Al-Qadisiyah Journal of Pure Science
ISSN(Printed): 1997-2490 ISSN(Online): 2411-3514
DOI: 10.29350/jops
Al-Qadisiyah Journal of Pure Science

Therapeutic Effect of Curcumin on Ethanol-Induced Gastric Ulcer and Its Association with GLP-1 and TNF-α in Male White Rats

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Received: 11/04/2025; Accepted: 21/04/2025; Published Online: 29/04/2025.

Abstract

A stomach ulcer is one of the most common disorders resulting from an imbalance between the stomach's defence mechanisms in the mucous membrane and factors causing damage to the stomach; inflammation and a weakening of protective factors are among the causes of gastric damage. The active compound curcumin, extracted from the plant Curcuma longa, possesses active properties that may help to strengthen the gastric mucosa, thereby helping to activate defence mechanisms and consequently reduce the inflammatory response in the stomach; however, its protective effect in relation to physiological mechanisms still requires further study. Conversely, glucagon-like peptide-1 (GLP-1) is one of a number of gut peptides with multiple effects; it may play a regulatory role in the defence mechanisms that protect the integrity of the gastrointestinal The aim of our current study is to investigate the protective role of curcumin on GLP-1 in rats with induced gastric ulcers, whilst examining GLP-1-related markers of mucosal protection and inflammation. Intestinal damage will be assessed based on ulcer indices, alongside measurements of serum GLP-1 levels and levels of prostaglandin E2 (PGE2) and tumour necrosis factor-α (TNF-α) in gastric tissue. The anticipated results may help clarify whether the GLP-1 pathway is associated with the protective effect of curcumin, and provide a clearer physiological

explanation of the mechanisms that may contribute to the maintenance of gastric mucosal integrity during experimental ulceration. The study was conducted on 36 healthy white rats and lasted 30 days, Gastric ulcers were induced using 96 percent absolute ethanol over a period of 6 days, using doses of (5 and 2.5) ml/kg body weight administered orally, Gastric ulcers were induced in three groups, with the exception of the control group (C), which was administered 10 ml/kg body weight of maize oil, used as a solvent for curcumin. In the first group (T1), gastric ulcers were induced throughout the duration of the experiment, Group 3 (T2) was administered curcumin at a concentration of 100 mg/kg dissolved in 10 ml/kg of maize oil, whilst Group 4 was administered curcumin at a concentration of 200 mg/kg dissolved in 10 ml/kg of maize oil, At the end of the experiment, the animals were sacrificed. The results showed reduced levels of GLP-1 and PGE2 in the animals in which gastric ulcers had been induced by ethanol, along with elevated levels of TNF-α in the gastric tissue, in contrast, the groups treated with curcumin at doses of 100 and 200 mg/kg showed an increase in GLP-1 and PGE2 levels, accompanied by a decrease in TNF-α levels.

The anticipated results may help to clarify whether the GLP-1 pathway is involved in the protective effect of curcumin, and provide a clearer physiological explanation of the mechanisms that may contribute to the preservation of gastric mucosal integrity during experimental ulceration.

Keywords:

Curcumin**,** Gastric Ulcer, Glucagon- like peptide-1 (GLP-1), Prostaglandin E_2(PGE2), Tumor Necrosis–alpha (TNF-α)

Introduction:

Stomach ulcers are one of the most common disorders of the digestive system, resulting from damage to the stomach lining. Approximately 10 per cent of people are at risk of developing them due to a variety of digestive disorders caused by the consumption of alcohol, caffeine and anti-inflammatory medicines, as well as the consumption of chemically processed foods and infection with Helicobacter

pylori. These factors contribute significantly to the stimulation of inflammatory reactions, with an increase in the production of inflammatory mediators such as cytokines, leading to increased gastric permeability as a result of damage to the mucosal layer (2).

The mechanism of gastric ulcer development depends on an imbalance between the defence mechanisms of the gastric mucosa and pathogenic factors. Physiologically, this imbalance—which increases the likelihood of developing gastric ulcers—is associated with reduced secretion of prostaglandin E2 (PGE2), bicarbonate and mucus in the stomach. Damage to the gastric mucosa causes a state of excessive oxidative stress, resulting in lipid peroxidation and consequently cell damage, which stimulates inflammatory mediators such as TNF-α, which in turn hinder the repair of damaged tissue (4).

