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RENOPROTECTIVE EFFICACY OF DIFFERENT EXTRACTS FROM PEPPERMINT (*Mentha piperita*) AS A NOVEL APPLICATION FOR THE TREATMENT OF NEPHROTOXICITY INDUCED BY GENTAMICIN

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ABSTRACT

Potential therapeutic approaches to protect (or) reverse gentamicin (GM) damage would be having very important clinical consequences of increasing the safety of the drug. Many literature reveal that the *Mentha piperita* found to be used in the traditional system of medicine. However nephroprotective activity of *M.piperita* has not been scientifically investigated. So, the present study was design to evaluate the protective effects of *M.piperita* on nephrotoxicity in rat model. Freshly prepared ethanolic and aqueous extracts of *M.piperita* (EMPet and AMPet) were orally administered to rats. The altered renal markers (Urea, uric acid, creatinine and BUN) after GM administered were normalized in extracts treated animals. The protective effects were confirmed by histopathology of renal tissues. In conclusion, the EMPet may emerge as a more putative nephroprotective agent than AMPet against nephrotoxicity. Further studies need to be undertaken in order to confirm these findings and its extrapolation in humans.

Keywords: Peppermint, *Mentha piperita*, gentamicin, nephrotoxicity and renal markers

INTRODUCTION

Mentha piperita is a peppermint, an aromatic and carminative herb cultivated throughout all regions of the world [1], have traditionally been used in folk remedy or in complementary and alternative medical therapy. Many studies reveals that peppermint has been ascribed a variety of biological properties, such as antiallergenic [2], antibacterial [3], anti-inflammatory [2], antimycotic [4], antitumor [5], antiviral [6], gastrointestinal protective [7], hepatoprotective [8] and chemopreventive [9]. It contains active ingredients, such as menthol, menthone, and menthyl acetate flavonoids, polymerized polyphenols, carotenes, tocopherols, saponin, and choline [1, 10-13] together with several other minor constituents, including pulegone, menthofuran and limonene [14].

Toxic chemical-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Acute kidney injury (AKI) is generally defined as a decline in kidney function resulting in accumulation of waste products in the blood stream. The main causes of AKI are nephrotoxins, aminoglycosides, oxytetracycline, and nonsteroidal anti-inflammatory drugs (NSAIDs) [15]. Gentamicin (GM) is probably one of the most commonly used aminoglycoside antibiotics for the treatment of serious and life-threatening infections caused by gram-negative aerobes [16].

GM nephrotoxicity accounts for 10–15% of all cases of acute renal failure and about 30% of patients show signs of nephrotoxicity [17]. GM-induced nephrotoxicity is characterized by morphological alterations including destruction, necrosis and apoptosis of kidney cells which eventually lead to AKI and dysfunction [18]. The renal toxicity is due to its selective accumulation in the renal proximal convoluted tubules and its long term stay subsequently leading to loss of brush border integrity [19, 20]. The nephrotoxicity exert toxic effects by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy [21].

Therefore, the clinical usefulness of GM is limited due to the development of nephrotoxicity [22]. Thus, a therapeutic approach to protect or reverse renal damage would have very important clinical consequences. To date, there is no specific agent used to protect against GM-induced

nephrotoxicity. In this regard, various medications have been used concomitantly with GM to prevent AKI in laboratory animal models [23-27]. Several natural agents have been used to ameliorate some toxic and carcinogenic and drugs toxicity. The survey of literature reveals that the *Mentha piperita* Linn. are found to be used in the traditional system of medicine has been ascribed a variety of biological properties. However nephroprotective activity of *M.piperita* has not been scientifically investigated. So, the present study was design to evaluate renoprotective efficacy of different extracts from peppermint (*Mentha piperita*) as a novel application for the treatment of nephrotoxicity induced by gentamicin.

