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Experimental Research Article

Comparing the Analgesic and Anti-Ulcer Properties of Green Tea Aqueous Extract with Licofelone

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ABSTRACT

Introduction: Green tea possesses gastroprotective effects via different mechanisms including lipoxygenase inhibition. We compared its protective effects with licofelone (as a potent lipoxygenase inhibitor) on reducing the incidence of gastric ulcers caused by indomethacin.

Methods: 48 rats received an aqueous extract of green tea (GTAE; 50, 100, and 200 mg/kg), licofelone (30 mg/kg), zileuton (100 mg/kg), or 0.18% Tween 80 in the presence of indomethacin (100 mg/kg). Two groups received only GTAE (200 mg/kg) or indomethacin (100 mg/kg). The gastric ulcer index and Malondialdehyde (MDA) in gastric tissues were evaluated. To investigate the analgesic effect in acute and chronic phases, 24 rats received GTAE (200 mg/kg), licofelone (30 mg/kg), indomethacin (30 mg/kg), or 0.18% Tween 80 in the presence of formalin (2.5%). The behavior of rats was monitored for 30 minutes (minutes 0 to 5 and 25 to 30) for licking and biting feet and tails.

Results: Indomethacin (100 mg/kg) produced clear macroscopic lesions compared to the control group. GTAE (100 and 200 mg/kg), licofelone, and Zileuton showed a significant decrease in wound score compared to indomethacin. GTAE (100 mg/kg and 200), licofelone, and zileuton displayed a significant decrease in the MDA content of gastric tissue compared to the indomethacin group. Notably, GTAE exerted greater benefits than licofelone. Besides, GTAE (200 mg/kg) showed a significant decrease observed in both acute and chronic stages of pain compared to licofelone (30 mg/kg).

Conclusion: GTAE (200 mg/kg) possesses anti-ulcer and analgesic effects similar to licofelone. The exact mechanism is probably via inhibition of lipoxygenase (LOX) and antioxidant effects.

Keywords:
Green tea
Lipoxygenase
Indomethacin
Gastric or peptic ulcer
Analgesic

Introduction

Peptic ulcer, a prevalent medical emergency condition globally, is linked to morbidity rates of up to 30% and even mortality (Malfertheiner et al., 2023; Xie et al., 2022). Clinical manifestations of peptic ulcer disease include upper abdominal pain, severe abdominal pain, he-

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matemesis, hematochezia, occult blood loss, and black or tarry stools (Andrade et al., 2024). The pathogenesis of peptic ulcers is complex, involving multiple factors. The onset of the condition is often the result of exposure to a range of risk factors, including but not limited to Helicobacter pylori infection (Malfertheiner et al., 2023), smoking (Liu et al., 2023b), drinking alcohol (Liu et al., 2023b), stress (Honcharuk et al., 2023), spicy food (Chan et al., 2021) and regular use of anti-thrombotic (like aspirin) (Hawkey et al., 2022), and non-steroidal anti-inflammatory (NSAID) (Xie et al., 2022) drugs is greater than protective factors such as buffers Carbonate, mucus gel, mucus phospholipid, prostaglandins (PGs) and stomach hormones (Tsai and Brooks 2019).

NSAIDs by widespread use in the world are known as potent anti-inflammatory, antipyretic, and analgesic drugs (Panchal and Sabina 2023). The inhibition of cyclooxygenase (COX) enzymes is known to impede the synthesis of numerous inflammatory mediators, like PGs, which exert great reducing inflammation, pain, and fever relief (Ali et al., 2023). On the other hand, PGs contribute to the protection of the gastromucosal barrier. The inhibition of PG production by NSAIDs, however, elevates the risk of severe vascular and upper gastrointestinal tract complications (Lanas et al., 2015; Pineda-Peña and Chávez-Piña 2023). Also, there is evidence that inhibition of COX by NSAIDs causes the transfer of arachidonic acid metabolism to the 5-lipooxygenase (5-LOX) pathway and more production of leukotriene. Leukotrienes (LTs; LTC4, LTD4, and LTE4) are involved in tissue ischemia, inflammation, vascular changes, and gastric mucosal damage (Aal-Aaboda et al., 2023). Moreover, NSAIDs by synthesizing nitric oxide (NO) and reactive oxygen species (ROS) trigger lipid peroxidation and inflammatory processes that play a crucial role in gastric damage (Majka and Brzozowski 2023; Mashayekhi-Sardoo et al., 2020).

Indomethacin, a potent NSAID, is deleterious to the gastrointestinal tract, causing noteworthy damage to the mucosa. As a result, this medication is frequently employed in research endeavors to scrutinize the adverse effects of NSAIDs on the gastrointestinal tract (Scarpignato and Hunt 2010). In addition, indomethacin in acute phases can enhance the levels of LTB4 (potent neutrophil chemoattractant) in the gastric mucosa (Aal-Aaboda et al., 2023; Mashayekhi-Sardoo et al., 2020).

