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Research Article
Effect of Basil Leaves Extract on Liver Fibrosis Induced by Thioacetamide in Male Rats

Mohammed Yahya Alomar and Atef Mohammed Al-Attar

Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia

Abstract

Background and Objective: Liver fibrosis is one of the most common chronic diseases worldwide. The current medical therapy of hepatic disorders is ineffective and till now there is no any therapy has successfully prevented the liver diseases and disorders. The present study aimed to investigate the effect of basil leaves extract on liver fibrosis induced by thioacetamide (TAA) in male rats. **Materials and Methods:** About 40 rats were randomly divided into four experimental groups. Rats of group 1 were served as controls. Rats of group 2 were given 300 mg kg^{-1} body weight of TAA by intraperitoneal injection, twice weekly. Rats of group 3 were orally supplemented with basil leaves extract at a dose of 300 mg kg^{-1} body weight/day. Moreover, they were intraperitoneally injected with TAA at the same dose given to group 2. Rats of group 4 were orally supplemented with basil leaves extract at same dose given to group 3. After 6 weeks of treatment, the blood samples and liver tissues were subjected to biochemical and histopathological evaluations. **Results:** Group 2 showed significantly increases of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase and total bilirubin. Significant decreases in the levels of liver glutathione and superoxide dismutase were observed in rats treated with TAA and basil leaves extract plus TAA. Noticeably decrease of liver catalase was observed in TAA treated rats. Malondialdehyde levels in liver were significantly increased in TAA and basil leaves extract plus TAA treated rats compared with control rats. In rats exposed to only TAA, liver sections showed an abnormal morphology characterized by noticeable fibrosis with extracellular matrix collagen contents and damage of liver cells structure. Administration of basil leaves extract to rats exposed to TAA led to inhibition of biochemical and histopathological alterations. **Conclusion:** These results confirmed that the protective role of basil leaves extract attributed to its antioxidant effects. Additionally, the obtained results clarify that the basil leaves extract is a potential protective natural therapy against liver fibrosis induced by exposure to TAA.

Key words: Liver fibrosis, liver diseases, basil leaves, thioacetamide, *Ocimum basilicum*, hepatic disorders, liver cells structure

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Corresponding Author: Atef Mohammed Al-Attar, Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, P.O. Box 139109, Jeddah 21323, Saudi Arabia Tel:+966504629915

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The liver is an important organ responsible for the metabolism, bile secretion, elimination of many substances, blood detoxifications, synthesizes and regulation of essential hormones[1]. Chronic liver disease is the 9th leading cause of mortality in western and developing countries[2]. Liver fibrosis is the result of excessive extracellular matrix (ECM) accumulation, characterized by scar tissue replacement and regenerative nodules occurring in hepatic perisinusoidal space[3]. Fibrotic formation results from liver impairment and its most common causes include hepatitis, alcoholism and other potentially damaging toxins[4]. Liver fibrosis was considered to be a passive and irreversible process due to the collapse of the hepatic parenchyma and its substitution with ECM components[5]. However, the reversibility of liver fibrosis has now been demonstrated both in patients and animal models[6].

In recent years, substantial traditional herbs that possess low adverse effects in the treatment of chronic liver diseases have created considerable interest as protective agents for reducing liver damage[7,8]. Basil (*Ocimum basilicum*) is an annual herb of the Lamiaceae family and is widely cultivated in different regions of the world. Basil is widely used in folk medicine to treat a wide range of diseases and has numerous pharmacological activities. Basil possesses high power against antioxidation[9]. The antioxidative effect of basil is mainly due to its content of phenolic components, such as flavonoids, phenolic acids, rosmarinic acid and aromatic compounds[10]. Additionally, basil had been found to contain linalool, eugenol, methyl chavicol, methyl cinnamate, ferulate, methyl eugenol, triterpenoids and steroidal glycoside known to exhibit antioxidant, chemopreventive, anti-inflammatory, bactericidal, antiulcer activities, a nervous system stimulant effect, modulatory effect on glutathione and antioxidant enzymes, antidiarrheal, antihypertensive, antiosteoporotic and antidiabetic influences[11-16]. Recently, there are no scientific studies on the effect of basil on liver fibrosis induced by thioacetamide (TAA). Therefore, the present study was designed to evaluate the effect of basil leaves extract on liver fibrosis induced by TAA in male rats.

