

Nephroprotective Effect of Apilarnil in Acetaminophen-Induced Acute Kidney Injury Model

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Abstract

Aim: High-dose and long-term acetaminophen (paracetamol; PAR) use can cause acute and chronic kidney damage. It was reported that apilarnil (AP), an apitherapy product obtained from drone larvae, has high antioxidative and anti-inflammatory effects. In this study, the effect of apilarnil on kidney tissue damage, oxidative status, and inflammation in an acetaminophen-induced renal injury model was investigated.

Method: A total of 32 adult male Wistar albino rats were used in this study. Rats were divided into 4 groups as control, paracetamol (PAR), paracetamol+apilarnil (PAR+AP) and apilarnil (AP) groups. A dose of 600 mg/kg PAR was used to create the acute kidney injury model. AP was administered at a dose of 0.8 mg/kg. Kidney tissue histopathology was evaluated with the hematoxylin-eosin (H&E) staining method. Renal tumor necrosis factor α (TNF- α) expression was determined by the indirect immunohistochemical method. Renal glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) levels were determined by the ELISA method.

Results: PAR administration caused an increase in MDA level in kidney tissue, while antioxidant enzyme levels of SOD, CAT and GPx decreased. PAR also caused an increase in renal TNF- α immunohistochemical expression. AP treatment provided a significant decrease in MDA level, while GPx and SOD levels increased. AP treatment also provided a decrease in renal TNF- α expression and tubular damage score.

Conclusion: This study is the first report showing that AP prevents paracetamol-induced renal damage. AP may be an option that can be used for the treatment of high-dose paracetamol-induced renal damage.

Keywords: Acetaminophen, apilarnil, acute kidney injury.

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ETHICAL STATEMENT: This study was carried out with the approval of the Ethics Committee of Tekirdağ Namık Kemal University, dated 14/03/2024 and numbered 2.

Asetaminofen ile İndüklenen Akut Böbrek Hasarı Modelinde Apilarnilin Nefroprotektif Etkisi

Öz

Amaç: Yüksek doz ve uzun süre Asetaminofen (parasetamol) kullanımı akut ve kronik böbrek hasarına neden olabilmektedir. Erkek arı larvasından elde edilen bir apiterapik ürün olan apilarnilin, yüksek antioksidatif ve antiinflamatuvar etkilere sahip olduğu belirtilmiştir. Bu çalışmada asetaminofen-uyarımlı renal hasar modelinde apilarnilin böbrek doku hasarı, oksidatif statü ve inflamasyon üzerindeki etkisi incelendi.

Yöntem: Çalışmada 32 adet erişkin erkek Wistar albino sıçan kullanıldı. Sıçanlar kontrol, parasetamol (PAR), parasetamol+apilarnil (PAR+AP) ve apilarnil (AP) olarak 4 gruba ayrıldı. Akut böbrek hasar modeli oluşturmada 600 mg/kg PAR kullanıldı. AP 0,8 mg/kg dozda uygulandı. Böbrek doku histopatolojisi hematoxilen – eozin (H&E) boyama yöntemi ile değerlendirildi. Renal TNF- α ifadesi indirekt immünohistokimyasal yöntemle belirlendi. Renal glutatyon peroksidaz (GPx), süperoksit dismutaz (SOD), katalaz (CAT) ve Malondialdehit (MDA) seviyeleri ELISA yöntemi ile belirlendi.

Bulgular: PAR uygulaması böbrek dokusunda MDA seviyesinde artışa neden olurken; antioksidan enzimler SOD, CAT ve GPx seviyelerinde azalmaya neden oldu. Ayrıca PAR, renal TNF- α immünohistokimyasal ifadesinde artışa neden oldu. AP tedavisi MDA seviyesinde anlamlı bir azalma sağlarken, GPx ve SOD seviyesinde artış sağladı. Ayrıca AP uygulaması renal TNF- α ifadesi ve tübüler hasar skorunda azalma sağladı.

Sonuç: Araştırmamız AP'nin parasetamol-uyarımlı renal hasarı engellediğini gösteren ilk rapordur. AP, yüksek doz parasetamol kaynaklı renal hasarın tedavisinde kullanılabilecek alternatif bir seçenek olabilir.

Anahtar Sözcükler: Asetaminofen, apilarnil, akut böbrek hasarı.

