The Protective Roles of Butein on Indomethacin Induced Gastric Ulcer in Mice

Rustem Anil Ugan[1], Harun Un[2]

ABSTRACT

Objective: Butein is a potential agent first isolated from Rhus verniciflua that has medicinal value in East Asia and has been used in the treatment of gastritis, gastric cancer, and atherosclerosis since ancient times. The aim of our study is to show, for the first time, the anti-ulcerative effect of butein in indomethacin induced gastric ulcer in mice.

Materials and Methods: A total of 42 mice were fasted 24 hours for the ulcer experiment, and 10, 20, and 40 mg/kg doses of butein were evaluated for their antiulcer activity. Famotidine 40 mg/kg was used as a positive control group. For ulcer induction, 25 mg/kg dose of indomethacin was administered to the mice and after 6 hours all stomachs were dissected out. After macroscopic analyses, tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), COX-1, and COX-2 mRNA levels of stomachs were evaluated by Real Time PCR, and Superoxide dismutase (SOD), glutathione (GSH), and malondialdehyde (MDA) were determined by ELISA.

Results: Butein administration exerted 50.8%, 65.9%, and 87.1% antiulcer effects at 10, 20, and 40 mg/kg, respectively. Butein administration decreased oxidative stress and inflammatory parameters in stomach tissues dose dependently. Furthermore, butein administration increased stomach PGE2 levels and decreased COX-1 and COX-2 mRNA levels.

Conclusion: Butein has been shown to have a healing effect on ulcers in macroscopic examinations in our study. We observed that butein has antioxidant and anti-cytokine properties in gastric tissue. Butein could be an important alternative in the treatment of indomethacin-induced ulcers. Whether butein is a partial agonist of the COX enzyme should be investigated in future studies.

Keywords: Butein, ulcer, mice, indomethacin

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[1]Department of Pharmacology, Ataturk University, Faculty of Pharmacy, Erzurum, Turkey
[2]Department of Biochemistry, Agri Ibrahim Cecen University, Faculty of Pharmacy, Agri, Turkey

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Correspondence to: Rustem Anil Ugan
E-mail: anil.ugan@atauni.edu.tr

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Introduction

There are various factors that could cause gastric ulcers. One of these factors is the use of non-steroidal anti-inflammatory drugs (NSAIDs). These drugs are widely used worldwide for their analgesic, anti-inflammatory, and antipyretic properties, although they cause serious gastrointestinal side effects [1]. Among NSAIDs, indomethacin is frequently used as a reference drug for the formation of the ulcer model in rats due to its high gastric toxicity [2]. The ulcer-forming mechanisms of indomethacin include the increased aggressive factors and oxidant parameters, decreased antioxidant parameters, and secretion of protective factors such as prostaglandin E2 (PGE2) [3]. Drugs that reduce gastric acid such as histamine H2 receptor blockers, proton pump inhibitors, antacids, and gastric protective drugs such as PGE2 analogs and sucralfate are used in the treatment of gastric ulcers [4]. In addition to these, natural compounds derived from plants have been used in the treatment of gastric ulcers for centuries because of their low side effects as well as significant medicinal effects [5].

Butein (3,4,2′,4′-Tetrahydroxychalcone) is a polyphenolic phytochemical from various plant sources [6]. Butein has been shown to have broad pharmacological effects, such as anti-inflammatory, anticancer, antioxidant, and antimicrobial, in experimental studies [7]. Butein was first isolated from Toxicodendron vernicifluum, formerly known as Rhus verniciflua [8]. Rhus verniciflua stokes (RVS) is widely known for its medicinal value in East Asia and has been used in the treatment of gastritis, gastric cancer, and atherosclerosis since ancient times [8].

However, the effects of pure butein on ulcers have not yet been shown. The aim of our study is to show, for the first time, the anti-ulcerative effect of butein on indomethacin-induced gastric ulcers in mice.

