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RESEARCH ARTICLE

The Anti-inflammatory effect of grape seed extract in rats exposed to Cadmium Chloride toxicity

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Abstract

Cadmium is considered as a very serious environmental health problem. It is absorbed via three different ways gastrointestinal duct, skin and respiratory system. The mechanism of cadmium toxicity like any other heavy metal toxicity induces the formation of reactive oxygen species which underlies tissue damages and physiological defects. In this study, we have used rats as an animal model for in vivo investigations. Different haematological parameters have been used to determine the inflammatory effect of cadmium toxicity and the anti-inflammatory role of grape seed extract. Here we demonstrate that daily oral intake of grape seed extract increases peripheral leukocytic counts and pro-inflammatory mediators CCL1, CCL2 and CCL12 .In addition, both inflammatory indicators TNF-α and neutrophils/lymphocytes ratio were reduced after tow months of cadmium chloride and grape seed extract co-treatment. Our data suggests that the oral intake of grape seed extract protects the experimental animals against inflammation due to both the anti-inflammatory action and immune response enhancement.

INTRODUCTION

Cadmium is a chemical element with atomic mass 112.41 and atomic number 48 (Haynes and Lide, 2011). The physical appearance of the metallic form of Cadmium is a soft, silver-white metal (Haynes and Lide, 2011). Naturally, Cadmium is usually present in ores of zinc, lead, and copper and form of complex oxides, sulphides, and carbonates (Haynes and Lide, 2011).

Human exposure to the cadmium is mainly referred to food in which 90 percent of exposure come from environmental contamination (Evangelisti *et al.*, 1994). In fact the major source of cadmium in the human diet is the agricultural products as a result of soil contamination (Nicholson *et al.*, 2003). Moreover, tobacco smokers might be exposed to cadmium more than non-smokers because cadmium is usually accumulates in tobacco plants (Scherer and Barkemeyer, 1983). Unfortunately, cadmium exposure and accumulation starts in childhood via both food intake and dust (Scherer and Barkemeyer, 1983). It has been found accumulated in different organs such as kidneys, bones (Scherer and Barkemeyer, 1983).

Nowadays, cadmium is considered as a very serious environmental health problem (Järup, 2002). It is absorbed via three different ways gastrointestinal duct, skin and respiratory system (Godt *et al.*, 2006). In normal individuals the blood levels of cadmium range from about 0.4 to 1.0 ug/l (Baron and Schweinsberg, 1989) . However, it is very toxic metal in which at low exposure levels were found associated with direct bone toxicity (Patel *et al.*, 2007). Several Published work have shown that cadmium toxicity induces renal damage and was associated with progressive renal defects (Dalgarno, 1980; Hotz *et al.*, 1999; Järup, 2002; Godt *et al.*, 2006). Acute overexposure to cadmium causes irritation in pulmonary system while the chronic exposure leads to passive accumulation in the kidneys which in turn damages the renal tubule (Nogue *et al.*, 2004). In fact, cadmium poisoning may also causes

cancers such as renal cancer, breast cancer, lung cancer and prostate cancer (Armstrong and Kazantzis, 1985; Arisawa *et al.*, 2001; Barrett, 2009; Beveridge *et al.*, 2010). Experimentally, cadmium caused a disturbance in ovarian steroids such as the production of progesterone and testosterone in rats (Piasek and Laskey, 1999). In addition, cadmium exposure can cause endocrine systems disturbances (Wang *et al.*, 2014).

