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Evaluation of The Gastroprotective Effect of Pantoprazole and The Therapeutic Role of Ginkgo Biloba in Indomethacin induced Gastric Ulcer in Albino Rat

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Abstract

Background: Gastric ulcers represent as a significant gastro-intestinal issue worldwide, Gastric mucosal damage could be triggered , by direct or indirect, through Reactive oxygen species production and cytokines.

Objective: for evaluation the gastroprotective action of pantoprazole and Therapeutic activity of Ginkgo biloba against indomethacin induces gastric ulcer.

Method: 32 albino rats were utilized for this research that divided in 4 groups as following, control group, induction group, Ginkgo biloba group which pretreated by indomethacin than treated by Ginkgo biloba , pantoprazole group, all drugs were administrated daily. Blood collection were obtained from retro-orbital veins for Tumor necrosis factor- alpha(TNF-α), Interleukin-6 (IL-6), Malondialdehyde (MDA), Total anti oxidant status(TAOS), after animals sacrifice, stomach excised for macroscopic and microscopic investigations.

Results: induction group showed elevation in TNF-α, IL-6, MDA and decreasing in TAOS levels, in contrast to the remaining groups which exerts reduction in TNF-α, IL-6, MDA with maintaining TAOS levels, The gross evaluation of gastric tissue showed remarkable protection of stomach.

Conclusion: Ginkgo biloba has therapeutic activity against indomethacin induce gastric ulcer, Ginkgo biloba exerts this action due to antioxidant and anti-inflammatory properties, also pantoprazole has protective action against indomethacin induced gastric ulcer ,the action of pantoprazole exerts as result of acid secretion inhibitor which act as primary activity of drug , also has anti-oxidant and anti-inflammatory action.

تقييم التأثير الوقائي للمعدة لدواء البانتوبرازول (Pantoprazole) والتأثير العلاجي لعشبة الجنكو (Ginkgo) لقرحة معدة الجرذان البيضاء المستحدثة بعقار الأندوميثاسين

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الخلاصة:
تعد القرحة من المشاكل الهضمية الأكثر انتشارا وتميزا على مستوى العالم. يمكن أن يحدث تلف الغشاء المخاطي للمعدة بشكل مباشر أو غير مباشر من خلال إنتاج أنواع الأكسجين التفاعلية والسيتوكينات. الهدف من هذا البحث تقييم التأثير الوقائي المعدي لدواء البانتوبرازول والنشاط العلاجي لنبات الجنكو بيلوبا (Ginkgo biloba) ضد قرحة المعدة المستحدثة بالإندوميثاسين . اثنان و ثلاثون من الجرذان البيضاء استخدمت في هذه الدراسة، وقسمت إلى 4 مجموعات كالآتي مجموعة السيطرة (Control)، ومجموعة الاستحداث (Induction)، ومجموعة الجنكو بيلوبا (بالإندوميثاسين ثم بالجنكو بيلوبا)، ومجموعة البانتوبرازول. أعطيت جميع الأدوية يوميا. تم جمع عينات الدم من الأوردة خلف المدار لقياس مستويات (TNF-α و IL-6 و MDA و TAOS). بعد قتل الحيوانات حسب ارشاد الاخلاقيات الموصى بها تم استئصال المعدة لإجراء الفحوصات العيانية والمجهرية. أظهرت النتائج أن مجموعة الاستحداث ارتفاعا في مستويات (TNF-α و IL-6 و MDA) وانخفاضا في مستوى (TAOS)، وذلك على النقيض من المجموعات الأخرى التي أظهرت انخفاضا في (TNF-α و IL-6 و MDA) مع الحفاظ على مستويات (TAOS). كما أظهر التقييم العياني لأنسجة المعدة حماية ملحوظة للمعدة. لقد تم استنتاج من هذه الدراسة أن نبات الجنكو بيلوبا تمتلك نشاطا علاجيا ضد قرحة المعدة المستحدثة بالإندوميثاسين، وذلك بفضل خصائصها المضادة للأكسدة والالتهابات. كما أن للبانتوبرازول له تأثيرا وقائيا ضد قرحة المعدة المستحدثة بالإندوميثاسين، ويعود تأثيره إلى تثبيطه لإفراز الحمض (وهو نشاطه الأساسي)، بالإضافة إلى امتلاكه خصائص مضادة للالتهابات والأكسدة.

الكلمات المفتاحية: مثبط الحمض، كاسح الجذور الحرة، التفاعل الالتهابي، الإجهاد التأكسدي.

