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Research Article

Protective Feature of Anzer Propolis in Contrast-Induced Nephropathy in Rats

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Abstract

Aim: The study aims to ascertain whether Anzer Propolis, a natural antioxidant compound, can protect the kidneys from iopromide.
Material and Method: This study was done in 2021. Four groups of 32 adult male Wistar albino rats, weighing between 250 and 300 g, were formed. Control (C) group contained eight rats. Intraperitoneal ethanol was administered to the Ethanol (E) group (n=8), 8 g/kg intraperitoneal iopromide to the contrast-induced nephropathy (CIN) group (n=8), and a 100 mg/kg dose of Anzer Propolis on the date of application to the Anzer Propolis group (AP) (n=8), as well as the prior day, by gastric gavage and then 8 g/kg iopromide was administered intraperitoneally. Termination was carried out at the 48th hour. Histopathological examination was performed for CIN in the right and left kidneys.
Results: Following has been examined as a part of the research: serum urea, creatinine, IL6, interleukin (IL)-1β, total oxidant status (TOS), tumor necrosis factor (TNF-α), total antioxidant status (TAS), myeloperoxidase (MPO). TAS had a statistically significant increase in AP, in comparison to CIN, C and E groups ($p<0.05$). The pathological examination showed, vacuolar degeneration formations in tubular epithelial cells, and increase in mononuclear cell infiltration areas in the interstitial region in CIN. CIN had significantly higher values in comparison to AP ($p<0.05$).
Conclusion: Propolis protects the kidney tissue against the toxicity caused by CIN and negative effects of free radicals; most likely due to the antioxidant and antitoxic properties. Propolis is a promising natural substance for preventing CIN. There is a need for further research on the properties of propolis.

Keywords: Anzer propolis, contrast induced nephropathy, acute kidney injury, rat

INTRODUCTION

Contrast-induced nephropathy (CIN) is iatrogenic acute kidney injury that can emerge after administrating iodinated contrast agent intravascularly for diagnostic imaging, interventional angiographic, or medical interventions (1). Although risk assessment and prevention strategies are applied for CIN before using iodinated contrast agents, it develops at a rate ranging from 1% to 25% in hospitalized patients and contributes to mortality and morbidity by increasing the length of hospital stay (2). Impaired renal perfusion are important in the pathogenesis of CIN (1,3). Iodinated contrast agents also increase oxidative stress by lowering antioxidant enzyme levels, which increases the production of reactive oxygen species (ROS) or oxidative stress (4). It is aimed to reduce oxidative stress so as to prevent and treat CIN (1). For this purpose, antioxidant supplements, such as ascorbic acid, and medications, such as N-acetylcysteine and sodium bicarbonate, are used for prophylaxis and treatment in CIN (2,1).

Anzer Propolis, which contains honey and other bee products, is a frequently used substance in alternative medicine (5). The antioxidant, antitumor, and immunomodulatory effects of propolis have beneficial effects in treating various diseases (6-8).

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The main antioxidant mechanism of propolis polyphenols is that ROS reduce the rate of the xanthine oxidase reaction. As a result, less free radicals are produced (9). Propolis efficiency is mainly related to its antioxidant and antitoxic properties. Previous studies showed that the ethanolic propolis extract contained important antioxidant compounds that inhibited ROS production (10-11).

Current investigation was done to determine how Anzer Propolis, which is indigenous to Türkiye's Eastern Black Sea Region, affected CIN.

MATERIAL AND METHOD

Following the US National Institutes of Health's Guidelines for the Care and Use of Laboratory Animals, all rats received compassionate treatment. The research was assigned the reference number 124-19 by Afyon Kocatepe University Experimental Animals Local Ethics Committee and granted approval on October 16, 2019. The Eastern Black Sea region of Türkiye is the only place where the endemic Anzer propolis employed in this research is found. This study was done in 2021.

Research Design

A standard climate environment was used to house 32 male Wistar albino rats that ranged in weight from 250 to 350 g. They were given free access to water and standard rat feed while being housed in individual cages. They had five days to adjust to the laboratory setting and later 4 groups of rats were created at random. All animals were manipulated in accordance with the US National Institutes of Health's Guidelines for the Care and Use of Laboratory Animals (NIH publication no. 85-23, was revised in 1996).

