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The protective effect of ashwagandha (*Withania somnifera*) against meloxicam-induced renal and hepatic damage in male rats

S. A. Razzaq*, Z. A. Aboshnin*, H. K. Abdul-Husseein**

**University of Al-Muthanna, Al-Muthanna, Iraq*
***University of Babylon, Babylon, Iraq*

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Department of Pharmacology and Toxicology, College of Pharmacy, University of Al-Muthanna, Al-Muthanna, Iraq.

Department of Clinical Pharmacy, College of Pharmacy, University of Babylon, Babylon, Iraq.

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Meloxicam is an effective member of the nonsteroidal anti-inflammatory drugs (NSAIDs) family, with the main use for relieving inflammation and moderate to severe pain, but its use for treatment of acute and chronic conditions is associated with several adverse effects on the liver and kidneys. Ashwagandha *Withania somnifera* (L.) Dunal (Solanaceae) is classified as an important component in Ayurvedic medicine due to its several health benefits, including antioxidant and anti-inflammatory properties, which may offer protective effects against meloxicam-induced hepatic and renal damage. This study aimed to evaluate the protective properties of ashwagandha against meloxicam-induced hepatic and renal damage. We conducted the study using 21 male rats. These rats were randomly divided into three groups, with 7 rats in each group. These were the control group: administered oral normal saline only, the meloxicam treated group: administered 1.5 mg/kg via oral route for 20 days; the ashwagandha-meloxicam treated group: administered a combination of ashwagandha (200 mg/kg) and meloxicam (1.5 mg/kg) orally for 20 days. The results revealed a significant decrease in the hepatic and renal parameters in the ashwagandha-meloxicam group compared to the meloxicam group. Histopathological study of the liver and kidneys shows a partial amelioration of the damage triggered by meloxicam in the ashwagandha-meloxicam group. This study concluded that the administration of ashwagandha may impart protective effects against meloxicam-induced hepatic and renal damage in male rats. The antioxidant and anti-inflammatory properties of ashwagandha may reveal its capacity to counteract the organ damage associated with NSAIDs use.

Keywords: ashwagandha; non steroid anti-inflammatory drugs; meloxicam; induced hepatic-renal injury.

Introduction

Induced kidney damage may be attributed to many medications, including antibiotics, diuretics, some antihypertensive drugs, and NSAIDs (Huang et al., 2021). The major clinical issue is that the use of drugs with nephrotoxic capability cannot be avoided due to the need for this group of drugs in a variety of clinical cases, which leads to an increase in the incidence of induced kidney injury. Acute kidney injury is described as a syndrome associated with a sudden reduction in glomerular filtration rate, which leads to creatinine and urea retention in addition to other substances filtered through the renal system. Moreover, this state is accompanied by high morbidity and mortality if untreated. NSAIDs are widely dispensed to treat a diversity of clinical conditions, including pain, fever, and inflammatory disorders (Lapi et al., 2013; Mahmood et al., 2024). Generally, NSAIDs are classified into several categories depending on either chemical characteristics, half-lives, or selectivity of inhibition for the target enzyme (Gupta et al., 2016; Ong et al., 2007). However, the underlying pathophysiology of renal injury induced by these medications may be attributed to their mechanisms of actions which involve the inhibition of prostaglandin synthesis from its precursor (arachidonic acid) either selectively or not (Burukoglu et al., 2016), since the filtration action of the renal system depends on the normal production of vasodilatory action of prostaglandins (Musu et al., 2011). So any factor that causes distortion of the normal pathway for prostaglandin production or action will lead to vasoconstriction and reduction of the renal perfusion, which ends with ischemic renal tissues and acute renal injury (Lucas et al., 2019). Another pathophysiological mechanism for NSAIDs- induced acute kidney injury is interstitial nephritis. The implication pathway of interstitial nephritis induced by NSAIDs is not fully clear, but it could be explained by an immune reaction in response to NSAIDs, especially in prolonged use, or be caused by improper arachidonic acid metabolism due to the action of NSAIDs ending with induced renal damage (Riella et al., 2003; Harirforoosh et al., 2013). Moreover, the administration of NSAIDs develops a wide range of hepatic complications that differ according to the chemical groups of agents such as meloxicam and piroxicam, which, related to the oxicam groups, can cause cholestasis, acute hepatitis, and massive or sub massive necrosis even with a moderate dose, while diclofenac use is associated with acute and chronic hepatitis in a dose-dependent manner (Bonkovsky et al., 2022). Other chemical groups are also involved in liver function abnormalities (elevation in liver enzymes, including AST and ALT), jaundice, and mixed liver damage (Sarges et al., 2015).