In recent years, multiple endeavors have been initiated to seek out a promising natural medicinal herb for relieving the peptic ulcers that occur with NSAIDs. Green tea is a traditional drink in Asia that derives from *Camellia sinensis* leaves (Ogar et al., 2023). This herb by containing different chemicals including phenolic compounds, catechin, caffeine, and theanine exhibits analgesic, anti-inflammatory, antioxidant, anti-diabetic, and anti-bacterial, as well as gastroprotective properties (Amirtha et al., 2023; Etemadi Sh et al., 2023; Żuchnik et al., 2022). Catechin can be considered the chief antioxidant compound of green tea. They potently neutralize the reactive oxygen and nitrogen species. The green tea catechin derivatives are epigallocatechin gallate (most potent), epigallocatechin, epicatechin, and epicatechin gallate (Fahmi et al., 2024). The gastroprotective mechanism of green tea is to maintain the mucus and glutathione (GSH) of gastric tissue (Lan et al., 2023). Moreover, green tea catechin inhibits the polymorphonuclear leukocyte 5-LOX activity and via inhibition of the LTB4 synthesis, prevents inflammatory reactions and oxidative damage (Choi et al., 2004).

Despite the fact that in the two recent decades following the prescription the proton-pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), and PGs analog drugs and cutback the Helicobacter pylori infection prevalence the cases suffered from peptic ulcer disease has become less (Begg et al., 2023; Kuipers 2018), there are insufficient therapeutic approaches regarding the peptic ulcers related to NSAID drugs. In previous studies, it was observed that water extract from green tea safely modulates inflammatory and oxidative stress biomarkers and exerts analgesic benefits (Coppock and Dziwenka 2016; Ghorbanoghli et al., 2019; Zainab Khudhur Ahmad et al., 2020). In the current study, we compared the analgesic and anti-ulcer effects of green tea aqueous extract (GTAE) with Licofelone, a dual inhibitor of COX-1/COX-2 and 5-LOX (Shahraki et al., 2023). Our goal was to determine whether GTAE has comparable or superior effects, which could suggest it as a suitable alternative to dual inhibitors of COX-1/COX-2 and 5-LOX.

Materials and methods

Animals

A total of 72 adult male Wistar rats with a weight range of 220-250 g were obtained from the Animals Laboratory of Mashhad University of Medical Sciences,

Mashhad, Iran, and enrolled in the present investigation. The animals were housed at the Laboratory Animal Facilities of the School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran, under standardized environmental conditions consisting of a 12-hour light/dark cycle, a temperature of 25±2 °C, and a humidity level of 60±10%. The animals were provided with ad libitum access to food and water, although a 4-hour fasting period was imposed prior to the commencement of the experiment. All animal procedures were performed in accordance with the guidelines established by the Ethical Committee for Animal Experimentation at the School of Pharmacy, Mashhad University of Medical Sciences, and were conducted under the approval of the committee (code: "details omitted for double-blind reviewing").

Chemicals and drugs

Tween 80 was obtained from Merck Co. (Germany). Indomethacin was purchased from Behdashkar (C.A.S: 53-86-1) (Tehran, Iran). Zileuton was acquired from Cayman (C.A.S: 111406 87-2) (Ann Arbor, Michigan). Licofelone powder was purchased from Tinab Shimi Khavarmianeh (C.A.S: 151767-02-1) (Mashhad, Iran). All other chemicals employed in the study were of analytical grade.

Extract preparation

In summary, a quantity of 100 grams of powdered dried green tea was subjected to maceration in 800 milliliters of deionized water at a temperature of 60 degrees Celsius. Following a duration of 20 minutes, the residual extracts were subjected to a single pass of smoothing utilizing a Buchner funnel and a subsequent pass with filter paper. The resultant filtered solutions were then transferred to Round-bottom balloons. In order to completely remove the solvent, the solvent was separately evaporated utilizing a Rotator-Evaporator. The extraction method yielded an efficiency of 21%. Upon complete removal of the solvents, the residues were stored in a glass container that was covered with aluminum foil, as the extract is light-sensitive. The storage temperature of the residues was maintained at -20 °C (Mashayekhi-Sardoo et al., 2020).

Study design

A) Designing study groups to scrutinize the anti-ulcer effect of GTAE and licofelone

The number of rats in each group is 6.

Group Indo: Indomethacin (100 mg/kg, orally) (Mashayekhi-Sardoo et al., 2020).

Group Indo+GTAE 50: GTAE (50 mg/kg, orally) + indomethacin (100 mg/kg, orally) (Mota et al., 2015).

Group Indo+GTAE 100: GTAE (100 mg/kg, orally) + indomethacin (100 mg/kg, orally) (Mota et al., 2015).

Group Indo+GTAE 200: GTAE (200 mg/kg, orally) + indomethacin (100 mg/kg, orally) (Mota et al., 2015).

Group GTAE: GTAE (200 mg/kg, orally) (Mota et al., 2015).

Group Indo+Zileu: Zileuton (a specific inhibitor of 5-lipooxygenase; as a positive control; 100 mg/kg, orally) + indomethacin (100 mg/kg, orally) (Mashayekhi-Sardoo et al., 2020).

Group Indo+Lico: Licofelone (dual inhibitor of COX1/2-5- LOX; as a positive control; 30 mg/kg, orally) + indomethacin (100 mg/kg, orally) (Singh et al., 2005).

Group Tween: Tween 0.18% (indomethacin solvent; as a negative control, orally).

B) Designing study groups to investigate the analgesic effect of GTAE

The quantity of rats in every assemblage is six.

Group Indo+formal: Indomethacin (30 mg/kg, intraperitoneally injection (IP) + formalin (50 µl; sub-plantar injection) (Mahdian Dehkordi et al., 2019).