The mechanism of cadmium toxicity like any other heavy metal toxicity induces the formation of reactive oxygen species which underlies tissue damages and physiological defects (Chatterjee *et al.*, 2009; Choong *et al.*, 2013; Nunes *et al.*, 2015; Wei *et al.*, 2015). In the same context, inflammatory mediators stimulate the production of reactive oxygen species which in turn cause DNA damage, mitophagy as well as autophagy (Kraaij *et al.*, 2014; Leavy, 2014; Wei *et al.*, 2015). Several studies have demonstrated that cadmium exposure induces inflammation in different target organs such as lungs, kidneys and cardiovascular system (Hsu *et al.*, 2009; Kataranovski *et al.*, 2009; Blum *et al.*, 2014; Colacino *et al.*, 2014). Moreover, inflammation is identified as an immune reaction caused by either infections, toxicity or injury which might lead to further risk progression such as tumorigenesis or chronic disease (Grivennikov *et al.*, 2010). Therefore, measurement of the inflammatory degree in the case of cadmium toxicity might be a useful tool for monitoring both severity of exposure and treatment of the physiological defect caused by that exposure. However, there are several parameters used for estimation the degree of inflammation such as leukocyte counts, serum cytokines and Neutrophils/Lymphocytes Ratio (NLR) (Varenko Iu *et al.*, 1985). Recently, this ratio became an useful prognostic tool for inflammation in which high NLR was found associated with increase serum levels of some inflammatory cytokines (Grivennikov *et al.*, 2010; Biyik *et al.*, 2013). Therefore, the NLR is used as a direct indicator for the inflammation caused by cadmium toxicity in this study.

2. Materials and Methods

2.1 Materials

Grape seed extract was purchased from General Nutrition Centers (GNC Corporation 300 Sixth Ave. Pittsburgh, PA 15222) , while the Cadmium chloride ($CdCl_2$) was purchased from Sigma Aldrich (St. Louis, MO, USA). Cytokines; cxcl1 Sandwich- ELISA kit , cxcl2 Sandwich- ELISA kit , cxcl13 Sandwich- ELISA kit and tumour necrosis factor- alpha (TNF-α) Sandwich- ELISA kit were purchased from Mybiosource® (San Diego, California, USA).

2.2 Animals and administration

Forty male Albino rats were purchased from King Fahad Research Center (Jeddah, Saudi Arabia) . All animal procedures were approved by the Ethical Committee Office of the dean of scientific affairs of Taif University, Saudi Arabia. The rats aged six weeks old were acclimatized to laboratory conditions for a further week before treatment. After acclimation, rats were weighed ranging from 204 to 227 g, then they were divided into four groups with 10 animals in each group. Group A was a control group (Normal feeding/ 2 months) , group B was exposed daily to Cadmium Chloride $CdCl_2$ (10mg/Kg B.W/ 2 months) which calculated as Cd, in group C rats were treated daily with grape seed extract (GSE) for (1g/Kg B.W / 2 months) and group D was treated daily with both (10mg/Kg B.W of $CdCl_2$) and (1g/Kg B.W of GSE). On the final day, samples were collected from experimental animals in which the whole blood for leukocytic counts and serums for the estimation of CXCl1, CXCl2 , CXCl13 and TNF-α.

2.3 Haematological and Serum Cytokines Studies

Haematological parameters were determined using Sysmex Xn100®. Cytokines; CCL1, CCL2, CCL12 and TNF-α were estimated using Sandwich- ELISA technology.

2.4 Statistical analysis

All the data were expressed as mean ± standard error of mean, and the analysis was performed using the Excel software version 2007.

3. Results

3.1 Leukocytic Counts Studies

The data presented in figure 1(A) have shown a clear reduction in white blood cell counts in rats were exposed to (10mg/Kg B.W/ 2 months) of Cadmium Chloride comparing with the normal feeding animals in which *P* value was < 0.01. However, there was a significant protection of the Grape Seed Extract in rats that administrated with both (10mg/Kg B.W of $CdCl_2$) and (1g/Kg B.W of GSE) in which the *P* value was < 0.002. Similarly, differential data

show that exposure to Cadmium Chloride significantly reduces the count of different types of leukocytes such as Neutrophils, Lymphocytes and Monocytes as shown in figure 1 (B), (C) and (D). On the other hand, the grape seed extract gives a clear protection in rats were treated with both (10mg/Kg B.W of $CdCl_2$) and (1g/Kg B.W of GSE) as demonstrated in figure 1 (B), (C) and (D).