Materials and Methods

Animals

This experiment was carried out using 48 Balb/c male mice weighing between 30–35 g. The mice were obtained from Ataturk University Medical Experimental Application and Research Center. The mice were housed in groups before and during the experiment, in plastic boxes with sawdust, in a 12/12-hour day/night cycle and 22°C temperature. Standard feed and tap water were given ad libitum. This study was approved by Ataturk University animal experiments local ethics committee (Decision no: 2018/221).

Chemicals

Indomethacin, famotidine, and thiopental sodium were obtained from Endol, Deva; Famodin, Sandoz; IE Ulagay, Istanbul, Turkey, respectively. Butein was obtained from Santa Cruz, Heidelberg, Germany. Indomethacin, famotidine, and butein were suspended in saline and administered orally. The same amount of saline was administered to the healthy group. Doses of indomethacin [2, 9, 10], famotidine [2], and butein [11] were selected according to previous studies.

Ulcer Model

Mice were randomly divided into seven groups (six mice in each group). Experimental groups are shown in Table 1. The mice were fasted for 24 hours; however, their access to water was not restricted. Butein and famotidine were given to the experimental groups with gastric gavage and five minutes later, indomethacin was given by gastric gavage to the groups three, four, five, six, and seven. Six hours after indomethacin administration, all mice were euthanized with intraperitoneal (i.p) thiopental sodium administration [12, 13]. The abdomen was excised, the stomach was removed, and ulcerative areas on the stomach surface were evaluated macroscopically. After this evaluation, the stomachs were stored in the laboratory under suitable conditions for biochemical and molecular investigations.

Main Points

- Butein could be an important alternative in the treatment of indomethacin-induced ulcers.
- Butein has antioxidant and anti-cytokine properties in the gastric tissue.
- Butein improved prostaglandin levels in the indomethacin-induced ulcer model.

Biochemical Analysis

All stomach tissues of mice were stored at -80°C and then were ground in liquid nitrogen on the TissueLyser II (Qiagen, Hilden, Germany). Approximately, 50 mg of powdered tissue was homogenized in 500 µl of PBS homogenate buffer and centrifuged. Superoxide dismutase (SOD) activity, glutathione (GSH), and malondialdehyde (MDA) levels were measured manually [14-17]; and prostaglandin E2 levels were measured with the kit from the supernatants of stomach tissues by ELISA reader. Protein amounts were measured manually using Lowry method. The mean absorbance of each sample and standard was calculated. All data were shown as mean±standard deviation (SD) relative to each mg protein.

Molecular Analysis

mRNA Extraction and cDNA Synthesis

mRNA extraction and complementary DNA (cDNA) synthesis were performed according to the methods described in our previous studies [18, 19]. mRNA extraction was performed from previously homogenized stomach tissue (pooled, 20 mg). Total mRNA was purified on the QIACUBE (Qiagen, Hilden, Germany) device according to the manufacturer's instructions using the RNeasy Mini Kit (Qiagen, Hilden, Germany). RNA samples were reverse transcribed to cDNA using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, CA, USA).

Relative Quantification of Gene Expression

Relative mRNA expression analyses of tumor necrosis factor-alpha (TNF-α, ID: Mm00443258_m1), interleukin-1β (IL-1β, ID: Mm00434228_m1), COX-1 (PTGS1, ID: Mm00477214_m1, and COX-2 (PTGS2, ID: Hs00153133_m1) from cDNAs obtained from RNAs of mice stomach was performed on StepOne Plus Real Time PCR instrument (Applied Biosystems) using the Taqman Gene Expression kit (Applied Biosystems). β-actin was used as housekeeping gene. All data were expressed as fold change in expressions compared to the control group using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

Biochemical and molecular data were applied to one-way ANOVA test in IBM SPSS 20.0 statistical program (IBM SPSS Corp.; Armonk, NY, USA). The differences between the groups were determined by Duncan multiple comparison test ($p < 0.05$). All results are expressed as mean±SD for each group.