Introduction

Acetaminophen (paracetamol; PAR) is one of the most commonly used antipyretic (fever reducer)-analgesic (pain reliever) drugs in many countries, and is available without a prescription¹. It is widely used for many ailments such as colds, sore throat, muscle-joint pain, and toothache². Easy access and widespread use also lead to the risk of toxicity^{3,4}. Experimental and clinical studies showed that PAR causes liver and kidney damage when used in high doses⁵⁻⁷. Kidneys have important physiological functions such as homeostasis, endocrine functions, acid-base and electrolyte balance⁸. The liver and kidneys are known to be more sensitive to toxic substances and are exposed to more toxicity compared to other organs⁹. PAR is mostly detoxified in the liver by conjugation with glucuronic acid. About 5% of the ingested PAR dose undergoes N-hydroxylation in the liver with the participation of cytochrome P450 enzymes (especially CYP2E1) and a very rapid toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is formed^{9,10}. This metabolite is a highly reactive compound that is excreted in urine. High doses of PAR cause overproduction of NAPQI and the level of NAPQI may exceed the detoxification capacity of glutathione (GSH). In addition, PAR is converted to p-aminophenol, a nephrotoxic metabolite, by deacetylation in the renal cortex. NAPQI and p-aminophenol produced during chronic use and by high doses of paracetamol cause kidney damage^{11,12}.

It was reported that excessive PAR intake causes vasoconstriction in the kidneys and a decrease in glomerular filtration rate^{13,14}. It was also suggested that GSH reduction and oxidative stress are important factors in nephrotoxicity caused by high-dose paracetamol intake¹⁵. Previous studies reported that acute high-dose PAR administration increases lipid peroxidation and weakens antioxidant mechanisms in kidney tissue^{16,17}. Although N-acetyl cysteine, which is used to alleviate PAR toxicity in clinics, prevents liver toxicity, it does not protect against kidney damage¹⁸. There is a need for new agents that are safe and have low toxicity risk and can be used as alternatives for PAR-induced kidney damage.

Apilarnil (AP), a current apitherapy agent with high antioxidant and anti-inflammatory properties, is a product obtained from drone larvae¹⁹. Elashal et al. (2024) reported that apilarnil prevents tissue damage by reducing the level of malondialdehyde (MDA) in testicular tissue against bisphenol-A (BPA) toxicity²⁰. Another study demonstrated that AP treatment significantly reduced the levels of the proinflammatory cytokines interleukin-1 beta (IL-1B), tumor necrosis factor alpha (TNF- α), and nuclear factor kappa beta (Nf-kB), while also preventing liver tissue damage in a lipopolysaccharide (LPS)-induced liver injury model²¹. In the current study, we intend to examine the kidney protective effects of AP in a PAR-induced rat nephrotoxicity model for the first time in the literature by determining histopathological, immunohistochemical, and tissue oxidative status.

Material and Methods

Chemicals

Parol (paracetamol 500 mg, Parol, Atabay Drug Industries, Turkey) was used to create the nephrotoxicity model. Apilarnil was purchased from Nutral Therapy (Erciyes University Technopark, Kayseri, Türkiye).

Experimental Model

The experimental investigations were conducted at Namık Kemal University Experimental Animal Research Center. During the experimental period, animals were fed with standard pellet diet and tap water ad libitum in a standard laboratory environment (40-60% humidity, 22 $\pm$ 2°C, and 12:12 h dark-light cycle).

Thirty-two adult male Wistar albino rats (200-240 g, 8 weeks old) were used in the study. Rats were divided into 4 groups (n=8); Control, PAR, PAR+AP and AP. Nephrotoxicity induction was performed by i.p. administration of PAR (dissolved in 1 ml physiological serum) at a dose of 600 mg/kg²². AP was administered by oral gavage at a dose of 0.8 mg/kg (dissolved in 1 ml of physiological serum)²¹. At the end of the 24th hour following PAR administration, rats were sacrificed by taking blood from the heart under ketamine-xylazine anesthesia. Kidney tissues were fixed with buffered neutral formalin for histological examination. The tissues were kept at -80°C for oxidative stress status analysis.

Histochemical Examinations

After 48 hours of fixation at room temperature, kidney tissues were washed with running tap water overnight. The tissues cleared of formalin were passed through graded ethanol (70-80-90 and 100%) for dehydration and cleared in toluene. Then, they were waxed in paraffin. The obtained tissue blocks were cut to 4-5 µm thick using a semi-motorized microtome (Leica RM-2245). To examine the histopathology of kidney tissue, sections were stained with hematoxylin-eosin (H&E). Tubular damage caused by paracetamol in kidney tissue was scored according to Ban et al. (2022)²³. Accordingly, scoring was 0, no damage; 1, 1-10% damaged area; 2, 11-25% damaged area; 3, 26-75% damaged area; and 4, 75% or more damaged area.

