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Hepatoprotective Effect of *Lavandula dentata* leaves extracts on Thioacetamide-Induced hepatic fibrosis in male albino mice

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ABSTRACT

This study is to investigate the effect of *L. dentata* leaves extracts on experimental liver fibrosis induced by thioacetamide (TAA) in male albino mice. The experimental mice were divided into four groups. The mice of the first group were served as control. The experimental animals of the second group were given 150 mg/kg body weight of TAA by intraperitoneal injection, twice weekly, for 8 weeks. The mice of the third group were exposed to TAA and supplemented with *L. dentata* leaves extracts. The animals of the fourth group were supplemented with *L. dentata* leaves extracts. The levels of plasma alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase were significantly decreased. Histopathological evaluations of hepatic sections from mice treated with TAA showed severe alterations including increase of fibrogenesis processes with structural damage. Administration of *L. dentata* leaves extracts reduced extent and development of fibrous septa, liver cells change, and biochemical alterations in mice exposed to TAA. The present findings suggests that the supplementation of these extract may act as antioxidant agents and could be an excellent adjuvant support in the therapy of hepatic fibrosis.

Keywords: *Lavandula dentate,* leaves extracts, liver, thioacetamide (TAA), male, mice

1. Introduction

Liver or hepatic fibrosis is a reversible physiological wound-healing process. When damage is sustained, however, this process becomes exacerbated and irreversible, leading to cirrhosis (Ramachandran and Iredale, 2012). Hepatic fibrosis after hepatocyte injury is a pathological process with deposition of extracellular matrix (ECM) proteins such as collagens (Lang *et al.,* 2011). A report of The World Health Organization (WHO) indicates that 10% of the world population has chronic liver disease, in addition about two million people worldwide die each year from hepatic failure (Schuppan and Afdhal, 2008).

Thioacetamide (TAA) was originally used to control the decay of oranges and then as a fungicide (Childs and Siegler, 1945). TAA is a potent hepatotoxicant which requires metabolic activation by the mixed-function oxidases. For its toxicity, thioacetamide requires oxidation to its S-oxide and then further to reactive S,S-dioxide form which ultimately attacks lipids and proteins (Hajovsky *et al.,* 2012). Further-more, the hepatic toxic chemical TAA has been widely used in the study of the underlying mechanisms of hepatic fibrogenesis and the therapeutic effects of potential antifibrosis drugs. Additionally, many experimental investigations showed that TAA induced hepatic fibrosis and cirrhosis in rats and mice (Al-Attar and Shawush, 2015; Meng *et al.,* 2015; Wang *et al.,* 2015).

Nature has been a source of medicinal treatments for thousands of years and plant derived products continue to play an essential role in the primary health care of about 80-85% of the world's population. Despite the trends of molecular biology and chemistry providing fast escalation of synthesized *de novo* drugs, plants still remain a traditional source of medicinal compounds; up to 40% of modern drugs may directly or indirectly be related to natural compounds (Solyanik *et al.,* 2004). Phytotherapy consists of the use of medicinal plants in order to prevent, cure or threat illnesses (López

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et al., 2017). Kingdom of Saudi Arabia has abundant and wide variety of medicinal plants whose therapeutic effects have not been adequately studied (Almalki *et al.,* 2019).

Lavender genus is an important member of the Lamiaceae family. *Lavandula* species are widely distributed in the Mediterranean region and cultivated in France, Italy and Spain. *Lavandula* is a plant with small purplish flowers which are mostly used to produce aromatic extracts (Dalilan *et al.,* 2013). Lavender which is well-known to people as a powerful aromatic and medicinal herb, is one of such alternatives that could be used as a feed additive (Salarmoini *et al.,* 2019). Previous phytochemical studies demonstrated that the most effective components of the aerial parts of lavender are monoterpenes linalool and linalyl acetate, coumarins and triterpenoids which cause its pharmacoactivity. It also contains aqueous phenolic compounds, such as hydroxycinnamic acids and flavone glycosides which are associated with its antioxidant activity (Büyükokuroğlu *et al.,* 2003; Hajhashemi *et al.,* 2003; Kageyama *et al.,* 2012; Mantovani *et al.,* 2013). Various pharmacological properties are attributed to lavender extract including anticonvulsant, sedative, analgesic, antioxidant and local anesthetic activity (Lehrner *et al.,* 2005; Lin *et al.,* 2007; Duda *et al.,* 2015; Bajalana *et al.,* 2016; Rahmati *et al.,* 2017). The plant is used in traditional and folk medicines of different parts of the world for the treatment of several gastrointestinal, nervous and rheumatic disorders (Rabiei *et al.,* 2014a).

