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Role Of Commiphora molmol In Prevention Of Indomethacin Induced Gastric Ulcers In Adult Male Albino Rats (A Histological And Biochemical Study)

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ABSTRACT

Background: Herbs used in traditional medicine comprise many components of medical importance. The Anti-ulcer actions of Commiphora Molmol(CM) were investigated and it was considered to be of value for its antioxidant properties.

Objective: The current work aimed to evaluate the protective effects of CM on indomethacin-induced gastric mucosal ulceration.

Material and Methods: Fourty adult male albino rats were included and categorized into four equal subgroups: Group I (control) received distilled water, group II (Indomethacin-induced gastric ulcers), group III received 250 mg/kg of oral CM for two weeks followed by intraperitoneal indomethacin; group IV received 500 mg/kg of oral CM for two weeks followed by intraperitoneal indomethacin. Indomethacin dose was 30 mg/Kg. At the end, animals were sacrificed and blood samples were collected to measure tumor necrosis factor-alpha (TNF-α). The stomach was obtained, opened through the greater curvature, washed with saline, fixed by pins over a cardboard plate and inspected for ulcers. Then, it was used for histopathological and immunohistochemical assessment.

Results: Administration of CM 250 or 500 mg/kg revealed a marked decrease in the ulcer index, when compared to group II (10.2, 7.6 versus 15.5). Additionally, there was a significant increase of malondialdehyde (MDA), TNF-α and matrix metalloproteinase-9 (MMP-9) in group II than the control group. The use of CM was associated with a significant reduction of all biomarkers than the indomethacin group. The ameliorative effect was more intense with a high dose of CM. However, values did not reach normal levels. Also, pretreatment with CM 250 or 500 mg/kg before indomethacin led to partial preservation of the mucus layer lining of the stomach. A better protective effect was observed with the high dose.

Conclusion: Oral administration of CM led to a protective effect in a dose-dependent manner against indomethacin induced gastric ulcers.

Keywords: Commiphora Molmol; Indomethacin; Gastric Ulcer; Inflammatory Markers; Antioxidant.

INTRODUCTION

Peptic ulcer disease (PUD) is a common disorder of the gastrointestinal (GI) tract. Its incidence had been recently decreased. However, the disease remains irritant to many individuals, especially the elderly **(Nabil et al., 2021).**

PUD is mainly due to infection by Gram-negative Helicobacter pylori, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), excessive alcohol intake, or endless stress **(Karbalaei and Keikha, 2020).**

Several mechanisms were proposed to clarify indomethacin (IND) harmful effects on the stomach. These include increased malondialdehyde (MDA) level, which enhances lipid peroxidation in gastric tissues, inhibition of cyclooxygenase enzyme, impaired production of prostaglandin E_2 leading to decreased synthesis of bicarbonate and mucus, with increased acids and free radicals production **(Nagi et al., 2021).**

Prostaglandin is a potential inhibitor of inflammatory markers production (e.g., tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)), resulting in the stimulation of inflammation and oxidative stress in the gastric mucosa. This led to the reduction of mucosal resistance and increased hostile factors as acid and pepsins**(Gong et al., 2018).**Also, several research works have showed that the gastric ulceration (GU) is linked to cleavage and remodeling of the extracellular matrix (ECM) by matrix metalloproteinases (MMP; mainly MMP-2 and MMP-9), MMP-2 may contribute in the functional turnover of the gastric ECM, whereas MMP-9 may be significant in the initial phase of the gastric ulcer development**(Kim et al., 2011, Lempinen et al., 2000).**

Anti-ulcer drugs (e.g, antacids, histamine (H_2) inhibitors, and proton pump inhibitors) were used in the past decades. However, these drugs have many side effects, like impotence, cardiac arrhythmia, arthralgia, gynecomastia, and many drug-drug interactions. These side effects make these drugs unsafe for use **(Armah et al., 2021).** Thus, there is a critical need to find newer safe and effective anti-ulcer drugs.

Several Herbal plants have been studied for their potential healing effects on peptic ulcer disease among them Myrrh, which is a natural resin obtained from a small, spiky tree species of the genus Commiphora. Myrrh resin has been used for centuries as a fragrance, incense, and drug. Its gum

(resin) is a yellowish extract of Commiphora myrrha, and the usually used name is Commiphora Molmol **(Al-Ruwaili et al., 2012).**

However, most experiments were conducted on the extract of the leaf, root and bark of this tree with little or no research on the gastro-protective and anti-oxidative activity of the myrrh **(Yahaya et al., 2021).**Thus, this research was carried out to evaluate the potential gastroprotective and antioxidant activities of CM in Indomethacin-induced gastric damage in albino rats.