INTRODUCTION

Gastric ulcer act as a multi-factorial disorder which result from imbalance between the protective factors such as nitric oxide, mucin, prostaglandins, the blood flow of mucosa, and the ability of epithelial regeneration and the aggressive agents such as smoking, non-steroidal anti -inflammatory drugs (NSAIDs), consumption of alcohol, releasing of pepsin, bile salts, gastric acid, and H. pylori infection [(1)]. The pharmacological management of gastric ulcer involves antacids, muscarinic receptor antagonists, proton pumps inhibitors, histamine (H2) receptor antagonists. These drugs have certainly decreased the frequency of gastric ulcer; however, they have a high risk of recurrence, drug-interactions, and adverse effects [(2)]. It has been demonstrated that 43% of people commonly administrated NSAIDs, and almost 30% of those persons subjects has gastric disorders [(3)]. Indomethacin is one of the classical NSAIDs that is used commonly in the management of inflammatory conditions. The pathogenicity of indomethacin in inducing ulcer are arising secretion of gastric acid, reducing level of ProstaglandineE2 [(4)]. Oxidative stress trigger, inflammation and apoptosis in gastric tissue, resulting in gastric ulcer Therefore, several studies have established indomethacin for inducing gastric ulcer in rats as a standard model of gastric ulcer in humans [(5,6)] .

Proton pumps inhibitors have a powerful healing action on gastric ulcer which exert their action through inhibition of gastric acid secretion by hindering the proton pump H + K + ATPase in the parietal cells of stomach [(7)]. Natural products and their medically active ingredients are extensively researched and investigated as possibly successful therapies for a several disorders [(8,9)]. These products are being utilized to offer gastroprotection in a multiple of situation, notably the prevention of chronic progressive gastric disorders and acute gastric ulcers[(10)]. Ginkgo biloba (G.biloba) is an herbal Chinese medication which contain several active ingredients in its composition that exerts multiple beneficial efficacy, Ginkgo biloba is a member of the botanical family: Ginkgoaceae . flavonoids and terpenoids are active chemical ingredients present in G. biloba leaves that exerts pharmacological action against bacteria, inflammation, allergic reaction and cytotoxicity [(11)]. Standardized preparation of ginkgo leaf extracts including 5–7 % terpene lactones and 22–27 % flavone glycosides [(12)]. Ginkgo biloba has multiple medication benefit such as management of gastric discomfort, cognitive impairment, inflammation of bronchi, asthma, and other disorders, Modern evaluations have confirmed its effectiveness as a nutritional supplement that may enhance cognitive function, in addition to treatment or prophylactic agent for Alzheimer's disease and other conditions of nervous system. as more as, Ginkgo biloba has

immune-modulating activity, inflammation suppression effect, neuroprotectant activity and scavenger of free radicals therefore act as therapeutic agent for cardiovascular disorders [11,13]. The purpose of current study is to investigate the Gastro-protective of pantoprazole and evaluated the therapeutic action of G. biloba , this will confer knowledge about the role of anti-oxidant and anti-inflammatory efficacy of present herbal compound and traditional medication that has been utilized in ulcer management.

MATERIAL AND METHOD

Experimental Animals

32 male Wistar albino rats that their weight ranged between (150-220 g) obtained from the animal house at the college of Veterinary, University of Tikrit (Iraq) which had been used in this experiment. The Rat s was housed in a clean, sterile, metallic cage and providing normal amount of water and rat chow; the animal room was well ventilated with a 12-hour(light-dark cycle) at room temperature and 45-50%humidity. All animals adapted for 2 weeks before processing in experiment . On day of experiment body weight of rat had been measured. The experimental procedures were reviewed and approved by the Pharmaceutical Research Ethics Committee (PREC),College of Pharmacy, University of Mosul, all animal procedures were performed according to international accepted guidelines for the care and using of laboratory animals, The Reference Code: PREC-25-1-15.

