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Hepatoprotective and toxicity assessment of *Cannabis sativa* seed oil in Albino rat

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Abstract

The present study was carried out on forty, male and female Wister white (albino) rats weighting 100-150 gm(s) to elucidate the hepatoprotective and toxicological effect of *Cannabis Sativa* oil on liver and Kidneys to explore the side effect of the oil for 4 weeks for toxicological parameter and 10 day for hepatoprotective activity. A daily doses of *Cannabis sativa* oil (0.01 ml/kg, 0.1 ml/kg and 1 ml/kg body weight/rat administered orally to three groups of rats (each group includes 10 rats) successively where a group of ten rats was taken as a control group. However, the results of study showed hepatorenal lesions but not causing death. Extracts of *C. sativa* showed no signs of abnormalities and no mortalities among off spring rats. No changes in the physiological behaviors were observed throughout the experiment. Moreover, the sections taken were characterized by pale kidney, generalized fatty changes in the liver during the experimental period (4 weeks). Also, the oil was tested for the hepatoprotective activity, the hepatotoixicty produced by administration of CCl_4 in paraffin oil 1:9 at a dose of 0.2 ml/kg for 10 days, was found to be inhibited by simultaneous oral administration of oil of *Cannabis sativa* seeds at a dose 1 and 0.5 ml/kg for 10 days, with evidence of decreased level of serum AST, ALT, ALP, and billirubin. In addition the concurrent administration of oil with CCl_4 for 10 days masked the liver changes induced by the hepatotoxic compound observed in the control rats and comparable with the hepatoprotective effect of the standard drug Silymarin.

Key words: Hepatoprotective, toxicity, *Cannabis sativa* oil, Albino rat, seed oil

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1. Introduction

Almost no plant has been studied as much as the cannabis plant (*Cannabis sativa*); more than 10.000 papers have been published describing various aspects of cannabis as a biologically active plant [1]. *Cannabis sativa* is grown and processed for many uses. Many plant parts are used as medicine for humans and livestock, whole seeds and seed oil are eaten by human, seeds and leaves are fed to animals, seeds oil and stalks are burned for fuel. Whole plants, leaves and wood have environmental uses and bark, fiber and seed are also of ritual importance [2]. The hemp seeds oil was dispensed in an open clinical trial involving in an outpatients, for the treatment of chronic ear, nose and throat (ENT) disorders external otitis, laryngitis, pharyngitis, sinusitis, tonsillitis, acute external otitis, and trauma [3]. The effects of marijuana (*Cannabis sativa)* and its *Cannabinoids* DELTA-9- hydrocannabinol on bacterial, protozoa and viral infections, immunity, and cytokinin, studied *in vitro* and *in vivo* [4]. Different extracts of *Apium graveolens* and *Croton oblongifolius* were tested for their hepatoprotective activity against CCl_4 – induced hepatotoxicity in albino rats. The methanolic extracts showed the most significant hepatoprotective activity comparable with the standard drug Silymarin [5]. Other extracts, of petroleum ether and acetone, also exhibited a potent activity. Ethanolic extracts of *Cassia tora* and its butanol fraction had hepatoprotective activities in rats.

Whereas, the benzene fraction was found to be inactive [6]. The powder and different extracts of whole plants of *Sida cordifolia* were tested for hepatoprotective properties against CCl_4, paracetamol (Acetaminophen) and total rifampicin- induced hepatotoxicities in rats. The methanolic, aqueous extracts showed significant anti-hepatotoxic activity comparable with that of Silymarin [7].

In northeastern India some of the plants species including *Cannabis sativa* have been used for treatment of specific human ailments such as allergies, burns, cuts and wounds, inflammation, leprosy, leucoderma, scabies, smallpox and sexually transmitted diseases [8]. The different preparation of *Cannabis sativa* has been used in Asian traditional medicine for treatment of variety of diseases including: inflammation, nausea, headache, hematochesia, diarrhea, and alopecia [9]. In ancient Iranian Avesta medicine, hashish (bhanga) was mixed with wine to deliver anesthesia [10-11].

