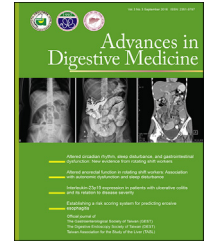




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ORIGINAL ARTICLE

# Gastroprotective effect of bezafibrate, a peroxisome proliferator activated receptor $\alpha$ agonist and its mechanism in a rat model of aspirin-induced gastric ulcer



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## KEYWORDS

Aspirin;  
Bezafibrate;  
Gastric ulcer;  
Nitric oxide;  
Rat

**Summary** *Background:* The aim of the present study was to demonstrate the antiulcer activity and mechanism of bezafibrate in a rat model of aspirin-induced gastric ulcer.

*Methods:* We used an aspirin-induced gastric ulcer model. Bezafibrate was administered orally in graded doses (10 mg/kg, 25 mg/kg, 50 mg/kg, 100 mg/kg, and 200 mg/kg) to detect the best effective antiulcer dose of bezafibrate. The parameters measured were: ulcer index, histopathological scoring of gastric ulcer, gastric juice analysis, gastric mucosal lipid peroxidation parameters, estimation of NO metabolite in blood, mRNA expression of inducible NO synthase iNOS and constitutive NO synthase (cNOS) in gastric mucosa, and gastric mucosal DNA fragmentation.

*Results:* The dose-dependent antiulcer activity of bezafibrate was shown by the ulcer index and histopathological score. Bezafibrate (100 mg/kg) significantly reduced total acidity, free acidity, and pepsin activity, and increased total hexoses and total proteins. Bezafibrate (100 mg/kg) also significantly reduced lipid peroxidation, inhibited iNOS expression, preserved cNOS expression, and inhibited DNA fragmentation.

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**Conclusion:** Bezafibrate can decrease aspirin-induced gastric mucosal injury via reducing lipid peroxidation, inhibiting iNOS expression, preserving cNOS expression, and decreasing DNA fragmentation.

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## Introduction

Peptic ulcer is a common disorder of the gastrointestinal system and millions of people suffer from this disease worldwide. The medical cost of treating peptic ulcer and its complications amounts to billions of dollars annually. The pathogenesis of peptic ulcer disease is multifactorial, including *Helicobacter pylori* infection, chronic use of nonsteroidal anti-inflammatory drugs, cigarette smoking, alcohol, and reactive oxygen species (ROS) [1–3]. Peptic ulcer is produced by the imbalance between gastroduodenal mucosal defense mechanisms and offensive factors [4]. Recent studies also indicate that programmed cell death or apoptosis plays a significant role in gastric ulceration [5–7]. Nitric oxide (NO) is a crucial mediator of gastrointestinal mucosal defense, but, paradoxically, it also contributes to mucosal damage [8]. This can be illustrated by the ability of different NO concentrations to produce completely opposite effects on the same tissue [9].

Nonsteroidal anti-inflammatory drugs such as aspirin is widely used as an anti-inflammatory, analgesic drug and in the prevention of cardiovascular events [10]. However, the major limitations of their clinical application are serious gastrointestinal side effects, especially peptic ulcerations and gastrointestinal bleeding [11]. Studies have demonstrated that the use of aspirin is associated with an elevated risk of symptomatic peptic ulcer [12]. The risk of peptic ulcer was elevated throughout treatment independently of its duration, was elevated with doses as low as 75 mg/d, and was no different from that with doses of 150 mg/d and 300 mg/d [13,14].

Bezafibrate, a peroxisome proliferator activated receptor (PPAR) $\alpha$  agonist, is often used in patients with diabetes mellitus and dyslipidemia. These patients are also taking aspirin for the prevention of cardiac events. So, we hypothesized that if bezafibrate demonstrated antiulcer activity against aspirin-induced gastric ulcer, then this combination can be used in patients with diabetes mellitus and dyslipidemia, with the additional benefit of the anti-gastric ulcer effect of bezafibrate.

Studies in animals have demonstrated the gastric anti-secretory activity of PPAR- $\alpha$  agonists like ciprofibrate, bezafibrate, and clofibrate [15,16]. Eason et al. [16] demonstrated significant inhibition of gastric secretion. Pathak et al. [15] demonstrated the effect of PPAR- $\alpha$  agonist, bezafibrate, on gastric secretion and gastric cytoprotection in various gastric ulcer models in rats, such as acetic-acid-induced chronic gastric ulcers, pylorus-ligation-induced gastric ulcers, ethanol-induced gastric ulcers, indomethacin-induced gastric ulcers, and ischemia–reperfusion-induced gastric ulcers. However, in the

aspirin-induced gastric ulcer model, the precise mechanisms for antiulcer and gastric cytoprotective effects of bezafibrate have not been studied.

To the best of our knowledge, no study has been carried out to investigate the mechanism of the anti-gastric ulcer effect of bezafibrate. Therefore, the present study was contemplated with the aim of studying the mechanism of bezafibrate as an anti-gastric ulcer agent. Keeping in view the diversity of defensive mechanisms, the present study was limited to exploring the oxidative stress, apoptosis, and NO pathways and their involvement in the mechanism of the anti-gastric ulcer effect of bezafibrate.

## Methods

### Experimental animals

Wistar rats of either gender weighing 200–250 g were used for the present study. The animals were obtained from Central animal House, PGIMER, Sector 12, Chandigarh, India. The animals were maintained at  $23 \pm 2^\circ\text{C}$  with a relative humidity of  $65 \pm 5\%$  in a 12-hour light/dark cycle. The animals had free access to standard pellet chow diet and tap water *ad libitum*. The rats were acclimatized to laboratory conditions for at least 7 days. Food was withheld for 36 hours and water for 1 hour prior to commencement of the study.

### Grouping

A total of 60 animals was divided into 10 groups (I–X) of six animals each as follows. Control Groups: Group I, normal control (normal saline); Group II, saline + aspirin (200 mg/kg); and Group III, ranitidine (50 mg/kg) + aspirin (200 mg/kg). For a dose–response study of bezafibrate to establish the best effective dose: Group IV, bezafibrate (10 mg/kg) + aspirin (200 mg/kg); Group V, bezafibrate (25 mg/kg) + aspirin (200 mg/kg); Group VI, bezafibrate (50 mg/kg) + aspirin (200 mg/kg); Group VII, bezafibrate (100 mg/kg) + aspirin (200 mg/kg); and Group VIII, bezafibrate (200 mg/kg) + aspirin (200 mg/kg). For mechanistic study with best effective dose: Group IX, best effective dose of bezafibrate (100 mg/kg) + aspirin (200 mg/kg); and Group X, L-N<sup>G</sup>-nitroarginine (L-NNA) (50 mg/kg) + best effective dose of bezafibrate (100 mg/kg) + aspirin (200 mg/kg).

### Ethical permission

Institutional Animal Ethics Committee (IAEC, PGIMER, sector 12, Chandigarh) approval (No. 42/IAEC/163 dated 24.09.2008) was obtained before the start of the study and

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