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The effect of sedr leaves (ziziphus spina-christi L.) on kidney and liver functions of injected rats with gentamicin

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Abstract

The hepatotoxicity and nephrotoxicity of gentamicin has been well documented in humans and animals, although the preventive strategies against it remain to be studied. Sidr Leaves (Zizyphus) is one of the traditional plants used in Egyptian folk medicine for the treatment of different diseases. Reports have revealed that the Sidr Leaves has a significant quantity of phytochemical molecules. The present study was designed to evaluate the possible protective effects of the Sidr Leaves against Gentamicin (GEN) induced oxidative stress and hepatorenal toxicity in rats. Fifty rats were divided into two main groups. The first main group (n=10 rats) served as negative control. The second main group (n=40 rats) were fed on basal diet and were intraperitoneally injected with GEN at (100 mg/Kg body weight) daily for 6 days, Random blood samples were obtained to analyze kidney and liver functions. Then rats were divided into 4 subgroups (10 rats each). One of them was served as a positive control group and the other three subgroups were supplemented with different concentrations of dried Sidr leaves (2.5%, 5%, 7%), respectively for 6 weeks. The results revealed that, following Sidr leaves treatment, renal function markers and serum activities of liver functions significantly improved compared with the GEN group ($P < 0.05$). Also, Sidr leaves could significantly ameliorate the levels of glucose and attenuate oxidative stress through a decrease of serum malondialdehyde and an increase of superoxide dismutase compared with the GEN group ($P < 0.05$). **Conclusion:** the results exhibited that Sidr Leaves have potential effects against GEN -induced hepatorenal toxicity in rat due to its antioxidant and free radical scavenger effects.

Keywords: Rats; Gentamicin; Ziziphusspina-christi; Hepatorenal toxicity; Lipid peroxidation; Oxidative stress; Antioxidants.

Introduction

Aminoglycoside antibiotics are commonly used for the treatment of severe Gram-negative bacterial infections, Gentamicin is one of these antibiotics which is commonly used ***(Reiter et al., 2002).*** However, aminoglycosides may cause nephrotoxicity ***(Takamoto et al., 2003)*** and hepatotoxicity ***(Sultana et al., 2016).*** Gentamicin increases the oxidative stress and generation of free radicals, this will cause damage to membrane lipids, proteins and nucleic acids, which leads to liver toxicity and dysfunction ***(Galaly et al., 2014).***

Natural antioxidants boost the internal antioxidants defenses from reactive oxygen species and counterbalance the reactive species ***(Ho et al., 1994).*** The malondialdehyde (MDA) is a marker of oxidative stress, and the superoxide dismutase (SOD) is an indicator of antioxidant capacity ***(Li et al., 2004 and Yoon and Yang, 2009).*** Amelioration of oxidative stress by sidr can be associated with its

ROS scavenging activity. Generally, herbs are considered effective and safe against many infections ***(Heeba et al., 2010).*** Bioactive components from natural sources have functional, pharmacological, and biological properties ***(Shahein et al., 2022).*** Among others, Sidr (*Ziziphusspina-christi*) is known as a multifunctional tree. Its leaves, fruits, and fruit juices are considered good sources of bioactive components. In addition to its good flavor, Sidr has antidiabetic, anti-inflammatory, sedative, analgesic activities ***(El Maaiden et al., 2019 and Cadi et al., 2020).***

The tree of *Ziziphusspina-christi* belongs to the botanical family Rhamnaceae and is known as " Sidr", the leaves are traditionally used in folk medicine. Leaf extract of this tree has a significant quantity of phytochemical molecules such as phenols, flavonoids, and tannins and vitamin C ***(Abdulrahman et al., 2022).*** These constituents have potential activities against liver complaints, urinary issues, digestive syndromes, obesity, diabetes, appetite loss and anemia ***(Bencheikh et al., 2021).***

The aim of the study: This study was conducted to investigate the effect of Sidr Leaves (*Ziziphusspina-christi* L.) on kidney and liver functions in rats injected with Gentamicin.

Materials and methods

Materials: Plant:

fresh Sidr (*Ziziphusspina-christi* L) leaves were obtained from the Agriculture Research Center. **Chemicals**: Casein, vitamins, minerals, cellulose and Gentamicin were purchased from El-Gomhoria Company, Cairo, Egypt. **Kits** for blood analysis were purchased from Alkan Company for Biodiagnostic Reagents, Dokki, Cairo, Egypt. **Animals**: adult male rats (Sprague Dawley strain) were obtained from Helwan Farm, Ministry of Health and Population, Cairo, Egypt.

