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Research Article

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Ameliorating Effect of Whey Proteins as a Dietary Supplement on the Cadmium-induced Toxicity in Male Wistar rats

Hassan Ahmed Rudayni (Ph.D.); Mohammed Mubarak (Ph.D.); Mohammed Al-Zhrani (Ph.D.); Mohammed Al-eissa (Ph.D.)
Department of Biology, College of Science,
Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11623, Saudi Arabia.
Address for correspondence: Dr. Mohammed Mubarak
Department of Biology, College of Science,
Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11623, Saudi Arabia.
E.mail: *mohammedahmed_62@yahoo.com*; **Mobile:** 00966563924677

Abstract

Background:
The liquid whey is a byproduct produced during cheese-making and its rich formula is prepared by multiple filtration processes to increase the protein concentration.
Cadmium is a highly hazardous heavy metal with a cumulative toxic effects that extend to damage various tissues and organs. The present study was carried out to elucidate the possible role of whey proteins to alleviate the cadmium-induced toxicological changes.

Materials and Methods:
Sixty male Wistar rats were randomly and equally allotted into three groups; group 1 served as untreated control, group 2 represented cadmium exposure and group 3 animals were exposed to cadmium and received a rich source of whey proteins (Impact Whey Isolate).

Results:
Both the hematological and biochemical profiles of cadmium exposed rats (group 2) manifested significant alterations compared with control. Animals exposed to cadmium and received why proteins exhibited increased erythrocytic indices and also showed relatively increased levels of total proteins, total thiols, glutathione and catalase, and decreased levels blood cadmium, creatinine, urea, bilirubin and malondialdehyde (MDA) compared with the animals exposed to cadmium (group 2).

Conclusion:
It was concluded that whey proteins contained in a rich dietary supplement may alleviate the toxic effects induced by cadmium as evidenced by the relatively restored hematological and biochemical parameters

Keywords: Whey proteins, cadmium, toxicity, antioxidant, hematological profile, biochemical changes.

Introduction

Cadmium is a highly hazardous heavy metal that exists naturally in the environment and implicated in a wide range of industries. There are occupational and non-occupational (environmental) forms of exposure to cadmium. Two ways of entry of this toxicant to inside the body were identified, namely ingestion of polluted feed and water and inhalation of industrial fumes. Cadmium-induced chronic toxicity is featured by progressive drastic effects due to a gradual accumulation of the toxicant heavy metal in different tissues (Sharma et al., 2015). Cadmium toxicity can provoke an oxidative stress with the associating damaging effects in the involved tissues and organs, especially kidney and liver (Li et al., 2015).

The liquid whey is raised as a byproduct from cheese-making, and can be exposed to sequential filtration steps to prepare special why products. The Initial filtration and purification is performed to remove the majority of fat and lactose contents, and the final ultrafiltration is done to increase the protein component to be higher than 90% in some whey products.

Oxidative activities are among the main events which eventually lead to cell and tissue damage. Inhibition and/or prevention of these activities is an ultimate function of the concerned antioxidative mechanisms. Human and animals possess a natural efficient antioxidant system for detection of the oxidative metabolites, such as free radicals, and preventing their damaging effects (Finkel and Holbrook, 2000; Mccord, 2000; Klaus and Heribert, 2004; Augus et al., 2011; Li et al., 2015). In other words, in normal physiological conditions there is a continuous stable balance between the oxidation and antioxidation states to avoid cellular damage and to maintain the integrity and functions of cells and tissues.

Natural antioxidants are greatly concerned (Yigit et al., 2017), and their medical applications have been extended for prevention of a number of major disease conditions including cancer, cardiovascular disorders, Alzheimer's, arthritis and also its role in alleviation of aging manifestations (Ames et al., 1993; Dreher and Junod, 1996, Diaz et al., 1997; Maxwell, 2000; Pham-Huy et al., 2008; Van Vugt et al., 2008).

