



Evaluation of antioxidant potential of natural xanthone mangiferin in myocardium- A rat model study

Binu Prakash, Abhilash S, Vineetha R C, Arathi P, Harikumaran Nair R*

Physiology Research Laboratory, School of Biosciences, Mahatma Gandhi University,
Kerala -686 560, India

*Corresponding author: harinair@mgu.ac.in

Abstract

Mangiferin, a glucosylxanthone found in *Mangifera indica*, reported to have a wide range of pharmacological properties. The objective of this study was to evaluate the antioxidant potential of mangiferin against arsenic trioxide induced myocardial oxidative stress in rats. Our earlier studies have revealed the oxidative stress inducing capacity of arsenic trioxide (As_2O_3), hence in the present study we have administered 4 mg/kg bwt of As_2O_3 to generate oxidative stress in myocardium. The antioxidant effect of mangiferin against arsenic induced toxicity was assessed by using biochemical parameters like reduced glutathione (GSH), glutathione-S-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and thiobarbituric acid reactive substances (TBARS). Cotreatment with mangiferin (100 mg/kg b.wt) for 30 days significantly ($p < 0.05$) inhibited the arsenic induced decrease in GSH, GST, GPx, SOD, and CAT levels. The mangiferin also protected the heart from lipid peroxidation. Taken together, our study revealed that mangiferin has potent antioxidant effect against arsenic trioxide induced toxicity in rat myocardium and which may be attributed to decrease in arsenic induced reactive oxygen species levels and resultant oxidative stress.

Keywords: Mangiferin, Natural Xanthone, Heart, Antioxidant, Oxidative stress, Arsenic trioxide.

Introduction

There is a strong current public interest in naturally occurring plant based remedies and dietary factors related to health and disease. In recent time there has been a remarkable increment in scientific research dealing with phytochemicals to mitigate oxidative stress. Antioxidants derived from medicinal plant source are gaining more attention as free radical scavengers as they protect against ROS induced oxidative stress or damage. Mangiferin, a polyphenolic compound consisting of several hydroxyl (-OH) groups which make it is an efficient free radical scavenger (Agarwal et al., 2015). Mangiferin is a molecule primarily obtained from the king of fruits

“*Mangifera indica*”, is a naturally occurring c-glycosyl xanthone extracted from the leaves. A number of studies reported that mangiferin has a broad range of therapeutic uses. Mangiferin is a heat stable molecule and it possesses antioxidant (Das et al., 2012), antidiarrhea (Sairam et al., 2003), dyslipidemic (Anila et al., 2002), antidiabetic (Aderibigbe et al., 1999) antiallergic (Garcia et al., 2003), antibacterial (Bairy et al., 2002) and anticancer (Yoshimi et al., 2001) activities. Instead of this mangiferin is recommend to treat immune deficiency diseases such as diabetes, hepatitis, arthritis and cardiac disorders (Sanchez et al., 2000).

Our previous studies in both *in vivo* (Mathews et al., 2012; Mathews et al., 2013; Binu et al., 2016) and *in vitro* (Vineetha et al., 2014; Mathews et al., 2016; Abhilash et al., 2016) experimental model reported that arsenic trioxide caused oxidative stress in heart and hepatic tissue. Arsenic trioxide treatment caused myocardial disorganization and interstitial edema in the heart (Raghu et al., 2009). So in this study we used the trivalent compound arsenic trioxide as an inducing agent for oxidative stress. In this background, the present study has been conducted to evaluate the antioxidant efficacy of mangiferin on the mitigation of arsenic induced oxidative stress in myocardium.

Materials and Methods

Chemicals and Reagents

Arsenic trioxide, Mangiferin (99%), Sodium pyruvate, Reduced glutathione (GSH), Oxidized glutathione (GSSG), Phenazine methosulphate (PMS), Nitroblue tetrazolium (NBT) were obtained from Sigma-Aldrich, Bangalore, India. 2,4-dinitro bis Nitro benzoic acid (DTMB), Nicotinamide adenine dinucleotide (NADH), Thiobarbituric acid (TBA), Nicotinamide adenine dinucleotide phosphate (NADPH), 1-chlor, 2,4 dinitro benzene (CDNB), Potassium chloride (KCl), Ethylene diamine tetra acetic acid (EDTA), Hydrogen peroxide (H₂O₂), Trichloroacetic acid (TCA) Magnesium sulfate (MgSO₄), were purchased from Merk Specialities Pvt. Ltd, Mumbai, India. Other chemicals and solvents of analytical grade were purchased from local retailer.

