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Research Article

Gastroprotective Effect of Bezafibrate and *Ginkgo biloba* in Ethanol-Induced Gastric Ulcer in Rats

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Abstract

Background: Gastric ulcer disease is a common and recurring gastrointestinal condition affecting millions annually. Several medications are available for the treatment of gastric ulcers; however, their adverse reactions attenuate their usefulness. ***Objective***: To evaluate the possible synergistic gastroprotective effects of combining bezafibrate with *Ginkgo biloba* (GKB) in ethanol-induced gastric ulcers. ***Methods***: Thirty male Wistar albino rats were randomly distributed into six groups, each of 6 rats, as follows: negative control, positive control, esomeprazole group, bezafibrate group, GKB, and bezafibrate + GKB. All the medications were administered orally on a daily basis, and a single dose of ethanol (1 ml) was administered on day 14 for groups III, IV, V, and VI. After scarification, blood samples were gathered, and the stomachs were excised for gross evaluation. ***Results***: The combination group showed decreased gastric free and total acidity and LDH and raised gastric pH and GSH levels. Gross evaluation of stomach images showed remarkable protection in the combination group. ***Conclusions***: The combination of bezafibrate with ginkgo biloba extract in the current study exerted more gastroprotective effect than each alone, comparable to the esomeprazole effect, suggesting they could work synergistically to guard the gastric mucosa from ethanol-induced destruction via decreasing gastric acidity and inflammatory mediators and boosting the antioxidant system.

Keywords: Antioxidant activity, Bezafibrate, Gastric ulcer, Ginkgo biloba, Gastric pH.

التأثير الوقائي للبيزافيبرات والجنكة في قرحة المعدة التي يسببها الإيثانول في الفئران

الخلاصة

الخلفية: مرض قرحة المعدة هو حالة معدية معوية شائعة ومتكررة تصيب الملايين سنويا. تتوفر العديد من الأدوية لعلاج قرحة المعدة. ومع ذلك، فإن ردود أفعالهم السلبية تخفف من فائدتها. **الهدف**: تقييم التأثيرات التآزرية المحتملة للوقائية المعدية لدمج البيزافيبرات مع الجنكة بيلوبا (GKB) في قرحة المعدة التي يسببها الإيثانول.**الطرائق**: تم توزيع ثلاثين فأرا من ذكور Wistar albino بشكل عشوائي إلى ست مجموعات، كل منها من 6 فئران، على النحو التالي: التحكم السلبي، والتحكم الإيجابي، ومجموعة esomeprazole، ومجموعة bezafibrate، و GKB ، و bezafibrate + GKB. تم إعطاء جميع الأدوية عن طريق الفم على أساس يومي، وتم إعطاء جرعة واحدة من الإيثانول (1 مل) في اليوم 14 للمجموعات الثالثة والرابعة والخامسة والسادسة. بعد الخدش، تم جمع عينات الدم ، وتم استئصال المعدة لتقييم إجمالي. **النتائج**: أظهرت المجموعة المركبة انخفاضا في الحموضة الخالية من المعدة والحموضة الكلية و LDH وارتفاع مستويات الأس الهيدروجيني في المعدة و GSH. أظهر التقييم الإجمالي لصور المعدة حماية ملحوظة في المجموعة المركبة. **الاستنتاجات**: كان لمزيج البيزافيبرات ومستخلص الجنكة بيلوبا في الدراسة الحالية تأثير وقائي للمعدة أكثر من كل منهما بمفرده، مقارنة بتأثير إيزوميبرازول، مما يشير إلى أنهما يمكن أن يعملوا بشكل تآزري لحماية الغشاء المخاطي في المعدة من التدمير الناجم عن الإيثانول عن طريق تقليل حموضة المعدة والوسطاء الالتهابيين وتعزيز نظام مضادات الأكسدة.

