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Original Article

Protective effect of curcumin against perfluorooctane sulfonate induced oxidative stress

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ABSTRACT

Background and Aims: The potential effects of perfluorooctane sulfonate (PFOS) on the environment and human health have aroused great concerns in recent years. To our knowledge, there are limited studies related with the effect of curcumin on PFOS induced damage in the literature. The existing studies are focused on DNA damage. No study has been found examining the effect on the antioxidant system. We planned this study to investigate the impact of curcumin on the antioxidant defense system response in rats exposed to PFOS.

Methods: The animals were divided into six groups, with the first group used as control. Groups II to VI were orally treated with curcumin (80 mg/kg), PFOS (1.25 mg/kg), PFOS (1.25 mg/kg) + curcumin, PFOS (2.5 mg/kg), and PFOS (2.5 mg/kg) + curcumin daily for 30 days, respectively. For oxidative stress, liver, kidney, and brain samples were homogenized. The activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) activities, and malondialdehyde (MDA) content were determined. Data from the experiments were statistically analyzed by SPSS 11.0 program.

Results: Our data showed that PFOS increased MDA level, while the activities of SOD and CAT decreased. It was observed that the application of curcumin together with PFOS decreased the MDA level and increased the antioxidant enzyme activities.

Conclusion: As an antioxidant, curcumin plays an important protective role against oxidative damage and inhibits PFOS-induced lipid peroxidation.

Keywords: Curcumin, perfluorooctane sulfonate, antioxidant, oxidative stress, lipid peroxidation.

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INTRODUCTION

Perfluorooctane sulfonate (PFOS, $C_8F_{17}SO^{3-}$) is an associate of the class known as fluorochemical compounds (PFCs). PFOSs are compounds that are synthesized in industry and are highly resistant to degradation (Endirlik & Gürbay, 2018). These compounds have a wide range of use in many industrial and commercial areas, such as carpets, leather, and food (repellent coatings), various surfactants, as well as cosmetics and firefighting foams (Dorts et al., 2011). People can be exposed to PFOS through consumption of contaminated food and drinking water, breathing air, and contaminated environments (Pachkowski, Post, & Stern, 2019). After exposure, PFOS enters the cells of various organs and then interacts with macromolecules such as protein and DNA, causing direct oxidative damage and a range of cytotoxic effects such as cell death (Zhang et al., 2015; Beesoon & Martin, 2015). After 24 h exposure to PFOS, increased reactive oxygen species (ROS) and significant DNA damage are observed in the human hepatoma cell line (HepG2) (Wielsøe, Long, Ghisari, & Bonefeld-Jorgensen, 2015).

It has been reported that PFOS causes a decrease in fertility in women, a decrease in sperm quality in men, low birth weight, hyperactivity, an increase in total and LDL cholesterol levels, and changes in thyroid hormone levels (Ceccatelli et al., 2018; Grasl-Kraupp et al., 2020). In addition to the above-mentioned disorders, it has been reported that there is an increased risk of developing prostate and bladder cancer in those working in the production facilities of such chemicals (Tsuda, 2016).

Aerobic organisms affect oxygen consumption due to cell growth that leads to the formation of reactive oxygen species (ROS). According to reports, the generation of ROS is a significant apoptotic signal. These ROS comprise radicals, like excited oxygen species, superoxide anion radicals, hydroxyl radicals, hydrogen peroxide, and singlet oxygen. Free radicals that occur during physiological events are kept with antioxidant activity. The levels of these reactive oxygen metabolites increase when antioxidant activity is inadequate or antioxidant activity is insufficient. Reactive oxygen metabolites can attack and damage macromolecules, including DNA. Furthermore, lipid peroxidation products formed by oxidative degradation of polyunsaturated fatty acids can cause cellular damage. DNA damage may cause changes in cell function. A large proportion of such DNA damage leads to carcinogenic events (Comporti, 1989).

