The Ameliorating Effects of Fennel Powder, Extract and Oil on Gentamicin Induced Nephrotoxicity in Rats

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Abstract: The current study was undertaken to evaluate efficacy of fennel powder, extract and oil on gentamicin induced nephrotoxicity in rats. 35 adult female sprague Dawley rats were classified into five groups. The first group was kept on standard diet all over the period of the experiment. The other groups administered gentamicin (100 mg/kg/day for 7 days i.p). These animals were assigned as control (+ve) group and treated groups which were fennel powder, extract and oil. The treatment period was 45 days. The obtained results showed that gentamicin induced nephrotoxicity was manifested by increase levels of kidney function indicator, serum nitric oxide (NO) and kidney malondialdyde (MDA) but showed a significant decrease in weight gain , food efficiency ratio(FER), and also antioxidants enzymes in serum and kidney and that appeared obviously in control(+ve) rat group. Gentamicin induced nephrotoxicity rat groups which treated with fennel powder, extract and oil could improve the levels of urea and uric acid in comparing to control (+ve). Also they showed improvement of antioxidant enzymes as increase of serum superoxide dismutase(SOD), catalase, and glutathione transferase (GST) and decrease of serum NO compared with control (+ve) group. Fennel oil group showed normal values of kidney antioxidant enzymes compared with normal group. The results of this study clearly indicate that fennel powder, extract and oil have a potent antioxidant and ameliorate in rats gentamicin induced nephrotoxicity in rats.
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1. Introduction

Nephrotoxicity is a major complication characterized by functional alterations including inhibition of protein synthesis, reduced glutathione depletion, lipid peroxidation and mitochondrial damage. Oxidative damage is thought to be one of the main mechanisms involved in nearly all chronic renal pathologies. Certain drugs may induce oxidative stress by forming drug-derived radicals that can not only deplete the antioxidant defenses but can also react directly with biomolecules **(Abd El-Ghany et al., 2012)**. Gentamicin has been used clinically due to its wide spectrum of activities against Gram-negative bacterial infections. In experimental research, Gentamicin used for study of acute kidney failure as it generates free oxygen radicals, leading to tissue injury such as nephrotoxicity and ototoxicity (**Laurent et al., 1990 and Conlon et al., 1999**).

Most research studies against gentamicin-induced nephrotoxicity are focused on the use of various antioxidants. Phytotherapy is considered as a complementary approach for preventing and treating simple disease **(Nidhal and Shatha 2012)**. Fennel (Foeniculum vulgare Miller) is an aromatic herb belonging to the parsley family. It is used as a spice and possesses a sweet taste that is similar to anise. It is an essential ingredient in the Mediterranean cuisine. It is native to the South European region. Fennel seed shape is oval and has a strong scent, while the fruit have a slightly sweet and slightly spicy. Essential oil of fennel is used as flavoring agents in food products such as beverages, bread, pickles, pastries, and cheese. It is also used as a constituent of cosmetic and pharmaceutical products. Sweet fennel oil is made up predominantly of anethole (50 to 80%), limonene, fenchone, and estragole. The seeds also contain fiber and complex carbohydrates **(Tanira et al., 1996 and Choi and Hwang 2004)**. Fennel seeds are generally eaten for the taste but also very healthy owing to the nutrition value attached to it. Fennel is also used for various health benefits that are derived from its anti-oxidants. These anti-oxidants are essential to curb unwanted free radical reactions in the body to prevent many diseases. Fennel seeds contain antioxidants as kaemoferol and quercetin that prevent degenerative reactions **(Alexandrovich et al., 2003)**.

Therefore the objective of this study was to investigate the ameliorative effect of fennel consumption either as powder, extract or oil against gentamicin induced nephrotoxicity in rats.

2. Materials and Methods

Materials:

Gentamicin drug and Kits for biochemical analyses were purchased from The Gamma Trade Company for Pharmaceutical and Chemicals, in Riyadh. The standared diet was prepared according to **Reeves et al., (1993**). Fennel (Foeniculum vulgare) seeds and oil were obtained and identified by agriculture research centre, Giza, Egypt. Thirty five male albino rats (Sprague Dawley strain), weighing 200±10g were provided from experimental animals center in Medicine collage of King Saud University in Riyadh.

