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The Genoprotective Activity of Resveratrol on Permethrin-Induced Genotoxic Damage in Cultured Human Lymphocytes

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ABSTRACT

The aim of this work was to investigate the genetic effects of resveratrol (RSV) at concentrations of 10, 15, 25, 40, 75 and 100 µM and its activities on the genotoxicity induced by the permethrin (PM) (200 µM). After the application of PM and RSV, separately and together, cultured human lymphocytes were assessed by chromosome aberrations (CA) and sister chromatid exchange (SCE) tests. According to results, the frequencies of CA and SCE rates in the peripheral lymphocytes were significantly increased by PM compared with the controls. However, RSV had no genotoxic effect. Furthermore, the findings revealed that PM-induced increases in the mean frequencies of both genotoxic indices were diminished by RSV in a clear dose dependent manner, indicating its protective role towards the cells from PM exerted injury. In conclusion, these effects of RSV should be considered while evaluating the possible use of RSV as a therapeutic agent.

Key words: Chromosome aberration, mutagenicity, permethrin, resveratrol, sister chromatid exchange

INTRODUCTION

Many pesticides often lead to environmental pollution and negative effects on human health (Sandal and Yilmaz 2010). Previous studies indicate that pesticide intoxication produces oxidative stress by the generation of free radicals and by inducing the tissue lipid peroxidation (LPO) in the mammals and other organisms (Çömelekoglu et al. 2000). Permethrin (PM), the most popular insecticide among the synthetic pyrethroids, has been used worldwide to control a wide range of insects in agriculture, forestry, public health, and homes (Zhang et al. 2008). Although exposure to a large proportions of the general population from the widespread use, information is limited concerning its potential carcinogenicity and mutagenicity. Mammalian and non-mammalian bioassays and toxicology studies have found potential liver carcinogenicity (Hakoi et al. 1992; Price et al. 2007). PM exposure has been reported to cause DNA damage in humans and experimental animals (Tisch et al. 2002; Gabbianelli et al. 2004; Undeğer and Başaran 2005); PM has also been reported to cause a genotoxic response upon generation of oxidative stress (Gabbianelli et al. 2009; Vadhana et al. 2010).

The resveratrol (RSV) (*trans*-3,4′,-5-trihydroxystilbene) is a polyphenolic plant-derived antioxidant abundantly found in certain food such as grapes, roots, berries, peanuts, cranberry, mulberry, lingberry, bilberry, partridgeberry, sparkleberry, deer berry, blueberry, jackfruit and

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red wine (Mukherjee et al. 2010; Gao et al. 2011). RSV contains two aromatic groups and has been reported to have a higher 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and hydroxyl radical-scavenging capacity than propyl gallate, vitamin C, and vitamin E (Soares et al. 2003). It provides a critical matter with antioxidant functions *in vivo* and in cell culture models (Pervaiz 2003; Mikstacka et al. 2010). Mechanisms behind the antioxidant properties of RSV are not fully understood but it has been recently revealed that it decreased the generation of ROS, LPO and nitric oxide (NO) content in the experimental animals (Kairisalo et al. 2011; Simao et al. 2011). RSV exhibited protective effects in cardiovascular diseases, cancer, and neurodegenerative diseases, partly as a result of its anti-oxidative, anti-inflammatory, and anti-mutagenic activities (Zhuang et al. 2003; Baur and Sinclair 2006).

In recent years, many efforts are being made to investigate the therapeutic substances that are capable of reducing the genotoxicity of various natural and man-made mutagens in human life (Türkez and Geyikoglu 2010). These include vitamins, sulfhydryl substances, microalga, some compounds and plant products (Edenharder et al. 1999; Geyikoglu and Türkez 2005; Yörük et al. 2005; Kandaz et al. 2009; Chattopadhyay et al. 2009; Bertolin et al. 2009). Since the complete avoidance of exposure to PM-producing mould is very difficult, chemoprevention is an attractive strategy for protecting the humans and animals from the risks caused by the exposure to this pesticide. Many physical, chemical and biological approaches employed to counteract the PM problem have been reported in the literature (Etang et al. 2007; Al-Eissa et al. 2008; Rossbach et al. 2010; Koutros et al. 2010; Issam et al. 2011). To the best of our knowledge, the efficacy of RSV on PM induced genotoxicity has not been investigated. Thus, this study investigated the efficacy of RSV against PM-induced genotoxic damages by CA and SCE assays.