Experimental Study Design

32 rats have been sub divided into four groups (8 rats per each group) rats were allocated to the experimental groups with consideration of base line body weight to achieve comparable weight :

- **Normal Control group;** rats administrated normal saline for 7 consecutive days orally (p.o)
- **Indomethacin group;** after adaptation gastric ulcer had been induced by administration of single dose of indomethacin drugs (30mg /kg, p.o). for inducing ulcer animals starved for 24 h .
- **Indomethacin group+ Ginkgo biloba (therapeutic);** after adaptation for 2 weeks , in first day of experiment , rats are pretreated with single dose of indomethacin (30mg/kg/ p.o) , in day 2 of experiment after ulcer induction ,rats treated by G. biloba (100mg\kg\p.o) for 7 consecutive days to evaluate its therapeutic effect.
- **Pantoprazole + indomethacin group (prophylaxis);** in first day of experiment, rats pretreated with pantoprazole (10mg/kg/i.p) for 7 consecutive days , in day 8 day of experiment animals administrated single dose of indomethacin (30mg\kg) to evaluate its prophylactic effect.

Preparation of Medications

Indomethacin: Each indomethacin capsule contained 25 mg of the active drug. The contents of one capsule were dispersed in 2 mL of distilled water to prepare a fresh suspension immediately before administration. The resulting suspension contained 12.5 mg/mL. indomethacin was administered orally at a dose of 30 mg/kg body weight. The required administration volume for each rat was calculated individually according to its body weight based on the concentration of the prepared suspension.

Ginkgo biloba: Each tablet of Ginkgo contains 120mg of drug. The tablet were dispersed in 10 mL of distilled water to prepare a fresh suspension immediately before administration. Ginkgo biloba was administered orally at a dose of 100 mg/kg body weight. The required administration volume for each rat was calculated individually according to its body weight based on the concentration of the prepared suspension.

Pantoprazole: Pantoprazole injection (40 mg/vial) was reconstituted with 10 mL of distilled water to obtain a final concentration of 4 mg/mL. The solution was freshly prepared immediately before administration. Pantoprazole was administered orally at a dose of 10 mg/kg body weight. The administration volume for each rat was calculated individually according to its body weight based on the concentration of the prepared solution.

Blood collection and Euthanasia

At experiment end, rat subject to anesthesia for blood sample collection from retro-orbital venous plexus of rats by utilizing capillary test tubes for analysis, then Samples were handled by centrifugation at 3000 rpm for 15 minutes for serum analyze; The obtained serum is preserved at –20 $^{\circ}C$ up to used. then animals were killed by cervical dislocation, the stomachs were excised from body of rat, longitudinally incision was made along the greater curvature of stomach and then cleaned gently with normal saline. Stomach placed on white corkboard and gastric lesion investigated microscopically , finally gastric samples maintained in 10% neutral buffered formalin for further histopathological examination. Histopathological evaluation and biochemical assays were performed by experienced specialists who were blinded to the experimental group allocation.

Biochemical Tests

All Following bio-chemical tests were determined by using a commercial ELISA kit (SunLong Biotech Co., Ltd., China) according to the instructions of Manufacture , the concentration could be calculated.

Table (1): Bio-chemical commercial ELISA kit.

Kit Name	Intra-Assay	Inter-Assay	Sensitivity
Tumor Necrosis Factor – alpha (TNF-α)	CV<10%	CV<12%	2.8ng\L
Interleukin-6(IL-6)	CV<10%	CV<12%	1.5ng/L
Malondialdehyde (MDA)	CV<10%	CV<12%	1.2ng\ml
Rat Total antioxidant status (TAOS)	CV<10%	CV<12%	0.01U\ml

Statistical analysis

Results were expressed as mean ± standard deviation of mean by using one-way ANOVA and Tukey HSD tests. The p value < 0.05 values were regarded as statistically significant. Analysis of Statistical was done by using IBM SPSS Statistics (Windows, Version 22.0 IBM Corp., Armonk, NY, USA). A Total of 32 rats were initially included in the study and randomly allocated into 4 groups (n = 8 per group). During tissue processing, one sample from each group was excluded from the statistical analysis. Consequently, statistical analyses were performed using seven samples per group (n = 7).

RESULTS

The inflammatory cytokine TNF-α and IL-6 and lipid peroxidation MDA serum level shown high serum level in indomethacin group in comparison with the normal control group ($p < 0.01$) (Tables 2,3,4 and 5).

The ginkgo biloba and pantoprazole groups exhibited a reduction in inflammatory markers TNF-α, IL-6 and lipid peroxidation MDA serum level in comparison with the indomethacin induction group ($p < 0.05$). MDA serum levels between pantoprazole group and G. biloba in a comparison with control group ($P > 0.05$).

The induction group showed considerable reduction in the serum levels of TAOS in comparison with the normal control group ($p < 0.01$), while Ginkgo biloba and pantoprazole demonstrated considerable elevated serum levels of TAOS in comparison with the indomethacin induction group ($p < 0.05$).

