Water Extract of Arabic Gum Ameliorates the Gentamicin-Induced Nephrotoxicity, Hepatotoxicity, Oxidative Stress Markers andCytokine Levels in Mice

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KEYWORDS
Gentamicin, Arabic gum, oxidative stress, cytokines, gene expression

ABSTRACT
Arabic gum is a natural exudate from Acacia trees, primarily composed of arabinogalactan, water soluble plan product that is rich in many important elements for the human body health such as K+, Mg2+ Ca2+ and others. The aim of this study is to investigate the beneficial effect of water extract of Arabic gum on the nephrotoxicity and hepatotoxicity induced by gentamicin. Forty mice were used to conduct this study which divided into five groups. The effects of the Arabic gum on the kidney and liver functions were estimated by investigating their function markers (AST, ALT, creatinine, urea). Oxidative stress was also investigated in liver tissues. The current results showed that gentamicin caused a state of hepatotoxicity and nephrotoxicity denoted by increasing liver enzymes AST and ALT, creatinine, urea, increased level of oxidative stress markers MDA, GSH and CAT and levels of pro-inflammatory cytokines such as tumor necrosis factor alpha and Interleukin 6 (TNF-α and IL-6).and anti-inflammatory cytokines IL-4 and IL-10, while the water extract of Arabic gum reduced the oxidative stress that increased by gentamicin. Arabic gum extract also found to modulate the kidney and liver function mediated by liver enzymes (AST and ALT) and kidney function markers, creatinine and urea. Results also stated that Arabic gum extract adjust the gentamicin-induced inflammation by regulating the levels of pro-inflammatory cytokines IL-6 and TNF-α, and anti-inflammatory cytokines IL-4 and IL-10. The current study suggested that Arabic gum can be added to the food as food supplements. However, further studies should be conducted for the approval of its safety.

Introduction

Gentamicin is stated to be very powerful aminoglycosides that are used for treatment of infections those caused by gram negative bacteria. Nephrotoxic effect is recorded to be the most dangerous adverse effect of Gentamicin[1,2]. This adverse effect limits gentamicin clinical use. The exact and clear mechanism of gentamicin-induced nephrotoxicity is not fully understood yet, but a remarkable increase in reactive oxygen species (ROS), inflammatory cytokines, lipid peroxidation increase were stated to have an important role in this mechanism. It was found to decrease the antioxidant renal enzymes assuperoxide dismutase (SOD), glutathione (GSH) and glutathione peroxidase (GPx) catalase[3,4]. Oxidative stress activation induces many mechanisms ends with up-regulation of caspase family of proteases those have apoptotic cell death effect[5,6]. 30% of the aminoglycosides patients showed a nephrotoxic effect within 7 days of administration. Many studies revealed that anti-inflammatory agents and antioxidants have a great role against Gentamicin adverse effects [7, 8].

Arabic gum is a water soluble fermentable dietary fiber from *Acacia senegal*exudates[9, 10]. It is a polysaccharide having a branched chain. Biochemical analysis revealed that Arabic gum is rich in containing Mg^{+}, K^{+} and Ca^{+}. Arabic gum is degraded in the colon by microorganisms (fauna and flora) into a short fatty acid [11]. Using AG as a dietary fiber found to have a protective effect on renal, cardiac and hepatic toxicity. Moreover, it is stated to decrease the blood cholesterol, and blood pressure[12, 13]. Arabic gum is also reported to increase the intestinal absorption for water and Na^{+}. Treatment with Arabic gum found to have an anti-carcinogenic effect where it alters expression of some genes which leads finally to inhibit tumor formation[14].

In this work we aimed to explain the renal and hepatic protective role of water extract of Arabic gum in gentamicin induced nephrotoxicity and hepatotoxicity throughout investigation of some pro-inflammatory cytokines (IL-1 and IL-6) and anti-inflammatory cytokines and (IL-4 and IL-10). Also, antioxidant enzymes (Catalase, Glutathione and Glutathione peroxidase) are investigated. AST, ALT, Urea and Creatinine as biomarkers for liver and kidney function also investigated.