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INTRODUCTION

Gastric ulcer disease is a common and recurring gastrointestinal disorder that affects millions of individuals each year and accounts for an expected mortality of 15 out of every 15,000 complications yearly [1,2]. It is widely acknowledged that gastric ulcers are multifactorial and seem to be caused by an imbalance between destructive elements (such as acid/pepsin, bile, H. pylori infection, NSAIDs, stresses, alcohol consumption, tobacco, and caffeine) and mucosal protective mechanisms (involving mucus secretion, mucosal blood flow, bicarbonate production, prostaglandin E, cellular repair mechanisms, and growth factors) [3]. High alcohol intake is the most common cause of stomach mucosal injury. As a result, the experimental model of ethanol-induced stomach ulcer is frequently used to screen anti-ulcer drugs [4]. Several medications are available to treat gastric ulcers; the most typical technique is to use H receptor antagonism and proton pump inhibitors or agents having mechanical protective action on gastric mucosa. However, long-term usage of these medications may have substantial

side effects. Current synthetic antiulcer drugs available on the market are often expensive and ineffective at preventing ulcer recurrence. Accordingly, there is a continuing interest in exploring new medications for the treatment of gastric ulcers [1,5]. Bezafibrate is a peroxisome proliferator-activated receptor alpha (PPARα) agonist. PPARs are a nuclear hormone receptor family that acts as ligand-activated transcription factors and forms heterodimers with the retinoid X receptor (RXR) when activated. This heterodimer interacts with a specific recognition sequence inside a PPAR-target gene regulation region. The PPAR family has three isoforms: PPARα, PPARβ/δ, and PPARγ. Each has a diverse tissue distribution and a different set of target genes. Some of their targets are nuclear-encoded RC genes, while others are mitochondrial biogenesis and fatty acid oxidation genes. The capacity of bezafibrate to upregulate the expression of nuclear-encoded mitochondrial genes explains some of the molecular mechanisms underpinning its effects on mitochondrial function and biogenesis [6,7]. PPAR is abundant in the small and large intestine mucosa, where dietary fatty acids are supplied. PPAR regulates genes involved in inflammation, cell cycle progression, angiogenesis, and lipid metabolism [8]. Studies have shown the effectiveness of numerous plants in treating gastroduodenal illness [9]. *Ginkgo biloba* (GKB) is an ancient plant that is believed to be a significant source of new herbal medicines with therapeutic effectiveness and various bioactive components that provide many health benefits to living organisms and contains many bioactive components, making it a chemically diverse plant [10]. The present study was designed to estimate the possible gastroprotective effect of combining GKB with bezafibrate.

METHODS

Experimental animals

Thirty male Wistar albino rats of (160-200g) weight were accommodated in the animal house of the College of Pharmacy, University of Sulaimani. The rats were held in well-ventilated plastic cages under regular conditions: temperature 25±2 °C and 12 hours of dark/light cycle. They were fed a conventional pellet diet and had unrestricted water access. Before starting the experiment, the animals were allowed to acclimate for one week. The experimental protocols were approved by the Ethical Committee of the University of Sulaimani, College of Medicine (certificate number 135; on 11th of December 2022) following the Institutional Animal Ethics Committee that met the Canadian Council on Animal Care (CCAC) guidelines.

Study design

A total of thirty rats were randomly distributed into six groups of 6 rats each as follows: Group I: Negative control rats received an equal amount of D.W. for 14 days. Group II: Positive control: received an equal amount of D.W. for 14 days; on day 14 received 1.0 ml of 90% ethanol to cause gastric ulcer. Group III: Esomeprazole group: received 30 mg/kg esomeprazole for 14 days. Group IV: Bezafibrate group: received 300 mg/kg for 14 days. Group V: The GKB group received 60 mg/kg for 14 days. Group VI: Bezafibrate + GKB group: received bezafibrate 300 mg/kg + GGKB 60 mg/kg for 14 days. All the medications were administered orally using a gavage tube, and a single dose of ethanol (1.0 ml) was administered orally on day 14 for groups III, IV, V, and VI. On the last 14th day of the experiment, all the animals were fasted for 24 hours with free access to water; they were euthanized one hour after the administration of ethanol. The doses of esomeprazole, bezafibrate, ethanol, and GKB used in this study have been based on previous studies [11-14].

Blood collection

Blood was collected through a cardiac puncture, centrifuged and sent for the measurement of biochemical markers including LDH, IL6, GSH and Catalase using ELISA kit (Bioassay Technology Laboratory, UK).