However, there were no substantial differences in TAOS serum levels between pantoprazole group and G. biloba in a comparison with control group ($P > 0.05$).

Histological Investigations

The outcomes demonstrated an observable induction of gastric ulcer (G.U) with significantly macroscopic changing in tissue sections of stomach in indomethacin group (B) in comparison with the control group (A).

However, both the ginkgo biloba (C) pantoprazole (D) groups showed fewer macroscopic changing of stomach than the induction group, resulting in a more lower degree of severity and extent of the experimentally generated ulcer, as shown in Figure1. The Histological section in the rat gastric wall of group A show normal architecture of gastric wall, mucosa, submucosa, tunica muscularis, (arrows) gastric pit. H&E stain, 100x as shown in figure 2A.

In contrast, the rat gastric mucosa of group B shows necrotic lesions in the gastric mucosa infiltration of inflammatory cells, and congested blood vessels. H&E stain, 100x as shown in figure 2B.

Additionally, light microscopic investigation of tissue of rats pretreated with Indomethacin for inducing ulcer , and then treated by Ginkgo biloba 100mg\kg for seven days shows mild necrotic lesions in the gastric mucosa, infiltration of inflammatory cells, regeneration of gastric epithelium, granulation tissue in lamina propria. H&E stain, 100x. as shown in figure 2C.

Finally, Histological investigation in the mucosa of rat stomach rats pretreated with pantoprazole (10mg/kg) for seven days and then treated with indomethacin (30mg/kg) shows normal architecture of gastric mucosa with mild vacuolar degeneration (arrows) in the cells of gastric glands, intact gastric pits and surface epithelium. H&E stain, 100x. as shown in figure 2D.

Table (2): Values of MDA.

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Control	7	25.03	3.4	1.3	21.8	28.2
Indomethacin	7	46.67	6.3	2.4	40.7	52.5
Ginkgo biloba	7	30.30	7.0	2.6	23.7	36.8
Pantoprazole	7	27.71	2.8	1.0	25.1	30.3
Total	28	32.43	9.9	1.8	28.5	36.2
MDA		**Df**		**Mean Square**	**F**	**Sig.**
Between Groups		3		663.850	23.932	**.000**
Within Groups		24		27.739		
Total		27				

Table (3): Values of TAOS.

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Control	7	.89	.10	.03	.80	.98
Indomethacin	7	.37	.09	.03	.28	.46
Ginkgo biloba	7	.78	.16	.06	.63	.92
Pantoprazole	7	.82	.17	.06	.66	.98
Total	28	.71	.24	.04	.62	.81
TAOS			**Df**	**Mean Square**	**F**	**Sig.**
Between Groups			3	.379	20.317	**.000**
Within Groups			24	.019		
Total			27			

Table (4): Values of TNF-α.

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Control	7	22.77	5.55	2.09	17.63	27.90
Indomethacin	7	41.54	5.56	2.10	36.39	46.69
Ginkgo biloba	7	27.56	5.65	2.13	22.33	32.79
Pantoprazole	7	23.39	5.93	2.24	17.90	28.87
Total	28	28.82	9.39	1.77	25.17	32.46
TNF-α		**Df**		**Mean Square**	**F**	**Sig.**
Between Groups		3		535.7	16.6	**.000**
Within Groups		24		32.2		
Total		27				

Table (5): Values of IL-6.

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Control	7	5.33	1.33	.50	4.10	6.57
Indomethacin	7	12.26	1.76	.66	10.62	13.89
Ginkgo biloba	7	6.82	1.26	.47	5.65	7.99
Pantoprazole	7	5.59	1.164	.44	4.52	6.67
Total	28	7.50	3.14	.59	6.28	8.72
IL-6		**Df**		**Mean Square**	**F**	**Sig.**
Between Groups		3		73.267	37.295	**.000**
Within Groups		24		1.965		
Total		27				

