

ORIGINAL ARTICLE

Protective Effect of Propolis in Proteinuria, Crystaluria, Nephrotoxicity and Hepatototoxicity Induced by Ethylene Glycol Ingestion

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Background and Aims. Propolis is a natural honeybee product with wide biological activities and potential therapeutic properties. The aim of the study is to evaluate the protective effect of propolis extract on nephrotoxicity and hepatotoxicity induced by ethylene glycol in rats.

Methods. Five groups of rats were used. Group 1 received drinking water, group 2 received 0.75% ethylene-glycol in drinking water, group 3 received 0.75% ethylene-glycol in drinking water along with cystone 500 mg/kg/body weight (bw) daily, group 4 received 0.75% ethylene-glycol in drinking water along with propolis extract at a dose of 100 mg/kg/bw daily, and group 5 received 0.75% ethylene-glycol in drinking water along with propolis extract at a dose of 250 mg/kg/bw daily. The treatment continued for a total of 30 d. Urinalyses for pH, crystals, protein, creatinine, uric acid and electrolytes, and renal and liver function tests were performed.

Results. Ethylene-glycol increased urinary pH, urinary volume, and urinary calcium, phosphorus, uric acid and protein excretion. It decreased creatinine clearance and magnesium and caused crystaluria. Treatment with propolis extract or cystone normalized the level of magnesium, creatinine, sodium, potassium and chloride. Propolis is more potent than cystone. Propolis extract alleviates urinary protein excretion and ameliorates the deterioration of liver and kidney function caused by ethylene glycol.

Conclusions. Propolis extract has a potential protective effect against ethylene glycol induced hepatotoxicity and nephrotoxicity and has a potential to treat and prevent urinary calculus, crystaluria and proteinuria. © 2016 IMSS. Published by Elsevier Inc.

Key Words: Propolis, Cystone, Ethylene glycol, Liver, Kidney, Toxicity, Crystal, Proteinuria.

Introduction

Ethylene glycol (EG) is a synthetic chemical liquid used in almost all radiator fluid products and used as solvent, emulsifier or surfactant. Its metabolites include glycolic acid, glyoxylic acid and oxalic acid. EG is a common cause of overdose and toxicity and also commonly used to induce nephrolithiasis (1,2). Ingestion of EG causes renal injury and exposure to EG in industries causes impairment in liver and kidney functions (3,4).

Toxicity occurs after EG is converted to its metabolites, glycolic acid and oxalic acid, which cause central nervous system and cardiovascular dysfunction, severe metabolic acidosis, and acute kidney failure (5–7). Calcium oxalate crystals accumulate in blood and other tissues including the renal cortex that result in kidney injury (8). In addition to supportive care, treatment of EG toxicity includes intravenous fomepizole, which inhibits alcohol dehydrogenase or hemodialysis (6,9–11). Reduction of urinary oxalate and other crystal levels can decrease calcium oxalate depositions and stone formation. There is no effective treatment that targets oxalate biosynthesis.

Propolis or bee glue is a resinous hive product that honeybees (*Apis mellifera L.*) collect from various plant species. Honeybees collect propolis from cracks in the bark

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of trees and leaf buds and enrich it with their salivary enzymes and beeswax. Propolis contains highly complex and variable chemical compositions, which are directly related to that of bud exudates. Basically, propolis is composed of 30% wax, 10% essential and aromatic oils, 50% resin and vegetable balsam, 5% pollens and 5% various other substances that include organic compounds and minerals (12).

Cystone is a polyherbal formulation, which is used for antilithic activity in traditional medicine at doses of 500 and 750 mg/kg/bw. It has a protective effect against experimentally induced urolithiasis in rats (13). Cystone is used to prevent and facilitate passage of cysteine kidney stones (13).

Propolis has antimicrobial, antifungal, antioxidant, anti-inflammatory, antitumor, radioprotective, and anti-ulcer activities as well as wound healing properties (14–20). These properties make propolis a candidate to be tested in inflammatory or pathological conditions such as toxicity challenges as well as due to a pathological entity resulting from the high oxidative process. Therefore, the objective of the present study was to assess the effects of hydroalcoholic extract of propolis (HAEP) as a preventive agent in EG-induced nephrotoxicity and hepatotoxicity in rats.

Materials and Methods

Experimental Animals

Adult male Wistar rats (150–220 g) were obtained from the Animal Housing Breeding Center, Department of Biology, Faculty of Sciences, Fés, Morocco and were used for the experiments. Animals were housed under standard environmental conditions ($25 \pm 1^\circ\text{C}$, $55 \pm 5\%$ humidity and 12 h/12 h light/dark cycle) and were maintained with free access to water and laboratory rat chow. All experiments were conducted in accordance with the internationally accepted principles for the care and use of laboratory animals. Approval from the ethics committee at the Faculty of Sciences, Fés, Morocco was obtained.

Collection and Extraction of Propolis

HAEP was prepared from propolis obtained from colonies of honeybees in the region of Salé (Morocco). The collected propolis was frozen at -20°C and ground in a chilled mortar. The ground powder (30 g) was then extracted with the use of 100 mL of ethanol 70% at ambient temperature and maceration under agitation for 1 week. The solution was then filtered through a Whatman filter paper and concentrated in a rotary evaporator under reduced pressure to get a solid residue. The residue was dissolved in a minimal volume of ethanol and stored at -20°C until use. During the experiment, distilled water was added to obtain the required propolis concentration that was given to the animals daily by gavage for 30 d.

Experimental Design

Animals were housed in metabolic cages 3 days prior to the start of the experiment for adaptation and they were divided into five groups, each containing six animals. Group I (control group) animals were maintained on regular food and received only drinking water ad libitum for 30 d. Group 2 (EG group) animals received 0.75% EG in drinking water ad libitum for 30 d. Group 3 (EG-cystone group) animals received 0.75% EG in drinking water ad libitum along with cystone 500 mg/kg/body weight (bw) daily by gavage for 30 d. Group 4; (EG-propolis 100 mg group) animals received 0.75% EG in drinking water ad libitum along with HAEP at a dose of 100 mg/kg/bw daily by gavage for 30 d. Group 5 (EG-propolis 250 mg group) animals received 0.75% EG in drinking water ad libitum along with HAEP at a dose of 250 mg/kg/bw daily by gavage for 30 d.

Collection and Urinalysis

Animals were kept in metabolic cages individually for the collection of 24-h urine samples on days 0, 7, 14, 21 and 30 of treatment. Urine pH and urinary volume were measured immediately after collection. Urine samples collected on day 30 were acidified by the addition of concentrated hydrochloric acid and stored at -20°C for determination of various parameters. Urine was analyzed for calcium, magnesium, inorganic phosphorus, sodium, potassium, chloride, creatinine, protein and uric acid. Urinary oxalate was not measured because the test was not available in Morocco.

Urinary Crystal Study

Urine was collected from all groups after 30 d of the interventions and microscopic examination was done to identify urinary crystals.

Blood Tests

After 30 d of the experiment, blood samples were collected from the anaesthetized animals in all groups by cardiac puncture. Blood was analyzed for creatinine, urea, uric acid, potassium, sodium, and magnesium. Creatinine clearance as a measure of renal function was calculated from serum and urinary creatinine levels. Hepatic function was evaluated by measuring serum alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Statistical Analysis

All data expressed are mean \pm SEM for six rats in each group. All statistical comparisons between groups were done by one-way analysis of variance (ANOVA) followed by post hoc Tukey's Multiple Comparison Test using Graph Pad Prism 5 software.

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