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Protective effect of *Berberis vulgaris* fruit extract against Paraquat-induced pulmonary fibrosis in rats

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ABSTRACT

Background: Pulmonary fibrosis induced by paraquat (PQ) has caused a large number of human fatalities all over the world, especially in Asian region. The main potential mechanism of PQ toxicity has been thought to be mediated by ROS. The present study was designed to evaluate the efficacy of the *Berberis vulgaris* fruit extract (BVFE) against PQ—induced pulmonary fibrosis in rats.
Methods: Forty male rats were randomly divided into five experimental groups each containing eight rats. Groups 1 and 2, served as a negative and positive control and received a single dose of intratracheal instillation of saline and PQ (20 mg/kg), respectively. Groups 3–5 were treated with different doses of BVFE (100, 200, 400 mg/kg/day, orally) 1 week before the PQ injection and continued for 3 weeks. The rats were sacrificed 21 days after PQ. Malondialdehyde (MDA), Hydroxyproline, inflammatory and fibrogenic cytokine tumor necrosis factor (TNF)-α, interleukin (IL)-6 and transforming growth factor (TGF)-β1 in lung tissue were determined. Presence of fibrosis, inflammatory cells, connective tissue and collagen deposition in lung were evaluated microscopically by hematoxylin and eosin (H&E) staining. Dried extract was standardized by amount of berberine by HPTLC methods by silica gel plate.
Results: The results showed that PQ could significantly increase the lung MDA, hydroxyproline, TNF-α, IL-6 and TGF-β1 levels. BVFE ameliorated the biochemical and histological lung alterations induced by PQ.
Conclusions: The present study indicates the hydroalcolic extract of *Berberis vulgaris* fruit has beneficial effects in rat pulmonary fibrosis induced by PQ in a dose-dependent manner, possibly by anti-oxidant and anti- inflammatory properties, which might be due to its berberine alkaloid content.
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1. Introduction

Pulmonary fibrosis is one of the main interstitial or diffuse parenchyma, lung diseases is characterized by a numerical expansion of fibroblasts that they synthesize excessive amounts of extracellular matrix, including collagen. Pulmonary fibrosis may result from a variety of acute and chronic diseases, including the idiopathic interstitial pneumonias, chronic inflammatory processes (sarcoidosis, Wegener's granulomatosis), infections, environmental agents, exposure to ionizing radiation and certain medications [1,2]. Although current therapies for fibrotic lung diseases are ineffective and lung transplantation is a viable option for patients with end-stage pulmonary fibrosis, control and prevention of inflammatory events might delay progress of the fibrotic events. Although the precise mechanisms that drive the numeric expansion of fibroblasts and collagen accumulation in pulmonary fibrosis remain incompletely understood, tissue fibrosis is often viewed as the aberrant wound healing following sequential lung injuries. Inflammation and immune mechanisms, oxidative stress and oxidative signaling, and procoagulant mechanisms may be responsible for the combination of altered lung fibroblasts, loss of alveolar epithelial cells, and excessive accumulation of extracellular matrix (ECM) that can initiate the

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tissue damages and result in pulmonary fibrosis [3–5]. Many xenobiotics, including paraquat (PQ) [6], butyrated hydroxytoluene [7] and Amiodarone [8] and bleomycin [9–11] are capableof producing lung fibrosis by stimulating the overproduction of ROS, such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), peroxinitrite ($ONOO^-$), and hydroxyl radical ($HO^{\bullet}$) that they are major mediators of lung inflammatory processes [12]. Among them, PQ (1, 1′-dimethyl-4, 4′-bipyridinium dichloride) is an effective and non-selective quaternary nitrogen herbicide, which is widely used in many countries for broadleaf weed control. However, acute PQ poisoning by accidental and/or voluntary ingestion of commercial liquid formulations of PQ has caused a large number of human fatalities, especially in Asian region. Although PQ has toxic effects on various organs, including liver, kidney, heart and central nervous system, the lung is the primary target organ in PQ poisoning and death mostly occurs due to lung damage and pulmonary fibrosis. PQ is mainly accumulated in the lung through the process by which active polyamine is transported into the Clara cells and alveolar type I and II epithelial cells [13–16]. The mechanisms of PQ cytotoxicity have not been fully explained. The main potential mechanism of PQ toxicity has been thought to be mediated by ROS produced by the enzymatic one-electron reduction of PQ, which generates $O2^-$ anions and other free radicals that interact with membrane lipids leading to cell death and lung tissue damage. Since there are no specific antidotes or effective treatment for PQ, the mortality rate of PQ poisoning has remained high [17,18].