Results

Stereological Results

Looking at our results of numerical densities of the ulcer hematoma areas (Figure 1), we found that the INDO group had 0.029±0.002 ulcer density per 1000 µm^2 of stomach area. The famotidine administration significantly reduced areas of ulcer hematoma and caused a 99.2% antiulcer effect. BUT 10, BUT 20, and BUT 40 groups showed significant antiulcer effect dose dependently (13.8%, 62.0%, and 86.2%, respectively)

Biochemical Results

Stomach Tissue Oxidative Stress Results

It was shown that SOD activity (Figure 2) and GSH levels significantly decreased, and MDA levels significantly increased in the INDO group when compared to those of the healthy control group. Oxidative stress parameters in the FAMO group were significantly different from that in the ULCER and HEALTHY groups. SOD activity, GSH levels, and MDA levels in ULCER+BUT40 group were significantly closer to the HEALTHY group ($p<0.05$).

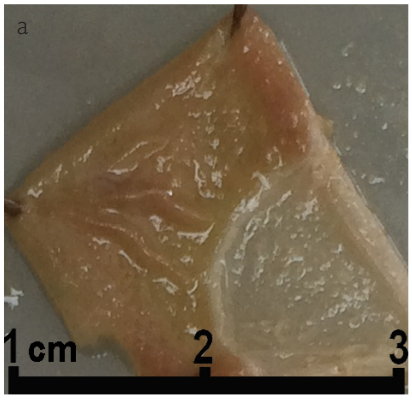
Stomach Tissue Prostaglandin E2 Results

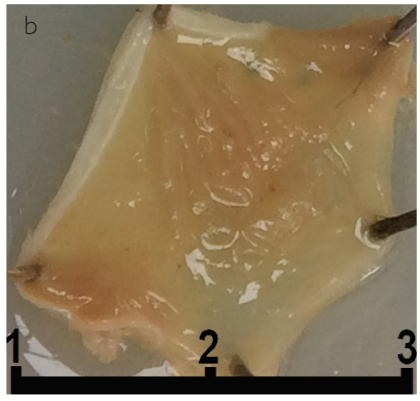
As shown in Figure 3, stomach PGE2 concentration significantly decreased with indomethacin

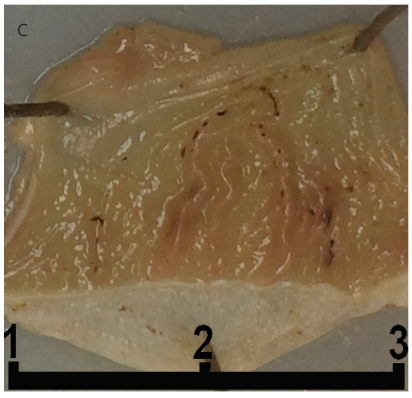
Table 1. Experimental groups

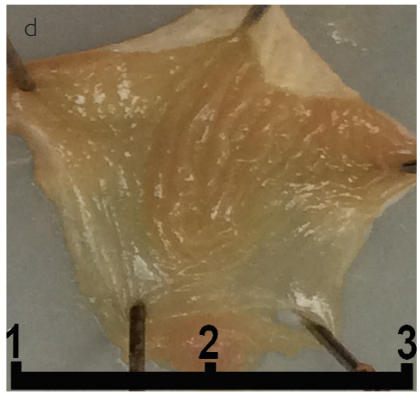
Groups	
HEALTHY	Control
BUT 40	Only butein 40 mg/kg
INDO	Only 25 mg/kg indomethacin
FAMO+INDO	40 mg/kg famotidine + 25 mg/kg indomethacin
BUT 10+INDO	10 mg/kg butein + 25 mg/kg indomethacin
BUT 20+INDO	20 mg/kg butein + 25 mg/kg indomethacin
BUT 40+INDO	40 mg/kg butein + 25 mg/kg indomethacin

