

Antimicrobial Activity and Histopathological Safety Evidence of *Ochradenus baccatus* Delile: A Medicinally Important Plant Growing in Saudi Arabia

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ABSTRACT

Background: The growing climatic condition affects plant constituents and biological activities. *Ochradenus baccatus* (Taily Weed) from *Resedaceae* family is a perennial shrub that is widely used in folk medicine in the Middle East. **Aim:** From the viewpoint that *O. baccatus* is regularly used in folk medicine, this study was designed to evaluate the antimicrobial activity and investigate the effect of *O. baccatus* on the biochemical and histopathological parameters of liver and kidney in experimental animals. **Methods:** The *O. baccatus* extracts were obtained by hot continuous extraction method. Agar diffusion and minimal inhibitory concentration assays were used for the antimicrobial activity. *O. baccatus* total extracts at doses of 100 mg/kg and 50 mg/kg were given to the first and second groups of rates, respectively, whereas the third and fourth groups received the vehicle olive oil and saline, respectively. The liver and kidney functions, as well as lipid profile and glucose levels, were measured by spectrophotometric technique on obtained blood samples. The liver and kidney tissues were evaluated for histopathological effect. **Results:** Ethanol and ethyl acetate extracts have similarly and potentially inhibited the bacterial micro-organisms, whereas *Candida albicans* was inhibited by n-hexane extract. *O. baccatus* total extract showed no significant effects on the kidney and liver functions ($P > 0.05$). However, it significantly reduced triglyceride level ($P = 0.04$). The histopathological investigation of liver and kidney tissues revealed no significant differences compared to control animals.

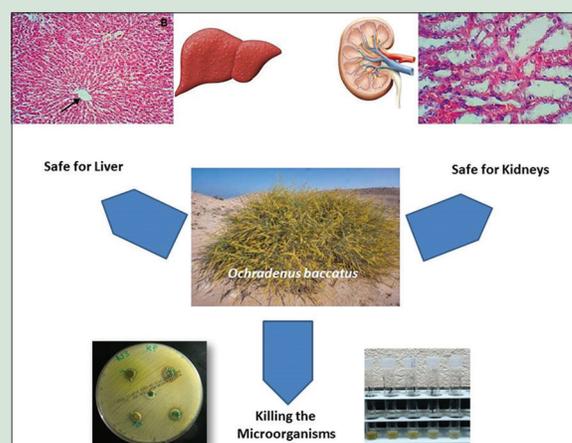
Conclusion: The medicinally important plant, *O. baccatus*, growing in Saudi Arabia showed no significant toxic effects on the livers and kidneys. Moreover, it demonstrated a potential antimicrobial activity besides a significant reduction in serum triglycerides in rats. These findings are in consistent with other reported results suggesting no environmental effects on the safety of this plant.

Key words: Antimicrobial activity, histopathology, kidney function, lipid profile, liver function, *Ochradenus baccatus*

SUMMARY

- Significant biochemical and histopathological evidence for the safety of *Ochradenus baccatus* growing in Saudi Arabia were conformed in animal models

- Ethanol and ethyl acetate extracts of *O. baccatus* had similarly and potentially inhibited the bacterial micro-organisms, whereas *Candida albicans* was inhibited by n-hexane extract
- The plant significantly reduced triglyceride level ($P = 0.04$).



Abbreviations Used: ALT: Alanine aminotransferase, AST: Aspartate transaminase, *C. albicans*: *Candida albicans*, *E. coli*: *Escherichia coli*, IZD: Inhibition zone diameter, IFCC: International federation of clinical chemistry, *O. baccatus*: *Ochradenus baccatus*, MIC: Minimal inhibitory concentration, *S. aureus*: *Staphylococcus aureus*.