Proteins that can protect the cells and tissues from the oxidative damaging action are known as antioxidant proteins (Feng et al., 2017). However, antioxidant proteins are not synthesized in the body and external sources of such type of proteins, as well as other micronutrients, are essential for sustaining the oxidation-antioxidation balance (Nichole et al., 2008; Huang et al., 2009; Lobo et al., 2010).

The results of *in vivo* and *in vitro* studies concerned with the capability of external sources of proteins to enhance the cellular antioxidative activities are either unclear or controversial (Nichole et al.,2008; Augus et al., 2011; Feng et al., 2016; Yong et al.,2017). Therefore, there is a need for a research trial to clarify some aspects of the possible role of external rich protein sources to enhance and maintain the endogenous antioxidative mechanisms.

The present study was carried out to test the possible antioxidant property of the proteins contained in one of the highly enriched whey products. The suggested antioxidative role of whey proteins was evaluated in the presence of an oxidative stress induced by cadmium toxicity in rats.

Materials and Methods

Experimental animals:

Sixty adult male Wistar rats, aging 4 months and weighing 170-210 g, were used in the present study. The rats were maintained according to the standard laboratory conditions (ambient temperature 24 ± 1 ^{o}C, 12-h dark-light cycle, relative humidity of 35% to 70%). All the guides and rules to care and use of laboratory animals stated officially by the Ethical Committee of Imam Mohammad ibn Saud University, Saudi Arabia, were accurately followed.

Cadmium and whey product:

Cadmium was used as analytical grade cadmium chloride (Cd Cl_2) (Merck, Germany).

The enriched whey product "Impact Whey Isolate" (MyProtein®, UK) as ready-to-mix powder was employed. According to the manufacturer, this why product is of bovine milk source and its absorption is remarkably fast. It is considered as one of the purest why supplements and officially certified as one of the best protein powders available. It is ranked as grade A for both quality and value. This whey product contains 90% proteins as well as emulsifiers, sweetener, sunflower lecithin and soya lecithin.

Experimental design:

After acclimatization for one week, the rats were randomly and equally allotted into three groups, of 20 animals each, and designated groups 1, 2 and 3. Rats in group 1 served as untreated control, i.e., not exposed to cadmium and didn't receive why product. Group 2 animals were exposed to cadmium, the rats were injected subcutaneously at the dose of 2 mg/kg b.w. in 0.1 ml saline, four times weekly. Control animals received an equal volume of saline via the same route of injection. Rats in group 3 were injected with cadmium and concomitantly received the whey protein isolate at the dose of 90 mg/day by oral gavage in a volume of 1 mL/kg b.w.

Experimentation period extended for 4 weeks and during this period feed (dry ration) and drinking water were supplied *ad libitum.*

All experimental animals were observed for behavioral activity, feed consumption, water intake and clinical signs.

Hematological and biochemical assays:

Blood samples were collected from animals in all groups at the end of experiment. The blood samples collected with an anticoagulant (EDTA) were used to measure the various hematological parameters, including RBCs and total WBCs counts, and other erythrocytic indices involving hemoglobin (Hb) concentration and packed cell volume (PCV) %.

For estimation of cadmium level in blood, 1 mL blood samples were subjected for digestion using a mixture of $HCIO_4^-$ and HNO_3, and blood cadmium level was estimated using atomic absorption spectrophotometer (CBC 906 AA).

Serum separated from the coagulated blood samples was utilized to assess the various biochemical parameters encompassing total proteins, total thiols, glutathione (GSH), creatinine, urea, blood urea nitrogen (BUN), bilirubin, albumin, globulin, malondialdehyde (MDA), catalase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).

Erythrocytic and totalleucocytic counts were estimated using the convenient hemocytometer. Packed cell volume (PCV) % was estimated by a micro-hematocrit method. Hemoglobin (Hb) concentration was assessed by Cyanmet-hemoglobin methods as described by Benjamin (1978) and Coles (1986).