Materials and methods

Drugs and chemicals

Indomethacin was supplied by the Nile Co. for Pharmaceuticals and Chemical Industries, Egypt. The phosphate buffer, formalin and all other chemical substances were of the highest commercially available purity grade. The oleo-gum-resin of CM was obtained, in the purest form available commercially, from a local market in Zagazig, Egypt. Five grams of the resin were crushed into a fine powder using a sterile pestle and mortar. The plant powder was then suspended in distilled water to have a final concentration of 500 mg/ml. The selection of this dose was based on earlier studies, showed that 500 mg/kg of CM has no toxic effects**(Qureshi et al., 1993).**

Animals

Animal handling was accepted by the Institutional Review Board for Research and Ethics Medical ethical committee, Damietta Faculty of Medicine, Al Azhar University, Egypt (IRB 00012367-21-06-007). Fourty adult male albino rats were chosen as an animal model for this study. They were kept in suitable cages (five rats/cage) at room temperature, with the natural light/dark cycle. They weighed 150 -170 g (average weight was 160g). They were kept for 15 days for adaptation to new environments before the start of the experiment. They were fed on a standard food with free water supply.

Induction of gastric ulcer

The stomach ulcer was induced by the method previously described by Okonkwo et al.**(Okonkwo et al., 2021).** The rats were received a single dose of indomethacin (30mg/kg). The food did not permitted. However, rats freely accessed to water 24 h. before the ulcer induction. Different grades of ulcer had been demonstrated six hours after administration of indomethacin. The animals were anaesthetized using diethylether, sacrificed and stomach was incised along the greater curvatureand ulceration was scored.

Experimental design

The rats were categorized into four equal groups (10 rats each): group I (control), received distilled water 1 ml/rat by oral gavage; group II indomethacin induced gastric ulcers; group III received 250 mg/kg of CM by oral gavage for two weeks followed by intraperitoneal (i.p.) injection of indomethacin 30 mg/kg in the last day, 20 min. after last dose of distilled water (DW); group IV received 500 mg/kg of CM by oral gavage, for two weeks followed by injection of indomethacin i.p. of 30 mg/kg in the last day, 20 min. from last dose of CM. Animals were sacrificed 6 h. after indomethacin injection. Blood samples were collected from the retro-orbital plexus for measurement of TNF-alpha serum levels. Then, abdomen was opened to access and remove the stomach. The stomach then opened through its greater curvature, and washed with saline. It was fixed by pins over a cardboard plate and inspected for ulcers. The ulcerated parts in the stomach

look like streaks 1-2 mm wide. The ulcer length was measured by a transparent millimeter scale with the aid of a magnifying lens. Results were calculated and expressed as the ulcer index (UI) that specifies the burden of ulcers. Then, preventive index (PI) was calculated as described previously**(Šćepović and Radmanović, 1984).** After gross examination of the stomach, pieces about 1 × ½ cm were excised and prepared for malondialdehyde (MDA) estimation. Then, other sections were fixed by formalin solution (10.0%). Paraffin sections were prepared and stained with hematoxylin, and eosin for histopathological examination. MDA estimation was previously described by**(Fong et al., 1973)** in which the tissue pieces were homogenized in TCA and suspended in thiobarbituric acid. After centrifugation, the clear pink supernatant optical density was measured at 532 nm. Malondialdehydebis (dimethyl acetal) was used as standard.

Determination of tissue MMP-9 immunostain expression

The specimens of the gastric tissue were fixed in paraformaldehyde 4% in tris-buffered saline (TBS) at 4°C for 18 h. Serial sections (4.0 µm) of paraffin-embedded tissues had been deparaffinized in xylene and dehydrated in ascending concentrations of ethanol alcohol. Antigen retrieval was completed by exposing the samples for heat (hot oven for 20 min. at 95°C) in a citrate buffer (pH 6.0). The blockage of the endogenous peroxidase was achieved by hydrogen peroxide (3%) for 10 minutes at room temperature. Afterward, a rabbit polyclonal MMP-9 antibody (cat. no. ab38898; Abcam, Cambridge, MA, USA) was used to incubate the sections at 1:250dilution at 4°C for an overnight. Then, washed by PBS, and incubated with horseradish peroxidase-labeled goat anti-rabbit immunoglobulin (cat. no. ab6721; Abcam) at a 1:1,000 dilution at 37°C for 30 minutes. The reaction visualization was achieved by 3,3'-diaminobenzidine. Finally, the sections were counterstained with Mayer's hematoxylin at room temperature for one minute. The primary antibody was substituted with non-immune rabbit serum (cat. no. AR0010; Boster, Wuhan, Hubei, China) which served as the negative control**(Britten et al., 1993).**