Meloxicam is an enolic acid derivative and is related to the oxicam group of NSAIDs (Fringuelli et al., 2005). Meloxicam binds to the active site of both forms of cyclooxygenase COX-1 and COX-2 and blocks the action of these enzymes (Xu et al., 2014). The incidence of adverse effects depends on the dosing regimen, including dose, dosing interval, course of therapy, and also route of administration, in addition to the presence of comorbid diseases that are considered risk factors for gastrointestinal, renal, and hepatic adverse effects (Papich et al., 2015).

Indian winter cherry, ashwagandha, or Indian ginseng – all these names found in herbal medicine, especially in Ayurveda, refer to *Withania somnifera* (L.) Dunal (Solanaceae), which is a plant native to India. In fact, ashwagandha has multiple actions on different targets, so it has gained special value in recent research (Langade et al., 2019). The name ashwagandha refers to its powerful ability to strengthen the body and supply it with energy; however, the anti-inflammatory, antioxidant, adaptogenic, antimicrobial, and neuroprotective action of ashwagandha make this herbal medicine a target for many experimental and clinical trials to reveal its therapeutic ability in management of many conditions associated with inflammation, oxidative stress, and neurodegenerative disease (Pandey et al., 2017). The chemical composition of ashwagandha shows many phytochemical compounds, including withanolides (representing the active constituents), flavonoids (mainly quercetin), and alkaloids. The pharmacological activity related to these phytochemical components changes in strength according to the age of the plant and the area of implantation

(John, 2014). Recent studies showed that the aqueous extract of ashwagandha roots can increase the scavenging activity for reactive oxygen species and free radicals, with the ability to inhibit lipid peroxidation (Minhas et al., 2011a). In addition to the antioxidant action, this extract also has anti-inflammatory properties achieved by a significant reduction in the levels of tumor necrosis factor (TNF)-α and interleukins-6 (IL-6) (Minhas et al., 2011b).

So depending on the pleotropic effect of the extract of ashwagandha roots, the role of ashwagandha can be explained in mice with induced hepatic and renal damage by protecting this vulnerable organ against the cytotoxic, oxidative, and inflammatory injury induced by different triggers (Sajida et al., 2021). The study aimed to investigate the protective role of ashwagandha against meloxicam-induced renal and hepatic damage by using rats as the animal model.

Materials and methods

Twenty-one male rats ranged in weight from 200 to 250 g during the 20-day course of the experiment. At the start of the study, the rats were kept in controlled conditions at a temperature of 27 °C along with 40–60% moisture and a light/dark environment; however, the rats were stabilized for one week before the treatment course and the experimental work for adaptation purposes. Meloxicam was dissolved in normal saline (0.9% N/S) (Kim et al., 2023) in the proper amount after determining its LD_{50} in such away that a 0.1 mL solution contained the required amount of meloxicam (1.5 mg/kg/day). A constant dose was orally administered to rats. Fresh *Withania somnifera* (ashwagandha) powder, purchased from a popular company, was dissolved in water (Langade et al., 2023) and a 0.1 mL oral daily dose of 200 mg/kg was administered in parallel with the meloxicam. The randomization step was achieved in the rats' selection to reduce the bias errors, so the rats in each individual group of 7 were taken randomly from the pool of rats. The division of groups was as follows: Group 1: also named control group or vehicle group, where the rats received normal saline through the oral gavage; Group 2: named the meloxicam-treated group, the treated rats received meloxicam through the oral gavage. Group 3: ashwagandha-meloxicam-treated group, where the rats were treated with the administration of the ashwagandha + meloxicam. After the administration of the last dose, we started with sample collection. The rats were anesthetized via a combination of xylazine (10 mg/kg) and ketamine (100 mg/kg) to perform the abdominal opening surgery. Blood samples were collected in special EDTA vials by direct puncture of the heart while the rats were under the effect of anesthesia, then the blood was centrifuged to obtain the serum, which was kept at –80 °C for measurement of liver function enzymes (AST, ALT, and ALP) and kidney function markers (urea, BUN, and creatinine). The time required for centrifugation was five minutes at 3000 rpm. Then, the rats were euthanized with a high dose of ketamine, and tissues were collected, preserved, and labeled for histopathological studies of the liver and the right kidney after washing them with distilled water and kept within a 10% formalin solution to focus on the histopathological changes in these target organs, which were attributed to meloxicam (Ur Rehman., 2023).