Total thiols were estimated by a total thiol colorimetric assay kit (Cell Biolabs Inc., USA). Glutathione (GSH) was measured by a reduced glutathione colorimetric assay kit (ElabScience, USA). Catalase level was determined by using catalase activity colorimetric assay kit (BioVision, Abcam, UK). Measurement of MDA was done by a colorimetric assay kitfor MDA (Elabscience, USA).

ALT, AST and ALP levels were determined by using diagnostic kits (BioMerieux, France). Urea level was measured by a colorimetric assay kit (BioVision, Biovision Incorporated, UK). BUN level was assessed by a colorimetric detection kit (ThermoFisher Scientific, USA). Other biochemical parameters including total proteins, creatinine, bilirubin, albumin and globulin were measured using the relevant colorimetric diagnostic kits (Interchim Diagnostics Biochemistry kits, France).

Statistical analysis:

All data were presented as means ± S.D. The obtained data from all animals were analyzed using a statistical analysis SPSS software (SPSS Inc. Chicago IL, USA). *p*-values less than 0.05 ($P < 0.05$) were considered statistically significant.

Results

Blood cadmium level was (0.0021 ± 0.0001 ppm) in control untreated rats, measured (0.493 ± 0.023 ppm) in rats exposed to cadmium and estimated (0.281 ± 0.026 ppm) in rats exposed to cadmium and received impact whey isolate.

Rats exposed to cadmium and didn't receive impact whey isolate (group 2) demonstrated decreased hematological parameters, the most noticeable were Hb concentration and PCV%. These parameters were comparatively restored toward the control levels in rats exposed to cadmium and received impact whey isolate (group 3).

Table (1) shows the hematological parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the control untreated rats.

Table (1). Hematological parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the untreated control rats

Parameter	Control	Cadmium	Cadmium and impact whey isolate
RBCs count ($10^6/mm^3$)	5.71 ± 0.08	4.21* ± 0.13	5.53** ± 0.02
Total leucocytic Count ($10^3/mm^3$)	6.87 ± 0.41	5.47* ± 0.29	6.40** ± 0.04
Hemoglobin (Hb) concentration (g/dL)	13.27 ± 0.39	9.86* ± 0.37	12.69** ± 0.45
Packed cell volume (PCV %)	46.14 ± 0.33	37.18* ± 0.61	43.82** ± 0.73

Values are means ± S.D., N=20.*Significantly different means from untreated control ($P < 0.05$),**Significantly different from cadmium group.