Glucagon-like peptide-1 (GLP-1), secreted by enter endocrine cells, plays a pivotal role in regulating appetite. It helps to stimulate insulin secretion via its receptors on β-cells in the pancreas, whilst regulating glucagon secretion from α-cells , which slows gastric emptying and thereby regulates blood glucose levels after a meal (9).

In addition to its metabolic effects, evidence suggests that activation of GLP-1 receptors may directly affect the gastrointestinal mucosa. Studies have shown that GLP-1 signalling promotes epithelial cell proliferation, mucus secretion and tissue repair, Furthermore, GLP-1 receptor activation has been associated with anti-inflammatory and antioxidant effects, including the suppression of pro-inflammatory cytokines and the alleviation of markers of oxidative stress (12).

Numerous studies have examined the relationship between GLP-1 and gastric mucosal protection. One experimental study in mice confirmed that activation of the GLP-1 pathway by liraglutide can reduce gastric mucosal damage by enhancing prostaglandin production and mucosal blood flow, as well as reducing gastric ulcer damage and TNF-α levels, thereby supporting the existence of a

functional link between GLP-1 signalling and the mechanisms of mucosal defence and inflammation in the stomach (6).

TNF-α is one of the most important pro-inflammatory cytokines; increased inflammatory activity associated with mucosal injury contributes significantly to increased damage whilst delaying the repair of damaged tissue. TNF-α is therefore used as a marker of inflammation in experimental studies relating to gastric ulcers. Conversely, prostaglandin E2 (PGE2) plays a protective role in the mucosa due to its direct involvement in improving the environment necessary for wound healing by activating the stomach's defence mechanisms. Numerous experimental studies have confirmed the association between gastric ulcer healing and increased levels of. (1) PGE2

Curcumin is a chemical compound (diferuloylmethane) extracted from the roots of the turmeric plant (Curcuma longa Linn) of the ginger family (Zingiberaceae). It is a perennial herb characterised by its anti-inflammatory and immunomodulatory properties, as well as its inhibitory effect on numerous enzymes that produce reactive oxygen species (7).

Curcumin has been used in traditional medicine to treat inflammation and impaired liver function, as well as for its role in scavenging reactive oxygen species (ROS). Studies have confirmed that curcumin intake helped to reduce oxidative stress caused by heavy metals, gentamicin and acetaminophen in rats (8).

Numerous studies have shown that curcumin helps improve inflammatory markers associated with gastric ulcers whilst reducing their incidence. Furthermore, a systematic review conducted on laboratory animals highlighted the efficacy of curcumin in improving a number of markers of upper gastrointestinal disorders, with a statistically significant reduction in ulcer incidence and certain inflammatory markers (11).

Although experimental studies have examined the protective effects of curcumin in isolation and its role in gastric protection or the inflammatory response, the

relationship between curcumin treatment and GLP-1 levels in conjunction with PGE_2 and TNF-α during gastric ulcer healing still requires further investigation, particularly in the ethanol-induced gastric ulcer model. Hence, our current study was initiated to investigate the relationship between the therapeutic effect of curcumin in an experimental gastric ulcer model and changes in GLP-1, PGE2 and TNF-α, which may provide a better understanding of the relationship between gut hormonal signalling, mucosal defence and the inflammatory response during the ulcer healing process.

Materials and methods

The experiment was conducted in the Animal House laboratory at the Faculty of Science, University of Al-Qadisiyah. The ARRIVE (Animal Research: Reporting of in Vivo Experiments) guidelines were followed, and we adhered to the institution's regulations on the care of laboratory animals. The experiment involved 36 adult male white rats weighing between 200 and 250 g and aged 8–10 weeks. They were housed under laboratory conditions at a temperature of 22 ± 2 °C and a moderate level of light/ dark cycles ranging from 14 to 10 hours. Throughout the experiment, they were provided with water and feed, they were allowed to acclimatise for one month prior to the start of the experiment and were then randomly divided into four groups, each comprising nine animals. Gastric ulcers were induced in these animals using ethanol, after which they were administered curcumin at a dose of (100–200) mg/kg body weight over a period of 30 days.

