

Evaluation of effects of white vinegar- induced gastric mucosal ulceration in rats

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Abstract:

This study was aimed to investigate the effects of white vinegar (WV) induced gastric mucosal ulceration in rats. Thirty rats were divided into three groups, group (1) was given distilled water as control group, group (2) was given WV with a dose [1 ml/kg (5%)] and group (3) was given WV with a dose [1 ml/kg (10%)] for 14 days. Results presented a significant decrease in the body weights and pH value of the gastric juice whereas, a significant increase occurred in gastric acid volume levels, total acidity, ulcer index and an ulcer score of stomach. Measurement of ulcer area of stomach showed, sever haemorrhagic areas covered with coagulated blood in group (3) while, group (2) showed, some spot ulcer and slight of haemorrhagic streaks compared with normal control group. The results of this study reveal that white vinegar has an effect on gastric mucosa from injury and ulcers in rats.

Key Words: White Vinegar, Gastric Mucosal, Ulcer, Rats.

تقييم آثار تقرح الغشاء المخاطي المعدي الناجم عن الخل الأبيض في الجرذان
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الملخص :

تهدف هذه الدراسة إلى تقييم تقرح الغشاء المخاطي المعدي الناجم عن الخل الأبيض في الجرذان. تم تقسيم ثلاثين جرذاً إلى ثلاث مجموعات ، المجموعة (1) أعطيت ماء مقطر كمجموعة ضابطة، المجموعة (2) أعطيت الخل الأبيض بجرعة [1 مل/كغ(5%)] والمجموعة (3) أعطيت الخل الأبيض بجرعة [1 مل/كغ(10%)] لمدة 14 يوماً. أظهرت النتائج انخفاضاً معنوياً في أوزان الجسم وقيمة الرقم الهيدروجيني لعصير المعدة بينما حدثت زيادة معنوية في مستويات حجم حامض المعدة والحموضة الكلية ومؤشر القرحة ودرجة تقرح المعدة. أظهر قياس منطقة القرحة بالمعدة وجود مناطق نزفية شديدة مغطاة بالدم المتخثر في المجموعة (3) بينما أظهرت المجموعة (2) وجود بعض القرحة الموضعية وظهور خطوط نزفية طفيفة مقارنة بالمجموعة الضابطة. أظهرت نتائج هذه الدراسة أن الخل الأبيض له تأثير على الغشاء المخاطي في المعدة وحدوث تقرحات في الجرذان.

الكلمات المفتاحية: خل أبيض، مخاطية معدية، قرحة، جرذان.

Introduction:

Gastric ulceration and the associated acute inflammation are caused by an imbalance between aggressive factors and protective mechanisms in the stomach [1], [2]. Furthermore, ulceration is an imbalance between the rate of secretion of gastric juice and the degree of protection afforded by the gastroduodenal mucosal barrier as well as the neutralization of the gastric acid by duodenal juice. Infection by the bacterial pathogen *Helicobacter pylori*, frequent usage of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), and high acid secretion are the main reasons for the induction of ulcers [3]. On the other hand, the gastric mucosal barrier is a complex and dynamic system that includes epithelial, immune, and vascular elements [4]. The functional integrity of the gastric mucosa and its secretory gland units are maintained in part by the constant renewal of the epithelium [5]. An imbalance of cell proliferation and apoptosis is implicated in the pathogenesis of gastric mucosal ulceration [2]. Additionally, epithelial cells located at the mucosal surface can secrete chemoattractant and pro-inflammatory cytokines in response to bacterial infections and inflammation. Cytokines play a vital role in maintaining gastrointestinal mucosal homeostasis. The epithelial cytokine response to pathogenic agents depends on various factors, including the site of infection and the specific pathogen. Thus, the epithelial cells act as early. The ulcer is defined as erosion in the lining of the stomach or duodenum and is caused by the disruption of the gastric mucosal defense systems. An ulcer in the stomach is called a gastric ulcer [3]. Moreover, Ulcer incidence varies with the type of ulcer, gender, and age [6]. A coating of mucus and other biochemical normally shield the duodenum from digesting themselves. When these protective mechanisms are disturbed, powerful digestive acids can erode into the lining of these organs and cause ulcers [3].

White vinegar (WV), the volatile organic acid that identifies the product as white vinegar consists of about 3 to 10% of acetic acid content and is responsible for the tart flavor and pungent, biting odor of kinds of white vinegar [7]. Moreover, the etiology of white vinegar-induced ulcers mimics human gastric and duodenal ulcers in location, chronicity, and severity [8]. WA is absorbed from the gastrointestinal tract and through the lungs and almost completely oxidized by tissues [9]. Additionally, the genesis of WA-induced gastric lesions is

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a multifactorial process that starts mainly with the depletion of gastric wall mucous content. Such depletion is often associated with the significant production of free radicals, causing damage to the cell and cellular membrane due to excessive oxidative stress. The generation of reactive oxygen species, for example, superoxide anion, hydrogen peroxide, and hydroxyl radicals may cause lipid peroxidation, especially in membranes, and results in tissue injury [10]. Local effects of WA ingestion represent corrosive injury to the upper gastrointestinal tract [11]. The WA produces round, deep ulcers in the stomach and duodenum, resembling a great extent human ulcer in terms of both pathological features and healing drugs [12]. The present study was aimed to evaluate of effects of white vinegar-induced gastric mucosal ulceration in rats.

Material and Methods:

Experimental chemicals:

White vinegar (WV) was obtained from the Omar Al-Mokhtar University. Animals were given white vinegar orally by gavage at a dose of 1 ml/kg/b.w./day [13] for 14 days. WV was given to animals in this study at two concentrations:

- Rats were given (5% of WV) according to [14].
- Rats were given (10% of WV) according to [15].

Experimental animals:

Healthy female albino rats (*Rattus norvegicus*) with an average weight of 180-225 g were used. Rats were obtained from the animal house of Zoology Department, Faculty Science, University of Omar Al-Mukhtar, El-Beida, Libya. All rats were allowed 3 weeks pre-experimentation period to acclimatize to laboratory conditions in order to avoid any complications along the course of the experiment. They were housed in cages at room temperature. Rats were fed with laboratory diet and water *ad libitum* with fresh daily supplies. All rats were weighted weekly and the weight were recorded before the experimental procedures and at the end of the experiment.

Experimental design:

A total of 30 female albino rats were used. All rats were abstained from food for 24 hours with given the water ad libitum prior to the experimental procedures then they were randomized into three groups (10 rats in each):

- Normal control group: Rats were given orally distilled water for two weeks
- Treated group: Rats were given orally WV (5%) by gavage at a dose of 1 ml/kg/b. w./day for two weeks.
- Treated group: Rats were given orally WV (10%) by gavage at a dose of 1 ml/kg/b. w./day for two weeks.

After the completion of treatment period, all rats were fasted for 24 hours. Animals were sacrificed then the stomach were removed.

Determination of body weight:

Body weight was evaluated in all animals at the beginning (initial weight) and at the end of the experiment (final weight) by using a sensitive electronic balance.