MATERIALS AND METHODS

Preparation of plant extracts

Approximately about 500 g of air-dried whole leaves (*M.piperita*) were pulverized into powdered form by using heavy duty commercial blender (Figure 1).

Ethanolic M.piperita extracts [EMPet]

The powder samples (50 g) were extracted with 95% ethanol (1:3 w/v) by using Soxhlet extractor at 37°C for two days. The total yield was 4.67 g (9.34 % w/w) of dark greenish extract. Because of very low aqueous solubility, the EMPet from *M.piperita* was reconstituted to a final concentration of 5% (w/v) using aqueous solution of gum acacia (5%) for further treatments [28].

Aqueous M.piperita extracts [AMPet]

The aqueous extracts of *M.piperita* leaves were prepared according to the method of Hossain *et al* [29]. *M.piperita* leaves yielded 13% light greenish semisolid which was stored at 0–4°C until used.

Chemicals

The antibiotics, GENTAM® were purchased from SPIMACO, Al–Qassim, Kingdom of Saudi Arabia and other chemicals and solvents used were of analar grade.

Animals

Healthy, male albino Wister rats (*Rattus norvegicus albinus*) each weighing 150-200 g were used for this study. The rats were housed in polypropylene cages and maintained under standard conditions (12 h light and dark cycles, at 25±3°C and 35-60 % humidity). Standard pelletized feed (Grain Silos & Flour Mills Organization, Riyadh, KSA) and tap water were provided ad libitum. The experimental design was approved by the Deanship of Research, University of Hail (Proposal No. CM4 2013, date 16-12-2014).

Figure 1: Photographs of *M.piperita* Linn. and its leaves powder

Induction of kidney damage

Kidney damage was induced in rats by administrating Gentamicin (GM) intraperitonially at the dose of 100mg/kg body weight for 6 consecutive days [30].

Experimental Design

The animals were grouped as follows and each group contains 6 rats. **Group I:** Normal animals received standard feed and water *ad libitum*. No other treatment. **Group II:** GM-induced group received gentamicin (100mg/kg body weight, ip) for 6 consecutive days along with standard feed and water *ad libitum*. **Group III:** Treatment group received GM as group II for 6 days followed by the treatment with EMPet orally (300 mg / kg b.wt per day for 10 days). **Group IV:** Treatment group received GM as group II for 6 days followed by the treatment with AMPet orally (400 mg / kg b.wt per day for 10 days). **Group V:** Drug alone treated group received EMPet orally (300 mg / kg b.wt per day for 10 days). **Group VI:** Drug alone treated group received AMPet orally (400 mg / kg b.wt per day for 10 days). The dosages of drugs were chosen according to our acute toxicity study [28].

The body weight of the animals was recorded throughout the experimental period starting from Day 0. After the experimental regimen,

the rats were fasted overnight and were sacrificed by cervical dislocation under light ether anesthesia, and the blood was collected on decapitation.

Histopathology

For histopathological studies, kidney tissues were fixed in 10% formalin and were routinely processed and paraffin embedded, 5µm sections were cut in a rotary microtome and were stained with hematoxylin and eosin.

Biochemical estimations

Biochemical estimations were carried out in blood and kidney tissue samples of control and experimental animals in each group.

Estimation of kidney markers

Urea concentration in blood was estimated by NED Dye method (colorimetric Fix Time test) [31]. Concentration of serum creatinine was measured by alkaline picrate method [32]. Blood urea nitrogen (BUN) was measured with the commercial kit developed by the Parsazmoon Company (Tehran, Iran) based on the method described by Talke and Schubert [33]. Serum uric acid was measured by using commercially available reagents [34]. Total protein level was estimated by colorimetric assay with modified Biuret end point method using protein estimation kit [35]. Serum albumin level was estimated by BCG method using albumin estimation kit [35].

Statistical analysis

The values are expressed as mean ± SD. The statistical comparisons were performed by one way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT), using SPSS version 16.0 for windows (SPSS Inc.Chicago; http://www.spss.com). The values are considered statistically significant if the p value was less than 0.05.

