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The Effects of Caffeic Acid Phenethyl Ester and Ellagic Acid on the Levels of Malondialdehyde, Reduced Glutathione and Nitric Oxide in the Lung, Liver and Kidney Tissues in Acute Diazinon Toxicity in Rats

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Abstract: The aim of this study was to investigate the effects of Caffeic Acid Phenethyl Ester (CAPE) and Ellagic Acid (EA) on acitivities of Malondialdehyde (MDA), reduced Glutathione (GSH) and Nitric Oxide (NO) in rat lung, liver and kidney tissues in acute Diazinon (DI) toxicity. Six groups of 6 Sprague Dawley rats were used comprising control, CAPE, EA, DI control, DI+CAPE and DI+EA. Tissue samples were analysed for GSH, MDA and NO levels in lung, liver and kidney tissues. Biochemical parameters were measured colormetrically by spectrophotometer. Control, CAPE and EA groups showed no statistically significant difference whereas DI+medication groups revealed that CAPE and EA increased the level of GSH in liver tissue by blocking the DI effect. NO levels in lung, liver and kidney tissues were significantly increased by DI but CAPE and EA attenuated those levels. In DI+medication groups, MDA levels showed no significant change in kidney and liver tissues but in lung tissues, CAPE and EA reduced the MDA level by blocking the DI effect. It was concluded that CAPE and EA which showed similar effects to each other could be used for protection and support against oxidative stress caused by acute DI intoxication.

Key words: Caffeic acid phenethyl ester, diazinon, ellagic acid, malondialdehyde, nitric oxide, reduced glutathione

INTRODUCTION

Organophosphates (OPs) are one of the main classes of insecticides in use since the mid 1940s (Gallo and Lawryk, 1991). Organophosphorus Insecticides (OPIs), widely used in agriculture show several interesting features for environmental safety such as limited persistence and selective toxicity to insects with respect to mammals (Vittozzi *et al*., 2001; Sutcu *et al*., 2007). Therefore, the toxic material chos for this study was Diazinon (DI) as an OPI often causing human and animal poisoning.

DI(o,o-diethyl-o-[2-isopropyl-6-methyl-4-pyrimidinyl] phosphorothioate) has been greatly and effectively used throughout the world with applications in agriculture and horticulture for controlling insects in crops, ornamentals, lawns, fruits, vegetables and as a pesticide in domestic applications (International Program on Chemical Safety and WHO, 1997; Garfitt *et al*., 2002; Dutta and Meijer, 2003; Amirkabirian *et al*., 2007). Whatever the route of exposure, DI by the process of inhibiting Acetylcholinesterase (AChE), affects particularly the nervous system causing poisoning. The indications of DI poisoning are nausea, vomiting, stomach cramps, slow

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pulse, diarrhea, headache, dizzyness, general weakness, anxiety, blurred vision, respiratory difficulties, coma and finally death. Previous studies have revealed the important role played by oxidative tissue damage in the pathogenesis of the toxic effects (hepatotoxicity, neurotoxicity, genetic toxicity, embryotoxicity, immunotoxicity, etc.,) of acute and chronic DI application (Bachowski *et al*., 1997; Dutta and Meijer, 2003). However, there are still insufficient studies on why DI cause oxidative damage and on protective and supportive medications for that damage. Therefore potentially protective materials selected for this study was Caffeic Acid Phenethyl Ester (CAPE) and Ellagic Acid (EA). CAPE is an active component of honeybee propolis and it is known to have powerful antimicrobial, anti-inflammatory, antineoplastic and anti-oxidizing effects (Koltuksuz *et al*., 2000). According to previous studies, CAPE exerts its beneficial effects by decreasing free oxygen radicals and prevents consumption of free radical scavenging enzymes acting in parallel to these antioxidant enzymes (Koltuksuz *et al*., 2000; Ilter *et al*., 2004; Ogeturk *et al*., 2005). It has been shown that CAPE suppresses lipid peroxidation, inhibits lipoxygenase activities and tumour promotion. At a concentration of 10 μmol, CAPE completely blocks production of Reactive Oxygen Species (ROS) in human neutrophils and Xanthine/Xanthine Oxidase (XO) system (Yilmaz *et al*., 2005).

