Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online): 0493-2137
E-Publication: Online Open Access
Vol: 56 Issue: 06:2023
DOI 10.17605/OSF.IO/XK6Z5

A COMPREHENSIVE OVERVIEW OF BIOCHEMICAL AND HISTOLOGICAL INDUCIBLE ALTERATIONS FROM FRANKINCENSE AQUEOUS EXTRACT ON WISTAR RATS

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Abstract

The use of frankincense for therapeutic purposes continues from ancient times till now. The traditional uses have given us vital information for its bioactivity. However, modern medicine needs to obtain scientific evidences to establish its uses. In our research, we have investigated and evaluated the degree of alteration which caused by exposing the white albino rat of Wistar strain to treatment of frankincense aqueous extract. The evaluation took place through two types of examinations in addition to measuring body weight; the first one was the biochemical examination and the second was the histological examination. The biochemical examination has been done through assessment of function tests of kidney and liver. The function tests for the liver show elevation of ALP in frankincense treated group, while bilirubin, AST and ALT levels were decreased. The biochemical assessment of the kidney reveals that there is an elevation of the serum urea level in the treated group on the contrary serum creatinine and uric acid which appeared slightly decreased. The histological examination has been completed using hematoxylin and eosin staining. The results stated that there is a disarrangement of hepatic strands, mild hepatocellular necrosis, dilation and congestion of blood vessels with mild hemorrhage in liver while the histological examination of kidney revealed degeneration and necrosis of glomeruli structure. Concerning body weight of wistar rats, there was a significant increase in body weight of the wistar rats treated by frankincense aqueous extract.

Keywords: Frankincense, Wistar Rats, Boswellia Extract, Albino Rats

1. INTRODUCTION

Frankincense is being identified as a gum resin of Boswellia plant species those cultivated in Somalia, India, and Yemen. It is characterized by the anti‑inflammatory activity and it is widely used as a traditional medicine in India, Africa, and Western Europe [1]. Frankincense has been utilized as an efficacious treatment regimen in treatment of different minor illnesses in traditional medicine [2]. It has been outlined that boswellic acids which are the main component in the extract of Boswellia could repress the

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biosynthesis of inflammatory cytokines [3]. Frankincense composition has been analyzed and appears to be consists of 60 to 85% resins which are mainly terpenes, 6 to 30% gums those are composed of polysaccharides and 5 to 9% exists as essential oil. Boswellic acids which are represented by the molecular formula $C_{32}H_{52}O_4$ constitute the major active ingredient of boswellia [4]. The use of medicinal plants and their extracts has been acknowledged as an effective strategy in lessening the damage caused by inflammation and oxidative stress on body tissues [5]. LPS which is considered a part of bacterial cell wall is released as endotoxin in the pathogenesis process that associated with gram-negative bacteria has been found to deteriorate the liver circulation and induce hepatic cell necrosis [6]. It has been stated that TNF-α excreted from Kupffer cells which have been exposed to LPS hinders liver from performing its normal function and that result in stimulation of hepatocyte apoptosis process [7]. The detrimental effects from accumulation of TNF-α caused by LPS on kidney function have been also approved [8]. Additional causes which are associated with liver diseases include alcoholic and non-alcoholic fatty liver disease and viral infections, like HCV, HBV and HAV [9]. Moreover, other risk factors for kidney diseases can include excessive accumulation of body fat [10], diabetes mellitus [11, 12], exposure to toxic materials [13], and tumors. Oleo-gum resin of Boswellia has been confirmed to cause an enhancement of the antioxidant capacity and decreasing the amount of inflammatory factors released like nuclear factor κB, IL-6, TNF-α and transforming growth factor-β [14]. Furthermore, studies reported that Boswellia extract could increase the antioxidant activity of enzymes such as catalase and superoxide dismutase. In regard to other effects those can be produced by Boswellia extract, it acts on a various targets particularly on 5-lipoxygenase, topoisomerases, angiogenesis, and cytochrome p450 enzymes. Also, concerning cell sort that is affected, Boswellic acid could induce of block mitogen-activated protein kinase particularly p38 [15, 16]. Other uses for Boswellia extract involve using it in the cosmetic preparation such as sun-block creams and face creams [17].

