



Research Article

Histopathological examination of the hepatoprotective effect of *curcumin* with *piperine* on thioacetamide induced hepatotoxicity in rats

Shamsher Shivhare, K. Shrman, Vidhi Gautam, Shreya Dubey

Abstract

Piperine possesses bio-enhancer characteristics, while *curcumin* has a long history of traditional use in reviving the liver and treating illnesses and dysfunction of the liver. Thus, the goal of the current investigation was to ascertain the hepatoprotective potential of *curcumin* and *piperine* after oral administration on albino rat liver damage caused by thioacetamide. In this study, the animals were divided into five groups, each containing four rats. Groups II (received thioacetamide on the eighth day), III (received *curcumin* orally for seven days), IV, and V received a single dose of thioacetamide on the eighth day of the experiment. For seven days, a group I received normal saline as a control. For seven days, Group III received 200 mg of *curcumin* per kg of body weight. Groups IV and V received *piperine* for 7 days combined with *curcumin* at doses of 200 and 400 mg per kg of body weight, respectively. Rats of all the groups were sacrificed on the 10th day of the study. The thioacetamide treated group showed severe necrosis, hemosiderosis, and mononuclear cell infiltration around the central vein. The *curcumin*-treated group showed minimal hepatic necrosis and mild degenerative changes indicating restoration of normal architecture due to the hepatoprotective property of respective treatments against thioacetamide. The histo-architecture of the kidney treated with thioacetamide showed pathological changes as evidenced by tubular degeneration and distorted architecture. Treatment groups showed improvement in renal pathology. Hence, the study concluded that *curcumin* provided hepatoprotection against thioacetamide-induced hepatotoxicity and in combination with piperine hepatoprotective activity of *curcumin* was observed to be reduced.

Keywords curcumin, histopathology, kidney, liver, piperine, thioacetamide

Introduction

Liver diseases have been treated with herbal medicines since the dawn of civilization. *Curcumin* has a long history of application in traditional medicine for reviving the liver and treating illnesses and dysfunction of the liver. Most of *Curcuma longa*'s therapeutic benefits are attributed to *curcumin*, a natural polyphenol found in the plant's rhizomes. It has been shown to help with conditions like diabetes, cystic fibrosis, atherosclerosis, and cancer [1-3]. Its antioxidant activity is the primary mechanism underpinning its positive effect. Reactive oxygen species are scavenged, and their production is prevented. *Curcumin* reduces the toxic

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Authors:

S. Shivhare ✉, K. Shrman, V. Gautam
Department of Veterinary Pharmacology and
Toxicology, College of Veterinary Science and
Animal Husbandry, NDVSU, Jabalpur, M.P.,
India

S. Dubey
Department of Veterinary Public Health and
Epidemiology, College of Veterinary Science
and Animal Husbandry, Kamdhenu University,
Anand, Gujarat, India

✉ shamsher1124@gmail.com

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and inflammatory damage to the liver, gut, and pancreas in the digestive system [4-5]. The acceptable Daily Intake (ADI) of *Curcumin* is 3 mg/kg b.wt. per day and total bioavailability was estimated to be around 1% [6]. Thioacetamide (TA), a potent centrilobar hepatotoxicant, the main reactive metabolites is TA-S, S-dioxide (TASO₂) formed by bioactivation CYP2E1 enzyme which converts TA to TA sulfoxide (TASO) and further dissociate into TASO₂. TASO₂ is responsible for liver and renal injury. An alkaloid called *piperine* is extracted from the seeds of *Piper nigrum* and *Piper longum* well recognized indigenous medicinal plants. The acceptable Daily Intake (ADI) of *piperine* is 10-50 mg/kg b.wt. per day. *Piperine* is a bio-enhancer compound known to increase the bioavailability of many drugs. The objective of the current investigation was to determine if *curcumin* alone or in combination with *piperine* has hepatoprotective effects on rat liver damage caused by thioacetamide by histological analysis of the liver and kidney.

