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Research Paper

Protective Effects of Co-Treatment With Hydroethanolic Extract of Origanum Vulgare on Gentamicin-Induced Renal Toxicity in Rats

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ABSTRACT

Objective Renal toxicity and ototoxicity are considered as the main side effects of aminoglycoside antibiotics, such as gentamicin. The present study aimed to investigate the effect of co-treatment by origanum vulgare extract on the gentamicin-induced renal toxicity.

Methods Adult male Wistar rats in the weight range of 200 to 250 grams were randomly assigned into four groups (n = 8): Control, renal toxicity (with the intraperitoneal injection of gentamicin [100 mg/kg/day], for eight days), co-treatment with OV extract and gentamicin vehicle (with the intraperitoneal injection of normal saline and OV extract gavage [40 mg/kg], for eight days), co-treatment with OV ethanolic extract (with the intraperitoneal injection of gentamicin [100 mg/kg/day] and OV extract gavage [40 mg/kg]), for eight days. The amount of urea, creatinine, sodium, potassium, and osmolality were measured in the plasma and urine samples. The left kidney was used for the histological study and the right kidney was used to measure MDA and FRAP.

Results treatment with OV ethanolic extract significantly decreased the blood concentrations of creatinine, urea, the absolute excretion of sodium, the fractional excretion of sodium and potassium, and MDA, compared with the renal toxicity group. Besides, co-treatment with ethanolic extract of origanum vulgare significantly increased creatinine clearance, urinary osmolality, and FRAP, compared with the renal toxicity group.

Conclusion The oral co-treatment with ethanolic extract of origanum vulgare has a protective effect on gentamicin-induced renal toxicity. This effect can be induced by reducing the oxidative stress caused by free radicals and reducing the amount of lipid peroxidation caused by gentamicin.

Extended Abstract

1. Introduction

Renal toxicity and ototoxicity are considered as the main side effects of the gentamicin [1]. These side effects are associated with the production of Reactive Oxygen Species (ROS). During gentamicin-induced renal toxicity, the tubular epithelial cell necrosis and glomerular damages create ROS. The ROS leads to the contraction of glomerular mesenchymal cells, increases renal vascular resistance, and reduces renal blood flow and glomerular filtration [1]. Thus, the selective aggregation of gentamicin in renal tissues damages various types of cells [2].

Origanum Vulgare (OV) from the mint family is a medicinal plant; the leaves and flower branches of this plant

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are used medicinally. OV includes several pharmaceutically active compounds, such as linalool, thymol, carvacrol, myrcene, caryophyllene, tannin, glycoside, saponin, and rosaniline acetate [6, 7]. The terpenes compounds of OV, like carvacrol acetate and thymol, have significantly decreased the ROS and nitrogen oxide levels [10]. Moreover, the phenolic compounds of OV have protective effects against ROS and strengthen the body's antioxidant system [13, 14]. Considering the antioxidant properties of the hydroethanolic extract of OV, the present study aimed to investigate the effect of co-treatment by OV extract on the gentamicin-induced renal toxicity.

2. Materials and Methods

This experimental study was conducted on a sample of 32 adult male Wistar rats with a weight range of 200 to 250 grams. The rats were assigned into four groups: Control, gentamicin, OV^+ normal saline, OV^+ gentamicin. The control group received no treatment. The gentamicin (100 mg/kg) was intraperitoneally injected to the rats of the gentamicin group, for eight days. Animals in the OV^+ normal saline group daily received the gavage of hydroethanolic extract of OV (40 mg/kg) and normal saline (0.5 ml), for eight days. Furthermore, the OV^+ gentamicin group received the gavage of hydroethanolic extract of OV (40 mg/kg) and intraperitoneal injection of gentamicin (100 mg/kg). On the ninth day of the experiment, the urine samples were collected, also, the blood pressure was measured from the Caudal artery. Next, the blood sampling was conducted from the abdominal aorta of the animals.

The blood samples were tested for Creatinine (Cr), Blood Urea Nitrogen (BUN), and the sodium and potassium concentrations. Also, the osmolality was measured in blood and urine samples. The observed values were used to Calculate Creatinine Clearance (CCR), absolute excretion of sodium (UNaVo) and potassium (UKVo), and fractional excretion of sodium (FENa) and potassium (FEK) using the suggested equations [17]. On the other hand, the kidneys were delivered to the pathology laboratory; the left and right kidneys were used to determine the tissue damage and measure Malondialdehyde (MDA) with FRAP test, respectively.

The one-way analysis of variance and Tukey test were performed to compare the treatment results' differences, in SPSS-21. Also, the histological results were analyzed with the Kruskal Wallis and Dunnett tests. The P-value of lower than 0.05 was considered as a significant result in the analysis.