Methods:

Experimental study was conducted according to the guidelines of Animal Care and Ethics Committee of the NRC as well as the biochemical analysis at the Post graduate Lab of Home Economics Faculty – Helwan University.

The scientific identification of these leaves was carried out at The Agriculture Research Center, Giza, Egypt .

Preparation of dried Sidr leaves: The fresh Sidr leaves were shade-dried for 4 days then they were milled into fine powder by electric blender.

Preparation of diets: The basal diet was prepared according to (AIN-93M) which consists of protein (14%), corn oil (4%), minerals mixture (3.5%), vitamins mixture (1%), fiber (5%), sucrose (10%), choline chloride (0.25%) and corn starch was being thoroughly mixed and formulated according to ***(Reeves et al, 1993).***

Induction of rats model:

Rats were fed on basal diet and injected intraperitoneally with Gentamicin (100 mg/Kg body weight) daily for 6 days ***(Pedraza-Chaverri, 2003 and Jafarey et al., 2014).*** Random blood samples were obtained to analyze kidney and liver functions.

Experimental Design:

The experimental animal was done using fifty male rats, with body weight 180 ±10 g. The rats were housed in cages under hygienic conditions, at temperature-controlled room 25°C. Vitamins and minerals mixture were prepared as described by ***(Reeves et al.,1993).*** The animals were randomly divided into two main groups as follows:**The first main group** (n= 10): was fed on basal diet and served as negative control group. **The second main group** (n= 40) was fed on basal diet and injected intraperitoneally with GEN (100 mg/Kg body weight) daily for 6 days. Then these rats will be divided into 4 subgroups as follow: **Subgroup (1):** Rats were fed on basal diet (positive control group). **Subgroups (2, 3 and 4):** Rats were fed on basal diet supplemented with 2.5%, 5 and 7 of dried Sidr leaves, respectively.

The amounts of food consumed and/or wasted, were recorded every day while total feed intake (FI) was calculated. In addition, body weight (BW) of rat's was recorded weekly and the body weight gain percent (BWG%) and feed efficiency ratio (FER) were calculated according to ***(Chapman et al., 1959).*** At the end of the experimental period (6 wks), rats were fasted overnight, then the blood was collected under slight ether anesthesia. The serum was separated by centrifugation at 3000 rpm for 15 min. which was stored at- 20°C until used for subsequent analysis.

Biochemical Analysis:

Serum was used to determine the following parameters: Uric acid was determined in the serum according to the method described by ***(Fossati et al., 1980).*** Urea nitrogen and Creatinine were determined according to ***(Young and Friedman 2001).*** Serum Aspartate amine transaminase (AST), Alanine amine transaminases (ALT) and alkaline phosphatase (ALP) were carried using the method of ***(Henry, 1974 and Young, 1975 ; Tietz, 1976 and Belfieled and Goldberg, 1971),*** respectively. Serum Malondialdehyde (MDA) was determined according ***to (Draper and Hadley, 1990),*** while Superoxide dismutase (SOD) was measured using the xanthine oxidase-cytochrome c method as described by ***(McCord and Fridovich, 1969).***

Statistical analysis:

Statistical analysis was performed using SPSS computer program (Graph pad software Inc, San Diego, CA, USA) version 20. One-way analysis of variance (ANOVA) followed Duncan's multiple tests were used to make a comparison among different groups. The probability value used for statistical significance was $p < 0.05$ ***(Snedecor and Cochron, 1989).***

Results

The data in Table (1) illustrated the effect of dried Sidr leaves at different levels on body weight status of experimental rats. The statistical analysis showed that the mean values of Final body weight (FBW), BWG % and FER of the positive control group (+ve) were significantly decreased ($P<0.05$), compared to the (- ve) control group However, there was no significant difference in the initial body weight (IBW) among all the groups. Treated rats with different concentrations of dried Sidr leaves had significant increase ($P<0.05$) in FBW, BWG%, FER, compared to the (+ve) control. Also, there were a significant differences in the FBW and BWG% among the treated groups. The most effective groups on FBW were in the group of rat fed on dried Sidr leaves dried Sidr leaves (7%) followed by (5%) then (2.5%).