Curcumin is an important polyphenolic compound obtained from the rhizomes of Curcuma longa L. (turmeric) (Bright, 2007). The medicinal properties of curcumin are due to the curcuminoids in its structure and the main component in the rhizome containing curcumin (diferuloylmethane)–(1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5,dione (Figure 1) (Maheshwari, Singh, Gaddipati, & Srimal, 2006). Curcumin, used as a traditional medicinal plant, has various therapeutic properties, which include anti-inflammatory, antibacterial, and anticancer (Rathore et al., 2020). Its antioxidant property is controlled by different enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxide (GPx) (El-Hack et al., 2021).

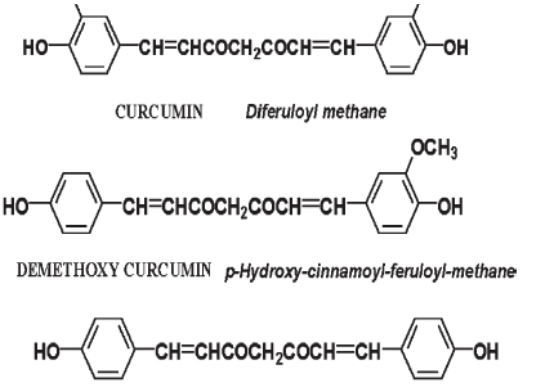

Figure 1. Chemical structure of curcumin. Curcuminoids, demethoxycurcumin, and bisdemethoxycurcumin curcumin which show anti-inflammatory and antioxidant properties[5].

Curcumin has more antioxidant effects than the antioxidant vitamins C and E (Mughal, 2019). Previous research has shown that curcumin has a defensive effect in various tissues against toxic agents (Hosseini & Hosseinzadeh, 2018). It has been also shown the ability of curcumin to protect against liver damage from some xenobiotics (Farzaei et al., 2018). Curcumin has been proven to be efficient in protecting against liver damage and fibrogenesis by reducing oxidative stress in the presence of carbon tetrachloride (CCl4) (Reyes-Gordillo et al., 2007; Fu, Zheng, Lin, Ryerse, & Chen, 2008). In addition, curcumin has been shown in various animal models to inhibit lipid peroxidation (Maheshwari, et al., 2006). The potential environmental and human health threats of exposure to PFOS have aroused great concerns in recent years. As with many environmental pollutants, in vivo and in vitro animal experiments are the main way to determine the human health risks and PFOS's toxic effects (Ceccatelli et al., 2018; Solan & Lavado, 2020).

In laboratory animal studies, exposure to PFOS has been reported to be associated with hepatotoxicity (Xu, Jiang, Liu, Liu, & Gu, 2017), neurotoxicity (Long et al., 2013), reproductive toxicity (Lopez-Doval, Salgado, Pereiro, Moyano, & Lafuente, 2014), immunotoxicity (Zheng, Dong, Jin, & He, 2009), pulmonary toxicity (Qin et al., 2017) and renal toxicity (Tang, et al., 2022). in numerous in vitro human cell lines.

Eke & Çelik (2016), showed that DNA damage in mouse peripheral blood using single-cell gel electrophoresis/comet test and a micronucleus test in vivo and showed that all PFOS concentrations increased the micronucleus frequency and curcumin reduced DNA damage induced by PFOS. These findings, and the associated epidemiological studies, confirm the damaging consequences of PFOS on human health (Ceccatelli et al., 2018; Qin, Ren, Zhao, & Guo, 2022). Although the toxic effect of PFOS has been investigated, more research is needed and as far as we know, but there are limited studies on the effect of curcumin on PFOS in the literature. These studies focused on DNA damage, and no studies examining the effect on the antioxidant system were found. In this study, it was aimed to determine whether curcumin substance has a protective effect against PFOS-induced oxidative damage.

MATERIALS AND METHODS

Chemicals

PFOS (CAS No.: 1763-23-1) and curcumin (chemical purity >99%) were purchased from Sigma (St. Louis, MO, USA). All other chemicals and reagents were purchased from Sigma-Aldrich, Merck and all were analytical grade.