Experimental protocol

The rats were divided into four groups of six rats each, a normal control group, a mangiferin control which received 100 mg/kg b.wt of mangiferin, one arsenic trioxide (4 mg/kg b.wt) administered group and a combination group treated with 4 mg/kg b.wt of arsenic trioxide and 100 mg/kg b.wt of mangiferin. 0.1 % dimethyl sulfoxide (DMSO) solution was used as vehicle for mangiferin administration. Experimental groups received this via oral intubation daily for a period of 30 days. At the end of the experimental period animals were decapitated and heart was removed immediately, washed in ice cold 0.15 M NaCl and blotted on a filter paper. Then the heart tissue was weighed and homogenized by using Teflon glass homogenizer (1/10th weight/volume) in ice cold tris-HCl buffer (0.2 M, pH 7.4). The homogenate was centrifuged at 10000 g for 20 min at 4 °C and the supernatant was used for the estimation of lipid

peroxidation and various enzymatic and non enzymatic assays.

Assay of tissue GSH

GSH was measured in tissue homogenate according to the method described by Ellman (1959). In the assay mixture contained 0.1 mL of sample, 0.85 mL of PBS (0.3 M, pH 7.4), and 0.05 mL of DTNB (10 mM). The reaction was read at 412 nm, and results were expressed as µmoles of GSH/g protein.

Assay of tissue GST

GST level was assayed by the method of Habig et al (1974) tissue was washed in 1.15% KCl and homogenized in phosphate buffer (pH=7.4), centrifuged at 9000 rpm for 20 minutes. After centrifugation, supernatant was mixed with 3 ml of reaction mixture (1.7 mL Phosphate buffer + 0.1 mL of CDNB + 1.2 mL GSH) and change in accordance was read at 340 nm for 5 minutes.

Assay of Glutathione Peroxidase (GPx)

The activity of GPx was determined by the method of Rotruck et al (1973). Briefly, the reaction mixture contained 0.2 mL of 0.4 M of Tris-HCl buffer (pH 7.0), 0.1 mL of 10 mM of sodium azide, 0.2 mL of homogenate (homogenized in 0.4 M of Tris-HCl buffer; pH 7.0), 0.2 mL of glutathione and 0.1 mL of 0.2 mM of H₂O₂. The tubes were incubated at 37^o C for 3 minutes, and the reaction was terminated by the addition of 0.5 mL of 10% trichloroacetic acid (TCA). To determine the residual glutathione content, the supernatant was removed after centrifugation and to this 1 mL of DTNB reagent was added. The color that developed was read at 412 nm against a reagent blank, and results were expressed as µg of GSH consumed/mg protein.

Assay of Superoxide dismutase (SOD)

SOD activity was determined by the method of Kakkar et al. (1984). The assay mixture contained 0.1 mL of sample, 1.2 mL of sodium pyrophosphate buffer (pH 8.3, 0.052 M), 0.1 mL of PMS (186 µM), 0.3 mL of NBT (300 µM), and 0.2 mL of NADH (750 µM). Reaction was started by the addition of NADH. After incubation at 30 °C for 90 seconds, the reaction was stopped by the addition of 0.1 mL of glacial acetic acid. The reaction mixture was stirred vigorously with 4.0 mL of n-butanol. The mixture was allowed to stand for 10 minutes, centrifuged, and the butanol

layer was separated. The color intensity of the chromogen in butanol layer was measured at 560 nm against n-butanol, and the concentration of SOD was expressed as units/g of renal tissue. One unit was taken as the amount of enzyme that gave 50% inhibition of NBT reduction/mg protein.

Assay of Catalase (CAT)

Catalase activity in the sample was measured according to the method of Aebi (1974) by measuring the decrease in absorbance of H₂O₂ at 240 nm.

Detection of lipid peroxidation

Lipid peroxidation was determined by detecting thiobarbituric acid reactive substances (TBARS) level. TBARS level was estimated by measuring the pink color chromophore formed by the reaction with thiobarbituric acid absorbing at 535 nm (Beuge and Aust, 1978).