Methodology

The study was carried out at Nanaji Deshmukh Veterinary Science University, Jabalpur, in the College of Veterinary Science and Animal Husbandry's Department of Veterinary Pharmacology and Toxicology (M.P). The investigation was conducted on adult, inbred albino rats of either sex, weighing 150–200 g. The rats were housed in clean conditions in polycarbonate cages in the Animal Lab House at the College of Veterinary Science and Animal Husbandry, Jabalpur. The rats had full access to water and were fed on a regular pellet diet. Before the start of the experiment, the animals were kept under close supervision for two weeks. Animals were subjected to a clinical examination during this period to rule out any potential health conditions. To prevent the animals from experiencing unnecessary stress, all appropriate management practices were implemented.

With IAEC No. 03/IAEC/Vety/2019, the Institutional Animal Ethics Committee (IAEC) approved the study's experimental design and animal usage. The CPCSEA requirements for the care and management of animals were followed throughout the entire experiment.

Experimental design

The study was conducted in 20 healthy inbred albino rats, divided into 5 groups, each consisting of 4 rats. Chemicals used in this study were Curcumin (95%), Piperine, Thioacetamide, and Normal saline (0.9%). Curcumin @200 and 400 mg/kg b.wt. [7] were given orally in respective groups; in 12 hours fasted animals with free access to drinking water, whereas piperine was administered @20 mg/kg b.wt. [8] orally. On the 8th day of the study, Thioacetamide was administered @200 mg/kg b.wt. [9] intra-peritoneally in 12 hours fasted animal. Detailed experimental design is shown in Table 1. Following is the detailed experimental design of the study:

Body weight

Body weights were evaluated on the 0th, 5th, and 10th day of the study.

Organ weight

The relative organ weight of the liver and kidney was recorded on the 10th day of the study after sacrificing rats.

Induction of liver damage

A single dose of thioacetamide (200mg/kg) was administered intraperitoneally from groups II to V on the eighth day of the experiment. The rats received thioacetamide following a 12-hour fast, but free access to extra water was permitted.

Sacrificing of rats



On the 10th day of the study all the rats from groups I to V were sacrificed by decapitation method. The liver and kidney were collected and removed for additional evaluation to check for alterations in gross and histological architecture.

Table 1. Design of experiment for hepatoprotective study

Groups	No. of rats	Experiment Schedule		
		DAY 1 to 7	DAY 8	DAY 10
I	4	Treated with saline (oral)	Treated with saline	Liver and kidney collection
II	4	Treated with saline (oral)	thioacetamide @ mg/kilogram body weight i/p	Liver and kidney collection
III	4	Curcumin@200mg/kilogram body weight (oral)	thioacetamide @ mg/kilogram body weight i/p	Liver and kidney collection
IV	4	Curcumin@ mg/kilogram body weight (oral) + piperine@20 mg/kilogram body weight (oral)	thioacetamide @ mg/kilogram body weight i/p	Liver and kidney collection
V	4	Curcumin@400 mg/kilogram body weight (oral) + piperine@20 mg/kilogram body weight (oral)	thioacetamide @200 mg/kilogram body weight i/p	Liver and kidney collection

Gross pathology

The liver and kidney were subjected to detailed post-mortem examination. Gross lesions in the liver and kidney were recorded. Rats showing gross lesions like necrosis, degeneration, vascular and other changes were suspected of histopathological changes.

Histopathological study

Liver and kidney tissue specimens were collected and processed for histological analysis in 10% formalin [10].

Processing of tissues

The tissue samples underwent dehydration, clarifying, and paraffin embedding processing before being cut into 5mm sections using a microtome. For histological analysis, the sectioned slides were mounted on glass slides, stained with Haematoxylin and Eosin, mounted with Distyrene Plasticizer Xylene (DPX), and covered with coverslips.

Statistical analysis: Statistical methodology is used for analysis

Snedecor and Cochran [11] recommended statistical methodology was used to analyze the data.