2. Materials and methods

2.1. Toxicity to Albino rats of oil of seeds of Cannabis sativa petroleum ether extract

a. Animals, housing and management

Forty, male and female Wister white (albino) rats weighting 100-150gm were obtained from the Medicinal and Aromatic Plants, Research Institute, National Center for Research, Khartoum, Sudan, where they were housed in cages and maintained in a room under standard environmental condition, controlled temperature (22 ± 2˚C), relative humidity (60%) with free access to water and formula rat feed (2.5 Mcal and 20% crude protein). Animals were apparently healthy and there were identified by color tail marks. One week was allowed as a preliminary adaptive period.

b. Administration and dose rates

At the end of the adaptation period, the animals were weight- distributed and allotted randomly to four groups, each of ten rats. Rats in group 1 were the untreated control *Cannabis sativa* oil was given orally in daily doses at 0.01ml /kg body wt/rat to group 2. Rats in group 3 received 0.1ml /kg body wt/rat/day, while rats in group 4 received 1ml /kg body wt./rat/day. Dosing continued for four weeks.

c. Parameters

Clinical signs were recorded. Blood samples were obtained from the ocular vein before the start of the experimental dosing and thereafter fortnightly for hematological investigations and serum analysis. Hemoglobin concentration (Hb), packed cell volume (PCV), red blood cell (RBC) and white blood cell (WBC) counts were estimated. Sera were analyzed for the activities of AST, ALT, ALP and for the concentrations of metabolic indicators, total protein, urea, albumin and calcium, lots of three rats from each group were anaesthetized with diethyl ether and sacrificed at the mid of the experiment and at week 4. Tissue specimens of liver, kidneys, hearts, spleen and brain were fixed in 10% neutral buffered formalin and processed for histopathology.

2.2. Hepatoprotective activity of seed's oil of Cannabis sativa petroleum ether extract to albino rats

a. Animals, housing and management

Twenty five adult male and female Wister albino rats, (95-150gm) were obtained from the Medicinal and Aromatic Plants Research Institute, National Center for Research, Khartoum, Sudan, where they were housed in cages and maintained in a room under standard environmental condition, controlled temperature (22 ± 2˚C), relative humidity (60%) with free access to water and formula rat feed (2.5 Mcal and 20% crude protein). Animals were apparently healthy and they were identified by tail color marks. One week allowed as a preliminary adaptive period.

b. Administration and dose rates

After adaptation period, the animals divided randomly into 5 groups of 5 rats each. Group 1 serving as control received only the vehicle liquid paraffin 0.2 ml/kg/day 1/p for 10 days. Group 2 serving as intoxicated control by given CCl_4 induced hepatotoxicity 0.2 ml/kg /day 1/p in liquid paraffin (1:9) for 10 days. Group 3 rats were given CCl_4 at 0.2 ml/kg /day 1/p in liquid paraffin (1:9) for 10 days and simultaneous dosed orally with the oil of *Cannabis sativa* at 1ml/kg. Group 4 rats were injected with CCl_4 at 0.2 ml/kg day/1/p in liquid paraffin (1:9) and simultaneous given orally the oil of *Cannabis sativa* seeds at dose 0.5 ml/kg. Group 5 serving as hepatoprotective drug control, rats were given CCl_4 0.2ml/kg/day1/p in liquid paraffin (1:9) for 10 days, and at the same time received orally Silymarin suspended in 5% acacia mucilage at dose 10 mg/kg/day.

c. Parameters

Blood samples were collected before treatment started at 0, and after 5 days and 10 days, and analyzed for various biochemical parameters. Rats were observed for signs of toxicity. The specimens of liver were collected immediately after slaughtering and were fixed in 10 % neutral formal saline for histopathology.

d. Preparation of the plant extract

The seeds of *Cannabis sativa* were obtained from Niala, South Darfur, Sudan, cleaned and dried. The oil was extracted as follows: The powder of *Cannabis sativa* seeds obtained was successively extracted with Petroleum ether for 4 hr, using soxhelt apparatus. The extract was occasionally shaken during the first four hours and was then filtrated. The filtrate was evaporated under vacuum, and the residue is brownish in color.

e. Histological methods

The specimens were collected immediately after slaughter and fixed in 10% formal saline, embedded in paraffin wax, sectioned at 5 um and stained with haemotoxylin and eosin (H & E) using Mayers haemalum.