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INTRODUCTION

Ochradenus baccatus (Taily Weed) is a perennial shrub belonging to family *Resedaceae* and is widely distributed in the Middle East. The plant is broadly growing in the southwest and focal areas in Saudi Arabia, Ethiopia, Egypt, Libya, and Center East and reaches out into Pakistan.^[1] *O. baccatus* has a great importance in the world, especially in the Arabian Peninsula, as it is used as an important source of food for some species of animals in the deserts.^[2] Furthermore, *O. baccatus* is an important medicinal plant and it contains high contents of antioxidants and anti-inflammatory agents.^[3-5] In addition, *O. baccatus* demonstrates therapeutic importance as it can reduce blood cholesterol levels and induce a potential effect against *Plasmodium falciparum*.^[4]

The plant is used in traditional medicine as an anti-inflammatory,^[6] in the treatment of male sexual disorders,^[7] and as an antibacterial agent.^[8]

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The nematocidal activity of the plant against the root-knot nematode *Meloidogyne javanica* was evaluated, and it has been found to contain exceptionally high levels of glucosinolates.^[9] The plant extract showed an antimalarial effect, and it induces apoptosis in HepG2 cells, which indicates that it has anticancer activity.^[10,11]

O. baccatus is equipped with antioxidant machinery which includes major antioxidant enzymes such as superoxide dismutase, catalase, ascorbate peroxidase, and glutathione reductase. In addition, the plant is also equipped by antioxidant secondary metabolite, particularly flavonoids. The mentioned antioxidant machinery is the protective pathway of the plant to overcome oxidative stress produced by salinity condition of the plant's environment.^[12]

Flavonoid glycosides, particularly flavonol-type glycosides, were isolated from the aerial part of *O. baccatus*. In addition, most of these flavonol glycosides have been elucidated as quercetin derivatives. New flavonoids quercetin 3-O- β -glucosyl (1 \rightarrow 2)- α -rhamnoside-7-O- α -rhamnoside and quercetin-3-O-pcoumaryl (1 \rightarrow 6)- β -glucosyl (1 \rightarrow 6)- β -glucoside-7-O- α rhamnoside, together with known compounds quercetin 3-gentiobioside, isoquercetin, quercetin, and kaempferol, were isolated from the aerial part of *O. baccatus*.^[12] Furthermore, *O. baccatus* also contains alkaloids, coumarins, saponins, and steroidal compounds.^[13]

Such medicinally important plant with huge number of bioactive secondary metabolites might affect the liver and kidney as they are important organs for metabolism and excretion of the metabolites.^[14-16] Accordingly, such plant needs to be investigated for its deleterious effects in the functions of liver and kidney. In that regard, a study was conducted for the *O. baccatus* ethanol extract that was collected from the Eastern Desert of Egypt. The study concluded that the plant is safe in animal trials.^[5] The current study evaluated the antimicrobial activity, liver and kidney effects, and histopathological changes induced by *O. baccatus* extracts collected from Saudi Arabia and widely used as a medicinal plant.

MATERIALS AND METHODS

Plant materials and extraction procedure

The plant was collected in September 2017 from Hnakyia in Medina Region in Saudi Arabia and identified as *O. baccatus* by Prof. Ahmed Al-Oglah taxonomist from the Department of Biology, Yarmouk University, Jordan. The whole plant was dried in open air shade and ground in 3 mm mesh mill.

Accurately, 400 g of the dried plant was extracted by Soxhlet extractor^[17] using n-hexane, chloroform, ethyl acetate, and ethanol in sequence (10 refluxes for each). The extracts were vacuum-dried at 40°C until complete dryness. In the same manner, ethanol was used to extract 400 g of *O. baccatus* to collect the total ethanol extract that was used in the animal experiments. The dried extracts were stored at -20°C for further steps. Each dry extract has been weighted and the extractive values were calculated using the equation:

$$\text{Extraction value (\%)} = \frac{\text{The weight of dried extract obtained from each solvent in gram}}{\text{Weight of dried plant materials}} \times 100$$

Antimicrobial assay of plant extract

Microbial strains

The micro-organisms were provided by the Medical Microbiology Department, College of Applied Medical Sciences, Qassim University, Buraydah, Saudi Arabia. Only three micro-organisms were used in the assay, which were Gram positive, *Staphylococcus aureus*; Gram negative, *Escherichia coli*; and the fungus, *Candida albicans*.