The images were photographed & the percentage area density of MMP-9 was measured using an Raywild B5 microscope with an RaywildM-300 digital camera with image-analyzing system (Mvi-mage program v12)**.**

Statistical analysis

Results were prepared, coded and fed to a statistical software for analysis. The package used was SPSS for Windows (version 25, IBM®SPSS®Inc., Chicago, IL, USA). Values of the measured parameters were expressed as mean (for central tendency) and standard deviation (SD; for dispersion). Differences and significances were verified by one-way ANOVA followed by the least significant difference (LSD) post hoc tests. P value ≤ 0.05 was considered statistically significant.

RESULTS

Gross appearance

Macroscopic examination of the stomach of the control group revealed normal pink coloration of the gastric mucosa with prominent rugae. Gastric mucosa of indomethacin-induced gastric ulcer group (II) revealed brownish hemorrhagic spots and streaks with pallor of the surrounding gastric mucosa. While, in the low dose of CM treated group, apparent normal gastric mucosa despite small tiny hyperemic spots were detected. Obvious improvement was detected in the gastric ulcer treated with a high dose of CM (Figure 1: a, b, c, d).

Light microscopic results

Hematoxylin and eosin-stained sections results

Examination of sections of the stomach of the control group stained by H&E revealed normal histological structure of the gastric mucosa, composed of epithelium that was interrupted by short narrow gastric pits, lamina propria and muscularis mucosa. The lamina propria was occupied by long tightly packed simple tubular fundic glands laying perpendicular to the surface. The fundic glands were differentiated into three regions; innermost isthmus, neck, and base regions. The simple columnar epithelial lining the surface, isthmus and the gastric pits (mucus-secreting) cells with pale cytoplasm and basal oval nuclei. The neck region was lined by groups of low columnar mucous neck cells with basal flattened nuclei and foamy cytoplasm interspersed with parietal cells. Oxyntic or parietal cells appeared large pyramidal with deeply acidophilic cytoplasm and centrally located rounded vesicular nuclei. The resulting mucosal lesions in the indomethacin-induced gastric ulcer group (II) revealed mucosal injury in the form of separated mucosa with distorted glandular histoarchitecture with widening of gastric pits and sloughing of epithelial cells at the ulcerated region into the gastric lumen. Some parietal and chief cells are vacuolated with darkly stained small nuclei. Moreover, congested blood capillaries along with diffuse inflammatory cellular infiltrations were prominent in the lamina propria in between the destructed fundic glands near the ulcerated area. The CM-treated group showed restoration of the histological architecture of the gastric mucosa with more or less similarity to the control group in the high dose-treated group (Figure 2, 3 (a, b, c, d).

Assessment of immunostaining expression of MMP-9

In the control group, there was no expression of MMP-9; the rat of the indomethacin-treated group showed strong expression of MMP-9 at the base, neck & isthmus of the gland. The rat of the low dose of CM-treated group showed minimal expression of MMP-9 in the mucosa, while rats of the high dose of CM-treated group showed more or less normal expression of MMP-9 in the mucosa (Figure 4: a, b, c, d).

Statistical and morphometric results

Ulcer index

Indomethacin-treated group (II) showed ulcers with a total number of 155 with mean 15.5 mm compared to 0 in the control group. Oral administration of CM in doses of 250 and 500 mg/kg showed a significant decrease in the ulcer index compared to the indomethacin-treated group as shown in table (1).

Assessment of oxidative status and pro-inflammatory marker & Immunohistochemical staining:

There was a significant increase in gastric tissue levels of MDA, serum levels of TNF alpha & immune expression of MMP-9 in the indomethacin treated-group compared to control, While, there was a significant decrease in gastric tissue levels of MDA, serum levels of TNF alpha & immune expression of MMP-9 in the CM treated groups compared to the indomethacin treated-group as shown in table (2).