MATERIALS AND METHODS

Extraction of basil leaves: The fine quality of basil leaves were purchased from local market, Jeddah, Saudi Arabia. The leaves were scientifically defined by the herbarium of Biological Sciences Department, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia. The method of Al-Attar and Abu Zeid[17] was used to prepare the extract with some modifications. The aqueous extract of leaves was prepared every 2 weeks. The dried olive leaves (200 g) were powdered and added to 7 L of hot water. After 3 h, the mixture was slowly boiled for 30 min. After boiling period, the mixture was cooled at room temperature and it was gently subjected to an electric mixer for 20 min. Thereafter the solutions of basil leaves were filtered. Finally, the filtrates were evaporated in an oven at 40°C to produce dried residues (active principles). With references to the powdered samples, the yield means of leaves extract were 17.6%. Additionally, the extract was stored in a refrigerator for subsequent experiments.

Animals: Male albino rats of the Wistar strain (*Rattus norvegicus*), weighing 236-284 g were utilized in the present study. The experimentations were conducted at the Experimental Animal Unit, Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia during July and August 2018. The experimental animals were housed in standard plastic cages and maintained under controlled room conditions of humidity (65%), temperature (20±1°C) and 12:12 h light:dark cycle. Rats were fed *ad libitum* on normal commercial chow and had free access to water. The experimental treatments were conducted in accordance with ethical guidelines of the Animal Care and Use Committee of King Abdulaziz University.

Experimental treatment: A total of 40 rats were randomly divided into 4 experimental groups, 10 of rats each. The experimental groups were treated as follows:

- Rats of group 1 were served as controls and intraperitoneally injected with saline solution (0.9% NaCl), twice weekly
- Rats of group 2 were given 300 mg kg^{-1} body weight of TAA (Sigma-Aldrich Corp., St. Louis, MO, USA) by intraperitoneal injection, twice weekly
- Rats of group 3 were orally supplemented with basil leaves extract at a dose of 300 mg kg^{-1} body weight/day. Moreover, they were intraperitoneally injected with TAA at the same dose given to group 2
- Rats of group 4 were intraperitoneally injected with saline solution (0.9% NaCl), twice weekly and were orally supplemented with basil leaves extract at a dose of 300 mg kg^{-1} body weight/day

Body weight determination: The body weights of rats were determined at the start of the experimental period and after 6 weeks using a digital balance. These weights were measured at the same time during the morning. Moreover, the experimental animals were observed for signs of abnormalities throughout the period of study.

Blood serum analyses: After 6 weeks, the experimental animals were fasted for 8 h, water was not restricted and then anaesthetized with diethyl ether. Blood samples were collected from orbital venous plexus in non-heparinized tubes, centrifuged at 2500 rpm for 15 min and blood sera were then collected and stored at -80°C.

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using the method of Reitman and Frankel[18]. Serum alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin were estimated using the methods of McComb and Bowers[19], Szasz[20] and Doumas *et al.*[21], respectively.

Liver oxidative markers estimation: After blood sampling, rats were dissected and the liver tissues were perfused with phosphate buffered saline solution, pH 7.4 containing 0.16 mg mL^{-1} heparin to remove any red blood cells and clorts. One gram tissue was homogenized in 5-10 mL cold buffer (50 mM potassium phosphate, pH 7.5. 1 mM EDTA) and centrifuged at 2500 rpm for 15 min at 4°C. The supernatant was removed and freezed at -80°C. Liver glutathione (GSH), superoxide dismutase (SOD), malondialdehyde (MDA) and catalase (CAT) were measured according to the methods of Beutler *et al.*[22], Nishikimi *et al.*[23], Ohkawa *et al.*[24] and Aebi[25], respectively.

Histopathological examination: After blood sampling, liver tissues from all experimental dissected groups were fixed in 10% buffered formaldehyde, sectioned and stained with hematoxylin and eosin. Moreover, liver sections were subjected to Masson's trichrome stain. All liver sections were observed under light microscope (Olympus BX61-USA) connected to motorized controller unit (Olympus bx-ucb-USA) and photographed by a camera (Olympus DP72-USA).