Gastric acid volume and pH measurement

After the ligation of the pyloric and cardiac regions, the stomach of each rat was removed. The gastric content was collected using separate graduated tubes, centrifuged at 3000 rpm/10 min, and the volume of the supernatant was determined [15] and was considered for pH measurement through a digital pH meter [16].

Total and free acidity assessment

The stomach juice was mixed with 0.1 N NaOH, and methyl orange was used to measure the total and free acidity. Once all the free hydrochloric acid was neutralized, the juice turned a salmon color. For the measurement of total acidity, an indicator, phenolphthalein, was used afterward, and methyl orange reagent (1–2 drops) was added to the gastric juice. The appearance of a bright red color was considered an indicator of the free acidity. The titration with 0.1 NaOH continued until a canary yellow color emerged. The volume of NaOH represented free HCl. Successively nonstop titration with NaOH continued after adding 1-2 drops of phenolphthalein until the red color emerged. The number of mL of NaOH used for the titration represented the total acidity [17]. Y = 0.1 N NaOH (mL) X 10, where Y = total acidity (mEq/L).

Gross gastric lesions assessment

The stomach was opened along great curvature,

rinsed using normal saline solution (0.9% NaCl) and considered for macroscopic assessment.

Statistical analysis

The statistical analysis was performed using GraphPad Prism 8. The values of the measured parameters were expressed as mean ± standard deviation (S.D.). For the comparisons between different groups, one-way analysis of variance (ANOVA), followed by Tukey multiple comparison tests, was used. Unpaired t-tests were used to compare each group with the positive control group. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Figure 1A shows the effect of esomeprazole and each of bezafibrate and GKB alone or in combination on gastric total acidity (GTA). Bezafibrate alone produced a significant decrease in GTA compared to the positive control group ($p< 0.05$).

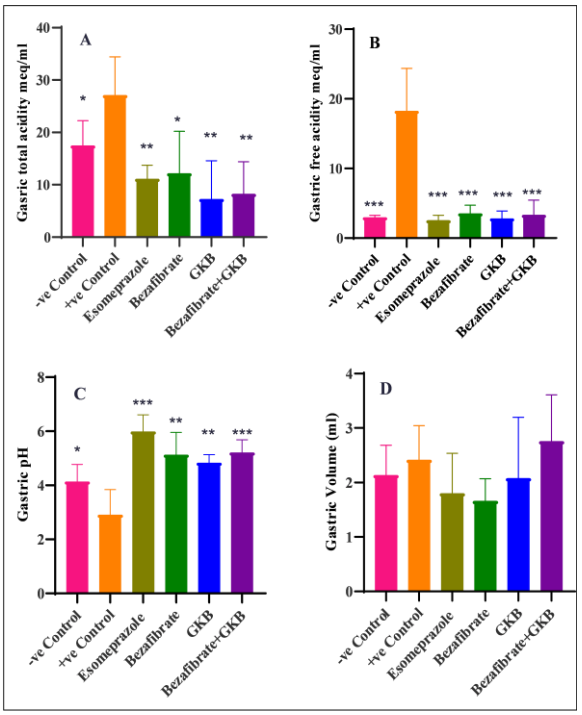

Figure 1: Effect of bezafibrate and GKB on (**A**) the gastric total acidity, (**B**) gastric free acidity, (**C**) gastric pH, and (**D**) gastric volume; * $p< 0.05$, ** $p< 0.01$, and *** $p< 0.001$ significantly different compared to the positive control group using one-way ANOVA and unpaired t-test.

The esomeprazole-treated group, GKB, and the combination group showed comparable effects that were more significant than the effect produced by bezafibrate alone ($p< 0.01$). Figure 1B shows the effect of esomeprazole and each of bezafibrate and KB alone or in combination with gastric free acidity (GFA). All the groups created a highly significant decrease in GFA compared to the positive control group ($p< 0.001$). Figure 1C shows the effect of esomeprazole and each of bezafibrate and GKB alone or in combination on gastric pH. All the groups studied created significant increases in gastric pH compared to the positive control group. However, the effect of esomeprazole along with bezafibrate and GKB combination ($p< 0.0001$) was more significant than the effect produced by bezafibrate and GKB alone ($p< 0.01$). Figure 1D presents the effect of esomeprazole and each of bezafibrate and GKB alone or in combination on gastric volume. No significant changes were observed in this regard. Figure 2A shows the effect of esomeprazole and each of bezafibrate and GKB alone or in combination on LDH. A significant elevation in the level of LDH was seen in the positive control group in comparison with the negative control group ($p< 0.01$).