This study was ethically approved by the University of Al-Muthanna committee (approval no. 1, date: 1/7/2024).

Mean ± standard deviation (x ± SD) was used to represent variables of the study. The parametric test, ANOVA (ANalysis of VAriance) with post-hoc Tukey's, test was applied to assess the differences in means. IBM SPSS software (version 26) was applied to represent data. The level of significance was considered at $P < 0.05$.

Results

The serum level of liver enzymes, including AST, ALT, and ALP, in the meloxicam-treated group showed significant elevation compared to the enzymes' level in the control group ($P < 0.001$, $P < 0.001$, $P = 0.002$, respectively), while a significant lowering in the levels of AST and ALT versus a non-significant lowering in the ALP level was noticed in the ashwagandha-meloxicam-treated group compared to the meloxicam-treated group ($P = 0.001$, $P = 0.043$, $P = 0.64$, respectively).

Serum urea and creatinine were used as parameters to indicate renal function in all groups. The levels of BUN (blood urea nitrogen), urea, and creatinine in the meloxicam-treated group were significantly elevated compared to the control rats ($P < 0.001$), while their levels in the ashwagandha-meloxicam-treated group were significantly lower compared to the meloxicam-treated group ($P < 0.001$, $P < 0.001$, $P = 0.014$, respectively, Table 1).

Table 1
The serum level of the liver enzymes (U/L) and renal parameters (in mg/dL) of the experimental animals (mean ± SD)

Groups	ALT	AST	ALP	BUN	Urea	Creatinine
Control group	48.6 ± 8.8	37.7 ± 18.9	131.0 ± 21.9	22.9 ± 1.8	49.0 ± 3.8	0.77 ± 0.09
Meloxicam-treated group	89.1 ± 7.5*	76.1 ± 9.6*	173.3 ± 12.6*	30.4 ± 1.2*	65.1 ± 2.6*	2.04 ± 0.56*
Ashwagandha-meloxicam treated group	78.4 ± 6.7†	42.1 ± 11.4†	164.3 ± 19.8	24.3 ± 2.1†	52.1 ± 4.5†	1.37 ± 0.38†

Notes: one-way ANOVA was used for calculation of P-value; * – $P < 0.05$ compared to control group; † – $P < 0.05$ compared to meloxicam group.

Histopathological examination of the hepatic tissues obtained from control rats revealed normal characteristics, which were indicated by normal hepatocytes, normal features of the hepatic artery, portal vein, and bile duct (Fig. 1), while the liver tissues belonging to the meloxicam-treated group showed deterioration, including atrophy of hepatocytes, widening of the sinusoid, dilation of the bile duct, and congestion of blood vessels (Fig. 2). On the other hand, an improvement in the liver tissues of the third group (the ashwagandha-meloxicam-treated group) was shown, which reflects the hepatoprotective action of ashwagandha (Fig. 3). Histopathological examination for renal tissue showed the same pattern as seen in hepatic tissues, including normal features in control rats, noticeable impairment in the meloxicam-treated group, and improvement in histological features for renal tissues taken from the ashwagandha-meloxicam-treated group (Fig. 4–6).

