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Effect of *Taraxacum officinale* L. ethanol extract against kidney injuries induced by paracetamol in rats

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Abstract

Background/Aim: The biochemical effects of dandelion (D) ethanol extract on blood and renal tissue in rats induced by paracetamol (PRC) were examined in this study.

Methods: In this study was utilized 36 Sprague Dawley male rats, aged 5 months. Rats were divided 6 groups of 6 rats each, randomly. Control group (C), D200 group, D250 group, PRC group, PRC+D200 group, PRC+D250 group, was given orally per os (p.o) in a single dosage (2 g/kg/b.w.) and dandelion extract (200-250 mg/kg) was given intraperitoneally (i.p) for 8 days.

Results PRC raised plasma levels of urea, uric acid, and creatinine, as well as malondialdehyde, nitrate, and nitrite in kidney tissue. Furthermore, antioxidant levels/activities in renal tissue were reduced. Dandelion reduced plasma levels of urea, uric acid, and creatinine, as well as lipid peroxidation, nitrat, and nitrit in kidney tissue, while simultaneously increasing antioxidant activities.

Conclusion: In this study was investigated that dandelion ethanol extract can be used excellent protection against PRC damage.

Keywords: Antioxidant; Dandelion; Kidney; Oxidative stress; Paracetamol

1. Introduction

Paracetamol which has been used analgesic and antipyretic, is a drug used safely even in children. The fact that PRC has a strong anti-inflammatory effect and is easily absorbed from the stomach and small intestine in the body when taken orally makes PRC attractive. However, overdose leads to liver and kidney toxicity [1, 2].

PRC nephrotoxicity is characterized by proximal tubular necrosis [3, 4]. Biochemical metabolism of paracetamol occurs in the liver and kidney by glucuronidation, sulphation, and microsomal oxidation (cytochrome p450) reactions [5]. The compound called NAPQI (N-acetyl p-benzokinoimine) that causes toxicity in the intake of paracetamol is formed in the oxidation step due to cytochrome p450. NAPQI is very suitable for free radical formation, so it is rapidly converted into non-toxic mercapturic acid and cysteine metabolites by binding with glutathione (GSH) in metabolism and excreted in the urine [6, 7]. However, if paracetamol is taken into the body in an overdose, it causes excessive consumption of glutathione and causes NAPQI accumulation. Thus, the NAPQI intermediate metabolite cannot be detoxified and covalently binds to macromolecules such as proteins, lipids, and DNA, consequently causing toxic effects [8, 9]. As a result of increased NAPQI concentration, it damages the liver [10] and kidneys [11, 12].

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Dandelion (Taraxacum officinale), a member of the Asteraceae family, has been used as a diuretic in folk medicine [13, 14]. Dandelion has a high amount of antioxidants and anti-inflammatory capacity, and its effects on serious diseases such as obesity, cancer, heart, diabetes have attracted attention in recent years [15-17]. Dandelion; contains such as terpenes, phenolic acids, flavonoids, calcium, potassium, vitamin A, nicotinic acid, vitamin C many vital compounds. [14, 18]. Phenolic compounds in the mixture extract of dandelion flowers and leaves; contains hydroxycinnamic acid derivatives [19, 20], various flavonoid glycosides [20-22], and the main carotenoid pigment of flowers, taraxanthin (lutein epoxide) diester [23]. All parts of the plant, including aerial parts (leaves, flowers, stems) and roots, have therapeutic effects [24, 25]. Treated rats with dandelion root and leaf extracts showed an improvement in antioxidant profile, which was in parallel with other studies [18, 26]. In a study, the antioxidant effects of the mixture created with leafy vegetables containing dandelion plants in mice fed high-fat and high-cholesterol diet were evaluated. According to this study, plasma, liver, heart, and kidney increased antioxidant levels (glutathione and β-carotene) and activities of antioxidant enzymes (superoxide dismutase, peroxidase, reduced glutathione) and lipid peroxidation decreased significantly [27]. Moreover, dandelion leaves are used to support kidney function [28].

In the present study, the biochemical and histopathological effects of dandelion (D) ethanol extract on plasma and kidney tissue in paracetamol (PRC) induced in rats were investigated.

2. Material and methods

2.1. Drug and extract

In this research, as PRC source Parol tablets (500 mg/tablet; Atabay Chemical Industry, Istanbul, Turkey) was used. PRC was administered 2 g/kg (suspended in 1% CMC in 1X PBS) 2ml, orally [29].