The positive control group had significant increase (P< 0.05) in the mean values of AST, ALT and ALP compared with the -ve control group due to GEN injection as seen at Table (2). All treated rats groups fed on different concentrations of supplemented diet with dried Sidr had significant decrease (P< 0.05) in the mean values of AST, ALT and ALP compared with the +ve control group. The results showed that there was a significant difference in serum AST and ALP among all the treated groups, However, there was no significant difference between the group fed on basal diet supplemented with(5%) and (7%) of dried Sidr leaves for serum ALT. The most decrease in the mean values of liver functions was recorded for group fed on dried Sidr leaves (7%).

The results in Table (3) showed injected rats with GEN had significant increase (P< 0.05) in mean values of kidney functions compared with the negative control group. Supplementation with dried Sidr at the three tested levels caused a significant decrease (P< 0.05) in the mean values of urea, uric acid and creatinine compared with the +ve control group. There were a significant differences in serum urea and uric acid among all the treated groups. In regarding to creatinine, there was no significant difference between the rats fed on (2.5%) and (5%) of dried leaves. However, there was a significant decrease in serum creatinine between the group fed on (7%) dried leaves and the other treated rats. The greatest decrease in the mean values of kidney functions was recorded for the group fed on dried Sidr leaves (7%).

The results showed that the positive control group had significant increase (P<0.05) in the mean value of MDA and significant decrease (P<0.05) in the mean value of SOD compared with control -ve group. In addition, treated rats with different concentrations of dried Sidr leaves had significant decrease (P<0.05) in mean values of MDA and had a significant increase in serum SOD compared with positive control group. The most decrease in the MDA was recorded for the group fed on dried Sidr leaves (7%).

Table (4)

The effect of dried Sidr leaves on SOD and MDA concentrations in rats injected with gentamicin

Parameters / Groups	SOD (µ/dl)	MDA (n mol/ml)
Control (-ve)	84.42±2.10a	39.72±0.69e
Control (+ve)	44.67±1.59e	88.00±1.49a
Dried Sidr leaves (2.5%)	57.40±1.63d	69.00±1.36b
Dried Sidr leaves (5%)	68.25±2.45c	51.32±1.30c
Dried Sidr leaves (7%)	75.96±1.69b	45.62±1.80d

Data are expressed as mean ± SE.

Values in each column which have different letters are significantly different at (P<0.05).

Discussion

The present study was to reveal the effects of sidr leaves on GEN induced hepatorenal toxicity in the rat. The obtained results demonstrated that the destructive effects of GEN on the rat's liver and kidney can be ameliorated by sidr leaves treatment. Similar to the results of the present finding the alterations in biochemical parameters in gentamicin toxicity were reported by various investigators ***(Abuelezz et al., 2016 ; Teo and Endre, 2017 and Govindappa et al., 2019).***
Concerning the effect of the sidr leaves on the body weight, the obtained results revealed that the mean body weights of gentamicin treated rats were significantly lower than those of the control. However, co-supplementation of Ziziphus leaf extract to gentamicin treated rats successfully restored the body weight near the normal.

Studies reported that weight is a significant and straight forward index of toxicity after exposure to toxic substances and showed that gentamicin exhibited toxicity signs such as depression, dullness, polyurea, restlessness, and reduced water and feed intake. ***Hassan et al., (2018) and Bencheikh et al., (2021)*** demonstrated that regular intraperitoneal injection of GM (80 mg/kg; b.w) to the rats resulted in a substantial reduction in weight gain in comparison with control group.

The data concerned with the modulatory role of Ziziphus spina Christi extract in the maintenance of body weight go parallel with the finding of ***(Missoun et al., 2010; Yossef et al., 2011 and Nale et al., 2012). Abalaka et al., (2011)*** reported that regular supplementation of Ziziphus fruit extract allows for regular assimilation of all body nutrients that maintain the growth rate. The daily administration of the antioxidant Zizyphus lotus L. (Desf.) fruit aqueous extract 3 h before the injection of GEN significantly restored this disorder provoked by the GEN.

Ali et al., (2019) showed that supplementation of goats with above 50% level of dried ZC leaves in their diet significantly increased feed intake and body weight gain by improving feed conversion efficiency of goats.