Statistical analysis: All data were expressed as mean±standard deviation (SD). One-way analysis of variance (ANOVA) was used to evaluate differences among experimental groups. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for windows, version 22.0. Differences with $p<0.05$ were considered statistically significant.

RESULTS

Body weight: Figure 1 represented the body weights of all experimental groups after 6 weeks. A gradual increase in the body weight gain of normal control rats and those supplemented with basil leaves extract was recorded as compare to TAA-intoxicated and basil leaves extract plus TAA treated rats.

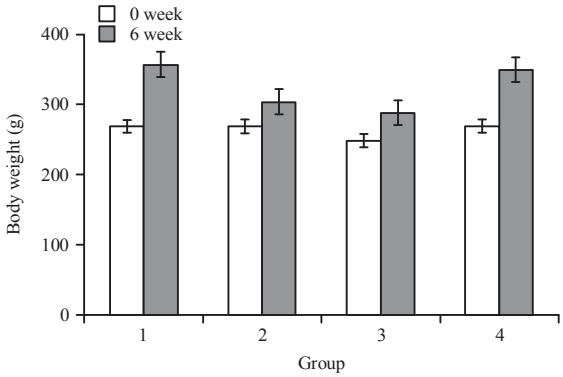

Fig. 1: Changes of body weight after 6 weeks in control (group 1), TAA (group 2), basil leaves extract plus TAA (group 3) and basil leaves extract (group 4) treated rats

Blood serum analyses: The levels of serum ALT, AST, ALP, GGT and total bilirubin in control, TAA, basil leaves extract plus TAA and basil leaves extract treated rats are shown in Fig. 2a-e. Statistically increases in the level of serum ALT were observed in rats exposed to TAA ($p<0.000$) and basil leaves extract plus TAA ($p<0.000$) compared with control and basil leaves extract treated rats. In comparison with control rats, the levels of serum AST were markedly increased in rats exposed to TAA ($p<0.000$) and basil leaves extract plus TAA ($p<0.001$). The TAA administration to normal rats significantly increased the level of serum ALP ($p<0.01$) compared with control rats. Significant elevations in the level of serum GGT were noted in rats treated with TAA ($p<0.000$) and basil leaves extract plus TAA ($p<0.000$) compared with control rats. Serum total bilirubin level was statistically enhanced in rats exposed to TAA ($p<0.002$) and basil leaves extract plus TAA ($p<0.01$).

Liver oxidative stress markers: Significant decreases in the level of liver GSH were observed in rats treated with TAA ($p<0.007$) and basil leaves extract plus TAA ($p<0.01$) compared with control rats. Relative to the control rats, the experimental rats treated TAA exhibited significantly decline in the level of liver SOD ($p<0.01$). The level of liver SOD was also statistically decreased in basil leaves extract plus TAA treated rats ($p<0.02$). The MDA levels in liver were significantly increased in TAA ($p<0.002$) and basil leaves extract plus TAA ($p<0.002$) treated rats compared with control rats. Noticeably decrease of liver CAT was observed in TAA treated rats ($p<0.002$) compared with control rats (Table 1).

Liver histopathological examination: Histopathological examination of liver sections of control, TAA, basil leaves extract plus TAA and basil leaves extract treated rats are represented in Fig. 3a-h. Control rats of group 1 (Fig. 3a) and