Additionally, it contains high levels of flavonoids, which possess a broad spectrum of chemical and biological activities, including radical scavenging properties (Rabiei *et al.,* 2014b). Akermi *et al.,* (2020) evaluated the neuroprotective effect of lavender essential oilagainst hydrogen peroxide (HP)- induced toxicity in mice. HP induced damage in histomorphological changes in the brain of mice, significant atrophy, as well as an important alteration of the genetic expression. The authors concluded that the essential oilof lavender offered significant protection against the toxicity of HP by restoring these parameters to normal, that's maybe attributed to its constituents.

2. Materials and Methods

2.1. Animals

Male albino mice of the SWRstrain, weighing 15.0–25.0 g were taken for the present study. The principles of laboratory animal care were followed throughout the duration of experiment and instruction given by King Abdulaziz University ethics committee was followed regarding experimental treatments. The mice were distributed into four groups (ten mice per group) and were housed in standard cages at an ambient temperature of 20 ±1 _C with 12-h light:12-h dark cycle and humidity of 65%. The mice were fed ad libitum on normal commercial chow and had free access to water.

2.2. Extraction of *L. dentata* leaves

The fresh leaves of *L. dentata* leaves extracts were directly collected from the outskirts of Albaha region of Saudi Arabia. The collected leaves were completely washed, air dried at room temperature and stored in a dry plastic container until use for extraction processes. The method of Al-Attar and Abu Zeid (2013) was used to prepare the extracts. The dried *L. dentata* leaves extracts (50 g) were powdered, added to 2 liters of cold water and mixed using an electric mixer for 20 min. Thereafter, the solutions of *L. dentata* was gently 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 mean yield of

L. dentata was 18.3%. Furthermore, these extracts were stored in a refrigerator for subsequent experiments.

2.3. Experimental design

The mice were randomly distributed into four groups of 10 each. Mice of group 1 were served as controls and intraperitoneally injected with saline solution (0.9% NaCl), twice weekly for eight weeks. Mice of group 2 were given 150 mg/kg body weight of TAA (Sigma–Aldrich Corp., St. Louis, MO, USA) by intraperitoneal injection, twice weekly for eight weeks. Mice of group 3 were intraperitoneally injected with TAA at the same dose given to group 2 and were orally supplemented with *L. dentata* leaves extract at a dose of 200 mg/kg body weight/day for eight weeks. Mice of group

4 were intraperitoneally received saline solution at the same dose given to group 1 and were orally supplemented with *L. dentata* leaves extract at the same dose given to group 3 for eight weeks.

2.4. Biochemical Analyses

At the end of experimental period, mice were fasted for 6 hours and anaesthetized with diethyl ether. Blood specimens were collected from orbital venous plexus in vacuum tubes containing EDTA (k3) as anticoagulants. Blood specimens were centrifuged at 200 ×g for 10 minutes, and the clear samples of blood plasma were separated. Plasma ALT, AST, GGT, ALP were estimated using an automatic analyzer (Reflotron Plus System, Roche, Germany). These serum samples were used to determine the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. The method of Reitman and (Frankel, 1957) was used to determine the levels of serum ALT and AST. The method of (Szasz, 1969) was used to measure the level of serum ALP. Serum level of GGT was estimated using the method of (Doumas *et al.,* 1973).

2.5. Histopathological examinations

Mice were dissected and the liver tissues were preserved in 10% buffered formalin immediately after removal from the animals, embedded with paraffin. After routineprocessing, paraffin sections of each tissue were cut into 4 lm thickness and stained with hematoxylin and eosin, Moreover, liver sections were subjected to Masson's trichrome stain. All liver sections were examined using a light microscope and photographed.

