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The Therapeutic Effect of *p*-Coumaric Acid on Lung Toxicity Induced by Methotrexate in Rats

Sıçanlarda Metotreksatın Neden Olduğu Akciğer Toksisitesi Üzerine *p*-Kumarik Asidin Terapötik Etkisi

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ABSTRACT

The use of methotrexate (MTX), a chemotherapy agent, is limited by a number of side effects, including pulmonary toxicity. Oxidative stress (OS) and inflammation are possible mechanisms of MTX-associated pulmonary toxicity. *p*-Coumaric acid (PCA) is a phenolic acid that has been demonstrated to exert a number of beneficial effects on human health, particularly in relation to antioxidant and anti-inflammatory activity. The potential effects of PCA in reducing MTX-induced pulmonary toxicity were investigated in the current study. After MTX (20 mg/kg) was administered to the rats on day 1, two different doses of PCA (2 and 4 mg/kg) were administered intraperitoneally for 3 days and the levels of OS, inflammation and apoptosis were assessed in the lung tissues collected on day 5. PCA applications largely eliminated MTX-induced OS, inflammation and apoptosis in lung tissue via enhancing the capacity of endogenous antioxidant system. The therapeutic effect of PCA against MTX-induced pulmonary toxicity should be re-evaluated in more systematic studies.

Keywords: Apoptosis, Inflammation, Methotrexate, Oxidative stress, *p*-Coumaric acid, Pulmonary toxicity

ÖZET

Bir kemoterapötik ajan olarak metotreksatın (MTX) kullanımı, akciğer toksisitesi de dahil olmak üzere bir takım yan etkiler nedeniyle sınırlıdır. Oksidatif stres (OS) ve inflamasyon, MTX ile ilişkili akciğer toksisitesinin olası mekanizmalarıdır. *p*-Kumarik asit (PCA), özellikle antioksidan ve anti-inflamatuar olmak üzere insan sağlığı üzerinde çeşitli yararlı etkileri olan bir fenolik asittir. Bu çalışmada PCA'nın MTX kaynaklı akciğer toksisitesini azaltmadaki potansiyel etkileri araştırıldı. Ratlara 1. günde MTX (20 mg/kg) enjeksiyonunu takiben 3 gün boyunca iki farklı dozda PCA (2 ve 4 mg/kg) intraperitoneal olarak uygulandıktan sonra 5.günde akciğer dokuları toplanarak OS, inflamasyon ve apoptoz düzeyleri değerlendirildi. PCA uygulamaları, endojen antioksidan sistemin kapasitesini artırarak akciğer dokusunda MTX'in neden olduğu OS, inflamasyon ve apoptozu büyük ölçüde ortadan kaldırdı. PCA'nın MTX kaynaklı akciğer toksisitesine karşı terapötik etkisinin daha sistematik çalışmalarla yeniden değerlendirilmesi gerekmektedir.

Anahtar Kelimeler: Akciğer toksisitesi, Apoptoz, İnflamasyon, Metotreksat, Oksidatif stress, *p*-Kumarik asit

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INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist that is employed in the treatment of various types of cancer, including leukaemia, breast cancer and lung cancer.[1] The antiproliferative effect of MTX on cancer cells is attributed to its suppression of thymidylate synthesis.[2] Several reports have shown that MTX can cause a number of adverse effects, including haematological, cutaneous, gastrointestinal, neuro-, nephro- and pulmonary toxicity.[3] In particular, pulmonary toxicity is a common adverse effect that may necessitate the discontinuation of treatment.[4] The incidence of MTX-induced lung disease is estimated to be approximately 7.6%.[5] The hypothesis has been put forth that MTX-related pulmonary injury is a consequence of heightened inflammation, a process which may culminate in the emergence of fibrosis, interstitial pneumonitis, and potentially significant alveolar destruction.[2] The aetiology of tissue damage associated with the use of MTX is complex and involves multiple mechanisms, with inflammatory and oxidative stress (OS) processes playing a significant role.[6] MTX has been demonstrated to induce parenchymal lung damage by causing an increase in the amount of reactive oxygen species (ROS) and a decrease in the capacity of the antioxidant defence system.[5,7-9] MTX also results in an elevation of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α).[5,10,11] This, in turn, contributes to the exacerbation of tissue damage.[12] It is therefore of the utmost importance to identify molecules that can prevent the lung injury induced by MTX.[4,13]

Phytochemicals are defined as non-nutritive secondary plant metabolites. Despite their low nutritional value, they are included in an ideal diet because of their various important biological activities, including antioxidant, antigenotoxic and anti-inflammatory properties.[14] *p*-Coumaric acid (PCA) is a member of the phenolic acid subgroup, which constitutes the most comprehensive phytochemical subgroup. It serves as an initial substrate for the production of numerous phenolic compounds in plants.[15] Particularly the antioxidant, antimicrobial and anti-inflammatory properties of PCA have increased its use in the food and cosmetic industries.[15,16] Although previous studies have demonstrated the potential of PCA to abolish cisplatin[17,18] and doxorubicin[19,20] induced tissue damage in experimental studies, no studies have evaluated the effectiveness of PCA against MTX-induced pulmonary toxicity to date. Therefore, the focus of this study was to investigate the therapeutic effect of PCA on MTX-induced pulmonary toxicity in rats through biochemical mechanisms.