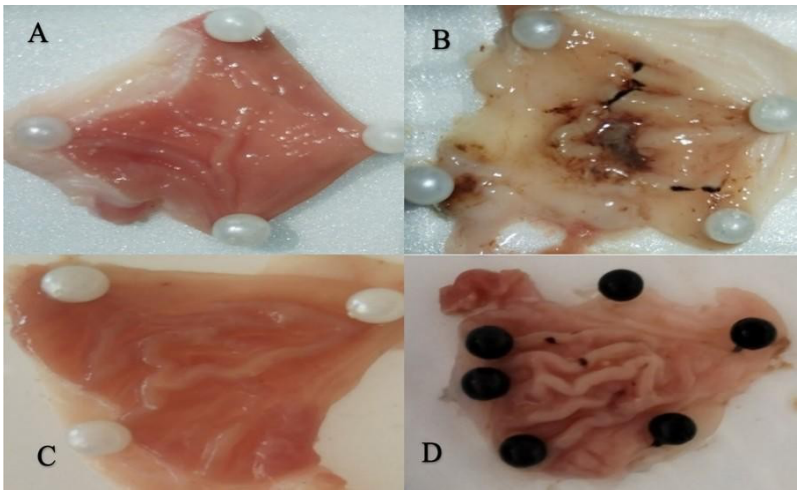

Figure (1): Macroscopic evaluation that demonstrated alteration in gastric of different research group: A= control group, B= indomethacin group, C= Ginkgo biloba group, D=Pantoprazole group.

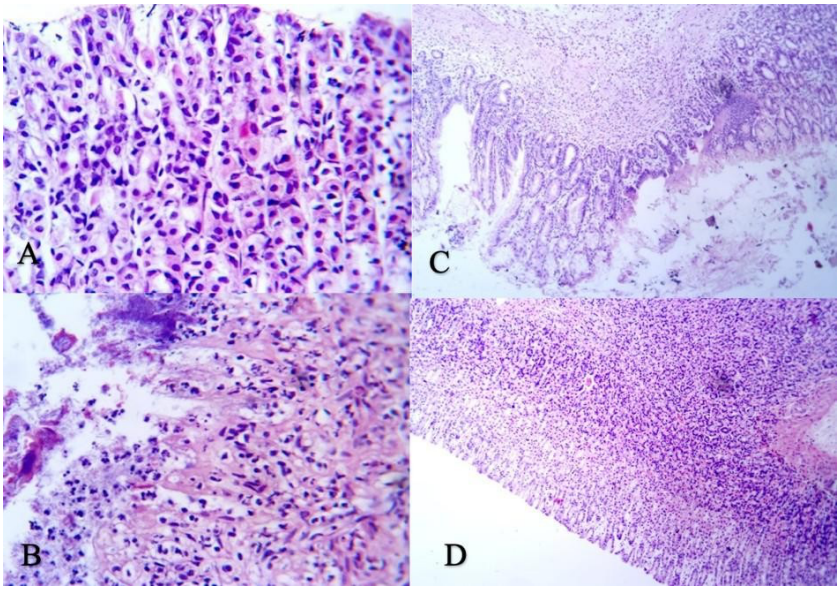

Figure (2): Histopathological Evaluation of different groups of rats. A = control group, B = Indomethacin group, C =Ginkgo biloba group (therapeutic), D=pantoprazole group (prophylaxis).

DISCUSSION

Gastric ulcers represent as a significant gastro-intestinal issue worldwide. The reason for preferred indomethacin for inducing ulcer in experimental setting than other members of NSAIDs due to the indomethacin drug exerts a greater ulcerogenic activity than other , Gastric mucosal damage could be triggered by direct or indirect, through ROS production and cytokines [14].

Dosage of 30 mg/kg was used for induction ulcers, our study was aligned with previous research such as Mugo N et al (2020), who also applied a dose of 30 mg/kg of indomethacin for induction gastric ulcers in Wistar rats [15] . According to Abdel-Tawab M et. al's study in 2020, Indomethacin group showed a significant elevation in ulcer index, volume of gastric acid, and serum levels of stress, inflammatory, and apoptotic markers in comparison with control group [16].

The current research demonstrated that administration of indomethacin to fasting rats exert ulcers that could be detected through macroscopical investigation and microscopically, the macroscopical evaluation observed as circular and linear hemorrhagic lesion while microscopic evaluation demonstrated that group treated with indomethacin shows necrotic lesion in the mucosa of stomach ,infiltration of inflammatory cell, hemorrhage. Also, indomethacin cause increase in MDA levels which reflect mucosal damage , while both pantoprazole and G. biloba were greatly reduced MDA level**.** Indomethacin exerts high inflammation grade in the mucosa of stomach, which expressed by the significant increase in mucosa of inflammatory cell infiltration in stomach, which exerts elevation in TNF-α and IL-6 levels, in comparison with control rats.