Group lico+formal: Licofelone (dual inhibitor of COX1/2-5- LOX; as a positive control; 30 mg/kg, IP) + formalin (50 µl; sub-plantar injection) (Singh et al., 2005).

Group GTAE+formal: GTAE (200 mg/kg, IP) + formalin (50 µl; sub-plantar injection) (Fernandes et al., 2022).

Group Tween +formal: Tween 0.18% (indomethacin solvent; as a negative control, IP) + formalin (50 µl; sub-plantar injection) (Fernandes et al., 2022).

Gastric ulcer induction

On the designated day of the experimental procedure, the rats underwent a fasting period of four hours. The targeted compounds were subsequently orally administered to the rats thirty minutes before the oral administration of indomethacin. Following four hours after the indomethacin administration, the rats were euthanized, and the stomach tissue was extracted and further sub-

jected to macroscopic examination to evaluate the incidence of Petechia or hemorrhagic lesions (Gandhi et al., 2012). Lesions were evaluated and assigned a score based on their length, utilizing the following scale: 1 denotes Petechia, 5 denotes lesions ranging from 1 to 3 millimeters in size, and 10 denotes lesions measuring up to 3 millimeters in size.

Upon completion of the lesion-scoring process, the samples were carefully placed within a microtube and subsequently stored in liquid nitrogen. The microtubes were then transferred to a freezer set at a temperature of -80℃ for preservation purposes. (Mashayekhi-Sardoo et al., 2020).

Measurement of lipid peroxidation indices (Malondialdehyde (MDA) level)

A mixture consisting of 10% homogenized stomach tissue and 1.15% potassium chloride was prepared. Subsequently, 0.5 ml of tissue sample solution was combined with 3 ml of 1% phosphoric acid and 1 ml of 0.6% Thiobarbituric acid (TBA). The resulting solution was subjected to boiling water for 45 minutes, leading to a pink coloration. Cooling of the samples was performed, followed by the addition of 4 ml of n-butanol to each tube, and vortexing for at least 1 minute. The tubes were then centrifuged at 4000 rpm for 20 minutes at a temperature of 4 °C. The resulting supernatant was separated, and the absorbance of samples was measured using a spectrophotometer (Jenway 6105 UV/vis, England) at a wavelength of 532 nm (Mihara and Uchiyama 1978).

Examining the analgesic effect

Indomethacin (30 mg/kg), GTAE (200 mg/kg), Tween 0.18%, and licofelone (30 mg/kg) were administered intraperitoneally to the rats. Subsequently, one hour later, Formalin was injected in the amount of 50 microliters into the soles of the rats' feet. The number of stinging in the injected foot or tail was checked and reported at two-time intervals. Specifically, the acute phase (0 to 5 minutes) and the chronic phase (25 to 30 minutes) were monitored meticulously (Fernandes et al., 2022; Hajhashemi et al., 2022).

Statistical Analysis

The Prism 8 software package was utilized to conduct statistical analysis, with a P-value of ≤ 0.05 being deemed indicative of significant statistical differences. The data was presented in the form of Mean ± SEM. A comparison of MDA levels and the analgesic effect was undertaken by employing the one-way ANOVA, followed by the post hoc Tukey-Kramer test. Additionally, the assessment of gastric ulcer scores involved the implementation of the Kruskal-Wallis test followed by Dunn's multiple comparisons test, with the median being used to represent the results.

Results

Effect of extract of green tea on the gastric ulcer index induced by indomethacin

The gastric ulcer index showed significant differences among the groups ($F_{(7, 40)}$ =93.33, P<0.0001). The results of the macroscopic evaluation revealed a marked elevation in the index of ulceration and bleeding in the gastric tissue of the Indo group, in comparison to the Tween group (P<0.001) (Figure 1). The groups pretreated with all doses of GTAE+Indo, GTAE, Indo+Zileu, and Indo+Lico groups displayed a significant decrease (P<0.001) in tissue damage compared to the Indo group.

Moreover, the Indo+Lico group exhibited a significant reduction of ulcers and bleeding in the stomach tissue in comparison to the Indo+GTAE 50 group (P<0.001) and the Indo+GTAE 100 group (P<0.05). While the Indo+GTAE 100 group did not have a significant difference compared to the Indo+Zileu and Indo+Lico groups (Figure 1, 2).

Effect of extract of green tea on lipid peroxidation (MDA) induced by indomethacin

The MDA levels indicated significant differences among the groups ($F_{(7, 40)}$ =186.5, P<0.001). In the stomach tissue, only in the Indo group, did the level of MDA increase significantly compared to the Tween group (P<0.001). Nevertheless, the Indo+GTAE 50, Indo+GTAE 100, Indo+GTAE 200 groups, and GTAE group, as well as the Indo+Zileu and Indo+Lico groups were able to significantly decrease the level of lipid peroxidation induced by the Indo group (P<0.001) (Figure 3). The GTAE group exhibited significant differences with the Tween group in MDA levels (P<0.001). Moreover, the MDA in the Indo+GTAE 200 group compared to the Indo+Zileu and Indo+Lico groups was significantly reduced (P<0.001).