Induction of gastric ulcers:

Gastric ulcers were induced after the animals had been fasted for 12 hours prior to stimulation on the first and sixth days over a six-day period, via oral administration of two doses of 96 per cent ethanol; A dose of 5 ml/kg body weight was used on days 1, 3 and 6, whilst a dose of 2.5 ml/kg body weight was used on days 2, 4 and 5 (3). The animals were fasted for 12 hours prior to the first

stimulation (on day 1) and the final stimulation (on day 6). On day 6, the animals were administered 96 per cent ethanol one hour prior to sacrifice.

Curcumin

It was obtained from a pharmaceutical pharmacy and administered to the animals after being dissolved in maize oil in accordance with the doses approved for the experiment, at concentrations of 100 mg/kg (10), and 200 mg/kg (7). The doses were dissolved in 10 mL/kg of maize oil.

Experimental design:

The experiment lasted 30 days. We used 36 healthy male white rats, which were then randomly divided into four groups, each comprising nine animals:

The first group served as the control group (C) and was administered maize oil at a concentration of 10 mL/kg body weight only for 30 days; the second group (T1) had ulcers induced with 96 per cent ethanol at two doses (5 and 2.0) mL/kg body weight during the experiment. In the third group (T2), ulcers were induced and the animals were then administered curcumin at a concentration of 100 mL/kg body weight throughout the duration of the experiment. In the fourth group (T3), ulcers were induced and the animals were then administered curcumin at a concentration of 100 mL/kg body weight throughout the duration of the experiment.

Sample collection:

At the end of the experiment, chloroform was used as an anaesthetic to collect blood serum via cardiac puncture for the necessary serological tests; the animals were then euthanised by placing them in a chamber filled with carbon dioxide (CO_2) and, after 2–3 minutes, the animals were removed after signs of respiratory arrest and pallor of the eyes were observed.

Gastric tissue was collected for ELISA assays to determine the levels of TNF-α and PGE2 using the ELISA technique.

Parameters studied:

GLP-1 levels in serum were measured by ELISA using a kit from Sunlong (China) with the serial number, No: SL0304Ra.

TNF-α levels in gastric tissue were also measured using a kit from Abcam (ab100785,Cambridge, UK) with the serial number ab100785.

A kit from MyBioSource (San Diego, CA, USA), with the catalogue number MBS262150, was used to measure PGE2 (14). The assay was performed in accordance with the manufacturers' instructions, and read by (Huma Reader HS, Germany) reader ELISA.

Statistical analysis

The results of the experiments were analysed using the SPSS statistical program, as the Least Significant Differences (LSD) was used to express the data, and the test was used. Anova) for multiple comparison between the studied groups and the control group, and the least significant difference was calculated to test the significance of the results.

Results and Discussion

Table (1) shows the effect of Curcumin on (GLP-1)in the serum of male rats in deferent concentration of Curcumin.

Group / Parameters	C	T1	T2	T3	LSD
GLP-1 pg/ml	75.2±5.3 ^a	43.3±4.7 ^d	59.8±3.0 ^c	71.0±3.5 ^b	4.06

Values are expressed as mean ± standard deviation (n=9). Means with different superscript letters within the same row are significantly different (p < 0.05). C: Control group. group; T1: Ethanol-Induced Gastric Ulcer. group; T2: Ethanol-Induced Gastric Ulcer given Curcumin **concertation 100ml/kg. group; T3 given Ethanol-Induced Gastric Ulcer given Curcumin concertation 100ml/kg.**

The results shown in Table 1 indicate a significant decrease in GLP-1 levels in rats in which gastric ulcers were induced by ethanol, with levels of 43.3 ± 4.7, compared with the control group, which had levels of 75.2 ± 5.3, This is attributed to the deleterious effect of ethanol, which causes gastric ulcers by dissolving the protective mucous layer as a result of penetrating the gastric mucosa and rendering it susceptible to hydrolytic and proteolytic factors, as well as its role in impairing the secretion of bicarbonate and protective mucus (3). In contrast, groups (T2, T3), which were treated with curcumin at two different doses (100

and 200 mg/kg), showed a statistically significant increase compared with group (T2); this is attributed to curcumin's anti-inflammatory role, which directly contributed to improved activation of the GLP-1 receptor in curcumin-treated rats. This was confirmed by our results, which showed that group (T3) exhibited greater improvement compared with (T2).