METHODS

Animals and experimental design

A total of thirty female Sprague-Dawley rats (aged 8-10 weeks) were housed in an environmentally controlled room at a temperature of 21±1°C under a 12-h light/dark cycle. The animals were given free access to standard laboratory chow and water and were acclimatised for one week prior to the study. The protocol was approved by the Local Animal Ethics Committee of Karadeniz Technical University (Protocol Number: 2023/06).

The animals were randomised into 5 groups: control, only MTX administered (MTX), MTX combined with PCA (2 and 4 mg/kg) and only high-dose PCA (4 mg/kg) administered. All drug administration was performed intraperitoneally. MTX and PCA (Sigma, St. Louis, MO, USA) were prepared by dissolving in physiological saline[21-23] and 20% ethanol[17,24], respectively.

Group I (Control): On the first day, the subjects received saline. Thereafter, for a period of three days, the subjects received 20% ethanol.

Group II (MTX): On the first day, the subjects received MTX (20 mg/kg). Thereafter, for a period of three days, the subjects received 20% ethanol.

Group III (MTX+low dosage PCA): On the first day, the subjects received MTX (20 mg/kg), followed by a 3-day course of PCA (2 mg/kg).

Group IV (MTX+high dosage PCA): On the first day, the subjects received MTX (20 mg/kg), followed by a 3-day course of PCA (4 mg/kg).

Group V (only high-dose PCA): On the first day, the subjects received saline. Thereafter, the subjects were administered PCA (4 mg/kg) for 3 days.

The experimental regimen and doses of MTX[21-23] and PCA[18,25] were determined based on previous studies. The 24 h after the last treatment, the animals were euthanised by cervical dislocation under general anaesthesia and the collected lung tissues were stored for further biochemical investigations.

Biochemical analysis

The samples (10% w/v) were homogenised in phosphate buffered saline (PBS), centrifuged at 1800xg for 10 min at 4ºC, and the clear supernatant was collected. Protein levels of the supernatants were determined using a commercially available colorimetric kit according to the

bicinchoninic acid protein assay (BCA) method[26], following the manufacturer's recommendations (Pierce BCA Protein Assay Kit, Thermo Scientific, Rockford, IL). Briefly, 25 µL of serially diluted bovine serum albumin (BSA) standards and supernatants (diluted 5-fold with PBS) were pipetted into the wells of a 96-well microplate, and 200 µL of BCA working reagent was added to each well and incubated at 37°C for 30 min. After incubation, the plate was cooled to room temperature and absorbances were measured at 562 nm in a microplate reader spectrophotometer (Versamax, Molecular Devices, CA, USA). A concentration vs. absorbance graph was then plotted for the BSA standards and the protein content of the samples was determined from this graph using the absorbance values of the samples.

MDA content was assessed using the previously described method.[27] The supernatant was mixed with 3 mL of 1% phosphoric acid and 1 mL of 0.672% thiobarbituric acid. The mixture was vortexed and then incubated in a boiling water bath for 1 h. The tubes were then allowed to cool at room temperature and centrifuged at 1800xg for 10 min. Two hundred microliters of each supernatant were transferred to a 96-well plate and the absorbance was read at 532 nm using a microplate reader (Versamax, Molecular Devices, CA, USA). 1,1,3,3-tetramethoxypropane was used as a standard, and the tissue MDA levels were expressed as nmol/mg protein.

The total antioxidant status (TAS) and the total oxidant status (TOS) in lung tissue were quantified using commercially available kits (Rel Assay Kit Diagnostics, Gaziantep, Turkey) and the OS index (OSI) was calculated.[28] The levels of the antioxidant system (with the superoxide dismutase (SOD) parameter), inflammation (with the TNF-α parameter) and apoptosis (with the caspase-3 (CASP3) parameter) in lung tissue were determined using commercial ELISA kits (BT LAB, Zhejiang, China).

Statistical analysis

Statistical analysis of data was performed using SPSS (Version 23.0, NY, USA). All results were presented as mean± the standard error of the mean (SEM). The Kolmogorov-Smirnov test was used to assess the suitability of the data for normal distribution. ANOVA was used to analyse data showing normal distribution, and Tukey's post-hoc test was used for comparisons between groups. The significance level was set at $p<0.05$.

RESULTS

The effect of PCA on MTX-induced lung toxicity was evaluated in terms of OS, inflammation and apoptosis parameters and the results were presented in Table 1. MTX administration resulted in a notable elevation in the levels of lung MDA, TOS and OSI, whereas PCA treatments demonstrated a dose-dependent reduction in MDA, TOS and OSI levels.

The antioxidant capacity of lung tissue in rats treated with MTX was evaluated using(TAS and SOD parameters. The administration of MTX was found to result in a significant reduction in the levels of lung TAS and SOD. Conversely, the administration of PCA demonstrated a dose-dependent improvement in TAS and SOD levels.