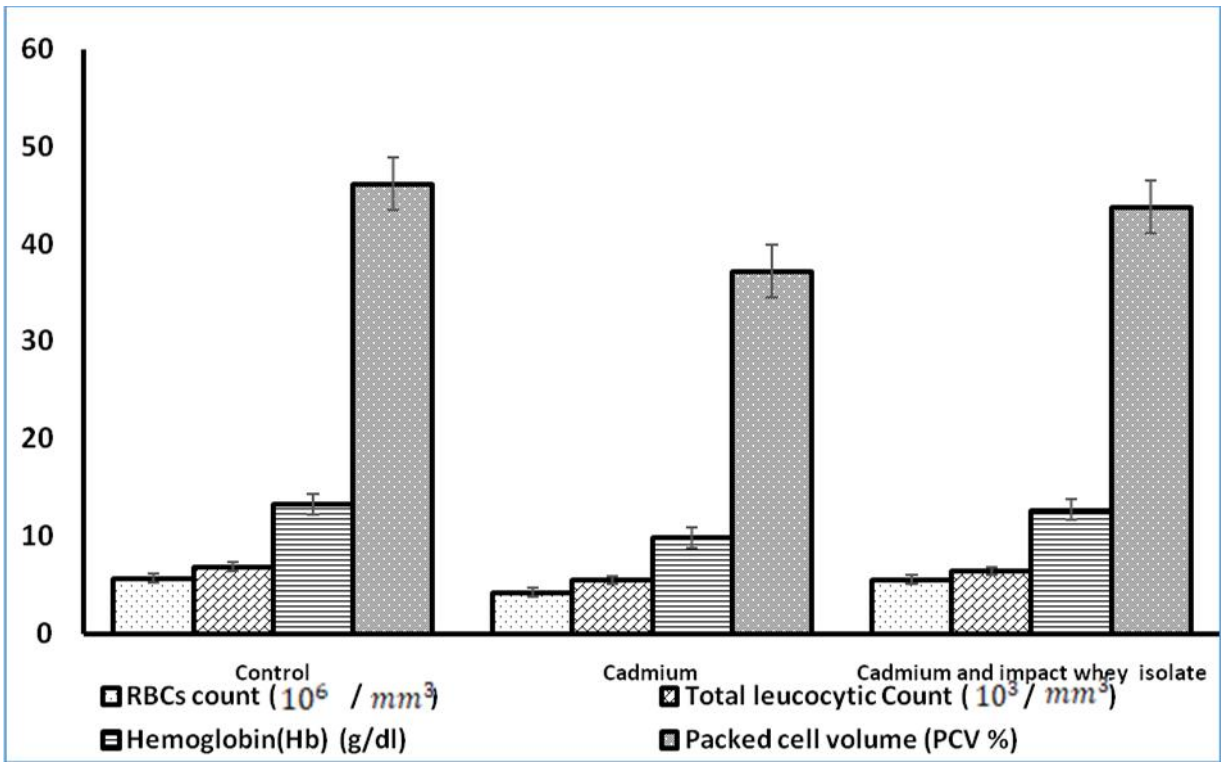

Figure (1). Hematological parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the untreated control rats.

Concerning the biochemical parameters, levels of total proteins, albumin and globulin were comparatively decreased in cadmium exposed animals which didn't receive impact whey isolate (group 2). Animals of this group exhibited significantly increased levels of creatinine, urea, BUN and bilirubin. The increased urea and BUN levels were remarkable.

Levels of total thiols, glutathione and catalase were decreased in the group of rats exposed to cadmium and had no access toimpact whey isolate.MDA level in animals of this group was significantly increased compared with the control level.

Table (2 a,b,c) shows the biochemical parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact why isolate compared with the control untreated rats.

Table (2). Biochemical parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the untreated control rats

a.Levels of total proteins (g/dL), albumin (g/dL), globulin (g/dL), creatinine (mg/dL), BUN (mg/dL) and bilirubin(mg/dL)

Parameter	Control	Cadmium	Cadmium and impact whey isolate
Total proteins	7.91 ± 0.11	5.88* ± 0.14	7.52** ± 0.13
Albumin	3.51± 0.05	2.40* ± 0.13	3.30** ± 0.15
Globulin	3.96± 0.02	2.78* ± 0.13	3.57**± 0.27
Creatinine	0.58± 0.01	0.84* ± 0.05	0.66** ± 0.31
BUN	16.31 ± 1.09	23.46* ± 1.41	17.83 ± 1.53
Bilirubin	6.74± 0.34	10.18* ± 0.23	8.89** ± 0.48

Values are means ± S.D., N=20
*Significantly different from untreated control ($P < 0.05$), **Significantly different from cadmium group.

b. Levels of alanine transferase (ALT) (IU/L), aspartate transferase (AST) (IU/L), alkaline phosphatase (ALP) (IU/L) and urea (mg/dL)

Parameter	Control	Cadmium	Cadmium and impact whey isolate
ALT	27.87 ± 1.02	56.11* ± 1.19	33.61** ± 1.05
AST	42.11 ± 1.07	117.14* ± 3.47	57.17** ± 1.14
ALP	24.67 ± 1.16	68.73* ± 1.49	30.89** ± 1.67
Urea	40.02 ± 0.71	69.08* ± 0.68	47.19** ± 0.73