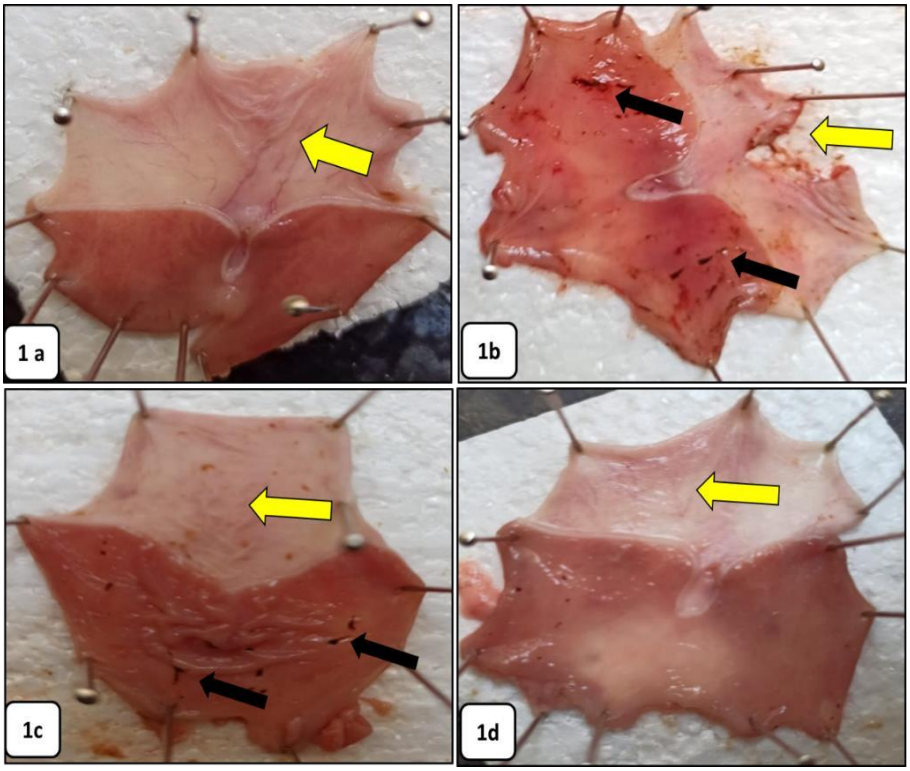

Figure 1: Gross examination of the gastric mucosa of all experimental groups showing: (1a) the control group has normal pink coloration with prominent rugae (yellow arrow). (1b): indomethacin-induced gastric ulcer group, showing a detachment of the mucosa (yellow arrow) brownish hemorrhagic spots and streaks (black arrows) among the gastric mucosa. (1c): low dose of CM treated group, small tiny hyperemic spots (black arrows) among the normal gastric mucosa (yellow arrow) is noticed. (1d): H. dose of CM-treated group showing: apparent normal pink gastric mucosa with prominent rugae (yellow arrow) more or less as the control. **Indom.: Indomethacin, CM.: Commiphora Molmol, L.: Low, H.: High.**