Results and Discussion

Body weight

The mean value of body weight in different groups has been shown in Table 2.

Relative body weight



The relative increase in body wt. from 0-5 days and 5-10 days of different groups are shown in Table 2. The increase in relative body weight from 0-5 days was observed in the control group (I) whereas, the same in Thioacetamide treated group II. The body wt. from 0-5 days in curcumin treatment group III was higher than in control and Thioacetamide treatment group II. In curcumin co-administered with piperine treatment group (IV) and (V), the mean value of relative body wt. was lower than curcumin alone treated group III.

Table 2. Effect of Curcumin with and without piperine against thioacetamide induced toxicity on body weight

Group	Treatment	0 days	5 days	10 days	Relative Increase in wt%(0-5 days)	Relative Increase in wt% (5-10 days)
I	Normal saline control	160.33	175.50	190.70	9.40 ^a ±1.24	8.63 ^a ±1.14
II	Thioacetamide control (8 th day)	161.83	178.83	185.83	10.84 ^b ±1.60	3.88 ^b ±0.53
III	Curcumin (1-7 day) + TAA (8 th day)	160.33	176.83	188.50	10.46 ^{ab} ±1.39	6.67 ^{ab} ±1.41
IV	Curcumin-1 + Piperine(1-7 Day) +TAA(8 th day)	165.17	180.83	186.80	9.60 ^b ±1.10	3.08 ^b ±2.17
V	Curcumin-2 + Piperine(1-7 Day) +TAA(8 th day)	167.17	181.83	190.70	9.00 ^{ab} ±1.71	4.86 ^{ab} ±2.43

Values are the mean of four observations

Significant differences between values with various superscripts exist (p 0.05). Their values are written with the standard error

From the above result, it can be concluded that the relative body weight from 0-5 days was found to increase in rats treated with curcumin. This may be due to increased appetite and absorption of nutrients from the gut. But when curcumin was co-administered with piperine treatment groups showed a reduction in relative body wt. in comparison to the curcumin alone treatment group.

A relative increase in body wt. from 5-10 days of study of a control group (I) is shown in Table 2. The effect of Thioacetamide administration on the 8th day of the study is reflected in all treatment groups given as shown in Table 2. In Thioacetamide treated group II, the relative increase in body weight was lower than in the control-treated group. The relative body wt. in the curcumin-treated group (III) was higher than Thioacetamide-treated group II. In curcumin co-administered with piperine treatment groups IV and V, the mean value of relative body wt. was lower than in curcumin-treated group III.

In Thioacetamide treated group the increase in relative body wt. from 5-10 days was drastically reduced. This might be due to Thioacetamide toxicity affecting the gastrointestinal tract causing a decrease in appetite and absorption of nutrients from the gut or may be due to direct toxicity of Thioacetamide. Curcumin treated group showed a relatively better increase in relative body wt for 5-10 days indicating curcumin reduced the toxicity of Thioacetamide. But with the addition of piperine along with curcumin the relative increase in body weight was somewhat closer to Thioacetamide treated group. This may be a result of piperine's abrogated effect on curcumin or due to piperine enhancing the toxicity of Thioacetamide.

Significant increases in the mean body weight of curcumin-treated albino rats having liver cirrhosis were previously observed [12]. Similarly, the findings of Kadir and colleagues recorded a marked decrease in body weight in thioacetamide-treated lab animals but after treatment with *Tinospora crispa*, the body weight significantly increased [13].



Organ weight

The mean value of organ weight (grams) of the liver and kidney was studied in different groups as shown in Table 3.