Values are means ± S.D., N=20.
*Significantly different from untreated control ($P<0.05$), ** Significantly different from cadmium group.

c. Levels of total thiols (mmol/L), glutathione (GSH)(µg/mL), catalase (IU/L) and malondialdehyde (MDA) (nmol/mL)

Parameter	Control	Cadmium	Cadmium and impact whey isolate
Total thiols	2.48 ± 0.42	0.29* ± 0.06	1.97** ± 0.46
glutathione	41.23 ± 1.14	16.03* ± 0.61	37.14** ± 1.35
Catalase	53.42 ± 1.63	31.17* ± 1.05	47.19**± 1.28
MDA	324.17 ± 3.11	420.31* ± 3.52	349.37** ± 3.61

Values are means ± S.D., N=20.
*Significantly different from untreated control (P<0.05), ** Significantly different from cadmium group.

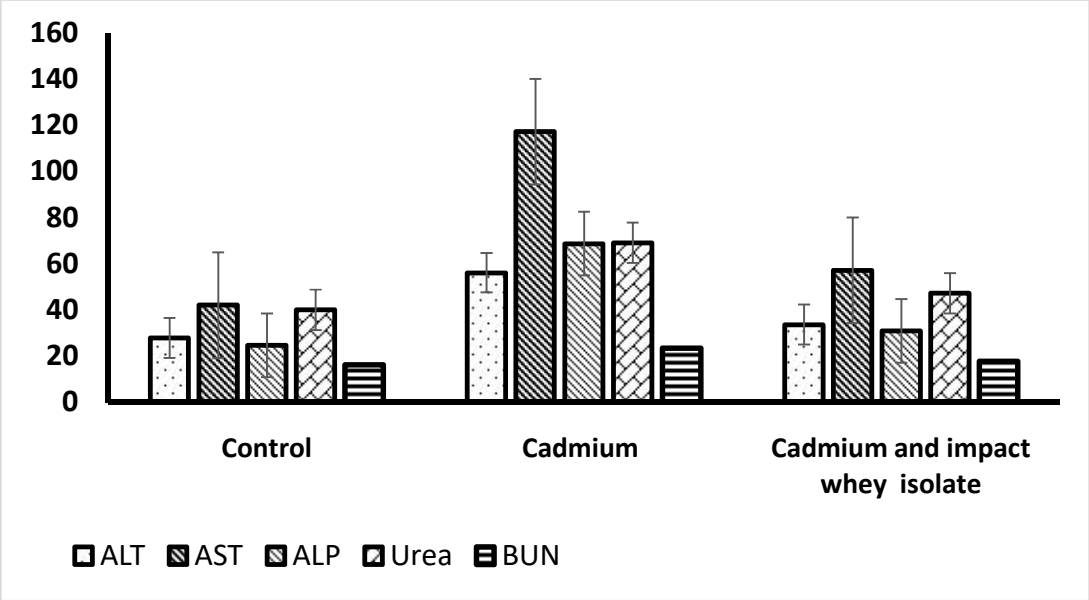

Figure (2). Biochemical parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the untreated control rats

b. Levels of alanine transferase (ALT) (IU/L), aspartate transferase (AST) (IU/L), alkaline phosphatase (ALP) (IU/L), urea (mg/dL) and BUN (mg/dL)

