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A study of the effect of prostodin and hydroalcoholic extract of Malva neglecta on kidney histopathology and renal factors in female rats

1Amineh Beyrami-Miavagi, 1Farah Farokhi, 2Majid Asadi-Samani

1Biology Dept., Urmia University, Urmia, I.R. Iran.
2Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, I.R. Iran.

ABSTRACT

Background: Prostaglandins naturally are saturated lipid acids and comprise three types, PGE1, PGE2, and PGF2a, each with a different function. Prostaglandins are formed by a variety of substances in plants, animals, and even from the human body. Prostaglandins are important in many physiological processes, such as the regulation of blood pressure and the control of inflammation. However, prostaglandins can also cause adverse effects, such as increased blood pressure and pain. Therefore, the search for a suitable alternative to prostaglandins is crucial.

Methods: In this study, the effects of prostaglandins on kidney function were compared with the effects of the hydroalcoholic extract of Malva neglecta, a plant that has been used in traditional medicine for its diuretic and sedative properties. The study involved 24 rats, which were divided into four groups: the control group received water and normal food, while the other groups received prostaglandins or the hydroalcoholic extract of Malva neglecta.

Results: The results showed that prostaglandins caused severe damage to the kidneys, including glomerular hypertrophy, decreased renal blood flow, and increased creatinine and urea levels. In contrast, the hydroalcoholic extract of Malva neglecta was found to have a protective effect on the kidneys, with no significant changes in renal function.

Conclusions: The results of this study suggest that the hydroalcoholic extract of Malva neglecta can be used as a suitable alternative to prostaglandins for treatment of kidney disease.

INTRODUCTION

Prostaglandins naturally are saturated lipid acids and comprise three types, PGE1, PGE2, and PGF2a, each with a different function. Prostaglandins are formed by a variety of substances in plants, animals, and even from the human body. Prostaglandins are important in many physiological processes, such as the regulation of blood pressure and the control of inflammation. However, prostaglandins can also cause adverse effects, such as increased blood pressure and pain. Therefore, the search for a suitable alternative to prostaglandins is crucial.

Nowadays, use of herbal medicines, instead of chemical ones, has been taken into consideration due to stupendous costs of chemical drugs and their adverse side effects on the body. With the advances in science and technology, various experiments have been conducted on plants in order to identify curative effects of the plants and the specific effect of each plant on a particular tissue and/or organ. Medicinal plants possibly cause fewer side effects thanks to containing natural substances, leading to health and decreasing the diseases, which is possibly due to various herbal chemical compounds with the antioxidant properties [3,4].

Malva neglecta is from the family Malvaceae. This family occurs in most regions worldwide, except the poles. M. neglecta contains malvin, mucilage, tannin, and glucose compounds as well as flavonoids and anthocyanins. Its leaves have a higher proportion of phenolic compounds. The therapeutic properties of this plant include relief of gastrointestinal and respiratory disorders, hemorrhoids, swollen eyes, some tumors and disorders, and renal diseases. M. neglecta is diuretic and sedative with anti-inflammatory properties [5-7].

Kidney contributes basically to filtration, metabolism, and excretion of metabolic products. Nephron is the main unit of kidney and blood infiltrator. Any change in different parts of nephron could be due to the damage to kidney. The substances excreted by the kidneys include urea, creatinine, and external ones like medications. Urea is produced from ammonia in the body. Its amount depends on the appropriate function of liver in its
synthesis and that of kidneys in its excretion. Creatinine is one of the products produced from phosphate creatinine decomposition in the muscles at a fixed rate [8]. The serum level of urea and creatinine is considered as one of the indices for measuring kidney function. The studies indicate that prostodin results in free radicals in and oxidative damages to the body tissues [1].

Regarding the contraceptive property of M. neglecta as well as its antioxidant activity, this plant was used in the present work. In this study, the effect of prostodin and hydroalcoholic M. neglecta extract was studied and compared on renal tissue and serum level of urea and creatinine in rats.