The analgesic effect of green tea in the acute phase

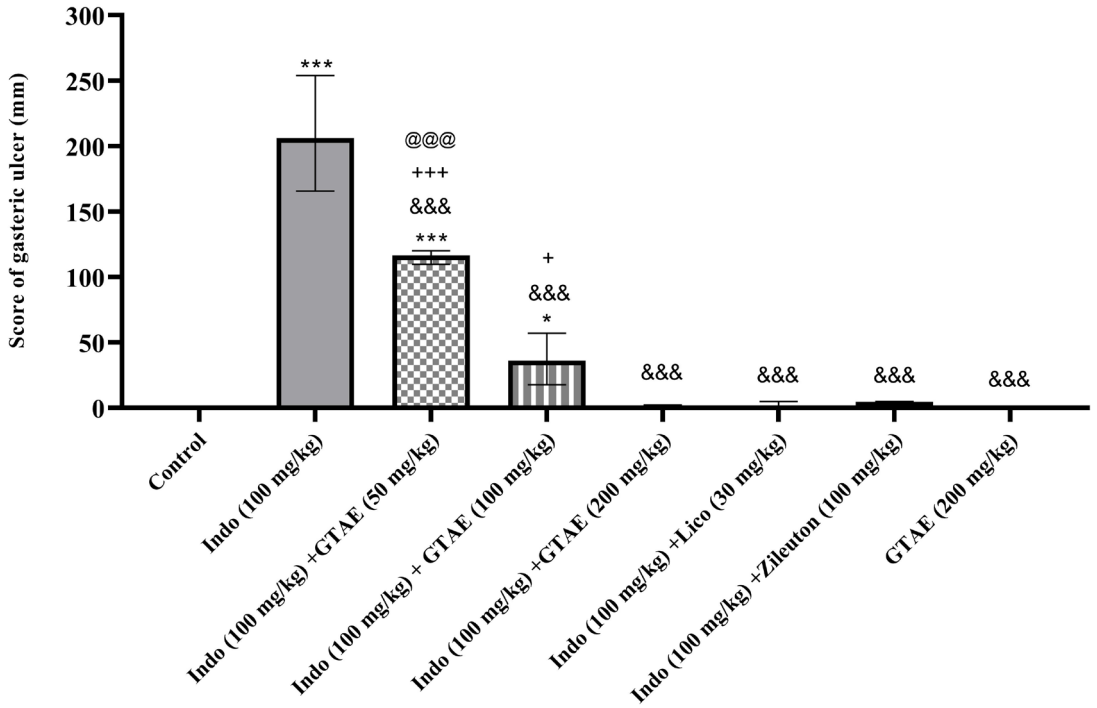

FIGURE 1. Effects of GTAE, licofelone, and zileuton on the gastric ulcers induced by indomethacin (100 mg/kg). GTAE, licofelone, and zileuton were administered by gavage. The number of rats in each group was 6. The data were reported as median±IQR after analysis by the Kruskal–Wallis test followed by Dunn's multiple comparisons test. $^{***}P<0.001$ for comparison with the control group; $^{\&\&\&}P<0.001$ for comparison with the indomethacin group alone; $^{+++}P<0.001$ and $^{+}P<0.05$ for comparison with the Licofelone group; $^{@@@}P<0.001$ for comparison with Zileuton. GTAE: green tea aqueous extract, indo: indomethacin, and Lico: Licofelone.

