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Original Research Article

Mangiferin protects rat myocardial tissue against cyclophosphamide induced cardiotoxicity

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ABSTRACT

Background: Mangiferin is a highly potent antioxidant present in mango leaves which is utilized for therapeutic purposes.
Objective: The present study was undertaken to evaluate the cardioprotective effect of mangiferin against cyclophosphamide induced cardiotoxicity.
Materials and methods: Rats were treated with 100 mg/kg of mangiferin in alone and interactive groups for 10 days. Apart from normal and mangiferin control groups, all the groups were subjected to cyclophosphamide (200 mg/kg, i.p.) toxicity on Day 1 and effects of different treatments were analyzed by changes in serum biomarkers, tissue antioxidant levels, electrocardiographic parameters, lipid profile and histopathological evaluation.
Results: Mangiferin treated group showed decrease in serum biomarker enzyme levels and increase in tissue antioxidant levels. Compared to cyclophosphamide control group, mangiferin treated animals showed improvement in lipid profile, electrocardiographic parameters, histological score and mortality.
Conclusion: The present findings clearly suggest the protective role of mangiferin as a powerful antioxidant preventing cardiotoxicity caused by cyclophosphamide.

1. Introduction

Evolution of cancer therapy has made cancer a manageable disease today than ever before. However, chemotherapy-induced cardiac complications are an important cause of morbidity and mortality. Patients are likely to suffer from a cardiac disease rather than recurrent cancer. It is therefore necessary to manage both, the neoplasm and associated toxicities of anti-neoplastic drugs, especially cardiotoxicity [1,2].

Cyclophosphamide (CYP) is perhaps the most widely used anti-neoplastic agent [3]. It is used for the treatment of chronic and acute leukemias, myelomas, lymphomas, and for bone marrow transplantation [4]. CYP is attributed to also possess highly potent immunosuppressant activity [3]. Apart from having tumor selective action, it also possesses many highly toxic side-effects. Dose-mediated cardiotoxicity is one of the most important toxic effects [5]. The incidence of fatal cardiomyopathy due to a single high dose of CYP is up to 17%, depending on the different regimens and patient populations [6]. In contrast to the delayed cardiotoxic effects of other anti-neoplastic drugs, CYP causes lethal cardiomyopathy within 1–10 days after first administration of the dose (180–200 mg/kg) [7,8]. The cardiotoxic effects of CYP consists of acute, dose-dependent cardiac damage, morphologically characterized by necrosis, hemorrhage and later development of fibrosis [4,9].

The anti-neoplastic activity of CYP is due to phosphoramide mustard, the therapeutically active metabolite, which possesses significant DNA-alkylating activity [10,11]. The other metabolite, acrolein interferes with antioxidant system producing highly reactive oxygen-free radicals – superoxide radicals and hydrogen peroxide [12]. These Reactive Oxygen Species (ROS) cause damage to the inner mitochondrial membrane of the heart, diminishing the oxygen radical detoxifying capacity of cardiac mitochondria [13].

Natural products are known to possess wide range of biological activity. Flavonoids and polyphenolic compounds are the active antioxidant principles found in large number of natural products.

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Apart from strong antioxidant activity, they also demonstrate a number of other biological activities like, hepatoprotective, anti-diabetic, anti-bacterial, and anti-cancer to name a few [14–16]. These phenolic compounds have the ability to suppress lipid peroxidation, prevent DNA oxidative damage, and scavenge free radicals. Free radicals cause depletion of the immune system antioxidants, change in gene expression, and induce abnormal proteins resulting in degenerative diseases and aging [17].

Mangifera indica L. (Mango) is an important plant of the Ayurvedic and other indigenous systems of medicine. Different parts of the mango tree are known to possess different bioactivities and have been extensively used in Ayurvedic system of medicine. The fruit and its juice are used as a restorative tonic, while the seeds are used in asthma. The bark finds use in diphtheria and rheumatism and the smoke of the dried leaves in prevention of hiccups and throat infections [18]. Leaves of *M. indica* L. are a rich source of phenolic compounds. Mangiferin, obtained from the leaves and bark of the tree, is a xanthone with wide range of pharmacological effects [19]. Bioactivity of mangiferin is attributed to its ability to decrease localized O_2 concentration and generation of mangiferin phenoxy radicals and metal–ligand complexes with iron, that prevent the formation of OH· radicals and oxo-ferryl groups that cause tissue damage. It also helps in maintaining the oxidant-antioxidant balance necessary for normal cellular function [20].