3.2 Neutrophils/Lymphocytes Ratio

Figure 2 shows that the Neutrophils/Lymphocytes Ratio NLR was increased in Cadmium exposed animals (10mg/Kg B.W/ 2 months) comparing to normal control animals, while in rats were treated with both cadmium and grape seed extracts the ratio was significantly decreased to about 50% of ratio that found in cadmium exposed rats in which *P* value was < 0.05.

3.3 Chemokines and TNF-α Studies

As seen in figure 3 (A), (B) and (C) Cadmium toxicity significantly (*P* value < 0.05) increases serum levels of monocytes chemoattractant CCL1, monocyte chemotactic protein- 1 (CCL2) and monocyte chemotactic protein 5 (CCL12), in animals were treated with cadmium Chloride only. However, grape seed extract add further stimulation in animals were co-treated with both (10mg/Kg B.W of $CdCl_2$) and (1g/Kg B.W of GSE) and that was significant *P* value < 0.05.
Figure 3 (D) clearly shows that cadmium toxicity significantly increases TNF-α serum levels *P* value < 0.05. On the other hand, the grape seed extract strikingly reduces the effect of Cadmium exposure which was significant *P* value < 0.05.

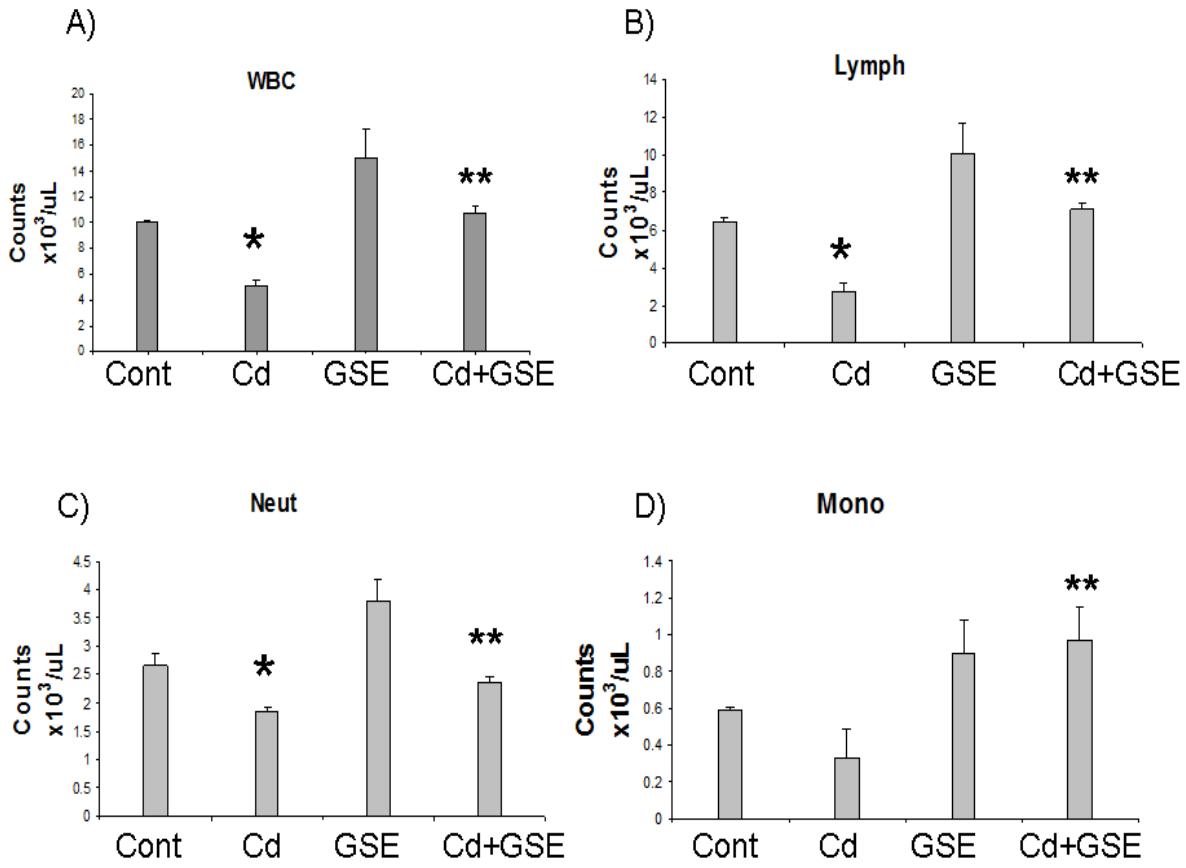