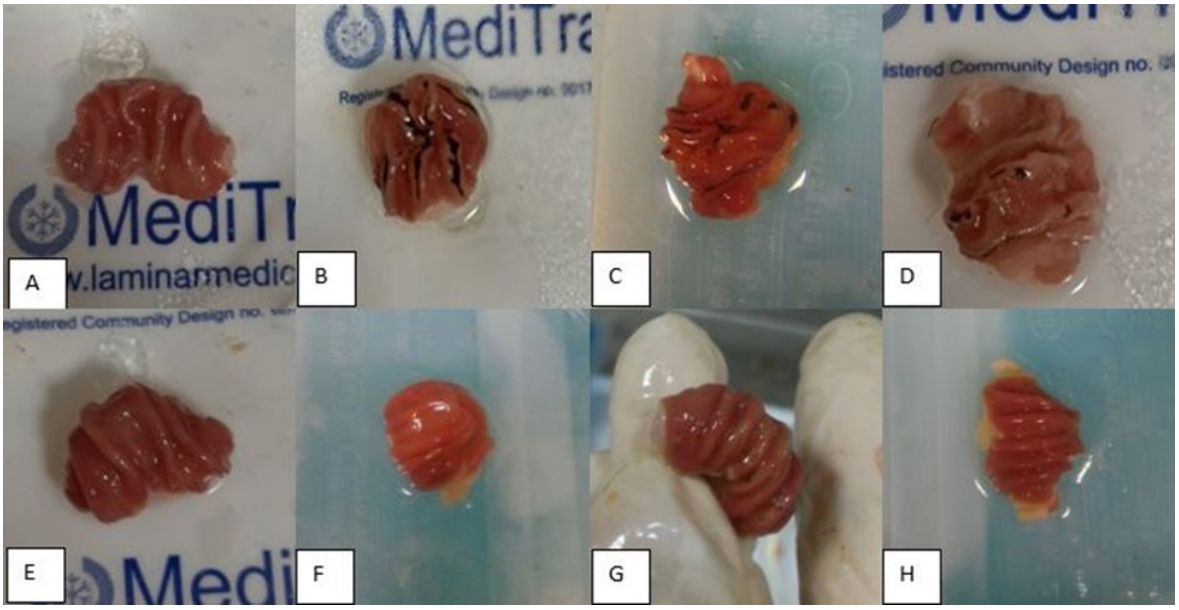

FIGURE 2. Protective effect of GTAE on indomethacin-induced gastric ulcer. A: control group, B: indomethacin group (100 mg/kg), C: GTAE group (50 mg/kg) + indomethacin group (100 mg/kg), D: GTAE group (100 mg/kg) + indomethacin group (100 mg/kg), E: GTAE group (200 mg/kg) + indomethacin group (100 mg/kg), F: Licofelone group (30 mg/kg) + indomethacin group (100 mg/kg), G: zileuton group (100 mg/kg) + indomethacin group (100 mg/kg), H: GTAE group (200 mg/kg). In all cases, the route of administration was oral (gavage).

The analgesic effect in the acute phase demonstrated significant differences among the groups ($F_{(3, 20)}=110.7$, $P<0.0001$). In the Indo, GTAE+formal, and Lico+formal groups, a significant decrease in the pain index was observed in the first 5 minutes (acute phase) compared to the Tween +formal group ($P<0.001$). Further-

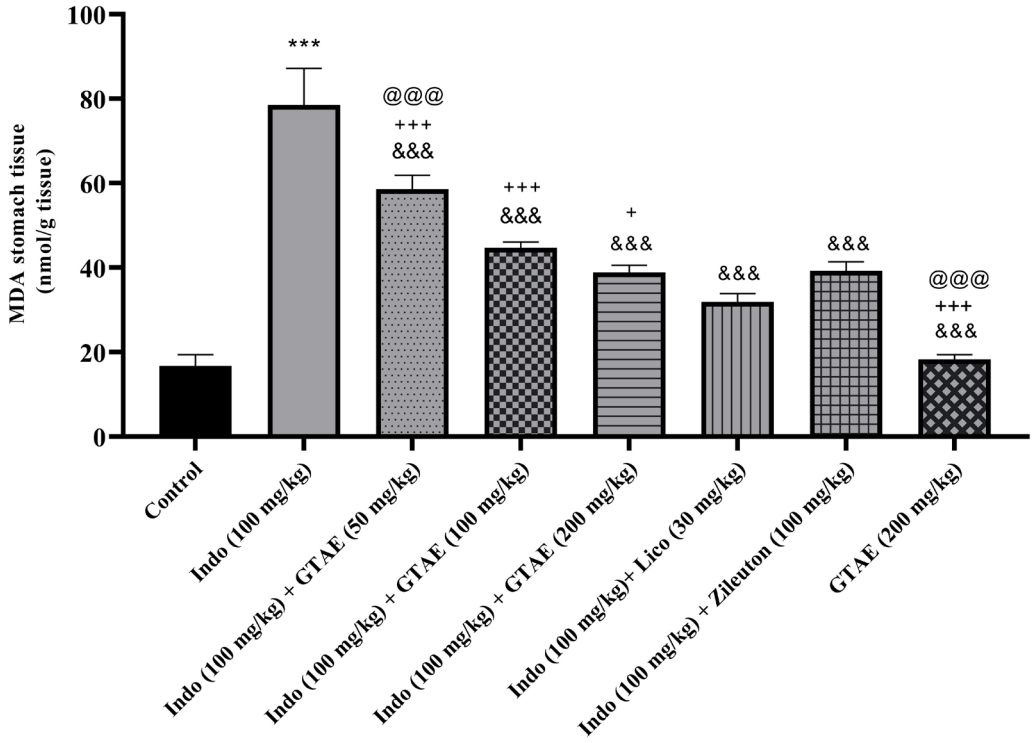

FIGURE 3. Effects of GTAE, licofelone, and zileuton on lipid peroxidation (MDA) induced by indomethacin (100 mg/kg). GTAE, licofelone, and zileuton were administered by gavage. The number of rats in each group was 6. The data were reported as median±IQR after analysis by the one-way ANOVA, followed by post hoc Tukey-Kramer tests. $^{***}P<0.001$ for comparison with the control group; $^{\&\&\&}P<0.001$ for comparison with the indomethacin group alone; $^{+++}P<0.001$ and $^{+}P<0.05$ for comparison with the licofelone group; and $^{@@@}P<0.001$ for comparison with the zileuton. GTAE: green tea aqueous extract, indo: indomethacin, and Lico: Licofelone.