2.6. Statistical analysis

The data were expressed as mean± standard deviation (SD) and were analyzed using the Statistical Package for Social Sciences (SPSS for windows, version 12.0). Statistical comparisons were performed by a two-way analysis of variance (ANOVA). The results were considered statistically significant if the P-values were less than 0.05.

3. Results

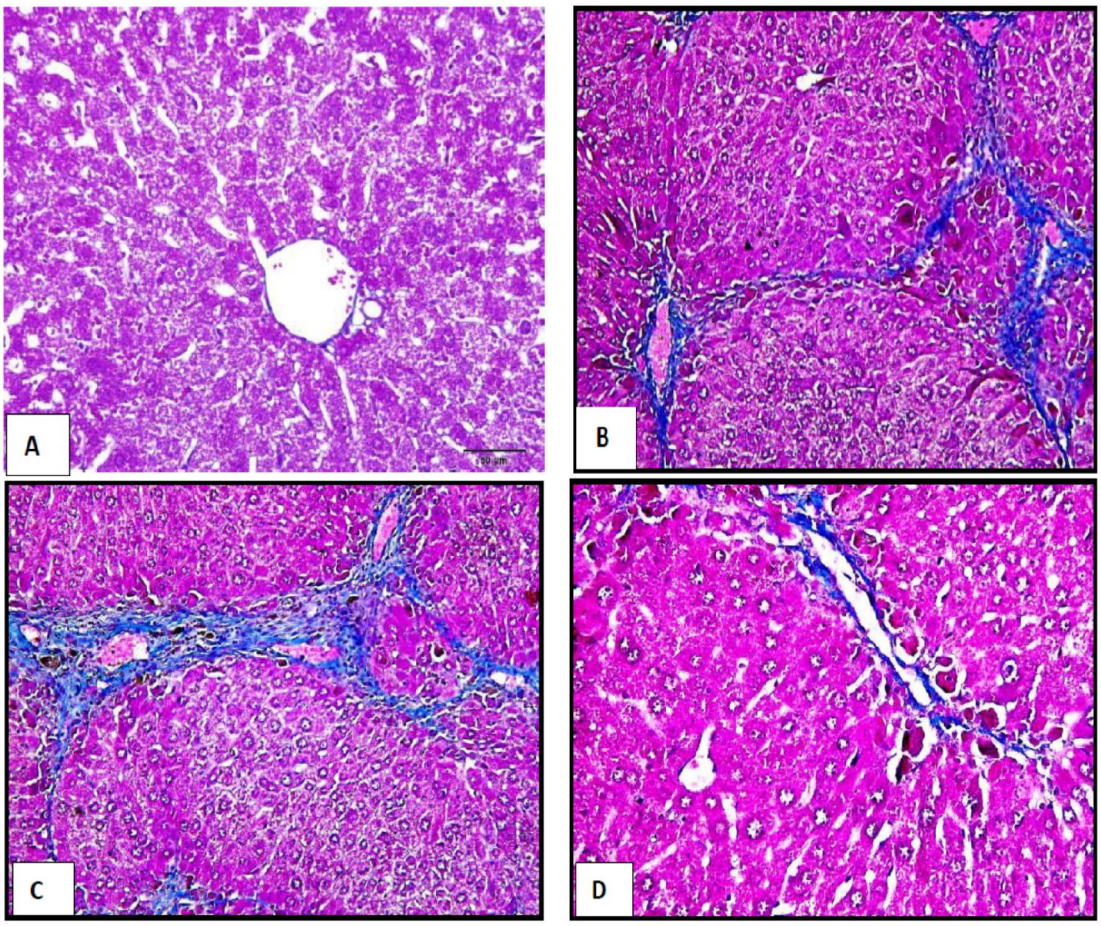
The body weights after eight weeks of all experimental groups are a gradual increase in the body weight gain of normal control mice (120.7%) at the end of eight weeks compared with their initial body weights. Significant decreases in the values of body weight gain were observed in mice treated with TAA, TAA plus *L. dentata* leaves extract. The minimum body weight gain was noted in TAA-intoxicated mice (34.8%). Supplementation with the tested extracts showed remarkable lowering effect on the percentage changes of body weight in mice treated with TAA plus *L. dentata* leaves extract. The change of body weight gain was 106.6% in normal mice supplemented with *L. dentata* leaves extract. The percentage change of body weight gain in normal mice fed with *L. dentata* leaves extracts is 104.4%.

