Open Access
Journal of the Faculty of Medicine Baghdad
Print ISSN: 0041-9419, Online ISSN: 2410-8057
DOI: https://doi.org/10.32007/jfacmedbaghdad2467.
Research Article

The Cytoprotective Effects of Melatonin on Gastric Ulcer: A Rat Model

Hela A. Muayad*[1], Huda I. AlQadhi[1]

[1] *Department of Pharmacology, College of Medicine, University of Baghdad, Baghdad, Iraq.*

Received: Sept. 2024
Revised: Nov. 2024
Accepted: Dec. 2024
Published: April 2025

Abstract

Background: Gastric ulcer is a prevalent gastrointestinal disorder caused by environmental factors and a higher intake of non-steroidal anti-inflammatory drugs (NSAIDs).

Objective: To investigate the prophylactic effects of melatonin on the histology, severity of gastric ulcers, and levels of inflammatory and oxidative stress markers (Interleukin-1beta (IL-1β) and Malondialdehyde (MDA)) in a rat model of indomethacin-induced ulcers.

Methods: This study was performed at Al-Mustansiriyah University's Research Center for Cancer and Medical Genetics from November 2023 to May 2024. Fifty healthy male albino rats weighing between 150 - 250 grams were used. After 24 hours of fasting, these rats were divided into five groups, each with 10 rats. **Group A:** Received 1 ml of indomethacin vehicle (carboxymethylcellulose 1%) orally (negative control). **Group B:** Received 60 mg/ kg of indomethacin orally (positive control). **Group C:** Received 20 mg/ kg of omeprazole orally 30 minutes before indomethacin induction. **Group D:** Received 20 mg/ kg of melatonin solution orally 30 minutes before indomethacin induction. **Group E:** Received 30 mg/ kg of pioglitazone solution orally. After 1 hour, rats received a melatonin solution of 20 mg/ kg and waited for 30 minutes before induction.

Results: The group that received melatonin pretreatment at a dosage of 20 mg/kg exhibited a statistically significant reduction in the severity of stomach ulcers and histological damage score. The administration of melatonin at a dose of 20 mg/kg to the pre-treated group reduced inflammatory and oxidative stress markers (IL-1β and MDA) levels similar to those observed with the reference medication.

Conclusions: Melatonin alone or a combination of pioglitazone and melatonin effectively reduce gastric mucosal injury, oxidative stress, and pro-inflammatory cytokine levels, comparable to standard omeprazole drugs.

Keywords: Indomethacin; Melatonin; Rats; Stomach Ulcer.

Introduction

About 20% of cases of gastric ulcer begin with a mild erosion of the epithelium lining the stomach lumen and progress deeper to the muscularis mucosa or submucosa, which is 5 mm in diameter or greater (1). The severity of the disease is related to age, gender, genetic variation, and geographic distribution.

It arises when the protective factors, like mucus gel, mucus phospholipid, bicarbonate buffers, PGs, and stomach hormones, are outweighed by the risk factors, such as smoking, alcohol, stress, spicy food, helicobacter pylori infection, and regularly using NSAIDs (2). The major serious complications of gastric ulcers include bleeding and perforation, which may even result in death (3).

Because of their dual anti-inflammatory and analgesic qualities, nonsteroidal anti-inflammatory medications (NSAIDs) are primarily given to treat pain and inflammation. They work by inhibiting the activity of an enzyme called cyclooxygenase (COX), which is involved in the production of various inflammatory chemicals, including prostaglandins (PGs), which are also responsible for the perception of pain (4). So NSAIDs cause stomach ulcers by disrupting PG synthesis by inhibiting COX enzymes, particularly COX-1 and COX-2 (5). Also, NSAIDs raise the expression of proinflammatory cytokines, including TNF-α, and encourage apoptosis (6). By suppressing constitutive nitric oxide synthase (cNOS), they also compromise the integrity of the stomach mucosa (7,8).

Indomethacin is a highly ulcerogenic drug commonly utilized in experimental animals to induce ulcers through multiple mechanisms. It reduces the production of PGs by non-selectively inhibiting the COX enzyme, which in turn weakens the body's defense mechanisms. This leads to oxidative damage caused by an increase in the generation of reactive oxygen species (ROS), in addition to causing permanent deactivation of gastric peroxidase (1). So, Indomethacin-induced gastric ulcers are due to various mechanisms, including suppressing PG synthesis, causing mucosal apoptosis, inhibiting angiogenesis, infiltrating neutrophils, and generating reactive oxygen species (ROS) (9).

The development of stomach ulcers has been linked to the inhibition of COX and ensuing PG function (10). Mitochondrial oxidative stress (MOS) is a significant pathway, independent on PGs that

* *Corresponding author: phhelamuayad@gmail.com.*

contributes to gastric mucosal injury caused by indomethacin. This pathway leads to an increase in proinflammatory reaction and neutrophil infiltration, which are involved in the development of gastric mucosal lesions through the overproduction of reactive oxidants (11,12).