RESULTS

Effects of *Mentha piperita* on body weight and kidney weight

Figure 2 show the effect of *M.piperita* on the physical parameters. In the present study, the body weight (Figure 2A) of rats administered with GM were reduced significantly (230.09±13.78 vs 225.86±9.02) (p<0.05) in comparison to the normal control group. Although there was increased in body weight of group III and group IV, the increased in body weight was not significant (p<0.05) compared to normal group. Rats treated with EMPet (Group V) and AMPet (Group VI) alone showed no significant difference in body weight status compared to control animals.

The levels of kidney weights of rats in control and all treated groups are showed in figure 2B. GM treatment induced a significant increase in the relative weight of

kidneys with respect to normal controls (0.93±0.05 vs 0.98±0.05) ($p < 0.05$). However, oral administration of EMPet (300 mg/kg b.wt) (Group III) and AMPet (400 mg/kg b.wt) (Group IV), reverted the weight of kidney to near normal range. Animals treated with EMPet (Group V) and AMPet (Group VI) alone showed no significant difference in kidney weight as compared to control animals.

Efficacy of *Mentha piperita* on renal function

Figure 3 shows the status of kidney markers in serum of the control and experimental groups. The concentration of serum creatinine, urea, uric acid and blood urea nitrogen were increased significantly in Group II (GM alone) as compared to control animals. Oral administration of EMPet (300 mg/kg b.wt) and AMPet (400 mg/kg b.wt) significantly decreased the levels of kidney markers. EMPet and AMPet (Groups VII and VIII) alone treated animals showed no significant difference in kidney markers as compared to control animals.

The levels of total protein were significantly increased in serum whereas decreased in albumin as compared to control animals. Oral administration of EMPet and AMPet at a dose of 300 mg / kg b.wt and 400 mg / kg b.wt to GM administered animals respectively revert back the status of total protein and albumin to near normal concentration. Rats treated with EMPet and AMPet alone showed no significant differences in serum total protein and albumin levels as compared to control animals.

Effects of *Mentha piperita* on renal histopathology

Table 1 shows the kidney histopathology of normal and experimental groups. In histologic examination, control samples of kidneys showed normal kidney morphology (Figure 4, group I). Gentamicin administered animals caused significant changes in tubular epithelium like vacuolization; desquamation, atrophy and necrosis; interstitial edema and inflammation in general architecture (Figure 4, group II). But, administration of EMPet and AMPet provided a well improvement in the renal morphology (Figure 4, group III & IV). Tubuler and glomerular structures were seen close to their normal structures in the EMPet treated group. No any kidney morphological changes were observed in EMPet and AMPet alone treated animals (Figure 4, group V & VI).