Agar well-diffusion assay

The procedure followed the method of Cooper and Woodman.^[18] The prepared microbial suspensions were incubated till turbidity/growth comparable to 0.5 McFarland tube was obtained. Sterile swaps were smeared on the agar surface and incubated for few minutes; then, 75 μ l of the extracts (prepared in DMSO 10 mg/ml) was pipetted to the designed cups. Positive control drug disc (10 μ g/ml amoxicillin, gentamicin, and clotrimazole) was placed onto the top of the inoculated agar plate. Plates were then incubated (Sheldon Manufacturing Inc., USA) for 24–72 h depending on the growth rate of each microbial organism and were checked every day, and inhibition zone diameters (IZDs) were measured to the nearest millimeter.^[19,20]

Minimal inhibitory concentration assay

The broth microdilution assay was used according to the method described by Candan *et al.*^[21] The bacterial organisms were cultured overnight at 37°C in Mueller Hinton broth supplemented with Tween 80 detergent (final concentration of 0.5% [v/v]), whereas *C. albicans* was cultured overnight at 30°C in Sabouraud dextrose broth + Tween 80. Serial dilutions of the extracts were prepared in a 96-well microplate and incubated at 37°C for 24 h for bacteria and at 30°C for 48 h for *C. albicans*. The white turbidity in well bottom indicates the bacterial growth.^[22]

Total extract effect on the liver, kidney, blood glucose, cholesterol, and triglyceride levels in the rats

Experimental animals

The experiment was performed using 24 male albino rats weighing 190–230 g that were obtained from animal house of College of Pharmacy, Qassim University, KSA. Animals were maintained at the animal house with standard conditions. The animals were divided randomly into four groups in which each group contains six animals. The study was approved by the Ethical Committee of College of Pharmacy, Qassim University, KSA. The handling and care of experimental rats were according to internationally accepted regulations.

Toxicity and determination of LD₅₀ of *Ochradenus baccatus* extract

The LD₅₀ of the *O. baccatus* ethanol extract was determined using the fifth group of the male albino rats and according to the method described by Lorke.^[23] The animals received 1000, 2000, or 4000 mg/kg of the extract and were investigated for 24 h.

Doses preparation and experimental study plan

50 mg/kg and 100 mg/kg of ethanol extract were used as therapeutic doses which are equal to 1/80 and 1/40, respectively, of the maximum dose (4000 mg/kg) that produces no mortality or acute toxicity. The first and second groups of the rats received 100 mg/kg and 50 mg/kg of the *O. baccatus* extract dissolved in olive oil, respectively. The third and fourth groups were used as placebo which received only olive oil vehicle and saline, respectively. All the doses were administrated to the rats orally using orogastric cannula for consecutive 30 days. By the end of therapeutic regimen, blood samples were obtained by retro-orbital puncture after anesthesia by diethyl ether. Serum was separated for biochemical assays using spectrophotometric procedure. For histopathological examination, livers and kidneys were dissected after rats' scarification, then fixed in 10% formalin, and left for 24 h for proper fixation.

Measurements of liver, kidney, lipid profile, and blood glucose levels

The serum level of total protein was measured photometrically using colorimetric test from human company, according to the method

of Weichselbaum in 1946.^[24] The determination of serum glucose, cholesterol, and triglycerides was determined by colorimetric methods.^[25] The serum level of ALT and AST was determined using optimized UV test according to the International Federation of Clinical Chemistry (IFCC).^[26] Serum creatinine was determined by kinetic method without deproteinization – Jaffe reaction. The urea was determined by enzymatic colorimetric, endpoint Berthelot method. All the kits were supplied from Crescent Diagnostics Company in Saudi Arabia.

Histological evaluation of liver and kidney tissues

The formalin-fixed tissue was processed using an automated tissue processor instrument (Leica TP1020), and paraffin-embedded sections were prepared. Serial 3–5- μ m sections were prepared using microtome (Leica RM2245) and stained by hematoxylin and eosin stain. All tissue sections were examined by light microscope (Olympus BX41) using $\times 4$, $\times 10$, and $\times 40$ magnifications, and images were taken through digital image camera (5MP Binocular Microscope Electronic Eyepiece USB Video CMOS Camera for Image Capture) and analyzed by ToupView image analyzer. Arteriolosclerosis was graded as described by Sommers *et al.*^[27] Grade 0 indicated unaltered arterioles, Grade 1 described minor localized thickening, and Grade 2 represented thickened wall that equaled to the lumen. Grade 3 described arterioles with wall thickness exceeding the diameter of the lumen.