Renal TNF-α Immunoreactivity

Renal TNF-α immunohistochemical labeling was determined with the indirect immunohistochemical method. Sections deparaffinized with xylene were dehydrated in a graded ethanol series and washed with phosphate buffer (PBS). The antigen retrieval step was performed by boiling in citrate buffer. Sections were treated with hydrogen peroxide (3%, aqueous H₂O₂ solution) for endogenous peroxide suppression. Slides rinsed with PBS were treated with block serum for 60 min and then treated with TNF-α antibody (TNF-α, 1:100 dilution, Elabsience) in a humid chamber for 90 min at 37 °C in an oven. 3-aminoethyl carbazole (AEC) was applied as a chromogen to the sections labeled with biotin and streptavidin antibodies, respectively. Background staining was performed with Mayer's hematoxylin. TNF-α staining intensity in the sections was evaluated according to Carter et al. (2004) (staining distribution 0.1, <25%; 0.4, 26–50%; 0.6, 51–75%; 0.9, 76–100% and staining intensity 0; no staining, 0.5; very little staining, 1; little staining, 2; moderate staining, 3; very strong staining). Immunohistochemical staining score = distribution x intensity²⁴.

Tissue Oxidative Stress Parameters

Levels of lipid peroxidation marker malondialdehyde (MDA) and the antioxidant enzymes catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) in kidney tissue were determined by the sandwich ELISA method using the procedures for the relevant commercial kit (MDA, SH0020; GPx, E1172Ra; SOD, SH0039; CAT, E0869Ra, BT Lab, Bioassay Technology Laboratory).

Ethical Statement

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Statistical Analyses

Analysis of data was conducted using SPSS (SPSS, IBM, Version 21, USA) and GraphPad Prism 8 software. Data are expressed as mean ± standard deviation value. Values were

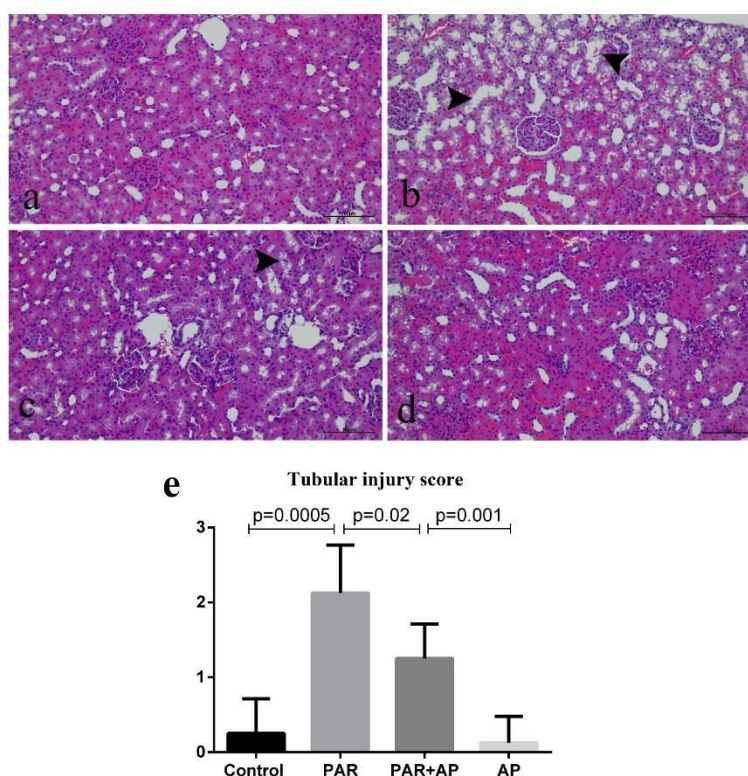
evaluated using a non-parametric test (Kruskal-Wallis). The significance of the values obtained in the groups after two-way comparisons was measured with the Mann-Whitney U test. A difference between groups was considered statistically significant if it was less than 0.05.

Results

AP Improved PAR-Induced Renal Histopathology

Kidney tissue histopathological findings are presented in Figure 1. The kidney structure in the control group was found to be normal. Degeneration and hemorrhage in tubular epithelial cells were detected in the PAR group. In the AP-treated group, tubular morphology was observed to be closer to normal compared to the nephrotoxicity group. The group only given AP had normal architecture of kidney tissue. Tubular damage scores for the groups are presented in Figure 1-e. The tubular damage score was significantly increased in the PAR group compared to the control group. In the PAR+AP group, the tubular damage score was significantly decreased compared to the PAR group.