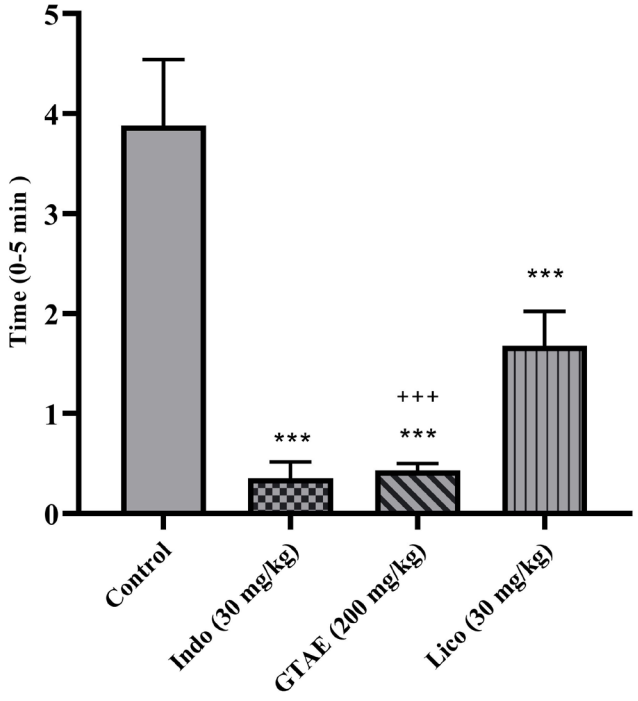

FIGURE 4. Investigating the acute analgesic effect of licofelone, indomethacin, and GTAE in the acute phase. GTAE, licofelone, and indomethacin were administered intraperitoneally (IP). The number of rats in each group was 6. The data were reported as median±IQR after analysis by the one-way ANOVA, followed by post hoc Tukey-Kramer tests. $^{***}P<0.001$ for comparison with the control group; $^{+++}P<0.001$) for comparison with the licofelone. GTAE: green tea aqueous extract, indo: indomethacin, and Lico: Licofelone.

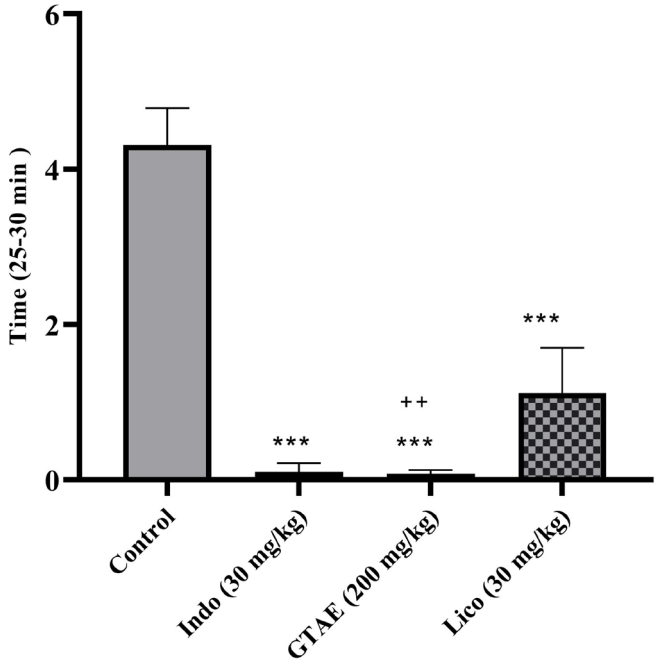

FIGURE 5. Investigating the chronic analgesic effect of licofelone, indomethacin, and GTAE in the chronic phase. GATE, licofelone, and indomethacin were administered intraperitoneally (IP). The number of rats in each group was 6. The data were reported as median±IQR after analysis by the one-way ANOVA, followed by post hoc Tukey-Kramer tests. $^{***}P<0.001$ for comparison with the control group; $^{+++}P<0.001$ for comparison with the licofelone. GTAE: green tea aqueous extract, indo: indomethacin, and Lico: Licofelone.

more, a significant decrease in pain index was seen in the GTAE+formal group compared to the Lico+formal group (P<0.001) (Figure 4).

The analgesic effect of green tea in the chronic phase

The analgesic effect in the chronic phase displayed significant differences among the groups ($F_{(3, 20)}$ =166, P<0.0001). The groups that received Indo, GTAE+formal, and Lico+formal, significantly decreased the pain index in the last 5 minutes (chronic phase) compared to the Tween +formal group (P<0.001). Furthermore, a significant decrease in the pain index was observed in GTAE+formal and Lico+formal (P<0.001) (Figure 5).

Discussion

Considering the antioxidant and enzyme inhibitory effects of GTAE, the purpose of the present research was to compare the analgesic and anti-ulcer effect of GTAE with licofelone so that if it has a positive and/or equal effect, this plant can be substituted for this new class of drugs (the dual inhibitors of COX1/2-5- LOX). The dual inhibitors of COX1/2-5- LOX, are analgesic drugs with less gastrointestinal adverse effect in comparison to NSAIDs. We observed the Indo+GTAE 200 group could significantly reduce the gastric ulcer induced by indomethacin (100 mg/kg). Moreover, GTAE significantly diminishes the area of gastric ulcer and lipid peroxidation index (MDA) to a greater extent than licofelone (30 mg/kg) and zileuton (100 mg/kg). Therefore, it can possess the same protective effect as licofelone (30 mg/kg) and zileuton (100 mg/kg). On the other side, the GTAE+formal group was able to reduce pain in both acute and chronic phases to a greater extent in comparison to the Lico+formal group.