Percentage change in body weight was calculated using this formula:

$$[(\text{final weight} - \text{initial weight}) / \text{initial weight}] \times 100 [16].$$

Measurement of gastric acid volume:

After dissection, stomachs of the rats were ligated from its two ends; the pylorus and lower esophagus were also ligated and inject with 2 ml distilled water. A small incision were made for each forestomach then the stomach contents were expelled [17], [18]. Gastric contents were collected in tubes and measured. Gastric juice were centrifuged at 3500 r/min for 15 min and the supernatant were used for determine of gastric acid output (volume) and total acidity. Overall, 1 ml of the supernatant liquid were pipetted out and diluted to 10 ml with distilled water. The solution were titrate 0.01N sodium hydroxide (NaOH) using phenolphthalein reagent as an indicator to the endpoint when the solution turned to pink color.

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Measurement of total acidity and pH in gastric fluid:

The volume of NaOH required were denoted to calculate the total acidity. The total acidity and pH of the supernatant were calculated, according [19].

Total acidity were calculated as follow:

Total acidity = [Vol. of NaOH × Normality of NaOH] / Vol. of gastric juice used

The total acidity were expressed as mEq/dl.

The pH of the supernatant and total acidity were measured according to [20], [18] respectively.

$$\text{pH} = - \text{Log} [\text{H}^+].$$

Macroscopic evaluation of an ulcer index and an ulcer score:

All samples of stomach and duodenum were opened along the greater curvature and washed by normal saline then examined by a blinding pathologist for macroscopic lesions in the glandular part under a dissecting microscope (6.5x).

The severity of macroscopic lesions formed were estimated using an ulcer index as previously reporting [21] using the following scale:

- 0 = normal mucosa;
- 1 = hyperemic mucosa up to 3 small patches;
- 2 = 4-10 small patches;
- 3 = more than 10 small or up to 3 medium-sized patches;
- 4 = 4 to 6 medium-sized patches;
- 5 = more than 6 medium-sized or up to 3 large patches;
- 6 = 4-6 large patches;
- 7 = 7-10 large patches;
- 8 = more than 10 large patches; and
- 10 = large patches of extensive necrotic zones.

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Where: A small patch: is defined as an area of lesion up to 2 mm across (maximum diameter), a medium-sized patch: as between 2 and 4 mm across, and a large patch: as more than 4 mm across [22].

Ulcer index will calculate according to the following formula [23].

$$UI = [UN + US + UA] \times 10^{-1}$$

Where: UI = ulcer index, UN = ulcer number, US = ulcer score, and UA= ulcer area.

Evaluation of degree of ulceration will express in terms of ulcer score which is calculating by [24].

$$\text{Ulcer score} = \frac{\text{Total number of ulcers in group}}{\text{Number of rats in group}}$$

Statistical analysis:

Results were expressed as mean \pm standard error. The macroscopic and microscopic lesion scores and other parameters were analyzed using significance by one way ANOVA. Means were separated using Tukey's test at $P < 0.05$. The T test also using for compared between two means. All statistical procedures were performed with the Minitab statistical analysis package program (Minitab version 17).

• Means with different superscript (a, b & c) were significantly different at $P < 0.05$, and means superscripts with the same letters mean that there is no significant difference ($P < 0.05$).

Results:

Determination of the body weights:

Averages of percentage of change in the body weights of rats belonging to the control and experimental groups are given in figure (1). Rats that given WV-5% and WV-10% showed a significant decrease ($P < 0.05$) in percentage of change in the body weights (14.843 ± 0.307) and (14.057 ± 0.545) respectively compared to control rats (21.671 ± 0.462). No significant effects were observed on percentage of change in body weights between WV-5% and WV-10%.

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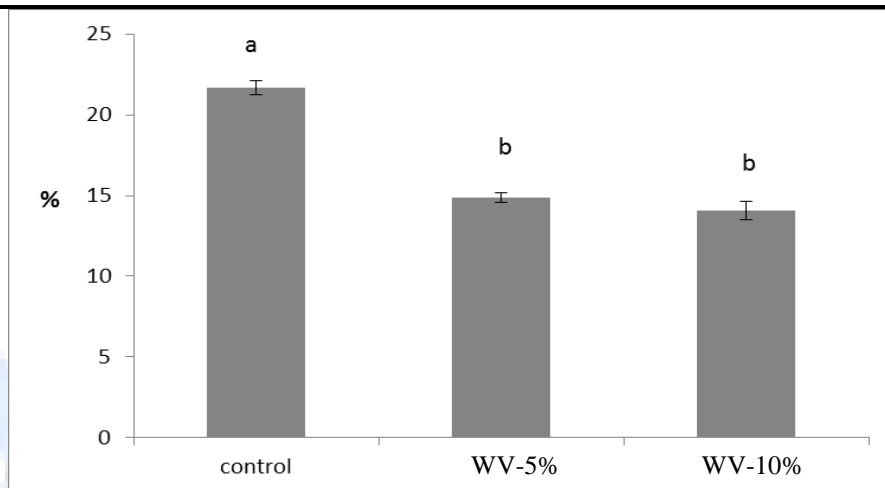


Figure 1: Averages of percentage change in the body weights in control and experimental groups (%).

Evaluation of gastric acid volume:

The mean values of gastric acid volume levels of control and experimental groups were presented in graphically represented by figure (2). A significant increase ($P < 0.05$) occurred in gastric acid volume levels in WV of rats in all treated groups with a mean value of (1.1857 ± 0.0769) in WV-5% groups and (2.100 ± 0.0816) in WV-10% groups as compared to (0.786 ± 0.103) of normal control group. Moreover, WV-10% group showed highly significant ($P < 0.05$) in gastric acid volume levels when compared with other groups.

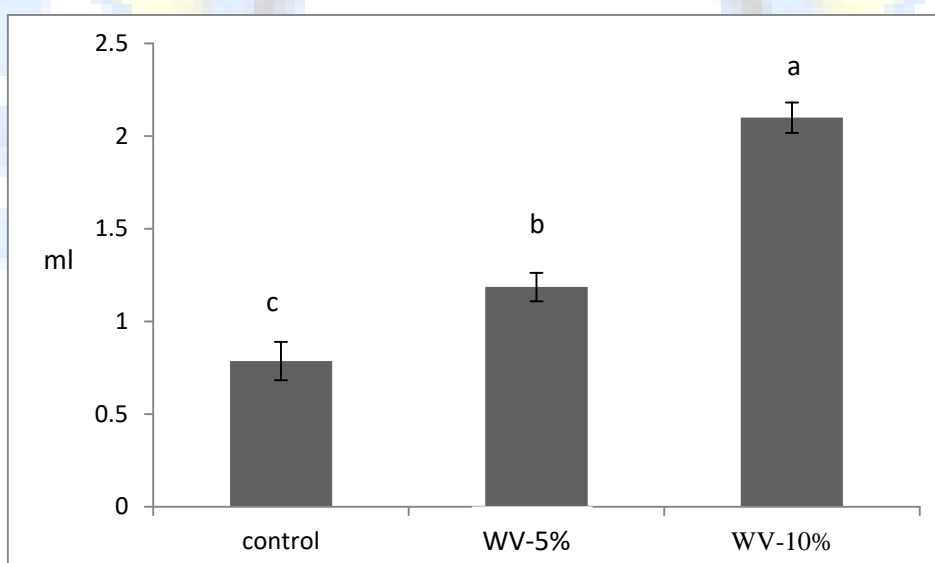


Figure 2: The mean values of gastric acid volume in control and experimental groups (ml).