Material and methods

Arabic Gum

Arabic Gum was provided from the market of Al-Ahsa region, Kingdom of Saudi Arabia (KSA). Arabic gum was rushed mechanically to reach very small size (Powder size). Overnight magnetic steered then filtered into a 50 ml tubes adjusting the concentration to 20 mg/ml and stored in normal refrigerator. Extract is prepared fresh every three days during injection. Gentamicin was purchased from Sigma Company. Chemicals for investigation of different parameters were purchased from Human Diagnostic Worldwide (Max-Planck-Ring 21, Wiessbaden, Germany).

Animals

Male Swiss Webster mice purchased from King Saud University were used in this study. Animals were kept under normal standard laboratory conditions of relative humidity and temperature. The dark/light cycle wasnormal, and animals allowed free access to food and water. All experiments had been carried out according to the guidelines of the animal ethical committee of KFU and with the NIH guide for the Care and Use of Laboratory Animals, NIH publication no. 85-23,1985.

Experimental protocol

Forty male mice of 25-30 gm weight were used in this experiment. Mice were randomly divided into five groups (8 mice for each). Mice are allowed to adapt to experimental conditions

for one week. The experimental span was around 4 weeks. Mice were assigned into the following groups. Group I: Control group received distilled water intraperitoneal (IP). Group II: injected with Gentamicin in concentration of 80 mg/kg of mice for 15 days followed by DW for 15 days. Group III: Injected with Arabic Gum in concentration of 300 mg/kg of mice for one month. Group IV: injected with gentamicin for 15 days followed by AG for another 15 days. Group V was injected by mix of gentamicin and Arabic gum at designed concentration of each for one month. Blood samples were collected from each group and centrifuged at 3000 rpm for 5 min. plasma were stored in -20^{0}C for estimating different blood parameters. Tissues (kidney and spleen and liver) were collected and stored in -80^{0}C for further studies.

Biochemical analysis

Kidney injury markers (creatinine and urea), pro-inflammatory cytokines such as, interleukin-6 (IL-6), tumor necrosis factor (TNF), anti-inflammatory ones such as interleukin-4 (IL-4), interleukin-10 (IL-10). Also, liver function was investigated throughout liver enzymes, aspartate transaminase (AST), and alanine transaminase (ALT). Oxidative stress was investigated throughout lipid peroxidation and reduced glutathione were carried out using kits for each parameter from Human Diagnostic, Germany according to the manufacturer manual.

Semi-quantitative PCR

Total RNA was isolated from kidney and liver. mRNA was purified from total one and then cDNA was synthesized using oligo-dt12-28 primer(GIBCO-Invitrogen, USA). Theobtained cDNA was extracted by phenol-chloroform, precipitated by ethanol then stored after resuspension in PCR grade water. Forward and reveres Primers were designed for pro-inflammatory cytokines (IL-6 and TNF) and anti-inflammatory ones (IL-4 and IL-10) (Table 1). PCR amplification was done, and the expression analysis was performed.

Table (1) primers sequence used in PCR amplification

Primer name	**Primer sequence**
TNF-α forward	5-atccgagatgtggaactg-3
TNF-α reverse	5-cacgtagtcggggcagcc-3
IL-6 forward	5-cttcttgggactgatgtt-3
IL-6 reverses	5-gtaagttgttcttcacaa-3
IL-4 forward	5-ccccaccttgctgtcacc-3
IL-4 reverses	5-tgagttcagaccgctgac-3
IL-10 forward	5-tgttgcctgccttactg-3
IL-10 reverses	5-gcagttgatgaagatgtc-3

Statistical analysis

Collected data were statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20. Statics were done for numerical results throughout mean, standard deviation and minimum and maximum of the range. All data were analyzed using one-way ANOVA test for comparison of the tested different groups followed by Tukey's post-hoc. Significant level was considered at (P value $\leq$ 0.05.)