The levels of inflammation and apoptosis in the lung tissue were evaluated using two distinct parameters: TNF-α and CASP3, respectively. MTX triggered a significant elevation in the levels of lung TNF-α and CASP3. Conversely, PCA treatments dose-dependently largely abolished inflammatory and apoptotic processes.

Table 1. Effect of PCA treatments on OS, inflammatory and apoptosis parameters

	Control	PCA (4 mg/kg)	MTX (20 mg/kg)	MTX+PCA (2 mg/kg)	MTX+PCA (4 mg/kg)
MDA (nmol/mg protein)	8.94±0.35	9.47±0.39	21.75±1.76***	12.09±0.52$^{\#\#\#}$	10.53±0.81$^{\#\#\#}$
TOS (µM H_2O_2 equivalent/L)	20.41±0.37	23.39±1.31	33.06±1.56**	25.79±1.98	23.98±3.38$^{\#}$
TAS (mM trolox equivalent/L)	8.47±0.09	8.11±0.28	3.72±0.40***	6.45±0.29$^{**,\#\#\#}$	7.27±0.43$^{\#\#\#}$
OSI (arbitrary unit)	0.24±0.01	0.29±0.02	0.94±0.09***	0.40±0.02$^{\#\#\#}$	0.34±0.05$^{\#\#\#}$
SOD (ng/mg protein)	0.39±0.03	0.38±0.03	0.20±0.02*	0.31±0.03	0.39±0.07$^{\#}$
TNF-α (pg/mg protein)	11.17±1.51	11.44±1.52	42.21±5.51***	24.03±3.01$^{*,\#\#}$	12.40±1.27$^{\#\#\#}$
CASP-3 (ng/mg protein)	0.27±0.02	0.21±0.01	0.71±0.08***	0.41±0.05$^{\#\#}$	0.23±0.04$^{\#\#\#}$

MTX: methotrexate, PCA: *p*-coumaric acid, MDA: malondialdehyde, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, SOD: superoxide dismutase, TNF-α: tumor necrosis factor-alpha, CASP3: caspase-3.
P-values according to one-way ANOVA test, post-hoc Tukey test. Data were expressed as mean±SEM.
Compared with control group $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$. Compared with MTX group $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$.

DISCUSSION

This study focused on elucidating the therapeutic potential of PCA in an *in vivo* model of MTX-induced pulmonary toxicity through biochemical mechanisms. Although the primary mechanism of MTX toxicity in the lungs remains to be fully elucidated, it is evident that OS, inflammation and apoptosis represent the principal mechanisms.[6,29] OS causes damage to nucleic acid, carbohydrate, lipid, protein and enzymes.[30] Lipids are biomolecules susceptible to OS, and increased ROS accelerate lipid peroxidation (LPO), resulting in the formation of various reactive aldehyde derivatives, including MDA.[20] The TOS, TAS and OSI have been employed with considerable frequency in recent years as straightforward and useful parameters for evaluating the overall OS degree in a biological sample.[31] SOD is an important cytoprotective enzyme that prevents the conversion of superoxide radicals to hydroxyl radicals.[32] Similar to previous literature[5,33,34], the findings indicated that MTX administration resulted in elevated LPO and OS levels in lung tissue and a diminished capacity of antioxidant system. Conversely, the administration of PCA following MTX has been observed to enhance the antioxidant system and to reduce LPO and OS levels dose-dependently. This observed improvement may be attributed to the potential of PCA as a phenolic acid to scavenge ROS and increase the endogenous cellular antioxidant capacity.[18,35] Similarly, the *in vivo* antioxidant activity of PCA has been previously determined in various experimental studies.[17,19,35,36]

Other mechanisms implicated in MTX-induced lung toxicity include inflammatory response and apoptosis.[5,18,37] Although inflammation is an acute adaptive response of the body to an invading attack, in the process of chronic inflammation, the sustained production of TNF-α increases tissue destruction, resulting in the activation of CASP3.[6] CASP3 activation is the main indicator that a cell has entered the irreversible apoptotic process.[29] In addition, high levels of MDA and TNF-α can induce apoptosis by activating CASP3.[5] Similar to previous literatures[5,8,13,29], findings showed that MTX administration triggered inflammatory and apoptotic processes. Conversely, the administration of PCA following MTX has been observed to suppressed these processes dose-dependently. It can be suggested that the potential antioxidant activity of PCA may be the main source of the improvement that was observed.[16,35] Similarly, the *in vivo* anti-inflammatory and anti-apoptotic activity of PCA has been previously determined in various experimental studies.[18,20,36,38]

CONCLUSION

Our findings provide new information that PCA may ameliorate MTX-associated pulmonary toxicity by suppressing OS, inflammatory, and apoptotic processes. However, this new information needs to be supported by more comprehensive analyzes in the future.

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Authorship contribution statement

Consept and desing: SD.

Acquisition of data: SD, NTA, EAD and AM.

Analysis and interpretation of data: SD, NTA, EAD, AM and YA.

Drafting of the manuscript: SD.

Critical revision of the manuscript for important intellectual content: YA.

Statistical analysis: AM.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol no: 2023/06) and performed according to the animal research reporting of in vivo experiments (ARRIVE) guidelines.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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