The study aim to assess and investigate the biochemical and histological changes those resulted from aqueous extract of boswellia plant on Wistar rats

2. MATERIALS AND METHODS

2.1 Animals Model

Male albino rats of the Wister strain (Rattus norvegicus), weighing 79-123.5 g were utilized in the present study. The experimental animals were obtained from the Experimental Animal Unit of King Fahd Medical Research Center, King Abdul-Aziz University, Jeddah, Saudi Arabia. Rats were acclimatized to the laboratory conditions for one week prior to the initiation of experimental treatments. The experimental animals were housed in standard plastic cages and maintained under controlled laboratory 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. All experiments were performed under protocols approved by Committee decision Taif

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University Research Ethics Committee and accordingly ethical approval was granted With No. (HAO-02-T-105) (From March 2022 to March 2023).

2.2 Frankincense Extraction

Frankincense is obtained from trees of Indian frankincense tree (Boswellia serrata) in the Dhofar region of Oman. Frankincense extracts were prepared by stirring of 20 gm. of the resin in 400 ml distilled water for 60 min at 80 ^{0}C after which the extract was cooled to room temperature, filtered and administered to the animals in drinking bottles daily [18].

2.3 Experimental Design

The rats were divided into 2 groups; the dose was given orally through special drinking bottles daily. The first group acted as control drinking water. The second group served as treated group and was given frankincense in the drinking water during the whole duration of the experiment. After 30 days.

2.4 Body Weight Determinations

The body weights of rats were determined at the start of the experimental period and after four weeks using a digital balance. These weights were measured at the same time during the morning [19]. Moreover, the experimental animals were observed for signs of abnormalities throughout the period of study

2.5 Blood Serum Analyses

At the end of four weeks, the experimental animals were fasted for 12 hours, water was not restricted, and then blood samples were drawn from diethyl ether anaesthetized rats via orbital venous plexus. Blood specimens were centrifuged at 2500 rpm for 15 min, and the clear samples of blood serum were separated and stored at –80 °C. Serum samples were used to determine the levels of alanine aminotransferase (ALT) [20], aspartate aminotransferase (AST) [21], alkaline phosphatase (ALP) [22], total bilirubin [23] , creatinine [24], urea [25], and uric acid [26], which were measured by Dimension (DAD BEHRING Company, USA).

2.6 Histopathological Examinations

After blood sampling, rats were dissected and the liver and kidney tissues were preserved in 10% formalin immediately after removal from the animals. The liver tissues were dehydrated by ascending grades of isopropyl alcohol by immersing in 80% isopropanol overnight and 100% isopropyl alcohol for 1 hour. The dehydrated tissues were cleared in two changes of xylene, 1 hour each. The wax impregnated tissues were embedded in paraffin blocks using the same grade wax. The paraffin blocks were cut with rotary microtome at 4 micron thickness. The sections were floated on a tissue floatation bath at 40°C and taken on glass slides and smeared with equal parts of egg albumin and glycerol. The sections were then melted in an incubator at 60°C and after 5 minutes the sections were allowed to cool. The sections were deparaffinized by immersing in xylene for 10 minutes in horizontal staining jar. The deparaffinized sections were washed in 100% isopropyl alcohol and stained in Ehrlich’s hematoxylin for 8 minutes in horizontal staining

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jar. After staining in hematoxylin, the sections were washed in tap water and dipped in acid alcohol to remove excess stain (8.3% HCl in 70% alcohol). The sections were then placed in running tap water for 10 minutes for bluing (slow alkalization). The sections were counter stained in 1% aqueous eosin for 1 minute and the excess stain was washed in tap water and the sections were allowed to dry. Complete dehydration of stained sections was ensured by placing the sections in the incubator at 60°C for 5 minutes. When the sections were cooled, they were mounted in DPX mountant having the optical index of glass, the sections were wetted in xylene and inverted on to the mount and placed on the coverslip [27]. All the liver and kidney tissues sections were examined and photographed using binocular digital microscope (SCO Tech GmbH, Germany).

2.7 Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for windows, version 22.0). Each value is expressed as mean ± standard deviation (S.D.). One-way analysis of variance (ANOVA) was used to evaluate differences among experimental groups. The results were considered statistically significant if the P-values were less than 0.05.

3. RESULTS

3.1 Body Weight

The data in (table 1) revealed that there were significant increase of treated group weight in comparing with the untreated group at 2nd week and forward. Meanwhile first day and 1st week show non-significant different between the treated and control one. And it was also observed during the experiment that an increase in the amount of eating for the treated groups compared to the control group (figure 1).