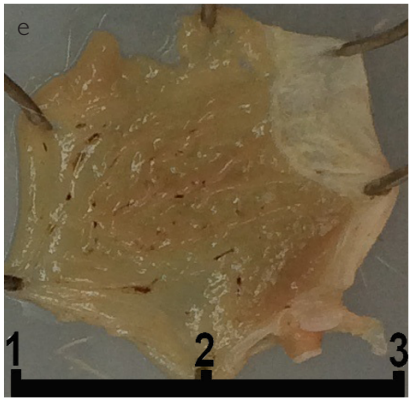
BUT: butein; INDO: indomethacin; FAMO: famotidine

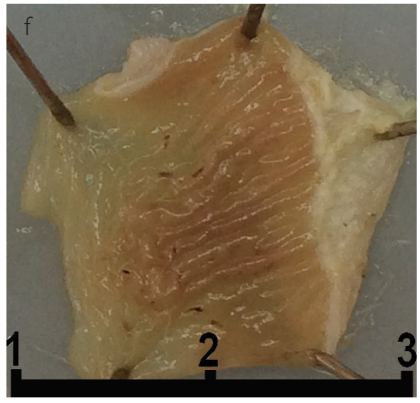


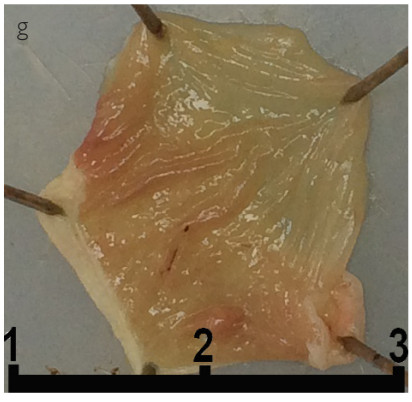












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Numarical Density of Ulcerated Areas	
HEALTHY	0.00
BUT40	0.00
ULCER	0.029±0.002
ULCER+FAMO	0.00
ULCER+BUT10	0.025±0.002
ULCER+BUT20	0.011±0.001
ULCER+BUT40	0.004±0.001

Figure 1. a-h. ample images; (a) Healthy, (b) BUT40, (c) INDO (ulcer), (d) INDO+FAMO, (e) INDO+BUT10, (f) INDO+BUT20, (g) INDO+BUT40, (h) Numerical densities of ulcerated hematomas from each group. In our study, numerical density of the ulcerated area has been calculated by dividing the total number of ulcer areas by total volume of stomach tissue

administration when compared to the healthy group. PGE2 levels in both the butein doses and FAMO groups were significantly higher than those in the indomethacin-induced ulcer group. Even 20 and 40 mg/kg of butein and famotidine increased PGE2 concentrations higher than that of the healthy group ($p<0.05$).

Molecular Results

Stomach COX Enzyme mRNA Expression

As shown in Figure 3, the mRNA expressions of COX-1 and COX-2 enzymes in the stomach tissues of mice significantly increased in the ULCER group, while the mRNA expressions of both enzymes in the FAMO group and butein administered groups significantly decreased. The mRNA expressions of COX-1 and COX-2 were decreased more significantly by butein 40 mg/kg.

Stomach Tissue Cytokine mRNA Expression

The mRNA expressions of TNF-α and IL-1β were significantly higher in the stomach tissue of the INDO group than the healthy group. All doses of butein and famotidine significantly decreased TNF-α and IL-1β mRNA expression dose dependently (Figure 4).

Discussion

In this study, antiulcer effects of three different doses of butein were examined in the indomethacin-induced ulcer model. The source point of our experiment is the considerable amount of butein in RVS, which has been used in the treatment of ulcers and gastric cancer in traditional East Asian medicine and as a food additive in Korea for a long time [20, 21]. Moreover, the use of food supplements in the treatment of gastric ulcers is common all over the world [5, 22].