Relative liver weight

Relative liver wt. (%) of different groups is shown in Table 3. In Thioacetamide treated group II, the relative liver wt. was higher than the control group. The mean value of relative liver wt. in curcumin treatment group III was lower than Thioacetamide treated group indicating some protection provided by curcumin. In curcumin co-administered with piperine treatment group (IV) and (V), the mean value of relative liver wt. was higher than only curcumin-treated group III. The liver injury and hepatic lesions were due to the toxic effect of Thioacetamide. The toxic effects caused by Thioacetamide were significantly reversed by the curcumin. This potential of curcumin can be applied as an ameliorative drug in Thioacetamide or their toxicity treatment. Similarly, a previous study reported that administering curcumin to Swiss male mice with nicotine-induced liver impairment resulted in significant decreases in liver weight [14]. Hsieh and co-workers observed an increase in liver weight through the administration of Thioacetamide-induced hepatotoxicity in rats [15].

Relative kidney weight

Relative kidney wt. (%) of different groups are shown in Table 3. The relative kidney weight in group II receiving thioacetamide was greater than in the control group. The relative kidney wt. of treatment group III was lower than Thioacetamide treatment group II. In the curcumin co-administered with piperine treatment group the relative kidney weight was increased in comparison to curcumin alone treatment group III. The increase in kidney weight caused by Thioacetamide toxicity may be due to the edema caused by tubular necrosis. But pre-treatment with the herbal drug curcumin reversed the effect of Thioacetamide on the kidney as evident in treatment groups. Similarly, a previous study observed a decrease in kidney weight after curcumin administration in cisplatin-induced nephrotoxic rats [16].

Table 3. Effect of curcumin with and without piperine against thioacetamide induced toxicity on organ weight

Group	Treatment	10-day Body wt	Liver wt	Relative liver wt %	Kidney wt	Relative Kidney wt %
I	Normal saline control	190.70	13.08	6.87 ^{cd} ±0.10	1.10	0.57 ^b ±0.03
II	Thioacetamide control (8 th day)	185.83	13.81	7.47 ^a ±0.30	1.38	0.74 ^a ±0.02
III	Curcumin (1-7 day) + TAA (8 th day)	188.50	13.15	7.03 ^{cd} ±0.30	1.20	0.63 ^b ±0.02
IV	Curcumin-1 + Piperine(1-7 Day) +TAA(8 th day)	186.80	13.57	7.25 ^{bc} ±0.08	1.22	0.65 ^{ab} ±0.03
V	Curcumin-2 + Piperine(1-7 Day) +TAA(8 th day)	190.70	13.55	7.10 ^d ±0.05	1.27	0.66 ^{ab} ±0.03

Values are mean of four observations

Significant differences between values with various superscripts (p 0.05). The standard error is listed with the values

Pathological studies

The gross and microscopic changes were recorded in rats during the experimental study. On the tenth day of the experiment, rats from each group were decapitated and slaughtered to see the progressive pathological abnormalities. Representative tissue from the liver and kidney was collected

for a detailed histo-architecture study. The pathological changes were more marked in Thioacetamide treated group as compared to other treatment groups. The gross and histopathological alterations observed in the above organs are described below.

Gross pathology

GROUP-1 (saline-treated control)

In the control group, there were no discernible gross or microscopic alterations in the liver or kidney (Figures 1A, B, and C).

GROUP-2 (Thioacetamide treated control)

Gross lesions and microscopic lesions

Grossly, hepatomegaly and yellowish discoloration on the surface of the liver were observed (Figures 2A) in Thioacetamide treated group II. In the liver section's histopathology, hemosiderosis and mononuclear cell infiltration were seen around the central vein (Figures 2B) in addition to significant hepatic necrosis (Figures 2C). A microscopic lesion in the kidney included tubular epithelial degeneration and necrosis in the thioacetamide-treated group (Figures 2D and E).

