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Evaluating the role of muscular exercise in modulating the progress of peptic ulcer treated by quercetin or dexilant in male albino rats

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***Abstract*---**Aim of the Work: Study the role of muscular exercise in modulating the progress of peptic ulcer treated by quercetin or dexilant in rats. Methods: 80 male rats divided into 8 equal groups: Control, gastric ulcer non-treated, gastric ulcer with exercise, dexilant treated gastric ulcer, quercetin treated gastric ulcer, dexilant treated gastric ulcer with exercise, quercetin treated gastric ulcer with exercise, quercetin and dexilant treated gastric ulcer groups. At the end, the collected samples were used to analyze PH, total gastric acidity, ulcer index(UI), curative index(CI), heat shock protein 70(HSP70), asymmetric dimethyle arginine(ADMA), tumor necrotic factor alpha(TNFα) levels. Histopathological and immunohistochemical analyses were done. Results: Non-treated group showed significant decrease of gastric levels of pH and CI with significant increase of gastric total acidity, UI, HSP70, ADMA and TNFα. Also, deterioration of histopathological and immunohistochemical expression of Bcl-2 with increase of NF-κB immunohistochemical expression compared to control group. In treated groups with exercise, dexilent and quercetin, dexilent with exercise and quercetin with exrcise, showed significant increase of gastric levels of pH and curative index with significant decrease of total acidity, ulcer index, HSP70, ADMA, MDA and TNFα with improvement of the histopathological appearance of gastric tissue, enhancement immunohistochemical expression of Bcl-2 with concomitant decrease NF-κB immunohistochemical expression as

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compared to non-treated group. All studied parameters significantly improved in quercetin and dexilent treated group as compared to non-treated and all treated groups. Conclusion: Combination of quercetin and dexilent could improve gastric ulcer induced by aspirin via anti-apoptotic, anti-inflammatory and antioxidant effects.

***Keywords*---**Muscular Exercise, Peptic Ulcer, Quercetin, Dexilant, ADMA, Bcl2, NF-kB.

Introduction

Peptic ulcer is a serious disease of the gastrointestinal tract (Lanas and Chan, 2017). It affects mainly in the stomach and duodenum (Prabhu and Shivani, 2014). Peptic ulcer disease is primarily caused by an imbalance between aggressive factors (acid, pepsin, non-steroidal anti-inflammatory drugs (NSAID), Helicobacter pylori infection, smoking, stress, and excessive alcohol intakes) and protective actions of the gastrointestinal mucosa, such as bicarbonate, mucus, and prostaglandins secretion (Fashner and Gitu, 2015).

Flavonoids are a class of naturally occurring chemicals that may be found throughout the plant kingdom as secondary metabolites (Tungmunnithum et al., 2018). Clinically, flavinoids have been shown to have anti-inflammatory, antioxidant, antiviral, anti-allergic, anticancer, and antitumor effects (Panche et al., 2016). Quercetin is one of flavonoid group, which has the most potent antioxidant activity (Olayinka et al., 2015). Quercetin has been shown to protect the stomach mucosa against acute lesions generated by various experimental models and necrotic agents, such as restraint stress, NSAID, and ethanol-induced gastric ulcers (David et al., 2016).

Proton pump inhibitors (PPIs) are the most widely used and the most often prescribed medication for peptic ulcer, they work by inhibiting the production of gastric hydrochloric acid (Kuna et al., 2019). The mechanism of action of PPIs is based on blocking the activity of the hydrogen/potassium adenosine triphosphatase (H/K ATPase) enzyme, that is called the proton pump and it has been found in the gastric parietal cells (Mossner, 2016).

Dexilant (Dexlansoprazole modified release (MR) is novel PPIs generation that display high efficiency in the treatment of symptoms gastric ulcer (Goh et al., 2016). Due to dexilant's ability to reach two peak concentrations at separate periods over two and five hours of treatment, two peak concentrations may be achieved. Dexilant's elimination rate is lower than that of older PPIs, therefore it may remain in circulation for a longer period of time (Fass and Frazier, 2017).

Physical activity has a lot of benefits for psychological and physical health (Shephard, 2017). The effect of physical activity on the development of peptic ulcer disease depends on severity and the period of the physical activity (Levenstein et al., 2015). Nystoriak and Bhatnagar, (2018) demonstrated that regular chronic moderate exercise, like walking, swimming, and cycling, has many benefits on cardiovascular, gastric and musculoskeletal systems. But the

mechanism of physical activity on peptic ulcer is still elusive. So, the aim of this work is to study the role of muscular exercise in modulating the progress of peptic ulcer treated by quercetin or dexilant in rats.