Methods:

Dried fennel seeds were washed with tap water to remove possible potential dust and exposed to air-circulated oven at 40°C to complete dryness then grinded to fine powder and stored in the refrigerator at 4°C until use. 3 kg of fennel powder was mixed five times with 5 L methanol. The extract was filtered and the filtrate was evaporated to dryness with a rotatory vacuum evaporator at 50°C to give 150 g **(Abdelaaty et al., 2012)**.

After acclimatization period(2 weeks), rats were divided into five groups of seven rats each: group (1) fed on the standared diet and kept as normal control group; the remaining four groups administered gentamicin at dose 100 mg/kg/day for 7 days intraperitoneal to induce nephrptoxicity according to previous studies as **Abd El-Ghany et al .,(2012)** then classified into group (2) which kept as control(+ve) group; groups (3), (4) and (5) treated with fennel powder(10% of diet), fennel extract(300 mg/kg b wt of rats by stomach tube) and fennel oil (750mg/kg) . Daily food intake and weekly body weight gain were recorded. Feed efficiency ratio (FER) was determined by **Chapman et al., (1950)**.

At the end of the treatment periods (45 days), rats were anaesthetized using diethyl ether and sacrificed by cervical dislocation. Blood samples were collected from jugular vein and centrifuged at 3000rpm for 15 min to obtain serum. Animals were quickly dissected and the kidney samples were immediately removed, washed, minced and homogenized in ice-cold sodium, potassium phosphate buffer (0.01 M, pH 7.4) containing 1.15% KCl in homogenizer. The homogenates were centrifuged at 3000rpm for 15 min for further biochemical analysis.

The following biochemical parameters were determined in the serum creatinine **(Bonsens and Taussky 1984),** urea **(Patton and Crouch 1977)**, uric acid (**Fossati et al., 1980),**total protein **(Bradford, 1976)**, albumin **(Doumas et al., 1977)**, and globulin **(Henry 2001)** . Activity of superoxide dismutase (SOD), catalase, glutathione transferase (GST) enzymes and nitric oxide (NO) were determined using commercial kits according to the methods described by **Kakkor et al.,(1984), Sinha (1972)**, **Ellman (1958) and Kirima et al .,(2003)** , respectively. Whereas superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione tranferase (GST) and malodialdehyde (MDA) were estimated in the kidney tissues according to **Misra and Fridovich (1972), Hissin and Hiff (1976), Beutler et al., (1963) and Draper and Hadley (1990)**, respectively.

2.9. Statistical analysis

Data are expressed as mean ± SD. Statistical analysis was done by using analysis of variance (ANOVA) followed by student's t-test and P values of 5% and less were considered to be significant according to **Snedecor and Cochran, (1989)**.

3.Results

The initial body weight of experimental animals was 200±10 gm. The weight gain during experimental period was121.19±12.10g and the food intake was 21.99±2.7 g/w and FER was 0.122±0.001 in normal rat group. Gentamicin induced nephrotoxicity rat group (control +ve) showed a significant decrease in weight gain and FER at $P < 0.001$ &0.01, respectively compared with normal group. Gentamicin induced nephrotoxicity rat groups which treated with fennel powder ,extract and oil showed a non significant difference in weight gain ,food intake and FER compared with normal group but showed a significant increase in weight gain and FER compared with control(+ve) group as shown in table(1).

It is known that serum creatinine concentration is a more potent indicator than the urea in the first phases of kidney disease. Gentamicin induced nephrotoxicity was manifested by increase levels of creatinine, urea and uric acid and that appeared obviously at $p< 0.001$ in control(+ve) rat group. Consumption of fennel powder and extract showed a significant increase of creatinine at $P < 0.01$& 0.05 compared with normal but could lower creatinine level as compared with control (+ve). Consumption of fennel powder ,extract and oil could improve the levels of urea and uric acid in comparing to control(+ve) and appeared within normal levels as illustrated in table(2).

Control +ve group showed a significant decrease in globulin at $P < 0.01$ and a significant increase in albumin /globulin ratio at $P < 0.001$ compared with normal group. Fennel powder ,extract and oil rat group showed a non significant difference in total protein, globulin, albumin and albumin /globulin ratio compared with normal group as obtained in table(3).

The effect of gentamicin on serum antioxidant enzymes was appeared in table (4). Control (+ve) group showed a significant decrease in serum SOD, catalase, and GST at P<0.001 and a significant increase in serum NO at P<0.001 compared with normal group. Consumption of fennel powder ,extract, and oil showed improvement of antioxidant enzymes as increase of serum SOD, catalase, and GST and decrease of serum NO compared with control (+ve) group.