Berberis vulgaris is a shrub belongs to the Berberidaceae family. It grows in central and southern Europe, northwest Africa, and western Asia. Dried fruit of *Berberis vulgaris* known as Zereshk or Sereshk in Iran, which used as condiment and cultivated in the south of Khorasan province [19]. Different parts of this plant (root, bark, leaf and fruit) have extensively been used in traditional medicine for the treatment and prevention of various diseases including discomforts of cardiovascular, respiratory, kidneys, urinary and gastrointestinal tract, skin and infectious diseases [20]. Recent studies have demonstrated that *Berberis vulgaris* extracts possess a plethora of biological activities including antiarrhythmic, antibacterial, anticholinergic, antihistaminic, antihypertensive, anti-inflammatory, antinociceptive, vasodilatory, anti-tumor effects [19–24]. It seems that these effects are due to its content of bioactive compounds such as are isoquinoline alkaloids such as berbamine, palmatine, and particularly berberine. A number of studies have suggested that Berberis species has antioxidant and free radical scavenger activity [25–28].

The present investigation was carried out with the objective of evaluating the protective effects of *Berberis vulgaris* fruit extract (BVFE) against PQ-induced pulmonary fibrosis in rats.

2. Materials and methods

2.1. Chemicals

Berberine hydrochloride, Trichloro acetic acid (TCA), Thiobarbituric acid (TBA), Bovine Serum Albumin (BSA), Hydroxyproline (HP), chloramine T and *p*-dimethylaminobenzaldehyde and Bradford reagent were purchased from Sigma–Aldrich Chemical Company (St. Louis, MO), USA. PQ was purchased from Afrashimi Co. (Iran). All chemicals and reagents used were analytical grade.

2.2. Animals

Forty male Sprague-Dawley strain rats, 8 weeks old, weighting 200 ± 25 g were obtained animal house and research center of Jundishapur University of Medical Sciences, Ahvaz, Iran. Rats were kept in polypropylene cages at a controlled condition of temperature (25 ± 2 °C) with a 12 h light: 12 h dark cycle. The animals were given standard rat chow and drinking water ad libitum. All experimental procedures were conducted according to the ethical standards and protocols approved by the Committee of Animal Experimentation of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

2.3. Extract preparation

Berberis vulgaris fruit (BVF) were purchased in Ahvaz, southwest of Iran. Fruit were identified at department of pharmacognosy, School of Pharmacy, Ahvaz, Iran.

The fruit (500 g) was soaked in a 70% aqueous ethanol solution in a large container for 3 days with occasional shaking. The extract was filtered through a clean cotton cloth and then was dried by using a rotary evaporator at 40 °C.

2.4. HPTLC assay

Dried extract was standardized by amount of berberine by HPTLC (Camag, Switzerland) methods by silica gel plate (20×10 cm 60 F 254 E MERCK KGaA co). Mobile phase n.propanol, water, formic acid (80:10:4). Standard of berberine (Sigma chemical Co, USA) was prepared in seven dilutions and calibrate for detection.

2.5. Experimental design

The animals were randomly divided into five experimental groups each containing eight rats. Groups 1 and 2, served as a negative and positive control and received a single dose of intratracheal instillation of saline and PQ (20 mg/kg), respectively. Groups 3–5 were treated with different doses of BVFE (100, 200, 400 mg/kg/day, orally) 1 week before the PQ injection and continued for 3 weeks. The rats were sacrificed 21 days after PQ.

2.6. Tissue collection

At the end of the treatment course, all rats were weighed and killed with a lethal dose (120 mg/kg, i.p.) of sodium pentobarbitone. After mid-line sternotomy, whole lung (include both lobes) was dissected out, separated from other tissues, and washed free of blood with ice-cold saline, then the whole lung weight was recorded and placed in a sterile plastic petri dish. One part of the right lung was fixed in formalin for histological examination, and the remaining lung tissues were immediately removed and washed in normal saline solution and frozen in liquid nitrogen.

2.7. Body weight and lung index

In the course of the experiment, the body weight of rats was measured every 7 days. After sacrifice, the lung index was expressed as the ratio of wet lung weight (mg) to body weight (g).

2.8. Hydroxyproline (HP) assay

The HP content of the lung tissue was determined using a colorimetric assay described else ware [29]. Briefly, 100 mg samples were homogenized in 6 molar HCl and hydrolyzed for five hours at 130 °C. The pH was adjusted to 6.5–7.0 with NaOH, and the sample volume was adjusted to 30 ml with distilled water. The sample solution (1.0 ml) was mixed with 1.0 ml of chloramine T solution (0.05 mol/L), and then the mixture was incubated at room temperature for 20 min. When 1.0 ml of 20% dimethyl benzaldehyde solution was added, the mixture was incubated at 60 °C for 20 min. The absorbance of each sample at 550 nm was measured. The results were calculated as mg HP per g wet lung weight using HP standards.

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