Interleukin-1beta (IL-1β) is a pro-inflammatory cytokine that has a role in the immunological response to infection by increasing the expression of adhesion factors on vascular endothelial cells, promoting extravasation of leukocytes to the infection site. Additionally, iL-1β resets the temperature regulation center in the hypothalamus, resulting in elevated body temperature (13). IL-1β plays a role in regulating gastric acid secretion and protecting cell activities in the gastric mucus (14).

Malondialdehyde (MDA) is a chemically active compound that is formed as a result of the breakdown of polyunsaturated fatty acids and lipids under the action of (ROS and the metabolism of arachidonic acid. MDA serves as a biological marker for oxidative stress and is documented to exist in animal tissues, particularly in cases of antioxidant insufficiency (15).

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone secreted mostly by the pineal gland in the brain, which maintains the body's circadian rhythm. Recent research has demonstrated that melatonin exhibits anti-inflammatory and antioxidant properties in living organisms. It is interesting to note that enterochromaffin-like cells (ECL) in the gastrointestinal tract (GIT) produce this indole derivative in a quantity 400 times higher than the pinealocytes. Prior research has demonstrated that melatonin protects against acute stomach damage brought on by stress, alcohol, aspirin, and ischemia-reperfusion (16). Due to its antiproliferative and antioxidative properties, melatonin has also been demonstrated to play many other roles, including an impact on immunological function (17,18).

Prior studies by Bilici *et al*. have demonstrated that melatonin provides protection against many forms of stomach ulceration, including ethanol-induced ulceration, by improving a reduction in glutathione levels, enhancing glutathione reductase activity, and reducing the infiltration of polymorphonuclear leukocytes (19,20). Additionally, melatonin prevents the formation of cold stress-induced ulcers by neutralizing the hydroxyl radical (OH•). In the same way, melatonin defends against acetylsalicylic acid and/ or ischemia reperfusion-induced gastropathy by removing ROS. Studies by Ganguly *et al*., indicated that melatonin provides protection against indomethacin-induced ulceration by increasing glutathione levels, decreasing myeloperoxidase activity, and reducing lipid peroxidation (9,21).

Melatonin's amphiphilic nature also contributes to its protective effect on the gastro-duodenal lining. This characteristic makes it possible for melatonin to freely enter each cell compartment, allowing it to scavenge ROS. Also Melatonin provides gastro-protection by maintaining tissue PG levels, which lower acid production, increase mucous and bicarbonate secretion, and improve blood flow (22).

The objective of this study is to investigate the cytoprotective and preventative effects of melatonin on the histology, severity of stomach ulcers, and indicators of oxidative and inflammatory stress (MDA and IL-1β).

Materials and Methods

Fifty male albino rats were used in the study. They were all in good health, with weights ranging from 150 - 250 g, and were obtained from Al-Mustansiriyah University Research Center for Cancer and Medical Genetics' animal house from November 2023 to May 2024. They were housed in standard conditions, with tap water and rodent food available. They were kept in polyethylene cages with a wire mesh floor and stainless-steel coverings to prevent coprophagy. The rats were kept in a 12-hour light/ dark cycle, with the temperature range maintained between 21 - 28°C, with a humidity range of 10% - 50%.

The faculty of Medicine/ Al-Mustansiriyah University ethics committee approved the protocol of this study, and all experiments were conducted according to institutional standards.

All the medications used in the experiment were dissolved using carboxymethylcellulose (CMC) 1% (Deiman®/USA). To generate a stock solution, one gram of CMC was dissolved in 100 milliliters of distilled water (DW). They were the following:

- Melatonin capsule 20 mg (Now foods®/USA); soluble in 1% CMC; (5 mg/ml),
- Omeprazole capsule 20 mg (Gasec®/Switzerland); soluble in a vehicle of $NaHCO_3$ and stirred strongly for 10 minutes until a clear suspension appears (concentration was adjusted to 4 mg/ml and kept in a dark reagent bottle),
- Indomethacin capsule 25 mg/kg (Mackline pure 99%®/China), and 60 mg/kg body weight of indomethacin was given orally via gavage.
- Ketamine vial (Alfasan®/Holland), Xylizin vial (VMD ®/Belgium), (D.W) from Iraq, Eosin stain (Sigma®/USA), Ethanol 99.9 % (Hayman®/UK), Formalin (37%) solution Alpha (Chemika®/India), Hematoxylin stain solution (BDH®/England), Normal saline (0.9% NaCl) (Fibco®/UAE).
- The following kits were used for the enzyme-linked immunosorbent test (ELISA): (Cat: ELK1272) (IL-1β) (ELK Biotechnology) and (Cat: ELK8612) (MDA) (ELK Biotechnology).

The rats were fasted for 24 hours before indomethacin administration because food causes a reduction in ulcerogenic activity, and water was held two hours before the beginning of the procedure.