MATERIALS AND METHODS

Experimental Design

Blood samples were obtained by vein puncture from three healthy non-smoking donors. PM (C21H20Cl2O3, CAS No. 52645-53-1, Sigma®, GERMANY; in concentration of 200 µg/ml) and RSV ($C_{14}H_{12}O_3$, CASNo. 501-36-0, Sigma®, USA; in concentrations of 10, 15, 25, 40, 75 and 100 µM) were dissolved in distilled water and a mixture of ethanol and water, respectively. These compounds were added to the cultures just before the incubation for cytogenetic analysis. Experiments were conformed to the guidelines of the World Medical Assembly (Declaration of Helsinki). The concentrations were selected according to the previous studies (Leiro et al. 2004; Undeğer and Başaran 2005). After the supplementation of RSV and PM, the blood was incubated at 37ºC for 72h to adjust the body conditions for testing the SCE. Each individual whole blood culture without RSV or PM was studied as a control group.

Genotoxicity Testing

SCE assay

The cultures were set up according to a slight modification of the protocol described by Evans and O'Riordan (1975). With the aim of providing successive visualization of SCEs, 5-bromo-20-deoxyuridine (Sigma®) was added at culture initiation. Exactly 70 h and 30 min after beginning of the incubations, demecolcine (N-Diacetyl-N-methylcolchicine, Sigma®) was added to the cultures. After hypotonic treatment (0.075 M KCl), followed by three repetitive cycles of fixation in methanol/acetic acid solution (3:1, v/v), centrifugation, and re-suspension, the cell suspension was dropped onto chilled, grease-free microscopic slides, air-dried, aged for three days, and then differentially stained for the inspection of the SCE rate according to the fluorescence plus Giemsa (FPG) procedure. For each treatment condition, well-spread twenty-five second division metaphases containing 42-46 chromosomes per cell were scored and the values obtained were calculated as SCEs per cell.

CA assay

A 0.5 ml aliquot of heparinized blood was cultured in 6.0 ml of culture medium (Chromosome Medium B; Biochrom, Berlin) with 5.0 mg/ml of phytohemagglutinin (Biochrom). The cultures were incubated in complete darkness at 37ºC for 72h. Two hours prior to harvesting, 0.1 ml of colchicine (0.2 mg/ml, Sigma®) was added to the culture flask. Hypotonic treatment and fixation were performed. To prepare the slides, 3-5 drops of the fixed cell suspension were dropped on a

clean slide and air-dried. The slides were stained in 3% Giemsa solution in phosphate buffer (pH 6.8) for 15 min. For each treatment, 30 well-spread metaphases were analyzed to detect the presence of chromosomal aberrations. Criteria to classify the different types of aberrations (chromatid or chromosome gap and chromatid or chromosome break) were in accordance with the recommendation of EHC (Environmental Health Criteria) 46 for environmental monitoring of human populations (IPCS, 1985).

Statistical analysis

Statistical analysis was performed using the SPSS Software (version 12.0, SPSS, Chicago, IL, USA). The two-tailed Student's t-test was used to compare the SCEs and CAs frequencies between the treated and control groups. Statistical decisions were made with a significance level of 0.05.

RESULTS

The frequency of CAs in human lymphocytes induced by the PM is shown in Figure 1. PM alone sharply increased the CA yield in human lymphocytes in a dose-dependent manner (Fig. 1). On the contrary, six RSV doses alone (10, 15, 25, 40, 75 and 100 µM) change the rate of CAs. However, combined application of PM and RSV significantly reduced the CA yields as their concentration increased compared to PM treated alone. The rate of SCEs in human lymphocytes induced by PM is shown in Figure 2. PM caused increases of SCE rates in the cultured human lymphocytes in a dose-dependent manner (Fig. 2). But, all the tested concentrations of RSV didn't change the rate of SCEs. Moreover, the combined application of PM and RSV significantly reduced the formations of SCEs in comparison with alone PM treated cultures.