Fig 1 : White Blood Cells Count. (A) Total White Blood Cells Count in $1x10^3$/uL, (B) Neutrophils Count in $1x10^3$/uL (C) Lymphocytes Count in $1x10^3$/uL (D) Monocytes Count in $1x10^3$/uL . Data are represented by Means

+/- SEM in Normal feeding/ 2 months rats (Cont), rats were exposed daily to 10mg/Kg B.W/ 2 months of Cadmium Chloride (Cd), rats were treated daily with 1g/Kg B.W / 2 months of Grape Seed Extract (GSE), rats were co-treated daily with both 10mg/Kg B.W of $CdCl_2$ and 1g/Kg B.W of Grape Seed Extract (Cd + GSE). * indicates *P* value < 0.05 corresponding to the control (Cont). ** indicates *P* value < 0.05 corresponding to the Cadmium exposed animals.

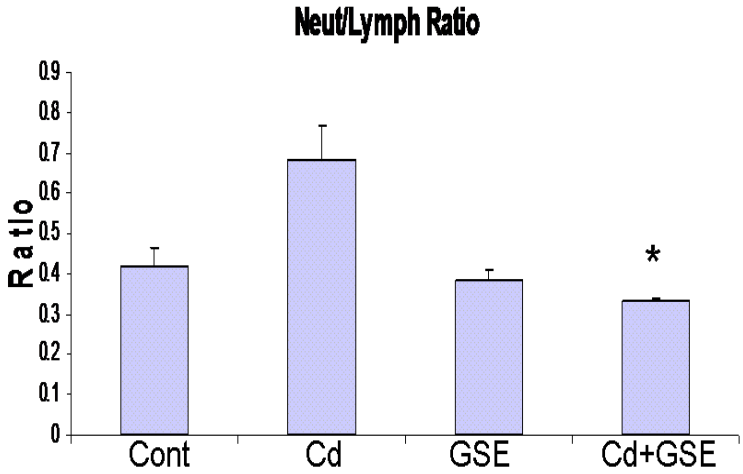

Fig 2: Neutrophils/Lymphocytes Ratio. Normal feeding/ 2 months rats (Cont), rats were exposed daily to 10mg/Kg B.W/ 2 months of Cadmium Chloride (Cd), rats were treated daily with 1g/Kg B.W / 2 months of Grape Seed Extract (GSE), rats were co-treated daily with both 10mg/Kg B.W of $CdCl_2$ and 1g/Kg B.W of Grape Seed Extract (Cd + GSE). Data are represented by Means +/- SEM. * indicates *P* value < 0.05 corresponding to the Cadmium exposed rats.