Table 1: Changes of body weight between control and treated groups after 4 weeks

Group	1st day	1st week	2nd week	3rd week	4th week
Control	110.30± 4.48	130.10± 3.31	148.66± 2.41	159.88± 1.28	171.90± 3.75
Treatment	105.98± 3.92	133.06± 4.82	165.18± 5.08*	173.36± 5.07*	189.06± 6.01*

Values are expressed as mean ± SE, * Significant at $p < 0.05$

Figure (1): Changes in body weight between control and treated groups after 4 weeks.

3.2 Histopathological Examinations

3.2.1 Liver

Histopathological examination indicated a normal structure of the liver in the normal control rats and it displays normal liver cells or hepatocytes with preserved cytoplasm, prominent nucleus and nucleolus, and well brought out central vein (figures 1a-1c). These cells are cuboidal epithelial cells arranged in anastomosing plates and cords. In classical lobules, the plates radiate from the central vein (CV) and cords alternate with sinusoids.

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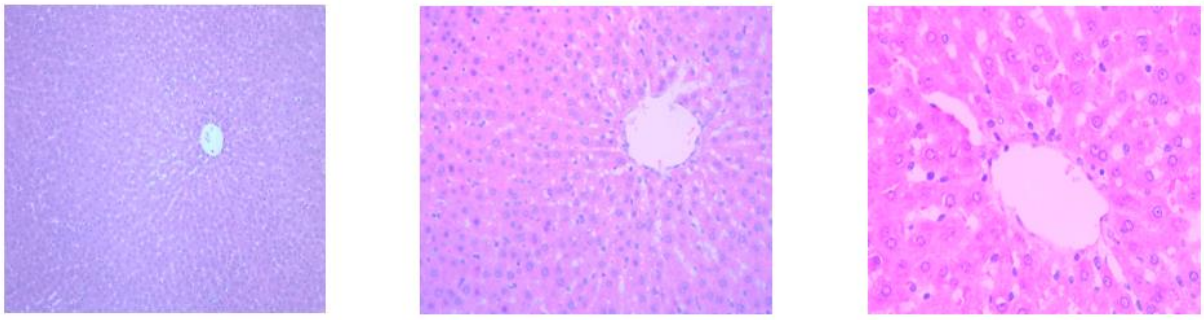
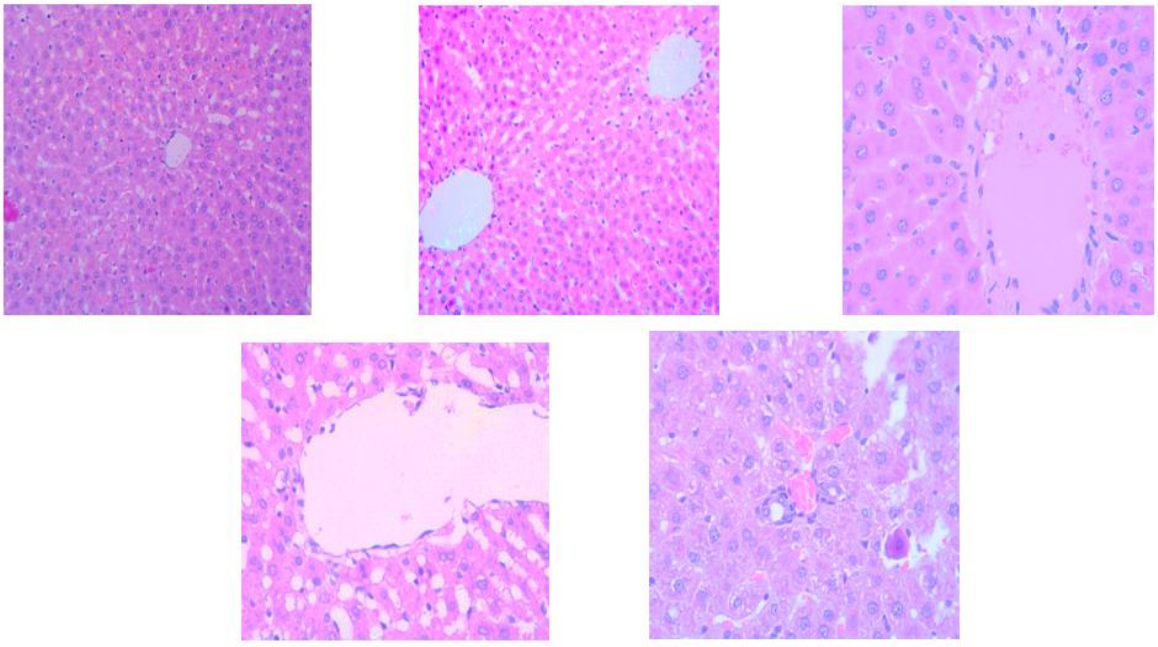
Histological section of rat liver from the control group (H&E) Section showing normal hepatic cell aggregation. Hepatocyte (H) appears in rows separated by hepatic sinusoids (S). Some of the Kupffer cells (K) are present. There is a central vein (CV) and a branch of the hepatic portal vein (PV). Liver structure of frankincense group rats changes including disarrangement of hepatic strands, rupture in liver cells (hepatocytes), mild hepatocellular necrosis, dilation and congestion of blood vessels with mild hemorrhage, dense lymphocytic infiltration around the central vein and dark stained hepatocytes nuclei indicating cell pyknosis (figures 2a-2e).