EA which is the other potentially protective agent to compare with CAPE in the this research is a polyphenol antioxidant found in certain fruits and nuts such as raspberries, strawberries, walnuts, loganberries, mango kernel and pomegranate (Thomas, 2001) which has been seen to have a variety of biological activities including potent anti-oxidant (Mican *et al*., 1992), anti-cancer (Shumilina *et al*., 2008) and anti-mutagen properties (Siebenlist *et al*., 1994) in a number of *in vitro* and small animal models. The aim of this study was to investigate the effects of CAPE and EA on acitivities of Malondialdehyde (MDA), reduced Glutathione (GSH) and Nitric Oxide (NO) in rat lung, liver and kidney tissues in acute DI toxicity.

MATERIALS AND METHODS

Animals, care and nutrition: A total of 36 adult female Sprague-Dawley rats weighing 200-250 g were used in the study. The rats were randomly allocated to 6 groups of 6 rats each. The animals were kept in laboratory conditions of a 12 h light/dark cycle at room temperature (21±3°C). The study was approved by Selcuk University Experimental Medical Research Centre Experimental Animals Ethics Committee.

Animals and treatment: The total 36 rats in the study were divided into 6 groups including 6 each: control (Group I) CAPE (Group II) (Sigma C8221) (10 μmol kg^{-1} dose administered intra peritoneal (ip)), EA (Group III) (E2250 Sigma, CAS Number: 476-66-4) (85 mg kg^{-1} dose administered orally (po)), DI (Group IV) (Basudin; Syngenta, Turkey) (200 mg kg^{-1} dose administered po) DI+CAPE (Group V) and DI+EA (Group VI). A total of 24 h after the medication administration, the animals were anesthetised with ketamine (50 mg kg^{-1} dose ip)+xylazine (5 mg kg^{-1} dose ip) then euthanised iva servical dislocation. Measurements were taken of Malondialdehyde (MDA), reduced Glutathione (GSH) and Nitric Oxide (NO) in the lung, liver and kidney tissues.

Biochemical parameters: Tissue samples from the liver, lung and kidney were collected for analysis of GSH, MDA and NO concentrations. Tissues were immediately removed and washed with 0.15 M KCl (at 4°C). The tissues were then homogenized in ice cold (A: 50 mM, H_2PO_4 ve B: 50 mM $Na_2HPO_4.2H_2O$A:B (v/v) = 1:1.5) by a homogenizator at 1600 rpm for 3 min. The homogenates were centrifuged at 5000 g at 4°C for 15 min. The supernatants were stored at -25°C until they were analyzed.

NO was measured colorimetrically using a spectrophotometer (PowerWave XS, BioTek, Instruments, Winooski, VT, USA) by the method of Miranda *et al*. (2001). For GSH and MDA concentrations, analyses (UV-1201, Shimadzu, Japan) were carried out by the method of Beutler *et al*. (1963) and Yoshioka *et al*. (1979), respectively.

Statistical evaluation: The data for biochemical parameters were analyzed by ANOVA then the post hoc Tukey test. All data were presented as mean±SE using SPSS Windows 10.0. A value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The results obtained and the statistical analysis of the results are shown in the Table 1. No statistically significant difference was determined between the groups in a comparison of the effects on MDA, GSH and NO parameters in liver kidney and lung tissue in the control CAPE and EA groups. These results showed that CAPE and EA used alone created no effect on MDA, GSH and NO levels in lung, liver and kidney tissues and as both medications showed similar effects on these molecules, their use alone in respect of oxidant-antioxidant defence mechanism did not generate any problems.