Contrast-Induced Nephropathy

The rats were dehydrated one day before the administration of iodinated contrast material in order to develop CIN. Intraperitoneally, 8 gr/kg iopromide (Ultravist 100 mL, Bayer, Berlin, Germany) was administered gradually. Regarding the occurrence of CIN, the clinical practice guidelines for Kidney Disease Improvement Global Outcomes (KDIGO) for acute kidney damage were taken as the basis. According to the KDIGO, CIN can be described as at least 0.3 mg/dL elevation (or 26.5 µmol/L) from baseline in serum creatinine (Cr) in the following 48 hours after contrast agent exposure or elevation that is more than 1.5x baseline within a week (7 days) after contrast agent exposure, or obtaining urine quantity that is less than 0.5 mL/(kg·h) at least six hours after the exposure (3).

Study Groups

The rats were designated into four groups to understand whether the results obtained in this study depended on the ethanol in the ethanolic propolis or the propolis substance.

Control group (group C, n=8): The rats were fed ad libitum and supplied with water. The rats were euthanized according to established protocols after 48 hours.

Ethanol (group E, n=8): The rats were fed ad libitum and supplied with drinking water. On 0th day intraperitoneal (i.p.) ethanol was administered. The rats were euthanized according to established protocols after 48 hours, using high-dose anesthetics (150 mg/kg thiopental sodium).

Contrast-induced nephropathy group (group CIN, n=8): In this group, 8 g/kg iopromide (Ultravist, Bayer, Berlin, Germany) was injected intraperitoneally at a slow pace. The rats were euthanized according to established protocols after 48 hours as in group Ethanol.

Anzer propolis+contrast-induced nephropathy group (group AP, n=8): On the first day of the experiment, the rats in this group were gastric gavaged twice with 2 mL of saline and 100 mg/kg of propolis from the Anzer region that had been dissolved in ethanol. On day 0, the procedure was applied to CIN. The rats were sacrificed according to established protocols after 48 hours like the other groups. The animals were weighed on day 0 and at the end of 48 hours Sacrificed rats' harvested kidneys were stored in 10% formol for histopathological examination.

Biochemical Analysis

Evaluation of renal functions

The values of urea, creatinine, and serum were measured using an autoanalyzer as the indicators of a decrease in glomerular functions, in blood samples obtained by an intracardiac puncture at the 48th hour.

Evaluation of neutrophil migration

Myeloperoxidase (MPO) activity was used to demonstrate the neutrophil infiltration in tissues. Rat MPO measurements were carried out by the ELISA method.

Biochemical measurements in blood samples

Determination of MPO, proinflammatory cytokines, and antioxidant status levels in serum

The serum MPO (Sunred Rabbit MPO ELISA Kit; Catalog. No: YLA0057RB; Shanghai YL Biotech Co., Ltd., China), IL-1β (Rat Interleukin-1β, Catalog No: YLA 0031RA; Shanghai YL Biotech Co., Ltd., -China.), IL-6 (Rat Interleukin-6 Catalog No: YLA 0031RA; Shanghai YL Biotech Co., Ltd. -China.), TAS (Rat Total Antioxidant Status; Catalog No: YLA 1389 RA; Shanghai YL Biotech Co., Ltd., -China.), TOS (Rat Total Oxidant Status; Catalog No: (YLA 1392 RA; Shanghai YL Biotech Co., Ltd., China), and TNF-α (Rat Tumor necrosis alfa; ELISA Kit; E0764Ra) were analyzed by ELISA kits using MVGt Lambda Scan 200 (Bio-Tek Instrument, Winooski, VT, USA).

Measurement of the serum electrolyte level

An autoanalyzer (Roche Cobas 8000, Germany) was employed to measure the levels of serum K+, Ca++, Na+, Cl-, and Mg++ in blood samples taken at the 48th hour from all groups.

Hemogram measurement

The blood samples were obtained from the groups, and the hemogram was measured in a hemogram-measuring Cell Counter device (Huma Cell Count 80 TS).