The data in the present study confirmed that gentamicin produces significant hepatotoxicity as evidenced by increase in serum AST and ALT. Transaminases (AST and ALT) were considered to be a more sensitive measure in evaluating liver function and damage ***(Wojciech and Vincent , 2005). Hatoff, (1980)*** reported that elevations in serum levels of these enzymes were mostly attributed to acute hepatocellular damage or extrahepatic obstruction, or both. The obtained results agree with other reports showing elevations of these enzymes in experimental animals exposed to gentamicin ***(Khan et al., 2011)*** It is well known that GEN can induce hepatotoxicity in rats through oxidative stress and apoptosis ***(Mohamadi et al., 2019; Khaksari et al., 2021 and Bulboaca et al., 2022).*** Following the sidr leaves treatment in our study, the serum activities of AST and ALT significantly decreased in hepatotoxic rats. Amelioration of transaminases activities by sidr leaves in our study may be associated with its antioxidant activities.

Also, ***Amin and Ghoneim, (2009)*** showed that ZSCF exerts a therapeutic effect on carbon tetrachloride (CCL_4) induced liver fibrosis in rats, possibly through its antioxidant action. Similarly, ***Yossef et al., (2011)*** concluded that ZSCF can protect the liver against CCL4-induce oxidative damage in rats, and the hepatoprotective effect might be correlated with its antioxidant and free radical scavenger effects.

El-Desouky et al., (2014) , reported that oral administration of ethanolic Ziziphus mauritiana leaf extracts resulted in a significant decrease in level of ALT and AST enzymes. As for kidney function markers, the obtained results exhibited that GEN injection to rats led to renal impairment, which was reflected by the increase of serum urea and creatinine. These observations are generally coincided with other studies ***(Mohammed et al., 2015).*** These outcomes are consistent with previous studies, which implied that GEN induces renal function impairment ***(Ataman et al., 2018; Yilmaz et al., 2018 and Medic et al., 2019).*** Significant elevations of serum urea and creatinine in GM intoxicated animals represent a decrease of glomerular filtration rate (GFR) ***(Abd-Elhamid et al., 2018).*** Moreover, the findings of our study have confirmed previous researches on the effects of other antioxidants in ameliorating kidney damages due to GEN that can refer to aminoguanidine ***(Polat et al., 2006)*** , gossypin ***(Katary and Salahuddin, 2017)*** and nigella sativa ***(Yaman and Balikci, 2010). Okasha et al., (2017)*** suggested that Sidr fruit extract slightly reduce the renal damage in experimental animals. Like liver, the antioxidant potentials of Sidr leaves are the cause behind their renal curative effects noticed in the present study.

The protective roles of sidr in reducing the levels of renal function markers may be associated with its antioxidant activities, as reported in the present study and above-mentioned previous studies. Another study showed that ZSCLE administration may prevent multiple-organ injury and can alleviate renal dysfunction associated with sepsis in mice ***(Dkhil et al., 2018).*** Similar trends have been observed by ***Al-Ghamdi et al., (2019)*** who found that methanol and aqueous extracts of Sidr leaves significantly decreased serum creatinine and uric acid. Furthermore, treatment with sidr leaf and flaxseed alone or in combination restored the level of urea, uric acid and creatinine significantly and reversed the nephrotoxicity induced by cyclosporine A. ***(El Seedy et al., 2021).***

In the present study, MDA significantly increased while the SOD were significantly decreased in all gentamycin treated rats. GEN promotes the production of ROS and reactive nitrogen species (RNS) and suppresses the antioxidant system ***(Heidarian, 2017;Ahmadvand , 2019; and Medic, 2019).*** The reduced enzyme activity in the gentamicin group is a generalized response, not specific to one enzyme indicating impaired function at several steps of the antioxidant pathway ***(Medic , 2019).*** In the current study, sidr leaves administration could reduce serum MDA concentration and clearly recovered activities of SOD in the treated groups. The radical scavenging properties of Sidr leaf extract might be due to the presence of bioactive antioxidants such as poly phenols and by this mechanism this plant is effective as traditional medicine ***(Rabiei et al., 2014).*** Also many researches showed that Z. spina christi is a strong antioxidant agent because of the presence of saponins glucosides and flavonoids. ***(Agata et al., 2009)*** , tannins ***(Adzu et al., 2001 and Guerra et al., 2005).***and carotenes ***(Guil-Guerrero, 2004).*** Most of the genus Ziziphus's plants have been reported to be potential antioxidants attributed to their polyphenolics, saponins, and triterpenoids, which are known to exhibit antioxidant activity ***(Sakna et al., 2019).***

Correspondingly, different studies also reported the antioxidant activity of Z. spina-christi extract. ***(Kumarappan et al., 2012 and Michel et al., 2011).*** The main phytochemical constituents of this plant include flavonoids, alkaloids and saponins. ***(Michel et al., 2011).*** It has been reported that plants with high antioxidant activity have ability to attenuate oxidative stress ***(Kumarappan et al., 2012). Alhakmani et al., (2014)*** showed that Z. spina christi extract has significant antioxidant activity and can be used to prevent oxidative stress and related diseases.