Animals groups and treatment

In this study, 36 adult male Wistar albino rats weighing 180-200 g were used. All experimental protocols were approved by the Mersin University Animal Experiments Local Ethics Committee (2010/ HADYEK/67). The rats were given standard rat chow and pipe water, with a 12 h light/12 h dark rhythm, in a room at a temperature (22±2 °C). The animals were divided into six groups, with the first group used as control. Groups II to VI were orally treated with curcumin (80 mg/kg), PFOS (1.25 mg/kg), PFOS (1.25 mg/kg) + curcumin, PFOS (2.5 mg/kg), and PFOS (2.5 mg/kg) + curcumin daily for 30 days, respectively.

All the concentrations of PFOS and curcumin used in the current study were selected based on earlier studies (Eke & Çelik, 2016).

The liver, kidney, and brain tissues of rats were isolated under anesthesia (ketamine 200 mg/kg i.p.) Then, the tissues were homogenized with phosphate buffer (25 mM, pH = 7.4) to make approximately 10% w/v homogenates. The obtained homogenates were centrifuged at +4 °C for 10 minutes at 13,000 rpm. Up until analysis, the supernatant portion was kept at -20 °C. The MDA levels, SOD, and CAT activities were examined in homogenized tissues.

Determination of SOD enzyme activity

This method is based on the reduction of nitroblue tetrazolium by superoxide radicals formed through the xanthine/xanthine oxidase (Sun, Oberley, & Li, 1988). The color (blue-violet) formed as a result of the reaction was measured spectrophotometrically at 560 nm. Specific activity was expressed as U/mg protein.

Determination of CAT enzyme activity

The CAT activity was assessed spectrophotometrically by the process described by Aebi (Aebi, 1984). The principle of the method is the catalytic degradation of the H_2O_2 substrate at 240 nm. The enzyme activities are given in U/mg protein.

Determination of lipid peroxidation

The MDA determination as the final product of lipid peroxidation was measured according to the process reported by Yagi, Nishigaki, & Ohama (1968). A total of 750 µL of thiobarbituric acid was added to 50 µL of tissue homogenate. Then, the obtained mixture was incubated at 95 °C for 30 min and then centrifuged at 3500 rpm for 15 min. Absorbance was measured at 560 nm by a spectrophotometer. The results were expressed as nmol/mg of protein.

Protein determination

Using a method created by Lowry, Rosebrough, Farr, & Randall (1951), the protein concentrations of the tissue homogenates were examined to identify the specific activity of the antioxidant enzymes. Bovine serum albumin was used as a reference protein. The total protein content of the samples was determined by measuring with a spectrophotometer at a wavelength of 750 nm.

Statistical analysis

The SPSS 11.0 statistical program was used for all statistical evaluations. The one-way analysis of variance test (ANOVA) with Tukey's post-hoc test was used to determine the statistical difference between groups. The reported data were presented as mean ± standard deviation, with values having p-value <0.05 considered to be significant.

RESULTS

Figure 2 presents the SOD antioxidant enzyme activity in the liver, kidney, and brain tissues of rats belonging to the control, PFOS and PFOS+curcumin groups. Significant decreases ($p < 0.05$) in SOD enzyme activity were observed in all experimental groups, except for the curcumin group, when compared to the control group (group I). Compared to the group I, 1.6, 1.6, and 1.7-fold change for liver, kidney, and brain tissues were observed in group III, respectively. In group V, 1.7, 1.7, and 1.9-fold change for liver, kidney, and brain tissues compared to the group I were obtained. The curcumin group displayed higher SOD activity in all tissues than the control group. Additionally, group IV and group VI exhibited higher SOD activities compared to group III and group V. A mean 1.6-fold change in liver, kidney, and brain tissues was observed when comparing group IV with group III, and a mean 1.8-fold change was observed for all of these tissues when comparing group VI with group V.