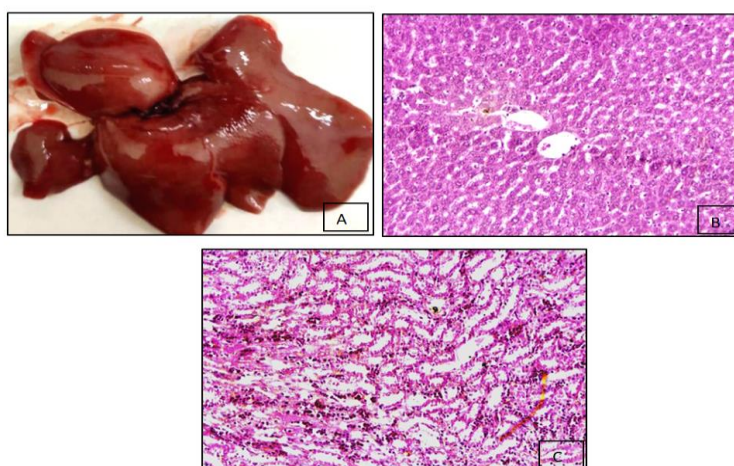


Figure 1. (A) Liver of normal saline treated rat (control group I) showing normal anatomy, (B) Microscopic section of liver showing normal hepatocyte in the control group (I) H&E X 100, (C) Microscopic section of kidney showing a normal tubular structure in rat treated with normal saline (group I) H&E X 100

Group III (Curcumin treatment group)

Gross lesions and microscopic lesions

The gross pathological changes observed in the liver as normal appearances with smooth surfaces suggesting a reversal of the Thioacetamide-induced liver damage (Figures 3A). The microscopic changes in the liver section of the curcumin-treated group were less marked. Mononuclear cell infiltration surrounding the major vein and minor hepatic necrosis was seen in the liver segment (Figures 3B). Microscopically, the kidney section showed a marked reduction in the extent of tubular damage, and normal tubular structure (Figures 3C).

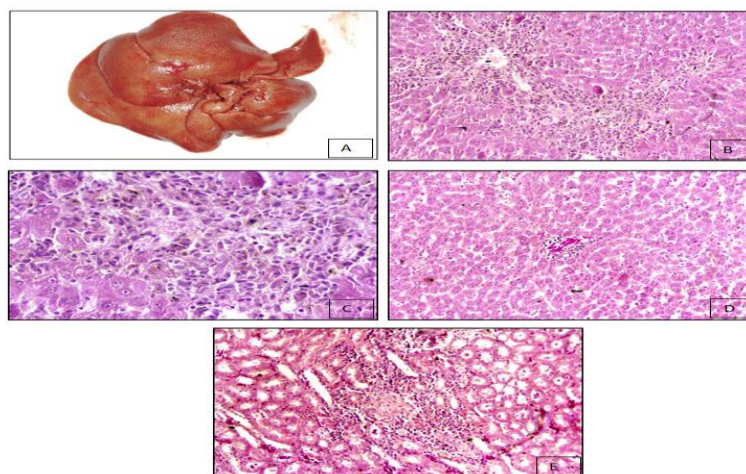


Figure 2. (A) Liver of thioacetamide treated rat (group II) showing hepatomegaly and yellowish discoloration on the surface of the liver, (B) Microscopic section of liver showing severe hepatic necrosis around the central vein in rat treated with Thioacetamide (group II) H&E X 100, (C) Microscopic section of liver showing severe hepatic necrosis, hemosiderosis and mononuclear cell infiltration around the central vein in rat treated with Thioacetamide (group II) H&E X 200, (D) Microscopic section of rat kidney showing tubular degeneration and increased capsular space in paracetamol treated group (II) H&EX400, (E) Microscopic section of kidney showing tubular necrosis in rat received Thioacetamide @ 200 mg/kilogram (group II) H&E X 100