3. Results

Gentamicin treatment increased the levels of Cr, BUN, FENa, FEK, UNaVo, and MDA, also, it reduced the CCR level and the FRAP value of the renal tissue (antioxidant power), and had no significant effect on UKVo. However, OV extract co-treatment decreased the levels of Cr, BUN, FENa, FEK, UNaVo, and MDA, also, it increased the CCR level, the FRAP value, and had no significant effect on UKVo (Table 1). Thus, gentamicin treatment caused renal toxicity. However, the systolic blood pressure did

Table 1. The statistics of the measured and calculated variables in the study sample

Parameters / Groups	Mean±SD							
	%FEK	%FENa	UKVo (mmol/min/kg)	UNaVo (mmol/min/kg)	CCr (ml/min/kg)	Crp (mg/dl)	BUN (mg/dl)	Osmolu (mOsm/kg H_2O)
Control	56.33±3.56	0.61±02.0	2.66±0.12	1.07±0.05	1.35±05.0	0.48±07.0	23.17±0.45	283±19.44
Gentamicin	150.13±35.9 ***	7.62±53.0 ***	2.42±32.0	3.57±20.0 ***	0.19±07.0 ***	2.91±13.0 ***	99.67±41.1 ***	295.60±74.30 ***
OV^+ normal saline	66.50±25.4 +++	0.64±06.0 +++	2.75±35.0	1.18±08.0 +++	1.52±05.0 **+++	0.48±05.0 +++	20.45±75.0 +++	285.55±50.33 +++
OV^+ gentamicin	60.25±40.6 +++	0.92±04.0 **+++	2.71±08.0	1.35±15.0 **++	1.45±04.0 ++	0.63±04.0 **+++	31.05±88.0 ***+++	289.8±15.33 +++

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FEK: Fractional Excretion of Potassium; FENa: Fractional Excretion of Sodium; UKVo: Absolute Excretion of Potassium; UNaVo: Absolute Excretion of Sodium; CCr: Creatinine Clearance; Crp: Plasma Concentration of Creatinine; BUN: Blood Urea Nitrogen; Osmolu, Urine Osmolarity;

**P<0.01; ***P<0.001; comparing with the control group; ++ P<0.01; +++ P<0.001; comparing with the gentamicin group

Table 2. The observed damages in the study sample

Parameters / Groups	Tubular Necrosis	Formation of Protein Templates	Tubular Obstruction	Vacuolation	Total Tubular Damage	Reduction of Red Blood Cells in Glomeruli	Increase in the Space of the Bowman Capsule	Total Glomeruli Damege
Control	0	0	0	0	0	0	0	0
Gentamicin	4 *	3 *	3 **	4 *	4 ***	3 *	4 *	4 *
OV+ normal saline	0 +	0 +	0 +	0 +	0 +++	0 +	0 +	0 +
OV+ gentamicin	1 +*	1 +*	1 +*	1 +*	2 +++***	1 +*	1 +*	1 +*

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*P<0.001: Comparing with the control group; +P<0.001: Comparing with the gentamicin group.

not differ between the rats with renal toxicity and those without gentamicin treatment.

Histological investigation results showed that gentamicin caused severe kidney tissue damage in the renal toxicity group, compared with the control group. The main observed damages include tubular necrosis, increase in the urinary space of the Bowman's capsule, vacuolation, formation of protein templates, reduction in the number of red blood cells of the glomeruli, and tubular obstruction. Again, the OV extract co-treatment mostly protected the kidney tissue against the observed damages (Table 2).

4. Discussion

In the present study, gentamicin increased the plasma levels of Cr and BUN, also, it reduced the clearance. However, OV extract co-treatment prevented the gentamicin-induced renal toxicity in rats. Also, the result showed that the parameters of oxidative stress and renal excretory function significantly differ between the control and gentamicin groups. Previous studies have shown that phenolic compounds reduce the plasma and urine levels of Cr because these compounds neutralize free radicals resulted from the gentamicin treatment. Thus, the phenolic compounds of hydroethanolic extract of OV can affect the development of renal toxicity due to a simultaneous gentamicin treatment [26, 27]. Besides, our results indicated that the antioxidant compounds of the OV extract can reduce the excretion of sodium and potassium; this occurs owing to the reduction of free radicals and oxidative stress by OV extract [31].

OV extract co-treatment prevented tissue damage in rats with gentamicin-induced renal toxicity. The hydroxyl group in the phenolic compounds of OV extract has regenerative properties and can trap free radicals. Also, the co-treatment with OV extract in rats receiving gentamicin decreased the amount of MDA in kidney tissue and increased the FRAP value. Previous studies have also reported that co-treatment with hydroethanolic extract of OV reduces the oxidative stress and has a protective effect on kidney tissue [25, 26].

5. Conclusion

The findings of this study showed that the antioxidant, anti-inflammatory, and vasodilatory properties of co-treatment with hydroethanolic extract of OV protects rats against gentamicin-induced renal damage. Further studies are needed to identify the active components of the ethanolic extract of OV, investigate the mechanism of their effect on the kidneys, and compare the effects of these compounds. Thus, OV extract could be recommended as a medicinal plant to prevent the renal toxicity of gentamicin.

Ethical Considerations

Compliance with ethical guidelines

The present study was confirmed by the Ethics Committee of the Arak University of Medical Sciences (Ethics Code, IR.ARAKMU.REC.1394284).

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Authors' contributions

Conceptualization, methodology, validation, and data analysis: Saeed Hajihashemi; Conducting research and

experiments, collecting data, and reviewing the sources of drafting, Razieh Rajabi and Atefeh Ghiasabadi Farahani.

Conflicts of interest

The authors declare no conflict of interest.

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