Induction of ulcers in rats

A pilot study examined three doses of indomethacin, administered orally via gavage after 24 hours of fasting, comparing 20 mg/kg, 30 mg/kg, and 60

mg/kg. The dose of 60 mg/kg was selected based on a pathologist's macroscopic assessment of the degree of gastric mucosal injury because it is the only dose that causes the highest injury and damage for the gastric mucosa.

Indomethacin is prepared by dissolving in a vehicle of 1% (CMC) at a dose of 15 mg/ml. Every rat was given an indomethacin solution according to their weight and waited for four hours until ulcer formation.

Preparation of groups

All drugs were freshly prepared on the day of the experiment. The 20 mg melatonin dosage was chosen based on an earlier investigation (23). After 15 days of adaptation, the experimental rats were randomly divided equally into five groups: Control groups (**A** and **B**) and study groups (**C**, **D**, and **E**) as follows:

Group A: Received 1 ml of indomethacin vehicle (carboxymethylcellulose 1%) orally by gavage tube after 24 hours of fasting (negative control).

Group B: Received 60 mg/ kg indomethacin orally by gavage after 24 hours of fasting (positive control).

Group C: Received 20 mg/ kg omeprazole orally after 24 hours of fasting and 30 minutes before indomethacin solution induction.

Group D: Received 20 mg/ kg melatonin solution orally after 24 hours of fasting, 30 minutes before indomethacin solution induction.

Group E: Received 30 mg/ kg pioglitazone solution orally by gavage after 24 hours of fasting. After 1 hour, rats received a melatonin solution of 20 mg/ kg and waited for 30 minutes before indomethacin solution induction.

After four hours of indomethacin administration, the rats were euthanized by cervical dislocation after being anesthetized with 0.8 ml xylazine and 0.2 ml ketamine (24). Their stomachs were then recovered and dried with filter paper. The stomach was divided into three segments, and stored at -20^{o}C for further biological examination. Whole portions of the gastric corpus were preserved in a 10% formalin solution for histological study. The histopathological changes were assessed and scored based on specific criteria (25). Protein expression quantification was assessed using 20X magnification light microscopy and ELISA for biochemical analysis of proteins like MDA and IL-1β.

Histopathology study

Fixation and Staining: The animals' stomachs were collected, cut open, rinsed with cold normal saline, preserved in 10% formalin, and paraffin was applied to embed the tissues. Xylene was injected to clean the tissues, forming a paraffin block after completing the process of embedding tissues (26), and a specimen was then examined under a microscope using hematoxylin and eosin (H&E) (27).

Statistical analysis

The data was analyzed using SPSS (Statistical Package for Social Science) version 26, with calculating means ± standard deviations and 95% confidence level. The ANOVA test was used to compare variables among various research groups, followed by the least squares differences test for comparable differences. A P value of < 0.05 was considered statistically significant.

The overall percentages of damage of the groups were calculated using the following formula:

$$\frac{\text{Total numbers of lesions}}{\text{Highest lesion number}}$$

The overall mean score of the groups were calculated using the following formula:

$$\frac{Mean\ score\ of\ the\ group}{Highest\ mean\ score}$$

Results

Oral-pretreated groups with indomethacin had more stomach ulcers, while groups pre-treated with omeprazole and melatonin showed significantly less ulcers. Pretreated groups with indomethacin had the highest mean number of lesions, while those given omeprazole had the lowest. Giving Melatonin or a combination of pioglitazone and melatonin showed no significant difference but they were significantly different from the healthy group and ulcer control group. Indomethacin significantly impacted mucosal injury, causing 82.5% damage, while omeprazole-pretreated groups showed the lowest damage at 22.5% and a higher inhibition rate of stomach ulcers at 77.5%. Melatonin and pioglitazone combined showed 25% damage with a 75% inhibition rate, not significantly different from the omeprazole group, but significantly different from the healthy and ulcer groups (Table 1).

Table 1: Mean±SD of number of lesions in the stomach and percent of damage in the five study groups

Study groups	Lesions	Damage %
	Mean ± SD	Mean ± SD
A. Healthy (negative control)	0 ± 0 A	0% ± 0% A
B. Indomethacin (positive control)	3.3 ± 0.5 B	82.5% ± 12.5% B*
C. Omeprazole + Indomethacin	0.9 ± 0.1 C	22.5% ± 10% C
D. Melatonin + Indomethacin	1 ± 0 C	25% ± 0% C
E. Pioglitazone and Melatonin + Indomethacin	1 ± 0 C	25% ± 0% C
p-value	<0.001 *	<0.001*

**Significant at 0.05 level by ANOVA test.*

Indomethacin administration at 60 mg/ kg led to a higher damage score and significant histological alterations in the healthy group, resulting in erythema, edema, inflammatory reaction, and congestion (Figure 1).

Microscopic examinations showed minimal damage in the gastric mucosal layers after pretreatment with omeprazole, melatonin, and a combination of (pioglitazone and melatonin) with no significant difference between them but significantly different

from the healthy and ulcer groups (Figures 2, 3, and 4).

