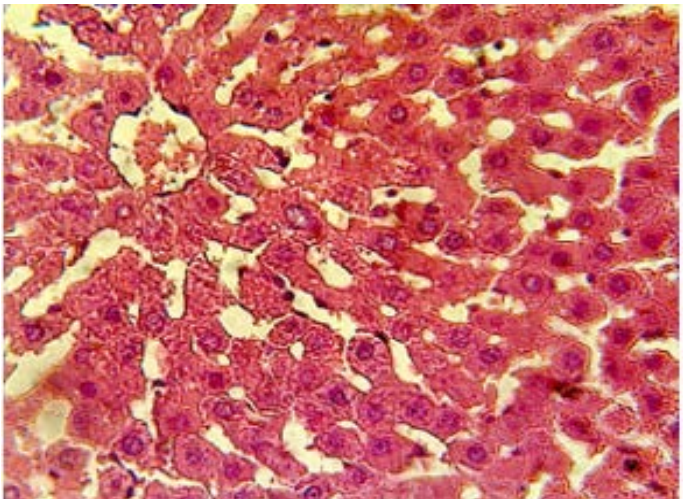

Figure 4: Section in the liver of G3 shows no clear lesions (H ' & E stain 400X)

DISCUSSION

The decreasing in RBCs counts or impairment of heme biosynthesis are likely to blame for the considerable drop in Hb concentration in the positive control group that was dosed with Meloxicam, this result agreed with Rehman et al. (2021), who mentioned immune-mediated anaemia in dogs was found in two field studies with initial subcutaneous injection of meloxicam (0.2mg/Kg.BW) on the first day followed by (0.1mg/Kg.BW) orally once a day for 13 days, it is possible that the decrease in haemoglobin levels in animals of the positive control group was due to high amounts of Meloxicam that penetrate the red blood cells, which is less than 10% after oral administration.

The increasing in RBC counts, PCV%, Hb concentration, and platelet counts in the ethanolic extract of the beetroots group compared to the positive control group after sub-chronic exposure to Meloxicam in rats may be attributed to beetroot treatment dramatically raised Hb concen-

tration and PCV% in anaemic rats, lead to prevent iron shortage (Indhumathi and kannikaparameswari, 2012; Cho et al., 2016). As well as, Beetroots are a good source of folic acid, which aids in the digestion and utilization of iron for hemoglobin formation. Hb concentration was considerably higher in the beetroots group than the positive control one, perhaps due to the dosage of beetroots may have boosted the biosynthesis of Hb and hence averted the deleterious effects of Meloxicam on RBC counts and Hb, as shown in this study. In addition, the statistically significant increase in almost all blood parameters in the animal group given the beetroots ethanolic extract at a dose of 2000mg/kg in combination with Meloxicam may be attributed to there is always a connection between the number of RBCs and the levels of hemobiotic parameters like Hb and PCV% and this study's findings that beetroot extract affects nearly all hematocrit measures lead to provide strong evidence that Hb incorporation into RBC and changes to RBC osmotic fertility and shape are responsible for these effects. (A debayo et al., 2005).

In this study, the PCV% of rats given beetroots in combination with Meloxicam was significantly higher than that of the positive control group, this result can be regarded to the benefits are strongest at large doses. Moreover, this study's findings corroborate another recent study (Al-Khazraji, 2018). As well as, the results had significantly longer clotting times when comparing Meloxicam-treated and untreated animals. Furthermore, Recent research has linked meloxicam to reduced platelet aggregation and possible bleeding by blocking thromboxane A2 (Mathews et al., 2001). It is fair to state that the lengthened clotting time directly results from the dramatic drop in platelet count.

During liver damage, often showed an increase in hepatic enzymes (AST and ALT) as a sign of hepatocellular necrosis. This makes the blood levels of these enzymes useful as quantitative indicators of the nature and extent of hepatic cell damage (Lozovoy et al., 2011). In addition, prior research has shown that free radicals caused by oxidative stress are major contributors to liver damage. (Ramadhan and khudair, 2019; Qinna and Ghanim, 2019).

