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Renoprotective effect of *Mangifera indica* polysaccharides and silymarin against cyclophosphamide toxicity in rats

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Abstract The present study aims to evaluate the possible protective role of polysaccharides extracted from the Egyptian mango *Mangifera indica* L. (MPS) and silymarin against cyclophosphamide (CP) nephrotoxicity in male albino rats. Male rats were randomly divided into, control group (administered distilled water orally for 10 days) and MPS (500, 1000 mg/kg, p.o.) and/or silymarin (150 mg/kg, p.o.) treated groups for 10 days. In the last 5 days of treatment rats were administered CP (150 mg/kg, i.p). The MPS revealed significant prophylactic effect against kidney injury induced by CP as demonstrated by enhancement of the kidney function via decreasing serum creatinine, urea and uric acid. Treatment of rats with MPS extract and/or silymarin significantly increased the level of reduced glutathione (GSH) and superoxide dismutase (SOD) activity while decreased the level of total malondialdehyde (MDA) and glutathione-S-transferase (GST). Also, histopathological examinations confirmed the protective efficacy of MPS and/or silymarin against CP nephrotoxicity. In conclusion, the obtained results of the present study support the protective antioxidant role of MPS and/or silymarin against CP-induced kidney disorder in rats.

Introduction

The kidney is a primary target for numerous toxic xenobiotics including drugs, environmental chemicals and metals. Acute kidney injury, induced by drugs and other stimuli, is a significant clinical problem, and accounts for the cessation of development of many promising drug candidates Shelton et al. (2013). Drug-induced nephrotoxicity is an extremely common condition and is responsible for a variety of pathological effects on the kidneys Dhodi et al. (2014). Cyclophosphamide (CP) is a potent anticancer agent. CP is effective against a wide spectrum of malignancies, such as leukemia, lymphoma, breast, lung, prostate, and ovarian cancers Khan et al. (2004). The usage of CP is severely limited by its physiological

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side effects, such as hepatotoxicity, nephrotoxicity, urotoxicity, cardiotoxicity and myelosuppression Motawi et al. (2010), Lameire et al. (2011) and Newton (2012). However, its clinical use is restricted because of its marked organ toxicity associated with increased oxidative stress and inflammation Nafees et al. (2015). Oxidative stress is reported to play important roles in CP-induced renal damage Abraham and Rabi (2011). Renal damage is one of the dose-limiting side effects of CP Abraham and Rabi (2011). It has been demonstrated that increased generation of reactive oxygen species (ROS) by CP in kidney tissues plays a critical role in the pathogenesis of CP-induced kidney damage Stankiewicz and Skrzydlewska (2003) and Abraham and Rabi (2009). So, free radical scavengers and antioxidants can be used in the treatment Sabolic (2006). Cyclophosphamide is now being used in combination with various detoxifying and protective agents with the purpose of reducing or eliminating its adverse toxic effects Neboh and Ufelle (2015) and Nurrochmad et al. (2015).

Silymarin, a bioflavonoid, is the main constituent of Silybummarianum (milk thistle). Chemically, silymarin is a flavonolignan that consists of a mixture of mainly three flavonoids, silibinin, silydianin and silychristin Kiruthiga et al. (2007). Silymarin has been reported to possess several pharmacological activities including antioxidant and anti-inflamma tory/immunomodulatory Manna et al. (1999), antifibrotic Crocenzi and Roma (2006), hepatoprotective, antibacterial, antiallergic, antimutagenic, antiviral, antithrombotic and vasodilatory actions Wellington and Jarvis (2001). Many studies reported that silymarin reduced CP-induced ROS generation Jnaneshwari et al. (2012). Silymarin was shown to have positive effects on preventing or decreasing severity of cyclophosphamide nephrotoxicity Eser et al. (2012). So it is the positive control used in this study.