Discussion

Meloxicam has powerful anti-inflammatory and analgesic properties, making it a good choice for many inflammatory disorders, including osteoarthritis and rheumatoid arthritis, and for relief of pain in different degrees, from back pain to postoperative pain (Kaye et al., 2020). Prolonged use and high doses of meloxicam administration have been associated with many complications especially nephrotoxic and hepatotoxic effects that have been reported previously (Pugh et al., 2017). This study evaluated the protective role of ashwagandha against the meloxicam-induced histological and biochemical changes in tissues of male rats ,taking into account the existence of many previous studies that report the reno- and hepatoprotective effects of ashwagandha (Lopresti et al., 2019; Wiciński et al., 2023; Murthy et al., 2024).

In the present study, histopathological changes were examined to support the results of measuring the liver and renal functions parameters. Histopathological examination of the liver tissues obtained from the control rats revealed normal characteristics, including normal lobular structure, central vein, sinusoids, and hepatic cords compared to those obtained from the meloxicam-treated group, which showed noted deterioration. These results were consistent with the results of other studies, which concluded that meloxicam can induce histopathological changes in the liver tissues, suggesting potential hepatotoxicity with prolonged periods or high-doses (Sheikhlangi et al 2023). The results of this study revealed the potential protective effect of the ashwagandha on the liver tissues as demonstrated by a significant decrease in AST and ALT levels in the ashwagandha-meloxicam-trea-

ted group compared to the meloxicam-treated group and marked improvement in the liver histology in which the tissues seemed closer to those of the control group.This result was similar to the results of other previous studies which showed a significant decrease in AST and ALT levels in the ashwagandha-treated rats and a marked improvement in the liver tissue structure, which was attributed to the antioxidant properties of ashwagandha, which aided in diminishing oxidative stress and protecting liver cells from damage (Mosa et al., 2022; Aboelhassan et al., 2024).