3. Results

3.1. Toxicity of Cannabis sativa oil to Albino rats

a. Clinical signs

Rats in groups 2 (0.01 ml/kg), 3 (0.1 ml/kg) and 4 (1 ml/kg), showed rough coat and long hair during the experimental period (4 weeks). No mortalities were recorded. No abnormal behaviors were recorded in the un-dosed control rats (group1) and also no mortalities recorded.

b. Pathological Changes

In test groups 2 and 3, the changes in the organs were characterized by slight fatty changes, and congestion in the liver and pale kidney, whereas in group 4 (1ml/kg) the liver was showed sever fatty change and kidneys showed fatty change and congestion (Table 1).

c. Histological changes

In group 4 (1ml/kg) the histopathological changes showed slight hepatic cell necrosis and fatty changes. The kidney showed slight necrosis of the renal tubule and the brain showed slight congestion, no changes in the intestine and spleen, while in group 2, 3 (0.01ml and 0.1ml) the same changes were seen with less severity (Figs. 1-2).

3.2. Effects of Cannabis sativa oil against CCl_4 induced liver damage in rats

a. Clinical findings

Rats in group 2 (CCl_4), group 3 (CCl_4 +1ml *C. sativa*) and in group 4 CCl_4 + 0.5 ml *C. sativa*), showed depression, slight convulsion, loss of appetite and no signs were observed in group 1 (control) and while these clinical sings were less in severity in group 5 (CCl_4 + silamyrin).

b. Post –mortem finding

In group 2 (CCl_4) there was fatty changes, peteheal heamorrhages and adhesions in all lobes of liver were observed.In group 3 (1 ml/kg + CCl_4) and group 4 (0.5ml/kg + CCl_4), the liver were fragile with generalized and sever fatty changes, also there were scattered spots of necrosis in the upper surface of liver especially in group 3. No significant changes were observed in group 1 (control).

c. Changes in serum constituents

The mean values of ALT, AST, ALP and billirubin are shows in Table 2. At day zero, the activates of AST, ALP, ALT and billirubin, Showed no significant changes ($p>0.05$) for all groups, normal values were recorded from the control group. Furthermore, in day 5 groups 2 (CCl_4) showed significant increase in the activities of AST, ALP, ALT and billirubin compared with the control group, and in groups 3, 4 (1ml and 0.5ml) showed significant decrease in the activities of AST, ALP, ALT and billirubin when compared with group 2 (CCl_4), while in group 5 (silymarin + CCl_4) showed significant decrease in the of AST, ALP, ALT and billirubin. At day 10 group 2 (CCl_4), showed significant increase in the activities of AST, ALP, ALT and billirubin , and in group 3, 4 (1ml and 0.5ml) showed significant decrease in the activities of AST, ALP, ALT and billirubin. There was significant decrease in the activities of AST, ALP, ALT and billirubin in group 5 (silymarin drugs) compared with group 2 (CCl_4) (Table 2).

d. Histopathological findings

Histological sections of the livers treated with *C. sativa* oil was presented in Fig. 3 (A-D). On microscopic the liver sections of the CCl_4 group (G2), showed contrilobular necrosis of hepatocytes, and congestion of the control vein (Fig. 3A).While group 3, 4 (CCl_4 + 0.5 ml), showed slight areas of necrosis and slight fatty change (Fig. 3B) and group 4 (CCl_4 +1 ml) showed scattered areas of necrosis of the hepatocytes (Fig. 3C), and the silymarin groups showed slight fatty changes and congestion of the hepatocytes (Fig. 3D).

