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RESEARCH ARTICLE

PROTECTIVE EFFECTS OF ETHANOL EXTRACT OF MANGOSTEEN (*GARCINIA MANGOSTANA L*) PERICARP AGAINST LEAD ACETATE-INDUCED HEPATOTOXICITY IN MICE

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ABSTRACT

Lead is one of the most toxic metals, producing severe organda mage in animals and humans. Oxidative stress reported to play an important role in lead acetate induced liver injury. This study was carried to investigate the role of ethanol extract of mangos teen pericarp in protecting against lead acetate-induced hepatoxicity in male mice.The sample used 50 male mice were divided into 5 groups: negative control (mice were given daily with aquadest); positive control (mice were given daily with lead acetate 20 mg/kg BW orally once in a day for 21 days); and the treatment group (mice were given the mangos teen pericarp extracts200 mg; 400 mg; 800 mg/kg BW orally once in a day for 25 days, and on 4th day, were given lead acetate 20 mg/kg BW one hour after the mangos teen pericarpextracts administration for 21 days). On day 25 measured levels of Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvate Transaminase (SGPT), Alkaline Phosphatase (ALP), Malondialdehyde (MDA), Superoxide Dismutase (SOD)and Glutathione Peroxidase (GPx). The SGOT, SGPT, ALP, MDA, SOD and GPx data were analyzed with one-way ANOVA, followed by LSD test. The results showed that, Oral administration of lead acetate 20 mg/kg BW for 21 days resulted in a significant increase in SGOT; SGPT, ALP and MDA level. Moreover, significant decrease in SOD and GPx. Treatment with the mangos teen pericarpextracts800 mg/kg BW but not 200 mg/kg BW and 400 mg/kg BW significantly ($P< 0.05$) decreased the elevated SGPT; SGOT, ALP and MDA levels as compared to positive control group. Treatment with the mangosteen pericarpextracts 800 mg/kg BW also significant increase in SOD and GPx as compared to positive control group. From the results of this study concluded that the mangos teen pericarpextractscould be a potent natural herbal product provide a promising hepato protective effect against lead acetate induced hepato toxicity in mice

INTRODUCTION

The environmental contamination by heavy metals has increased drastically along with the rapid development of modern industry. Among these metals is lead, of which its levels have increased substantially during the last few years. Lead-exposure occurs through the respiratory and gastrointestinal systems and lead which is ingested and absorbed is stored mainly in liver, kidney and bone. Elevated lead levels in the body have been associated with nephrotoxic, hepatotoxic, neurotoxic and cardiovascular disease (**Mudipalli, 2007; Adikwu *et al.*, 2013**). In living systems, liver is considered to be highly sensitive to toxic agents. The study of lead acetate in enzyme activities such as SGOT, SGPT and ALP have been found to be of great value in experimental liver damage (**Akilavalli *et al.*, 2011**). The mechanism behind lead hepatotoxicity is the oxidative stress and it develops when there is an imbalance between the generation of reactive oxygen species (ROS) and the scavenging capacity of antioxidants in the liver (**Hsu *et al.*, 2002; Patrick, 2006**). A previous study confirmed the possible involvement of reactive oxygen species (ROS) or free radicals such as superoxide ion (O_2^-), nitrogen oxide (NO) and hydroxyl radical (OH^-) in lead-induced toxicity (**Xu *et al.*, 2008; Mehana *et al.*, 2010**). MDA, one of the well known secondary products of lipid per oxidation after exposure to reactive oxygen species and free radicals, may be used as an indicator of cell membrane injury. The increase in MDA levels in liver suggests enhanced lipid per oxidation leading to tissue damage and failure of antioxidant defense mechanisms to prevent formation of excessive free radicals (**Kosem, 2007; Ibrahim *et al.*, 2012**). The most widely used assay for lipid per oxidation is the MDA formation. The level of MDA, the end product of lipid per oxidation is measured by the thiobarbituric acid reactive substance (TBARS) method. The concentration of MDA is the direct evidence of toxic processes caused by free radicals (**Attia *et al.*, 2013**).

