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Radical scavenging and gastroprotective activity of methanolic extract of *Gmelina arborea* stem bark

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ABSTRACT

Background: *Gmelina arborea* (GA) is widely used in traditional medicine for treating a number of ailments including gastrointestinal tract disorders.
Objective: To evaluate the gastroprotective effect of GA stem bark against ethanol-induced gastric ulcer in Wistar rats.
Materials and methods: All animals were fasted for 36 h and received GA extract 250 and 500 mg/kg body weight (bw), 1 h before the administration of ethanol. The animals received ranitidine 50 mg/kg bw which served as the standard. The rats were sacrificed after 4 h. Then, the injuries to the gastric mucosa were estimated through gross evaluation of ulcer lesions and histology. The antioxidant parameters such as level of lipid peroxidation, superoxide dismutase (SOD), reduced glutathione (GSH), and glutathione peroxidase (GPx) in gastric tissue were also determined.
Results: GA treatment at a dose of 500 mg/kg bw offered 91.98% inhibition of ulcer formation, which is higher than that of ranitidine. The ethanol treatment extensively increased lipid peroxidation and it was significantly ($P < 0.01$) reduced in GA-treated group that eventually helped to prevent free radical accumulation. The GA enhanced the gastric mucosal antioxidant system, as indicated by a dose-dependent increase in the level/activities of GSH, GPx, and SOD. GA also attenuated the severity of histological signs of cell damage. Further, GA extract showed *in-vitro* 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity with IC_{50} value of 124.39 μg/ml.
Conclusion: The results indicate that the gastroprotective effect of GA is probably related to its antioxidant activities that protect gastric mucosa against oxidative damage and antilipid peroxidative activity that maintain membrane integrity.
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1. Introduction

Gastric ulcer is one of the most widespread diseases in the world and occurs with stress, nonsteroidal anti-inflammatory drugs, *Helicobacter pylori* infection, and alcohol ingestion [1]. Ulceration occurs when there is an imbalance between aggressive (acid-pepsin secretions) and protective factors such as mucus secretion, mucosal barrier, cell regeneration, blood flow, and prostaglandins [2]. Most of the drugs used for the treatment of gastric ulcers, show numerous adverse effects [3]. In the search for new drugs, metabolites derived from plants used in traditional medicine provided an alternative source of therapeutic drugs [4]. Plant extracts containing a wide variety of antioxidants such as phenolic and flavonoid compounds, are some of the most attractive sources of new drugs and have been shown to produce promising results in the treatment of gastric ulcers [5].

Gmelina arborea (GA), Gambhari in Sanskrit, a popular commercial timber grows naturally in the warm temperate regions of Mediterranean and South Asia [6]. The plant is widely used in Ayurveda, one of the major traditional forms of medicine in India. The root of the plant is a member of "*brihat panchamoola*," which is a major constituent of many ayurvedic preparations [7] used for treating chronic fever, hemorrhages, urinary tract infections, anuria, etc. The plant forms one of the ingredients of Dashamoolarishta—a reputed restorative tonic and Shriparnyadi

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Kwath—prescribed in bilious fever [8]. The bark is bitter, tonic, and stomachic and is useful in curing fever and dyspepsia [9]. The Ayurvedic Pharmacopoeia of India recommends the use of bark and stem in treating inflammatory diseases and edema [10].

GA has been widely used in Ayurveda and Siddha for curing gastrointestinal tract disorders as well as, the leaf juice is used for ulcer treatment [8]. The plant is reported to contain a plenty of phytochemicals such as alkaloids, flavonoids [11], lignans, and iridoid glycosides [6]. Arboreol, paulownin, gmelinol, and epi-eudesmin [12] are reported to be in the heartwood of the plant. Tyrosol (2-[4-hydroxyphenyl] ethanol), balanophonin, gmelinol, phenylethanoid glycoside, 2,6-dimethoxy-p-benzoquinone, and 3,4,5-trimethoxyphenol were identified in the bark [13]. Considering its medicinal value and poor availability of scientific data to prove the gastroprotective effect, the present study was conducted to evaluate the antiulcer properties of 70% methanolic extract of GA stem bark against ethanol-induced gastric ulcer in rats and its comparison with that of the standard drug ranitidine.

2. Materials and methods

2.1. Plant material and extraction

The stem bark of GA was collected from the institute's ayurvedic garden. The plant was authenticated by Dr. P. Sujanapal, Scientist—B, Silviculture Department, KFRI, Peechi, Thrissur—680 653, Kerala (Voucher specimen No: KFRI/SILVA/GEN/07/11). The stem bark was dried at 45–50 °C for 7 days, powdered, and extracted with 70% methanol using Soxhlet apparatus. The extract was filtered, evaporated to dryness, and the dried extract was redissolved in distilled water for further studies.