4. Discussion

The present study has been attempt to elucidate the hepatoprotective properties for 10 days and toxicological effect of *Cannabis sativa* oil on liver and Kidney for 4 weeks. In this study the daily doses of *Cannabis sativa* oil administered orally to rats did not caused death but showed hepatorenal lesions, the changes in the organ section were characterized by pale kidney, generalized fatty changes in the liver during the experimental period (4 weeks). These observations were reported also by Twadu [12]. In this study, the daily dosing of *Leptadenia arborea* extract via oral administration caused changes in the vital organs and tissues of the treated rats included dilatation of kidney tubules, fatty changes in the liver and sever fatty changes and areas of necrosis of liver hepatocytes. In previous studies both a CB1 (cannabidiol) antagonist and a CB2 agonist have been shown to ameliorate the brain and liver damage that occurs in liver disease and HE (Hepatic encephalopathy) [13-15].

Recent evidence elucidating the complicated mechanisms involved in the release of hepatocyte cytosolic enzymes such as ALT and AST in the blood Their appearance in blood does not necessarily indicate cell death and also that enzyme release during reversible cell damage occurs with an apparent lack of histological evidence of necrosis [16]. Inadequacy of treatment with conventional drugs and possible hazards associated with their use prompted our search for better and safer hepatopretectives of herbal origin [17] As measurement of serum levels of enzymes such as ALT and AST renders a reliable means of assessment of liver damage [18].

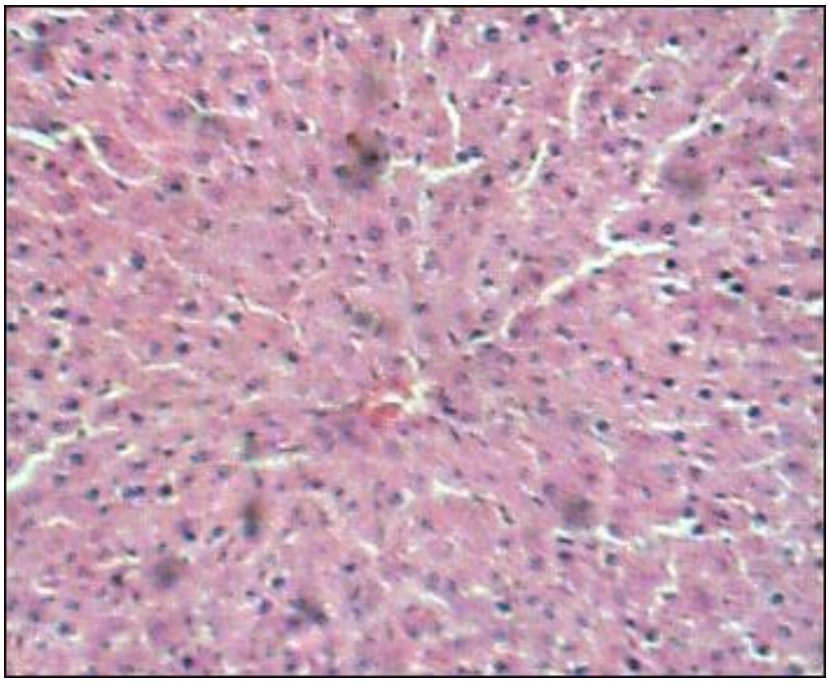

Figure 1. Focal areas of necrosis and fatty change in a liver of a rat dosed with 1ml/kg/day of *C. sativa* oil. H&E x10