**Methods:**

**The animals and experiment conditions:**

In this experimental study, 24 female rats weighing 150 to 150gr were used. The animals were obtained from the growth and maintenance center of animals, the Faculty of Sciences, University of Urmia. The diet was standard and water was freely placed at their disposal. The room conditions were 12h light/12h darkness cycle, 20-25°C temperature, and relative humidity 25-30%. To do this research, we assigned the rats into four groups of six each.

**Preparation of the hydroalcoholic extract:**

To prepare alcoholic extract of the plant, we supplied the plant’s leaves and had Herbarium of Biology Department, Faculty of Sciences, University of Urmia approve them (Herbarium No:4904). Then, we dried the leaves in a dark room and pulverized them using an electronic mill. 100 gr of the prepared powder was mixed with ethanol at 1:8 proportion and placed on the shaker at laboratory temperature for 48 hours [9, 10]. Then, the solution was infiltrated using filter paper and the obtained fluid was concentrated using rotary and incubator for solvent evaporation. Finally, a black, highly consistent extract with was obtained, and then different required concentrations were prepared at mg/kg body weight dose using normal saline.

**Test step:**

The mice were randomly assigned into 4 groups of 6 each. One group was determined as control and received normal food and water. Groups 2 and 3 received M. neglecta extract at respectively 200 and 300 mg/kg/day as oral (gavage) [11]. Group 4 received prostodin at 2 mg/kg/day as intraperitoneal injection [12]. The treatment was on a daily basis, continued for 18 days, and was done at a predetermined hour for all groups.

Blood taking and biochemical factors assessment:

All rats were anesthetized using chloroform after treatment completion and blood was taken from the hearts. Blood samples were centrifuged (3000 rounds per 15 minutes) in heparinized tubes and serum samples were isolated. Serum levels of urea and creatinine were measured per instructions of specific kits (Zist Chemi, Iran) using spectrophotometry method.

**Histopatologic study:**

Tissue samples were isolated from the kidneys and placed in a fixed formalin 10% buffer. After fixation, the tissues were dehydrated using alcohol, made transparent in xylol, and after preparation of paraffin blocks, the fragments with 6µ in diameter were prepared and studied using an optical microscope after staining with hematoxylin-eosin.

**Data analysis:**

Data were analyzed by SPSS13 using one-way ANOVA and Tukey’s test. P<0.05 was considered as the level of significance.

**Results:**

**Biochemical findings:**

The results obtained from biochemical experiments of blood serum factors indicated that creatinine level in the groups treated with M. neglecta extract decreased significantly (P<0.05), in a way that the decrease was more remarkable in the group receiving the extract at 500 mg/kg/day than the extract at 200 mg/kg/day. In the prostodin group, a significant increase (P<0.05) was observed in serum level of creatinine compared to the control (Figure 1a). Urea level in the M. neglecta group at 500 mg/kg/day dose had a significant increase (P<0.05), but in the M. neglecta group at 200 mg/kg/day and prostodin group, no significant increase was noted in blood serum level of urea (Figure 1b).
Histopathologic findings:

According to the conducted microscopic investigations of the profile obtained from kidney tissue, the structure and morphology of glomeruli and renal tubules were normal in the control group (Figure 1). In the prostodin group, glomerular hypertrophy and vascular dilation were noted and urinary space declined, in a way that in some points in glomeruli network, Bowman capsule was seen due to increased size in vicinity of external wall (Figure 2). In addition, dilation of blood vessels and accumulation of lymphoid cells around glomeruli network was observed. The presence of lymphoid cells in this region is the reason for inflammation in the interstitial tissue (Figure 3). But, in the groups receiving M. neglecta, the structure of glomeruli was natural and a small tubular damage was observed in some of the tubes (Figures 4).

Fig. 1: The blood serum level of creatinine (A) and urea (B) in the groups under treatment

Fig. 2: Profile of kidney tissue in the control group; G (normal glomeruli); Arrow 1 (proximal tube); arrow 2 (distal tube); hematoxylin and eosin staining at 40X magnification.
Fig. 3: Profiles of kidney tissue in the prostodin-treated group; A: Arrow 1 (proximal tube), arrow 2 (distal tube), G (dilated glomeruli); B: Arrow 3 (lymphoid cells accumulation and inflammation development); * (Blood vessels dilation); hematoxylin and eosin staining at 40X magnification.