Statistical analysis

One-way ANOVA followed by Tukey-Kramer multiple comparison test using SPSS (IBM Cooperation) statistical program was used in the analysis of data, and $P < 0.05$ was considered statistically significant.

RESULTS

The extractive values and antimicrobial activity of *Ochradenus baccatus* extracts

Different polar solvents were used to extract *O. baccatus* in hot continuous extractor (Soxhlet apparatus) extract. The extractive values were determined for each solvent by calculating the percentage of the dried extract materials obtained from dried plant powders as extracted by n-hexane, chloroform, ethyl acetate, and ethanol in sequence. The results obtained from extractive value calculations indicate that more polar solvents such as ethanol and ethyl acetate have the ability to extract the plant materials more than less polar solvents [Table 1]. The antimicrobial testing of *O. baccatus* was conducted for plant extracts against three microbial organisms including Gram positive (*S. aureus*), Gram negative (*E. coli*), and *C. albicans*. The results showed that the growths of the two tested bacterial micro-organisms were strongly inhibited by ethanol and ethyl acetate extracts which were similarly inhibited the growth of *S. aureus* and *E. coli* by 17 mm and 12 mm IZD, respectively. However, ethanol extract showed smaller minimal inhibitory concentration (MIC) values compared to ethyl acetate

extract against both micro-organisms [Table 1]. Both ethanol and ethyl acetate extracts were inactive against *C. albicans*. Inversely, *C. albicans* was strongly inhibited by n-hexane and chloroform extract with 19 mm IZD (3.5 mg/ml MIC) and 15 mm IZD (11 mg/ml MIC), respectively [Table 1].

Biochemical results

This study showed no significant differences in the serum levels of blood urea, serum creatinine, and blood glucose between the treated rats' groups (1 and 2) and the controls' groups (3 and 4) as $P = 0.9$, 0.26, and 0.57, respectively. With regard to the effect of *O. baccatus* on liver function, the study also showed no significant difference in the serum level of ALT, AST, and total protein between the treated rats' groups (1 and 2) and the controls' groups (3 and 4) with resultant $P = 0.16$, 0.30, and 0.18, respectively [Table 2]. These results indicated that *O. baccatus* is safe to the kidneys and livers with no effect on the level of blood glucose [Table 3].

Furthermore, *O. baccatus* total extract showed no significant difference in the serum level of cholesterol in the treated rats' groups compared with the controls' groups as $P = 0.22$. However, the serum levels of triglycerides were significantly decreased in Group 1 that received 100 mg/kg of the *O. baccatus* extract compared to the control groups ($P = 0.04$), and these findings suggested a hypolipidemic effect of *O. baccatus* extract [Table 2 and Figure 1].

Histopathological evaluation of rats' livers and kidneys

This study showed no significant difference in both the mean glomerular diameter and the mean Bowman's space diameter between the tested rats' groups and the controls' groups with $P = 0.133$ and 0.1473, respectively.

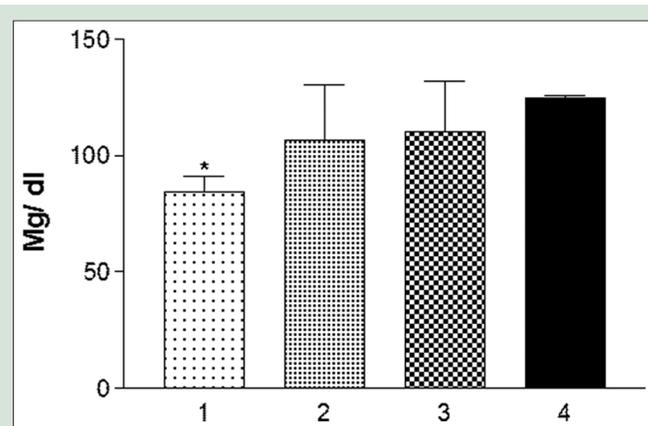


Figure 1: The serum level of triglycerides in treated rats with *Ochradenus baccatus* as compared to controls