Figures (1a), (1b) and (1c) are revealing Photomicrograph of liver section of control rats showing normal histological structure (hematoxylin and eosin staining). Original magnification X100



Figures (2a), (2b), (2c), (2d) and (2e) are revealing disarrangement of hepatic strands, rupture in liver cells (hepatocytes), mild hepatocellular necrosis, dilation and congestion of blood vessels with mild hemorrhage

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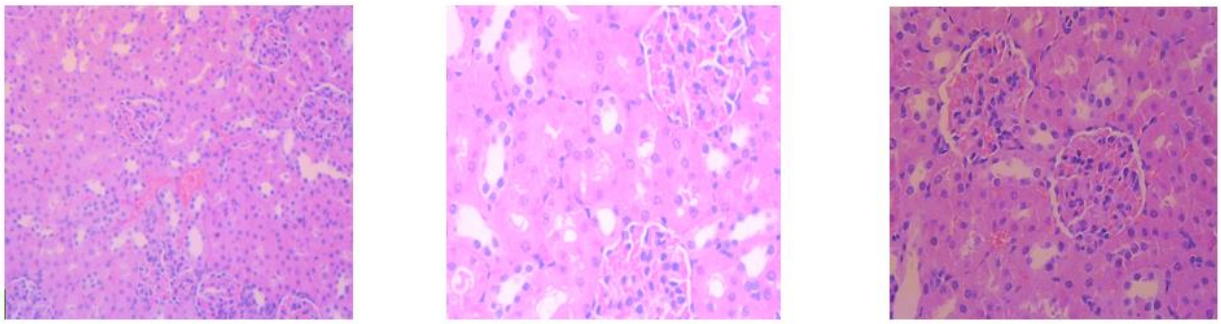
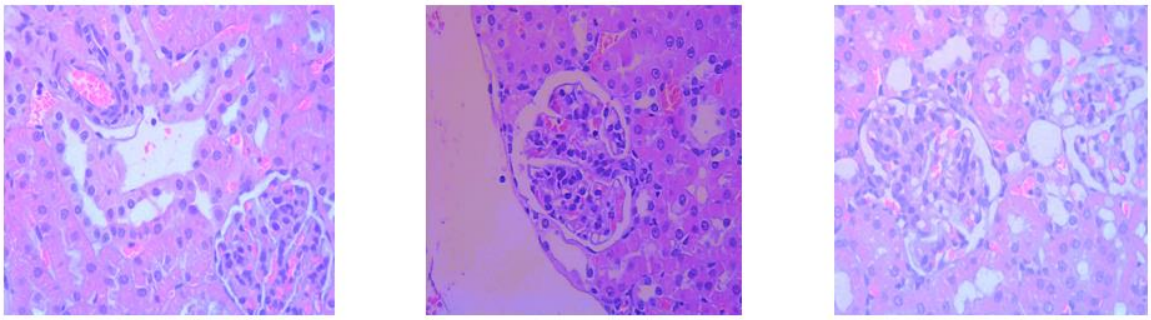
3.2.2 Kidney