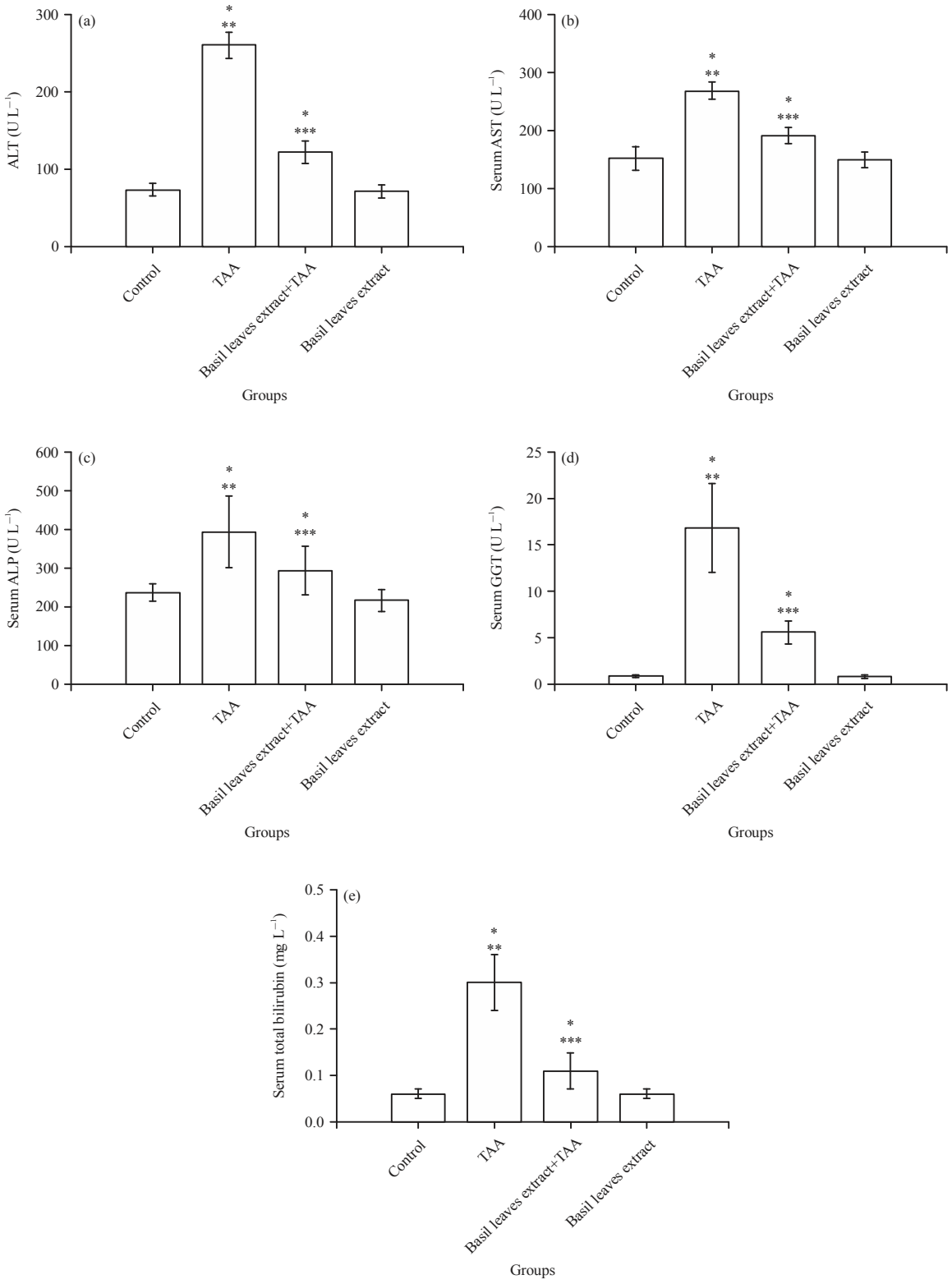

Fig. 2 (a-e): Levels of serum (a) ALT, (b) AST, (c) ALP, (d) GGT and (e) Total bilirubin in control, TAA, basil leaves extract plus TAA and basil leaves extract treated rats

*Indicates a significant difference between control and treated groups, **Indicates a significant difference between group 2 (TAA) and groups 3 (basil leaves extract+TAA) and 4 (basil leaves extract) treated rats, ***Indicates a significant difference between groups 3 and 4