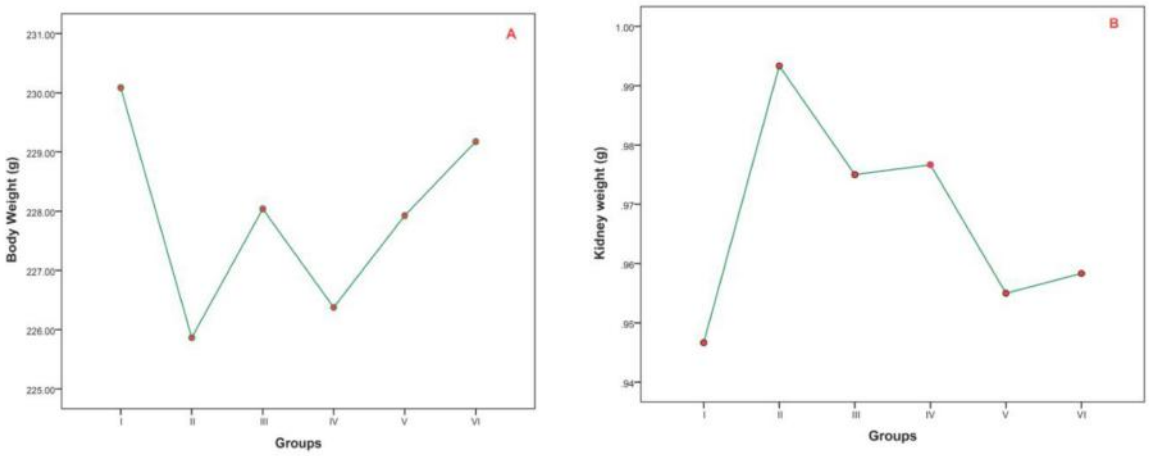

Figure 2 A & B: Effects of *M.piperita* on body weight and kidney weight in normal and experimental rats

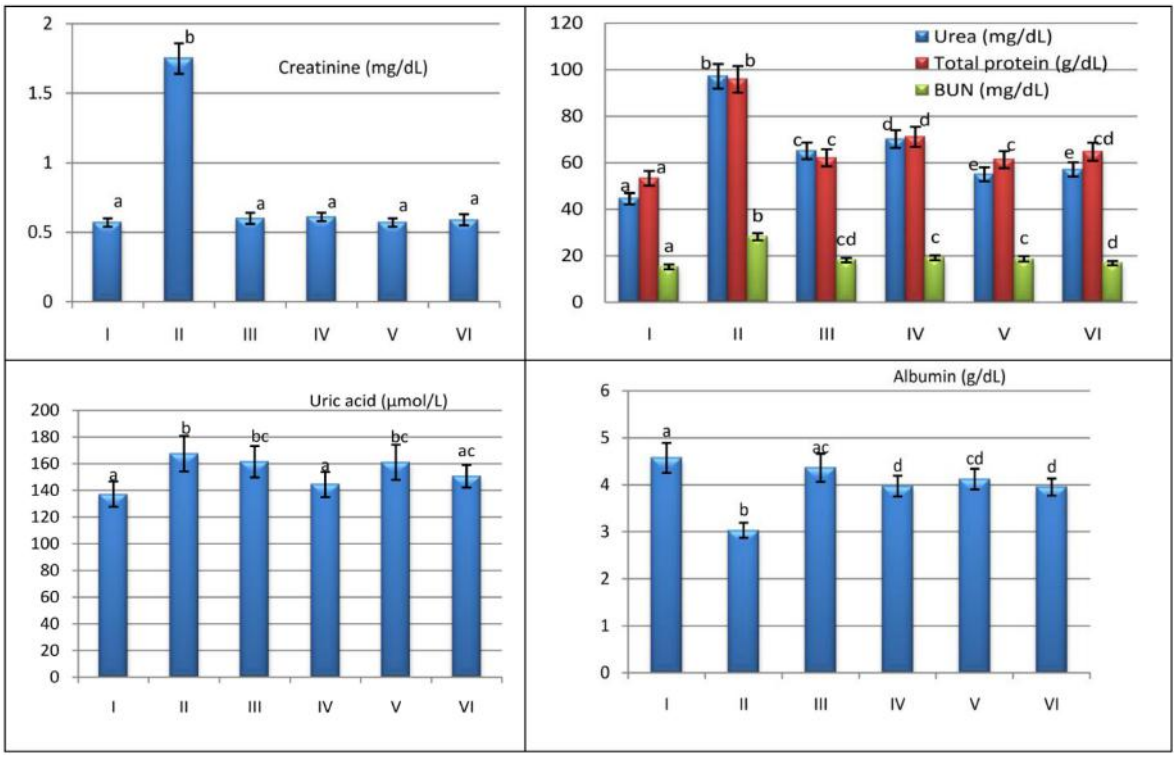

Figure 3: Effects of M.piperita on kidney markers in gentamicin induced nephrotoxicity
Values are expressed as mean ± SD for 6 animals in each group.
Values not sharing a common superscript letter differ significantly at p<0.05 (DMRT).
EMPet-Ethanolic M.piperita extracts; AMPet-Aqueous M.piperita extracts