Table 1: Extractive values and antimicrobial activity of *Ochradenus baccatus* extracts

Extracts	Extractive values (%)	Antimicrobial activity					
		<i>Staphylococcus aureus</i>		<i>Escherichia coli</i>		<i>Candida albicans</i>	
		IZD*	MIC**	IZD	MIC	IZD	MIC
Ethanol	3	17	7.5 \pm 0.25	12	17.0 \pm 1.22	0	ND
Ethyl acetate	2.77	17	8.25 \pm 0.22	12	20.1 \pm 0.97	0	ND
Chloroform	2.15	12	22.5 \pm 1.19	0	ND	15	11.0 \pm 0.75
n-hexane	1.25	0	ND	10	ND	19	3.5 \pm 0.14

*IZD was calculated to the nearest millimeter; **MIC was calculated in mg/ml from three independent measurements \pm SD. ND: Indicating that MIC not detected until 100 (mg/ml) of the extracts. MIC: Minimal Inhibitory Concentration; IZD: Inhibition zone diameters, SD: Standard deviation

Moreover, there was no significant arteriosclerosis nor significant inflammatory cells infiltrate between all the studied groups [Table 4].

The histopathological evaluation of the renal tissues obtained from Groups 1, 2, and 3 revealed that the glomerular structures, interstitium, blood vessels, and renal tubules were preserved and well organized without evidence of inflammatory cellular infiltration or necrosis which indicated insignificant histopathological changes. Group 4 showed significant hyaline droplets in the renal tubules and on other significant changes in the other renal structures [Figures 2 and 3]. The liver tissue from all the four groups showed

that the liver architecture, sinusoids, central vein, and portal tract were intact and well preserved without any evidence of porto-portal or porto-central inflammation, or necrosis which signifies no histopathological changes [Figure 4].

DISCUSSION

O. baccatus is a medicinally important plant used in different areas of traditional medicine in many countries. The plant is the reach of complex natural secondary metabolites, particularly flavonoids, alkaloids, saponins, and sterols. One previous study had investigated the

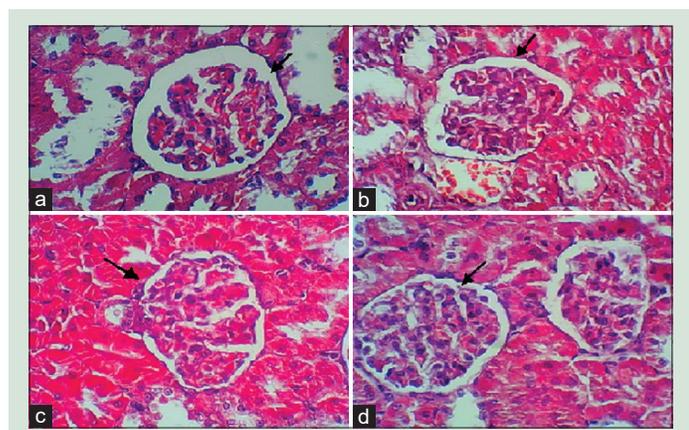


Figure 2: Renal glomeruli showed insignificant changes, (a) Group 1, (b) Group 2, (c) Group 3, (d) Group 4

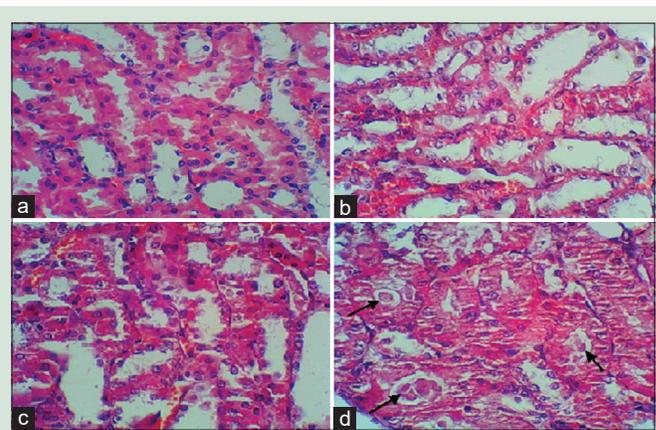


Figure 3: Renal tubules, (a) Group 1, (b) Group 2, (c) Group 3, (d) Group 4 showed significant hyaline droplets (arrow)