Evaluation of the total acidity in gastric fluid:

Data recorded for total gastric acid (total acidity) were presented in figure (3), a significant increase ($P < 0.05$) found in WV-5% and WV-10% in total acidity than control group rats. The mean values of WV-5% and WV-10% (17.86 ± 2.57 and 32.86 ± 4.74) respectively as compared to mean values of control groups (5.857 ± 0.404). Furthermore, the data showed highly significant ($P < 0.05$) in total acidity was established in WV-10% group as compared with WV-5% group rats.

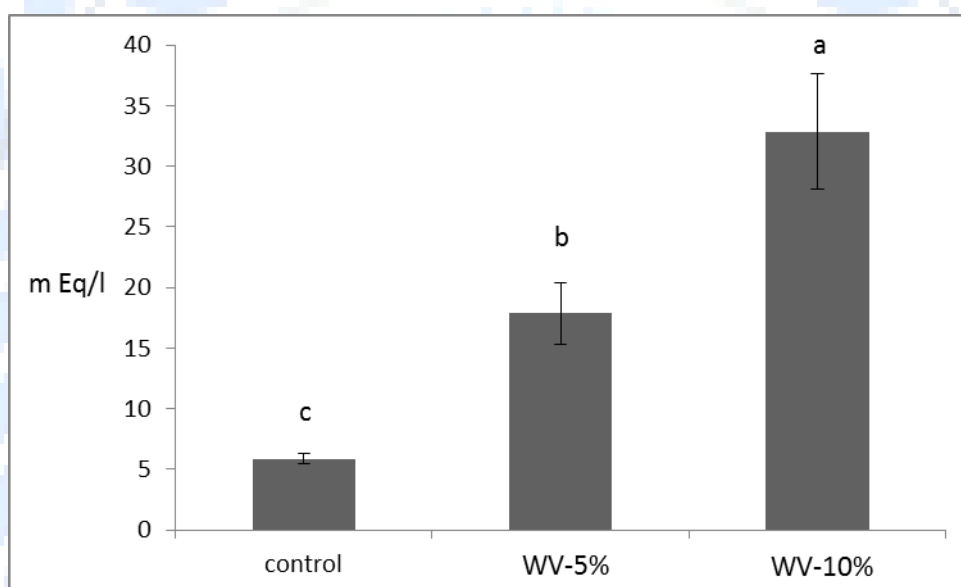


Figure 3: The mean values of the total acidity in control and experimental groups (m Eq/l).

Evaluation of the pH value of the gastric juice:

From the result recorded for pH value of the gastric juice were presented in figure (4). A significant decrease ($P < 0.05$) in the mean pH value occurred in the WV-5% groups (0.3357 ± 0.0500) and WV-10% (0.4843 ± 0.0490) groups as compared to normal control rats (2.071 ± 0.240).

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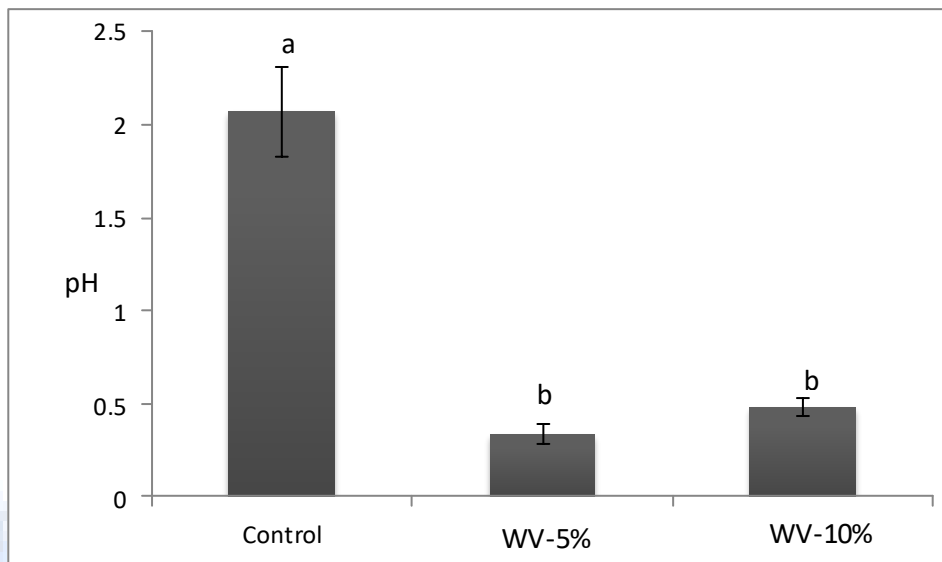


Figure 4: The mean values of pH level in control and experimental groups.

Evaluation of an ulcer index:

No ulcers were detected in the control rats (0.0 ± 0.0). Whereas, significant increase ($P < 0.05$) in an ulcer index of stomach in WV groups with the mean values (3.143 ± 0.265) in WV-5% groups and (4.936 ± 0.221) in WV-10% groups compared to control groups in the data graphically represented by figure (5).

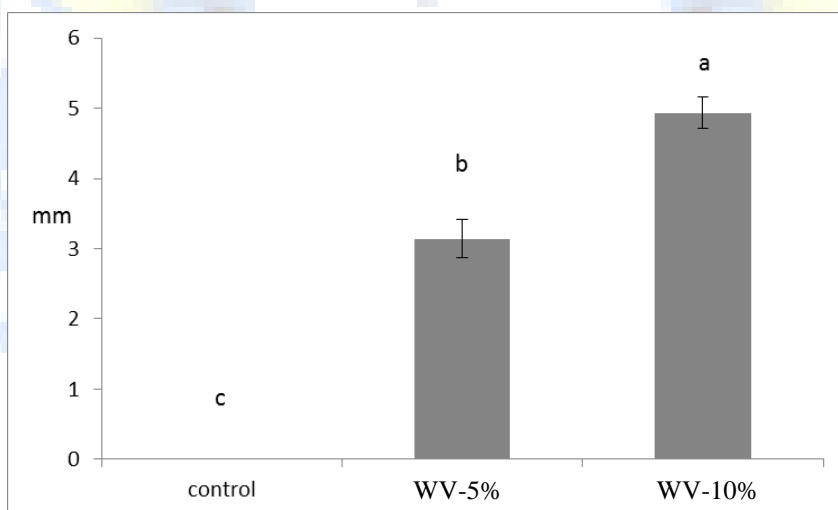


Figure 5: The mean values of ulcer index level in control and experimental groups (mm).