Results

Figure 1 and table 2 explain the effect of Arabic gum on the gentamicin-induced changes in the liver functions mediated by AST and ALT. Inboth enzymes, gentamicin significantly upregulated their levels in the serum and Arabic gum did not change their serum level. Treatment with Arabic gum after gentamicin treatment could lower the serum level of AST and ALT to the subnormal level as in AST or normal level as ALT. However,co-administration of gentamicin and Arabic gum significantly lowered the serum level of both AST and ALT.

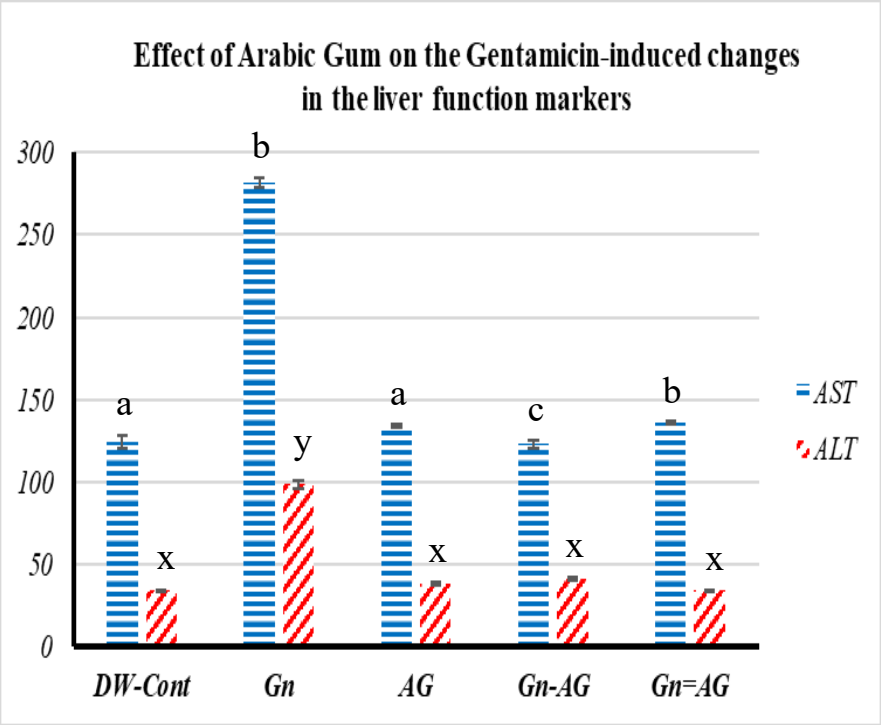

Fig. 1. Effect of Arabic gum on the gentamicin-induced changes in the function markers mediated by AST and ALT enzymes. ***DW-Cont***: control group received saline only;***Gn***: mice received gentamicin only;***AG***: mice received Arabic gum only;***Gn-AG***: mice received gentamicin for 15 daysfollowed by Arabic gum and ***Gn=AG***: mice received gentamicin and Arabic gum, simultaneously. Values were expressed as mean value of each experimental group ±SEM. Different letters within the same examined marker indicating significant difference. Significant difference was considered at *p value*≤0.05.

Figure 2 and table 2 represent the treatment effects of Arabic gum on the gentamicin-induced changes in the nephrotoxicity expressed by the serum levels of creatinine and urea. Gentamicin treatment significantly increased the serum levels of both creatinine and urea. Arabic gum did not affect the serum level of creatinine;however, it increased the level of the urea in the serum. Compared to the gentamicin group, Arabic gum significantly decreased the levels of creatinine and urea either in the group received it after gentamicin treatment or co-administered it with gentamicin, decreased level of creatinine reached the level of control group. Although the level of urea was decreased significantly with Arabic gum, it was significantly higher than the control group.