Histopathological Evaluation

The 10% buffered neutral formaldehyde solution was used to fix the kidneys. After 48 hours, they were cut and transferred to cassettes for further tissue analysis. The tissues underwent a series of alcohol and xylene treatments before being blocked in paraffin. After that, blocks between 4 and 5 microns thick were cut using a microtome and mounted on slides. Following hematoxylin-eosin (HE) staining, the sections were examined under an optical microscope. The pathological changes in the kidneys were assessed and are presented in Table 1.

Table 1. Classification of renal pathology after CIN

Degree	Damage	Pathological definition
0	None	Normal tubule
1	Light	Slight swelling and loss of brush-like edge
2	Light	Intense swelling and moderate vacuolization
3	Moderate	Nucleus shrinkage and severe vacuolization
4	Severe	Necrosis and rupture of the basal membrane of apoptotic cells
5	Necrosis	Tubular necrosis in its entirety

Statistical Analysis

Mean±standard deviation values were used to present the data, and to identify variations in the biochemical, electrolyte, and oxidative stress parameters, non-parametric ANOVA tests were employed. Furthermore, to determine the significance level a Tukey test was used. Microsoft's Statistical Package for Social Sciences (SPSS) version 24.0 was used to analyze the data (USA). It was deemed significant if $p<0.05$.

RESULTS

The difference between the groups in serum urea and creatinine levels is shown in Table 2.

Compared to C, E, and AP, CIN's WBC levels significantly decreased ($p=0.000$). While the Hb level did not change for others, there was a significant increase in AP's Hb levels ($p=0.005$) (Table 3).

The differences between the groups for serum MPO, proinflammatory cytokines and antioxidant status levels are shown in Table 4.

The histopathological differences observed between the groups are shown in Table 5. The pathological examinations of all groups are shown in Figure 1.

Upon analysis, we discovered that Anzer Propolis utilized in the research contained high levels of ethyl oleate (10.23%), 5-hydroxy (9.07%), and 4H-1 benzopyran-4-one (12).

Table 2. Kidney function tests in the groups (n=8) (Mean±SD)

Groups	Creatinine mg/dL	Na^{++} mmol/L	K^{+} mmol/L	Cl^{-} mmol/L	Ca^{+2} mg/dL	Urea mg/dL	Mg^{++} mg/dL
C	0.37^{b}±0.04	140.13±2.42	5.24^{b}±0.28	99.80±0.58	9.75^{b}±0.28	37.60^{c}±0.65	2.69±0.27
E	0.44^{a}±0.05	141.88±1.13	5.69^{b}±0.25	99.78±1.53	10.45^{a}±0.40	43.81^{ab}±3.48	2.58±0.14
CIN	0.41^{ab}±0.03	142.38±3.74	6.15^{a}±0.62	101.04±2.77	10.24^{a}±0.25	44.51^{a}±4.72	2.57±0.11
AP	0.38^{b}±0.03	141.50±1.60	5.62^{b}±0.49	101.79±1.68	10.34^{a}±0.29	40.36^{bc}±3.63	2.47±0.20
P	0.008*	0.307	0.003*	0.093	0.001*	0.001*	0.165

K^{+}: potassium; Cl^{-}: chlorine; Ca^{++}: calcium; Mg^{++}: magnesium. *: $p<0.01$; a, b, c: kidney function tests values ($p<0.05$) with different letters in the same column are statistically significant

Table 3. Hematological parameters in the groups (n=8) (Mean±SD)

Groups	WBC 10^{9}/L	RBC 10^{12}/L	HGB g/dL	HCT %	MCV fL	PLT 10^{9}/L
C	**5.85**^{a}±0.73	9.02±0.49	15.73^{b}±0.52	54.61^{a}±2.29	54.61±2.29	690.25^{b}±65.08
E	6.18^{a}±1.69	9.16±0.36	15.58^{b}±0.34	51.53^{bc}±1.49	55.65±1.10	818.75^{a}±50.38
CIN	3.32^{b}±1.17	8.80±0.55	15.33^{b}±0.70	49.43^{c}±2.64	56.23±2.48	912.13^{a}±117.73
AP	6.90^{a}±1.79	9.40±0.26	16.48^{a}±0.79	53.68^{ab}±2.56	57.11±2.05	814.75^{a}±134.14
P	0.000*	0.064	0.005*	0.000*	0.124	0.001*