Evaluation of an ulcer score:

On detecting an ulcer score of stomach were presented in figure (6). Rats treated with WV showed a significant increase ($P < 0.05$) in the mean value of WV rats (0.3594 ± 0.0613) in WV-5% rats and (1.864 ± 0.240) in WV-10% rats compared to control rats (0.0 ± 0.0).

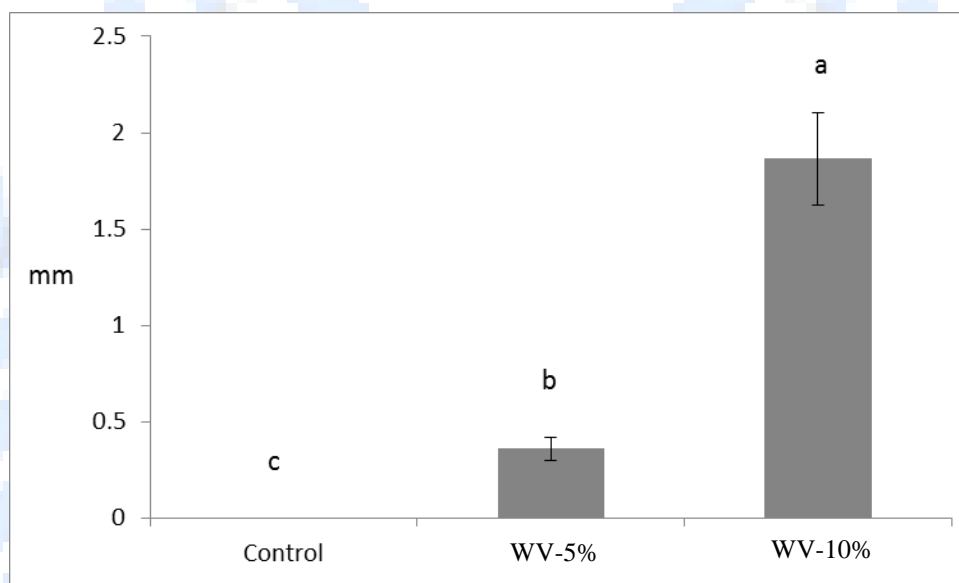


Figure 6: The mean values of ulcer score level in control and experimental groups (mm).

Macroscopic evaluation of the stomach ulcer:

The macroscopic findings of the opened stomach are shown in (Figure7). Sever haemorrhagic gastric ulcers covered with coagulated blood were more apparent in the WV (10%) group than the WV (5%) group, where showed some spot ulcer and slight of haemorrhagic streaks in the dissected stomach of rats compared with normal pattern of control group.

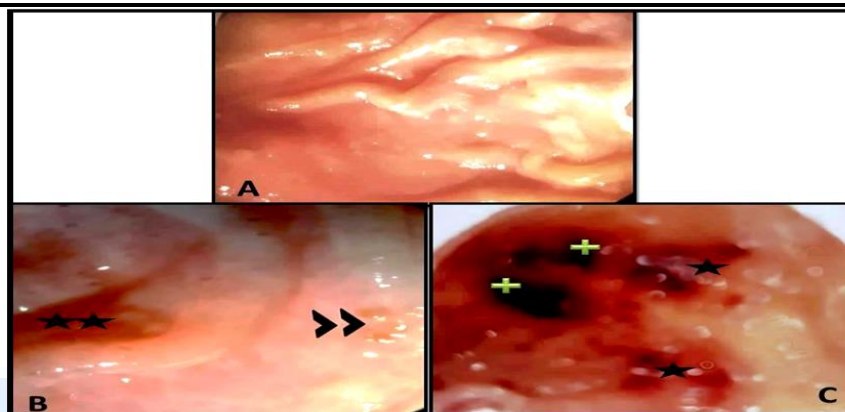


Figure 7: The macroscopic findings of stomach from control groups and experimental groups showing, normal pattern of control group (A), some spot ulcer (>>) and slight of haemorrhagic streaks (***) in the (WV-5%) group (B), and severe haemorrhagic gastric ulcers covered (+) with coagulated blood (*) in the (WV-10%) group (C) (D.M., X 6.5).

Discussion:

Ulceration of the gastric wall is manifested by heartburn, nausea, stomach pain, and discomfort and if not treated can lead to bleeding, perforation, and loss of weight. The symptoms and discomfort accompanied with the gastric ulcer influence the quality of life and accordingly has social and economic implications [25], [26], and [27]. The harmony between the immunological and hormonal systems assists the renewal of the gastric endogenous protective mechanism. A mechanism consisted of a succession of events among them a mucosal wall, blood flow, prostaglandins, epidermal growth factor, heat shock proteins, cathelicidins, lipoxins, nitric oxide, and hydrogen sulfide [28]. On the other hand, hydrochloric acid, pepsin, and other chemicals irritate the lining of the stomach wall thus factors enhancing mucus production and/or suppressing stomach acid production can alleviate the pain and soothe the mucosal damage [26], [29], [27].

The gastric mucosa is constantly exposed to potentially noxious substances, hydrochloric acid, and proteolytic enzymes, but the stomach usually remains its structural and functional integrity because of tight intercellular junctions and secretion of bicarbonate to neutralize the gastric acid [30]. Furthermore, gastric lesions are certainly a major human disorder that affects nearly 5% of the global population. The pathophysiology of peptic ulcer

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disease has centered on an imbalance between aggressive and protective factors in the stomach [31]. Moreover, they said the mucosal defense against these aggressive factors includes the function of the mucus-bicarbonate barrier, surface-active phospholipids, prostaglandin (PG), mucosal blood flow, cell renewal and migration, anti-oxidative enzymes, and some growth factors. However, prostaglandin E₂ (PGE₂) is the most abundant gastrointestinal prostaglandin and it regulates functions of the gut, including motility and secretion. PGE₂ has also been shown to exert a protective action on the stomach through the activation of prostaglandin EP receptors. According to many studies by [30] reported that prostaglandins synthesis through two cyclooxygenases (COX) isoforms, COX-1 and COX-2. COX-1 appears to be responsible for the production of PGs that is physiologically important for homeostatic functions, such as maintenance of mucosal integrity and mucosal blood flow. Under physiological conditions, prostanoid synthesis depends upon the availability of arachidonic acid and the COX-1 activity. While COX-2 is not constitutively expressed in most of the tissues but is dramatically upregulated during inflammation and injury.

Results obtained in the present study showed that there was a significant decline in the percentage of change in body weights of treated rats that were given white vinegar at a dose of 5% and 10% as compared to control rats. These results have been supported by the findings of [15], [32], [33], [14] who suggested that white vinegar causes inhibiting of body weight. These decreases in body weight gain may be due to gastric mucosal lesions and an increase in acidic activity, also due to increased degeneration of lipids and proteins or decreases in nutrient digestion and absorption. Moreover, the administration of white vinegar produced side effects such as deep ulcers in the stomach. The genesis of white vinegar induced gastric lesions is a multifactorial process that starts mainly with the depletion of gastric wall mucous content, such a depletion is often associated with significant production of free radicals, causing damage to the cell and cellular membrane due to excessive oxidative stress then decrease nutrient absorption [10]. In addition [34] showed that the symptoms of gastrointestinal disease caused loss of appetite by a reduction in food intake. This is due to the irritation of the gastrointestinal tract and the inflammatory processes that characterize the disease. Also, [35] elucidated that the reduction in body weight of animals treated with white vinegar might be through excessive nutrient losses through diarrhea, histological changes in

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the intestines revealing the presence of decreased villi and decrease number of goblets cells. The decrease in the numbers of villi in the intestine decrease nutrient absorption due to a decrease in the surface area of the intestine.