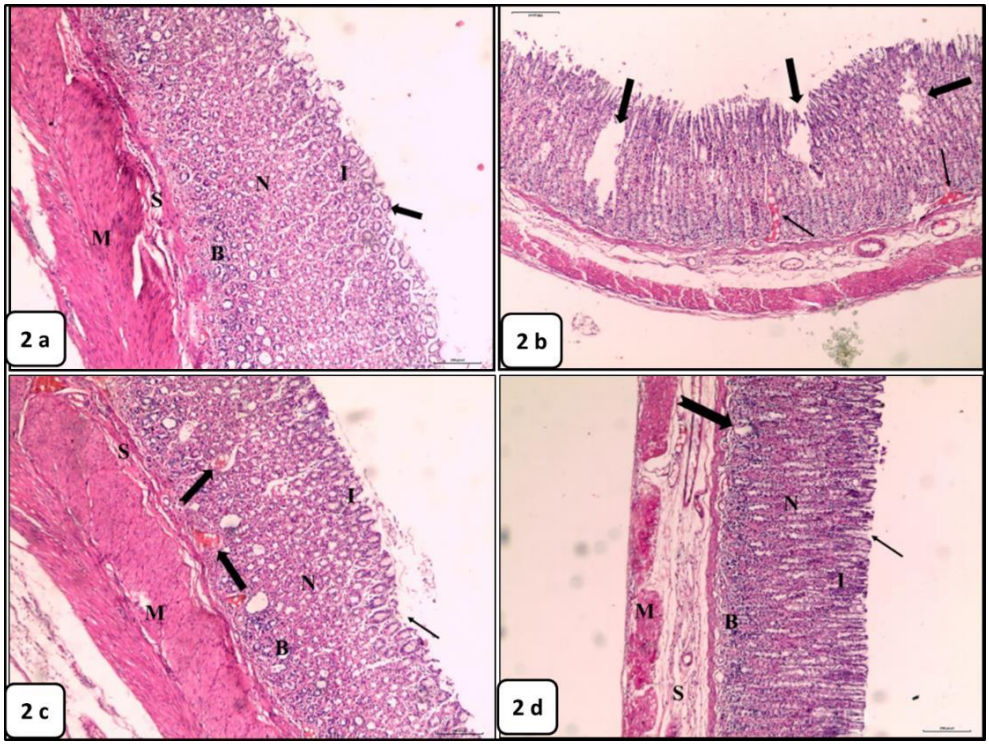

Figure (2): Photomicrographs of the stomach region of the studied groups showing:(2a): the rats of the control group (G.I) showed normal gastric mucosal architecture, intact epithelial surface (thick arrow) consisting of packed glands formed of isthmus (I), neck (N) and base (B) with normal submucosal (S) and musculosal layers (M). (2b): the rat of indom. group (G.II) showed multiple mucosal ulcers in the form of epithelial detachments (thick arrows), and mucosal congestion at the base of gastric glands (thin arrows). (2c): the rat of the low dose of CM-treated group showed minimal distortion of mucosal architecture, with minimal widening of superficial gastric pits (thin arrow), & with minimal capillary congestion (thick arrow) at the neck (N) and mild glandular separation and capillary congestion (notched thick arrow) at the base of the mucosal glands (B) with normal submucosal (S) and musculosal layers (M). (2d): while that of the rats of the high dose of CM-treated group showed, more or less restoration of normal histological architecture of the gastric region of the stomach consisting of packed glands formed of isthmus (I), neck (N) and base (B) with minimal widening of gastric pits (thin arrow), and minimal vacuolation (notched thick arrow) at the base of the glands (B) with normal submucosal (S) and musculosal layers (M)**(H & E. X100).** Scale bar 200 pixel.

Indom.: Indomethacin, CM.: CommiphoraMolmol, L.: Low, H.: High.