Table 1: The effects on MDA, GSH and NO parameters in liver kidney and lung tissue in the control CAPE and EA groups

	Experimental groups (n = 6)			
Parameters	Control	CAPE	Ellagic Acid (EA)	p-value
Liver				
MDA (nmol g^{-1} protein)	16.41±1.320	13.59±1.4900	11.94±1.4800	NS
GSH (μg g^{-1} protein)	15.53±1.050	16.34±0.9800	16.80±0.8200	NS
NO (nmol g^{-1} protein)	275.55±41.40	250.94±30.750	266.31±30.740	NS
Kidney				
MDA (nmol g^{-1} protein)	10.78±0.880	10.59±1.2100	10.65±1.0500	NS
GSH (μg g^{-1} protein)	9.95±0.360	11.61±0.8800	9.98±0.8800	NS
NO (nmol g^{-1} protein)	271.96±24.00	266.74±53.980	268.47±136.18	NS
Lung				
MDA (nmol g^{-1} protein)	25.56±2.800	24.61±1.7000	22.64±1.4600	NS
GSH (μg g^{-1} protein)	15.44±1.850	12.32±0.8100	14.18±2.1900	NS
NO (nmol g^{-1} protein)	962.23±138.8	930.65±192.41	950.55±144.07	NS

Values are expressed as means±SD for groups; Ns: Not statistically significant

Table 2: The effects on MDA, GSH and NO levels in liver kidney and lung tissue in the DI+CAPE, DI+EA and DI groups

	Experimental groups (n = 6)				
Parameters	Control	Diazinon	DI+CAPE	DI+Ellagic acid	p-value
Liver					
MDA (nmol g^{-1} protein)	$16.41±1.320^{a}$	15.60±0.65	15.53±1.480	15.42±1.7500	NS
GSH (μg g^{-1} protein)	$15.53±1.050^{ab}$	$15.07±2.24^{abc}$	$15.69±0.900^{ab}$	$17.13±1.3600^{a}$	p<0.05
NO (nmol g^{-1} protein)	$275.55±41.40^{c}$	$405.99±63.15^{abc}$	$365.28±39.190^{bc}$	$364.89±45.420^{bc}$	p<0.01
Kidney					
MDA (nmol g^{-1} protein)	10.78±0.880	13.27±1.190	13.25±1.5500	13.15±1.4700	NS
GSH (μg g^{-1} protein)	9.95±0.360	9.46±0.590	10.83±0.4000	8.50±0.9900	NS
NO (nmol g^{-1} protein)	$271.96±24.00^{b}$	$1134.01±183.5^{a}$	$762.34±106.89^{c}$	$929.19±120.19^{ac}$	p<0.001
Lung					
MDA (nmol g^{-1} protein)	$25.56±2.800^{c}$	$26.01±2.060^{a}$	$19.94±2.5900^{ab}$	$23.54±1.5400^{b}$	p<0.05
GSH (μg g^{-1} protein)	$15.44±1.850^{b}$	$22.87±3.170^{a}$	$17.44±1.4200^{ab}$	$15.32±1.9100^{b}$	NS
NO (nmol g^{-1} protein)	962.23±138.8	932.25±129.1	927.99±90.010	929.18±247.95	NS

Values are expressed as means±SD for groups; NS: Not statistically Significant; (a-c) Mean values with same superscripts (a-c) within the same row are different

An examination of the statistically significant values showed that in acute DI intoxication, CAPE and EA increased the level of the antoxidant agent GSH in the liver tissue by blocking the DI effect. In particular, EA was observed to increase the GSH level in the liver by a greater amount, in comparison with CAPE. When the DI, DI+CAPE and DI+EA groups were compared in respect of NO levels, DI had increased the NO levels in both liver and kidney tissues by a significant amount in comparison to the control group. The reason for DI to cause a great increase in NO levels orginates from a large amount of DI having been administered over an acute 24 h period thus creating severe damage so the conclusion was reached that excessive amounts of DI increase NO expression. In a comparison of MDA levels between the DI, DI+CAPE and DI+EA groups, no significant change was determined in the kidney and liver tissues. However, in the lung tissues, it was determined that the increase in MDA level caused by DI had been reduced by CAPE and EA blocking the DI effect (Table 2).