Statistical Analysis

The experimental results were expressed as mean \pm SD. Statistical analysis was evaluated by one-way analysis of variance (ANOVA) using SPSS software (version 20.0, SPSS Inc, Chicago, IL, USA). Values were considered significantly different if $P < 0.05$.

Results

Effects of mangiferin on non enzymatic antioxidant GSH level

Figure 1 illustrates the alterations in the level of GSH in the heart tissue of control and experiment rats. A significant decrease ($p < 0.05$) in the level of GSH in the heart tissue was observed in rats treated with arsenic when compared to the control. Administration of mangiferin along with arsenic significantly increased the level of this non enzymatic antioxidant to near normalcy when compared with arsenic treated rats.

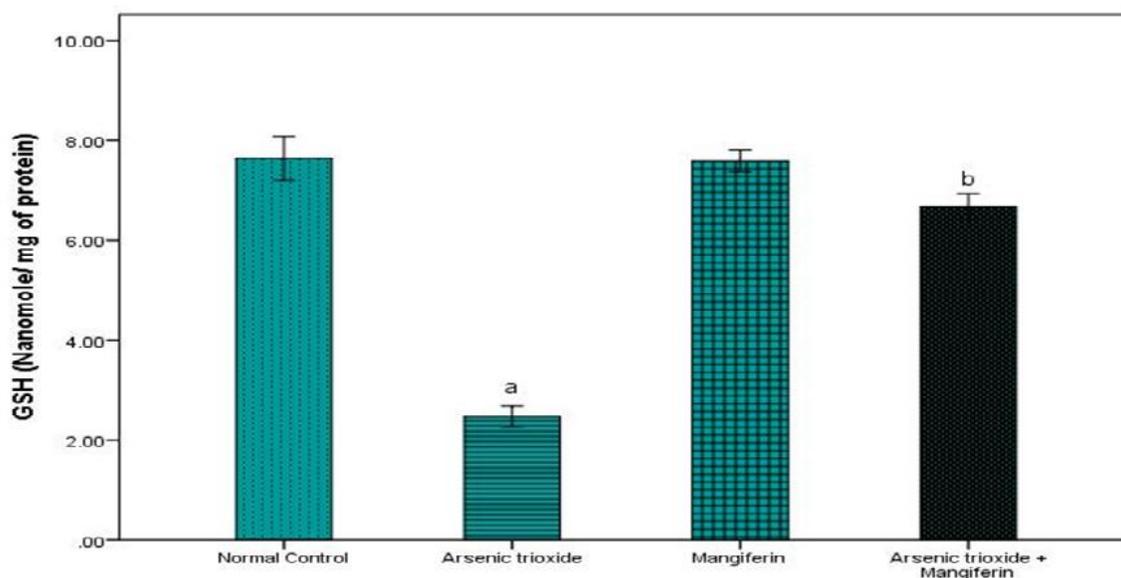


Figure 1. Effect of mangiferin non-enzymatic antioxidant GSH in heart tissue. Normal control, Arsenic trioxide – 4 mg/ kg b.wt, Mangiferin- 100 mg/kg b. wt, and Arsenic trioxide - 4mg/ kg b.wt) + Mangiferin- 100 mg/ kg b.wt. Data represented as mean \pm SD, n=6. **a** (significant difference between Normal control and Arsenic trioxide), **b** (significant difference between Arsenic trioxide and Arsenic trioxide + Mangiferin). $P < 0.05$

Effects of mangiferin on glutathione-s- transferase (GST) activity in heart

Figure 2 represents the activity of enzymatic antioxidant glutathione-s- transferase, which was significantly ($p < 0.05$) decreased in the heart tissue of

arsenic treated rats when compared with control rats. Administration of mangiferin along with arsenic intoxicated rats significantly ($p < 0.05$) protect the level of GST in heart tissue. Mangiferin alone treated group also shown significant ($p < 0.05$) difference with that of normal control group.