Pharmacotherapy using natural substances can be currently regarded as a very promising future alternative to conventional therapy Wang et al. (2013). Plants have been the major source of therapeutic agents for curing the human diseases Zahid et al. (2013). Mango (*Mangifera indica* L.) is one of the most important and popular tropical fruits, mainly due to its attractive flavor Chen et al. (2012). *M. indica* L. is an important member of the family Anacardiaceae and belongs to genus Mangifera order sapindales Ross (1999). In recent years, some bioactive polysaccharides isolated from natural sources have attracted much attention in the field of biochemistry and pharmacology Wang et al. (2013) and Xue et al. (2015). Some polysaccharides isolated from natural sources show various important biological activities, such as antitumor, immunomodulatory, and anti-inflammatory effects, which are strongly affected by their chemical structures and chain conformations Liu et al. (2015). It has been well documented that polysaccharides increase immunity through production of interleukins and antibodies Yang et al. (2008) and therefore could be explored as novel prospective antioxidants Sun et al. (2010) and Chen et al. (2012). Polysaccharides can be currently regarded as a very promising future alternative to conventional therapy in kidney diseases Chiu et al. (2014) and Lu et al. (2014). When multiple antioxidants are used in combination, they protect against vulnerability to other agents and synergistically potentiate their antioxidant properties Aleisa et al. (2013). So, the present study was designed to evaluate the efficacy of polysaccharides extracted from the mango pulp (MPS) and/or silymarin against renal injury induced by cyclophosphamide in male albino rats.

Materials and methods

Chemicals and reagents

Methanol 95%, ethanol, absolute acetone, and cyclophosphamide (Endoxan) were purchased from Bexter Oncology GmbH (Germany), silymarin was purchased from SEDICO Pharmaceutical Co. (6 October City, Egypt). All other chemicals were of analytical grade. Kits for all biochemical parameters were purchased from *Biodiagnostic* Company (El-Dokki, Giza, Egypt).

Collection of Mangifera indica L.

Mature green mango (*M. indica* L.) cv. Fagrkelan fruits were freshly harvested from Egypt fields through a local Dealer in September 2012, *M. indica* washed thoroughly with running tap water, seeds and peels are removed from mango.

Extraction of polysaccharides from Mangifera indica L.

Polysaccharides extracted from mango pulp by the technique described by Devaki et al. (2009) with some modifications. Briefly, 1670 g of mango pulp was boiled in 16.7 L of distilled water at 100 °C for 3 h. The slurry was separated by gauze and then, was filtered. The filtrate was dialyzed against tap water for 48 h, and then concentrated to about 350 ml under reduced pressure using rotary evaporator. Then, the concentrated filtrate was precipitated using four volumes of 95% ethanol to one volume of the extract (about 1400 ml 95% ethanol). The extract was washed with absolute acetone, filtrated and then dried in a vacuum desiccator over anhydrous calcium chloride. About 65 g of polysaccharides extract is obtained and used for animals' experiments.

Animals

The experimental animals used in this study were adult male albino Wistar rats (*Rattus norvegicus*) weighing (150–160 ± 5 g). The animals were obtained from the National Research Center (NRC, Dokki, Giza). Animals were grouped and housed in polyacrylic cages (Five animals per cage). Animals were given food and water *ad libitum*. Rats were maintained in a friendly environment with a 12 h/12 h light–dark cycle at room temperature (22–25 °C). Rats were acclimatized to laboratory conditions for 7 days before commencement of the experiment. The protocol was approved by the Cairo University, Faculty of Science Institutional Animal Care and Use Committee (IACUC), Egypt (CUFS/S/PHY/28/14), and all the experimental procedures were carried out in accordance with international guidelines for care and use of laboratory animals.

Toxicity study (OECD 420)

Adult male albino rats (*R. norvegicus*) weighing (150–160 ± 5 g) were used for acute toxicity studies. The rats were divided into control and test groups containing five animals each. The rats were administered orally with polysaccharides extract of mango at dose levels of 5000 mg/kg (high dose)