The most important feature of DI and OPI toxicity is related to their irreversible blood AChE inhibition which at high doses could lead to animal and human death (Neishabouri *et al*., 2004). However, some studies indicate that oxidative stress could be an important component in the mechanism of toxicity of OPIs. OPIs may induce oxidative stress, leading to generation of free radicals and alterations in antioxidants (Bagchi *et al*., 1995; Ahmed *et al*., 2000; Gultekin *et al*., 2000; Sutcu *et al*., 2007). The cell has several mechanisms to deal with the effects of oxidative stress either by repairing the damage or by directly diminishing the occurrence of oxidative damage by means of enzymatic and nonenzymatic antioxidants. Some studies have shown that LPO has been suggested as one of the molecular mechanisms involved in OPI-induced toxicity (Yamano and Morita, 1992; Bagchi *et al*., 1995; Sutcu *et al*., 2007).

Acute exposure of rats to dimethoate was found to alter the activity of several antioxidant enzymes in the liver and brain (Sharma *et al*., 2005). Following acute administration of chlorpyrifos in rats, levels of Thiobarbituric Acid Reactive Substances (TBARS) increased in the liver (Bagchi *et al*., 1995), brain (Verma and Srivastava, 2001), kidney (Oncu *et al*., 2002) and erythrocytes (Gultekin *et al*., 2001). High doses of diisopropylfluorophosphate (an OP not used as an insecticide) were found to trigger excessive nitric oxide production in the brain (Gupta *et al*., 2001). Repeated

administrations of malathion, endosulfan or chlorpyrifos to rats were also found to increase lipid peroxidation and alter antioxidant enzymes in blood, liver and lungs (Ahmed *et al*., 2000; Akhgari *et al*., 2003; Bebe and Panemangalore, 2003). When various antioxidants were administered, they were reported to antagonize the oxidative stress induced by OPs (Ahmed *et al*., 2000; Gultekin *et al*., 2001; Gupta *et al*., 2001; Karaoz *et al*., 2002; Oncu *et al*., 2002; Cankayali *et al*., 2005; Giordano *et al*., 2007).

This study researched the effects of CAPE and EA on MDA, NO and GSH levels in acute DI toxicity. One of the marker agents of this study, NO has been implicated in the mechanisms of cell injury and long-term physiological changes in cellular excitability. Celik *et al*. (2007) found that NO levels were significantly increased in the Pyelonephritis groups (PYN) caused by Escherichia coli compared with the control group ($p<0.05$). On the other hand, CAPE treatments significantly decreased the pathogen-induced elevation in NO levels similar to that seen with MDA.

Altug *et al*. (2008) found that CAPE treatment significantly attenuated the elevation of plasma MDA content ($p<0.05$) whereas it significantly increased the levels of plasma GSH and NO ($p<0.05$) in adult male New Zealand rabbits which was induced by microsurgical procedures producing right focal Permanent Middle Cerebral Artery Occlusion (PMCAO).

Ozyurt *et al*. (2007a) revealed that I/R injury led to increases in MDA and NO levels in both skeletal muscle tissue and plasma. In contrast, CAPE led to a decrease in MDA and NO levels in both plasma and muscle tissue.

Ozyurt *et al*. (2007b) found that Malondialdehyde (MDA) and Nitric Oxide (NO) enzyme activities were found to be increased significantly in the Prefrontal Cortex (PFC) of MK-801 (dizocilpine maleate) group compared to the control group. In CAPE treated rats, prefrontal tissue MDA and NO enzyme activities were significantly decreased.

Devipriya *et al*. (2007) studied the antioxidant properties of EA against alcohol-induced toxicity and determined that EA resulted in a signifcant decrease in the levels of Thiobarbituric Acid Reactive Substances (TBARS) in both the liver and kidneys. The levels of NO were significantly increased in the alcohol-fed rats when compared to the rats in the control group. Treatment with EA restored the levels of NO to near normal.