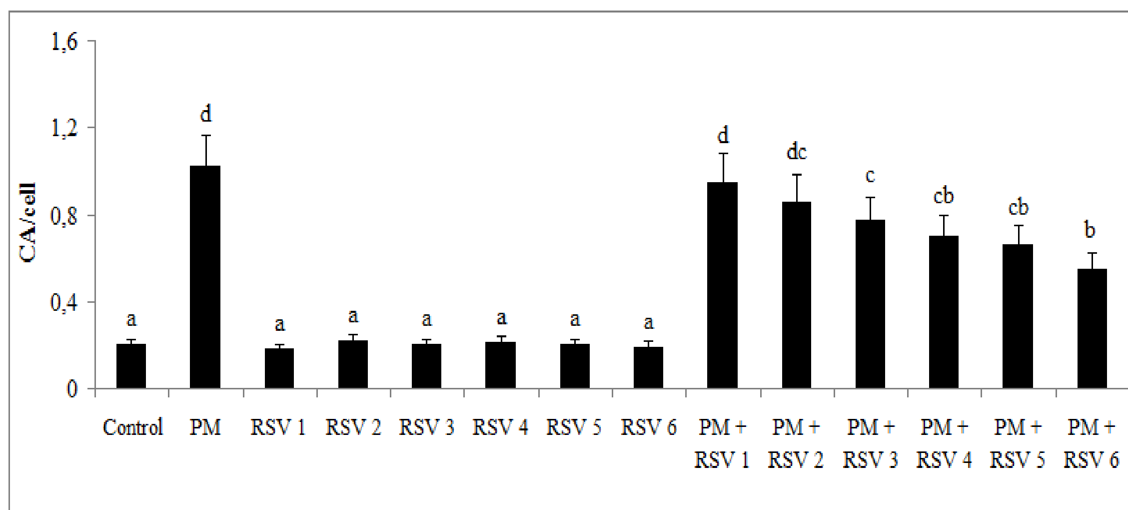

Figure 1 - Effect of RSV on PM induced chromosomal aberrations in human peripheral lymphocytes. (Values are expressed as mean for three cultures in each group; means in the figure followed by the different letters present significant differences at the $p<0.05$ level; PM: 200 µM permethrin; RSV1:10 µM resveratrol; RSV2:15 µM resveratrol; RSV3:25 µM resveratrol; RSV4:40 µM resveratrol; RSV5:75 µM resveratrol; RSV5:100 µM resveratrol.)