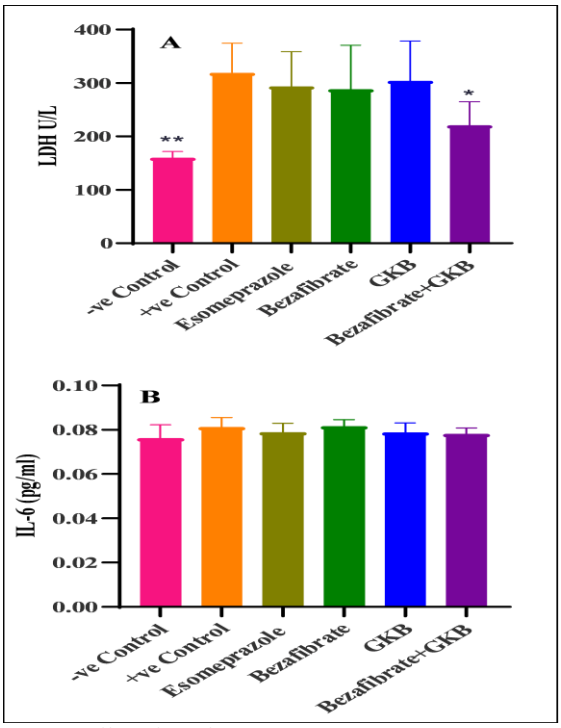

Figure 2: Effect of bezafibrate and GKB on (**A**) LDH, and (**B**) IL-6; ** $p< 0.01$) significantly different compared to the positive control group using one-way ANOVA and unpaired t-test.

However, none of the treated groups were able to produce significant amelioration except for the combination group ($p< 0.05$) compared to the positive control group. Figure 2B shows the effect of esomeprazole and each of bezafibrate and GKB alone or in combination on IL6. Although the combination group attenuated the level of IL6, the result was statistically not significant in each of the treated groups. Figure 3A shows the effect of esomeprazole and each of bezafibrate and GKB alone or in combination with GSH. The study displayed a significant increase in GSH produced by esomeprazole ($p< 0.05$) and each of bezafibrate and GKB alone and in combination ($p< 0.01$) in comparison to the positive control. Figure 3B shows the effect on catalase. Esomeprazole and each of bezafibrate and GKB alone and in combination increased the level; however, they didn't reach a significant level compared to the positive control.

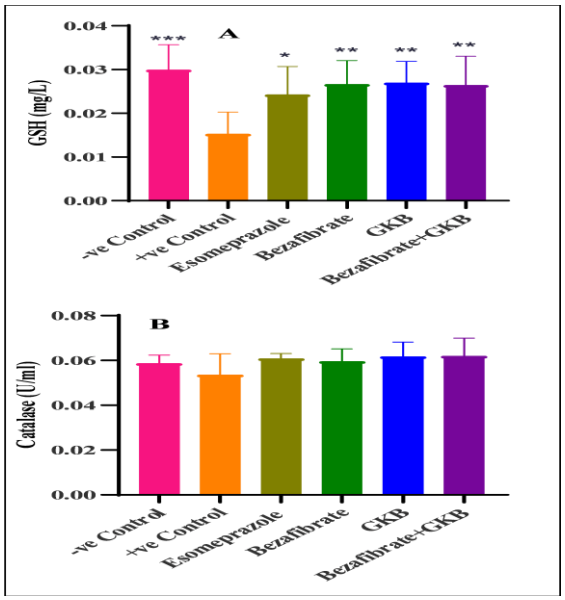

Figure 3: Effect of bezafibrate and GKB on (**A**) GSH, and (**B**) Catalase; * $p< 0.05$, ** $p< 0.01$), and *** $p< 0.001$ significantly different compared to the positive control group using one-way ANOVA and unpaired t-test.

Figure 4 shows the effect of esomeprazole and each of bezafibrate and GKB alone or in combination on total body weight. Esomeprazole and each of bezafibrate and GKB alone and in combination caused no significant effect on total body weight compared to the positive control.