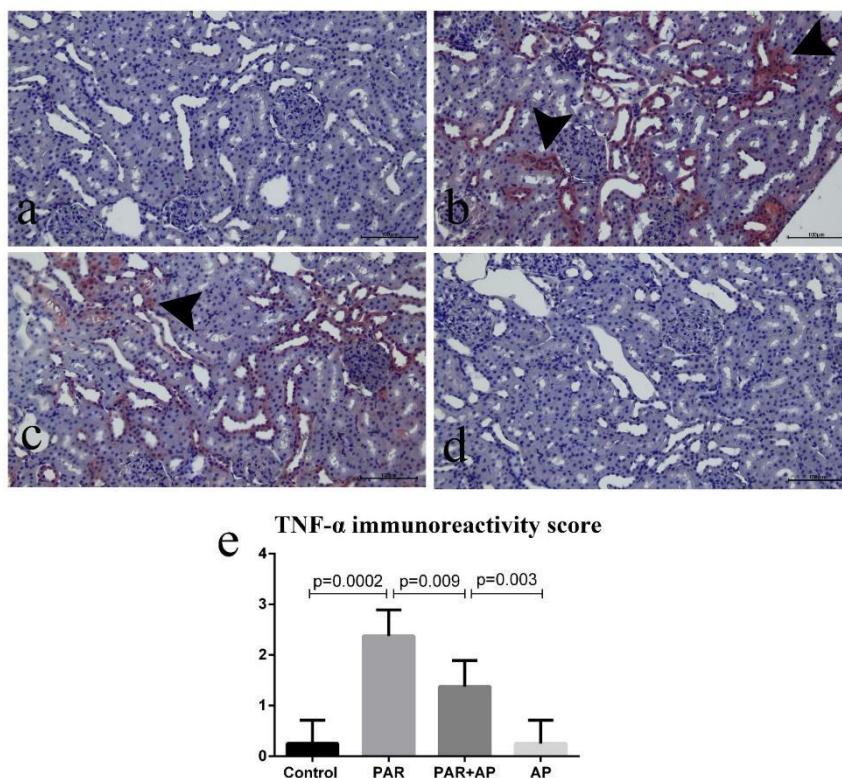
Figure 1. The effect of AP on PAR-induced acute renal injury. a; control, b; PAR, c; PAR+AP, d; AP, e; tubular injury scores of groups, (arrowhead; tubular epithelial shrinking, dye; hematoxylin and eosin, magnification; 200x)



AP Alleviated Renal TNF- α Expression

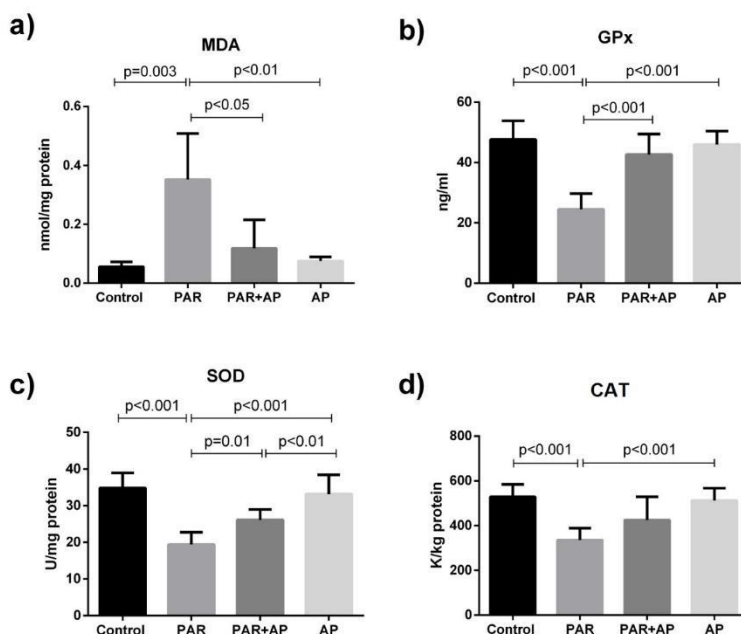
Figure 2 shows the immunohistochemical expression of TNF- α in kidney tissue. TNF- α expression was concentrated especially in tubular epithelial cells in kidney tissue. AP treatment provided a significant decrease in TNF- α immunohistochemical expression.