2.2. 2,2-Diphenyl-1-picrylhydrazyl radical scavenging activity

The antioxidant activity of the GA extract was measured by the scavenging activity of the stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical [14]. The radical form of DPPH has an absorption peak at 515 nm, which reduces upon reduction by an antioxidant compound. Different concentration of the extract was incubated with freshly prepared DPPH solution in a total volume of 2 ml (0.25 g/l in methanol). Absorbance at 515 nm was measured 20 min after starting the reaction. Vitamin C was used as a standard. Concentration of extract necessary to decrease the initial concentration of DPPH by 50% (IC_{50}) was calculated.

2.3. Experimental animals

Wistar rats were purchased from the Small Animal Breeding Station, Kerala Veterinary and Animal Sciences University, Mannuthy, Kerala, India. The animals were maintained under standardized environmental conditions (temperature: 22–30 °C, relative humidity: 60–70%, and 12 h of dark/light cycle) with free access to standard rat feed (Lipton, India) and water *ad libitum*. They were kept in a group of three in polypropylene cages with husk paddy as the bedding with stainless steel top grill having facilities for providing food and water. All animal experiments were conducted during the present study got prior permission from Institutional Animal Ethical Committee (IAEC) (Register Number: ACRC/IAEC/15/02-[2]) and followed the internationally accepted laboratory animal use and care guidelines and rules of IAEC.

2.4. Acute oral toxicity

For acute oral toxicity analysis, female Wistar rats (170–180 g) were divided into five groups of five animals each. Before the initiation of experiment, the animals were fasted overnight and then a single dose of GA extract at concentrations 50, 500, 1000, 2000, and 5000 mg/kg body weight (bw) was administered orally. The animals were observed for behavioral changes and mortality, periodically for the first 24 h and then daily for 14 days according to the Organisation for Economic Cooperation and Development-423 Guideline. Changes in body weight, food, and water intake of the animals were also recorded during the period.

2.5. Experimental design

Thirty male Wistar rats, weighing 180–200 g were randomly divided into five groups of six animals each.

- Group I: Normal – 1 ml distilled water
- Group II: Control – 1 ml distilled water
- Group III: Standard – Ranitidine (50 mg/kg bw.)
- Group IV: *G. arborea* extract low concentration (GALC) (250 mg/kg bw.)
- Group V: *G. arborea* extract high concentration (GAHC) (500 mg/kg bw.).

Before the start of the experiment, the rats were deprived of food for 36 h and water for 12 h. After 1 h of oral treatment as per the above schedule, all groups except Group I (normal) were administered with 1 ml of 80% ethanol orally to induce gastric ulcer. The animals were sacrificed after 4 h of ethanol administration, with an overdose of ether. Stomach of each experimental animal was carefully dissected and opened along the greater curvature. The stomachs were washed with ice-cold normal saline (0.9%).

2.6. Gross lesion evaluation

The ulcer index (U.I.) was calculated by severity of gastric mucosal lesions graded as erosions, 1 mm or less Grade 1; 1–2 mm Grade 2, and more than 2 mm Grade 3. Calculation of U.I was done according to Main and Whittle [15]. The percentage inhibition (I%) of ulcer formation was calculated by the formula, I% = ([UI of control − UI of test]/UI of control) × 100.

2.7. Biochemical analysis

Mucosa of glandular stomach homogenate (10% in Tris buffer, pH 7.0) was prepared and used for the biochemical analysis of lipid peroxidation by measuring the color produced by the reaction of thiobarbituric acid with malondialdehyde (MDA) [16]. The supernatant obtained after centrifugation of homogenate at 10,000 rpm for 1 h was used for further estimations. Reduced glutathione (GSH) was measured by its reaction with 5,5'-dithio-bis-(2-nitrobenzoic acid) to give a yellow colored complex [17]. Glutathione peroxidase (GPx) was estimated by measuring the amount of unconsumed GSH, as the enzyme degrades hydrogen peroxide in the presence of GSH [18]. Superoxide dismutase (SOD) was assayed based on the ability of the enzyme to inhibit superoxide radical mediated reduction of nitroblue tetrazolium salt [19]. Total protein was also measured [20].

2.8. Histopathological analysis

Histological evaluation was performed on the glandular stomach of rats. The tissue samples were preserved in 10% buffered formalin and processed for routine paraffin block preparation. Sections about 5 μm in thickness were cut and stained with hematoxylin and eosin [21].

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