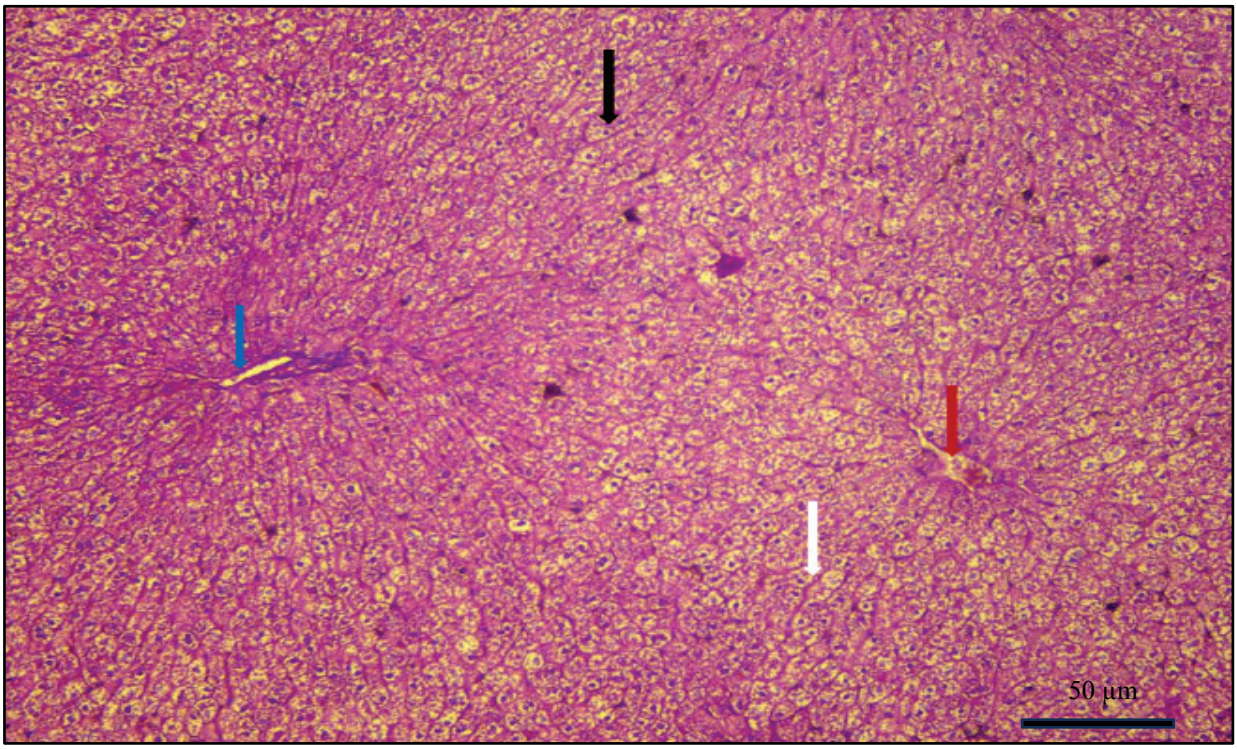

Fig. 1. Liver from the control group, where the canaliculi (black arrow), hepatocytes (white arrow), central vein (red arrow), and portal area (blue arrow) show normal characteristics.

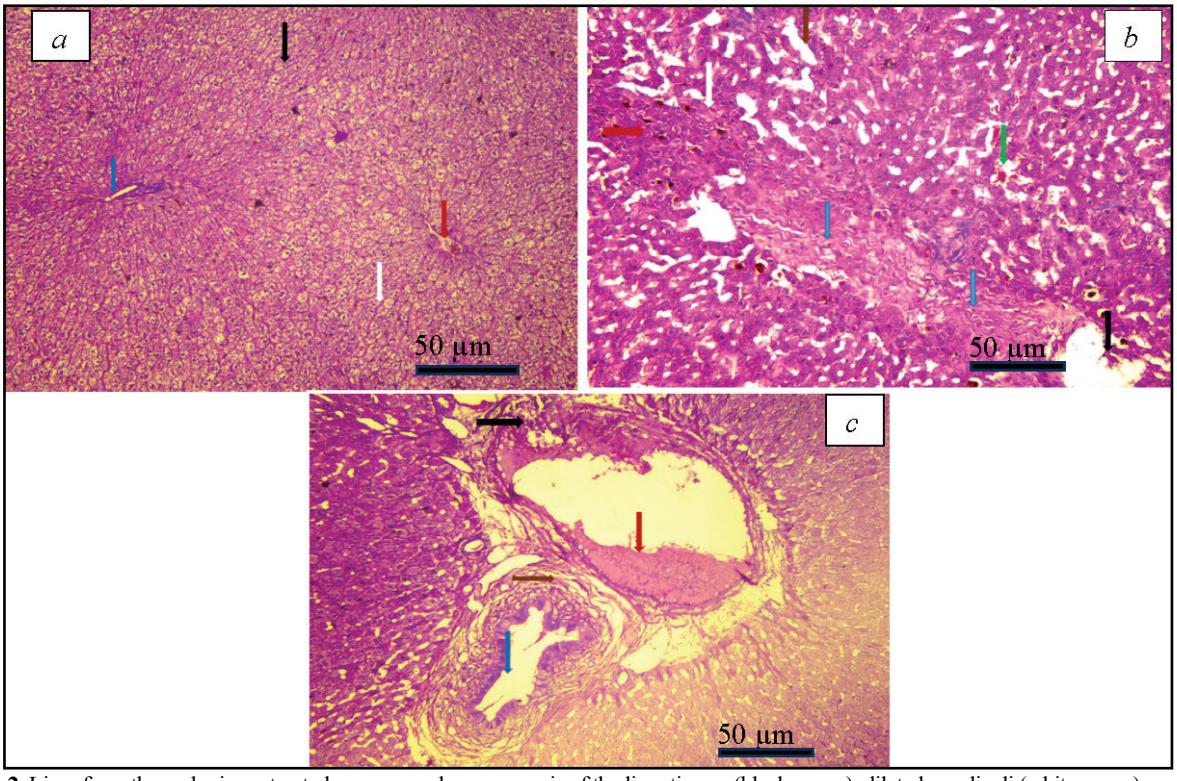

Fig. 2. Liver from the meloxicam-treated group: *a* – shows necrosis of the liver tissues (black arrow), dilated canaliculi (white arrow), central vein congestion (red arrow), and severely congested area of blood vessels (blue arrow); *b* – shows necrosis of the liver tissue (black arrow), dilated canaliculi (brown arrow), inflammatory cells (red arrow), accumulation of cholestasis, kupffer cells (white arrow) and fibrosis of the portal area (blue arrow); *c* – shows the necrosis of the portal area (black arrow), congested portal vein (red arrow), bile duct (blue arrow), and fibrosis of the portal area (brown arrow)