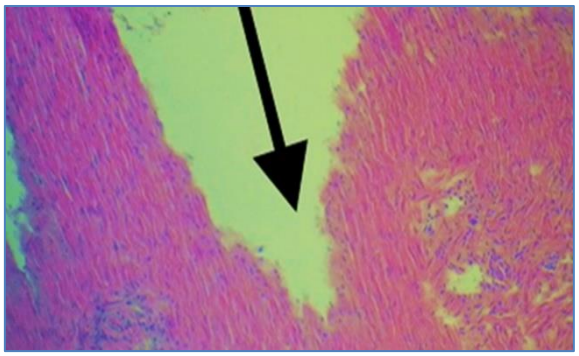

Figure 1: Marked degeneration of surface mucus epithelium of indomethacin [black arrow] and marked infiltration of inflammatory cells (H&E: 20X)

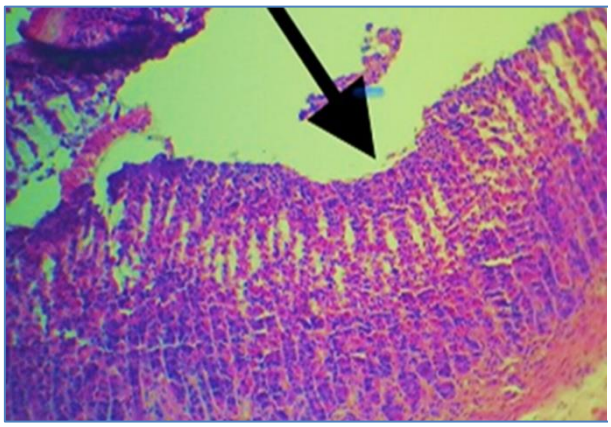

Figure 2: Marked erosion of gastric surface epithelium of omeprazole [black arrow] (H&E: 20X)

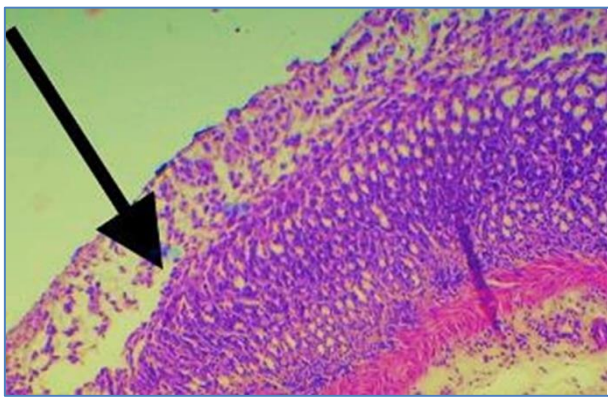

Figure 3: Marked erosion of gastric surface epithelium of melatonin [black arrow] (H&E: 20X)

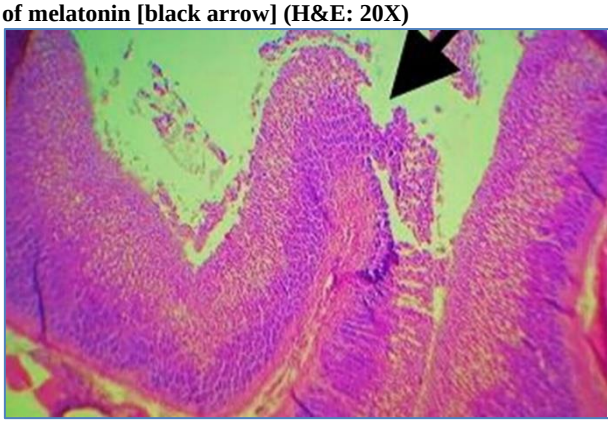

Figure 4: Marked erosion of gastric surface epithelium of pioglitazone and melatonin [black arrow] (H&E: 20X)

Indomethacin caused the highest mucosal damage (96.7%), while pre-treatment with omeprazole, melatonin, or their combination significantly reduced damage to 33.3% – 36.7%, with no significant difference among the treatment groups (Table 2).

Table 2: Mean±SD of scores and damage % in the stomach in the five study groups

Study groups	Scores	Damage %
	Mean ± SD	Mean ± SD
A. Healthy (negative control)	0 ± 0 A	0% ± 0% A
B. Indomethacin (positive control)	2.9 ± 0.3 B	96.7% ± 10.5% B*
C. Omeprazole + Indomethacin	1 ± 0 C	33.3% ± 0% C
D. Melatonin + Indomethacin	1.1 ± 0.3 C	36.7% ± 10.5% C
E. Pioglitazone and Melatonin + Indomethacin	1 ± 0 C	33.3% ± 0 % C
p-value	<0.001*	<0.001*

**Significant at 0.05 level by ANOVA test.*

Indomethacin significantly improved IL-1β expression in pretreated groups, while melatonin and omeprazole showed no significant difference (Table 3).