Yildirim *et al*. (2003) found that NO level in the kidney tissue was increased by the cisplatin management and erdosteine prevented this increment at a statistically significant level. Increasing evidence suggested that NO has an important role in modulating oxidant stress and tissue damage. Peresleni *et al*. (1996) showed that oxidant stress to the epithelial cells caused an increase in immunodetectable Inducible NO Synthase (INOS) which results in an elevation in NO release, nitrite production and decreased cell viability. Yilmaz *et al*. (2005) found a marked elevation in NO level in damaged liver tissue of cisplatin treated rats and CAPE significantly attenuated this increment. Song *et al*. (2002) demonstrated that CAPE inhibited NO production.

Similar to the findings reported by Yildirim *et al*. (2003) and Peresleni *et al*. (1996), the results of this study determined that the reason for severe damage in liver and kidney tissues was connected to the oxidative stress created by DI because of an increase in NO release and by the process of CAPE and EA reducing the greatly increased NO levels there was a balanced attenuation of NO levels.

Malondialdehyde (MDA) and TBARS levels are known to be indicators of lipid peroxidation, free radical generation and oxidative stress which result either from increased oxidant production or reduced antioxidant levels and increase at the end of lipid peroxidation. In some *in vitro* and *in vivo* studies, MDA formation increased with the administration of chlorpyrifos-ethyl, fenthion, phosalone and DI (Gultekin *et al*., 2001; Altuntas *et al*., 2002, 2003, 2004; Sutcu *et al*., 2007).

However, some studies have reported no change in MDA levels from the application of OPI and DI. For example, Yildirim *et al*. (2003) found that the unchanged MDA levels in a cisplatin administrated group seemed to be contrary when compared to the NO levels. MDA is the breakdown product of the major chain reactions leading to oxidation of polyunsaturated fatty acids and thus serves as a reliable marker of oxidative stress-mediated lipid peroxidation in the liver. The unchanged MDA level in liver tissue leads us to think that the catabolic pathway for MDA is very rapid in the liver. MDA released by lipid peroxidation in liver tissues might be metabolized immediately by a mitochondrial MDA-metabolizing enzyme (low specific aldehyde dehydrogenase) and an increase in MDA level is not seen.

In the present study, similar to the reason mentioned by Yildirim *et al*. (2003), no significant change was noted in the MDA levels of the kidney and liver tissues from DI and the lasting effect of DI in the DI+CAPE and the DI+EA groups. However, in contrast the results of Gultekin *et al*. (2001), Altuntas *et al*. (2002, 2003, 2004) and Sutcu *et al*. (2007) reported that although DI had caused increased MDA levels in the lung tissue, CAPE and EA by blocking the effect of DI had reduced the MDA level.

GSH is a major player in cellular defence against reactive oxygen species. GSTs catalyze the conjugation of

GSH with electrophilic metabolites which are involved in the detoxification of both reactive intermediates and oxygen radicals. Increased activities of GST are known to serve as protective responses to eliminate xenobiotics (Smith and Litwack, 1980). Elevated GSH activity may reflect the possibility of better protection against pesticide toxicity and it is used as a biomarker for environmental biomonitoring. When GSH activity is inhibited, accumulation of lipid peroxidation products occurs. GSH play a primary important role in celluer detoxification of toxic aldehydes (Ozcan *et al*., 2006; Oruc, 2010).

Pari and Sivasankari (2008) found that EA increased levels of GSH would therefore be important in protecting cells with significant hepatoprotection against CsA-induced toxicity. In addition, it was repoted that the levels of TBARS and hydroperoxides were significantly decreased and the levels of enzymic and non-enzymic antioxidants significantly increased on treatment with EA in the liver (Pari and Sivasankari, 2008). An examination of the statistically significant levels in the present study determined that DI had reduced the GSH level in the liver tissue but looking at the DI+CAPE and DI+EA groups CAPE and EA had increased the GSH levels against the reducing effect of DI. EA especially, in comparison to CAPE was determined to have increased the GSH level by a greater amount in the liver.

CONCLUSION

It is concluded that CAPE and EA showed positive effects similar to each other on oxidative stress in acute DI intoxication and as such could be used for protective purposes against acute DI poisoning.

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