Previous research was aligned with current study, Macroscopic investigation demonstrated that indomethacin cause hemorrhagic lesions in the long bands form in mucosa of stomach , pinpoint lesions with ulcerative inflammation, degeneration of stomach and necrosis, death of epithelial cell with localize or multiple hemorrhagic ulcers. This may be attributed to the high expression of various inflammatory cytokines and chemokines that are chemotactic to leukocytes and other inflammatory process cells as well as oxidative stress induction. The increased gastric ulcer index observed in indomethacin-induced rats confirmed the strong ulcerogenic activity of indomethacin, consistent with previous studies [17–20].

Additionally ,the histological investigation from previous research which provide additional support for our results. The histological evaluation of ulcerated rats gastric tissue demonstrated gastric mucosal erosion with bleeding lesions that extending into deep layer of mucosa. As more as, pathological indicators, such as extensive edema and infiltration of leukocyte in the layer of submucosa were observed in the induction group [21].

The extract and pantoprazole inhibit infiltration of inflammatory cell in stomach and caused a remarkable reduce in mucosal Tumor necrosis Factor-α and interleukin-6 level, indicating an anti-inflammatory role of Ginkgo biloba and pantoprazole. The current research medications (Ginkgo biloba and pantoprazole) reduced the inflammatory marker and exert results as close as result of control groups.

Ginkgo biloba activity against gastric ulcer was related to the capacity of Ginkgo biloba to resist inflammatory and oxidative stress. In our study the antioxidant activity of ginkgo biloba demonstrated by reduction in lipid peroxidation marker (MDA) of gastric tissue, and maintenance in TAOS level. The main factors that contributed to the role of Ginkgo biloba as gastroprotective agent in the present study are antioxidants activity by scavenging free radicals. G. biloba product is rich in flavonoids and terpenoid, that has antioxidant features; it effectively exerts free radicals scavenging activity, decreases lipid peroxidation, and protects the gastric mucosa from oxidative injury. Ginkgo biloba exerts anti-inflammatory action by reduction the level of TNF-α and IL-6, the current results were aligned with previous research[22].

As more as previous studies reported that pre-treatment with extract Ginkgo biloba 761 decrease the MDA gastric level and serum level of C-reactive protein in rats that treated by indomethacin. Both flavonoid and ginkgolide ingredients are contributed to the anti-oxidant and free radical scavenging capabilities of extract Ginkgo biloba 761, which decrease tissue reactive oxygen species levels and prevent lipid membrane peroxidation [23,24].

According to previous research , ginkgolides ingredients of ginkgo biloba leaves show anti-inflammatory action via suppression of interleukin-6 and tumor necrosis factor –alpha formation by inhibition the gene expression of NF-κB [25].

However, treatment with Ginkgo biloba extract and pantoprazole exerts low damage of mucosa in comparison with induction group.

Several studies have demonstrated that PPIs could prevent gastric mucosal damage by other mechanisms over the action of its specific acid inhibition [26]. However, suppression of gastric acid increases the susceptibility to enteric infections and alters gastritis distribution in H. pylori infected individuals. Favoring the predominant gastritis development with gastric atrophy, these pathological changes are known as the risk factors for gastric adenocarcinoma and intestinal metaplasia. In addition, decreasing gastric acid negatively affects the intestinal calcium absorption and vitamin B12, thereby increasing the risk of bone fracture and anemia [27].

CONCLUSION

Indomethacin is a member of NSAIDs which has ability for inducing ulcer , the herbal extract (G. biloba) has therapeutic activity and improving action on gastric mucosa due to antioxidant and anti-inflammatory properties. Pantoprazole has prophylactic action in gastric ulcer that induced by indomethacin gastric ulcer. This activity occurred as result of gastric acid secretion inhibition which act as a main activity of drug ,additionally has anti -inflammatory and antioxidant action.

LIMITATION

This study has certain limitation. One limitation of this study is that Ginkgo biloba was evaluated as a therapeutic intervention after indomethacin-induced gastric ulcer, whereas pantoprazole was evaluated as a prophylactic intervention before ulcer induction. Therefore, the two interventions were assessed under different experimental conditions and dosing schedules, and direct head-to-head comparisons should be interpreted with caution. Future studies using identical treatment timing and comparable dosing regimens are warranted to enable direct comparisons . A priori power analysis was not performed before the study. The sample size was determined based on animal availability and resource constraints. This is acknowledged as a limitation of the study.

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CONFLICT OF INTEREST

The authors declare there is no Conflict of Interest

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