Table 3: Comparison of IL-1β marker level, according to study groups

Study groups	IL-1β	
	Mean	SD
A. Healthy	99	3.6 A
B. Indomethacin	375.5	66.8 B*
C. Omeprazole + Indomethacin	137.4	10 C
D. Melatonin + Indomethacin	125.7	13.7 C
E. Pioglitazone and Melatonin+ Indomethacin	147.8	9 C
p-value	<0.001*	

**Significant at 0.05 level by ANOVA test.*

A higher MDA score was found in the indomethacin-treated group (452±33.3) compared to the healthy group and all other study groups, while the lowest score was found in the pre-treated groups (Table 4).

Table 4: Comparison of MDA marker level, according to study groups

Study groups	MDA	
	Mean	SD
A. Healthy	121	6.7 A
B. Indomethacin	452	33.3 B*
C. Omeprazole + Indomethacin	132.6	7.9 A
D. Melatonin + Indomethacin	128.1	8.1 A
E. Pioglitazone and Melatonin+ Indomethacin	134.2	3.6 A
p-value	<0.001*	

**Significant at 0.05 level by ANOVA test. N=5 Healthy, Indomethacin (60mg/kg), Omeprazole (20mg/kg), Melatonin (20mg/kg), combination of (Pioglitazone 30mg/kg and Melatonin 20mg/kg).*

Discussion

The current study found that oral indomethacin significantly enhances the severity of gastric ulcers in the ulcerated group, consistent with previous research by Song *et* al (28). It was also found that a significant increase in the pro-inflammatory markers, such as IL-1β (the neutrophil recruitment indicator), and the oxidative stress marker, such as MDA after indomethacin administration. These findings align with previous studies (11,29) and can be attributed to the fact that indomethacin harms mitochondria by disrupting respiration stages and producing free radicals, which enhance inflammatory cytokine activity and neutrophil movement, leading to the development of inflammatory illnesses. These results align with our findings (30,31).

According to Lichtenberger *et* al, free radicals impair the functions of antioxidant enzymes and trigger lipid peroxidation, a crucial process in the harmful mechanism of indomethacin (12,32). According to Bindu *et* al, inflammation plays a crucial role in the pathogenesis of gastric injury (31,33).

Inflammation is considered the primary indicator of stomach ulcers (33). Abdel-Tawab *et. al*, found that administrating melatonin as a cytoprotective drug, significantly reduces pro-inflammatory cytokines like IL-1β, while enhancing MDA levels due to its anti-inflammatory properties (34). However, Konturek *et. al*, determined that the gastro-protective impact of melatonin arises from the stimulation of the COX1 enzyme pathway, as COX1 enzyme is constitutively expressed in gastric mucosa and generate PGs which is involved in gastrointestinal mucosal protection through vasodilation, stimulation, mucus and bicarbonate secretion, forming a protective barrier to acid injury, increased gastric and mucosal blood flow, increased angiogenesis, and scavenging of free radicals (35).

This study may be the first study that evaluates melatonin in indomethacin-induced experimental gastric ulcers. It found that administering melatonin 30 minutes before indomethacin administration significantly reduced pro-inflammatory cytokines and oxidative stress markers like IL-β and MDA which is compatible with the findings of Celinski *et* al (36). Melatonin's antioxidant activity effectively counteracts oxidative stress caused by indomethacin, as documented in Pal *et* al when 20 mg/kg of omeprazole and 5 mg/kg of melatonin were used for 21 days to treat an ulcer that had developed after taking indomethacin for five days (37).

Melatonin's anti-inflammatory and antioxidant properties may reduce ulcer severity. Combining pioglitazone and melatonin 90 minutes before indomethacin administration reduced pro-inflammatory cytokines and oxidative stress markers, indicating the combination's antioxidant and anti-inflammatory effects.

Conclusions

Melatonin alone or a combination of pioglitazone and melatonin effectively reduces gastric mucosal injury, oxidative stress, and pro-inflammatory cytokine levels, comparable to standard omeprazole drugs.

Authors Declaration

We hereby confirm that all the Figures and Tables in the manuscript are ours. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the local ethical committee in the College of Medicine, University of Baghdad. According to No. 03-7, dated March 24, 2024.

Conflicts of Interest: None.

Funding: None.

Author contributions:

Study conception:(Hela and Huda), Study design: (Hela and Huda), Literature search: (Study conception: Hela and Huda), Data acquisition: (Hela). Data analysis & interpretation: (Hela and Huda). Manuscript preparation: (Hela and Huda). Manuscript editing & review: (Hela and Huda).

References

1. Imad R, Al-Qadh HI. The protective effects of Cilostazol on indomethacin-induced gastric ulcer in rat model. HIV Nurs. 2022;22(2):3578-83.