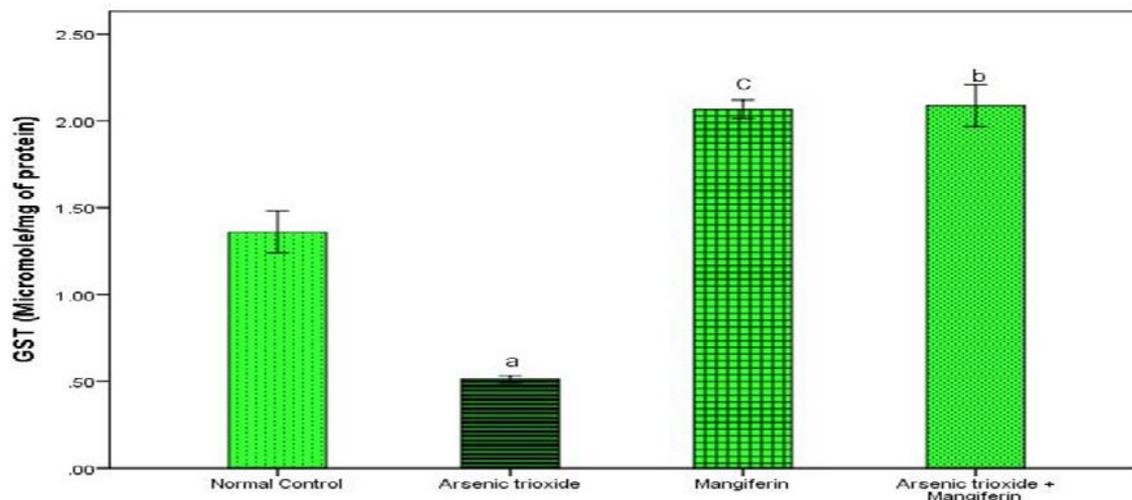


Figure 2. Effect of mangiferin enzymatic antioxidant GST level in heart tissue. Normal control, Arsenic trioxide – 4 mg/ kg b.wt, Mangiferin- 100 mg/kg b. wt, and Arsenic trioxide – 4mg/ kg b.wt) + Mangiferin- 100 mg/ kg b.wt. Data represented as mean \pm SD, n=6. a (significant difference between Normal control and Arsenic trioxide), b (significant difference between Arsenic trioxide and Arsenic trioxide + Mangiferin), c (significant difference between normal control and mangiferin). $P < 0.05$

Effect of mangiferin on glutathione peroxidase (GPx) level in heart

Arsenic induced changes of GPx activity and the protective role of mangiferin are shown in Figure 3. Oral administration of arsenic trioxide resulted in

significantly ($p < 0.05$) decreased the level of GPx as compared to controls, whereas co-administration of mangiferin exhibited a significant increase in the enzyme level with respect to arsenic alone treated group.