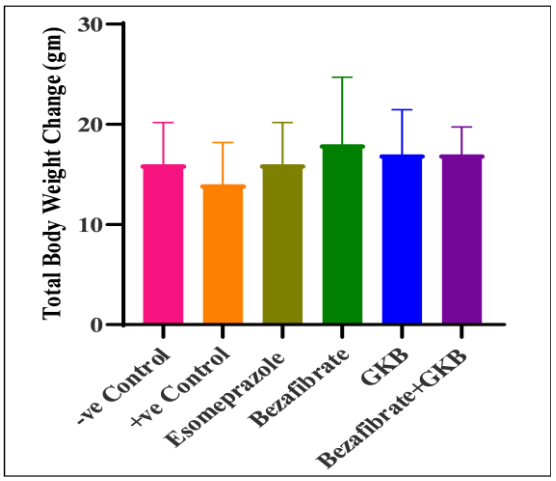

Figure 4: Effect of bezafibrate and GKB on total body weight change.

Figures 5A–F represent the images of the six treated groups. Macroscopic examination demonstrates a gastroprotective effect of bezafibrate and GKB; however, the combination group produced a maximum protective effect. The combination therapy (Figure 5F) in ethanol-induced gastric ulcers resulted in a protective effect comparable to that of the esomeprazole group (Figure 5C), and it was clearly observed when compared with the positive control group (Figure 5B).

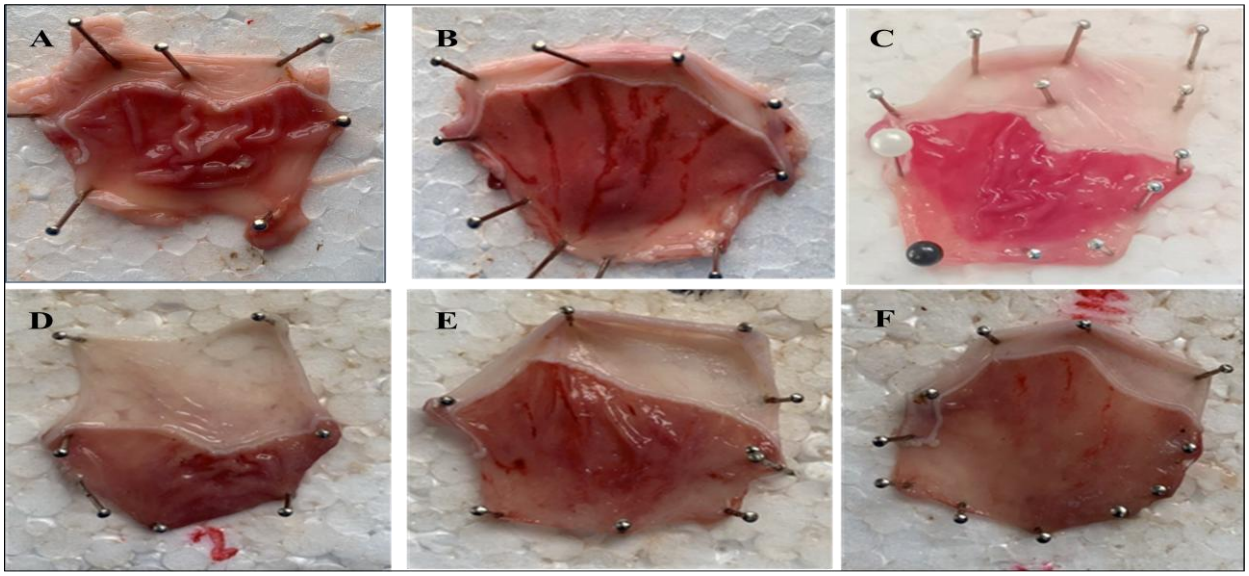

Figure 5: Representative images of stomachs from experimental groups: (**A**) Negative control group, (**B**) Ethanol-treated group, (**C**) Esomeprazole-treated group (30mg/kg), (**D**) Bezafibrate-treated group (300mg/kg), (**E**) GKB-treated group (60mg/kg), and (**F**) Bezafibrate and GKB-treated group.