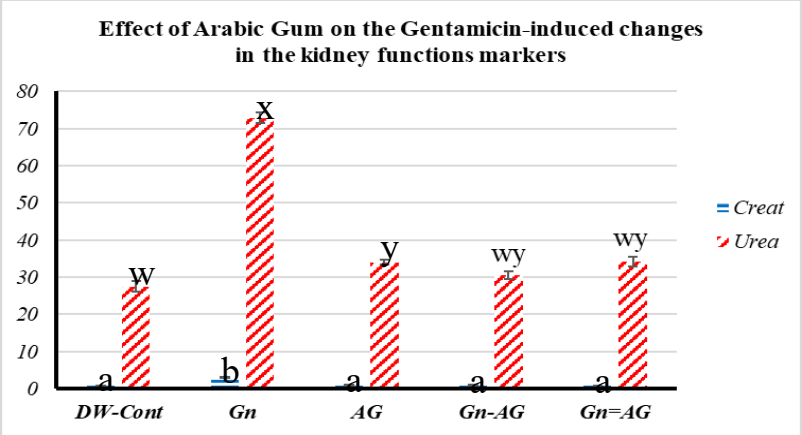

Fig. 2. Effect of Arabic gum on the gentamicin-induced changes in the kidney function markers mediated by creatinine and urea. ***DW-Cont***: control group received saline only; ***Gn***: mice received gentamicin only; ***AG***: mice received Arabic gum only; ***Gn-AG***: mice received gentamicin for 15 days followed by Arabic gum and ***Gn=AG***: mice received gentamicin and Arabic gum, simultaneously. Values were expressed as mean value of each experimental group ±SEM. Different letters within the same examined marker indicating significant difference. Significant difference was considered at *p value*≤0.05.

Table (2). Effect Arabic gum on the gentamicin-induced changes in the liver and kidney function markers. Different letters indicating significant difference between the experimental groups of the same marker.For more details, refer to Fig. 2.

	Liver Function Markers		**Kidney Functions Markers**	
	AST	***ALT***	***Creatinine***	***Urea***
DW-Cnt	124.0 ± 3.73^{a}	34 ± 0.63^{w}	0.898 ± 0.01^{a}	27.4 ± 1.43^{w}
Gn	281.9 ± 2.77^{b}	98.8 ± 2.42^{x}	2.963 ± 0.19^{b}	72.9 ± 1.47^{x}
AG	134.1 ± 1.03^{a}	38 ± 1.09^{w}	0.897 ± 0.02^{a}	34 ± 0.71^{y}
Gn-AG	122.8 ± 2.69^{c}	40.9 ± 1.22^{w}	0.994 ± 0.02^{a}	30.6 ± 1.11^{wy}
Gn=AG	135.9 ± 0.83^{b}	34 ± 0.72^{w}	0.856 ± 0.03^{a}	34.1 ± 1.39^{wy}

Figure 3 and table 3 show the results of Arabic gum treatment on the gentamicin-induced changes of MDA, GSH and CAT oxidative stress markers. Compared to the saline control group, gentamicin significantly elevated the levels of MDA, GSH and CAT, whereas Arabic gum treatment did not affect the levels of MDA and CAT, however the level of GSH was significantly increased by Arabic gum. Compared with the gentamicin group, co-administration of Arabic gum with gentamicin or simultaneous treatment could significantly lower the levels of MDA and CAT to the level of the control group; on the other hand, GSH was decreased significantly by Arabic gum, however its expression was still significantly higher than that of the saline control group.