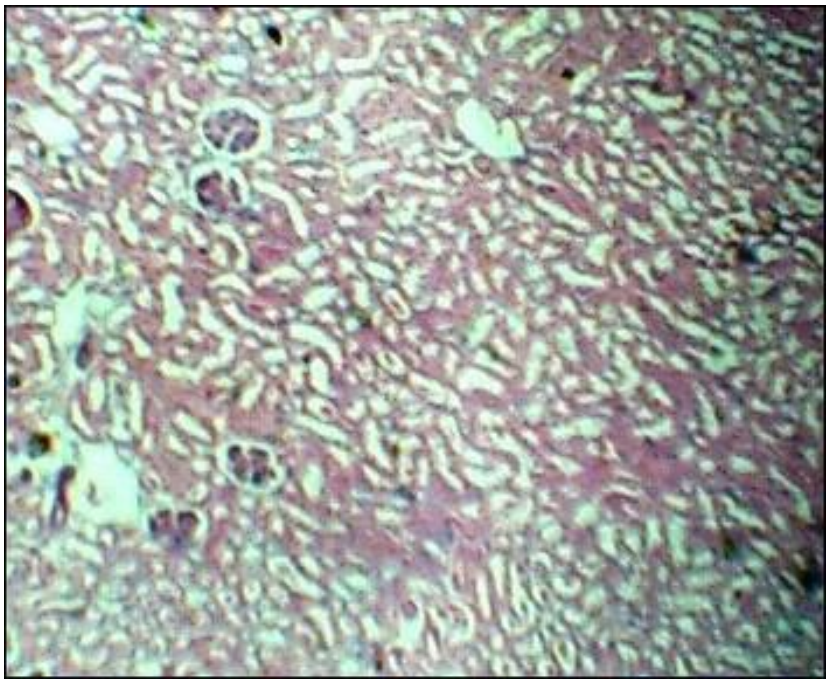

Figure 2. Scatted areas of necrosis of the renal tubules in kidneys of rats dosed with 1ml/kg of *C. sativa* oil H&E x10.