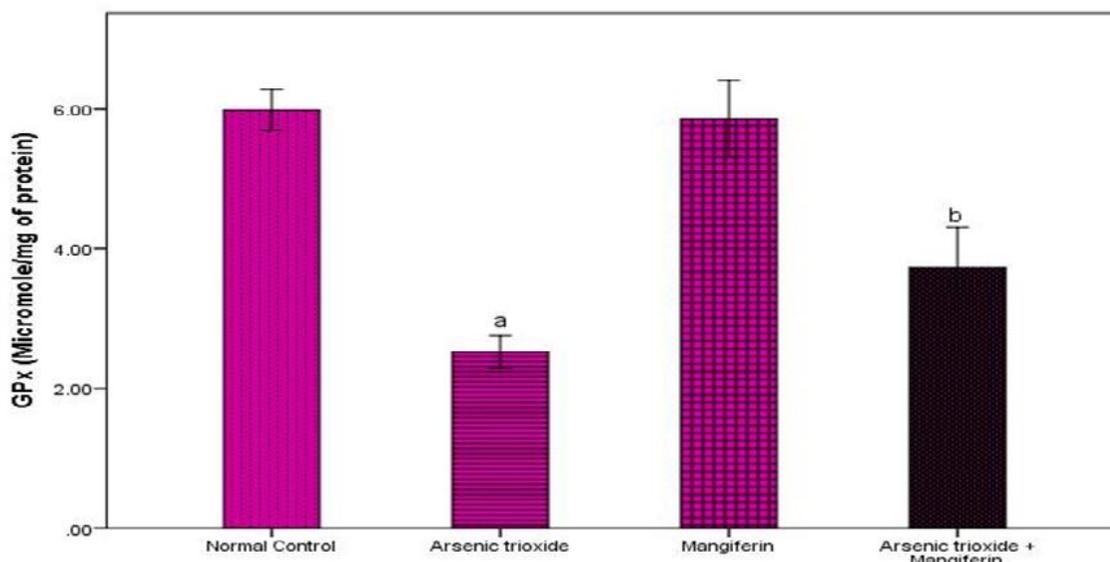


Figure 3. Effect of mangiferin enzymatic antioxidant GPx level in heart tissue. Normal control, Arsenic trioxide – 4 mg/ kg b.wt, Mangiferin- 100 mg/kg b. wt, and Arsenic trioxide – 4mg/ kg b.wt) + Mangiferin- 100 mg/ kg b.wt. Data represented as mean \pm SD, n=6. a (significant difference between Normal control and Arsenic trioxide), b (significant difference between Arsenic trioxide and Arsenic trioxide + Mangiferin). $P < 0.05$

Effect of mangiferin on superoxide dismutase activity (SOD) in heart

Superoxide dismutase activity in the cardiac tissue after arsenic administration and mangiferin treatment

is indicated in Figure 4. A significantly ($p < 0.05$) decreased activity of SOD in heart tissue was observed in arsenic treated group. Treatment of rats with both arsenic and mangiferin significantly ($p < 0.05$) maintain the level of SOD.

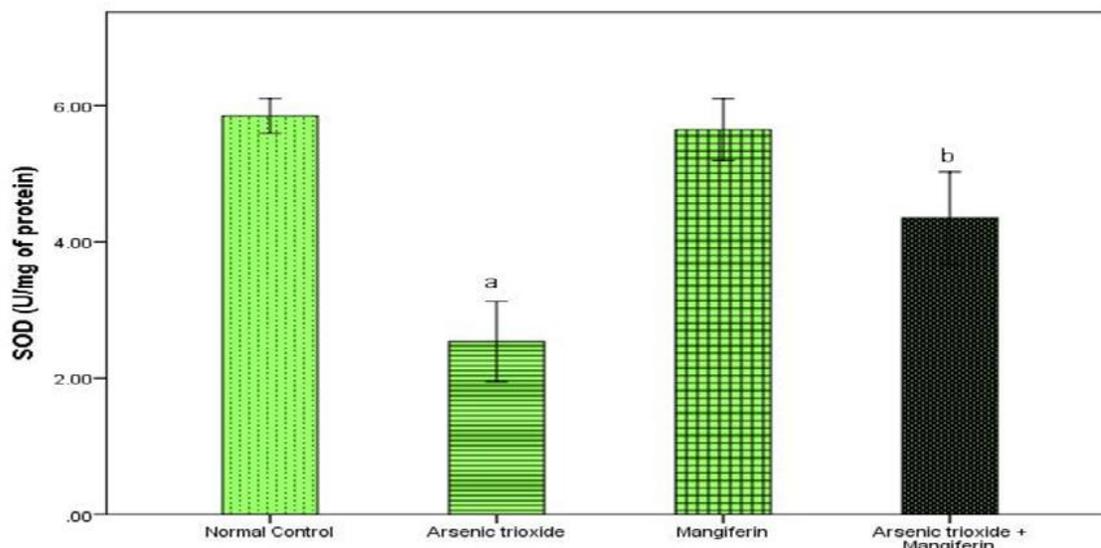


Figure 4. Effect of mangiferin on superoxide dismutase activity (SOD) level in heart. Normal control, Arsenic trioxide – 4 mg/ kg b.wt, Mangiferin- 100 mg/kg b. wt, and Arsenic trioxide - 4mg/ kg b.wt) + Mangiferin- 100 mg/ kg b.wt. Data represented as mean \pm SD, n=6. **a** (significant difference between Normal control and Arsenic trioxide), **b** (significant difference between Arsenic trioxide and Arsenic trioxide + Mangiferin). $P < 0.05$

Effect of mangiferin on catalase (CAT) activity in heart

A significant ($p < 0.05$) decline in catalase (CAT) was noted in heart tissue of rats treated with arsenic when

compared with normal control rats (Figure 5). Cotreatment with mangiferin exhibited significant ($p < 0.05$) increase in CAT level compared with arsenic group.