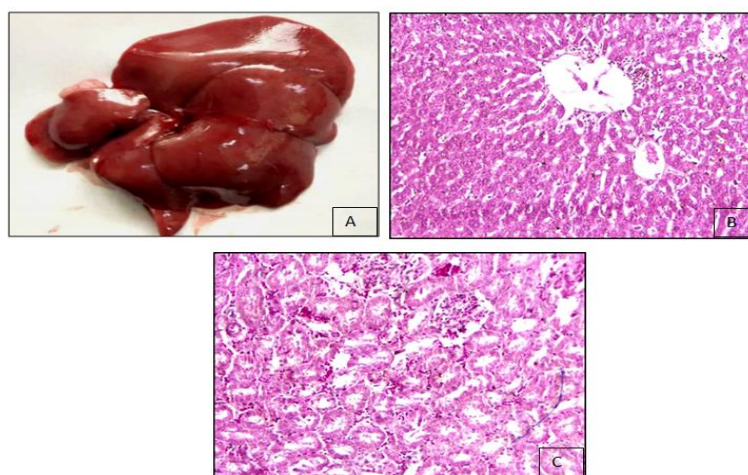


Figure 3. (A) Liver of Curcumin treated rat (group III) showing normal coloration and anatomy, (B) Microscopic liver segment of rat given 200 mg/kg of curcumin, demonstrating minor hepatic necrosis and mononuclear cell infiltration around the central vein (group III) H&E X 100, (C) Microscopic section of kidney showing normal tubular structure in rat received curcumin @ 200 mg/kilogram (group III) H&E X 100

GROUP-IV (curcumin@200 co-administered with piperine@20)

Gross lesions and Microscopic lesions

In the curcumin co-administered with a piperine-treated group, the gross pathology of the liver revealed mild swelling, pallor, and foci of yellowish discoloration (Figures 4A). The microscopic section of the liver showed mild hepatic necrosis with mononuclear cell infiltration in treated group IV (Figures 4B). In the kidney, the microscopic lesion revealed mild tubular necrosis (Figures 4C).

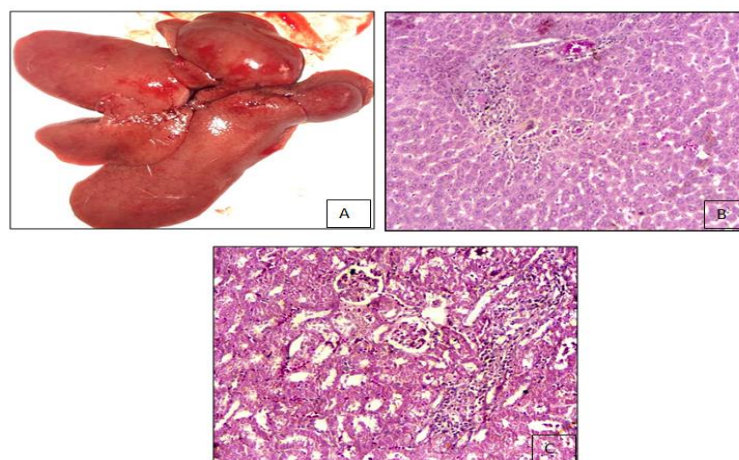


Figure 4. (A) Liver of group IV rat showing pallor and foci of yellowish discoloration, (B) Microscopic section of liver showing mild hepatic necrosis with mono nuclear cell infiltration in rat received curcumin 200 mg / kilogram + piperine 20 mg/kilogram (group IV) H&E X 100, (C) Microscopic section of kidney showing mild tubular necrosis in rat received curcumin @ 200 mg/kilogram + piperine 20 mg/kilogram (group IV) H&E X 100

GROUP-V (curcumin@400 co-administered with piperine@20)

Gross lesions and Microscopic lesions

The gross lesion of the liver showed mild foci of yellowish discoloration (Figures 5A). The microscopic changes in curcumin @400 with piperine @20 mg/kg body wt. treatment group of the liver showed mild hepatic necrosis with mononuclear cell infiltration observed (Figures 5B) indicative of protection from the Thioacetamide induced damage. In the kidney section mild tubular degeneration was observed. Even greater dosages of curcumin combined with piperine did not boost curcumin's hepatoprotective effect against Thioacetamide-induced liver damage in albino rats, according to histopathological lesions in the current study's group V.