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Antioxidant activity or inhibition of generation of free radicals plays a crucial role in providing protection against such hepatic damage. Vitamins are ideal antioxidants to increase tissue protection from oxidative stress due to their easy, effective and safe dietary administration in a large range of concentrations (**Upadhyay *et al*., 2009**). Antioxidants such as vitamin E and vitamin C were found to improve hepatic conditions significantly when treated in animals with lead acetate induced damage. The antioxidant activity of vitamin E is targeted primarily towards the lipid component of cells. Antioxidants such as vitamin E and vitamin C have been shown to inhibit free radical formation and are effective in minimizing lipid per oxidation in several different biological systems. Vitamin E and vitamin C is a natural antioxidant and prevents the increased production of free radicals induced by oxidative damage to lipids and lipoproteins in various cellular compartments and tissues (**Aziz *et al*., 2014**).

Recently, there has been an increased interest in the therapeutic potential of plant products or medicinal plants having antioxidant properties in reducing free radical-induced tissue injury. Medicinal plants are commonly used for the treatment of various ailments, as they are considered to have advantages over the conventionally used drugs that are much expensive and known to have harmful side effects (**Vishnu Priya *et al*., 2010; Jackie *et al*., 2011**). Many authors tried various ameliorating agents like Rosemary; *Curcuma longa*; Ginger; green tea; *Tinospora cordifolia* against lead toxicity (**Sharma and Pandey, 2010; Abd El Kader *et al*., 2012; Baxla *et al*., 2013; Mannem, 2014**). Mangosteen (*Garcinia mangostana L*.) is one of the most famous fruits in Indonesia. Previous studies have shown that the mangosteen extracts from various parts contain varieties of secondary metabolites such as prenylated and oxygenated xanthones. Xanthones such as α, β-, and γ-*mangostins, garcinone E,* 8-*deoxygartanin*, and *gartanin* could be isolated from pericarp, whole fruit, bark, and leaves of mangosteen (**Jung *et al*., 2006**). Several studies have shown that obtained xanthones from mangosteen have remarkable biological activities such as antioxidant, antitumoral, anti-inflammatory, antiallergy, antibacterial, antifungal, and antiviral activities (**Pedraza-Chaverri *et al*., 2008; Zerena, 2009; Ngawhirunpat *et al*., 2010**). The present study is intended to investigate hepaprotective activity of ethanolic extract of the mangosteen peel against lead acetate induced liver damage in mice.

MATERIALS AND METHODS

Chemicals

Lead acetate was purchased from Sigma-Aldrich chemic (USA). All other chemicals and solvents used in this study were of highest purity and analytical grade, and purchased from Sigma-Aldrich chemic (USA). Reagent kits for assay of SGPT, SGOT and ALP were obtained from Kristalindo (Indonesia). Reagent kits for determination of MDA, GPx and SOD were purchased from Kristalindo (Indonesia).

Experimental animal

Male Swiss albino mice (Mus musculus L) weighing approximately 25–30 g (2.5-3 months) were obtained from Veterinary Farma Surabaya Indonesia for experimental purpose. They were housed in plastic cages in an air-conditioned room with temperature maintained at 25^{o}C ± 3^{o}C, relative humidity of 50%± 5% and 12h alternating light and darkcycles. The mice were provided *ad libitum* with tap water and fed with standard commercial mice chow. The Animal Ethics Committee of Airlangga University, Surabaya Indonesia has approved experimental protocol.

Preparation of ethanol extract of mangosteen pericarps

Plant material and extract preparation Mangos teen pericarps were collected from Surabaya, Indonesia. Fruits were cleaned with running tap water and fresh pericarps were chopped into pieces. They were dried under shade at ambient temperature for 5 days and the air-dried pericarps were then ground to powder for extraction. The powdered pericarp (1 kg) was macerated with ethanol (5 L) for a week at 37°C. The supernatant was then collected and filtered through Whatman No. 1 filter paper in a Buchner funnel under vacuum. The filtrate was concentrated by evaporation with a vacuum rotary evaporator at 45°C. The extract was dried at reduced pressure, stored at 0-4^{o}C and used for the experimentation.

Experimental Design

The fifty male mice (Mus musculus) were divided randomly into five groups as the following: negative control group (mice were given daily with aquadest) ; positive control group (mice were given daily with aquadest and lead 20 mg/kg BW orally once in a day for 21 days); and the treatment group (mice were given the mangos teen pericarp extracts ethanol200 mg; 400 mg; 800 mg/kg BW orally once in a day for 25 days and lead acetate 20 mg/kg BW were given on 4th day, one hour after the mango steen pericarp extracts administration for 21 days). On day 25, blood samples were taken by cardiac puncture into chilled tubes and centrifuged at 3000 rpm for 20 minutes; then sera were stored at -85C^{0} until assay.