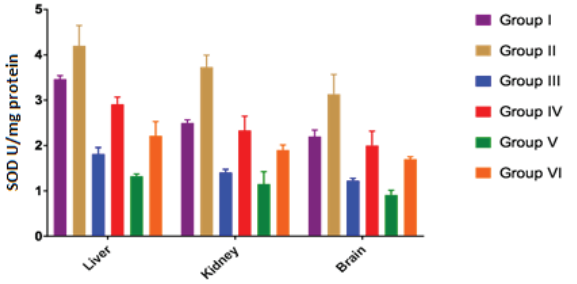

Figure 2. Activities of SOD in control, PFOS and PFOS+ Curcumin groups in liver, kidney, and brain tissues of rats.
Groups I: control, Groups II: curcumin (80 mg/kg), Groups III: PFOS (1.25 mg/kg), Groups IV: PFOS (1.25 mg/kg) + curcumin, Groups V: PFOS (2.5 mg/kg), Groups IV: PFOS (2.5 mg/kg) + curcumin

The findings of the CAT activity in the liver, kidney, and brain tissues are illustrated in Figure 3. No significant difference was observed between the control group and the curcumin group (group II) in all tissues ($p > 0.05$). However, when comparing the other groups (groups III-V) with the control group, CAT enzyme activity significantly decreased ($p < 0.05$). Group III exhibited a 0.5-fold change in liver tissue, a 0.4-fold change in kidney tissue, and a 0.3-fold change in brain tissue compared to the control group (group I). In group V, a 0.2-fold change was observed for all the tissues studied compared to group I. CAT activity declined in animals treated with low-dose PFOS (group III) and high-dose

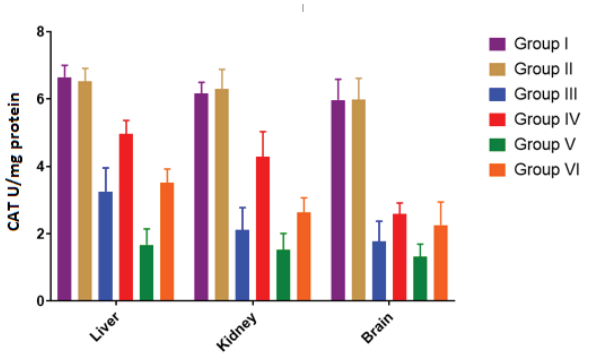

Figure 3. Activities of CAT in control, PFOS and PFOS+Curcumin groups in liver, kidney, and brain tissues of rats.
Groups I: control, Groups II: curcumin (80 mg/kg), Groups III: PFOS (1.25 mg/kg), Groups IV: PFOS (1.25 mg/kg) + curcumin, Groups V: PFOS (2.5 mg/kg), Groups IV: PFOS (2.5 mg/kg) + curcumin.

PFOS (group V), while a significant increase in CAT enzyme activities was observed in the groups exposed to PFOS+curcumin (group IV, group VI). Comparing group IV with group III, a mean 1.7-fold change was observed for liver, kidney, and brain tissues, while a mean 1.9-fold change was observed for all these tissues when comparing group VI with group V.

The levels of MDA in the tissues are given in Figure 4. A comparison between the results of the control and curcumin groups showed no significant difference. However, lipid peroxidation, as indicated by MDA levels, significantly increased in the PFOS groups compared to the control group (group I) ($p < 0.05$). Compared to the control group (group I), 2.5-fold change for liver tissue, 5-fold for kidney tissue, and 9.4-fold for brain tissue were observed in group III. In group V, 4.7-fold change for the liver, 6-fold for the kidney, and 10.5-fold for the brain were detected. The highest increase was defined in the group exposed to high-dose PFOS. Treatment with curcumin after PFOS exposure significantly decreased the MDA levels. In the comparison of group IV with group III, a mean 0.34-fold change was observed for liver, kidney and brain tissues. Furthermore, when group VI was compared with group V, a mean 0.45-fold change was discerned for all of these tissues.