The result indicated that rats treated with Thioacetamide (@200mg/kg b.wt.) exhibited severe histopathological changes in the liver such as necrosis of hepatocytes and occasional infiltration of inflammatory cells. Kidney changes include tubular epithelial degeneration and tubular necrosis in PCT. The finding indicated that a single dose of Thioacetamide was toxic to cause severe hepatic and renal damage. The evidence of hepatic damage by Thioacetamide has been well documented [17-18]. Thioacetamide administration induced hepatic and renal damage in the rats. Thioacetamide is transformed into the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) via metabolite activation, which causes free radical damage, more severe Glutathione (GSH) depletion, and enormous synthesis of reactive metabolites. Additionally, these intermediaries create a covalent bond with tissue-specific biological proteins [19]. Homeostasis is upset by this process, which also starts apoptosis, or programmed cell death, which causes tissue necrosis and, eventually, organ malfunction. Our observation in the present study, suggests that oral administration of curcumin in all treated groups showed a marked reversal in Thioacetamide induced hepatic and renal damage. Curcumin @ 200 and 400 mg/kg maintain cellular integrity of hepatic and renal tissue and helped in regeneration. This might be caused by curcumin's increased detoxification and excretion properties, its antioxidant properties, improved protein synthesis during liver regeneration, or any combination of these. Similar to our findings, other studies also reported that administration of curcumin lessened kidney and liver damage [20-21]. The histological lesions of the liver and kidney revealed a small decline in curcumin's protective effect against Thioacetamide-induced damage when it was co-administered with piperine. Contrary to our findings, many authors reported that piperine augments curcumin's protective action against the toxic effects of thioacetamide [22-23].

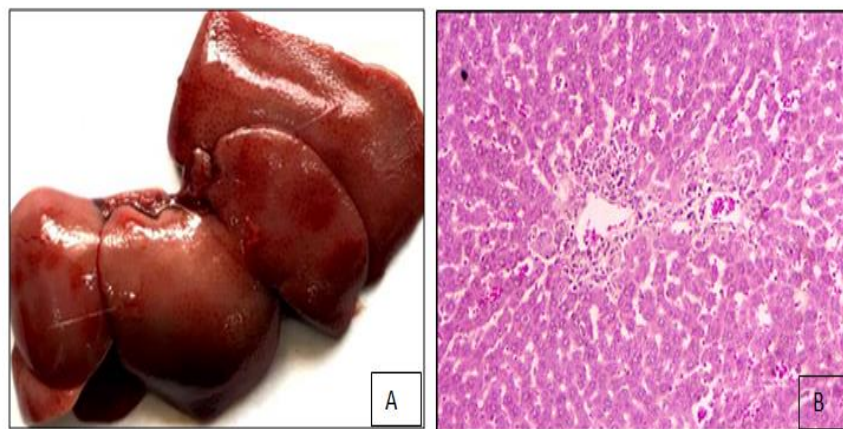


Figure 5. (A) Liver of group V rat showing mild foci of yellowish discoloration, (B) Microscopic section of liver showing mild hepatic necrosis with mono nuclear cell infiltration in rat received curcumin @ 400 mg/kilogram + piperine @ 20mg/kilogram (group V) H&E X 100

Conclusion

Histopathological characteristics demonstrated that curcumin when administered orally, protected the liver from the hepatotoxicity of thioacetamide. When piperine was administered combined with curcumin, it was shown that curcumin's hepatoprotective activity against Thioacetamide-induced liver damage was less effective than when curcumin was administered alone. Even an increased dosage of curcumin coupled with *piperine* did not enhance curcumin's ability to protect the liver from damage induced by thioacetamide in albino rats.

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Ethical approval

With IAEC No. 03/IAEC/Vety/2019, the Institutional Animal Ethics Committee (IAEC) approved the study's experimental design and animal usage. The CPCSEA requirements for the care and management of animals were followed throughout the entire experiment.

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