Table 2: The serum level of alanine aminotransferase, aspartate transaminase, total protein, cholesterol, and triglycerides in treated rats with hexane extract of *Ochradenus baccatus* compared to controls

Groups	Mean±SD				
	ALT	AST	Total protein	Total cholesterol	Triglycerides
Group 1	38.71±13.81	56.48±15.24	5.66±0.27	64.99±7.91	79.67±4.72
Group 2	23.85±5.28	35.22±11.70	5.92±0.72	76.21±1.18	106.7±23.73
Group 3	31.09±5.73	30.78±25.76	6.54±0.23	81.53±7.57	110.3±21.59
Group 4	42.26±10.58	39.98±5.03	6.78±0.94	76.02±14.08	125.1±0.85
P	0.16 (NS)	0.30 (NS)	0.18 (NS)	0.22 (NS)	0.04*

Results are expressed as mean±SD. Group 1: Treated rats with 100 (mg/kg) of extract, Group 2: Treated rats with 100 (mg/kg) of extract; Group 3: Treated rats with olive oil as a vehicle; Group 4: Rats received saline. ALT: Alanine aminotransferase; AST: Aspartate transaminase; SD: Standard deviation; NS: Not significance

Table 3: The serum level of urea creatinine and glucose in treated rats with hexane extract of *Ochradenus baccatus* compared to controls

Groups	Mean±SD		
	Blood urea	Serum creatinine	Blood glucose
Group 1	68.31±1.28	0.718±0.10	118.4±13.78
Group 2	68.51±2.02	0.837±0.07	98.25±13.29
Group 3	67.92±1.46	0.8087±0.06	116.2±32.38
Group 4	68.61±0.59	0.8967±0.15	118.8±15.2
P	0.9 (NS)	0.26 (NS)	0.57 (NS)

Results are expressed as mean±SD. Group 1: Treated rats with 100 (mg/kg) of extract, Group 2: Treated rats with 100 (mg/kg) of extract, Group 3: Treated rats with olive oil as a vehicle, Group 4: Rats received saline. SD: Standard deviation; NS: Not significance

Table 4: Mean glomerular and Bowman's space diameter±standard deviation, grade of arteriosclerosis, and degree of inflammation

	Group 1	Group 2	Group 3	Group 4	P
Mean glomerular diameter±SD (µm)	170.08±2.32	168.77±1.38	170.97±0.64	169.93±1.30	0.133
Mean Bowman's space diameter±SD (µm)	22.73±0.70	22.55±0.44	21.78±0.24	22.40±0.54	0.1473
Arteriosclerosis	Grade 0	Grade 0	Grade 0	Grade 0	
Inflammatory cell infiltrate	Insignificant	Insignificant	Insignificant	Insignificant	

Results are expressed as mean±SD. Group 1: Treated rats with 100 (mg/kg) of extract, Group 2: Treated rats with 100 (mg/kg) of extract, Group 3: Treated rats with olive oil as a vehicle, Group 4: Rats received saline. SD: Standard deviation