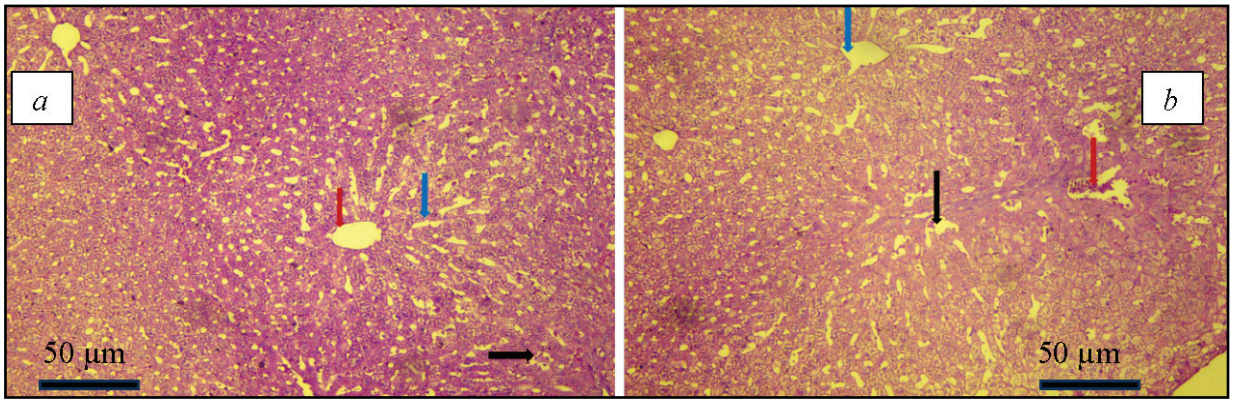

Fig. 3. Liver from the ashwagandha-treated group: *a* – shows a decrease in the area of liver tissues necrosis (black arrow), canaliculi (blue arrow), and central vein (red arrow); *b* – show decrease of the area of liver tissues necrosis (black arrow), reduction in congested blood vessels area (red arrow), and central vein (blue arrow)