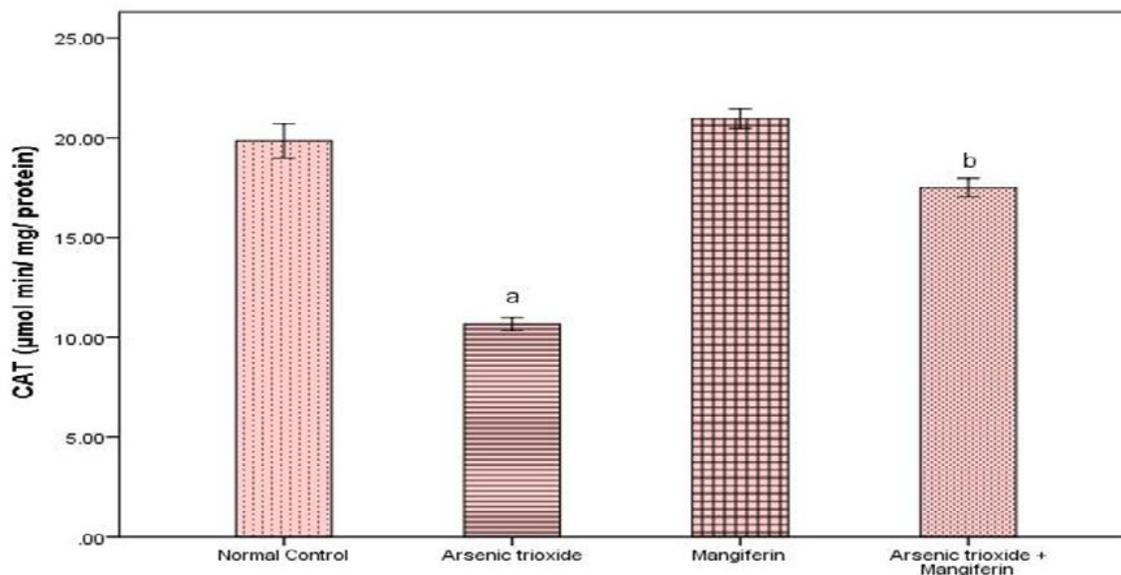


Figure 5. Effect of mangiferin on catalase in heart tissue. Normal control, Arsenic trioxide – 4 mg/ kg b.wt, Mangiferin- 100 mg/kg b. wt, and Arsenic trioxide - 4mg/ kg b.wt) + Mangiferin- 100 mg/ kg b.wt. Data represented as mean \pm SD, n=6. **a** (significant difference between Normal control and Arsenic trioxide), **b** (significant difference between Arsenic trioxide and Arsenic trioxide + Mangiferin). $P < 0.05$

Effect of mangiferin on lipid peroxidation in heart

Compared to the control group, arsenic trioxide treated group had a significant ($p < 0.05$) increase in TBARS

level in heart tissue (Figure 6). Furthermore arsenic along with mangiferin significantly ($p < 0.05$) prevent lipid peroxidation with low TBARS level in heart as compared with arsenic alone treated group.