According to the data showing in Table 1, the levels of serum ALT, AST, GGT, ALP of control and treated mice after eight weeks are shown in TAA at the dose of 150 mg/kg body weight induced significant increases ($P < 0.05$) of plasma ALT (+117.6%), AST (+101.5%), GGT (+141.2%), ALP (+53.0%) were statistically decreased ($P < 0.05$) in mice of group 2 compared with control (group 1), TAA plus *L. dentata* leaves extracts (group 3), and *L. dentata* leaves extracts (group 4) treated mice. The level of plasma ALT (+26.9%) was statistically elevated in mice treated with TAA plus *L. dentata* leaves extracts compared with control and *L. dentata* leaves extracts treated mice. The level of plasma GGT (+19.7) was increased in mice treated with TAA plus *L. dentata* leaves extracts compared with mice supplemented with only *L. dentata* leaves extracts. Additionally, the levels of plasma AST, ALP were significantly unchanged in mice treated with TAA plus *L. dentata* leaves extracts. Furthermore, insignificant changes of plasma ALT, AST, GGT, ALP were observed in mice treated with only *L. dentata* leaves extracts.

Table 1: Plasma ALT, AST, ALP, GGT levels (mean ± SD) of control, TAA, TTA plus *L. dentata* leaves extracts, and *L. dentata* leaves extracts treated mice (n = 7). Percentage changes are included in parentheses.

	Parameters			
Treatments	**ALT (U/L)**	**AST (U/L)**	**ALP (U/L)**	**GGT (U/L)**
Control	24.61 ± 3.03	39.37 ± 4.10	118.55 ± 8.61	4.78 ± 0.50
TAA	58.00 ± 12.15 (+117.6%)	82.50 ± 22.40 (+101.5%)	180.63 ± 24.28 (+53.0%)	11.55 ± 2.31 (+141.2%)
TAA + *L. dentata* leaves extracts	33.62 ± 7.35 (+26.9)	48.86 ±11.64 (+19.5)	126.38 ± 16.78 (+6.4)	3.63 ± 1.33 (+19.7)
***L. dentata* leaves extracts**	24.75 ± 3.01 (−7.1)	41.00 ± 5.93 (−0.9)	118.13 ± 8.86 (+0.5)	4.53 ± 0.48 (−5.2)

Liver histopathological results were depicted in Figure 1(A-F) showed the normal structure in control and *L. dentata* leaves extract. The liver sections of control and *L. dentata* leaves extract treated mice showed normal liver cells or hepatocytes with preserved cytoplasm, poeminent nucleus and nucleolus, and well brought out central vein. These cells are cuboidal epithelial cells arranged in anastomosing plates and cords. In classical lobules, the plates radiate from the central vein and cords alternate with sinusoids. After eight weeks of TAA treatment (group 2), the treated mice revealed an abnormal morphology characterized by noticeable structural damage with the extracellular matrix collagen fibrosis processes in the liver (Fig1. B –C). In mice treated with TAA plus *L. dentata* leaves extract (Fig1. D –E), liver sections showed a reduced extent and development of fibrosis. In addition, the liver cells showed slight alterations compared with liver cells structure of mice treated with only TAA.