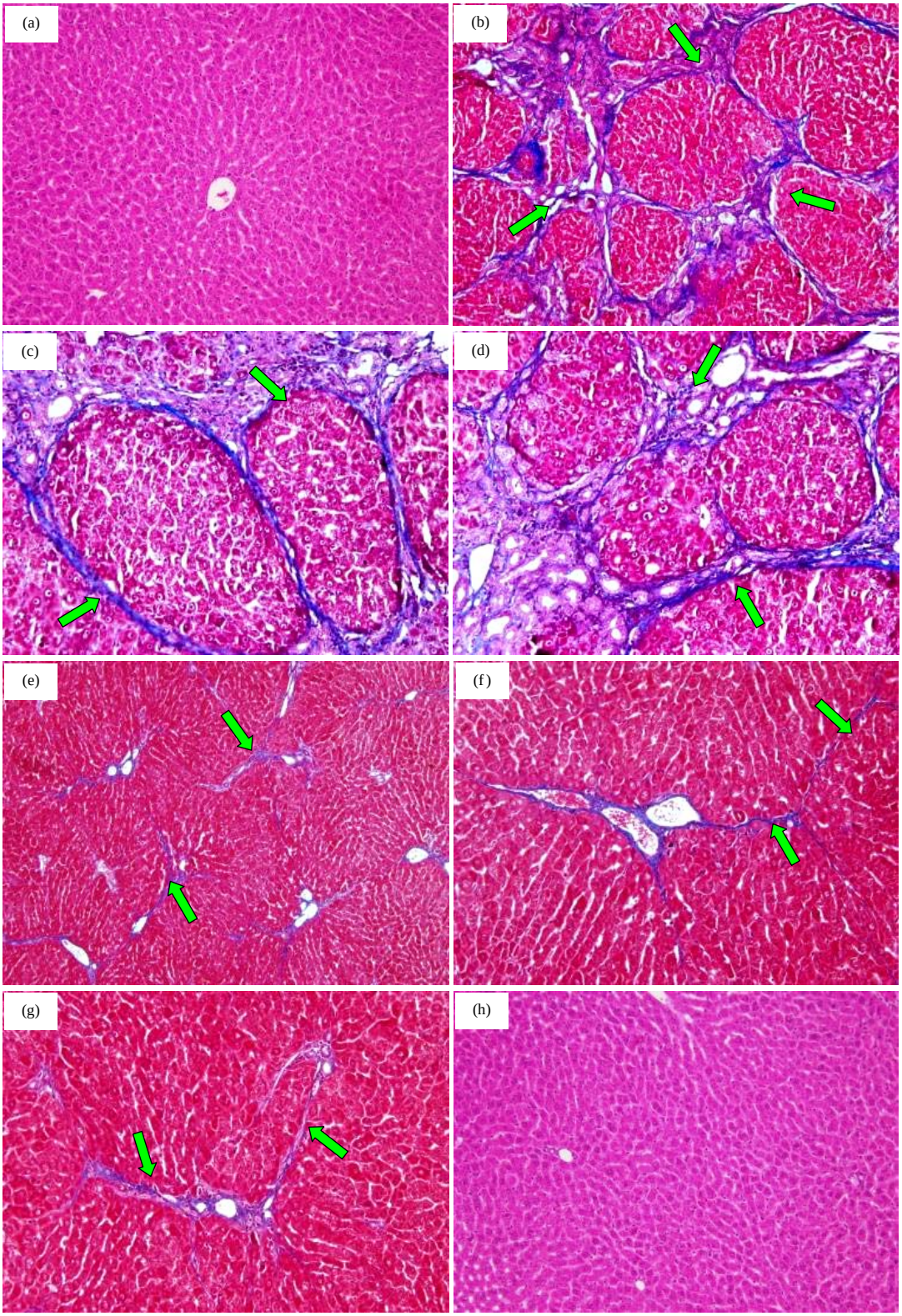

Fig. 3(a-h): Photomicrographs of liver sections from control rats showing normal histological structure (a X200), TAA treated rats showing the fibrosis with mixed sized nodules and fibrotic septae, arrows, (b X100, c and d X200), basil leaves extract plus TAA treated rats showing a mild fibrosis with mixed sized nodules and fibrotic septae, arrows, (e X100, f and g X200) and basil leaves extract treated rats showing normal histological structure (h X200)

Table 1: Levels of liver GSH, SOD, MDA and CAT in control, TAA, basil leaves extract plus TAA and basil leaves extract treated rats after 6 weeks. Percentage changes are included in parentheses

	Treatments			
Parameters	Control	TAA	Basil leaves extract+TAA	Basil leaves extract
GSH (mg g^{-1})	21.36±0.87	16.68±2.63a (-21.9)	17.24±1.21a (-19.3)	20.12±1.65 (-5.8)
SOD (U g^{-1})	20.02±2.07	16.14±1.69 a (-19.4)	16.48±0.85ac (-17.7)	19.66±0.83 (-1.8)
MDA (nmol g^{-1})	15.44±0.67	21.06±1.69ab (+36.4)	19.36±2.29a (+25.4)	17.24±1.27 (+11.7)
CAT (U g^{-1})	118.06±1.99	102.56±3.34ab (-13.1)	111.64±4.17 (-5.4)	117.36±6.07 (-0.6)