In light of this information, we conducted this study to elucidate whether butein alone had an anti-ulcerative effect. To this end, we administered butein at doses of 10, 20, and 40 mg/kg to indomethacin-treated mice and compared the results with famotidine, a histamine receptor blocker currently used in the treatment of ulcers. Our results showed that butein administration significantly increased antioxidant levels, decreased oxidative parameters, and reduced elevated cytokine levels such as TNF-α and IL-1β. According to stereological examinations, we observed that severe ulcers developed in indomethacin-treated groups, and the ulcer areas disappeared in famotidine-treated groups. In the butein groups, we found that ulcer areas decreased in a dose-dependent manner.

Looking at the mechanisms of gastric ulcer formation, the increase of free radicals and oxida-

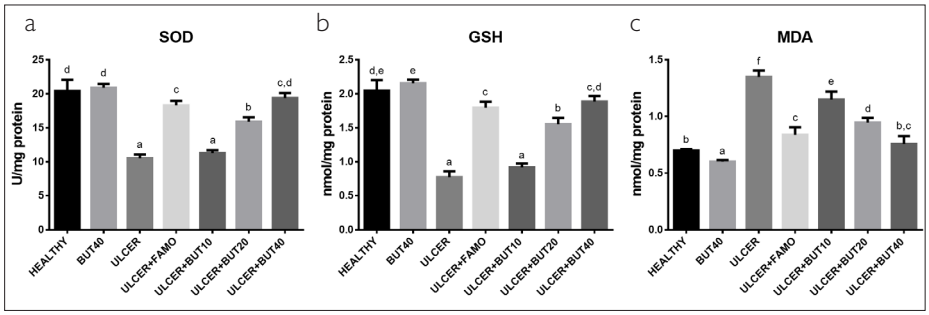

Figure 2. a-c. (a) Stomach tissue SOD activity, (b) GSH level, and (c) MDA level. Means with the same letter are not significantly different; means with different letters indicate significant differences between the groups according to the Duncan test ($p < 0.05$). Results are mean±SD. N=6 animals per group

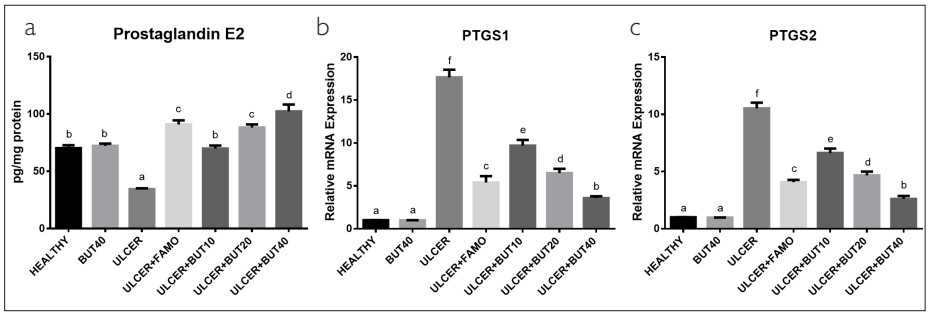

Figure 3. a-c. Stomach tissue PGE2 concentration (a) COX-1 (b) and COX-2 (c) mRNA expression. Means with the same letter are not significantly different; means with different letters indicate significant differences between the groups according to the Duncan test ($p < 0.05$). Results are mean±SD. N=¼ 6 animals per group