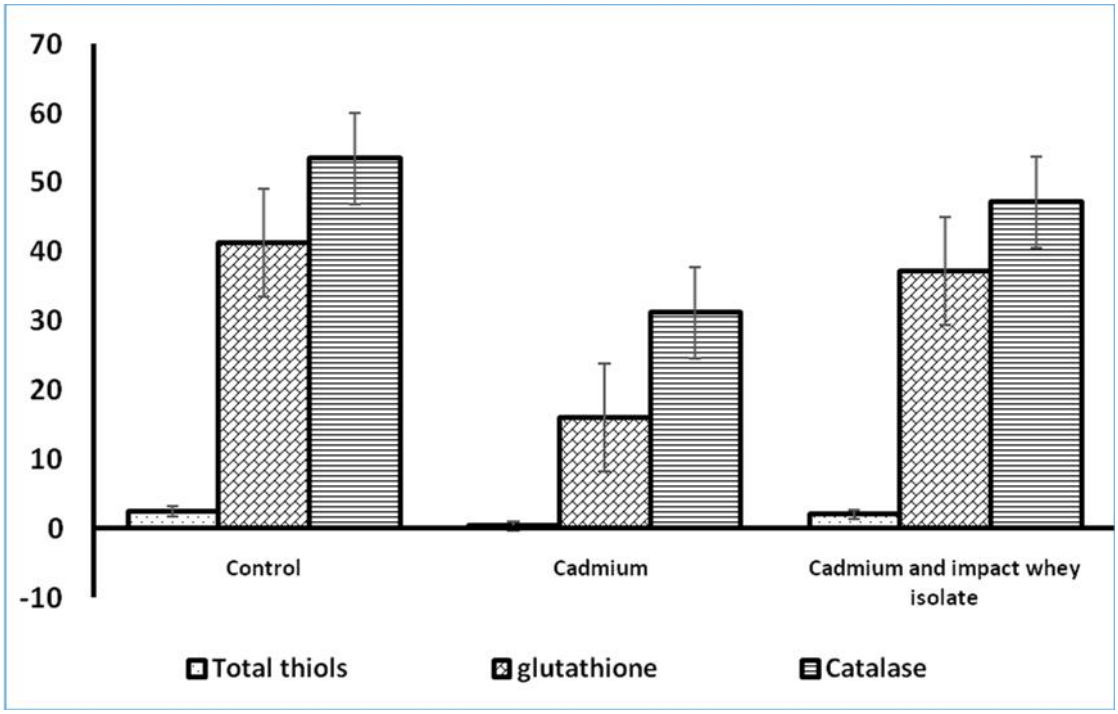

Figure (2). Biochemical parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the untreated control rats

c. Levels of total thiols (mmol/L), glutathione (µg/mL)and catalase(IU/L).