Hb: hemoglobin, HCT: hematocrit, MCH: mean corpuscular hemoglobin, PLT: platelet, RBC: red blood count, WBC: white blood count; Hematological values ($p<0.05$) with different letters in the same column are statistically significant

Table 4. Biochemical parameters in the groups (n=8) (Mean±SD)

Parameters/groups	CIN	E	AP	C	P value
TOS (U/mL)	5.5950±.21537[a]	4.8638±.08401[b]	4.7775±.13872[b]	4.9525±.04636[b]	0.001
TAS (U/mL)	11.0650±.43727[b]	10.7500±.28069[b]	12.9388±.25721[a]	11.2437±.23140[b]	0.001
IL-1β(ng/mL)	26.0250±1.65571[a]	20.8525±1.15944[b]	19.0463±.89201[bc]	16.9063±.34428[c]	0.001
IL-6 (ng/L)	35.0338±1.76343[a]	19.5363±1.51576[c]	25.0113±1.29203[b]	20.9962±.59118[c]	0.001
Hyp (ng/L)	260.0000±13.56203	271.5850±5.33029	289.6250±7.33372	281.4688±5.51215	0.110
MPO (ng/mL)	22.6013±.71762[a]	16.3200±.41467[c]	15.8700±.42172[c]	18.0788±.22303[b]	0.001
TNF-α(ng/mL)	44.6950±3.18151[a]	25.9275±1.34338[b]	23.0063±1.16015[b]	24.2250±1.08938[b]	0.001

Hyp: Hydroxyproline, IL-1: Interleukin-1, IL-6: interleukin-6, MPO: myeloperoxidase, TAS: total antioxidant status, TOS: total oxidant status, TNF: tumor necrosis factor. Letters next to biochemical parameters indicate statistical significance (p<0.05)

Table 5. Pathological evaluation of the groups (n=8)

Groups	Enlargement of the glomerular Bowman's space	Vacuolization formation in the glomerular capillary ball	Vacuolar degeneration formations in tubular epithelial cells	MNC infiltration areas in the interstitial region
C	0.00d±0.00	0.00d±0.00	0.00c±0.00	0.00b±0.00
E	0.88b±0.35	1.25b±0.46	1.00b±0.00	0.38b±0.52
CIN	1.88a±0.35	1.88a±0.35	2.25a±0.89	2.50a±0.76
AP	0.50c±0.53	0.75c±0.46	0.63b±0.52	0.38b±0.52
P	**0.000***	**0.000***	**0.000***	**0.000***

*: a, b, c, d: Letters next to renal histopathological values indicate statistical significance (p<0.05); MNC: mononuclear cell

DISCUSSION

Despite the risk assessment and prevention strategies for CIN before the use of iodinated contrast agents, it develops at a rate ranging from 1% to 25% of hospitalized patients. However, patients with high risk, like diabetics, geriatrics and those who suffer from chronic kidney diseases, this rate increases to 50%, increasing the length of hospital stay and contributing to mortality and morbidity (2,13). The pathogenesis of CIN is still not fully elucidated. However, there are various mechanisms suggested in the pathogenesis. These mechanisms are direct toxicity due to iodinated contrast agents, renal medullary hypoxia, and increased apoptosis (14). All these mechanisms cause increased oxidative stress, tissue damage and acute kidney injury. Iodized contrast agents increase oxidative stress through the increase of ROS production, or by decreasing antioxidant enzyme levels (6). For this reason, studies that aim to reduce oxidative stress were conducted to prevent the development of CIN (1,4,15). In this study, the protective properties of Anzer propolis against CIN were investigated biochemically and histopathologically.

Propolis is a natural substance broadly utilized both in folkloric and alternative medicine along with other bee products such as royal jelly, bee pollen, beeswax, and honey (5). Health benefits of propolis have been shown in the treatment of various diseases resulting from its antiviral, antitumor, antioxidant, immunomodulatory, and anti-inflammatory effects (6-8). The main antioxidant mechanism of propolis polyphenols is that ROS and reactive nitrogen radical species (RNS) reduce the xanthine oxidase reaction. Thus, they reduce the formation of free radicals (9). Several investigation indicated that ethanolic propolis extract contains important antioxidant compounds can inhibit ROS production (10-11).