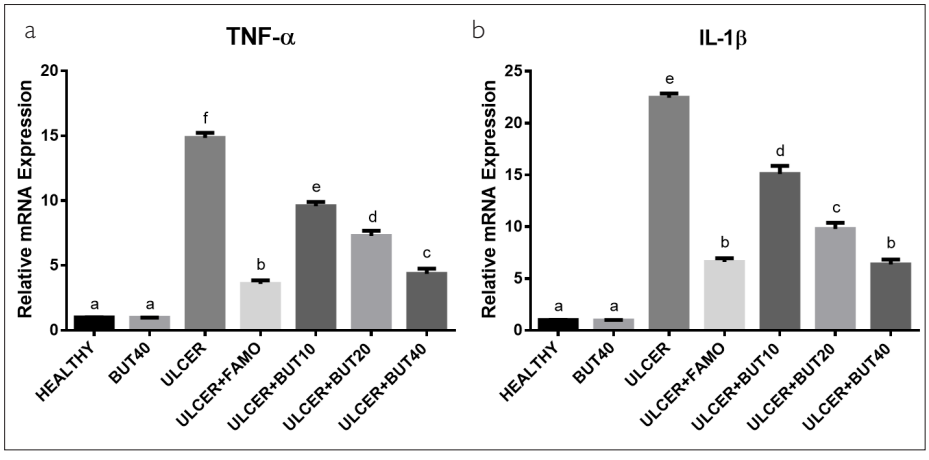

Figure 4. a, b. Stomach tissue TNF-α (a) and IL-1β (b) mRNA expression. Means with the same letter are not significantly different; means with different letters indicate significant differences between the groups according to the Duncan test ($p < 0.05$). Results are mean±SD. N=¼ 6 animals per group

tive processes contribute strongly to the ulcer disease. Therefore, the relationship between ulcer and antioxidants is a very interesting subject [2]. In the literature, useful results have been demonstrated by using antioxidant agents in gastric ulcer treatment and regulating the antioxidant/oxidant balance. For example, quercetin, known to have antioxidant properties, has been shown to be able to reduce ulcer damage by regulating oxidant and antioxidant parameters in both ethanol and indomethacin-induced gastric ulcers [23, 24]. Similarly, EGCG, an antioxidant in green tea, administered to ulcerated mice demonstrated beneficial results against gastric ulcers [25]. Based on this information, in our study, we evaluated the effect of butein on oxidative stress parameters in the stomach tissues of mice in order to explain its antiulcer mechanism. According to our results, indomethacin increased MDA (a lipid peroxidation indicator) levels [2], while butein dose dependently decreased MDA levels. Additionally, indomethacin decreased antioxidant parameters. In our study, indomethacin administration decreased SOD activity and GSH levels, while butein dose dependently increased both. Similarly, recent studies suggest that butein has antioxidant properties. Chen et al. indicated that butein may be more effective than the α-tocopherol by using the density functional theory (26). In another study, it was shown that butein had a dose-dependent inhibitory effect on lipid peroxidation in rat brain, and its antioxidant activity was dependent on free radical scavenging action and metal ion chelation [27]. Sogawa et al. suggested that butein decreased the production of superoxide anion and exhibited a potent inhibitory effect on H_2O_2-induced hemolysis on oxidative cell damage caused by carbon tetrachloride [28]. Another study investigated the restorative properties of butein on reduced activities of antioxidant enzymes (SOD) and GSH content in glutamate-injured HT22 cells [29]. Similar to butein studies, it was seen that antioxidant activity of RVS corresponds to well-known enzymatic and non-enzymatic antioxidants [30]. In another study, Lee et al. found that the ethanol extract of RVS showed stronger ROS scavenging and antioxidant activity against hydroxyl radicals compared to other extracts of RVS [31]. The same researchers later found that butein was one of the responsible compounds for the antioxidant property of the ethanol extract of RVS [32].

On the other hand, increased cytokine levels contribute to ulcer damage as well as increased oxidative stress [2]. Proinflammatory cytokines, mainly TNF-α and IL1β, are secreted in addition to oxidant release in almost all inflammatory responses [33]. In this context, we investigated the effects of butein administration on cytokine content in indomethacin-induced gastric ulcer. Both TNF-α and IL1β levels in the ulcer group were significantly higher than those of the healthy group. Butein administration significantly reduced TNF-α and IL-1β levels dose dependently. Previous studies support our results. It was shown that butein effectively inhibit TNF-α induced airway inflammation and ROS generation [34]. Butein suppressed TNF-α production in LPS-stimulated RAW264 cells [34, 35]. In a study about colitis, it was shown that butein administration decreased IL-1β and IL-6 expression levels [36].