Comparison of the anti-ulcer effect of aqueous extract of green tea with similar studies

Indomethacin, an NSAID, serves to modulate the metabolic processes of arachidonic acid in neutrophils by redirecting the COX pathway towards the 5-LOX pathway, ultimately resulting in an augmentation of LT levels (Gandhi et al., 2012). Previous research stated that LTs including LTB4, LTC4, or LTD4 play an important role in forming mucosal erosions and vascular injuries in gastric tissue (Liu et al., 2023a). In similar studies, it has been proven that the oral administration of indomethacin (100 mg/kg) causes peptic ulcers along with an elevation in the degree of MDA has been observed

in the stomach tissue (Mashayekhi-Sardoo et al., 2020). The inhibition of the COX enzyme leads to a reduction of mucus synthesis and bicarbonate secretion. The reduction of these factors results in the occurrence of vascular damage in the tissues and the formation of ulcers in the digestive system, especially the stomach (El-Ashmawy et al., 2016; Mashayekhi-Sardoo et al., 2020). Since the overproduction of metabolites in the 5-LOX pathway develops gastric damage, the LTs antagonists and 5-LOX inhibitors can reverse the gastric injuries that occur by indomethacin (Rainsford 1987). Besides, NSAID by development of the lipid peroxidation process results in the overproduction of free radicals, and MDA levels that progress gastric ulcers (Turan et al., 2013). Likewise, the results of our study validate that the administration of indomethacin to rodents results in a noteworthy elevation in MDA concentration in contrast to the Tween cohort. Gandhi in 2012 stated curcumin (inhibitor of COX and LOX) exerted protective effects on the gastric ulcers induced by indomethacin. Hence, curcumin through a decrease in LT synthesis, resulted in diminished neutrophil adherence (Gandhi et al., 2012). In 2017, Katary et al. carried out a study in which they administered vanillin at a dose of 100 mg/kg for a period of five days to a rat model of indomethacin-induced gastric ulcer. This intervention yielded a reduction in gastric ulcer index, content volume, gastric acid, total acidity, and histopathological damages caused by indomethacin. Additionally, it reduces the oxidative stress in the stomach and also increases the antioxidant activity of gastric enzymes (Katary and Salahuddin 2017). In another study in 2019, safranal (one of the components of saffron; 1, 0.25, 0.063 mg/kg), normalized the stomach volume, stomach pH, and the gastric ulcer area caused by indomethacin (50 mg/kg). Therefore, safranal exhibited obvious protective effects against indomethacin that induced stomach tissue and biochemical changes. Likewise, our previous experiment showed that aqueous and especially ethanolic extracts of *Lemon verbena* exert a protective effect against indomethacin (100 mg/kg)-induced gastric ulcer. Accordingly, administration of ethanolic (200 mg/kg), and aqueous extract (200 mg/kg) of *lemon verbena* significantly decreased the gastric ulcer occurred by indomethacin. Moreover, ethanolic extracts (100 and 200 mg/kg) and aqueous extract (200 mg/kg) of *lemon verbena* significantly diminished the increased MDA levels (Mashayekhi-Sardoo et al., 2020). All these studies confirm the induction of clear and macroscopic stomach ulcers by indomethacin and the mechanisms described in this section. According to these studies, we chose indomethacin with a dose of 100 mg/kg to cause gastric ulcers.

Previous research indicated that green tea and its effective flavonoid, epigallocatechin exert great anti-wounding activity. This protective effect is based on the antioxidant and LOX/COX inhibitory mechanisms (Choi et al., 2004; Mota et al., 2015). Green tea polyphenols are potent antioxidants that deal with the regulation of the essential signaling pathways such as programmed cell death pathways, transcription nuclear factor-kappa B mediated I kappa B kinase complex pathways, as well as intervention with inflammatory biomarkers like COX-2 and cytokine synthesis (Oz 2017). Alcoholic extract of green tea and three other plants with doses of 100, 400, and 800 mg/kg, exerted a protective effect against gastric ulcers caused by NSAID in rats (Fallah Huseini et al., 2015). The administration of green tea root extract (at a dose of 10 mg/kg) to rats with ethanol-induced gastric ulcers following a pre-treatment period of 10 days was observed to contribute significantly to a reduction in the severity of the gastric wound caused by ethanol. Moreover, the amounts of GSH and glutathione peroxidase (GPx) reduced by ethanol increased using this extract (Maity et al., 2003). Omar and colleagues 2020 showed that the administration of 50 mg/kg of ethanol extract from green tea for 14 days to rats-induced gastric ulcers by *Helicobacter pylori*, significantly reduced gastric ulcers and had therapeutic and preventive effects (Omar et al., 2020). Administration of a dosage of 1 mg/kg of GTAE twice daily for a duration of 15 days in mice resulted in a substantial decrease in the wound index by 76.12%. Furthermore, a notable enhancement in the epithelial lining was observed. Within the group that received this extract, an integration of surface mucin gel layer and polysaccharide content was detected in the stomach tissue (Rakshit et al., 2018). Administration of green tea catechin to rats chronically poisoned with cadmium led to the inhibition of activities of genes encoding Phospholipase A2 (PLA2), COX, and 5'-Lipoxygenase (Lpx). Moreover, catechin ameliorated the Prostacyclin (PGI2)/thromboxane A2 (TXA2) ratio and returned LTB4 synthesis to normal condition. Green tea catechin like Epigallocatechin gallate (EGCG) exerts potent inhibitory effects on leukotriene B4 release

(Kim et al., 2014; Matsuo et al., 1996). Moreover, catechin of green tea extracts inhibits the phosphorylation and expressions of inflammatory biomarkers and then regulates the associated metabolic pathways (Chu et al., 2014). It is documented that catechin promisingly suppresses the synthesis of oxidative stress biomarkers and oxidized proteins. Hence, green tea catechin by modulating the 5'-lipoxygenase activity blocks leukotriene B4 generation (Choi et al., 2004). Additionally, Singh in 2018 (Singh et al., 2018) stated green tea extract can be considered a supplement along with the anti-leukotriene drug for alleviating the oxidant damage. Therefore, green tea catechin can be considered an anti-inflammatory and antithrombotic agent (Choi et al., 2002). Our study is consistent with the mentioned results that the aqueous extract of green tea can significantly reduce the gastric ulcer induced by indomethacin and prevent ulcers and bleeding in the stomach.