DISCUSSION

Ethanol-induced gastric ulcers are among various other factors that contribute to the pathogenesis of gastric ulcers, and they have been used in the current study as a model. The underlying mechanisms include significant damage to gastric mucosa by increasing oxidative stress, inflammation, and apoptosis in gastric tissues [18]. The new approach in drug discovery partly depends on repurposing the already-known medications for other therapeutic purposes [19]. Research has explored various natural and pharmacological agents for their gastroprotective effects [20,21]. Herbal medicine has promptly become popular in the prevention and treatment of many human illnesses, including drug-induced gastric ulcers. Because of their safety and effectiveness, they are given more consideration. Their exceptional antioxidant and anti-inflammatory properties, along with their phytonutrient content, have made them useful in the management of various health problems [21]. GKB is the world's oldest

extant tree species, and its extract is one of the most commonly used herbal preparations. It is one of the most widely utilized medicinal plants in the world for treating different conditions, and several studies have demonstrated its strong antioxidant activity across various tissues ranging from human subjects to animal models [2]. Bezafibrate exhibits dose-dependent antiulcer activity in rats [8,23]. In the present study, combining bezafibrate with Ginkgo biloba has shown potential for protecting against ethanol-induced gastric ulcers via decreasing gastric acidity and inflammatory markers and elevating antioxidant capacity with no significant effects on total weight. Bezafibrate, as a PPAR-α agonist, modulates lipid metabolism and exhibits anti-inflammatory effects. It reduces the production of pro-inflammatory cytokines, which can help minimize gastric mucosal damage [25]. Bezafibrate combination with GKB has been studied and verified to protect against hepatotoxicity, along with cardiac injury, by restoring injury markers and IL-6, as well as improving the lipid profile, atherogenic index, and cardiac risk ratio. These effects might result from the cumulative anti-inflammatory and antioxidant effects of this combination [14,26]. Additionally, the herbal extract GKB exerts anti-inflammatory effects primarily through inhibiting the release of inflammatory mediators [27]. Another important factor that contributes to the protection against gastric ulcers in the current study is the antioxidant capacity offered by the combination group. Bezafibrate acts through upregulating antioxidant enzymes and reducing the generation of reactive oxygen species (ROS) in gastric tissues [26]. On the other hand, Ginkgo biloba is rich in flavonoids and terpenoids, which enable it to act as a potent antioxidant. It scavenges free radicals, reduces lipid peroxidation, and protects the gastric mucosa from oxidative damage. Studies have shown that GKB has a positive effect on improving gastrointestinal function, attributing to its antioxidant properties and anti-inflammatory potential [28], besides its ability to improve gastric pH, preserve gastric mucus, and increase GSH. Their phytonutrient contents, along with their outstanding anti-inflammatory and antioxidant characteristics, have enabled them to play an important role in the treatment of numerous human ailments [24,29,30]. Furthermore, studies showed that bezafibrate might aid in mucosal defense mechanisms by enhancing mucin production, a protective mucus layer in the stomach, thereby providing a physical barrier against ethanol-induced injury [23]. Ginkgo biloba also contributes to mucosal defense enhancement by improving blood flow [31] and enhancing the microcirculation within the gastric mucosa [32]. Ginkgo biloba supports the maintenance of mucosal integrity and promotes the healing of gastric lesions [33]. Moreover, Ginkgo biloba extract can impede ethanol-induced apoptosis in gastric cells, likely through its antioxidant effects and modulating signaling pathways involved in cell survival. Inhibition of apoptosis is another suggestive mechanism of gastric protection [34]. Researchers found that bezafibrate can lower apoptosis in gastric epithelial cells by changing the levels of proteins that help and hurt apoptosis. This protects the integrity of the lining of the stomach [23,35]. The macroscopic examination of gastric images clearly demonstrates the gastroprotective effects of the combination group, which produced effects comparable to those exerted by esomeprazole.

Conclusion

The combination of bezafibrate with ginkgo biloba extract in the current study showed promising results that suggest they could work synergistically to protect the gastric mucosa from ethanol-induced damage via decreasing gastric acidity and inflammatory mediators and boosting the antioxidant system.

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Conflict of interests

The author declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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