Table 1: Histopathological changes in kidney tissues of *M.piperita* leaf extracts treated and gentamicin administered animals

Histopathological changes	Group I Normal	Group II GM	Group III GM + EMPet	Group IV GM + AMPet	Group V EMPet	Group VI AMPet
Tubular necrosis	-	+	-	+	-	-
Tubular dilatation	-	++	+	-	-	-
Tubular epithelial desquamation	-	+	-	+	-	-
Tubular atrophy	-	+	+	+	-	-
Interstitial inflammation	-	+++	+	-	-	-
Interstitial edema	-	+	+	+	-	-
Tubular casts	-	+	-	-	-	-

EMPet-Ethanolic *M.piperita* extracts; AMPet-Aqueous *M.piperita* extracts
Quantification scores (-): no meaningful histopathologic change (+): mild degree; (++): moderate degree; (+++): severe degree

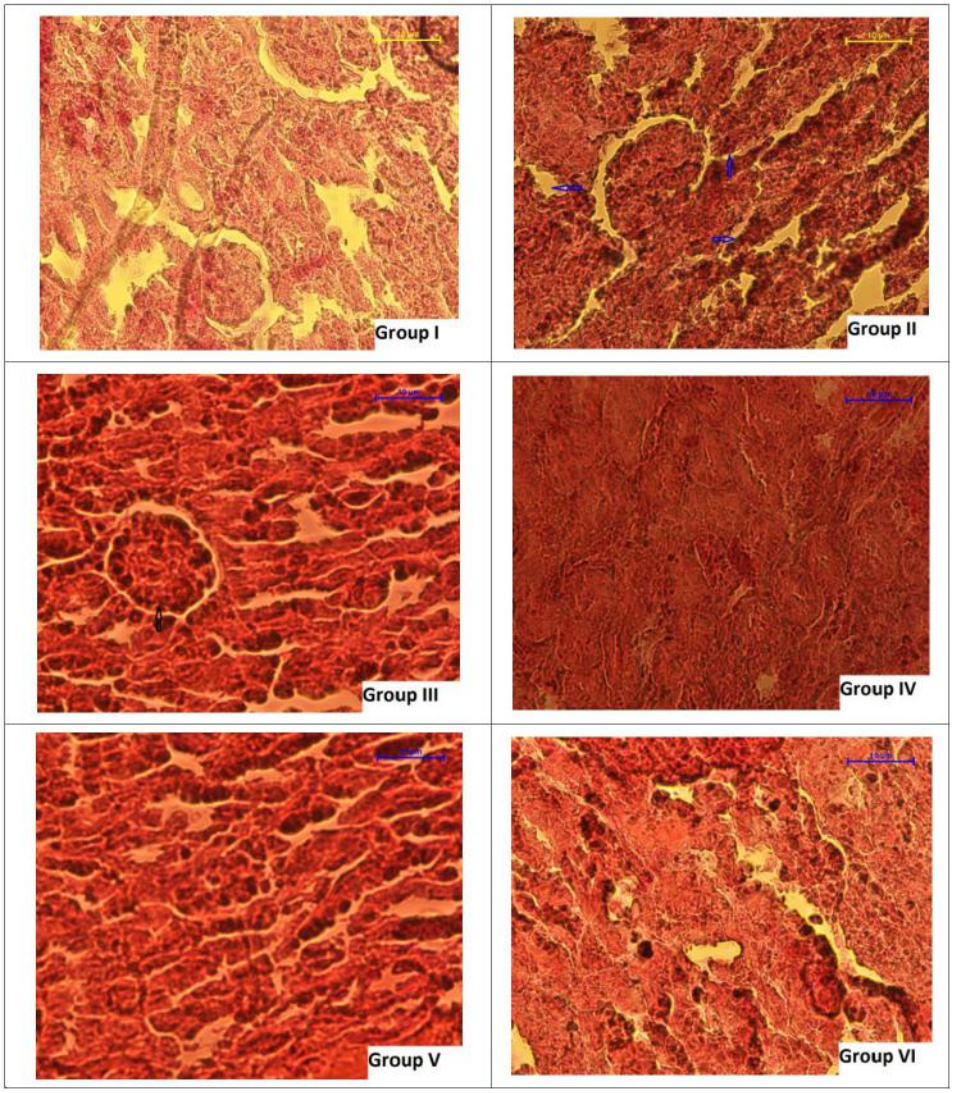

Figure 4: Photomicrographs of renal sections in all experimental groups. Group I - Control rat showing normal tubular architecture, tubules, and glomerules that appear normal. Group II - The epithelial cell vacuolization, desquamation, interstitial inflammation, luminal casts and dilatation of renal tubules are clearly observed in the kidney of gentamicin administered rats. Group III&IV, V&VI - Almost all morphology is preserved in EMPet and AMPet treated rats respectively (Mild degeneration and tubular dilatation and atrophy are observed in some tubules) [H&E stain X 200]

DISCUSSION

About 20% of hospital admissions due to acute kidney injury (AKI) are related to drug-induced nephrotoxicity. Nephrotoxic drugs can lead to alteration in intra glomerular hemodynamics, tubular epithelial cell damage, tubulointerstitial disease, glomerular disease, renal vasculitis and thrombosis, and obstructive nephropathy [36]. The main causes of AKI are nephrotoxins, aminoglycosides, oxytetracycline, and nonsteroidal anti-inflammatory drugs (NSAIDs) [15]. Gentamicin (GM) is probably one of the most commonly used aminoglycoside antibiotics for the treatment of serious and life-threatening infections caused by Gram-negative aerobes [16]. Therefore, the clinical usefulness of this drug is limited due to the development of nephrotoxicity [22]. Thus, a therapeutic approach to protect or reverse renal damage would have very important clinical consequences. Several natural agents have been used to ameliorate some toxic and carcinogenic and drugs toxicity.