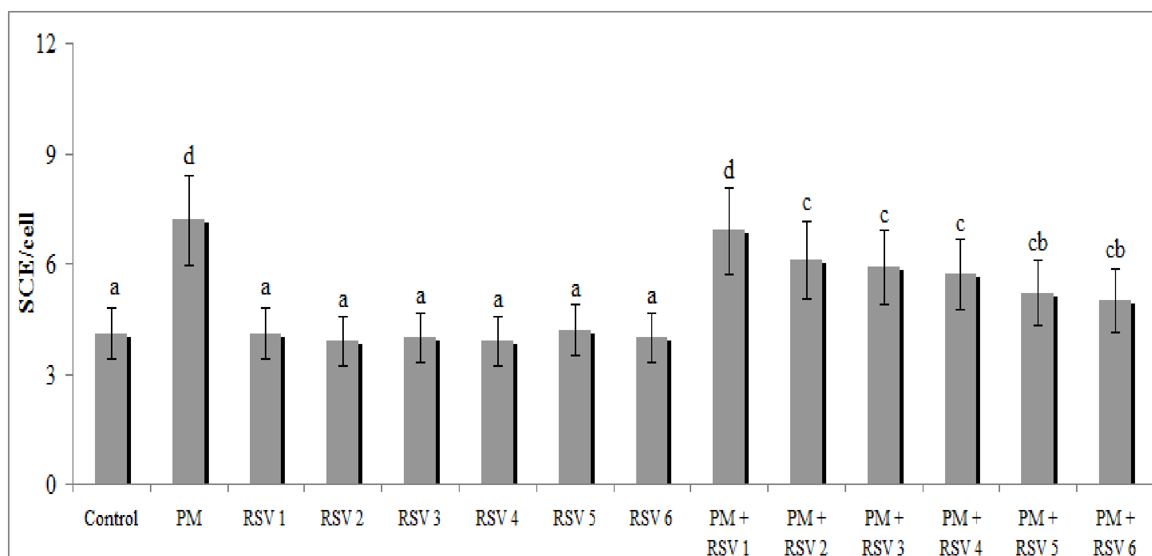

Figure 2 - Effect of RSV on PM induced sister-chromatid exchanges in human peripheral lymphocytes. Abbreviations are as in Figure 1.

DISCUSSION

The PM is among the most potent genotoxic agents known. It has been reported to cause nuclear DNA damage (single- and double-strand breaks in striatum cells) in the rats (Falcioni et al. 2010). Also, PM induces those micronuclei, CA, DNA damage on human peripheral lymphocytes (Barrueco et al. 1992; Barrueco et al. 1994; Undeğer and Başaran 2005). The normal human white blood cells stimulated to produce toxic oxygen metabolites cause SCEs in the cultured mammalian cells (Weitzman and Stossel 1981; Weitberg et al. 1983). A recent study showed that the ROS generation and malondialdehyde (MDA) (a LPO production) were increased by the PM treatment but the activity of antioxidant enzymes such as superoxide dismutase and catalase and glutathione (GSH) content had declined in the rats (Hu et al. 2010).

The health-protecting properties of the RSV have been well described as an antioxidant, anti-inflammatory, cardioprotective, neuroprotective, cancer, ageing related diseases, chemoprotective and anti-apoptotic (Mukherjee et al. 2010; Gutiérrez-Pérez et al. 2011), anti-aging (Ungvari et al. 2011), modulator of lipoprotein metabolism (Soleas et al. 1997), inhibitor of platelet aggregation (Pace-Asciak et al. 1995) and vasorelaxing agent. The most important beneficial effect of RSV is its cancer chemopreventive activity. Jang et al. (1997) reported that RSV had antimutagenic properties. Boyce et al. (2004) reported the anti-mutagenic effect of RSV on the bacterial and eukaryotic cells. RSV also interfered with the cellular events, leading to tumor initiation, promotion and progression and has been shown to inhibit the proliferation of a variety of cancer cells in culture, including human colon cancer cells, breast epithelial cells, prostate cancer cells, primary pancreatic cancer cells and leukemic cells (Mgbonyebi et al. 1998; Schneider et al. 2000; Cardile et al. 2003; Shankar et al. 2011; Niu et al. 2011). Several investigations have reported the possible role and protective effects of RSV against certain forms of oxidant damage, through a hydrogen-electron donation from its hydroxyl groups (López-Vélez et al. 2003). The consequences are capacity to scavenge the ROS, a protective effect against DNA damage and LPO in cell membrane (Leonard et al. 2003). It is probable that multiple mechanisms, including the effect on the metabolic activation of mutagens or the influence on detoxification enzymes and blocking DNA-adducts formation are involved in the anti-mutagenic effect of RSV. The present results supported the fact that RSV were in agreement with the results of Bárta et al. (2006) who detected a significant decrease of mutagenicty of three mutagens, aflatoxin (AFB1), 2-amino-3-methylimidazo [4,5-f] chinoline (IQ) and N-nitroso-N-methylurea (MNU),by RSV in

micronucleus (MN) test. Quincozes-Santos et al. (2010) reported that RSV prevented hydrogen peroxide-increased MN formation in C6 glioma cells.

In conclusion, diet may be considered as a very important factor influencing favorably the pathophysiological processes in the organism and may be a very effective factor in the prevention strategy against various diseases, including diseases with genotoxicological etiology. The study of chemo protective effects of RSV or the study of their interactions and knowledge of the mechanisms of their effect should lead to a wider use of this substance as dietary supplements or as a part of functional foods in the prevention of many diseases, including tumors.

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