Also, our findings are in parallel with the study of ***Asgarpanah, (2012)*** that revealed ZSCL crude methanolic extract exerted strong free radical and peroxide scavenging activities which agree with ***Setorki, (2016) and Alnahdi et al., (2017)*** reports. Other antioxidants such as lycopene, curcumin, and melatonin appear to be well in the improvement of oxidative stress status. ***(Karahan, 2005).*** Modern studies have confirmed that triterpenes and triterpenic acids, isolated from Ziziphus exert biological functions, the most important of which is antioxidant activity ***(Song et al., 2020).***

Conclusion

According to the obtained results, it was concluded that the destructive effects of GEN on the rat's liver and kidney can be ameliorated by sidr leaves treatment. In addition. Antioxidant activities of sidr might be responsible for its beneficial effects.

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تأثير أوراق السدر على وظائف الكبد والكلى في الفئران المحقونة بمادة الجنتاميسين (*ziziphus spina-christi* L).

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تم توثيق السمية الكبدية والسمية الكلوية للجنتاميسين (GEN) بشكل تام في البشر والحيوانات، على الرغم من ذلك فإن الاستراتيجيات الوقائية ضد السمية لا تزال بحاجة إلى الدراسة. إن أورق السدر (زيزيفوس) هو أحد النباتات المستخدمة تقليديا في الطب الشعبي المصري لعلاج الأمراض المختلفة. وقد كشفت التقارير أن أوراق السدر تحتوي على كمية كبيرة من الجزيئات الكيميائية النباتية. لذا تم تصميم هذه الدراسة لتقييم التأثيرات المحتملة لأوراق السدر ضد الإجهاد التأكسدي والتسمم الكبدي الكلوي في الفئران الناجم عن الجنتاميسين (GEN). تم تقسيم خمسين فأرا إلى مجموعتين رئيسيتين. كانت المجموعة الرئيسية الأولى (عددها = ١٠ فئران) بمثابة مجموعة ضابطة سالبة. تم تغذية المجموعة الرئيسية الثانية (عددها = ٤٠ فأراً) على الغذاء الأساسي وتم حقنها بالجنتاميسين (GEN) داخل الغشاء البريتونى بجرعة (١٠٠ ملجم/كجم من وزن الجسم) يومياً لمدة ٦ أيام. وبعد ذلك تم تقسيمها إلى ٤ مجموعات فرعية (١٠ فئران لكل منها). تم تقديم إحداها كمجموعة ضابطة موجبة وتم تغذية المجموعات الفرعية الثلاثة الأخرى بتركيزات مختلفة من أوراق السدر المجففة (٢.٥%، ٥%، ٧%) على التوالى لمدة ٦ أسابيع. أظهرت النتائج أنه بعد العلاج بأوراق السدر، تحسنت دلائل وظائف الكلى وأنشطة وظائف الكبد بشكل ملحوظ مقارنة بمجموعة الجنتاميسين ($P < 0.05$). وكذلك أيضا يمكن لأوراق السدر أن يعمل على تحسين مستويات سكر الجلوكوز بشكل كبير وتخفيف الإجهاد التأكسدي من خلال تخفيض المالونديالدهيد (MDA) بالدم وزيادة فوق أكسيد الديسميوتيز (SOD) مقارنة بمجموعة الجنتاميسين ($P < 0.05$). الخلاصة: كشفت النتائج أن أوراق السدر لها تأثيرات محتملة ضد التسمم الكبدي الكلوي في الفئران الناجم عن الجنتاميسين وذلك بفضل آثارها المضادة للأكسدة والكاسحة للجذور الحرة .

الكلمات المفتاحية: الفئران؛ الجنتاميسين ؛ زيزيفو سبينا كريستي ؛ سمية الكبد ؛ بيروكسيد الدهون ؛ الإجهاد التأكسدى ؛ مضادات الأكسدة.