The results of this study presented a significant increase happened in gastric acid volume levels in white vinegar of female rats that taken WV-5% and WV-10% when compared to normal control rats. These results are in agreement with [36], [37] who described that administration of white vinegar to rats produced of increase in gastric acid volume levels in rats .

Besides, the data were presented in the present work showed a significant increase in the total acidity of treated animals (WV-5% and WV-10%) compared with control group rats. These results were supported by the findings in [31], [33], [38] who reported that the white vinegar caused increased in the total acidity of treated animals.

On the other hand, results recorded in this study exhibited a significant decrease in the pH value of the gastric juice followed in rats given white vinegar at doses of 5% and 10% as compared to normal control rats. The reduction in pH value of the gastric juice of the WV-treated animals is in agreement with that obtained by [31], [33], [39], [40]. Jaikumar *et al.* [41] stated that the increase in the gastric volume of the ulcerated rats is due to the increased production of HCl as is evident from the total acidity of the gastric juice. The increase in protein content of the gastric juice in the ulcer group indicates the damage to the gastric mucosa as the result of plasma proteins leak into the gastric juice. PGE₂ is one of the major protective factors in gastric tissue which inhibits gastric acid secretion. Thus, PGE₂ might indirectly take part in ulcer relapse via acid secretion [42]. On the other hand, [42], [19], [43] reported that inhibition of prostaglandin synthesis interferes with protective mechanisms, (mucus, bicarbonate secretion, surface epithelial hydrophobicity, and mucosal blood flow). Furthermore, a very brief cessation of mucosal blood flow results in a rapid decrease in the pH within the mucoid cap, which in turn, results in the formation of hemorrhagic erosions. The increase in total acidity of gastric juice, gastric acid volume values, and decrease in pH level by WV may be due to increasing the aggressive factors (acid and pepsin) but decreased pH level because of so-called back diffusion of HCl through

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the broken barrier, inhibition of mucosal blood flow, acute inflammation and a decrease in the synthesis of sulfated mucus glycoprotein has been implicated in the etiology of gastric ulcer [36]. Furthermore, increasing acid secretion by increasing the H^+ ion transport/back diffusion of H^+ ions [44]. So, the increase in total acidic activity and decrease in pH value of the ulcer group is undoubtedly due to the increased production of HCl as it is evident from the total acidity of the gastric juice [45]. In parietal cells, anion exchanger 2 (AE_2) mediates the exchange of Cl^-/HCO_3^- in the basolateral membrane and compensates for luminal H^+ pumping while providing Cl^- for apical secretion. Gastric acid secretion across the apical membrane of the parietal cell is closely related to the AE_2 activity. WV might be caused by increasing the stimulating gastric acid secretion by blocking the activity of AE_2 [30].

Significant increase in an ulcer index and an ulcer score of the stomach in white vinegar groups compared to control groups in the data documented in the study. Additionally, the macroscopic findings of the opened stomach are showed severe haemorrhagic gastric ulcers covered with coagulated blood were more apparent in the white vinegar (WV-10%) group, while the (WV-5%) group showed some spot ulcer and slight haemorrhagic streaks in the dissected stomach of rats as compared with a normal pattern of the control group. Similarly, in studies carried out on rats, [46], [31], [33], [38], [47] they determined that the administration of the white vinegar caused an increase in ulcer index and lesions areas of gastric ulcer in treated groups. In general, the formation of gastric mucosal lesions may be due to the reduction of gastric blood flow, which results in a rapid decrease in the pH within the mucoid cap, causing the formation of haemorrhagic erosions [48]. In addition, induction of gastric ulcer after exposure to necrotic agents, such as white vinegar is associated with various mechanisms such as, decreased gastric blood flow and solubilization of mucus constituents in the stomach which causes an elevated influx of Na^+ and K^+ ions along with loss of H^+ ions that results in increased secretion of pepsin into gastric mucosa [38]. Adequate blood flow through microcirculation plays an essential role in the protection and regeneration of the mucous membrane in the gastrointestinal tract. Research on animals has shown that exposure of the gastric mucous membrane to potentially harmful substances results from damage to gastric tissues. So, the restriction of blood flow through the mucosa results in the formation of large gastric ulcers [49]. Abdul-Aziz [43] supposed changes that