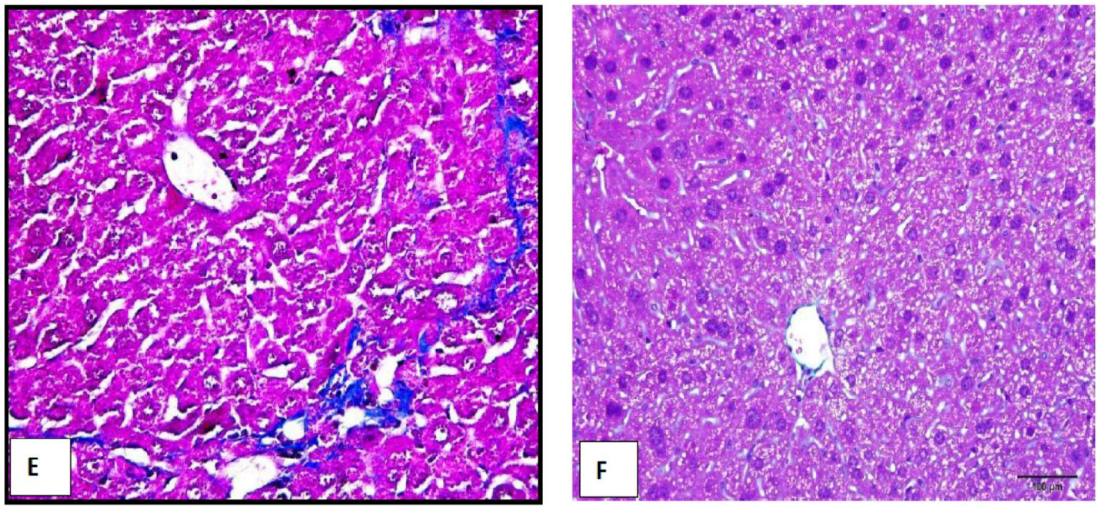


Fig. 1 (A- F): Photomicrograph of liver section in each group.(A) control (X400), (B and C) TAA (X400 and X400),(D and E) TAA plus *L. dentata* leaves extract (X400 and X400), (F) *L. dentata* leaves extract treated mice for eight week.

4. Discussion

The cirrhosis of liver is a common end consequence of a variety of CLD. Its underlying pathology, fibrosis, represents the common response of liver to toxic, infectious, or metabolic agents (Schuppan and Kim, 2013). Currently, hepatic fibrosis still contributes to the high incidence and morbidity rates of cirrhosis as the latter is irreversible. Thus, researchers are dedicated to find out specific treatment targets that contribute to the development of hepatic fibrosis (Qin *et al.,* 2014).

The present study is the first experimental investigation designed to evaluate whether supplementation of *L. dentata* leaves extracts would have protective influences on TAA induced hepatic fibrosis with physiological disturbances and histological injuries in male mice. TAA intoxication has shown significant increases in the levels of serum ALT, AST, GGT and ALP. Similar observations were noted in experimental animals treated with TAA (Al-Attar, 2011, 2012; Salama *et al.,* 2013; Zargar, 2014; Kim *et al.,* 2014; Al-Attar *et al.,* 2016). Moreover, necrosis or membrane damage releases these enzymes into circulation, which agrees with the previously reported results.

Moreover, this work showed that the treatment of mice with *L. dentata* leaves extracts reduced the liver fibrosis process and tissues damage induced by TAA administration as verified by the values of liver function markers (ALT, AST, GGT, and ALP) and liver histopathological observations. This indicated the effectiveness of this extracts in prevention of TAA toxicity. The main constituent of the *L. dentata* leaves extracts are alkaloids, indicaxanthin, neobetanin, and various flavonoids which are thought to be responsible for pharmacological effects . Furthermore, Chemopreventive effect on oxidative stress and genotoxicity was also recently investigated. This plant yield high values of important nutrients such as minerals, vitamins as well as further antioxidants , this is in line with (Hancianu *et al.,* 2013; Hui *et al.,* 2010; Wang *et al.,* 2012). Hohmann *et al.,* (1999) suggests that Phenolic components in lavender toothed extracts were evaluated for antioxidant activity.

One of the most important findings in the present study is the observation that the studied extracts of *L. dentata* leaves extracts was effective in reducing the TAA induced liver fibrosis, that were proven by physiological analysis and histopathological evaluation. Collectively, the results of this study suggest that the effects of these extracts against TAA-induced hepatic fibrosis possibly due to antioxidant properties of their natural chemical constituents. Moreover, this study is from the first investigations that apply scientific methodology to looking at how these extracts exert its role in the protection action against physiological disturbances and histopathological alterations in hepaticfibrosis cases and may be in its complications. Additional physiological, biochemical and histopathological investigations are needed to explore the possible use of different doses of these extracts and their constituents as potential natural therapeutic agents in therapy of hepatic fibrosis against TAA and may be against other fibrogenic factors.

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