In addition to changes in cytokines, changes in the COX enzyme, which plays an important role in the inflammation process, and PGE2 synthesis are important in the pathogenesis of gastric ulcer [2]. These are more important particularly in gastric ulcers caused by an NSAID such as indomethacin [2, 37]. Studies have shown that COX-1 and COX-2 enzymes are inhibited and therefore PGE2 synthesis is reduced, and

ulcers are exacerbated by the use of NSAIDs [37]. For that reason, prostaglandin synthesis enhancing treatments are currently considered in the treatment of NSAID-induced ulcers. For example, the H2 receptor blocker, famotidine, is one of the first preferred drugs in treatment because it decreases acid synthesis as well as increases prostaglandin synthesis and shows gastric protective activity. However, the prostaglandin analogue, misoprostol, is abused due to its miscarriage effect and its use is restricted [38]. Therefore, alternatives in the treatment of ulcer with fewer side effects are being sought, and hence research is shifting to substances with natural antioxidant activity [22]. Therefore, we examined the effects of butein on COX-1 and COX-2 mRNA expression levels and serum prostaglandin levels in indomethacin-induced ulcer and compared the results with famotidine. Compared with the ulcer group, we found that butein dose dependently increased COX-1 and COX-2 mRNA levels and as a result increased PGE2. However, we found that the improvement in these values was not as good as that with famotidine. Initial studies with butein in the literature support our findings. Nakadate and Aizu et al. investigated the effects of butein on lipoxygenase and cyclooxygenase enzyme activities and found that butein reduced lipoxygenase activity in all doses but increased COX activity up to 3 μM concentration and reduced COX activity at higher doses [39, 40]. Additionally, Nakadate and Aizu et al. suggested that butein may be effective on tumors with lipoxygenase inhibition and may reduce histamine secretion, but it is unlikely that butein can inhibit COX activity because it has little effect on epidermal COX activity [39, 40]. In another study, Lau et al. suggested that butein down regulates phorbol 12-myristate 13-acetate (PMA)-induced COX-2 transcriptional activity and reduces PGE2 levels in cancerous and non-cancerous breast cells. Similarly, Li et al. specified that butein induced cell apoptosis and reduced COX-2 expression in A549 lung cancer cells [41]. In another study, butein was also shown to inhibit LPS-induced COX-2 and TNF-α expressions [35]. In a paw edema study, the percentage of COX inhibition and anti-inflammatory activity of butein were compared with ibuprofen, and the activity of butein was found to be about half of that of ibuprofen [20].

According to a summary of all these results, butein activates COX enzyme at low doses and inhibits at it at high doses. Butein decreases the COX-2 synthesis when it is induced by PMA; however, in our study, butein increased COX-2 synthesis when it was reduced by indomethacin. Moreover, the percentage of COX inhibition and anti-inflammatory activity of butein was found to be half of that of ibuprofen. All these studies suggest that butein could be a partial agonist of the COX enzyme.

Therefore, we conclude that butein partially inhibits COX enzyme in the absence of NSAID or in the presence of PMA and activates COX in the presence of NSAID. On the other hand, it has been shown in previous studies that butein reduces histamine synthesis and anti-inflammatory response by the inhibition of lipid peroxidation [39]. These pathways may have contributed to the effect of butein on gastric ulcer healing and warrants further investigation in future studies.

In conclusion, although butein appears to be at a disadvantage in terms of treating gastric ulcer due to COX enzyme inhibition in previous studies, we have shown it to have ulcer healing effect on macroscopic examinations in our study. This leads us to believe that butein is a partial agonist of the COX enzyme, and our study demonstrates that it has antioxidant and anti-cytokine properties in the gastric tissue, which implies that butein could be an important alternative in the treatment of indomethacin-induced ulcers. New clinical and experimental studies on this subject should be done in the future.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Animal Experiments of Ataturk University (Decision no: 2018/221).

Informed Consent: We complied with NIH guidelines for use of laboratory animals.

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Conflict of Interest: Authors have no conflicts of interest to declare.

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