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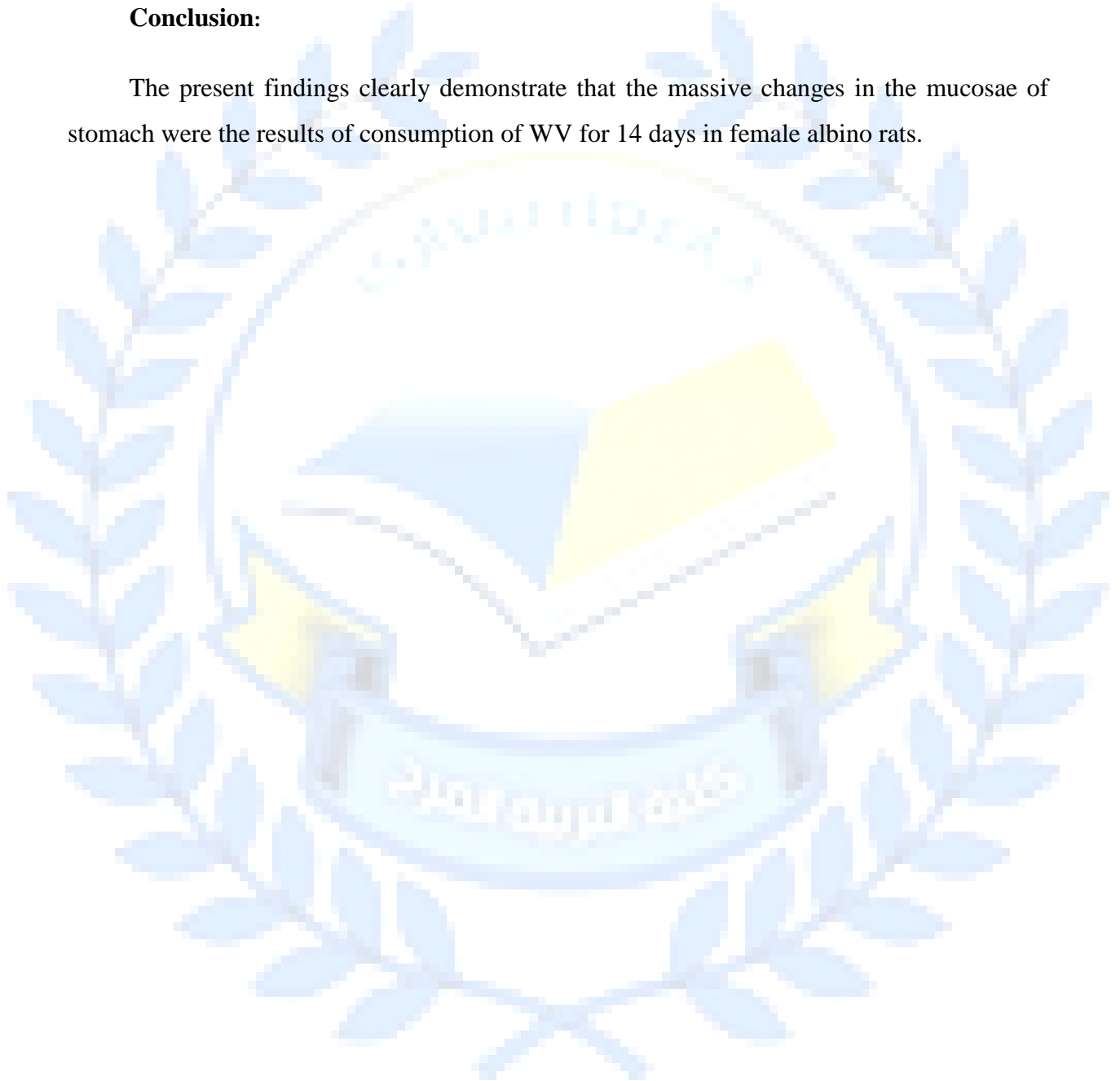
permit back diffusion of acid into the mucosa could directly lead to vascular leakage and aggressive damaging effect in the basement membrane of both epithelial and mucosal cells in the gastric wall, which could inhibit the restitution processes in the injured mucosa and induce a progression of apoptosis to deeper layers of the mucosa. On the mucosal epithelial factors, it decreases mucin surface-active phospholipids bicarbonate secretion mucosal proliferation and on the microvasculature produced damage by formation of free radicals [50]. Also, WV may occur damage in the gastrointestinal mucosa, causing lesions ranging from trivial petechial and superficial erosions to potentially serious deep peptic ulcers that will lead to gastric distress and gastrointestinal blood loss [51]. Wang *et al.* [52] stated that the PGE₂ content and proinflammatory cytokines interleukin and tumor necrosis factor play important parts in the genesis of gastric mucosal damage. It has been reported that increases in nitric oxide synthase activity are involved in the gastrointestinal mucosal defense and also in the pathogenesis of mucosal damage. Furthermore, oxidative stress plays an important role in the pathogenesis of ulcers. The radicals also promote mucosal damage by causing degradation of the epithelial basement membrane components, complete alteration of the cell metabolism. The damage to the membrane proteins decreases membrane permeability, activities of enzymes and receptors, and activation of cells [53]. A similar result in a study made by [54] suggested that the ulcer forms as a result of non-steroidal anti-inflammatory drugs administration may involve several mechanisms which are reducing gastric blood flow, thereby contributing to the development of necrosis and haemorrhage and solubilization of mucus constituents in the stomach. These actions result in an increased pepsin secretion and flux of Na⁺ and K⁺, with a decrease in histamine and H⁺ ions into the lumen. Additionally, [55] reported that the damage to the gastric tissue was accompanied by a significant depletion of the gastric mucus. Ethanol-induced gastric ulceration is associated with a reduction in gastric mucosal blood flow, gastric mucus, vascular permeability, enhanced release of histamine, and the production of free radicals. In addition, ulcerogenic agents cause dispersal of the gastroprotective mucus gel and the associated phospholipids layers leading to acid back diffusion and injury to the gastric mucosa.

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Macroscopic findings in this study showed, white vinegar caused gastric haemorrhagic lesions in the glandular mucosa, which appeared as prominent cellular damage at the light microscopic level demonstrating true ulcer formation.

Conclusion:

The present findings clearly demonstrate that the massive changes in the mucosae of stomach were the results of consumption of WV for 14 days in female albino rats.



References:

- [1]: Malfertheiner, P., Chan, F. K. and McColl, K. E. 2009. Peptic ulcer disease. *Lancet*. 24: 1449-1461.
- [2]: Bakaeva, Z. V., Sangadzhieva, A. D., Tani, S., Myasoedov, N. F., Andreeva, L. A., Torshin, V. I., Wallace, J. L. and Tanaka, T. 2016. Glyprolines exert protective and repair-promoting effects in the rat stomach: Potential role of the cytokine GRO/CINC-1. *Journal Physiology Pharmacology*.67: 253-260.
- [3]: Gopinathan, S. and Naveenraj, D. 2013. Gastroprotective and anti-ulcer activity of *Aloe vera* juice, *Papaya* fruit juice and *Aloe vera* and *Papaya* fruit combined juice in ethanol induced ulcerated rats. *International Journal of Drug Development and Research*. 5 (4): 300-11.
- [4]: Wallace, J. L. 2008. Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn't the stomach digest itself. *Physiological Reviews*. 88: 1547-1565.
- [5]: deFoneska, A., Kaunitz J. D. 2010. Gastroduodenal mucosal defense. *Current Opinion in Gastroenterology*. 26: 604-610.
- [6]: Gopinathan, S. and Nija, S. 2014. Gastric ulcer curative potential of *Mollugo oppositifolia* Linn. Extract-A preclinical study. *World Journal of Pharmaceutical Research*. 3 (7): 929-948.
- [7]: Mahmoodi, M., Hosseini-zijoud, S., Hassan, S. G., Nabati, S., Modarresi, M., Mehrabian, M., Sayyadi, A. and Hajizadeh, M. 2013. The effect of white vinegar on some blood biochemical factors in type 2 diabetic patients. *Global Journal Hematology Endocrinology*.1 (1): 51-54.
- [8]: Okabe, S. and Amagase, K. 2005. An overview of acetic acid ulcer models-the history and state of the art of peptic ulcer research. *Biological and Pharmaceutical Bulletin*. 28: 1321-41.