The blood urea and creatinine are often regarded as reliable markers for renal function status [37]. The gentamicin induced neprotoxicity were confirmed by an increase in serum creatinine, uric acid, urea and blood urea nitrogen levels and severe proximal renal tubular necrosis, followed by deterioration and renal failure [22, 38] in group II animals (Figure 3), are in agreement with a previous study done by Begum *et al* [39]. High values of blood urea and serum creatinine indicate renal damage [40, 41] and this may be correlated with the significant and progressive body weight loss and kidney weight gain in the GM administered group II (figure 2). These parameters were almost significantly normalized by oral administered *M.piperita* leaf extracts (groups III and IV). This result is consistent with many previous studies done using other traditional plants [42], and is strongly attributed to the scavenging free radicals and reduced lipid peroxidation mechanisms.

The GM administered animals were caused severe histological damages, mainly tubular epithelial desquamation and interstitial edema in kidney tissues of group II rats. Finally, it is clear that GM administration can cause an imbalance in kidney markers and histological damage in rat kidney tissue. Our results clearly showed that EMPet and AMPet treatment successfully protect kidney from damage caused by gentamicin and also its indicates that EMPet have more protective role than AMPet.

CONCLUSIONS

This study revealed that the concurrent administration *M. piperita* successfully prevented renal damage associated with gentamicin, explored by various biochemical and histological examinations. Alteration in mean body weight, blood urea nitrogen, creatinine and uric acid associated with gentamicin were reduced by treating animals simultaneously with extract of *M. piperita*. In conclusion, the results of the present study indicate that *Mentha piperita* may emerge as a putative nephroprotective, agent against nephrotoxicity. Further studies need to be undertaken in order to confirm these findings and its extrapolation in humans.

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