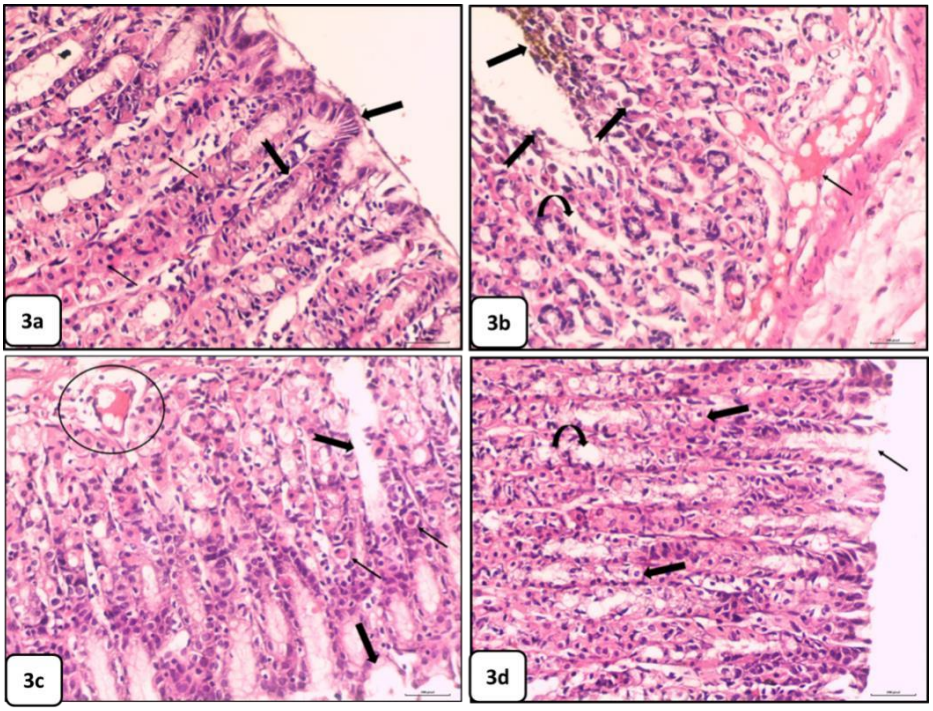

Figure (3) Photomicrographs of higher magnification in the stomach region of the studied groups showing:(3a): the control adult male albino rat (G.I) with long, straight, packed gastric glands lined with normal surface columnar cells with basal oval nuclei (thick arrow), mucous neck cells with basal flattened nuclei (notched thick arrow) and parietal cells with central rounded nuclei (thin arrow). (3b): the gastric mucosa of the rat of the indomethacin group (G.II) showed, mucosal ulcers in the form of epithelial detachments with multiple superficial streaks of hemorrhage (thick arrow), abnormally degenerated superficial parietal cells, (notched thick arrows) with widening of the space between them (curved arrow) and mucosal congestion at the base of gastric glands (thin arrow). (3c): the rat of the low dose of CM-treated group (G.III) showed, restoration of epithelial continuity of the mucosa with minimal widening of gastric pits (thick arrow), some parietal cells appear with vacuolated cytoplasm (thin arrow). with minimal capillary congestion (circle). (3d): while that of the rats of the high dose of CM-treated group(G.IV) showed, more or less normal histological architecture of the gastric region of the stomach with minimal widening of gastric pits (thin arrow), few apoptotic parietal cells (thick arrows) and minimal vacuolation at the base of the glands (curved arrow)(Hx& E. X400). Scale bar 200 pixel.

Indom.: Indomethacin, CM.: Commiphora Molmol, L.: Low, H.: High.

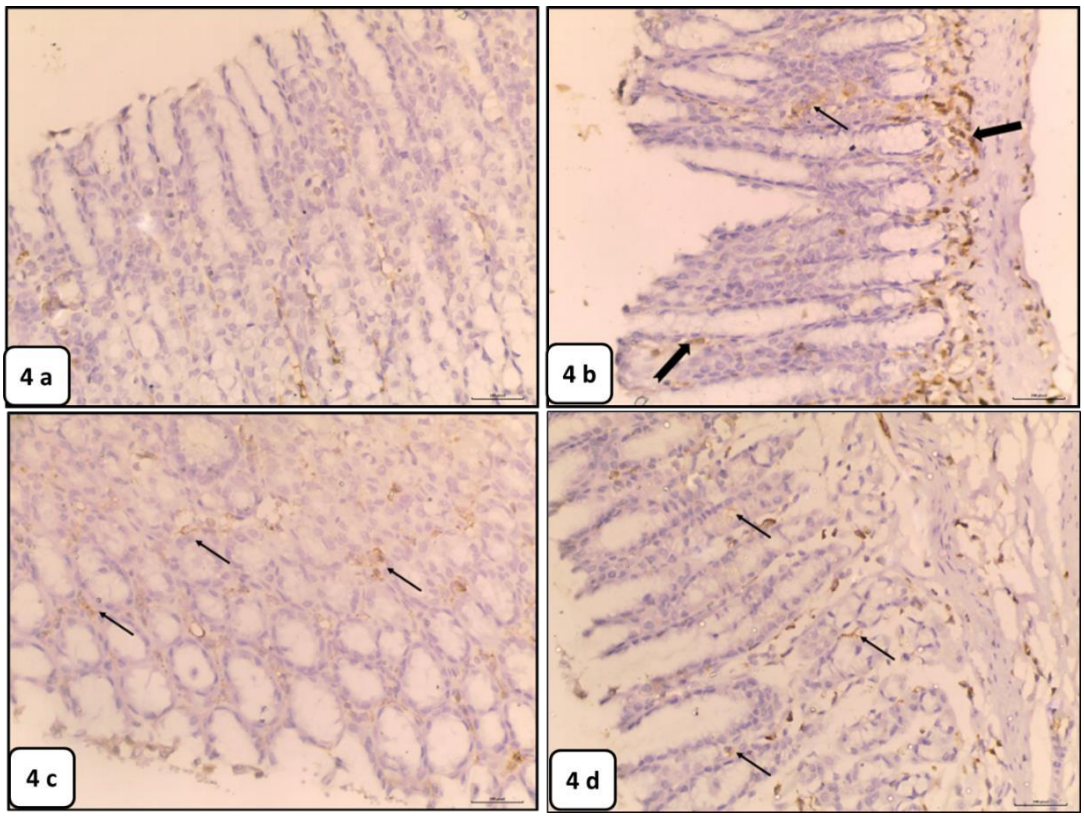

Figure (4): Photomicrographs of Immunohistochemical staining of MMP-9 in gastric sections in all of the experimental groups showing: (4 a): the control rat group showed no expression of MMP-9, (4 b): the rat of the indomethacin group showed strong expression of MMP-9 (brown color) at the base of the gland (thick arrow), neck (thin arrows) & at the isthmus (thick notched arrow). (4 c): the rat of the low dose of CM-treated group showed minimal expression of MMP-9 in the mucosa (thin arrows), (4 d): the rats of the high dose of CM-treated group showed, more or less normal expression of MMP-9 in the mucosa (thin arrows)(MMP-9 immunohistochemical staining. X400). Scale bar 200 pixel.