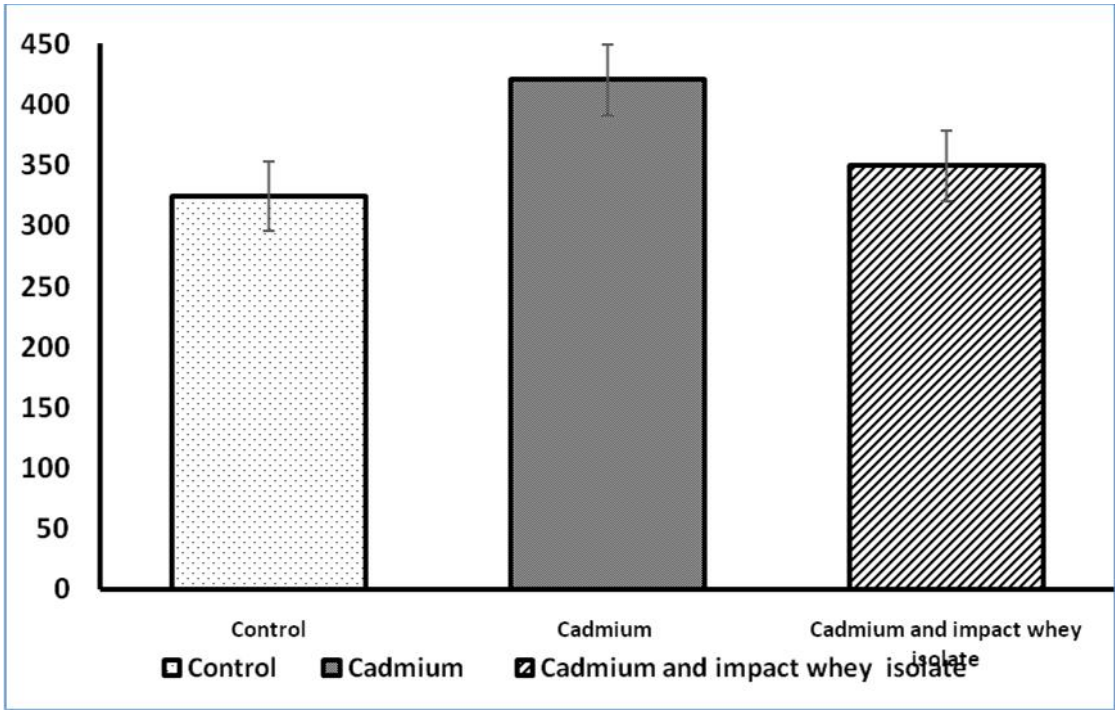

Figure (2). Biochemical parameters in rats exposed to cadmium, and rats exposed to cadmium and received impact whey isolate compared with the untreated control rats

d. Level of malondialdehyde (MDA) (nmol/mL).

Discussion

A limited magnitude of free radicals is required to carry out some physiological metabolic activities such as detoxification and cell respiration. Reactive oxygen species (ROS) include a component of free radicals, such as hydroxyl and superoxide radicals, and another component of non-radicals exemplified by hydrogen peroxide (Case, 2017). Excess magnitude of ROS, encompassing free radicals, is highly oxidizing to cell molecules and create a state of oxidative stress (oxidative damage) which affects cell proteins, DNA and even expression of some genes (Urso and Clarkson, 2003; Lee et al, 2004; Li et al., 2015). Lipid peroxidation, mainly affecting cell and organelles membranes, is among the most deleterious effects provoked by ROS (Staudacher et al., 2018).

The highly potent endogenous antioxidation system, existing in human and animals, is a highly sensitive detector to excess free radicals, especially reactive oxygen species, and acts to prevent and/or block their deleterious actions (Finkel and Holbrook, 2000; Mccord, 2000; Klaus and Heribert, 2004; Augus et al., 2011; Yigit et al., 2014 ; Li et al., 2015). Superoxide dismutase, catalase and glutathione peroxidase are endogenous antioxidant enzymes, while metallothionins are example of non-enzymatic antioxidants (Viarengo et al., 2000; Mruk et al., 2002; Pisoschi and Negulescu, 2011).All these endogenous antioxidants contribute, by different mechanisms, in elimination of excess free radicals (Alfonso-Prieto et al., 2009; Case, 2017; Staudacher et al., 2018).

The endogenous antioxidant mechanisms may be impaired in case of heavy metals toxicity, this occurs under effect of the overwhelming oxidative stress which depletes the active antioxidant molecules. In other words, the effect and magnitude of the oxidative molecules, exemplified by free radicals, exceed the counteracting action of antioxidative molecules (Li et al, 2015). In such cases, external additive source of antioxidants is required, preferably in the form of additive nutrients, to restore the oxidation: antioxidation balance. The antioxidative activity of these nutrients is proposed to support the endogenous antioxidation capacity in various ways. One of these ways is the prevention of lipid peroxidation which is one of the main functions of potent antioxidants (Pham-Huy et al., 2008). If proteins are selected as additive nutrients, then the main role of these external natural proteins to function as efficient antioxidant, synergistically with the endogenous antioxidant system, is to inhibit lipid peroxidation and thus preventing cell damage. This is accomplished through elimination (scavenging) of free radicals and binding (chelation) with pro-oxidative molecules, as well as enhancing reduction of reactive oxygen species (Feng et al., 2017; Pisoschi and Negulescu, 2011).