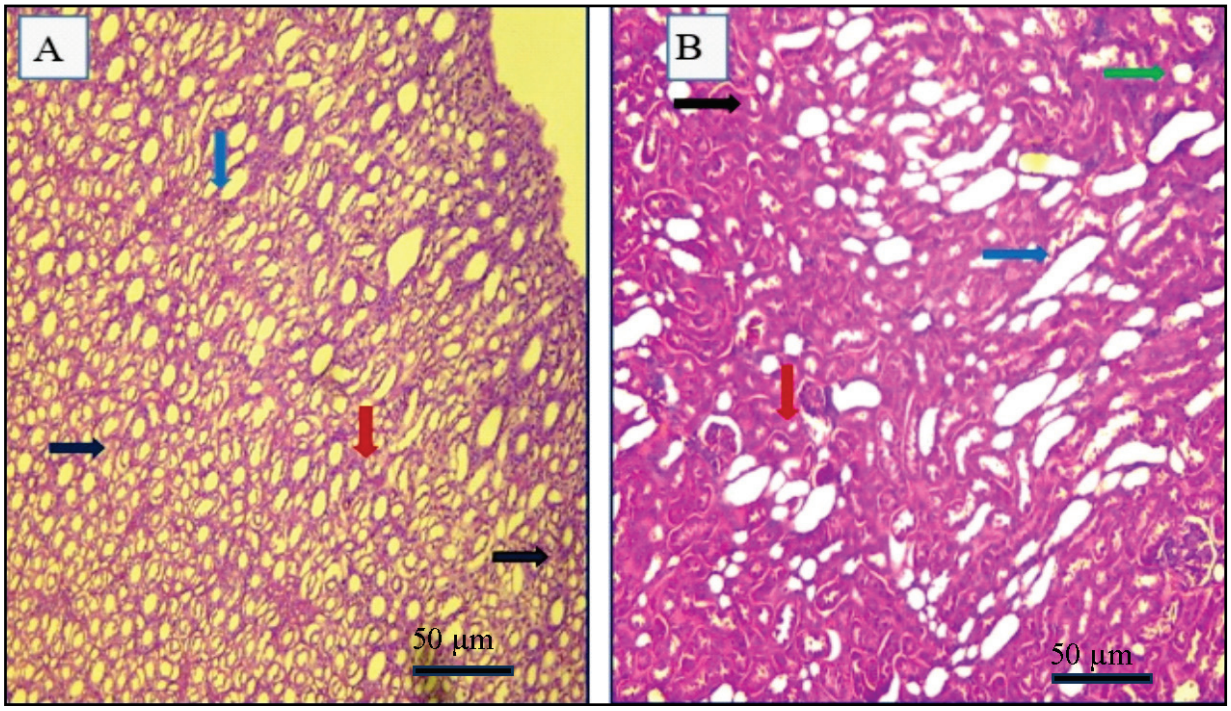

Fig. 4. Kidney from the control group: *a* – the cortex shows glomeruli (black arrow), proximal tubule (red arrow), and distal tubule (blue arrow) with normal characteristics, while on the left side; *b* – the medulla also shows the normal structure of thick descending tubule (black arrow), thick ascending tubule (red arrow), papillary duct (blue arrow), and pelvic space (green arrow)

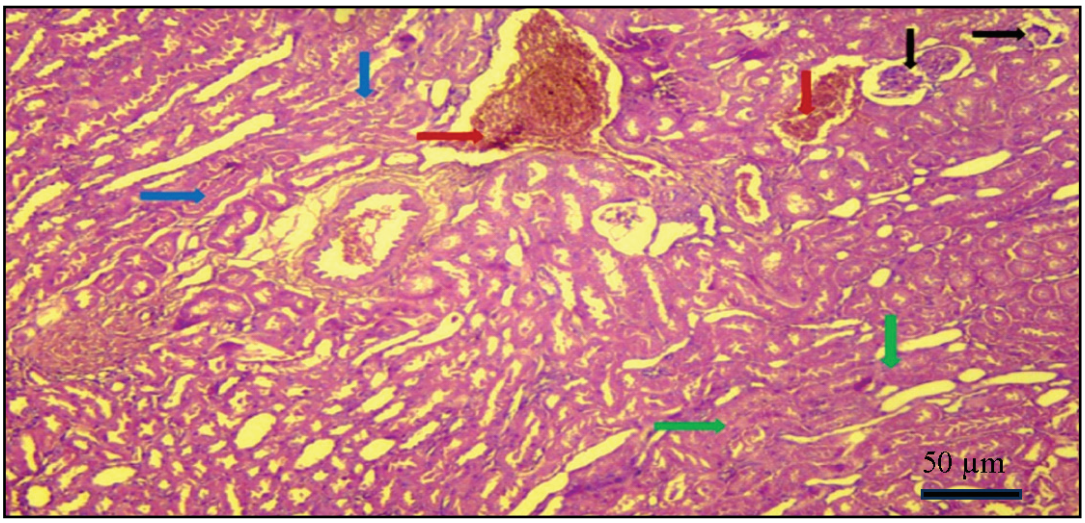

Fig. 5. Kidney from the meloxicam-treated group (cross section), the cortex showing degeneration and necrosis of glomeruli (black arrow), congested blood vessels (red arrow), casts (blue arrow), and degenerated tubules (green arrow)