Indom.: Indomethacin, CM.: Commiphora Molmol, L.: Low, H.: High.

Table (1): showing ulcer index and preventive index in the studied groups.

Parameters / Groups (n=10)	Ulcer index		Preventive index (%)
	The sum of the lengths of ulcers in mms/group (Total)	Mean lengths of ulcers in mms/rat (Mean)	
Control	0	0	-
Indomethacin	155	15.5	-
Indom. + low dose of Com. molmol	102	10.2	34.19%
Indom.+ high dose of Com.molmol	76	7.6	50.96%

Table (2): Changes in MDA and TNF alpha in different groups.

Groups / Parameters	Group I	Group II	Group III	Group IV
MDA (n mol/ gram tissue)	22.45±2.41	134.63±6.74*	66.81±5.21*	46.76±3.44*
TNF alpha	29.33±2.89	144.67±6.89* P<0.05	54.27±4.73* P<0.05	35.41±4.23* P<0.05
MMP-9	0.236±0.05	0.325±0.04*	0.272±0.06*	0.253±0.03*

DISCUSSION

In the current work, acute exposure of the rats' gastric mucosa to the indomethacin in a dose of 30 mg/kg led to lesions similar to those developed in patients with gastric ulcers. Hence, it was obvious that the administration of indomethacin resulted in gross damage to gastric mucosa, such as loss of normal color, and hemorrhage. These changes are in agreement with the findings of Samir &Aicha **(Samir and Aicha, 2021).** Additionally, the results of macroscopic examination were supported by the histopathological findings of gastric mucosa in rats of the GU model group as it showed gastric ulcers with epithelial detachment and loss of the superficial mucosal layer in rats subjected to the indomethacin administration. These changes coincide with the previously recorded a significant damage and erosion in the mucosal layer of the stomach tissue in the indomethacin- treated groups **(Maity et al., 2021, Samy El-Ficky et al., 2018).**

The ulcerogenic effect of the indomethacin was confirmed by the increased UI in study than the control group. Our results agree with Boushra et al.**(2019)** who stated that UI and gastric volume were increased in the indomethacin-treated than the control rats.

The gastric damage produced by indomethacin was due to the suppression effects of prostaglandin production, reduction of the mucus secretion, and reduced mucosal blood circulation **(Kim et al., 2019).**

Also, the effect of the indomethacin on the synthesis of prostaglandin was associated with free radicals formation, as observed in ulcerated gastric tissues in other studies **(Sabiu et al., 2016, Vivatvakin et al., 2017).** This may be explained by free radical's production or decreasing synthesis of prostaglandins. Where decreased prostaglandin levels may result in decreased gastroprotection, increased gastric acid secretion, diminished blood flow and mucous secretion which are the main cause of mucosal ulceration**(Bjarnason et al., 2018).**

Oxidative stress play a crucial role in the pathogenesis of GU. The oxidative stress caused by the increased levels of reactive oxygen species (ROS). Therefore, injury to the gastric tissues occurs by destruction of membranes and cellular biocomponents such as proteins, nucleic acids and lipids **(Adhikary et al., 2011).**

GU is associated with a reduction of the gastric mucin content leading to reduction in the mucosal membranes' ability to safeguard the mucosa against physical damage and hydrogen ions back diffusion. Additionally, it prevents the recovery of epithetical tissues. The inhibition of PGs production lead to a reduction in mucin secretion then hydrogen ions and pepsins could diffuse from

the lumen into the mucosa. So, acid and pepsin back diffusion into the tissues induce more acid and pepsin secretion to lead to more destruction**(Srivastava et al., 2021).**So, using anti-oxidant medicinal plants could reduce the production of ROS and prevent its destructive effects on the gastric mucosa.

In the present study, treatment with CM decreased the size of the gastric lesions produced by the indomethacin pretreatment by CM in a dose of 250 mg/kg and 500 mg/kg to the indomethacin treated rats led to a reduction in the UI in a dose-dependent pattern when compared to the indomethacin- treated group with a protection ratio of 34.19% and 50.96% respectively. These results agreed with AL-Yahya **(2015)** who concluded that myrrh increases the healing of chronic GU due to acetic acid in rats and it stimulates the healing of GU with ranitidine treatment.

In this study, CM resulted in a significant protection on gastric mucosa against indomethacin-induced ulcer. This protective effect of CM was apparent by the reduced ulcer length. The CM cytoprotective effect was approved in the present work by macroscopic and microscopic investigations as the hemorrhage severity, ulcerations, infiltration by inflammatory cells and submucosal edema were reduced.