Cadmium, as a highly toxic heavy metal, was employed in the current study to induce a state of oxidative stress in rats.After absorption, cadmium is distributed to different tissues and organs, and start to accumulate especially in liver and kidney (Sharma et al., 2015). The accumulated cadmium induces oxidative damage in these organs through indirect generation of free radicals (Templeton and Liu, 2010). Induction of oxidative stress and direct action of cadmium on lipid peroxidation of cell membranes are main events in progression of cadmium cytotoxicity (Klaudia and Marian, 2011).Lipid peroxidation of mitochondrial membranes drastically affects ATP production and associated with sharp decrease in mitochondrial glutathione (Nigam et al., 1999). Moreover, cadmium exerts a suppressive effect on antioxidative enzymes, and thus accentuates the already existing oxidative stress. Finally, apoptosis takes place in cadmium toxicity as a result of caspases activation (Dorta et al., 2003).

The presently encountered elevations of serum enzymes ALT, AST and ALP reflect the cadmium-induced hepatic damage. Increased serum levels of hepatic enzymes is strongly linked with hepatotoxicity (Dhu et al., 2004). The damaged lysosomal membranes due to lipid

peroxidation become more permeable with leakage of hepatic enzymes and subsequent increase of their serum level. Also, biochemical parameters indicating kidney functions, including urea and creatinine, were increased in the presently cadmium-intoxicated rats. This points to a nephrotoxic effect and impaired renal functions caused by cadmium toxicity. Metallothioneins, especially in hepatic tissues, contribute to the antioxidation activities through their property to bind the pro-oxidative metals (Viarengo et al., 2000). Cadmium-induced nephrotoxicity is presumably ascribed to the released cadmium-metallothionein complexes originating from the damaged hepatic tissue.

The presently estimated levels of total thiols, glutathione and catalase, which reflect the oxidative stress and the antioxidative status, were all decreased in rats exposed to cadmium. Oxidation activity of ROS, generated by toxicities, extend to involve most of such antioxidant molecules which may loss their activity. Glutathione and catalase are actively incorporated in scavenging free radicals, and catalase acts as a potent antioxidant by destructing hydrogen peroxide and thus eliminate one of the major factors causing lipid peroxidation (Alfonso-prieto et al, 2009). Deletion of these antioxidants gives the opportunity to free radicals to provoke more intensive lipid peroxidation (De Cavanagh et al., 2000). In the presence of an oxidative stress, glutathione-related proteins may be converted to reduced forms (The'venod, 2009). This may interpret the decreased glutathione level in rats currently exposed to cadmium Level of total thiols was also decreased in the presently cadmium intoxicated rats. Thiols, involving glutathione, under oxidative stress may undergone oxidation and their role to scavenge singlet oxygen and hydroxyl radicals is minimized (Sato and Berrnner, 1993). The presently encountered increased level of MDA is a direct expression of the existing oxidative damage, since MDA is produced as a result of lipid peroxidation of the cellular membranous structures.

It has been stated that dietary antioxidants protect against cell damage induced by the excess free radicals and thus alleviate the effect of oxidative stress (Feng et al., 2017). In the present study, cadmium blood level was significantly decreased in rats intoxicated with cadmium and received whey proteins compared with rats exposed to cadmium. This might be ascribed to a postulated indirect chelating activity of whey proteins through enhancing the formation of cadmium complexes with metal binding proteins. Undoubtedly, minimizing the pool of cadmium in blood reduces greatly the eventual power of oxidative stress induced by the main insult (cadmium). This subsequently gives the chance to the endogenous antioxidant system to relatively recovers and restart to counteract the effect of excess free radicals. In presence of the postulated antioxidant role of whey proteins, which act synergistically with the endogenous antioxidant molecules, the overall antioxidant status is much improved. This was finally expressed on the hematological and biochemical profiles of rats intoxicated with cadmium and received whey proteins. The estimated parameters were relatively restored and reversed toward the control levels. This might be considered as an evidence of the antioxidative activity of whey proteins against the tremendous oxidative damage caused by cadmium toxicity. More investigations are recommended to be done to define the detailed molecular mechanisms relevant to the antioxidative role of dietary proteins.

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