Table (5) illustrated that control (+ve) group showed a significant decrease in kidney SOD, GPX and GST at P<0.001 and a significant increase in kidney MDA at P<0.001 compared with normal group. Fennel powder rat group showed a significant decrease in kidney SOD and GST at P<0.05 while fennel extract group showed a significant decrease in kidney GST at P<0.05 but fennel oil group showed normal values of kidney antioxidant enzymes compared with normal group. Consumption of fennel powder ,extract, and oil showed a significant increase in kidney SOD , GPX and GST and a significant decrease in kidney MDA compared with control (+ve) group as shown in table (5).

Table (1): Effect of fennel consumption on feeding and growth performance in experimental rat groups

Groups / Variables	Normal	Gentamicin induced nephrotoxicity rat groups			
		Control(+ve)	Fennel powder	Fennel Extract	Fennel oils
Weight Gain (g)	121.19±12.10a	87.88±5.11c***	103.45±8.17ab	107.11±9.91ab	125.71±11.21a
Food intake (g/w)	21.99±2.71a	18.71±1.80ab	20.41±2.14a	21.19±2.05a	22.33±2.01a
FER	0.122±0.001a	0.104±0.003bc**	0.112±0.004ab	0.112±0.005ab	0.125±0.007a

Significant with control (-ve) group * P < 0.05 * * P < 0.01 *** P < 0.001
Mean values in each raw having different superscript (a,b,d,c…..) are significantly different at P < 0.05

Table (2): Effect of fennel consumption on creatinine, urea and uric acid in experimental rat groups

Groups / Variables	Normal	Gentamicin induced nephrotoxicity rat groups			
		Control(+ve)	Fennel powder	Fennel Extract	Fennel oils
Creatinine (mg/dl)	0.77±0.10c	1.88±0.25a***	0.93±0.01b**	0.89±0.03b*	0.79±0.11c
Urea (µ /mg)	40.11±4.51b	80.77±8.11a***	45.66±5.17b	39.40±4.27b	35.71±5.71bc
Uric acid (mg/dl)	4.19±1.21b	6.14±1.54a***	4.30±1.27b	4.11±1.40b	4.01±1.31b

Significant with control (-ve) group * P < 0.05 * * P < 0.01 *** P < 0.001
Mean values in each raw having different superscript (a,b,d,c…..) are significantly different at P < 0.05

Table (3): Effect of fennel consumption on total protein, albumin, globulin and albumin /globulin ratio in experimental rat groups

Groups / Variables	Normal	Gentamicin induced nephrotoxicity rat groups			
		Control(+ve)	Fennel powder	Fennel Extract	Fennel oils
Total protein (g/dl)	6.99±1.41a	5.45±1.14ab	6.13±1.17a	6.41±1.18a	7.03±1.51a
Albumin (g/dl)	3.40±0.57a	3.41±0.45a	3.02±0.55a	3.12±0.71a	3.33±0.68a
Globulin (g/dl)	3.59±0.44a	2.04±0.21b**	3.11±0.41a	3.29±0.39a	3.71±0.33a
Albumin / Globulin	0.94±0.030b	1.67±0.55a***	0.97±0.44b	0.94±0.43b	0.89±0.40b

Significant with control (-ve) group * P < 0.05 * * P < 0.01 *** P < 0.001
Mean values in each raw having different superscript (a,b,d,c…..) are significantly different at P < 0.05

Table (4): Effect of fennel consumption on serum SOD, catalase, GST and NO of the experimental groups

Groups / Variables	Normal	Gentamicin induced nephrotoxicity rat groups			
		Control(+ve)	Fennel powder	Fennel Extract	Fennel oils
SOD (mmol/l)	35.71±4.71a	18.41±1.71c***	31.21±3.20ab	34.32±4.27ab	37.16±4.11a
Catalase (µ /l)	288.70±28.11a	104.31±10.12c***	211.17±20.11b*	209.41±22.11b*	271.40±27.11a
GST (mmol/l)	121.11±12.13a	66.77±6.61c***	105.54±10.41ab	108.11±11.21ab	119.17±13.15a
NO (mmol/l)	8.11±1.21b	15.21±2.41a***	6.99±0.88bc	6.88±0.97bc	7.91±1.10b

Significant with control group * P<0.05 ** P<0.01 *** P<0.001.
[abcd] Mean values in each raw having similar letters were not significantly different