The anti-ulcer effect of CM observed in the current work, agree with the study of Su et al. **(2012)** and Alfkyet al. **(2018).**

Several studies showed that CM can affect the healing process of ulcer by different mechanisms. It increases mucus production, nucleic acid synthesis, and non-protein sulfhydryl compound requiredto maintain health of the gastrointestinal mucosa **(Younis and Mohamed, 2021).**

Myrrh also has a powerful antioxidant and antimicrobial effects that can share in the process of GU healing. It inhibits the growth of diverse bacteria and fungi. This antibacterial effect contributes to the healing actions exerted by this herb. Additionally, the gastroprotective effect of CM extract was resulted from the interaction between anti-secretory, cytoprotective, anti-inflammatory, and antioxidant actions **(Khalil et al., 2020, Ashry et al., 2010).**

Moreover, recent study showed that the anti-ulcer activity of CM could be resulted from its anti-inflammatory effect. The researchers suggested that the GU healing induced by ethanol is improved by CM extract through reduction of the inflammatory mediators serum levels, and prostaglandin E_2 (PGE_2)**(Weber et al., 2020).**

In the present work, the indomethacin-treated group showed an increase in TNFα than the control group. These results agree with the results of recent studies **(Mahmoud et al., 2021, El-Demerdash et al., 2021)** which revealed that TNF-α is a chief mediator causing NSAID induced gastropathy. It stimulates transcription factors such as nuclear factor kappa B (NF-κB) with synthesis of various inflammatory cytokines and stimulation of neutrophil infiltration of the gastric mucosa.

TNF-α initiates the expression of adhesion molecules that stimulate neutrophil invasion in the gastric mucosa. Furthermore, TNF-α has a pro-apoptotic and cytotoxic activity with consequent damage to cells in the gastric mucosa **(Yildirim et al., 2015, Fakhri et al., 2021).**

Our study showed that the indomethacin-treated group significantly increases the gastric tissue level of MDA when compared to the control group. These results were in line with earlier studies **(Liu et al., 2015, Gomaa et al., 2018).** The raised MDA level showed an improved lipid peroxidation

in thegastric tissues **(Kolgazi et al., 2021).**

Also, our results demonstrated that pretreatment by CM in a dose of 250 mg/kg and 500 mg/kg to the indomethacin treated rats led to a significant decrease in TNF-α when compared to the indomethacin-treated group. These results agreed with the results of Mahmoud et al.**(Mahmoud et al., 2017)** who reported that the use of resin markedly attenuated ammonia-induced liver injury, reduced circulating ammonia, and TNF-α in hyperammonemic rats.

Moreover that, our results were agree with a previous study **(Su et al., 2015)** showed that both the frankincense and the CM have favorable effects on inflammation, and the co-administration of the two substances has a well synergistic anti-inflammatory action with a significant reduction of inflammatory cytokines expression (e.g., interferon-gamma (INF-γ), interleukin-2 (IL-2), IL-1β, IL-12, TNF-α, PGE2, nitric oxide (NO), and MDA).

Our results showed up-regulation of MMP-9 gene expression in the indomethacin-treated group when compared to the control one. Several studies have recorded that the indomethacin up-regulates MMP-9 expression through prostaglandin independent pathways. which is in agreement with our findings **(Singh et al., 2011, Hegab et al., 2018).**

But administration of CM in a dose of 250 mg/kg and 500 mg/kg to the indomethacin treated rats led to down-regulation of MMP-9 gene expression when compared to the indomethacin-treated group.

The effect of CM on MMP-9 gene expression could be resulted from its strong antioxidant effect, as ROS regulate MMP gene expression through indirect regulation of redox-dependent MMP gene transcription or direct modification of MMP structure. MMPs selectively destroy the ECM components and play a significant role in its remodeling. Therefore, its inhibition could repair the balance between matrix degradation and deposition, thus, preventing gastric injury **(Hegab et al., 2018).**

The ECM degradation in GU is induced by the MMPs action, which also related to the inflammatory and oxidative tissue changes. This refers to the negative participation of these MMPs in gastric healing. The increased expression of MMP-2 in gastric mucosa is often linked to the initiation and progress of GU**(Li et al., 2013).**

In conclusion, CM (Myrrh) had an anti-ulcer effects in indomethacin-induced GU through regulation of MMP-9 expression and activity of MDA and TNF alpha. These data approve its traditional use for GU treatment.

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