Research suggests that mangiferin possesses anti-diabetic effect on streptozotocin induced diabetes in mice and rats, possibly by reducing intestinal absorption of glucose [21,22]. It is known to prevent isoproterenol induced myocardial infarction in rats [23]. Previous studies have also revealed protective effects of mangiferin on rat brain by inducing peroxidation of phospholipids and prevention of DNA damage by bleomycin [24]. Immunomodulatory activity of mangiferin is evident in its action to inhibit TNF-induced activation of NF-κB in mice [25]. Apart from these bioactivities, mangiferin is also attributed to possess antimicrobial [26], anti-allergenic [27], anti-inflammatory, analgesic [28], and hepatoprotective [29] activities among many others.

However, till now, there have been no studies carried out to demonstrate the protective effect of mangiferin against cardiotoxicity caused by anti-cancer drugs. This study is designed to evaluate the protective effect of mangiferin on cardiotoxicity caused by CYP.

2. Materials and methods

2.1. Animals

Wistar rats of both sexes, weighing between 200 and 250 g, were obtained from the animal facility of Shree Devi College of Pharmacy, Mangalore, India. The rats were maintained in an animal house with standard facilities. The animals were housed in clean cages and maintained at 25 ± 5 °C and humidity at 30–70% under 12 h light–dark cycles, and were fed with standard feed with free access to purified drinking water. Animals were acclimatized for one week to laboratory conditions before starting the experiment. All experiment protocols were conducted according to the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), the Ministry of Social Justices and Empowerment, Government of India. Prior to the commencement of the experiment Institutional Animal Ethics Committee (SDCP/IAEC-07/2012-13) approval was obtained.

2.2. Isolation of mangiferin

M. indica L., leaves were obtained from cultivated trees from Mangalore area. The plant was identified at the Herbarium, Department of Pharmacognosy, Shree Devi College of Pharmacy, Mangalore. The leaves were shade dried and powdered. The powdered material was defatted with petroleum ether (60–80 °C). Defatted powdered leaves were extracted in a Soxhlet apparatus with required quantity of ethanol for 21 h and concentrated under reduced pressure to yield semisolid mass. The ethanolic mass was then subjected to hydrolysation and followed by treatment with ethyl acetate. The ethyl acetate fraction was then precipitated with ethanol and crystallized. Briefly, the compound purity was confirmed through high performance liquid chromatography (HPLC) (Data not shown). The product was stored in a desiccator to prevent humidification and the weighed dose was dissolved in Dimethyl sulfoxide (DMSO) and used for the present study.

2.3. Experimental protocol

After the end of 1 week acclimatization, animals were divided into 4 groups of 6 animals each.

- Group I (*Normal Control*) served as normal control and received 1% Dimethyl Sulfoxide (DMSO) (i.p.) for 10 days.
- Group II (*CYP Control*) served as toxic control, in which the animals received single injection of CYP (200 mg/kg, i.p.) on the first day of experimental period to induce cardiotoxicity [30].
- Group III (*MANG*) received mangiferin (100 mg/kg body weight i.p.) for 10 days, dissolved in 1% DMSO [23].
- Group IV (*MANG + CYP*) received CYP (200 mg/kg, i.p.) on the first day and mangiferin (100 mg/kg body weight, i.p.) for 10 days.

Acute & chronic toxicity studies [31] and pharmacological studies [23] conducted on mangiferin were used as reference in deriving the current dose of 100 mg/kg.

2.4. Biochemical analysis

At the end of the experimental period, all the rats were anaesthetized under light ether anesthesia and blood was collected by the retro-orbital route using microcapillaries. Serum was then separated from blood and used for the estimation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate (ALP), creatine kinase-MB (CK-MB), creatine kinase-NAC (CK-NAC) and lactate dehydrogenase (LDH). Then, the animals were sacrificed by mild ether anesthesia and four hearts from each group were homogenized with ice cold 0.25 M sucrose solution [32,33] for estimation of superoxide dismutase (SOD), catalase and Reduced Glutathione (GSH). SOD activity was determined on the capacity of the enzyme to reduce nitro blue tetrazolium [34]. The absorbance was measured at 560 nm. Ellman method was followed for the estimation of GSH [35], while method of Aebi was followed to estimate catalase [36].

2.5. Electrocardiographic studies

Twenty-four hours after the last treatment, the animals were anesthetized with the combination of ketamine (75 mg/kg, i.p.) and xylazine (8 mg/kg, i.p.). The leads were attached to the dermal layer of both the front paws and the hind legs and recordings were made with the help of a digital physiograph (Model number – DI-2, INCO, Ambala, India). The changes in heart rate, QRS, QT, PR and RR intervals were determined.

2.6. Lipid profile assay

Serum cholesterol and triglyceride levels were measured by commercial kits with the help of a semi-autoanalyzer.

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