The aerial parts of the dandelion plant were collected in the flowering period and dried in the shade. After that, the plant was grinded and kept in ethyl alcohol at Ataturk University Faculty of Agriculture, Essential Oil Laboratory for 48 hours, and filtered. After the solvent has removed with the help of a rotary evaporator, the extracts were stored in the refrigerator at +4ºC [30]. The extracts were dissolved in 5% Dimethyl sulfoxide (DMSO) and applied to rats intraperitoneally (i.p) [31].

2.2. The animals

The rats used for the study were provided by the Medical Experimental Research and Application Center of Ataturk University. The ethical approval is obtained from Ataturk University Animal Researches Ethic Committee in the session held on 25.03.2013 (decision number 36643897-475). 36 Sprague-Dawley rats, 5 months old, were used for the study. Rats weighing 250-300 g were kept at room temperature of 24-25ºC for 12 hours in a light/dark cycle. Rats, adapted to the environment for a week, were fed ad-libitum with standard pellet feed and tap water throughout the study.

2.3. Experimental application

Rats were randomly divided into 6 groups with 6 rats in each group. The animals in paracetamol given groups were fasted for 24 hours. 1 hour after the extract is administered, 2 g/kg p.o. PRC was given.

- Control Group (C): 5% DMSO (i.p),
- D200 Group: 200 mg/kg/day/i.p. dandelion extract,
- D250 Group: 250 mg/kg/day/i.p. dandelion extract,
- PRC Group: 2 g/kg/p.o. paracetamol,
- PRC + D200 Group: 2 g/kg/p.o. Paracetamol + 200 mg/kg/day/i.p dandelion extract,
- PRC + D250 Group: 2 g/kg/p.o. Paracetamol + 250 mg/kg/day/i.p dandelion extract was applied for 8 days.
- Animals were decapitated under sevoflurane (Sevorane liquid 100%, Abbott Laboratories, Istanbul, Turkey) anesthesia, and blood and kidney tissue samples were collected rapidly. Biochemical analysis were done in blood and kidney tissues.

2.4. Sample collection

Blood samples were transferred to lithium heparin tubes, and their plasma was separated by centrifugation at 3000 rpm for 10 minutes at +4ºC. Along with kidney tissues taken, they were stored in the deep freezer at -20 ºC until biochemical analysis. After the kidney tissues obtained from rats were homogenized with a 1/10 ratio of 0.1 M, pH 7.4 phosphate buffer, and centrifuged at 1700xg, supernatants were used for the experiment.

2.5. Renal function analysis

Urea, uric acid, and creatine (Cre), were measured at renal function analysis meter from Medasia.store (Hangzhou Medasia Trading, China), sodium (Na) and potassium (K) levels were measured using the same brand commercial kit of Beckman Coulter autoanalyzer.

2.6. Analysis of oxidants and antioxidants

Malondialdehyde (MDA) in plasma [32], glutathione (GSH) levels [33] and catalase (CAT) [34], SOD [35] and GPx [36] activities in kidney tissue; MDA [37], GSH levels [38, 39] and Nitrite and Nitrate [40] levels were measured spectrophotometrically in the kidney tissue (Biotech Epocha UV-Visible EIA Spectrophotometer).

2.7. Statistical Analysis

Analysis of variance was performed using the SPSS 22.0 package program (One Way ANOVA) for the importance of the difference between all groups. Tukey test was used for multiple comparison.

3. Results

Plasma urea, uric acid, Cre, Na and K levels of the control and experimental groups are shown in Table 1.

PRC raised plasma levels of urea, uric acid, and Cre, as well as malondialdehyde, nitrate, and nitrite in kidney tissue. Furthermore, Na and K levels and antioxidant levels/activities (SOD, CAT, GPx activities and GSH levels) in renal tissue were reduced in PRC group. Dandelion reduced plasma levels of urea, uric acid, and creatinine, as well as lipid peroxidation, nitrat, and nitrit in kidney tissue, while simultaneously increasing antioxidant activities, Na and K levels.