2. Dafalla SE, Alghamdi HYA, Alsaedi AM, Alzain MAI, Alsaedi ODA, Khormi MA, et al. Awareness of the general population in Jeddah about peptic ulcer disease. Int J Med Dev Ctries. 2021;5(2):656-62. https://doi.org/10.24911/IJMDC.51-1609363527.

3. Al-Marzooq TJ, Naji RE, Al-Majidi AK, Abbas Y. The use of serum Amylase as a predictive factor for mortality in Perforated Duodenal Ulcer. J Fac Med Baghdad. 2015;57(4):295-8. https://doi.org/10.32007/med.1936/jfacmedbagdad.v57i4.8.

4. Jahnavi K, Reddy PP, Vasudha B, Narender B. Non-steroidal anti-inflammatory drugs: an overview. J Drug Deliv Ther. 2019;9(1-s):442-8. https://doi.org/10.22270/jddt.v9i1-s.2287.

5. Ju Z, Li M, Xu J, Howell DC, Li Z, Chen FE. Recent development on COX-2 inhibitors as promising anti-inflammatory agents: The past 10 years. Acta Pharm Sin B. 2022;12(6):2790-807. https://doi.org/10.1016/j.apsb.2022.01.002.

6. Zhang M, Xia F, Xia S, Zhou W, Zhang Y, Han X, et al. NSAID-associated small intestinal injury: an overview from animal model development to pathogenesis, treatment, and prevention. Front Pharmacol. 2022;13:818877. https://doi.org/10.3389/fphar.2022.818877.

7. Matloub SYN, Manna MJ. The cytoprotective effect of different doses of Sildenafil on indomethacin-induced gastric mucosal damage in rats. J Fac Med Baghdad. 2010;52(4):426-31. https://doi.org/10.32007/jfacmedbagdad.524950.

8. Mohamed YT, Naguib IA, Abo-Saif AA, Elkomy MH, Alghamdi BS, Mohamed WR. Role of ADMA/DDAH-1 and iNOS/eNOS signaling in the gastroprotective effect of tadalafil against indomethacin-induced gastric injury. Biomed Pharmacother. 2022;150:113026.