Biochemical assays

Serum biochemical markers activities of SGPT, SGOT and ALP were assayed spectrophotometrically according to the standard procedures using commercially available diagnostic kits. The level of serum MDA was determined spectrophotometrically with a thiobarbituric acid (TBA) solution. In brief to 150µl serum sample added the followings: 1ml trichloroacetic acid (TCA) 17.5 %, 1ml of 0.66 % TBA, mixed well by vortex, incubate it in boiling water for 15 minutes, & then allowed to cool. Then add 1ml of 70 % TCA, and let the mixture to stand at room temperature for 20 minutes, centrifuged at 2000 rpm for 15 minutes, and take out the supernatant for scanning spectrophotometrically. Portions of liver was immediately washed in ice cold physiological saline and homogenized in 50mM potassium phosphate (pH 7.4) to render 10% homogenate. The homogenate was centrifuged at 4000 rpm for 15 min at 4 °C. The supernatant was used for SOD, and GPx analysis.

Statistical analysis

Data were presented as means ± standard errors. One-way ANOVA was carried out, and the statistical comparisons

among the groups were performed with LSD test using a statistical package program (SPSS version 17.0).

RESULTS

Effects of mangosteen pericarp extract on lead acetate induced changes in the serum hepatic enzymes

An increase in the serum hepatic marker enzymes (SGOT, SGPT and ALP) indicates liver damage. Analysis of these hepatic marker enzymes has been done to evaluate the hepatoprotective effect of ethanol extract of mangosteen pericarp in lead acetate treated mice. Positive control (lead acetate treated mice) showed a significant (p <0.05) increase in serum hepatic enzymes (SGOT, SGPT and ALP) comparing with the negative control. In contrast, the groups pretreated with ethanol extract of mangosteen pericarp (800 mg/kg BW) showed significantly (P <0.05) decreased enzyme (SGOT, SGPT and ALP) level in a dose dependent manner with respect to the positive control to towards normalization and close to the negative control group (Table 1).

Table 1. Effects of mangosteen pericarp extract on lead acetate induced changes in the serum hepatic marker enzymes

Groups	Means ± SD		
	SGOT (U/L)	SGPT (U/L)	ALP (U/L)
Negative Control	$66.30^{a} \pm 3.27$	$27.70^{a} \pm 2.75$	$164.36^{a} \pm 7.71$
Positive Control	$92.10^{b} \pm 5.59$	$43.40^{b} \pm 2.63$	$225.62^{b} \pm 9.45$
Mangosteen 200 mg/kg BW	$90.00^{b} \pm 4.55$	$45.30^{b} \pm 2.21$	$216.81^{b} \pm 8.93$
Mangosteen 400 mg/kg BW	$85.80^{b} \pm 4.77$	$42.20^{b} \pm 2.15$	$209.84^{b} \pm 9.82$
Mangosteen 800 mg/kg BW	$77.80^{c} \pm 5.51$	$39.80^{c} \pm 2.15$	$187.52^{c} \pm 8.61$

Superscript within each column indicate significant difference between the means ($p < 0.05$)

Effects of mangosteen pericarp extract on lead acetate induced changes inantioxidant and MDA

Lead acetate enhances the intracellular formation of reactive oxygen species causing hepatic damage. In the present study we analyze the hepatic levels of several antioxidants (SOD and GPx) and MDA. Positive control (lead acetate treated mice) showed significant (P<0.05) decrease in the level of SOD and GPx compared with negative control group, meanwhile a significant (P<0.05) increase in MDA level was detected.