Histological section of the cortex has been obtained from the kidneys of the control group (H&E x10) and it is showing normal cellular structure with intact glomeruli and regular tubular contour (figures 3a-3c). The urinary corpuscles which are formed from Bowman's capsule (BC) surrounding the glomerulus (G) and separated by urinary space are seen. Notice the contour of the proximal (PT) and distal (DT) convoluted tubules is intact and regular with intact nuclei (N) of the endothelial cells. Areas of renal cortex containing renal corpuscles and associated tubules were showed some pronounced changes in frankincense treated group in compared to normal control. The Histological section of cortex from the kidneys of the rats given frankincense showing abnormal cellular structure with degeneration of glomeruli structure, mild hepatocellular necrosis, dilation and congestion of blood vessels with mild hemorrhage (figures 4a-4c).



Figures (3a), (3b) and (3c) are displaying Photomicrograph of Kidney section of control rats showing normal histological structure (hematoxylin and eosin staining). Original magnification X200



Figures (4a), (4b) and (4c) are displaying Photomicrograph of kidney section of tissue frankincense group rats showing degeneration and necrosis of glomeruli (hematoxylin and eosin staining).Original magnification X 400

3.3 Blood Serum Analysis

The data in (table 2) revealed that there were significant increase of frankincense group ALP in comparing with the group control, in contrast serum ALT, AST and bilirubin show significant decrease of frankincense group in comparing with control one. The level of

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serum ALT and AST was significant decrease in frankincense group by 4.53% and 8.51% respectively and increase ALP by 6.98% (figure 5). Bilirubin shows significant decrease of treated group in comparing with control one by 0.002% (figures 6). Insignificant alterations of serum uric acid and urea levels were noted in frankincense group in comparing to the control group (table 3) (figure 7). Meanwhile creatinine show significant decrease of treated groups by 0.012% in comparing to normal control group (figure 8).

Table 2: Level of serum ALP, ALT, AST and total bilirubin in control and frankincense groups

Group	ALP	ALT	AST	Bilirubin
Control	192.04± 2.53	114.98± 1.63	161.78±3.46	0.080±0.007
Treatment	269.60± 6.98 *	68.04± 4.53*	123.92± 8.51*	0.034±0.002*

Values are expressed as mean ± SE, * Significant at p < 0.05

Table 3: Level of serum urea, uric and creatinine

Group	Urea	Uric	Creatinine
Control	43.20±1.62	3.67±0.05	0.28±0.007
Treatment	44.00± 2.30	3.34± 0.42	0.23± 0.012*

Values are expressed as mean ± SE, * Significant at p < 0.05

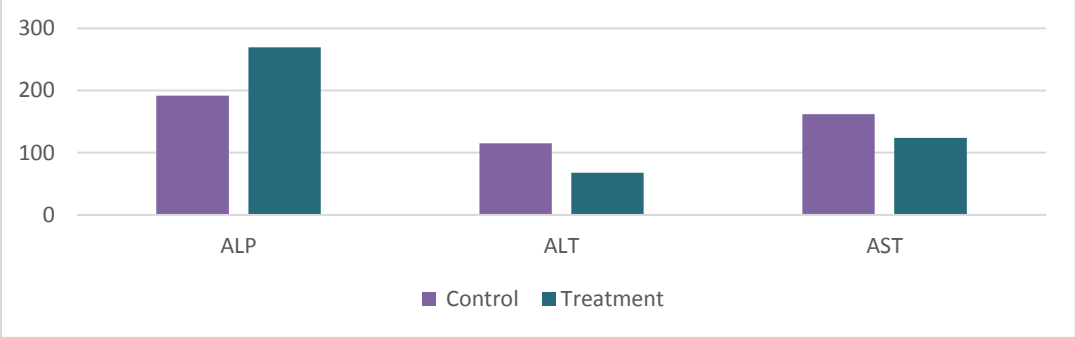

Figure 5: shows serum levels of ALP, ALT and AST in control and frankincense groups