Materials & Methods

The present work was be carried on 80 male albino rats. The rats were be housed in an isolated animal cages (5 rats in each cage), in research lab of physiology department. They were freely supplied with water and food all over the period of the work. They were maintained in a 12-hour light-dark cycle at 23°C ambient temperature. The experiment was carried out in accordance with the guidelines of the Tanta University, Faculty of Medicine's ethics committee. (Approval Code Number: 33236/07/19). The rats were be randomly divided into eight groups, each consists of 10 rats as the following:

1- Group I (Control group): They were received normal saline via oral gavage as a vehicle.
2- Group II (Gastric ulcer non-treated): Rats were received aspirin in a dose of 500 mg/kg via oral gavage (Das and Roy, 2012) for 2 weeks for induction of gastric ulcer, then they were received saline once daily via oral gavage as a vehicle for 4 weeks.
3-Group III (gastric ulcer with exercise): Rats were received aspirin as in group II. Then, they were exposed to chronic moderate exercise by swimming test for 4 weeks (Shephard, 2017).
4- Group IV (Dexilant treated gastric ulcer): Rats were received aspirin as in group II, then they were treated with dexilant in a dose of 60mg/kg once daily via oral gavage (Wu et al., 2016 b) for 4 weeks.
5- Group V (Quercetin treated gastric ulcer): Rats were received aspirin as in group II, then they were treated with quercetin in a dose of 50 mg/kg via oral gavage (Abourehab et al., 2015) for 4 weeks.
6- Group VI (dexilant treated gastric ulcer with exercise): Rats were received aspirin as in group II, then they were treated with dexilant as in group IV and they were exposed to chronic moderate exercise by swimming test for 4 weeks.
7- Group VII (quercetin treated gastric ulcer with exercise): Rats were received aspirin as in group II, then they were treated with quercetin as in group V and they were exposed to chronic moderate exercise by swimming test for 4 weeks.
8- Group VIII (quercetin and dexilant treated gastric ulcer): Rats were received aspirin as in group II, then they were treated with quercetin as in group V and they were treated with dexilant as in group IV at the same time.

Drug preparation

Aspirin, dexilent and quercetin were obtained from Sigma Aldrish CO., (Louis, Mo, USA) as powders and they were dissolved in normal saline.

Swimming test

This test was used for chronic exercise training**.** The animals were submitted to swimming exercise test after induction of gastric ulcer by aspirin for 2 weeks. But group VI and group VII were submitted to swimming test after administration of dexilant and quercetin respectively (treated gastric ulcer). The rats were

acclimated to swimming for 15 min in a water tank (diameter; 40 cm; depth, 70 cm) at a temperature of 35±1°C every day for two weeks. Then the animals were helped out of the water and were returned back to their home cages for recovery (Matsakas, et al.2006).

Statistical analysis

The previously mentioned data were statistically expressed as the mean ± standard deviation. Statistical comparison between different groups was carried out by using one–way ANOVA. Significant results of analysis of variance were subjected to post hoc analysis (Tukey-Kramer multiple comparisons). P-values <0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) for Microsoft Windows (version 25).

Results

Gastric pH, Total acidity, UI and CI levels in all studied groups:

As regard to the comparison with gastric ulcer group, the gastric pH level and gastric CI exhibited significant increase in all gastric ulcer treated groups. On the other hand, the gastric total acidity and gastric UI exhibited significant decrease in all gastric ulcer treated groups. In the same way, the gastric pH levels and gastric CI were significantly increase in all gastric ulcer treated groups as compared to the gastric ulcer group exposed to exercise. But, the gastric total acidity and gastric UI exhibited significant decrease in all gastric ulcer treated groups.

It was noticed that the gastric pH level and gastric CI were significantly lower in quercetin treated group as compared to dexilent treated group. However the gastric pH levels and gastric CI were significantly higher in dexilent treated group with exercise and both quercetin and dexilent treated group as compared to dexilent treated group. But, the gastric total acidity level and gastric UI were significantly higher in quercetin treated group as compared to dexilent treated group. However the gastric total acidity level and gastric UI were significantly lower in dexilent treated group with exercise and both quercetin and dexilent treated group as compared to dexilent treated group.

In comparison with quercetin treated group, the gastric pH levels and gastric CI showed significant increase in all gastric ulcer treated groups except the gastric ulcer group exposed to exercise. However, the gastric total acidity level and gastric UI showed significant decrease in all gastric ulcer treated groups except the gastric ulcer group exposed to exercise as compared to quercetin treated group. It was observed that the gastric pH level and gastric CI were significantly lower in quercetin treated group with exercise as compared to dexilent treated group with exercise. However the gastric pH levels and gastric CI were significantly higher in both quercetin and dexilent treated group as compared to dexilent treated group with exercise. However, the gastric total acidity level and gastric UI were significantly higher in quercetin treated group with exercise as compared to dexilent treated group with exercise. However the gastric total acidity level and

gastric UI were significantly lower in both quercetin and dexilent treated group as compared to dexilent treated group with exercise. Finally, as compared to quercetin treated group with exercise the gastric pH level and gastric CI were significantly higher in group treated with both quercetin and dexilent. But, as compared to quercetin treated group with exercise the gastric total acidity level and gastric UI were significantly lower in group treated with both quercetin and dexilent (Table 1).