Table (5): Effect of fennel consumption on kidney SOD, GPX, GST and MDA in experimental rat groups

Groups / Variables	Normal	Gentamicin induced nephrotoxicity rat groups			
		Control(+ve)	Fennel powder	Fennel Extract	Fennel oils
SOD (µ /mg)	75.21±6.36a	31.14±2.17c***	61.11±6.36b*	65.30±7.14ab	77.19±7.41a
GPX (µ /mg)	60.34±7.11a	22.33±3.21b***	56.14±6.41a	55.50±5.57a	56.11±6.14a
GST (µ /mg)	3.11±0.22a	1.66±0.05c***	2.51±0.01b*	2.44±0.31b*	2.99±0.14ab
MDA (µmol /g)	6.88±1.27b	14.39±2.11a***	7.14±1.03b	7.08±1.27b	7.41±1.31b

Significant with control (-ve) group * $P < 0.05$ * * $P < 0.01$ *** $P < 0.001$

Mean values in each raw having different superscript (a,b,d,c…..) are significantly different at $P < 0.05$

4. Discussion

The improvement of nutritional results of rats was related to composition of fennel where it is composed of 9.50% water, 50% carbohydrates, 17.7% protein, 14.6% fiber, ash and fat, minerals. Fiber helps balance the metabolism, aids in digestion and cleanses the colon and easing constipation condition. The content of vitamins on fennel seeds is vitamin A, B and C (Tanira **et al., 1996)**. Fennel seeds are concentrated source of minerals like copper, iron, calcium, potassium, manganese, selenium, zinc, and magnesium. Copper is required in the production of red blood cells. Iron is required for red blood cell formation. Zinc is a co-factor in many enzymes that regulate growth and development, sperm generation, digestion and nucleic acid synthesis. Potassium is an important component of cell and body fluids that helps controlling heart rate and blood pressure. Manganese is used by the body as a co-factor for the powerful anti-oxidant enzyme, superoxide dismutase **(Singh et al., 2006)**.

The results of this study showed that gentamicine administration to rats produced a typical pattern of nephrotoxicity which was manifested by marked increase in serum creatinine, urea and uric acid levels. On the other hand, many substances have been identified in fennel including estragole, hydroxycinnamic acid derivatives, flavonoid glycosides, flavonoid aglycons, quercetin, kaempferol, chlorogenic acid, eriocitrin, rutin, miquelianin, rosmarinic acid, and caffeoylquinic acid. Most of these substances in fennel are antioxidants **(Conforti et al., 2006 and Miguel et al., 2010)**. Fennel volatile oil is a mixture of different chemicals and the main ingredients are anethole, fenchone and estragole.It was reported that fennel oil possessed antiinflamatory, antioxidant and pro-oxidant activities **(Cosge et al., 2008)**.

Gentamicin increases generation of reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, hydrogen peroxide, and reactive nitrogen species in the kidney **(Balakumar et al., 2008)**. Gentamicin induced kidney damage is linked with lipid peroxidation, and protein oxidation in the renal cortex with reducing activity of renal antioxidant enzymes **(Stojiljkovic et al., 2008 and Lopez-Novoa et al., 2011)**.

Antioxidant defense mechanisms are important for the protection of cells and tissues against oxidative damage. The major endogenous antioxidant enzyme-systems include superoxide dismutase, catalase, selenium-dependent glutathione peroxidase, glutathione peroxidase, and glutathione reductase. The major non-enzymatic endogenous antioxidants include glutathione and vitamin E **(Abd El-Ghany et al., 2012)**.

Fennel seeds and extract reduced oxidative stress and improve antioxidant defense by reducing MDA level and increasing plasma SOD as well as CAT activities. Aqueous extracts of fennel provide to have antioxidant activity higher than some well known antioxidant such as ascorbic acid **(Singh et al., 2006, and Celik and Isik 2008)**. This effect may be due to fennel content of phenolic and flavonoid compounds by scavenging or quenching free radicals, by chelating metal ions, or by inhibiting enzymatic systems responsible for the generation of free radical and enhance the activity of antioxidant system. D-limonene compound presented in fennel increased the concentration of liver glutathione which is used by several enzymes that participate in the formation of the correct disulfide bonds of many proteins **(Demarino et al., 2007 and Singh and Kale, 2008)**.

From these results, it is concluded that fennel has potent antioxidant activity and can lower gentamicine induced nephrotoxicity in rats.

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