Table 2. Effects of mangosteen pericarp extracton lead acetate induced changes in antioxidant and MDA

Groups	Means ± SD		
	MDA (nmol/mL)	SOD (U/mg)	GPx (U/mg)
Negative Control	$4.97^{a} \pm 0.86$	$8.32^{a} \pm 0.98$	$43.36^{a} \pm 4.71$
Positive Control	$8.04^{b} \pm 0.86$	$4.61^{b} \pm 0.82$	$31.45^{b} \pm 3.52$
Mangosteen 200 mg/kg BW	$8.34^{b} \pm 0.80$	$4.37^{b} \pm 0.93$	$34.21^{b} \pm 5.83$
Mangosteen 400 mg/kg BW	$7.84^{b} \pm 0.79$	$5.01^{b} \pm 1.01$	$35.62^{b} \pm 4.96$
Mangosteen 800 mg/kg BW	$7.02^{c} \pm 0.72$	$6.92^{c} \pm 0.73$	$40.57^{c} \pm 2.45$

Superscript within each column indicate significant difference between the means ($p < 0.05$)

Groups pretreated with ethanol extract of mangos teen pericarp (800 mg/kg BW) showed a significant (P <0.05) increase in the level of SOD and GPx with significant (P<0.05) decrease in MDA level compared with lead acetate treated mice towards the normal level and close to the negative control (Table 2).

DISCUSSION

Lead is one of the most toxic metals, producing severe organdamage in animals and humans. Studies have shown that the liver is one of the primary targets in lead associated toxicity (**Adikwu *et al.*, 2013**).Lead produces oxidative damage in the liver by enhancing lipid peroxidation and cause liver dysfunction and increase free radical damage (**Haleagrahara *et al.*, 2010; Wang *et al.*, 2012**). Antioxidant enzyme levels are applied as markers of oxidative stress. Based on the present study lead induced toxicity might result in decreased tissue activities of enzymatic antioxidants SOD and GPx. The decrease of SOD and GPx activities might predispose the examined tissue of mice to oxidative stress, because these enzymes catalyze the decomposition of ROS (**Xu *et al.*, 2008; Newairy and Abdou, 2009**). The levels of these antioxidants might provide a clear indication on the extent of cytotoxic damage that occurs in hepatic tissue. Therefore, some authors have postulated that antioxidants should be one of the important components of an effective treatment of lead poisoning (**Hsu *et al.*, 2002; Patrick, 2006**).

Mangosteen is one of the famous fruits and its pericarp extracts have been widely used in traditional medicine. Most of the scientific researchers have been focused on phytochemical studies in order to find novel constituents. Pharmacological activities and mechanisms of actions are scarcely available. From phytochemical studies, mangosteen pericarp consists of more than 90 % xanthones as major polyphenolic compounds, especially α-*mangostin* (80–90 %) and β-mangostin (5–10 %), named *panaxanthone* (**Jung *et al.*, 2006**) These xanthones are of great interest because of biological and pharmacological properties, such as antioxidant, antitumor, anti-inflammatory, antibacterial, antifungal, and antiviral properties (**Pedraza-Chaverri *et al.*, 2008; Zarena and Sankar, 2009**). The present study is intended to investigate hepaprotective activity of ethanolic extract of the mangosteen pericarp against lead acetate induced liver damage in mice.

Liver injury following lead exposure is well characterized by elevated levels of plasma hepatic marker enzymes which indicate cellular leakage and loss of functional integrity of hepatic membrane architecture. The serum enzyme SGOT, SGPT and ALP are recommended for the assessment of hepatocellularinjury in preclinical studies as it is considered a more specific and sensitive indicator of liver damage. Low levels of SGOT, SGPT and ALP are normally found in the blood, but when the liver is damaged or diseased, it releases SGOT. SGPT and ALP into the bloodstream, which makes SGOT. SGPT and ALP levels go up. Most increases in SGOT. SGPT and ALP levels are caused by liver damage (**Moussa and Bashandy, 2008; Grattagliano *et al.*, 2009**). The current work revealed an increase in the level of SGOT, SGPT and ALP in lead acetate treated mice in comparison to the negative

control and this may be due to the degeneration of hepatocytes by necrosis which causes leakage of these enzymes into blood circulation. Similar observation was reported by **Moussa and Bashandy, (2008). Mehana *et al*, (2010) and Attia *et al*, (2013)** have reported that lead acetate treatment induced significant elevation of serum SGOT, SGPT and ALP activities. Furthermore, **Ibrahim *et al*, (2012)** reported that the high SGOT, SGPT and ALP activities are accompanied by high liver microsomal membrane fluidity, free radical generation and alteration in the liver tissue. Our results indicated that ethanol extract of mangosteen pericarp has ahepato protective activity against lead acetate-induced hepatotoxicity, where the pretreated groups with ethanol extract of mangosteen pericarp800 mg/kg b.w, showed an improvement in the SGOT, SGPT and ALP levels. This might be through its direct action on free radicals of lead acetate to protects the liver cellular damage by maintaining its membrane integrity. Reduction of serum transaminases near normal levels suggested regeneration of hepatocytes with healing of hepatic parenchyma.