Figure 2. Effect of AP on renal TNF- α immunoreactivity, a; control, b; PAR, c; PAR+AP, d; AP, e; TNF- α immunoreactivity scores for the groups (arrowhead; TNF- α positive cells, magnification; 200x, counterstain; Mayers hematoxylin)



Oxidative Status Findings

Figure 3 displays the MDA, SOD, CAT, and GPx results for the groups. MDA levels were significantly higher in the PAR group compared to the control group. MDA levels decreased in the PAR+AP group compared to the PAR group. SOD, CAT and GPx levels decreased significantly in the PAR group compared to the control group. GPx and SOD levels increased significantly in the PAR+AP group compared to the PAR group.

Figure 3. Effect of AP on MDA, GPx, SOD and CAT enzyme levels

Discussion

The beneficial effects of products obtained through beekeeping, such as honey, propolis, pollen, royal jelly, and bee bread, have been known by people for a long time, and these products are used for various purposes²⁵. The role of apilarnil, an apitherapy product that is becoming popular around the world in recent years, in PAR-induced nephrotoxicity was examined for the first time in this study.

High doses of PAR, one of the most common painkillers sold without a prescription, can cause liver and kidney damage³. The frequency of nephrotoxicity due to high-dose PAR use was reported as 2-10% in the literature²⁶. The fact that kidney damage can develop without signs of liver damage due to PAR use makes the issue more remarkable²⁷. Several natural products and phytochemicals were reported to alleviate the PAR-induced hepatorenal toxicity to date^{2,28,29}.

In the pathogenesis of PAR-induced renal damage, inadequacy of GSH capacity to detoxify the increased production of NAPQI plays an important role³⁰. For this reason, GSH stands out as a key parameter in studies examining acetaminophen-induced renal damage in the literature^{31,32}. Canayakin et al. reported decreased GSH levels in a PAR-induced renal damage model³². In this study, AP treatment significantly increased the decreased GSH-px level caused by PAR. In PAR-induced renal damage models, various agents used for therapeutic purposes were reported to increase GSH levels and improve oxidative damage markers and renal histopathology^{16,33}. Oxidative stress also contributes to tissue damage in PAR-induced nephrotoxicity³⁴. Tissue damage may be aggravated due to the increase in free radicals due to the increase in NAPQI and the decrease in

enzymes that have antioxidant effects such as SOD and CAT, especially due to GSH depletion^{33,35}. In this study, a significant decrease in SOD and CAT enzyme levels was determined together with GPx in the PAR group. In line with previous literature, MDA, an important marker of tissue damage, was found to be significantly higher in the PAR group. Experimental studies reported the positive effects of natural agents containing various polyphenolic compounds in the suppression of PAR-induced renal damage and oxidative stress^{29,36}. AP, which contains many phenolic and polyphenolic components in its structure, has high antioxidant and radical scavenging properties in experimental studies^{25,37,38}. Doganyigit et al. (2020) reported that AP treatment provided significant improvements in MDA, SOD and CAT enzyme levels in the LPS-induced sepsis model. Elashal et al. (2024) reported that AP treatment prevented tissue damage along with improvements in testicular MDA and GSH levels in a BPA-induced testicular injury model²⁰. In line with the aforementioned studies, AP administration alleviated the severity of tissue damage by providing a significant increase in the oxidative stress parameters of SOD and GPx. Unlike these studies, CAT level increased in the PAR+AP group, but it was not found to be statistically significant. In previous studies, the role of inflammation in the pathogenesis of PAR-induced nephrotoxicity was reported^{27,28}. Following high-dose PAR application, increased TNF- α levels activate the inflammatory cascade in kidney tissue, causing the release of proinflammatory cytokines¹⁸. El-Boshy et al. (2019) and Ozatik et al. (2019) reported TNF- α levels in a PAR-induced acute kidney injury model^{17,39}. In line with the aforementioned studies, increased TNF- α levels in kidney tissue were shown immunohistochemically in the present study. AP treatment provided a significant decrease in TNF- α levels. Inandikcioglu et al. (2021) reported that AP administration provided a significant decrease in TNF- α levels in the LPS-induced renal injury model⁴⁰.

This study has some limitations. In this study, BUN and creatinine levels, which are biochemical markers of renal injury, could not be determined. In addition, the findings are valid for the experimental model in this study and lack clinical data. In order to better elucidate the role of AP in PAR-induced renal injury, further studies are needed using advanced methods with different doses and durations.

Conclusion

In conclusion, we determined that AP administration suppressed the inflammatory cascade in a PAR-induced acute renal injury model and protected the tissue structure by preventing oxidative damage. We think that AP can be used as a potential product for the treatment of high-dose PAR-induced renal injury.

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