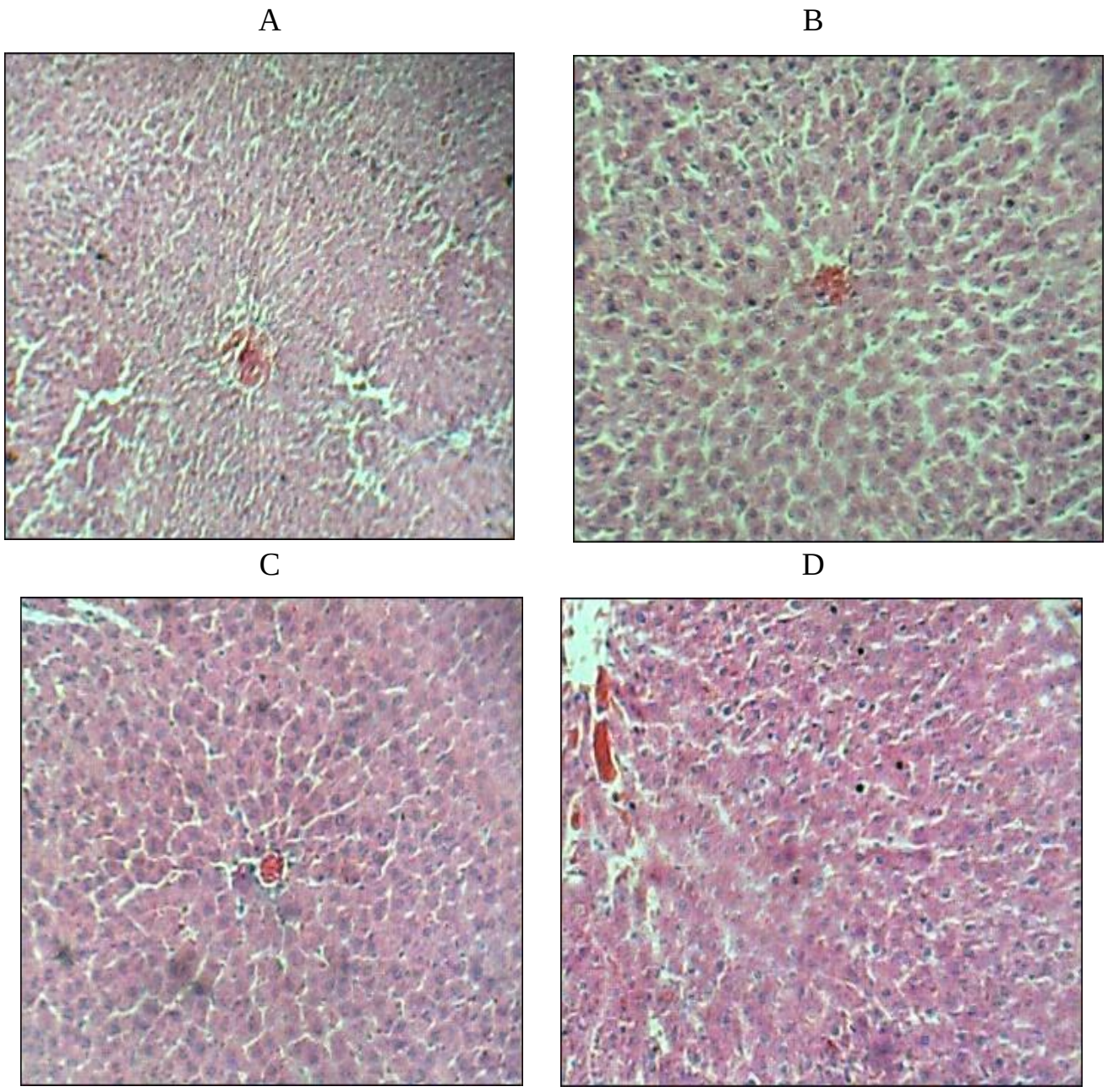

Figure 3. Sections of livers of rats treated with *Cannabis sativa* and CCl_4

A- Centrilobular necrosis of hepatocytes and congestion of the central vein in aliver of rat dosed with CCl_4 (G2).
B- Slight necrosis of hepatocytes and fatty change in a liver of a rat dosed with 0.5ml/kg/day of *C. sativa* + CCl_4 (G3).
C- Scattered areas of necrosis of the hepatocytes in a liver of rat dosed with 1ml/kg/day of *C. sativa* oil+ CCl_4 (G4).
D- Slight fatty changes and congestion of the hepatocytes in a liver of a rat with dosed 10mg/kg/day silamyrin + CCl_4 (G5).

Table 1. Average (mean ± S.E) values of serum constituents of rats treated with *Cannabis sativa* seed's oil for 4 weeks Week zero

Groups	**ALT (i.u/I)**	**AST (i.u/I)**	**ALP (i.u/I)**	**T.protein(mg/ dL)**	**Albumin (g/ dL)**	**Urea (mg/ dL)**	**Calcium (mg/ dl)**
G1	54.25±2.06a	228.75±14.33a	270.00±24.79a	7.73±0.36a	3.38±0.11a	42.25±2.29a	10.15±0.13a
G2	57.50±3.57a	241.75±16.11a	328.25±17.90a	7.45±0.25a	3.30±0.09a	39.25±2.1.4a	9.20±0.30a
G3	58.75±5.66a	227.75±25.17a	338.75±23.58a	7.58±0.19a	3.58±0.08a	37.50±2.55a	9.95±0.52a
G4	65.50±4.17a	273.25±22.42a	332.50±43.99a	7.83±0.46a	3.70±0.20a	29.75±7.95a	9.935±0.5a
Week two							
Groups	ALT (i.u/I)	AST (i.u/I)	ALP (i.u/I)	T.protein(mg/ dL)	Albumin (g/ dL)	Urea (mg/ dL)	Calcium (mg/ dl)
G1	42.00±5.70b	167.50±18.32c	296.50±28.01c	7.73±0.36a	3.38±0.11b	42.25±2.29b	10.15±0.13b
G2	47.25±4.64ab	184.50±11.59bc	451.50±52.53ab	27.13±0.19a	3.48±0.13b	50.75±2.10a	10.28±0.31b
G3	65.75±8.46a	226.25±16.10ab	350.75±39.58bc	7.75±0.19a	3.90±0.08a	46.25±2.84ab	11.00±0.09a
G4	58.75±3.20ab	257.50±12.10a	508.50±46.39a	7.45±0.10a	3.68±0.08ab	39.50±1.55b	10.83±0.26ab
Week four							
Groups	ALT (i.u/I)	AST (i.u/I)	ALP (i.u/I)	T.protein(mg/ dL)	Albumin (g/ dL)	Urea (mg/ dL)	Calcium (mg/ dl)
G1	38.50±0.87c	119.00±7.95c	307.50±16.83c	7.03±0.31a	3.88±0.26a	55.00±1.78a	11.15±0.57a
G2	47.00±2.45b	135.00±1.68b	373.50±30.43bc	7.45±0.41a	3.60±0.11a	47.00±3.42a	9.28±0.49b
G3	51.00±2.04ab	145.75±1.80ab	408.25±27.82b	7.75±0.29a	3.68±0.17a	48.50±2.72a	10.65±0.49ab
G4	55.25±2.17a	157.50±3.23a	533.75±11.71a	7.83±0.22a	3.88±0.06a	49.50±2.84a	9.95±0.52ab