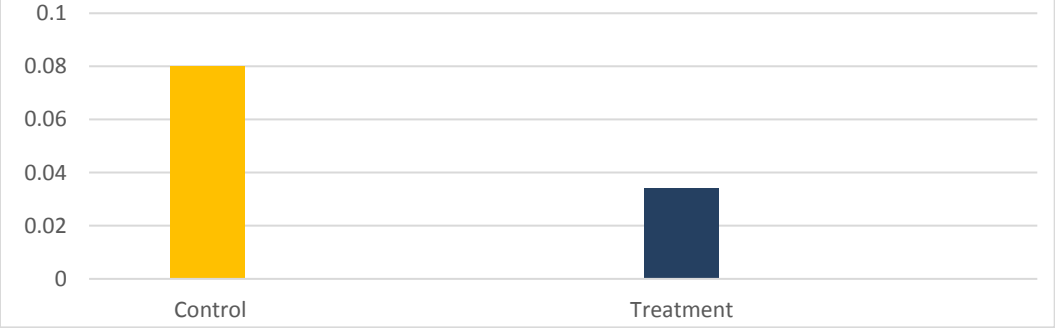

Figure 6: shows serum level of bilirubin in control and frankincense groups

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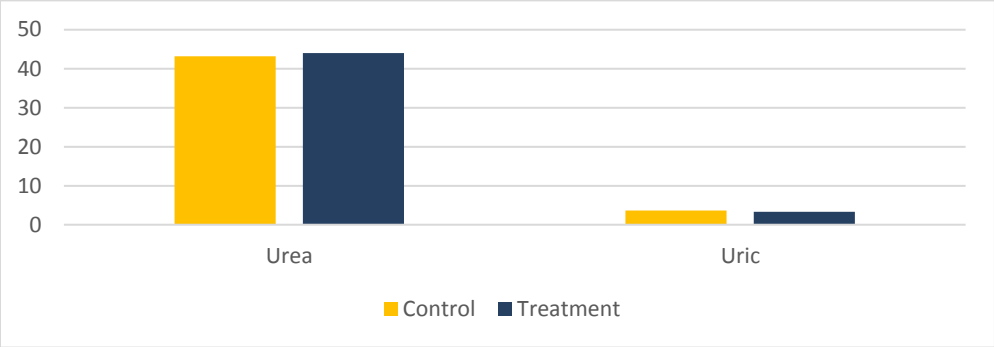

Figure 7: shows serum levels of urea and uric acid in control and frankincense groups

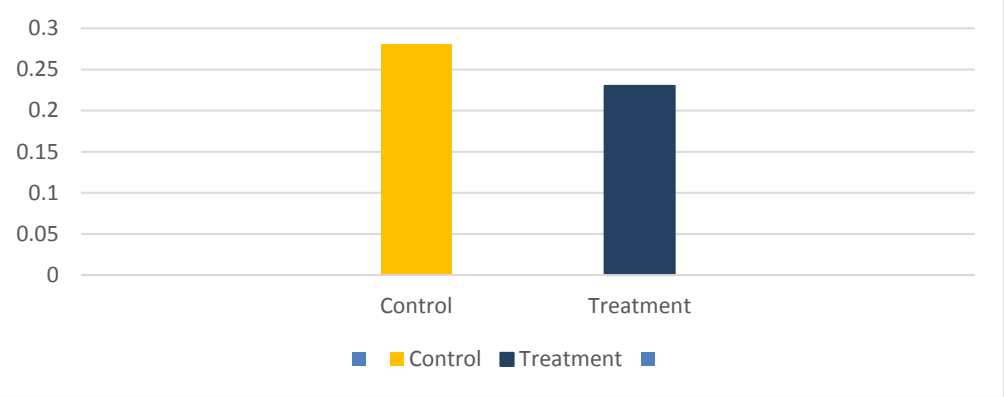

Figure 8: shows serum level of creatinine in control and frankincense groups

4. DISCUSSION

Medicinal plants have great benefits since ancient times and were used as a treatment for many diseases .During the last two decades the use of phyto-constituents has increased due to their low side effects beside their benefits in keeping health and wellness. Additionally, several research reports indicate of their ability to combat diseases including diabetes, HIV, inflammation, cancer, obesity and toxicant-induced organ injuries [28-31]. The current study has been designed for the sake of evaluating the safety and effects on kidney and liver of the aqueous extract of frankincense. The results evident that there were no symptoms to indicate that the animals were adversely affected by the doses or treatment given throughout the period of the study. This observation is further supplemented by the fact that all the animals were alive at the end of the study and this agrees with former researches [32]. In our research, an increase in the weight of animals those were treated with frankincense extract was observed, and this is due the effect of the compounds of the frankincense extract on the secretions of the thyroid gland which affects the metabolism. The results were revealed that there was significant increase of frankincense group ALP in comparing to the control group. Meanwhile serum ALT, AST and bilirubin show significant decrease of frankincense treated group in comparing to