Fig. 4: Profiles of kidney tissue in the M. neglecta-treated group; A: M. neglecta group at 200 mg/kg/day dose; B: M. neglecta group at dose 500 mg/kg/day; G (normal glomeruli), arrow tips (1-4): samples of tubular analysis; hematoxylin and eosin staining at 40X magnification.

Discussion:

Prostodin, as an artificial compound from F2a prostaglandins causes adverse complications including destruction of body tissues. According to the conducted studies, prostaglandin causes development of free radicals in and oxidative damages to the body tissues [8]. By the study conducted by Sharma et al. (2010) PGF2a in the individuals with endometriosis increased significantly and led to oxidative stress [14]. The latest works indicate that oxidative stress results in kidney damage. Kidneys are one of the most important organs damaged throughout animal experiments using chemical compounds [13].

The serum level of urea and creatinine is considered as one of the important indices of kidney function measurement. Mora et al reported that creatinine serum level signaled the risk of chronic renal failures [15]. The findings of the present study indicated that prostodin caused increased serum level of creatinine. The increase in blood creatinine is caused by the damage to and disorder in nephrons’ function and hence disorder in the process of kidney treatment.

According to the experiments, the increased prostaglandins caused damages to the kidney tissue [1, 16]. Some of researchers reported that excessive intake of proteins increased prostaglandins in the body and hence the kidneys size and glomerular hypertrophy [17, 18], which is consistent with the present study.

Dilation of glomeruli and increase in their size could cause vasodilatation and hence decrease in blood pressure in the vessels. Reported that prostaglandins caused decrease in blood pressure [1]. This study compared
the effects of M. neglecta with those of prostodin on kidneys because of the contribution of M. neglecta and prostodin to abortion.

M. neglecta is rich in antioxidant substances including flavonoids [6, 19]. Antioxidants, directly and/or indirectly, protect the cells against the damages to free radicals [20]. The important biological activities of plant flavonoids, particularly anti allergic, anti-inflammatory, and anti cancer, have been already demonstrated [21, 22]. According to the investigations on the flavonoids, these compounds cause recovery and protection of the damaged cells through increasing capacity of antioxidant enzymes such as glutathione, glutathione reductase, glutathione peroxidase, and catalase [23].

The works indicate that M. neglecta contribute importantly to treatment of kidney stone and relief of the pain due to it thanks to being diuretic. In addition to being diuretic, this plant is astringent and laxative [5, 6, 24]. In this study, a significant decrease was observed in urea and creatinine levels in the groups treated with M. neglecta, indicating lack of serious damages to kidneys. Histopathologically, M. neglecta caused tubular damage in some regions, but no damage and/or change was observed in the structure of glomeruli and Bowman capsule as the most important parts of the kidneys. In addition, no inflammation and/or accumulation of lymphoid cells was observed in the kidneys in the groups treated with M. neglecta, in contrast to the prostodin group, which could be explained by anti-inflammatory property of M. neglecta. Marouane et al found that treatment with vanadium caused damage to the kidneys, in a way that vanadium led to glomerular hypertrophy, decreased urinary space in kidney nephrons’ Bowman capsule, and increased serum creatinine through inducing lipid peroxidation and increasing serum creatinine. But, the mice treatment with M. sylvestris specious decreased free radicals and tissue damages developed by vanadium as well as serum creatinine and kidneys protection against oxidative damages due to the presence of antioxidant compounds like flavonoids in this plant [25].

Conclusions:
Biochemical and histopathologic investigations of this study indicated that prostodin caused increased blood serum creatinine and urea and Bowman capsule diameter, decreased urinary space, as well as glomerular dilution (glomerular hypertrophy), resulting in disorder in renal function, lack of proper blood treatment, and finally further increase in serum creatinine. However, M. neglecta caused decline in serum creatinine and no damage to the glomeruli as the most important parts of nephrons and protected the kidneys against serious damages. Therefore, it could be concluded that M. neglecta might be a suitable alternative to chemical drugs in abortion therapy thanks to its contraceptive property and fewer side effects (lack of obvious complications).

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