G1= (UN – dosed control), G2 = (0.01 ml/kg/day cannabis sativa), G3= (0.1 ml/kg/day cannabis sativa), G4= (1 ml/kg/day cannabis sativa)
Means in the same column with the same letter are not significantly different (P>0.05).

Table 2. Average (mean ±S.E) Level of serum constituents in rats treated with *Cannabis sativa* oil administered simultaneously with CCl_4

Group \dose	ALT (i.u/I)			AST (i.u/I)			ALP (i.u/I)			Billirubin mg/dL)		
	Day Zero	Day5	Day10	Day Zero	Day5	Day10	Day Zero	Day5	Day10	Day Zero	Day5	Day10
G1	26.0±2.77[a]	37.00±3.03c	68.25±24.06b	89.6±4.87a	119.50±8.13b	134.25±5.19d	313.7±32.92a	246.25±34.96c	307.50±70.50c	0.12±0.06a	0.15± 0.02c	0.18±0.03b
G2	30.6±5.41[a]	70.00±4.95a	146.75±24.33a	120.4±3.84a	226.75±29.52a	467.75±27.30a	473.2±37.82a	568.25±87.24a	592.00±59.66a	0.51±0.09a	0.80±0.06a	1.05±0.43a
G3	31.7±2.20[a]	58.25±6.05a	77.00±11.11b	115.6±13.08a	219.25±16.10a	303.00±19.47b	376.4±27.07a	435.00±31.65ab	508.50±46.39ab	0.22±0.002a	0.55±0.26ab	0.68±0.06ab
G4	30.6±5.41[a]	55.00±5.12ab	61.75±2.87b	180.0±10.1a	211.50±22.44a	222.50±12.67c	255.52±5.26a	388.25±34.26bc	451.50±52.53abc	0.18±0.04a	0.12±0.05c	0.33±0.19b
G5	31.2±1.18[a]	40.50±5.95bc	43.25±3.66b	159.0±21.45a	167.50±28.03ab	182.75±16.62cd	252.2±7.98a	328.75±27.57bc	407.75±31.25bc	0.11±0.03a	0.22±0.02c	0.33±0.13b

G1= (control), G2= (CCl_4 0.2 mL/kg), G3= (CCl_4 0.2 ml/kg/day + 1ml cannabis sativa oil), G4= ($CCl_4$0.2 ml/kg/day + 0.5ml cannabis sativa oil), G5= (CCl_4 0.2 ml/kg/day + 10 mg/kg/day silymarin), Means in the same column with the same letter are not significantly different (P>0.05).

Our result using the model of CCl_4 induced hepatotoxicity in rats demonstrated that the oil of *Cannabis sativa* (0.5-1 ml), caused remarkable significant decreased of AST, ALT, ALP as well as billirubin concentration in serum. However, sever necrotic hepatic lesions precipitated by CCl_4 revered high levels of these enzymes. Similar type of hepatoprotective activity of *solanum nigrum* and *Khaya senegalensis* in rats is shown in literature [19-20]. Antiinfammatory activity of *Cannabis sativa* seed oil in rats is previously approved [21]. These findings indicate that the hepatoprotective effect of the seeds of *Cannabis sativa* is more expressed in rat receiving high doses of the extraction for longer period.

5. Conclusion

We conclude that administration of *Cannabis sativa* seed oil extract to rats for 4 weeks resulted in mild hepatorenal damage at higher dose of 1ml/kg/day but no death was recorded. The oil of *Cannabis sativa* contain hepatoprotective ingredient that protect the liver from carbon tetrachloride damage.

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