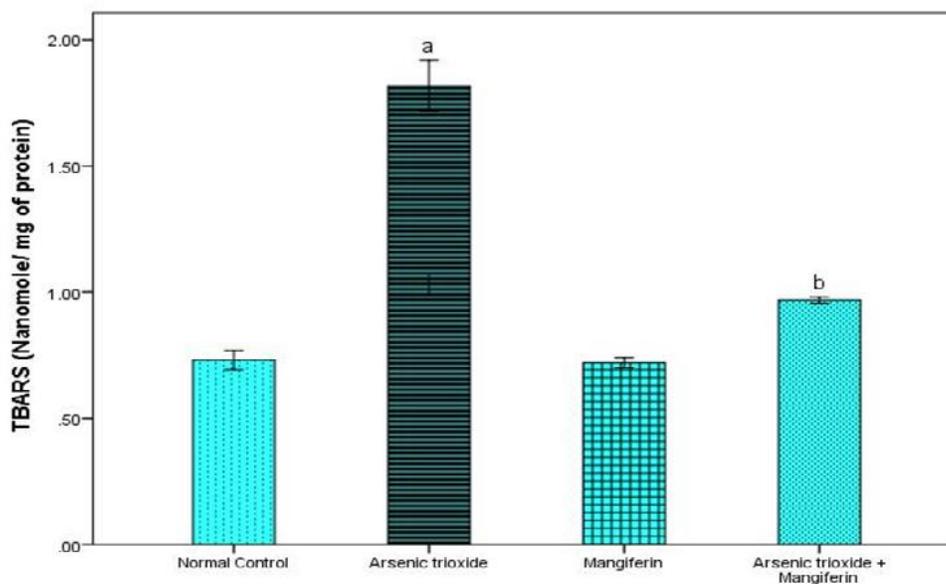


Figure 6. Effect of mangiferin on TBARS activity in heart tissue. Normal control, Arsenic trioxide – 4 mg/ kg b.wt, Mangiferin- 100 mg/kg b. wt, and Arsenic trioxide - 4mg/ kg b.wt) + Mangiferin- 100 mg/ kg b.wt. Data represented as mean \pm SD, n=6. a (significant difference between Normal control and Arsenic trioxide), b (significant difference between Arsenic trioxide and Arsenic trioxide + Mangiferin). $P < 0.05$

Discussion

Antioxidant enzymes as well as nonenzymatic antioxidants are from the first line of defense against ROS induced oxidative damage in a living organism. The oxidant-antioxidant system is in equilibrium in normal conditions. An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions. Low levels of antioxidants or inhibition of the antioxidant enzymes cause oxidative stress and may damage or kill cells. Arsenic induced toxic changes in several organs have been previously described and shown to be the results of induction of ROS and depletion of antioxidant defenses (Reghu et al., 2009; Mathews et al., 2016). Therefore, the theory of increasing antioxidant capacity in tissues to ameliorate the toxic effects caused by arsenic was investigated in the present study. For this purpose here we select and utilized antioxidant potential of natural xanthone mangiferin.

The antioxidant status of our body includes the concerted action of both antioxidant enzymes and nonenzymatic antioxidants. In the current study level of reduced glutathione (GSH) was declined during treatment with oxidative stress inducer arsenic in heart tissue. Reduced glutathione acts as a free radical scavenger and is involved in the repair of radical caused biological damage, and the decrease in the GSH content may alter antioxidant enzymes. The decrease in the level of GSH in tissues may be due to increases in the utilization or decrease the rate of synthesis of this antioxidant in cause of oxidative stress. GSH and other thiol containing proteins play a very crucial key role in cellular defense against arsenic toxicity. Curello et al (1985) reported that reduced glutathione (GSH) donates protons to membrane lipids and protects them from oxidant attacks. Diminish in GSH content because of oxidative stress reduce the actions of GST and GPx with a concomitant decrease in the activity of GSH stimulating enzyme. These results suggest that the xanthone compound mangiferin cotreatment maintain the activity of GSH near to normal range which may be due to the inhibition of sulfhydryl (SH) group oxidation or radical scavenging capacity of mangiferin. The primary antioxidant mechanism of mangiferin seems to be

mediated through enhancing glutathione levels (Amazzal et al., 2007). Jha et al (2007) reported that mangiferin having two hydroxyl groups at the 6 and 7 positions of B ring generally have strong antioxidant potency.

Glutathione-S-transferase (GST) can remove free radicals and its levels can reflect the antioxidant capacity in the body. The present studies showed that GST levels were lowered in arsenic treated rats as compared with normal control rats. GST is a phase 2 enzyme that is also critically involved in the detoxification of ROS (Landrigan et al., 1989; Yang et al., 2001). Seven classes of cytosolic GST are identified in mammalian, designated Alpha, Mu, Pi, Sigma, Theta, Omega, and Zeta (Hayes et al., 1995; Armstrong et al., 1997). During nonstressed conditions, class Mu and Pi GSTs interact with kinases Ask1 and N-terminal kinases JNK respectively, and inhibit these kinases and GSTP1 dissociates from (JNK) in response to oxidative stress (Cho et al., 2001). Treatment with mangiferin led to a significantly enhancement of tissue GST activity. This may be due to the capability of mangiferin to induce the gene level expression of GST. In addition to this there might be a possibility of inducible expression of rat GSTA2 gene occurs through Nrf2 based pathway.

Another enzymatic antioxidant glutathione peroxidase (GPx) was declined during arsenic induced oxidative stress condition. GPx is the general name of an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage. GPx reduces lipid hydroperoxides into lipid alcohols (Wang et al., 1997). GPx is a selenium containing enzyme and it was well established that arsenic interacts with selenocysteine moiety of GPx to form inactive As-selenium complex (Milton et al., 2012). This was resulting in the inhibition of GPx activity or altering the expression and synthesis of GPx. GPx are major enzymes that remove hydrogen peroxide generated by SOD in cytosol and mitochondria (Chance et al., 1979). Cotreatment with mangiferin maintains the tissue GPx activity near to normalcy. This may be positive indication of antioxidant potential activity of mangiferin over arsenic induced oxidative stress.