Lead toxicity leads to generation of free radical damage by two separate pathways including hydroperoxides, singlet oxygen, and hydrogen peroxides, evaluated by MDA levels as the final products of lipidperoxidation, and the direct depletion of antioxidant reserves (**Newairy and Abdou, 2009**). The present investigation resulted significantly increase of MDA levels in the liver of lead acetate treated mice in comparison tothe negative control. This means that it increased the oxidative stress in the lead acetate treated mice. It is known that lead acetate-induced oxidative stress tissue damage could be caused by two mechanisms: increased generation of ROS, and by causing direct depletion of antioxidant reserves (**Patrick, 2006; Ibrahim *et al*., 2012**). Intense lipid peroxidation caused by lead exposure may affect the mitochondrial and cytoplasmic membranes causing more severe oxidative damage in the tissues and consequently releasing lipid hydroperoxides into circulation which reflects the induction of oxidative stress (**Sharma and Pandey, 2010; Aziz *et al*., 2014**). The ethanol extract of mangosteen pericarp, which behaves as a powerful antioxidant and free radical scavenger, can decrease MDA level perturbed by lead acetate in mice liver, as observed in this study.

Treatment of mice with ethanol extract of mangosteen pericarpat a dose of 800 mg/kg body weight prevented the levels of lipid peroxidation (MDA) to rise when the mice were challenged with lead acetate. This means that ethanol extract of mangosteen pericarpminimized the toxic effect of lead acetate via its antioxidant activity. The antioxidant protective mechanism decreases the oxidative stress and scavenges the free radical which responsible for the liver damage and thus inhibit the lipid peroxidation (MDA).The findings of this study suggest that ethanol extract of mangosteen pericarp could attenuate oxidative stress by decreasing the lipid peroxidation (MDA level) in lead-treated liver. A similar result had been showed that vitamin C and Vitamin E enhanced the antioxidant status and inhibited lipid peroxidation (MDA) in rats with lead acetate induced liver injury. These findings indicate that the antioxidant activity of Vitamin C and vitamin E are targeted primarily towards the lipid component of cells. Antioxidants such as Vitamin C and viyamin E have been shown to inhibit free radical formation and are effective in minimizing lipid peroxidation in several different biological systems (**Aziz *et al*., 2014**). SOD and GPx are important antioxidant enzymes. They constitute a mutually supportive defense mechanism against ROS. SOD decomposes superoxide radicals (O_2-) to produce H_2O_2. GPx is a selenoenzyme which plays a major role in the reduction of H_2O_2 and hydroperoxide to produce nontoxic products. Therefore, the activities of these enzymes have been used to assess oxidative stress in cells. Many studies have shown that lead has high affinity for SH groups in several enzymes such as SOD and GPx, thus it can alter antioxidant activities by inhibiting functional SH groups in these enzymes (**Hsu and Guo, 2002**).

In the present study, the activity of SOD and GPx in mice liver was dramatically decreased by lead acetate treatment. This suggested that lead acetate exposure induced oxidative stress by inhibiting the activity of this antioxidant enzyme. Interestingly, the administration of ethanol extract of mangosteen pericarp increased the activities of SOD and GPx in the liver of lead-treated mice, which might be due to the ability of ginger to reduce the accumulation of free radicals. Ethanol extract of mangosteen pericarp acts as a scavenger for the oxygen-derived free radicals, thus protecting from cellular damage. This decreased SOD and GPx activity with lead acetate treatment is in agreement with previous studies (**Haleagrahara *et al*., 2010; Wang *et al*., 2012**). It could be concluded that, ethanol extract of mangosteen pericarp may exert its protective actions against lead-induced hepatic injury in rats possibly through its antioxidant mechanisms. Ethanol extract of mangosteen pericarp can be a future natural product for counteract the lead acetate intoxication. This Results showed that ethanol extract of mangosteen pericarp has a potential hepatoprotective effect in a dose dependant manner that minimize or diminish compounds the hepatotoxic effect induced by lead acetate intoxication.

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