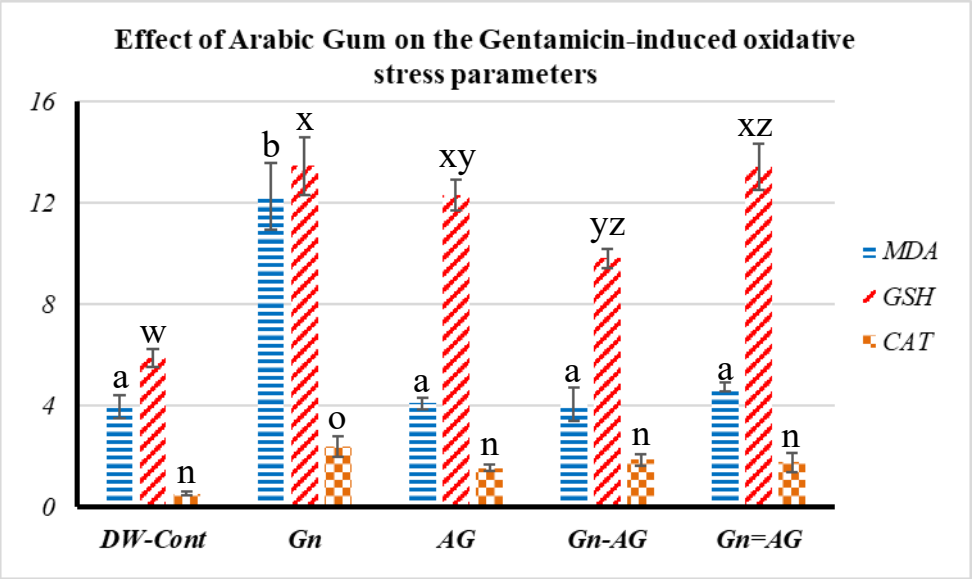

Fig. 3. Effect of Arabic gum on the gentamicin-induced changes oxidative stress markers mediated by MDA, GSH and CAT.***DW-Cont***: control group received saline only; ***Gn***: mice received gentamicin only; ***AG***: mice received Arabic gum only; ***Gn-AG***: mice received gentamicin for 15 days followed by Arabic gum and ***Gn=AG***: mice received gentamicin and Arabic gum, simultaneously. Values were expressed as mean value of each experimental group ±SEM. Different letters within the same examined marker indicating significant difference. Significant difference was considered at *p value*≤0.05.

Table (3) Effect of gentamicin on the oxidative stress status markers. Different letters indicating significant differences between the experimental groups of the same markerFor more details, refer to Fig. 3.

	Oxidative Stress Markers		
	MDA	***GSH***	***CAT***
DW-Cnt	3.96 ± 0.46^{a}	5.88 ± 0.35^{w}	0.53 ± 0.07^{n}
Gn	12.25 ± 1.32^{b}	13.43 ± 1.13^{x}	2.4 ± 0.4^{o}
AG	4.08 ± 0.22^{a}	12.29 ± 0.61^{xy}	1.54 ± 0.12^{n}
Gn-AG	4.04 ± 0.67^{a}	9.8 ± 0.37^{yz}	1.87 ± 0.23^{n}
Gn=AG	4.71 ± 0.18^{a}	13.4 ± 0.93^{xz}	1.76 ± 0.37^{n}

The effects of Arabic gum on the gentamicin-induced changes in the expression of pro-inflammatory cytokines TNF-α and IL-6 expressed in the kidney were shown in figure 4 and table 4. Compared to the saline control group, gentamicin significantly increased the expression levels of TNF-α and IL-6 and Arabic gum treatment did not affect their levels. Compared to the gentamicin treated group, treatment with Arabic gum after gentamicin treatment or either-or simultaneous treatment with both gentamicin and Arabic gum could significantly return the expression levels of TNF-α and IL-6 to their saline control group.