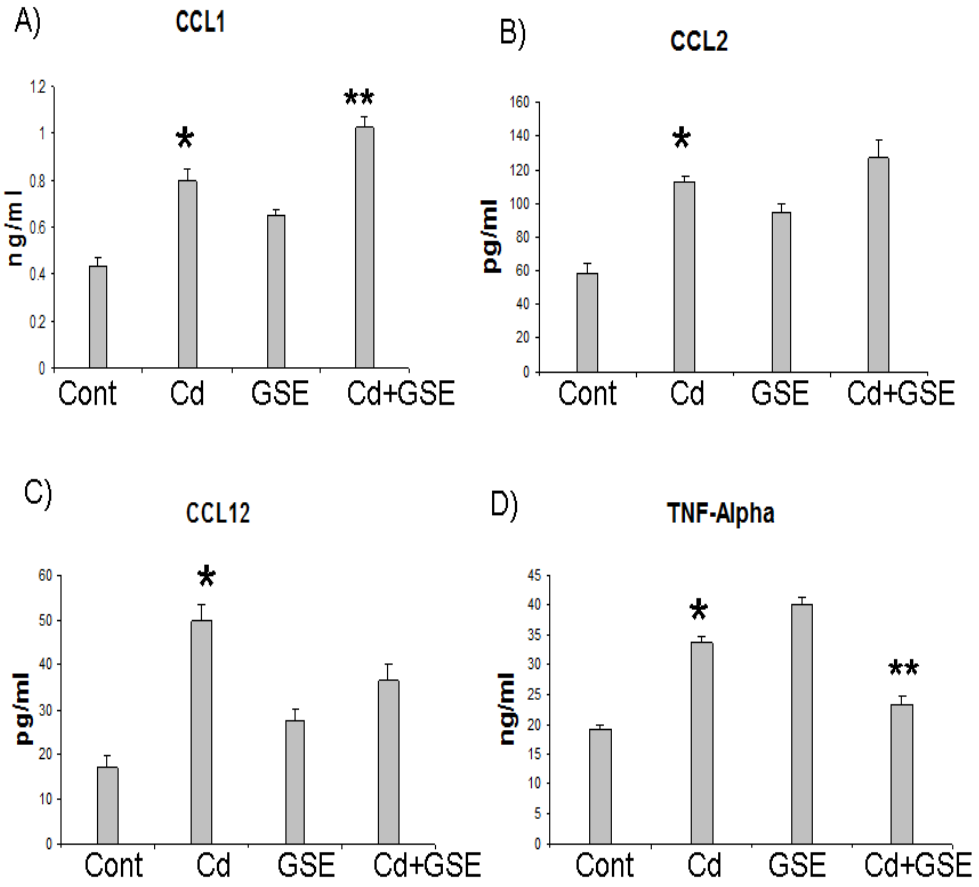

Fig 3: Serum levels of Cytokines. A) Serum CCL1 levels in ng/ml, B) Serum CCL2 levels in pg/ml, C) Serum CCL12 levels in pg/ml and D) Serum TNF-α levels in ng/ml. Data are represented by Means +/- SEM in Normal feeding/ 2 months rats (Cont), rats were exposed daily to 10mg/Kg B.W/ 2 months of Cadmium Chloride (Cd), rats were treated daily with 1g/Kg B.W / 2 months of Grape Seed Extract (GSE), rats were co-treated daily with both 10mg/Kg B.W of $CdCl_2$ and 1g/Kg B.W of Grape Seed Extract (Cd + GSE). * indicates *P* value < 0.05 corresponding to the control (Cont). ** indicates *P* value < 0.05 corresponding to the Cadmium exposed animals.

4. Discussion

Dietary nutrients are the oldest treatment way for several diseases. In fact, many antioxidants are naturally distributed in a variety of fruits, vegetables, herbs and flowers. Grapes and grape seed extract are rich of polyphenols, catechin, and vlavanols which all are bioactive antioxidants (Terra *et al.*, 2011; Ahmad *et al.*, 2014; Yang *et al.*, 2014). Grape seed extract reduces airway inflammation and hyper-responsiveness in a murine model of Asthma (Zhou *et al.*, 2011). In a mouse model of carrageenan-induced pleurisy, the grape seed extract have been shown to exert a clear protection (Ahmad *et al.*, 2014). Furthermore, Irandoost and his colleagues have reported that grape seed oil improves inflammatory conditions and insulin resistance in overweight women (Irandoost *et al.*, 2013). In this study, rats were treated with Cadmium chloride in either presence or absence of the grape seed extract in which the direct effect was assessed using complete blood counts, neutrophils/lymphocytes ratio and serum levels of inflammatory mediators CCL1, CCL2, CCL12 and tumour necrosis factor- alpha (TNF-α).