https://doi.org/10.1016/j.biopha.2022.113026.
9. Choudhary P, Roy T, Chatterjee A, Mishra VK, Pant S, Swarnakar S. Melatonin rescues swim stress induced gastric ulceration by inhibiting matrix metalloproteinase-3 via down-regulation of inflammatory signaling cascade. Life Sci. 2022;297:120426.
https://doi.org/10.1016/j.lfs.2022.120426.
10. Matloub SYN. Captopril versus enalapril in the protection of the gastric mucosa against NSAID induced gastric mucosal injury in rats. J Fac Med Baghdad. 2011;53(2):236-40.
https://doi.org/10.32007/jfacmedbagdad.532882.
11. Küçükler S, Kandemir FM, Yıldırım S. Protective effect of chrysin on indomethacin induced gastric ulcer in rats: role of multi-pathway regulation. Biotech Histochem. 2022;97(7):490-503.
https://doi.org/10.1080/10520295.2021.2014569.
12. Panchal NK, Sabina EP. Non-steroidal anti-inflammatory drugs (NSAIDs): A current insight into its molecular mechanism eliciting organ toxicities. Food Chem Toxicol. 2023;172:113598.
https://doi.org/10.1016/j.fct.2022.113598.
13. Rébé C, Ghiringhelli F. Interleukin-1β and cancer. Cancers (Basel). 2020;12(7):1791.
https://doi.org/10.3390/cancers12071791.
14. Wang J, Liu H, Wang Y, Wu J, Wang C, Liu K, et al. The polymorphisms of interleukin-12B gene and susceptibility to inflammatory bowel diseases: a meta-analysis and trial sequential analysis. Immunol Invest. 2021;50(8):987-1006.
https://doi.org/10.1080/08820139.2020.1863981.
15. Ajao AA, Sibiya NP, Moteetee AN. Sexual prowess from nature: A systematic review of medicinal plants used as aphrodisiacs and sexual dysfunction in sub-Saharan Africa. South African J Bot. 2019; 122:342-59.
https://doi.org/10.1016/j.sajb.2018.08.011.
16. Chrustek A, Olszewska-Słonina D. Melatonin as a powerful antioxidant. Acta Pharm. 2021;71(3):335-54.
https://doi.org/10.2478/acph-2021-0027.
17. Waleed S, Taha ATM, Uthman AT. Effect of Salivary Melatonin on Ionizing Radiation Worker and its Effect on Periodontal Disease. J Fac Med Baghdad. 2024;66(1):79-84.
https://doi.org/10.32007/jfacmedbagdad.6612183.
18. Ivanov DO, Evsyukova II, Mironova ES, Polyakova VO, Kvetnoy IM, Nasyrov RA. Maternal melatonin deficiency leads to endocrine pathologies in children in early ontogenesis. Int J Mol Sci. 2021;22(4):2058. https://doi.org/10.3390/ijms22042058.
19. Bilici D, Süleyman H, Banoğlu ZN, Kiziltunç A, Avci B, Çiftçioğlu A, et al. Melatonin prevents ethanol-induced gastric mucosal damage possibly due to its antioxidant effect. Dig Dis Sci. 2002;47:856-61. https://doi.org/10.1023/A:1014764705864.
20. Morvaridzadeh M, Sadeghi E, Agah S, Nachvak SM, Fazelian S, Moradi F, et al. Effect of melatonin supplementation on oxidative stress parameters: a systematic review and meta-analysis. Pharmacol Res. 2020;161:105210.
https://doi.org/10.1016/j.phrs.2020.105210.
21. Ganguly K, Maity P, Reiter RJ, Swarnakar S. Effect of melatonin on secreted and induced matrix metalloproteinase-9 and-2 activity during prevention of indomethacin-induced gastric ulcer. J Pineal Res. 2005;39(3):307-15.
https://doi.org/10.1111/j.1600-079X.2005.00250.x.
22. Majumder R, Datta M, Chattopadhyay A, Bandyopadhyay D. Melatonin promotes gastric healing by modulating the components of matrix metalloproteinase signaling pathway: a novel scenario for gastric ulcer management. Melatonin Res. 2021;4(2):213-31.
https://doi.org/10.32794/mr11250092.
23. Sánchez AB, Clares B, Rodríguez-Lagunas MJ, Fábrega MJ, Calpena AC. Study of melatonin as preventive agent of gastrointestinal damage induced by sodium diclofenac. Cells. 2020;9(1):180.
https://doi.org/10.3390/cells9010180.
24. Bhatia A, Saikia PP, Dkhar B, Pyngrope H. Anesthesia protocol for ear surgery in Wistar rats (animal research). Anim Model Exp Med. 2022;5(2):183-8. https://doi.org/10.1002/ame2.12198.
25. Jafari A, Andishfar N, Esmaeilzadeh Z, Khezri MR, Ghasemnejad-Berenji M. Gastroprotective effect of topiramate on indomethacin-induced peptic ulcer in rats: Biochemical and histological analyses. Basic Clin Pharmacol Toxicol. 2022;130(5):559-68.
https://doi.org/10.1111/bcpt.13718.
26. Nonaka H, Mino T, Sakamoto S, Oh JH, Watanabe Y, Ishikawa M, et al. Revisiting PFA-mediated tissue fixation chemistry: FixEL enables trapping of small molecules in the brain to visualize their distribution changes. Chem. 2023;9(2):523-40.
https://doi.org/10.1016/j.chempr.2022.11.005.
27. Ekbbal R, Iqubal A, Ansari MA, Ahmad S, Haque SE. Evaluation of cardioprotective potential of isolated swerchirin against the isoproterenol-induced cardiotoxicity in wistar albino rats. Pharmacogn Mag. 2022;18(77).
https://doi.org/10.4103/pm.pm_500_20.
28. Song H, Hou X, Zeng M, Chen X, Chen X, Yang T, et al. Traditional Chinese Medicine Li-Zhong-Tang accelerates the healing of indomethacin-induced gastric ulcers in rats by affecting TLR-2/MyD88 signaling pathway. J Ethnopharmacol. 2020;259:112979.
https://doi.org/10.1016/j.jep.2020.112979.
29. Antonisamy P, Arasu MV, Dhanasekaran M, Choi KC, Aravinthan A, Kim NS, et al. Protective effects of trigonelline against indomethacin-induced gastric ulcer in rats and potential underlying mechanisms. Food Funct. 2016;7(1):398-408.
https://doi.org/10.1039/C5FO00403A,
30. Maity P, Bindu S, Dey S, Goyal M, Alam A, Pal C, et al. Indomethacin, a non-steroidal anti-inflammatory drug, develops gastropathy by inducing reactive oxygen species-mediated mitochondrial pathology and associated apoptosis in gastric mucosa: a novel role of mitochondrial aconitase oxidation. J Biol Chem. 2009;284(5):3058-68.
https://doi.org/10.1074/jbc.M805329200.

31. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020;180:114147. https://doi.org/10.1016/j.bcp.2020.114147.
32. Lichtenberger LM, Zhou Y, Dial EJ, Raphael RM. NSAID injury to the gastrointestinal tract: evidence that NSAIDs interact with phospholipids to weaken the hydrophobic surface barrier and induce the formation of unstable pores in membranes. J Pharm Pharmacol. 2006;58(11):1421-8. https://doi.org/10.1211/jpp.58.10.0001.
33. Bindu S, Mazumder S, Dey S, Pal C, Goyal M, Alam A, et al. Nonsteroidal anti-inflammatory drug induces proinflammatory damage in gastric mucosa through NF-κB activation and neutrophil infiltration: Anti-inflammatory role of heme oxygenase-1 against nonsteroidal anti-inflammatory drug. Free Radic Biol Med. 2013;65:456-67. https://doi.org/10.1016/j.freeradbiomed.2013.07.027
34. Abdel-Tawab MS, Tork OM, Mostafa-Hedeab G, Hassan ME, Elberry DA. Protective effects of quercetin and melatonin on indomethacin induced gastric ulcers in rats. Reports Biochem Mol Biol. 2020;9(3):278. https://doi.org/10.29252/rbmb.9.3.278.
35. Konturek SJ, Konturek PC, Brzozowski T. Melatonin in gastroprotection against stress-induced acute gastric lesions and in healing of chronic gastric ulcers. J Physiol Pharmacol. 2006;57:51. https://pubmed.ncbi.nlm.nih.gov/17233075.
36. Celinski K, Konturek SJ, Konturek PC, Brzozowski T, Cichoz-Lach H, Slomka M, et al. Melatonin or l-tryptophan accelerates healing of gastroduodenal ulcers in patients treated with omeprazole. J Pineal Res. 2011;50(4):389-94. https://doi.org/10.1111/j.1600-079X.2011.00855.x.
37. Pal PK, Chattopadhyay A, Bandyopadhyay D. Functional interplay of melatonin in the bile duct and gastrointestinal tract to mitigate disease development: An overview. Melatonin Res. 2021;4(1):118-40. https://doi.org/10.32794/mr11250086.

How to Cite this Article:
Muayad HA, AlQadhi HI. The effects of melatonin on IL-1β and MDA levels in Indomethacin induced gastric ulcer in rat model. J Fac Med Baghdad. 2025;67(1). Available from:
https://iqjmc.uobaghdad.edu.iq/index.php/19JFacMedBaghdad36/article/view/2467

تأثيرات الميلاتونين على مستويات IL-1β و MDA في قرحة المعدة الناجمة عن الإندوميتاسين في نموذج الجرذان

هلا مؤيد[1]، هدى القاضي[1]
[1] فرع علم الأدوية، كلية الطب، جامعة بغداد، بغداد، العراق.

الخلاصة
الخلفية: قرحة المعدة هي اضطراب معدي معوي منتشر ناتج عن عوامل بيئية وخيارات نمط الحياة. وتناول كميات كبيرة من مضادات الالتهاب غير الستيرويدية.
الهدف: دراسة التأثيرات الوقائية للميلاتونين على أنسجة وشدة قرحة المعدة ومستويات علامات الإلتهاب والإجهاد التأكسدي (IL-1β) و(MDA) في نموذج الجرذان المصابة بقرحة المعدة بسبب الإندوميتاسين.
المنهجية: أجريت هذه الدراسة في مركز أبحاث السرطان والوراثة الطبية بجامعة المستنصرية من نوفمبر 2023 إلى مايو 2024. تم استخدام خمسين فأرًا ذكرًا سليمًا من الفئران البيضاء يتراوح وزنهم بين 150 - 250 جرامًا. بعد 24 ساعة من الصيام، تم تقسيم هذه الفئران إلى (5) مجموعات تحتوي كل منها على (10) فئران. المجموعة أ: تلقت 1 مل من مركب الإندوميثاسين (كاربوكسي ميثيل سلولوز 1٪) عن طريق الفم (مجموعة تحكم سلبية). المجموعة ب: تلقت 60 مجم / كجم من الإندوميثاسين عن طريق الفم (مجموعة تحكم إيجابية). المجموعة ج: تلقت 20 مجم / كجم من أوميبرازول عن طريق الفم قبل 30 دقيقة من تحريض الإندوميثاسين. المجموعة د: تلقت 20 مجم / كجم من محلول الميلاتونين عن طريق الفم قبل 30 دقيقة من تحريض الإندوميثاسين. المجموعة هـ: تلقت 30 مجم / كجم من محلول بيوجليتازون عن طريق الفم. بعد ساعة واحدة، تم إعطاء الفئران محلول الميلاتونين بجرعة 20 ملغ / كجم وانتظرت لمدة 30 دقيقة قبل التحريض.
النتائج: أظهرت المجموعة التي تلقت العلاج المسبق بالميلاتونين بجرعة 20 مجم/كجم انخفاضاً ملحوظاً إحصائياً في شدة قرحة المعدة ودرجة التلف النسيجي. كما أدى إعطاء الميلاتونين بجرعة 20 ملجم/كجم للمجموعة المعالجة مسبقًا إلى خفض مستويات علامات الإلتهاب والإجهاد التأكسدي (IL-1β)و (MDA) بشكل مماثل لما لوحظ مع الدواء المرجعي.
الاستنتاجات: يعمل الميلاتونين بمفرده أو مزيج من البيوجليتازون والميلاتونين بشكل فعال على تقليل إصابة الغشاء المخاطي في المعدة والإجهاد التأكسدي ومستويات السيتوكينات المؤيدة للالتهابات، بشكل مماثل لأدوية أوميبرازول القياسية.
الكلمات المفتاحية: الإندوميثاسين؛ الميلاتونين، الجرذان؛ قرحة المعدة.