In our study, it was shown that serum creatinine level increased significantly in CIN and E, in comparison to C and AP (p=0.008). The similarity of serum creatinine levels in AP and C may be related to propolis phenols' nephroprotective properties due to their antioxidant and antitoxic properties. Likewise, in a previous experimental work of Baykara et al. (16), the nephroprotective effect of propolis against iodinated contrast agents was demonstrated. After administration of iodinated contrast, a significant increase in plasma urea level was observed in CIN, in comparison to C.

Nevertheless, AP's levels of plasma urea were significantly lower than CIN. Past studies reached similar conclusions (16-17).

Exposure to iodinated contrast agents triggers oxidative stress, increasing the production of ROS (14). In a previous

study, it has been shown that the TOS level increases and the TAS level decreases after application of iodinated contrast material (18). In our study, CIN's levels of TOS and TAS production were significantly higher than AP's. This result is related to the antioxidant and antitoxic properties of Anzer Propolis phenols (19).

In previous studies, it has been shown that CIN causes an increase in the level of interleukins (4,9). We observed significant decrease in IL-1 levels in AP, in comparison to E and CIN ($p<0.05$). Propolis has a rich content of flavonoids that inhibit nitric oxide, IL-1 and IL-6 production (20). It has been demonstrated that the acute phase reactant IL-6 contributes to renal autoimmune and inflammatory diseases by locally activating the classical and transsignal pathways. Podocytes, endothelial, mesangial, and tubular epithelial cells, among others, canare able to secrete IL-6 in kidneys (21). In the study of Hudzig B., et al. (22), there was an increase in patients' IL-6 levels who developed CIN. In our study, a statistically significant decrease in IL-6 levels was observed in AP and E, compared to CIN ($p<0.05$). The low levels of IL-1 and IL-6 in AP in our study may be due to the effect of flavonoids in AP content.

It has been shown that the level of MPO, a proinflammatory enzyme, increases in CIN (23). Increased MPO levels in the kidney are directly correlated with neutrophil infiltration and tissue inflammation brought on by contrast media. Activation of MPO can generate glomerular morphological changes, endothelial and mesangial cell damage and platelet activation, as well as glomerulonephritis (24). In our study, Anzer Propolis has been shown to reduce the level of MPO.

One of the proinflammatory mediators whose levels increase in contrast-related nephropathy is TNFα (25). It has been shown that the increase in TNFα level causes damage to renal tubular cells (26). In a single-center study, it was shown that the baseline level of TNFα is useful in demonstrating the prognosis in patients who develop CIN (27). For this reason, studies have been carried out to reduce the level of TNF α (25,26). In this study, Anzer propolis was shown to reduce TNFα level.

An increase in WBC level has been shown in contrast-related nephropathy (28). In the current study, WBC levels were statistically significantly higher in CIN and E than in AP ($p<0.05$). Anemia can trigger CIN progress by causing hypoxia due to reduced oxygen carrying capacity (29). Statistically significant increases were observed in hemoglobin and Hct values in AP compared to others ($p<0.05$). This result may be related to the antioxidant effect of Anzer Propolis.

The pathological effects of contrast agents on the kidneys are vacuolization in proximal epithelial cells, interstitial inflammation and cellular necrosis (30). In the pathological evaluation of our study, enlargement of the Bowman's space of the glomerulus in CIN, vacuolization formation in the glomerular capillary ball, vacuolar degeneration formations in the tubular epithelial cells and mononuclear cell (MND) infiltration areas in the interstitial region were detected. These findings were significantly higher in CIN compared to AP ($p<0.05$). As a result of this pathological evaluation, it was revealed that AP protects kidney tissue with its antioxidant and antitoxic effects.

Since AP extract used in our study contains ethanol, it was revealed both biochemically and pathologically that the results obtained were related to the effect of AP, not ethanol.

CONCLUSION

CIN is iatrogenic acute kidney damage that prolongs hospital stays and increases mortality and morbidity. According to the literature, pathophysiological mechanisms leading to CIN have still not been fully explained. There are ongoing studies for preventing and treating CIN. Propolis protects the kidney tissue against the toxicity caused by CIN and negative effects of free radicals; most likely due to the antioxidant and antitoxic properties. Propolis is a promising natural substance for preventing CIN. There is a need for further research on the properties of propolis.

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