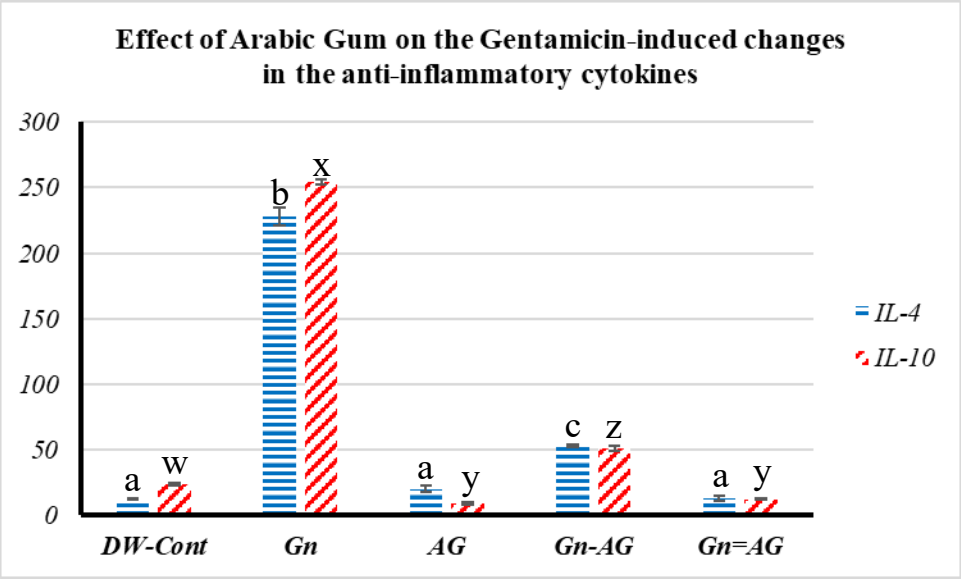

Fig. 4. Effect of Arabic gum on the gentamicin-induced changes in the expression levels of pro-inflammatory cytokines TNF-α and IL-6 in kidney tissue.***DW-Cont***: control group received saline only; ***Gn***: mice received gentamicin only; ***AG***: mice received Arabic gum only; ***Gn-AG***: mice received gentamicin for 15 days followed by Arabic gum and ***Gn=AG***: mice received gentamicin and Arabic gum, simultaneously. Values were expressed as mean value of each experimental group ±SEM. Different letters within the same examined marker indicating significant difference. Significant difference was considered at *p value*≤0.05.

Table (4): Effect of gentamicin on the level of pro-inflammatory cytokines. Different letters indicating significant difference between the experimental groups of the same marker. For more details, refer to Fig. 4.

	Pro-inflammatory Cytokines		**Anti-inflammatory Cytokines**	
	TNF-α	***IL-6***	***IL-4***	***IL-10***
DW-Cnt	63.8 ± 1.62^{a}	63.4 ± 1.33^{x}	12.2 ± 0.37^{a}	23.4 ± 0.93^{w}
Gn	642 ± 14.28^{b}	348.6 ± 5.52^{y}	228 ± 7.18^{b}	254.6 ± 2.04^{x}
AG	68.2 ± 0.86^{a}	65.8 ± 1.16^{x}	20 ± 2.63^{a}	8.6 ± 0.75^{y}
Gn-AG	80.4 ± 3.19^{a}	66.6 ± 0.93^{x}	53.2 ± 1.07^{c}	51.2 ± 1.83^{z}
Gn=AG	69.8 ± 6.13^{a}	65.5 ± 1.69^{x}	12.8 ± 1.68^{a}	12.2 ± 0.86^{y}

The effects of Arabic gum on the gentamicin-induced changes in the anti-inflammatory cytokines IL-4 and IL-10 were illustrated in figure 5 and table 4. Gentamicin significantly increased the levels of the anti-inflammatory cytokines IL-4 and IL-10. Compared to the saline control group, Arabic gum did not affect the expression level of IL-4 but decreased the expression level of IL-10. Compared to gentamicin treated group and saline control group, Administration of Arabic gum after gentamicin significantly downregulated the expression levels of both IL-4 and IL-10 however their expression levels were still higher than the control group. Co-administration of Arabic gum with gentamicin significantly decreased the expression level of IL-4 to the levels of the saline control group whereas the expression level of IL-10 decreased to a level lower than the saline control group.