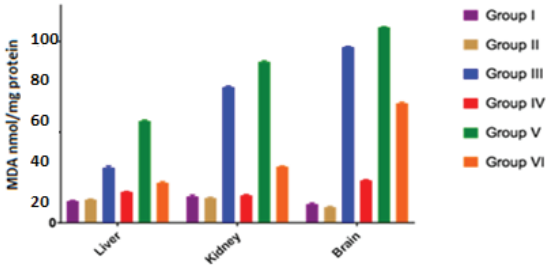

Figure 4. Level of MDA in control, PFOS and PFOS+ Curcumin groups in liver, kidney, and brain tissues of rats.
Groups I: control, Groups II: curcumin (80 mg/kg), Groups III: PFOS (1.25 mg/kg), Groups IV: PFOS (1.25 mg/kg) + curcumin, Groups V: PFOS (2.5 mg/kg), Groups IV: PFOS (2.5 mg/kg) + curcumin

DISCUSSION

Oxidative stress occurs as a result of an imbalance between free radicals and the antioxidant defense system. This can lead to the loss of the functions of these basic biomolecules and the formation of many diseases (Xu, Meng, Li, Gan, Li, & Li, 2018).

Curcumin is widely used as colorant and spice. This bright yellow curcuminoid includes various functional antioxidant groups, such as the β-diketo group, carbon-carbon double bonds, and phenyl chains. Due to these properties, curcumin converts to a phenoxy radical by removing lipid radicals in the cell membrane. Therefore, this compound is accepted as a very effective natural antioxidant. It was also found that curcumin inhibited lipid peroxidation and neutralized reactive oxygen species (superoxide, hydroxyl radicals) (Farzaei et al., 2018).

PFOS is a member of the Per- and Polyfluoroalkyl Substances chemical class (PFAS). The exceptional resistance of PFOS to environmental degradation is due to the strong chemical bond between carbon and fluorine atoms. The motility, toxicity, and bioaccumulation possibility of this chemical cause potential adverse effects on the environment and human health (Torres, Redko, Limper, Imbiakha, Chang, & August, 2021; Endirlik & Gürbay, 2018). A thorough research of the potentially harmful effects on living things has become more important as a result of the increasing usage of PFOS in industries and cosmetic applications. (Dhore & Murthy, 2021).

There is no study in the literature about the effects of curcumin with antioxidant properties on oxidative damage caused by PFOS in rat liver, kidney, and brain tissues. In this study, we investigated whether oxidative damage induced by PFOS on the liver, kidney, and brain tissues of rats and curcumin have a possible protective effect against this oxidative damage or not. Our study's findings demonstrated that PFOS administered at different concentrations in rat liver, kidney, and brain tissues caused oxidative damage. Furthermore, a reduction in SOD and CAT enzyme activities was detected in the PFOS treated tissues. There was a significant increase in the MDA levels. Moreover, our findings correlate with previous studies showing that the toxicity of PFOS is closely related to ROS production and the induction of oxidative stress (Xu et al., 2013; Wang et al., 2020) Xing et al. (2016) treated liver tissue homogenates of adult male C57BL/6 mice with PFOS at different doses (2.5, 5 or 10 mg PFOS/kg BW/day) for 30 days and examined the SOD, CAT and MDA levels. They found that SOD and CAT activities in the liver decreased significantly depending on the increased PFOS dose, while MDA levels were significantly higher compared to the control (Xing et al., 2016).

Mandour et al. (2022) exposed adult male albino rats to PFOS (20 mg/kg/day) for 28 days and determined that the antioxidant enzyme levels (SOD and CAT) in the liver tissue of the rats decreased significantly and MDA levels increased (Mandour, Maher, Abd El, & Moawad, 2022). Treatment with 100 µM PFOS for 24 hours has been reported to induce ROS production in renal tubular cells (Lee et al., 2022). It was determined that the levels of MDA, a critical marker for oxidative stress, in the kidney tissues of rats exposed to PFOS (20 µM