Data represent the Means±SD of 7 animals per group. [a]Significant difference between control and treated groups, [b]Significant difference between group 2 (TAA) and groups 3 (basil leaves extract+TAA) and 4 (basil leaves extract) treated rats, [c]Significant difference between groups 3 and 4

rats supplemented with basil leaves extract (Fig. 3h) showed a normal hepatic architecture. In rats exposed to only TAA (group 2), liver sections showed an abnormal morphology characterized by noticeable fibrosis with ECM collagen contents and damage of liver cells structure (Fig. 3b-d). Liver sections from basil leaves extract plus TAA treated rats showed a reduced extent and development of fibrosis processes (Fig. 3e-g). Moreover, the hepatocytes showed slight alterations compared with hepatocytes structure of rats treated with only TAA.

DISCUSSION

The present study was the first experimental investigation designed to evaluate whether supplementation of basil leaves extract would have protective effect on TAA induced liver fibrosis with physiological disturbances and histological injuries in male rats. In the present study the administration of TAA at a dose of 300 mg kg^{-1} body weight twice weekly for 6 weeks caused liver fibrosis accompanied with physiological and histopathological alterations in experimental rats. Physiologically, it is known that TAA toxicity is generally associated with hepatic fibrosis induction, complicated metabolic disorders and health problems[26].

The present study showed that the administration of TAA for 6 weeks induced an elevation in the levels of serum ALT, AST, ALP, GGT and total bilirubin with histopathological changes in rats. The observed increase in the levels of ALT, AST, ALP, GGT and total bilirubin are the major diagnostic symptoms of hepatic damage and diseases[27-29]. Moreover, many experimental studies showed that these parameters were significantly increased with histopathological changes in experimental animals treated with TAA[26,30-36]. Current findings indicated that TAA induced oxidative stress which confirmed by the decreases of liver GSH, SOD and CAT levels and an increase of MDA level. These findings clearly showed that TAA induced oxidative stress in experimental rats. Both enzymatic and non-enzymatic antioxidant system are essential for cellular response in order to deal with oxidative stress under physiological condition. Therefore, as SOD and CAT and non-enzymatic electron receptors such as GSH and MDA are antioxidant enzyme such affected and used as indexes to evaluate the level of oxidative stress[37-40].

It was observed that the treatment with basil leaves extract attenuated the physiological and histopathological alterations induced by TAA in rats. This indicated the effectiveness of basil leaves extract in prevention of TAA toxicity. From the present findings, the possible mechanism of the studied extract attributed to its antioxidant roles which evaluated by GSH, SOD, MDA and CAT levels. Basil possesses high power against antioxidation[9,41]. The antioxidative effect of basil is mainly due to its content of phenolic components, such as flavonoids, phenolic acids, rosmarinic acid and aromatic compounds[10]. The antioxidant activity of phenolic compounds is mainly caused by their redox properties, which permit them to act as reducing agents, hydrogen donors and singlet oxygen quenchers[42]. Moreover, previous studies showed that the basil extracts attenuated physiological, biochemical and histopathological alterations and exert protective effects that might be attributed to its antioxidants and free radicals scavenging properties[43-46]. To strengthen this study, further physiological, histopathological and pharmacological investigations are required to evaluate the effect of different doses of basil leaves extracts as a therapeutic factor on liver fibrosis induced by TAA and other related fibrogenic and pathogenic agents.

CONCLUSION

The present study indicated that the basil leaves extract significantly exerts noticeable of biological and pharmacological influences. The effect of basil leaves extract including attenuation of hepatic fibrosis and oxidative stress markers. Moreover, this study confirmed that the effect of basil leaves extract attributed to its antioxidant role.

SIGNIFICANCE STATEMENTS

This is the first study designed to investigate the protective effect of basil leaves extract against liver fibrosis and oxidative stress induced by TAA. The present study demonstrates that basil leaves extract can be beneficial for the treatment of liver fibrosis. The obtained results will help researchers to explore the important pharmacological roles of basil leaves and its active constituents as possible novel natural therapy for liver fibrosis and other diseases.

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