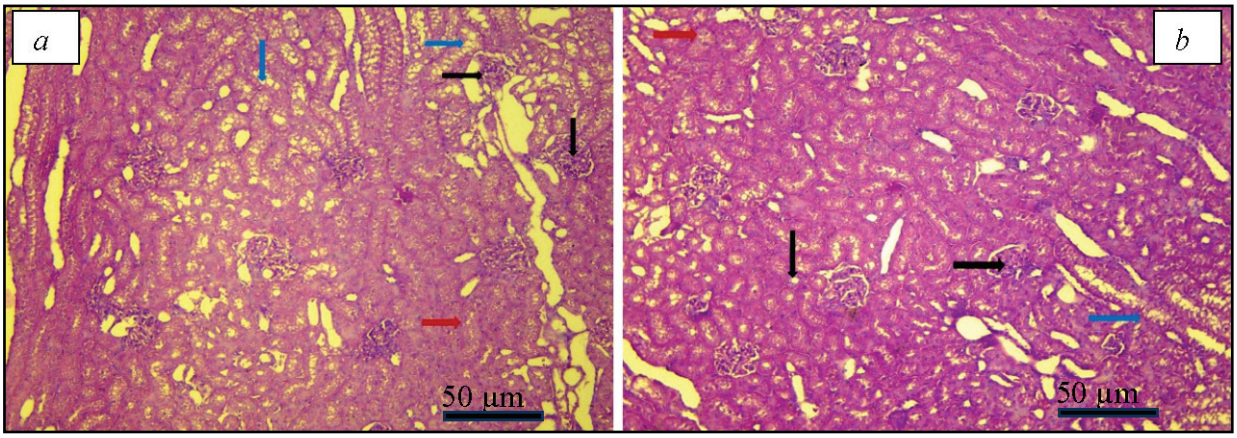

Fig. 6. Kidney tissues from the ashwagandha treated group: *a* – show mild necrosis with enlargement of glomeruli (black arrow), decrease in the degeneration area of tubules (red arrow), and vaculation in epithelia of tubules that reduce the urinary space of glomeruli (blue arrow); *b* – show normal glomeruli and tubules (black arrow), decrease in the degeneration area of tubules (red arrow), and mild vaculation in epithelia of tubules (blue arrow)

Khalil et al. (2021) suggest a mechanism by which ashwagandha exerts its hepatoprotective effects against meloxicam-induced hepatotoxicity via the activation of the Nrf2/HO-1 pathway, which has a vital role in reducing oxidative stress damage to liver cells. Moreover, ashwagandha inhibits the NF-κB/MAPK signaling pathway, which in turn reduces inflammation and cellular stress in the liver (Khalil et al., 2021). Regarding histological changes that were seen in the meloxicam-treated group, including mild necrosis in the medulla and cortex, degeneration of tubules and a decrease in the urinary space of the glomeruli as compared with the control group – these manifestations resembled those that have been reported by Sharma et al. (2017) and Grunz-Borgmann et al. (2015), who reported that meloxicam increased urea and creatinine levels, which reflect kidney damage , a finding supported by kidney histopathological examination that revealed severe renal injury. As explained in the results, ashwagandha has a renoprotective effect through reduction in urea and creatinine with improvement in kidney histopathological changes. Kiki et al. (2014) revealed that ashwagandha has renoprotective effects by reducing urea and creatinine serum levels in male rats and showed improvement in histopathological changes following radiation exposure by reduction of nitric oxide level and malondialdehyde, increasing antioxidant enzyme activity such as superoxide dismutase thereby reducing oxidative stress activity. Moreover, Shimmi et al. (2012) explainned that the nephroprotective effects of ashwagandha and urea and creatinine reduction were due to its capacity to scavenge free radicals, inhibit lipid peroxidation and normalize kidney weight in addition to its active phenolic and flavonoids components which increased glomerular filtaration rate, while ashwagandha's anti-inflammatory properties and its role in improving free radical scavenging enzymes were responsible for improving histopathological changes in the kidney.

Conclusion

This study concludes that ashwagandha may have a protective effect against meloxicam induced hepatic and renal injury in male rats as it significantly reduced biomarkers and improved tissue damage induced by meloxicam. These results necessitate further investigation into the potential use of ashwagandha as an adjuvant therapy to diminish NSAID-associated organ damage.

No conflict of interest.

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