العدد الخامس والخمسون / يناير / 2022

- [9]: Chibishev, A., Sikole, A., Pereska, Z., Chibisheva, V., Simonovska, N. and Orovchanec, N. 2013. Severe renal function impairment in adult patients acutely poisoned with concentrated acetic acid. *Archives of Industrial Hygiene and Toxicology*. 64 (1): 153-158.
- [10]: Almasaudi, S. B., Abbas, A. T., Al-Hindi, R. R., El-Shitany, N. A., Abdel-dayem, U. A., Ali, S. S., Saleh, R. M., Al Jaouni, S. K., Kamal, M. A. and Harakeh, S. M. 2017. Manuka honey exerts antioxidant and anti-inflammatory activities that promote healing of acetic acid-induced gastric ulcer in rats. *Evidence-Based Complementary and Alternative Medicine*. 1-12.
- [11]: Kamijo, Y., Soma, K., Iwabuchi, K. and Ohwada, T. 2000. Massive noninflammatory periportal liver necrosis following concentrated acetic acid ingestion. *Archives of Pathology and Laboratory Medicine*. 124 (1): 127-129.
- [12]: Kang, J. M., Kim, N., Kim, B., Kim, J. H., Lee, B. Y., Park, J. H., Lee, M. K., Lee, H. S., Kim, J. S., Jung, H. C. and Song, I. S. 2010. Enhancement of gastric-ulcer healing and angiogenesis by *Cochinchina momordica* seed extract in rats. *Journal of Korean Medical Science*. 25 (6): 875-881.
- [13]: Pastrelo, M. M., Ribeiro, C. C. D., Duarte, J. W., Gollücke, A. P. B., Artigiani-Neto, R., Ribeiro, D. A., Miszputen, S. J., Oshima, C. T. F. and Paiotti, A. P. R. 2017. Effect of concentrated *Apple* extract on an experimental colitis induced by acetic acid. *International Journal of Molecular and Cellular Medicine*. 6 (1): 38-49.
- [14]: Soykan, D., Muzaffer, C., Giray, A., Erdinc, Y., Semra, H. and Mohanraj, R. 2015. Methylene blue inhibits the inflammatory process of the acetic acid-induced colitis in rat colonic mucosa. *International Surgery*. 100: 1364-1374.
- [15]: Souza, M. M. D., Aguilar-Nascimento, J. E. D., Gomes-Da-Silva, M. H. and Junior, R. C. 2007. Effects of budesonide and probiotics enemas on the colonic mucosa of rats with experimental colitis. *Acta Cirúrgica Brasileira*. 22 (1): 34-38.

العدد الخامس والخمسون / يناير / 2022

- [16]: Abd Allaha, E. S. H., Makboul, R. and Mohamed, A. O. 2016. Role of serotonin and nuclear factor-kappa B in the ameliorative effect of ginger on acetic acid-induced colitis. *Pathophysiology*. 23: 35-42.
- [17]: Hsu, D., Chu, P., Chandrasekaran, V. R. and Liu, M. 2009. Sesame *Lignan sesamol* protects against aspirin-induced gastric mucosal damage in rats. *Journal of Functional Foods*.1: 335-349.
- [18]: Alshailabi, E. M. 2016. Effects of omeprazole on healing of non-steroidal anti-inflammatory drug (NSAID)-induced peptic ulceration in rats and protective role of indole-3-carbinol. *Art and Science Journal*.1-8.
- [19]: Al-dalain, S., El-kutry, M. S. and Ibrahim, H. S. 2008. Inhibitory effect of aqueous extracts of *Barley* and *Fenugreek* on ulcer induction in rats. *World Applied Sciences Journal*. 5 (3): 332-339.
- [20]: Vinothapooshan, G. and Sundar, K. 2010. Anti-ulcer activity of *Mimosa pudica* leaves against gastric ulcer in rats. *Research Journal of Pharmaceutical Biological and Chemical Sciences*.1 (4): 606-614.
- [21]: Yam, M. F., Ang, L. F., Salmanm, I. M., Ameerm, O. Z., Lim, V. and Ong, L. M. 2009. *Orthosiphon stamineus* leaf extract protects against ethanol-induced gastropathy in rats. *Journal of Medicinal Food*. 12: 1089-1097.
- [22]: Boligona, A. A., De Freitas, R. B., Bruma, B. T., Waczuqc, E. P., Klimaczewskic, C. V., Vilac, D. S., Athaydea, M. L., and Bauermannb, L. F. 2014. Antiulcerogenic activity of *Scutia buxifolia* on gastric ulcers induced by ethanol in rats. *Acta Pharmaceutica Sinica*. 4 (5): 358-367.
- [23]: Minaiyan, M., Ghannadi, A. R. and Karimzadeh, A. 2006. Antiulcerogenic effects of ginger (*Zingiber officinale roscoe*) on cysteamine induced duodenal ulcer in rats. *DARU Journal of Pharmaceutical Sciences*.14 (2): 97-10.

العدد الخامس والخمسون / يناير / 2022

- [24]: El-Shinnawy, N. A., Abd-Elmageid, S. A. and Alshailabi, E. M. 2014. Evaluation of antiulcer activity of indole-3-carbinol and/or omeprazole on aspirin-induced gastric ulcer in rats. *Toxicology and Industrial Health*. 30 (4): 357-375.
- [25]: Yuan, Y., Padol, I. T. and Hunt, R. H. 2006. Peptic ulcer disease today, Nature Clinical Practice. *European Journal of Gastroenterology and Hepatology*. 3: 80-89.
- [26]: Hajrezaie, M., Golbabapour, S., Hassan, P., Gwaram, S., Hadi, A. and Mohd, A. H. 2012. Acute toxicity and gastroprotection studies of a new schiff base derived copper (II) complex against ethanol induced acute gastric lesions in rats. *PloS one*. 7: 51537.
- [27]: Hajrezaie, M., Salehen, N., Karimian, H., Zahedifard, M., Shams, K., Al Batran, R., Majid, N. A., Khalifa, S. A., Ali, H. M., El-Seedi, H. and Abdulla, M. A. 2015. Biochan in a gastroprotective effects in ethanol-induced gastric mucosal ulceration in rats. *Plos One*. 10 (3): 1-13.
- [28]: Mohamed, M. and El-Sheikh, A. 2011. Prevention of gastric ulcers. *Peptic ulcer disease*. 437-460.
- [29]: Ketuly, K. A., Hadi, A., Golbabapour, S., Hajrezaie, M., Hassandarvish, P. and Mohd, H. 2013. Acute toxicity and gastroprotection studies with a newly synthesized steroid. *PloS one*. 8: e59296.
- [30]: Zhao, W., Zhu, F., Shen, W., Fu, A., Zheng, L., Yan, Z., Zhao, L. and Fu, G. 2009. Protective effects of DIDS against ethanol-induced gastric mucosal injury in rats. *Acta Biochimica et Biophysica Sinica*. 41 (4): 301-308.
- [31]: Hitesh, K. R., Harish, C. H. and Ramesh, K. R. 2012. Antiulcer potential of ethyl cellulose floating microspheres containing ranitidine hydrochloride in experimental rodents. *Asian Journal of Pharmaceutical and Clinical Research*. 5(3): 205-209.
- [32]: Soltan, S. S. and Shehata, M. M. E. M. 2012. Antidiabetic and hypocholesrolemic effect of different types of vinegar in rats. *Life Science Journal*. 9 (4): 2141-2151.