Serum hepatic enzyme levels were significantly higher in the G2 positive control group, indicating that Meloxicam had a hepatotoxic impact at the doses utilized in the current investigation, this finding agreed with other research recorded by Al-Asmari et al. (2020) who has indicated that Meloxicam caused an oxidative stress by building up in liver tissues, leading to elevated liver enzymes in the positive control group, liver damage, and cell necrosis. Hepatic necrosis may result from this buildup, which may initiate programmed cell death (apoptosis). While the decreasing blood levels of alanine aminotransferase (AST) and alanine aminotransferase (ALT) in rats treated with an ethanolic extract of beetroots and meloxicam may be indicated to a return to pre-hepatotoxic levels in the rats which is may be regarded to the antioxidant and anti-inflammatory effects of beetroots and nitrate stimulation of metabolic processes may account for their therapeutic effects (Clifford et al., 2017).

As well as, these findings corroborated a study that employed beetroots and highlighted their antioxidant and protective effects on liver tissue by in-vivo enzyme assays. The tension is caused by paracetamol (Vulić et al., 2014).

Furthermore, beetroot extracts' ability to lower AST and ALT activity after Meloxicam-induced liver injury indicates tissue recovery. Also, beetroot ethanolic extract may have contributed to our results by lowering liver enzyme levels by stabilizing cell membranes and protecting the liver from noxious chemicals and free radical-mediated toxicity. In contrast, the extract promotes the liver's proper function by increasing the organ's cellular regeneration rate. Nitrate, betalains, phenolics, and ascorbic acid are only a few of the active chemicals in the ethanolic extract of beetroots that may be responsible for its potent hepatoprotective effects; betalains, in particular, play an essential role in inflammation and oxidative stress. (Clifford et al., 2017).

Our liver histological results, which showed varied lesions in the G2 group, this result can be discussed by a considerable elevations in AST and ALT levels which is observed in the Meloxicam-positive control group's blood lead to this pathological changes in liver tissues, this is congruent with the findings of Ulrich et al. (1998), who discovered a high concentration of Meloxicam in the tissue of the liver and kidney following multiple oral doses of Meloxicam 1mg/Kg, suggesting that the largest tissue concentration of Meloxicam is in the liver.

The an improvement in liver tissue in rats treated with extract may be attributed to the plant extract is a powerful free radical scavenger that can assist in the avoidance of diseases caused by oxidative stress, this explaining agreed with Georgiev et al. (2010). In addition to phytochemical investigations on ethanolic extracts of Beta vulgaris roots have identified polyphenols, alkaloids, tannins, and flavonoids as the primary active ingredients "(Mroczek et al., 2012; Mokhtari-Dehkordi et al., 2014). Furthermore, Rose et al. (2014) and Nahla et al. (2018) found similar outcomes in their research. Liquid chromatography-mass spectrometry analysis of red beetroots also revealed the presence of five phenolic acids (ferulic, vanillic, syringic, ellagic, and caffeic) and three flavonoids (quercetin, kampferol, and myricetin) with antioxidant, anti-inflammatory, and tumor-proliferation properties (Farah et al., 2013).

In addition, a more recent study (Rehman et al., 2021) demonstrated the antioxidant activity of *B. vulgaris* leaves and roots extract, which may be connected to the presence of phenols, as it demonstrated superior radical scavenging capacity due to the presence of phenols in larger abundance".

CONCLUSIONS & RECOMMENDATIONS

Beetroot ethanolic extract may protect against the hepato-toxic effects of Meloxicam because it restores the body's natural antioxidant systems and blocks the generation of free radicals, both of which contribute to Meloxicam's negative side effects. Together, Meloxicam and beetroot ethanolic extract were more effective than Meloxicam alone. When given at a high enough dose, Beetroots showed an anti-anaemic impact that was particularly strong in anaemia, suggesting that they may be useful as a therapy for the condition. Additional research is necessary to determine the extract's mechanism of action and isolate and purify the active components responsible for its pharmacological and physiological actions.

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NOVELTY STATEMENT

The study's novel aspects consist of (1) examining the potential for changes in haematological and liver function parameters following sub-chronic exposure to Meloxicam, a new nonsteroidal anti-inflammatory drug, and (2) determining a novel herbal protection against these changes or any toxic effects by using Beetroots extract.

AUTHOR CONTRIBUTION

The contributed was done by Salma Jameel Askar alone.

CONFLICT OF INTEREST

There are no competing interests for the author to consider.

DATA AVAILABILITY

Author will provide all data at the reasonable request.

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