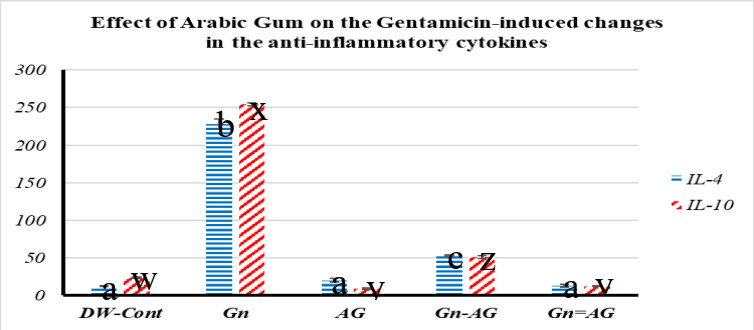

Fig. 5. Effect of Arabic gum on the gentamicin-induced changes in the expression levels of anti-inflammatory cytokines IL-4 and IL-10 in kidney tissue.***DW-Cont***: control group received saline only; ***Gn***: mice received gentamicin only; ***AG***: mice received Arabic gum only; ***Gn-AG***: mice received gentamicin for 15 days followed by Arabic gum and ***Gn=AG***: mice received gentamicin and Arabic gum, simultaneously. Values were expressed as mean value of each experimental group ±SEM. Different letters within the same examined marker indicating significant difference. Significant difference was considered at *p value*≤0.05.

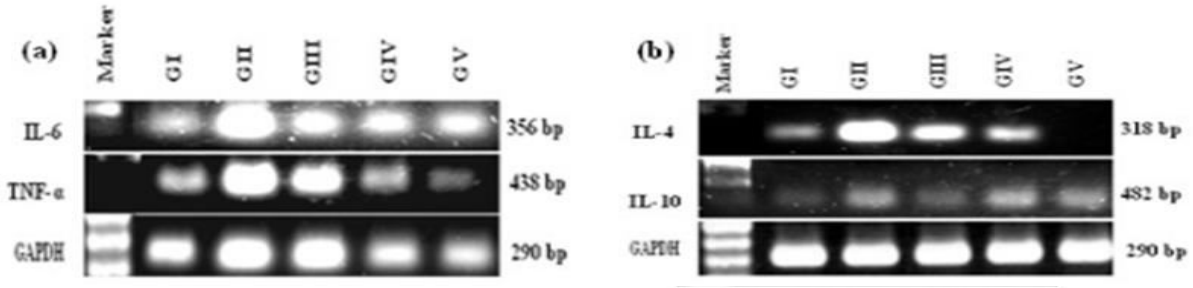

Fig.6. Expression profile of pro-inflammatory cytokines (a) and anti-inflammatory ones (b) in liver. GI: mice receive saline only, GII: mice receive gentamicin only, GIII: mice receive Arabic gum only, GIV: mice receive gentamicin for 15 days then followed by Arabic gum and GV: mice receive gentamicin and Arabic gum at the same time.

Fig. 7. Expression profile of pro-inflammatory cytokines (a) and anti-inflammatory ones (b) in kidney. GI: mice receive saline only, GII: mice receive gentamicin only, GIII: mice receive Arabic gum only, GIV: mice receive gentamicin for 15 days then followed by Arabic gum and GV: mice receive gentamicin and Arabic gum at the same time.

Discussion

Our work investigates the effect of water extract of Arabic gum on the alteration of the renal and hepatic function of mice. Injection of 100 mg/kg of gentamicin through intraperitoneal rout results in nephrotoxicity and hepatotoxicity after 15 days by the elevation of serum creatinine, urea as kidney biomarkers, AST and ALT as liver function enzymes. Gentamicin also increasesoxidative stress and inflammation which finally leads to apoptosis. These experimental results come in accordance with several previous studies [15, 16]. Hepatocyte damage was estimated by the significant elevation of liver enzymes in plasm. TheArabic gum extract reduced all liver enzymes (Fig.1 and Table 2) significantly indicating the protective role of this extract on hepatocytes. Protective effect of other plants on liver cells damaged by gentamicin [17]. Other groups which receive both of gentamicin and Arabic gum extract or following gentamicin by

extract of Arabic gum extract only showedresults near to control group. Co-administration of gentamicin with plants extract showed ameliorative effect on liver function markers[18,19].