and 60 μM) for 24 hours were significantly higher than the control group (Tang, Yu, Zhuge, Chen, Zhang, & Jiang, 2022). In one study, it was determined that PFOS (100 μM) exposure for 1, 3, 6 and 24 hours significantly increased ROS production in renal tubular cells (Wen, Chen, Lee, Ko, Chou, & Juan, 2021). Antioxidant enzymes like SOD and CAT are crucial in mammalian cells for blocking superoxide and hydroxyl ions (Sankar, Telang, & Manimaran, 2018). It has been shown that PFOS causes oxidative stress in a dose-dependent manner, not only by producing ROS, but also by reducing levels of antioxidants like SOD and CAT. This has been shown to cause a weakening of the antioxidant defense systems and induce tissue damage. In addition, in this study, the increase in lipid peroxidation value shows impairment of the membrane foundation. These changes in the MDA, CAT, and SOD values were more strong in the high dose PFOS-exposed rats as compared to rats treated with low dose PFOS. The response of the antioxidant system to oxidative stress shows variations among species (Adonaylo & Oteiza, 1999). In our study, the highest decrease in SOD and CAT enzyme activities and increase in MDA levels were detected in the brain tissue treated with PFOS. The brain was found to be more vulnerable to oxidative damage than the liver and kidney. The brain, which contains large amounts of polyunsaturated fatty acids, may be particularly sensitive to oxidative damage. When the natural structure of these organs is disturbed by toxicants or other stimulants, all of the essential physiological processes may get imbalanced. Their toxicities are fundamental biosafety assessment markers for novel medicines (Kanwal et al., 2019).

In our study, the antioxidant enzyme activities increased while there was a significant decrease in the MDA levels in the PFOS+curcumin treated group compared to the group treated with PFOS. The antioxidant mechanism of curcumin interacts with the oxidative cascade and can neutralize free radicals. Curcumin inhibits MDA production to improve antioxidant levels in PFOS-treated sensitive to oxidative stress.

Studies have shown that curcumin can directly remove free radicals and prevent ROS production (Tapia et al., 2014). In a study conducted by reducing the amount of curcumin oxidative stress, inflammation, and apoptosis, the colistin-induced nephrotoxicity and neurotoxicity was determined to be decreased (Edrees, Galal, Monaem, Beheiry, & Metwally, 2008). Curcumin has been found to have an important hepatoprotective effect against liver damage induced by ochratoxin A, CCl_4, sodium florid, and heavy metals in adult rats (Damiano et al., 2021; Park, Jeon, Ko, Kim, & Sohn, 2000; Moghaddam et al., 2015; García-Niño &

Pedraza-Chaverrí, 2014). In a previous study, rats treated with PTZ (pentylenetetrazole) for 35 days were given different doses of curcumin (50, 100, 200 mg/kg) and a dose-dependent reduction in MDA levels in brain tissue (Agarwal, Jain, Agarwal, Mediratta, & Sharma, 2011). In a study performed by AL-Harbi et al., curcumin application (60 mg/kg) was found to have hepatoprotective effects on oxidative stress induced by sodium fluoride, and it also decreased hepatotoxicity and liver enzyme activities (AL-Harbi, Hamza, & Dwary, 2014). In a previous work, it has been shown that Turmeric reduces cell viability in the L-02 human fetal hepatocyte cell line, prevents oxidative stress, and inhibits SOD activities and GSH levels. (Dai, Tang, Li, Zhao, & Xiao, 2015). In another study, curcumin administered to rats exposed to cadmium, a common environmental heavy metal pollutant, has been shown to have the capability to reduce lipid peroxidation and increase GSH levels (Eybl, Kotyzová, & Bludovská, 2004). Singh et al. stated that curcumin can be a powerful protective agent on lindane-induced hepatotoxicity (Singh & Sharma, 2011).

In conclusion, our study demonstrates that curcumin has a protective effect against oxidative damage caused by PFOS in the liver, brain, and kidney tissues of rats. These protective effects of curcumin are basically related to its antioxidant properties. Our findings highlight the toxicity of PFOS exposure and indicate that careful consideration should be given to PFOS use because it may have detrimental effects on humans.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- P.E., D.E.; Data Acquisition-P.E., S.Y.; Data Analysis/Interpretation- A.E.Y., P.E.; Drafting Manuscript- P.E., D.E.; Critical Revision of Manuscript- A.Ç., A.E.Y.; Final Approval and Accountability P.E., D.E., S.Y., A.Ç., A.E.Y.

Ethics Committee Approval: This study was approved by the Ethical Animal Research Commite of Mersin University.

Conflict of Interest: The authors have no conflict of interest to declare.

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