SOD and CAT are two key enzymes in detoxifying intracellular O_2^- and H_2O_2 . SOD catalyzes the dismutation of superoxide anions and prevents the subsequent formation of hydroxyl radicals (Imlay et al., 1988). As shown in results, a significant decrease of SOD and CAT activity in the heart tissue was

observed in the arsenic treated groups compared with control group. Cotreatment with mangiferin preserved the level of SOD and CAT activity in heart tissue. A reported from Leiro et al (2003), observed that mangiferin is capable for superoxide anion scavenging which is responsible for the inhibition of ROS production. Catalase catalyzes the conversion of the H_2O_2 generated in the cells normally or under conditions of oxidative stress into water and oxygen thereby protecting the cells against damage caused by peroxide radicals. The diminished activity of SOD and CAT in arsenic exposed rats was due to the enhanced production of superoxide radical anions and insufficient supply of NADPH (Rana et al., 2012; Zahng et al., 2013). Antioxidant property which normalized the levels of cellular defense enzymes has been mainly ascribed to the catechol moiety possessed by mangiferin.

Treatment with arsenic induces oxidative stress via ROS generation, depletion of cellular endogenous antioxidant reserve (Gupa et al., 2003). GSH, GST, GPx, SOD and CAT replenishment on mangiferin supplementation for the entire period reflects a favourable balance between potentially harmful oxidants and protective antioxidants.

Arsenic (III) compounds can inhibit enzymatic antioxidants especially the GSH-dependent enzymes, such as glutathione-S-transferases (GST), glutathione peroxidase (GPx) and non enzymatic GSH reductase through binding to their sulfhydryl (-SH) groups (Schiller et al., 1977; Waalkes et al., 2004). Oxidation of sulfhydryl groups or methionine residues of proteins cause conformational changes, protein unfolding, and degradation. Esra et al (2012) observed that higher production of ROS in body may change DNA structure, result in modification of proteins and lipids, activation of several stress-induced transcription factors. This may be altering the gene level expression pattern of these antioxidants. Restoration of these antioxidants near to normalcy during mangiferin treatment might be due to the ability of this compound to protect the SH group from the oxidative damage. It is well known that the antioxidant activity of polyphenols is basically attributed to their ability to release hydrogen atoms. It has been proposed that the catechol moiety with a 6,7-dihydroxylated structure, together with its aromatic bonds, is responsible for its antioxidant property (Wauthoz et al., 2007). The antioxidant system replenishment due to mangiferin supplementation for 30 days reflected a favorable balance between potentially harmful oxidants and protective antioxidants in the heart tissue.

Our results also showed decreased level of lipid peroxidation marker TBARS during cotreatment with mangiferin in heart tissue, is suggestive for lowered oxidative stress. The lipid radical and peroxide are risky to the body cells and allied with tissue damage. Shyamala et al (2006) observed that mangiferin reduced the lipid peroxide formation during isoproterenol induced myocardial infarction in rats. Therefore mangiferin might have scavenged these free radicals and lowered the peroxidation resulting in decreased oxidative stress in rat myocardium. In the present study, we observed that arsenic decreased the antioxidant enzyme level along with elevation of lipid peroxidation markers in heart tissue of rats. Mangiferin possess the ability to scavenge ROS, a causal inducer of oxidative stress, inhibit lipid peroxidation, and increase the reduced glutathione content, thus establishing itself as a good antioxidant. Instead of this the enzymatic antioxidant defense systems are the natural protector against lipidperoxidation. So antioxidant property of this xanthone, mangiferin enhances antioxidant system and through by reduces the membrane peroxidation rate.

Conclusion

Our data suggest that mangiferin has the capacity to counteract arsenic-induced oxidative damage in the heart; this could be due to its antioxidant nature, including its free radical scavenging and membrane stabilizing properties. Thus, the present study has shown that mangiferin is a heart protective natural xanthone against oxidative damage. Further detailed investigations are in progress to elucidate the exact mechanism by which mangiferin elicits its modulatory properties in myocardium.

Acknowledgments

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