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control one and insignificant alterations of serum uric acid levels were noted in of frankincense groups. Serum creatinine shows significant decrease in the treated group's liver and kidney. Harmful effects to the liver is the most frequently reported histopathological response, the importance of the liver as a marker for pathological change reflects the central role of mammalian hepatic tissue in nutrition, lipid and carbohydrate storage, synthesis of protein and enzymes, fatty acid metabolism, and biotransformation and elimination of wastes [33]. The biochemical changes are somewhat minor to cause any detected histopathological change in both liver and kidney. Our result is concurred with the previous studies which have evaluated the acute toxicity of Frankincense extract in vitro on human skin-derived cell lines [34]. Furthermore, former papers proved that ingestion of rat's frankincense aqueous extract daily for 30 days showed adverse effects on livers and kidneys as it induce abnormal liver and kidney functions [35]. The author concluded that frankincense is not absolutely safe. Through the biochemical analysis of these results, it may be inferred that the decrease of AST and ALT in serum is caused by the decrease in amino acid followed by decrease in protein synthesis and then by lipid peroxidation of kidney tissue. The slight alterations of the level of uric acid are due to the process of the breakdown of purine base in DNA and the amount of purine bases those exposed to the breakdown process decides which the results could be. The tenuous increase of the serum urea level is resulted from increased synthesis from the liver. Preceding studies declared that at low concentrations, polyphenols, flavonoids and triterpenoids which considered as the major phytochemicals in the gum resin enhance the expression of genes provoking protective mechanisms [36]. However, to the contrary, on increasing their concentrations, these compounds additionally activated the caspase pathway, leading to apoptosis. Further increments to supra-pharmacological concentrations would inevitably lead to nonspecific necrotic cell death. So, oral ingestion of large amounts of phenolic compounds in the form of a concentrated supplement may not be considered safe until their cytotoxicity is evaluated.

5. CONCLUSION

In our recent research work about the effects of aqueous extract of boswellia on kidney and liver tissues. We have utilized male albino rat of Wistar strain as an animal model for running our examinations on it, whether were histological examinations or biochemical ones or even measuring body weight. The body weight showed a significant increase in frankincense treated rats comparable to control group which was given only water. Biochemical assessment revealed that ALP was elevated in frankincense treated group, while bilirubin, AST and ALT levels were decreased. In regard to kidney function tests, the results showed that there is a slight elevation of the serum urea level in the treated group in contrast to serum creatinine and uric acid which appeared slightly decreased. With respect to the histological changes, the results of the liver tissue in frankincense treated group have showed disarrangement of hepatic strands, mild hepatocellular necrosis, dilation and congestion of blood vessels with mild hemorrhage. The histological alterations of kidney caused by the frankincense treatment revealed degeneration and necrosis of glomeruli structure.

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Data availability statement

The original contributions presented in the study are included in the article Material; further inquiries can be directed to the corresponding author.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or fi-nancial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors would like to thank Deanship of Postgraduate Studies at Taif University for supporting provided for this work.

Author Contributions

Conceptualization: Fawziah A. Al-Salmi, Sultan Abdurazag AL salmi; Formal analysis: Najwa Saleh Salem Bin Salman; Funding acquisition: Fawziah A. Al-Salmi; Investigation: Noha Adel Badri; Methodology: Fatimah Abdullah Ali Bin Othman; Project administration: Fawziah A. Al-Salmi, Sultan Abdurazag AL salmi; Resource: Najwa Saleh Salem Bin Salman; Supervision: Fawziah A. Al-Salmi, Sultan Abdurazag AL salmi; Validation: : Noha Adel Badri; Visualization Fatimah Abdullah Ali Bin Othman; Writing original draft: : Fawziah A. Al-Salmi, Sultan Abdurazag AL salmi; Writing -review edition: All authors have confirmed the final version of the manuscript.

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Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online): 0493-2137
E-Publication: Online Open Access
Vol: 56 Issue: 06:2023
DOI 10.17605/OSF.IO/XK6Z5

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