العدد الخامس والخمسون / يناير / 2022

- [33]: Salami, A. T., Ndukauba, N. G., Iyoila, T. O., Agbola, O. F., Oluwole, F. S. and Olaleye, S. B. 2014. Gastroprotective properties of manganese chloride on acetic acid induced ulcer in Wistar rats. *African Journal of Biomedical Research*. 17 (2):109-117.
- [34]: Abubakar, S. D., Adisa, J. O., Sahabi, S. M., Abdullahi, K., Abubakar, U., Fasogbon, S. A. and Zakariya, A. A. 2017. Beneficial effects of *Guiera senegalensis* on selected parameters in acetic acid-induced colitis in Wister rats. *Journal of Complementary and Alternative Medical Research*. 4 (4): 1-13.
- [35]: Olamilosoye, K. P., Akomolafe, R. O., Akinsomisoye, O. S., Adefisayo, M. A. and Alabi, Q. K. 2018. The aqueous extract of *Ocimum gratissimum* leaves ameliorates acetic acid-induced colitis via improving antioxidant status and hematological parameters in male Wistar rats. *Egyptian journal of Basic and Applied Sciences*. 1-8.
- [36]: Jainu, M., Mohan, V. and Devi, S. 2006. Gastroprotective effect of *Cissus quadrangularis* extract in rats with experimentally induced ulcer. *Indian Journal of Medical Research*. 123: 799-806.
- [37]: Keshavarzi, Z., Rezapour, T. M., Vatanchian, M., Hesari, M. Z., Haghighi, H. N., IZanlu, M., Sabaghian, M. and Shahveisi, K. 2014. The effects of aqueous extract of *Aloe vera* leaves on the gastric acid secretion and brain and intestinal water content following acetic acid-induced gastric ulcer in male rats. *Avicenna Journal of Phytomedicine*. 4 (2): 137-143.
- [38]: Sarkar, S., Sengupta, A., Mukhrjee, A., Guru, A., Patil, A., Kandhare, A. D. and Bodhankar, S. L. 2015. Antiulcer potential of *Morin* in acetic acid-induced gastric ulcer via modulation of endogenous biomarkers in laboratory animals. *Pharmacologia*. 6 (7): 273-281.
- [39]: Abourehab, M. A., Khaled, K. A., Sarhan, H. A. and Ahmed, O. A. 2015. Evaluation of combined famotidine with quercetin for the treatment of peptic ulcer: in vivo animal study. *Drug Design Development and Therapy*. 9: 2159-2196.

العدد الخامس والخمسون / يناير / 2022

- [40]: Ur Rehman, Z., Ul Haq, A., Akram, N., Abd El-Hack, M.E., Saeed, M., Rehman, S. U., Meng, C., Alagawany, M., Sayab, M., Dhama, K. and Ding, C. 2016. Growth performance, intestinal histomorphology, blood hematology and serum metabolites of broilers chickens fed diet supplemented with graded levels of acetic acid. *International Journal of Pharmacology*. 12 (8): 874-883.
- [41]: Jaikumar, S., Ramaswamy, S., Asokan, B. R., Mohan, T. and Gnanavel, M. 2010. Anti-ulcer activity of methanolic extract of *Jatropha curcas* (Linn.) on aspirin-induced gastric lesions in Wistar strain rats. *Research Journal Of Pharmaceutical Biological and Chemical Sciences*. 1 (4): 886-897.
- [42]: Wang, G., Huang, G., Yin, G., Zhou, G., Guo, C., Xie, C., Jia, B. and Wang, J. 2007. Aspirin can elicit the recurrence of gastric ulcer induced with acetic acid in rats. *Cellular Physiology and Biochemistry*. 20: 205-212.
- [43]: Abdul-Aziz, K. K. 2011. Comparative evaluation of the anti-ulcer activity of *Curcumin* and omeprazole during the acute phase of gastric ulcer. *Food and Nutrition Sciences*. 2: 628-640.
- [44]: Giri, M. A. A., Bhalke, R. D. A. and Pal, S. C. 2010. Gastroprotective effect of hydroalcoholic leaves extract of *Pongamia pinnata*. *International Journal of Pharmacy and Biological Sciences*. 1: 1-6.
- [45]: Potrich, F. B., Allemand, A., Silva, L. M., Santos, A. C., Baggio, C. H., Freitas, C. S., Mendes, D. A. G. B., Andre, E., Werner, M. F. P. and Marques, M. C. A. 2010. Antiulcerogenic activity of hydroalcoholic extract of *Achillea millefolium* L.: Involvement of the antioxidant system. *Journal of Ethnopharmacology*. 130: 85-92.
- [46]: Mahgoub, A. A., El-Medany, A. A., Hager, H. H., Mustafa, A. A. and El-Sabah, D. M. 2003. Evaluating the prophylactic potential of zafirlukast against the toxic effects of acetic acid on the rat colon. *Toxicology Letters*. 145 (1): 79-87.

العدد الخامس والخمسون / يناير / 2022

- [47]: Périco, L. L., Rodrigues, V. P., Ohara, R., Bueno, G., Nunes, V. V. A., Dos Santos, R. C., Camargo, A. C. L., Júnior, L. A. J., De Andrade, S. F., Steimbach, V. M. B. and De Silva, L. M. 2018. Sex-specific effects of *Eugenia punicifolia* extract on gastric ulcer healing in rats. *World Journal of Gastroenterology*. 24 (38): 4369-4418.
- [48]: Wallace, J. L. 2005. Recent advances in gastric ulcer therapeutics. *Current Opinion in Pharmacology*. 5 (6): 573-577.
- [49]: Matuszyk, A., Ceranowicz, P., Warzecha, Z., Cieszkowski, J., Ceranowicz, D., Gałazka, K., Bonior, J., Jaworek, J., Bartuś, K., Gil, K. and Olszanecki, R. 2016. Exogenous ghrelin accelerates the healing of acetic acid-induced colitis in rats. *International Journal of Molecular Sciences*. 17(9): 2-16.
- [50]: Sairam, K. A., Priyambada, S. A., Aryya, N. C. B. and Goel, R. K. 2003. Gastroduodenal ulcer protective activity of *Asparagus racemosus*: An experimental, biochemical and histological study. *Journal Ethnopharmacology*. 86: 1-10.
- [51]: Sener, G., Paskalog, K., Arbak, S., Hurdag, C. and Ayanoglu, G. 2001. Protective effect of famotidine, omeprazole and melatonin against acetylsalicylic acid-induced gastric damage in rats. *Digestive Diseases and Sciences*. 46 (2): 318-330.
- [52]: Wang, Z., Hasegawa, J., Wang, X., Matsuda, A., Tokuda, T., Miura, N. and Watanabe, T. 2011. Protective effects of ginger against aspirin-induced gastric ulcers in rats. *Yonago Acta Medica*. 54: 11-19.
- [53]: Thamocharan, G., Sekar, G., Ganesh, T., Saikat S., Chakraborty, R. and Kumar, S. N. 2010. Antiulcerogenic effects of *Lantana camara* Linn. leaves on *in vivo* test models in rats. *Asian Journal of Pharmaceutical and Clinical Research*. 3: 1-3.
- [54]: Tour, N. S. and Talele, G. S. 2011. Gastric antiulcer and anti-inflammatory activities of *Calotropis procera* stem bark. *Brazilian Journal of Pharmacognosy and Phytochemistry*. 21 (6): 1118-1126.

العدد الخامس والخمسون / يناير / 2022

- [55]: Al Asmari, A., Al Shahrani, H., Al Masri, N., Al Faraidi, A., Elfaki, I. and Arshaduddin, M. 2016. Vanillin abrogates ethanol induced gastric injury in rats via modulation of gastric secretion, oxidative stress and inflammation. *Toxicology Reports*. 3: 105-113.