Our findings were consistent with a study by Böhm in 2025 on the effect of liraglutide on an ethanol-induced gastric ulcer model, which was associated with the activation of GLP-1 signalling in gastric tissue, accompanied by an improvement in the defence factor PGE_2 in the gastric mucosa and, consequently, a reduction in inflammatory mediators (6).

This may also be attributed to the anti-inflammatory role of curcumin in activating the GLP-1 axis, which may be linked to the enhancement of mucosal defence and repair mechanisms and a reduction in local inflammation, These findings are consistent with a study conducted in 2025 suggesting that activation of the GLP-1 receptor can have a positive effect on the integrity of the gastric mucosa; the use of liraglutide in an animal model of indomethacin-induced gastric ulcers contributed to the activation of the GLP-1 receptor, and a reduction in ulcer area, whilst levels of PGE_2, EGF and VEGF-A increased and levels of TNF-α and IL-6 decreased in gastric tissue (5).

Table (2) shows the effect of Curcumin on (TNF-α, PGE2) in the stomach tissue of male rats in deferent concentration of Curcumin.

Group / Parameters	C	T1	T2	T3	LSD
TNF-α (pg/mg protein)	345.2±10.2 ^d	578±9.4 ^c	460±9.1 ^b	400±8.9 ^a	9.5
PGE2 (pg/mg tissue)	23.4±2.3 ^b	17.3±1.6 ^c	24.3±1.5 ^b	28.3±1.6 ^a	1.8

Values are expressed as mean ± standard deviation (n=9). Means with different superscript letters within the same row are significantly different ($p < 0.05$). C: Control group. group; T1: Ethanol-Induced Gastric Ulcer. group; T2: Ethanol-Induced Gastric Ulcer given Curcumin **concertation 100ml/kg. group; T3 given Ethanol-Induced Gastric Ulcer given Curcumin concertation 100ml/kg.**

The results showed a statistically significant increase in TNF-α levels in group (T1) compared with group (C), and, conversely, a statistically significant decrease in PGE2 levels in group (T1) compared with group (C), This is attributed to the effect of ethanol in inducing gastric ulcers in rats, which caused tissue damage resulting in severe inflammatory reactions in the gastric mucosa. This contributed to a reduction in blood flow to the tissue, causing oxidative stress due to the formation of reactive oxygen species (ROS) (13). In contrast, groups (T2) and (T3) showed improvements in TNF-α and PGE2 levels compared with group (T1), in which gastric ulcers were induced by ethanol, This is attributed to the role of curcumin in inhibiting inflammation, depending on the duration of treatment and the dose administered; group (T3), which received a dose of 200 mg/kg, showed greater improvement than group (T2), which was treated with a dose of 100 mg/kg . This efficacy is attributed to curcumin's role in inhibiting the activation of NF-κB, a key transcription factor involved in regulating the expression of pro-inflammatory cytokines, including TNF-α, as well as the role of its active compounds in stabilising cell membranes and reducing the accumulation of neutrophils within them (15).

Conclusion

The present study demonstrated that the induction of gastric ulcers with ethanol contributed to a statistically significant increase in TNF-α—one of the most important pro-inflammatory cytokines—along with a decrease in the levels of PGE2 and GLP-1 compared with the control group, In contrast, treatment with curcumin showed an improvement in the levels of these parameters under investigation, confirming its active anti-inflammatory role, which directly contributed to reducing inflammatory mediators whilst raising PGE2 levels in the gastric mucosa, as well as its role in raising serum GLP-1 levels. The study therefore suggests that curcumin possesses therapeutic and preventative effects that help to limit the damage associated with gastric ulcers by regulating inflammatory factors and GLP-1 receptors in the gastric mucosa.

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