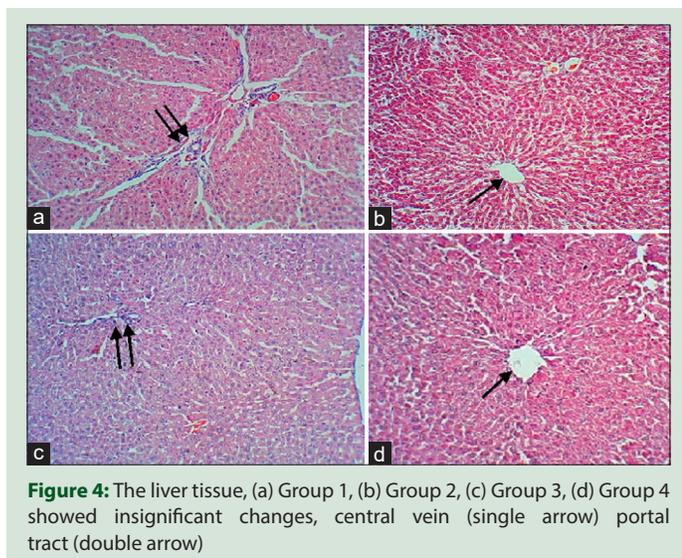


Figure 4: The liver tissue, (a) Group 1, (b) Group 2, (c) Group 3, (d) Group 4 showed insignificant changes, central vein (single arrow) portal tract (double arrow)

acute and chronic toxicity of *O. baccatus* growing in Egypt. The study concluded that the plant growing in that climatic region was safe until 4000 mg/kg as a daily dose in rats.^[5] The differences in climatic condition such as temperature and humidity regularly affect the plant constituents, therapeutic effects, and toxicity.^[28-31] The biochemical markers were investigated in the present study for *O. baccatus* growing in Saudi Arabia. Moreover, the histopathological effects on the liver and kidney tissues of treated and controlled rats were investigated.

Antimicrobial activity of *O. baccatus* was conducted on different plant extracts. Polar extracts (ethanol and ethyl acetate extracts) of *O. baccatus* were active against bacterial micro-organism *S. aureus* and *E. coli*, whereas non-polar extracts (chloroform and n-hexane extracts) had exerted activity against fungal strain *C. albicans*.

The serum level of ALT, AST, and total protein showed no significant differences in treated rats with extract of *O. baccatus* as compared to controls [Table 2]. The same results were provided by histopathological examination of liver tissues of treated rats with extract in comparison with the control group where all the groups showed no detectable changes in liver histology of sinusoids, portal tracts, or central vein [Figure 4]. These results are in accordance with the results obtained from *O. baccatus* growing in Egypt^[5] and insure that the extract of *O. baccatus* is considered safe to the liver cells without signs of hepatic toxicity.

The extract of *O. baccatus* has significantly reduced the serum level of triglycerides, especially in the first group of animals which received the dose of the extract (100 mg/kg) with $P = 0.04$. Although there was no significant effect on the serum level of cholesterol and glucose in the treated group compared to the control group in this study [Table 2], another study done by Barakat *et al.* showed a significant hypocholesterolemic effect of *O. baccatus* in rats, and they attributed their findings to the flavonoid contents.^[12] Furthermore, Saleh *et al.* indicated that the antioxidant and anti-inflammatory effect of the *O. baccatus* extract may result in a hypolipidemic of this extract.^[5]

Concerning the effects on the kidneys, this study indicated that *O. baccatus* extract showed no significant differences on blood creatinine and urea; the main kidney function tests of the treated rats were compared with controls, which indicated that there is no toxic effect on the kidney [Table 3]. In correlating the chemical findings to the histopathological examination, the mean glomerular diameter and the mean diameter of the Bowman's space in all the studied four groups showed no statistically significant differences between groups using

one-way ANOVA test with $P = 0.133$ and 0.1473 , respectively [Table 4]. In all studied groups the renal arterioles showed no wall thickening, hyaline changes or fibrinoid necrosis. Moreover, no significant inflammatory cellular infiltrate was seen. However, the renal tubules demonstrated prominent hyaline droplets in Group 4 that treated with saline, these findings open future challenges for further studies on the effect of saline in renal tubules [Figure 3].

CONCLUSION

O. baccatus extracts showed potential antimicrobial activity against *S. aureus*, *E. coli*, and *C. albicans*. In addition, the total plant extract was considered to be safe and has no toxic effects in kidney and liver in treated rats for 30 days with 50 mg/kg and 100 mg/kg compared to controls as evidenced by biochemical and histopathological evaluation. Moreover, the extracts significantly reduced the serum level of triglycerides, especially at the higher dose. Similar results were reported for *O. baccatus* growing in a different climatic region, i.e., Egypt, which suggests no environmental effects on the safety of this plant.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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