Table 1 Urea, uric acid, Cre, Na and K levels of the control and experimental groups

Groups	Urea (mg/dL)	Uric acid (mg/dL)	Cre (mg/dL)	Na (mmol/L)	K (nmol/L)
C	35.67 ± 1.23^{ab}	0.87 ± 0.18^{b}	0.20 ± 0.00	138.83 ± 0.87^{ab}	4.46 ± 0.15^{c}
D200	31.83 ± 1.49^{c}	1.17 ± 0.06^{b}	0.18 ± 0.02	141.33 ± 0.80^{a}	4.10 ± 0.25^{c}
D250	32.33 ± 2.94^{c}	1.32 ± 0.07^{b}	0.20 ± 0.02	137.33 ± 1.58^{ab}	6.81 ± 0.59^{ab}
PRC	40.67 ± 0.15^{a}	1.85 ± 0.07^{a}	0.22 ± 0.00	135.16 ± 1.54^{b}	3.95 ± 0.09^{c}
PRC+D200	35.33 ± 1.15^{ab}	1.03 ± 0.12^{b}	0.18 ± 0.02	140.00 ± 1.48^{ab}	7.60 ± 0.07^{a}
PRC+D250	37.67 ± 1.12^{ab}	1.13 ± 0.18^{b}	0.20 ± 0.00	137.33 ± 0.56^{ab}	6.00 ± 0.46^{b}
P	**	***	NS	*	***

^{a,b,c} Means superscripted with different row are significantly different (***(P<0.001; ** P<0.01; *P<0.05 NS: Non-significant). Data are expressed as mean ± SEM (n = 6)

Table 2 The effects of dandelion extract on kidney tissues biochemical parameters

Groups	MDA (nmol/g)	SOD (EU/mg)	CAT (kU/g)	GSH mmol/g	GPx U/mg	Nitrate (mg/kg)	Nitrite (mg/kg)
C	47.60±0.97	17.13 ± 0.80^{ab}	183.66 ± 4.65^{ab}	2.63 ± 0.04^{ab}	1.58 ± 0.12^{bc}	27.80 ± 1.73^{a}	3.08 ± 0.22^{ab}
D200	45.44±1.51	18.00 ± 0.42^{a}	190.90 ± 1.84^{a}	2.74 ± 0.05^{a}	2.52 ± 0.11^{a}	22.08 ± 1.08^{b}	2.87 ± 0.28^{ab}
D250	47.26±1.09	17.13 ± 0.63^{ab}	190.79 ± 1.76^{a}	2.700 ± 0.06^{a}	2.03 ± 0.13^{ab}	22.55 ± 1.45^{b}	2.22 ± 0.08^{b}
PRC	49.89±1.70	14.13 ± 0.65^{c}	172.56 ± 6.00^{b}	2.47 ± 0.05^{b}	1.52 ± 0.67^{c}	28.83 ± 1.06^{a}	3.94 ± 0.51^{a}
PRC+D200	46.01±0.99	15.48 ± 0.41^{bc}	192.39 ± 4.86^{a}	2.57 ± 0.04^{ab}	2.53 ± 0.11^{a}	20.85 ± 0.76^{b}	1.94 ± 0.11^{b}
PRC+D250	46.61±0.62	14.50 ± 0.33^{c}	182.99 ± 3.96^{ab}	2.49 ± 0.05^{b}	2.19 ± 0.17^{a}	20.96 ± 0.66^{b}	1.99 ± 0.12^{b}
P	NS	***	*	**	***	***	***

^{a,b,c} Means superscripted with different row are significantly different (***(P<0.001; ** P<0.01; *P<0.05 NS: Non-significant). Data are expressed as mean ± SEM (n = 6).

In the Table 2 the kidney tissue levels of MDA levels, SOD, CAT activities, GSH levels, GPx activities, Nitrat and Nitrit levels are shown.

4. Discussion

The reason why paracetamol becomes attractive is that its analgesic effect is mild compared to other analgesics, it has almost no side effects in the gastrointestinal tract and can be used safely even in pregnant women. However, many studies reported that PRC might be caused by nephrotoxicity in long-term use [12, 41].

Blood urea nitrogen and creatinine are supplied endogenously and exogenously and excreted in the urine. However, in various kidney disorders, the production rate of urea in the blood exceeds the clearance rate and causes accumulation [42, 43]. Urea, creatinine, BUN and uric acid levels are important markers in the evaluation of kidney function, and their levels increase when exposed to toxicity [44]. Administration of PRC in various doses increases blood urea and creatinine levels, causing renal tubular necrosis and a decrease in glomerular filtration rate [3].