Licofelone has a significant protective effect on reducing gastric ulcers, blood neutrophils, and lipid peroxides that had been changed by indomethacin administration. In addition, licofelone inhibits the increased LTB4 levels in the gastric mucosa that are induced by indomethacin. Thus, licofelone by inhibition of both 5-LOX and COX can reduce the level of LTB4 in mice (Ozleyen et al., 2023).

Through a comparative analysis of the efficacy of Indo+GTAE 200, GTAE, and Indo+Lico groups in treating ulcers, it was observed that there was no statistically significant difference between the two groups. Based on this finding, it can be inferred that GTAE extract presents a viable alternative to licofelone for individuals seeking to prevent peptic ulcers caused by indomethacin.

Comparison of analgesic effect of aqueous extract of green tea with similar studies

The formalin test in the acute phase mainly determines the centrally active analgesic drugs. Besides, in the chronic phase painkillers that act peripherally can respond to this test. As a result, this test can differentiate between inflammatory pain (chronic pain phase) and non-inflammatory pain (acute pain phase) (Fernandes et al., 2022). Cseh and colleagues stated that the injection of an inflammatory substance in the paw can cause inflammation and pain in both the primary and secondary phases (Cseh et al., 2020). In a study conducted by Medeiros and colleagues on neuropathic pain, formalin was injected into the sole to induce acute and chronic phases of pain (Medeiros et al., 2020).

Licofelone functions as an inhibitor of 5-LOX/COX, thereby reducing the secretion of inflammatory mediators, specifically LTs and PGs. This results in a decrease in the levels of these intermediaries which are known to contribute to inflammatory processes (Nikoui et al., 2020). According to the current study, the analgesic effect of licofelone 30 mg/kg was evaluated and it was observed that this drug has significant analgesic effects. NSAIDs, including indomethacin, aspirin, and ibuprofen exhibited their analgesic effects by inhibiting the COX. On the other hand, it has been found that PGs cause acute pain by affecting and stimulating the peripheral nerves (Abbasifard et al., 2021). Administration of indomethacin has a great effect on the chronic phase of pain. Accordingly, 30 mg/kg indomethacin was used as an anti-inflammatory drug of the PG pathway and it was observed that it had a significant analgesic effect compared to the control group. We observed both licofelone and indomethacin exerted a significant effect on pain relief. However, licofelone can be used as an auxiliary drug in pain control. Our study has revealed a noteworthy finding about the analgesic effect of indomethacin in both acute and chronic phases of pain. It is remarkable that this drug, which is typically known for its anti-inflammatory and COX enzyme-inhibiting properties in chronic pain, has demonstrated analgesic efficacy in both phases of pain. This observation is significant due to the temporal proximity between the two pain phases. Khazaeli and colleagues in 2020 indicated mucous paste containing green tea extract three times a day for 10 days can reduce the pains caused by Aphthous stomatitis (Movaghari Pour et al., 2020). Another study investigated the analgesic effect of acetaminophen, chewing gum, and green tea after orthodontic appliances were placed in the mouth. It was observed that green tea gargling was more effective compared to other treatments (Elvina et al., 2018). In a clinical study conducted on 80 patients with gastric cancer who underwent laparoscopic surgery, Liu and colleagues observed that administration of 2.5 g of GTAE on the first postoperative day and continued with 5 g until the day of discharge, caused a significant decrease in pain and the time to tolerate solid food came faster. It was also observed that the healing of the gastric wounds caused by the operation was done faster (Liu et al., 2021). All aforementioned studies con-

firm the analgesic effect of GTAE. In the contemporary investigation, it was noted that the GTAE+formal group evinced significant analgesic effects in both the acute and chronic phases compared to the Tween +formal group. In this study, only the dose of 200 mg/kg of green tea was used in comparison with 30 mg/kg of licofelone and 100 mg/kg of indomethacin, and it was observed that in both phases, GTAE significantly decreased the pain sensation time. Compared to licofelone it has more analgesic effect.

At the culmination of this investigation, it is discernible that the administration of GTAE at a dose of 200 mg/kg confers superior analgesic efficacy over licofelone while exhibiting comparable anti-ulcer activity. Thus, it can be posited that GTAE could be regarded as a viable alternative for furnishing both analgesic and anti-ulcer properties akin to licofelone.

Conclusion

The findings of this investigation have demonstrated that Indo+GTAE 200, and GTAE groups could elicit a protective effect akin to that of the Indo+Lico group in response to bleeding and gastric ulcers induced by indomethacin (100 mg/kg). In addition, the Indo+GTAE 200 group could reduce the increased amount of lipid peroxidation caused by indomethacin. Moreover, it has been observed that GTAE exhibits a greater analgesic efficacy in comparison to licofelone at a dose of 30 mg/kg, in both the acute and chronic phases of treatment. Finally, it can be concluded that the GTAE can probably be a suitable substitute for licofelone and other dual inhibitors of COX and LOX.

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