Creatinine and urea as renal markers were estimated in this work and showed a highly significant increase after treating gentamicin (Fig. 2 and table 2) so the creatinine and urea clearance from the blood was affected reflecting the impair of renal function. Many research groups reported similar results which support our results [22-24]. The result of our study showed a significate modulation effect of the Arabic gum extract on kidney and liver impairment induced by gentamicin. Therefore, Arabic gum exerts a great antioxidant effect as shown by our results. These antioxidant effects will take the body away from some dangerous diseases such as cancer and hyperlipidemia [25, 26].

The oxidative stress had been reported to have the main role in nephrotoxicity and hepatotoxicity. The increase of free radicals causes lipid peroxidation. In this work there is a significant increase in MDA (peroxidation indicator) in mice injected by gentamicin when compared with the control ones (Fig. 3 and table 3).Many previous studies support presentresults[20]. GSH level was decreased significantly in renal homogenate. This low level of GSH which is considered the main factor inthe integrity of the cell membrane protein and lipid and protect it against the damage produced by oxidative stress indicates the harmful effect of gentamicin on renal function by affecting the cell membrane configuration[21]. Catalase enzymes also report a significant decrease due to gentamicin administration and come near to the normal level in other groups which have the extract of Arabic gum (Table Fig. 3 and table 3).

The role of oxidative stress produced by gentamicin in inflammation of both kidney and liver was investigated by semi-quantitative polymerase chain reaction (PCR) for pro-inflammatory cytokines (IL-6 and TNF-α) and anti-inflammatory ones (IL-4 and IL-10). The expression profile of the pro-inflammatory cytokines and anti-inflammatory cytokines was confirmed in the kidney and liver tissues in all of the experimental groups (Figs. 6 and 7). The expression rate of pro- inflammatory cytokinesTNF-α and IL6 showed significantly high level in gentamicin challenged group in kidney(Fig. 4). These resultsagree with other studies that showed an increase in these cytokines by gentamicin at both protein and gene level[27].

The elevation of expression rate of pro-inflammatory may lead to kidney and liver damage which confirmed before by oxidative stress estimation studies (table: 3). The anti-inflammatory cytokines (IL-4 and IL-10) expression rate were also investigated in both kidne. The expression rate (Fig.5) showed nearly a very near profile of pro-inflammatory ones. This expression rate is enhanced as an immune response form the kidney and liver to face the kindly and liver damage induced by gentamicin. Both kidney tubules and liver cells are highly enriched with blood so the inflammation process will be urgent by diapedesis of and filtration of mass number of macrophage to the kidney and liver secreting pro-inflammatory and anti-inflammatory cytokines in kidney and liver tissue cells this may explain the expression rate in gentamicin treated group. Co-administration of Arabic gum extract with gentamicin or treatment of mice with Arabic gum after gentamicin showed decreasing of both pro-inflammatory and anti-inflammatory cytokines (Figs. 4, 5) indicating that treatment with Arabic gum extract reduces inflammatory effects induced by gentamicin.

Conclusion

In the work we can conclude that Arabic gum extract has a high concentration of different antioxidants thatappear in its antioxidant effect on both kidney and liver. Arabic gum extracts inhibit the inflammatory effect produced from different oxidants, so Arabic gum can be safely added for dietary supplements as a vital body organs protector.

Declaration of Conflicting Interests

The author hereby declares that there is no conflict of interest with respect to the research authorship and/or publication of the results of this work

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