In a paracetamol-induced nephrotoxicity study (2g/kg) in rats, it was reported that serum urea and creatinine levels increased significantly, but there was no difference in Na^+ and K^+ levels [45]. In another study, it has stated that 500 mg/kg dose of paracetamol increased the plasma urea and creatinine levels of the rats, and the Na^+ and K^+ levels decreased compared to the control group but were not statistically significant [46].

In a study where different dandelion leaf methanol extracts (250, 500 and 750 mg/kg) were examined for cisplatin nephrotoxicity, it was stated that all doses reduced serum creatinine and urea levels (the most effective dose; 500 mg/kg) and the extract did not have any side effects [47]. Dandelion extracts applied in different doses against nephrotoxicities caused by various chemicals (CCl_4, cisplatin, etc.) have been supported by studies in which blood BUN, urea, uric acid, creatinine, Na + and K + levels can decrease [48, 49].

In this study, the PRC groups had higher plasma urea, uric acid, creatinine levels, and lower Na and K levels than the control group. Hyponatremia and hypokalaemia are caused by decreased in electrolyte levels. This result clearly demonstrates a decrease in the kidney's ability to filter waste products or preserve cations efficiently.

Active oxygen derivatives of free radicals, called oxidants, affect the enzymatic events of vital molecules, the structure of genetic materials such as DNA and RNA, and the structure of the cell membrane, causing cell damage. While these oxidants are in a certain balance in living organisms; They are inactivated by antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) and reduced glutathione (GSH) [50-52]. Oxidative stress develops with an increase in free radical species (ROS) and a decrease in the antioxidant defense system that cannot resist it [53]. ROS sources, such as peroxides, xanthine oxidase, nitric oxide synthase (NOS) and NAD (P) H oxidase, increase lipid and protein in the blood, causing glomerular changes in the kidney and are ultimately characterized by kidney damage [50, 51, 54].

Previous studies have indicated that PRC is directly related to GSH. GSH tolerates the toxic compound NAPQI, which is formed by the metabolism of PRC taken at a therapeutic dose. GSH, which will detoxify the NAPQI metabolite, is not sufficient in PRC taken at high doses. Thus, the NAPQI compound is covalently bound to cellular proteins to initiate lipid peroxidation and, consequently, oxidative stress [55-57]. All these processes are followed by kidney damage and chronic kidney diseases [2, 58]. Oxidative stress is evaluated with the malondialdehyde (MDA) biomarker, an important end product of lipid peroxidation [59]. In the PRC nephrotoxicity (1 g/kg) study conducted by [12], MDA level increased, GSH level, SOD, and CAT activity decreased compared to the control group. In another study that caused nephrotoxicity from paracetamol (1g/kg); It was reported that PRC group kidney MDA level increased, and GPx activity decreased [60]. In other study, it is stated that different doses of PRC (500mg-2 g/kg) decrease the activity/level of rat kidney tissue SOD, CAT, GPx, GSH, and increase the level of MDA [58].

Dandelion, which is widely found in the world, has a diuretic effect, and this is attributed to the richness of sesquiterpene lactone content [60]. In a rat study where dandelion leaves methanol extract (500 mg/kg) was applied against cisplatin nephrotoxicity; it was reported that the extract increased SOD activity and GSH level and further decreased LPO level [47]. In an experiment given dandelion extract (100 mg/kg) against kidney damage caused by carbon tetrachloride in rats; it lowered the level of MDA, but there was no statistical difference in GSH and GPx level/activity [49]. Dandelion has previously been supported by different studies that it has antioxidant effects [30, 61-63].

5. Conclusion

While long-term paracetamol usage induces liver failure, the study also points out that nephrotoxicity can occur independently of liver failure, depending on the frequency of paracetamol exposure. The administration of a 200 mg/kg dandelion dose reduced kidney damage, decraised oxidative stress, avoided free radical production, boosted antioxidant activity, improved kidney function tests, Na and K levels, and reduced nephrotoxicity, according to biochemical results. According to the findings, the ethanol extract of dandelion can be used to protect against PRC damage.

Compliance with ethical standards

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Disclosure of conflict of interest

Esra AKTAS SENOCAK and Betul APAYDIN YILDIRIM declare that they have no conflict of interest. All institutional and national guidelines for the care and use of laboratory animals were followed.

Statement of ethical approval

The ethical approval is obtained from Ataturk University Animal Researches Ethic Committee in the session held on 25.03.2013 (decision number 36643897-475).

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