Several animal studies have reported that Cadmium toxicity negatively effects different systems and organs such as endocrine system, Kidneys and liver due to increases the oxidative stress (Hussain *et al.*, 1987; Stoica *et al.*, 2000; Boldogh *et al.*, 2005; Prozialeck and Edwards, 2012). The current study indicates that oral exposure to Cadmium significantly reduces the total White Blood Cells and differentially Neutrophils, Lymphocytes and Monocytes as shown in figure 1 and that reaction was via either extrinsic apoptotic effect of Cadmium on the leukocyte itself or bone marrow toxicity (Hamada *et al.*, 1997; Yan *et al.*, 1997; Mehranjani and Mosavi, 2011; Bao *et al.*, 2012). On the other hand, the grape seed extract administration have shown a significant protection as shown strikingly in

figure 1 (A),(B),(C) and (D), and that might be a direct antioxidant effect via the extract components; polyphenols or flavenols. Moreover, the increased Neutrophils to lymphocytes ratio is an indicator for a systemic inflammation (Wouters, 2005; Kurtul *et al.*, 2015). Figure2 is clearly demonstrated that oral exposure to cadmium increases the Neutrophils/Lymphocytes ratio which might be the oxidative stress outcomes while the co-treatment with both Cadmium Chloride and the grape seed extract have shown a significant decrease in that ration which suggests that the oral intake of the grape seed extract has a powerful anti-inflammatory effect.

Chemokines are secondary pro-inflammatory mediators that became an important indicator for the inflammatory process (Miller and Krangel, 1992;Koch *et al.*, 1993; Kim *et al.*, 1995 ; Kawano *et al.*, 2004). Consistently, cadmium toxicity significantly stimulates both CCL1 and CCL2 which are a pro-inflammatory cytokines as clearly shown in figure 3 (A) and (B), and that might be as a result of the highly oxidative effect. Similarly, oral exposure to cadmium significantly elevates another pro-inflammatory mediator (CCL12) which was consistent with the whole data presented in this study. However, the oral intake of the grape seed extract shows a synergic effect on both CCL1 and CCL2 serum levels which was significant in CCL1 and that was in rats co-treated with both Cadmium Chloride and the grape seed extract. This synergic effect was not observed in the case of CCL12 serum levels as shown in figure 3 (C). These data suggests that the oxidative stress caused by Cadmium toxicity activates leukocytes as a positive feed back. In addition, grape seed extract might exerts its effect differently as shown in figure 3, there is an elevation of serum CCL1 and CCL2 in animals were treated with grape seed extract alone. This result might highlights that the oral intake of grape seed extract might enhance the immune system and might be a useful anti-inflammation treatment. The interesting point is that grape seed extract does not show any clear effect on CCL12 serum levels which might need a further molecular biology investigation to identify which mediator/s are used in that reaction.

In the same context, tumour necrosis factor-α is an inflammatory response regulator stimulates different cellular responses including differentiation, migration, proliferation, survival and apoptosis (O'Donnell *et al.*, 1995; Vandenabeele *et al.*, 1995; Rolfe *et al.*, 1997; Bradley, 2008). In the present study, Cadmium toxicity increases serum TNF-α levels in the experimented animals, while grape seed extract have shown a significant reduction in animals were co-treated with both Cadmium Chloride and grape seed extract. These data are nicely fit the data presented previously in which the grape seed extract exerts an anti-inflammatory effect via different pathways leukocytic cells production, proliferation, inflammatory mediators induction and anti-oxidant reaction.

5. Conclusion

In this study, we confirmed that Grape Seed Extract (GSE) exhibited protective effects against Cd-induced inflammation as confirmed by the reduction of Neutrophils/ Lymphocytes ratio, enhancement of antioxidant status via improved leukocytic counts, and reduction of serum TNF-α levels. The presented data suggests that Grape Seed Extract (GSE) enhances the immune response and might exerts its anti-inflammatory effects via different ways as demonstrated in CCL1, CCL2 and TNF-α results.

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