Table (1): Gastric pH level, Total acidity level (mEq/L/100g), ulcer index (mm) level and curative index (%) level in all studied groups

Parameters	Control Group I	Gastric ulcer Group II	Gastric ulcer with exercise Group III	Dexilant treated Group IV	Quercetin treated gastric Group V	Dexilant treated with exercise Group VI	Quercetin treated with exercise Group VII	Quercetin and dexilant treated group VIII
Gastric pH level	2.82±0.18	1.24±0.07 [a]	1.55±0.09 [a,b]	2.16±0.05 [a,b,c]	1.91±0.04 [a,b,c,d]	2.41±0.12 [a,b,c,d,e]	2.12±0.07 [a,b,c,e,f]	2.80±0.18 [b,c,d,e,f,g]
Total acidity (mEq/L/100g	52.59±2.49	88.70±2.96 [a]	79.25±2.01 [a,b]	60.84±1.16 [a,b,c]	69.34±1.47 [a,b,c,d]	57.69±0.92 [a,b,c,d,e]	64.16±2.41 [a,b,c,d,e,f]	53.62±2.81 [b,c,d,e,f,g]
UI (mm) level	0.026±0.019	39.99±0.93 [a]	35.55±0.44 [a,b]	5.35±0.63 [a,b,c]	19.58±0.37 [a,b,c,d]	3.08±0.15 [a,b,c,d,e]	15.11±0.25 [a,b,c,d,e,f]	1.33±0.066 [b,c,d,e,f,g]
CI (%) level	99.99±0.015	0±0 [a]	22.42±0.16 [a,b]	86.91±0.23 [a,b,c]	51.71±0.40 [a,b,c,d]	90.74±0.311 [a,b,c,d,e]	55.39±0.51 [a,b,c,d,e,f]	98.57±1.04 [b,c,d,e,f,g]

UI: ulcer index, CI: curative index

a b c d e f g denotes statistical significance at p≤ 0.05. [a] shows significance as compared to group I, [b] shows significance as compared to group II , [c] shows significance as compared to group III, [d] shows significance as compared to group IV, [e] shows significance as compared to group V, [f] shows significance as compared to group VI, [g] shows significance as compared to group VII

Heat shock protein 70 levels in all studied groups:

As compared to gastric ulcer group, there was significant increase in HSP 70 in gastric ulcer group with exercise, dexilent treated group with exercise and quercetin treated group with exercise. However, there was significant decrease in HSP 70 in dexilent treated group, quercetin treated group and in group treated with both quercetin and dexilent as compared to gastric ulcer group.

In addition, HSP 70 levels were significantly decrease in all gastric ulcer treated groups as compared to the gastric ulcer group with exercise. Comparing with dexilent treated group, it was noticed that the HSP 70 level was significantly higher in quercetin treated group, dexilent treated group with exercise and quercetin treated group with exercise. But, HSP 70 level was significantly lower in both quercetin and dexilent treated group as compared to dexilent treated group.

As regard to quercetin treated group, there was significant increase in HSP 70 level in dexilent treated group with exercise and quercetin treated group with exercise. But, HSP 70 level was significantly lower in both quercetin and dexilent treated group as compared to dexilent treated group. As compared to dexilent

treated group with exercise, HSP 70 level significantly increase in quercetin treated group with exercise, but significantly decrease in both quercetin and dexilent treated group as compared to dexilent treated group with exercise. Moreover, HSP 70 level were significantly decrease in both quercetin and dexilent treated group as compared to quercetin treated group with exercise (Table 2).

Table (2): Heat Shock Protein 70 levels in all studied groups

Parameter	Control Group I	Gastric ulcer Group II	Gastric ulcer with exercise Group III	Dexilant treated Group IV	Quercetin treated gastric Group V	Dexilant treated with exercise Group VI	Quercetin treated with exercise Group VII	Quercetin and dexilant treated group VIII
HSP 70 (pg/ml)	36.74±4.46	79.03±3.29 [a]	148.73±4.6 [a,b]	57.9±5.2 [a,b,c]	64.4±3.4 [a,b,c,d]	100.61±4.51 [a,b,c,d,e]	120.6±3.33 [a,b,c,d,e,f]	37.80±4.72 [b,c,d,e,f,g]

HSP 70: Heat Shock Protein 70

a b c d e f g denotes statistical significance at p≤ 0.05. [a] shows significance as compared to group I, [b] shows significance as compared to group II , [c] shows significance as compared to group III, [d] shows significance as compared to group IV, [e] shows significance as compared to group V, [f] shows significance as compared to group VI, [g] shows significance as compared to group VII

Asymmetric Dimethyle Arganine and Tumor Necrotic Factor α levels in all studied groups:

As regard to the comparison with gastric ulcer group, the ADMA level and the TNF α level exhibited significant decrease in all gastric ulcer treated groups. In addition, the ADMA levels and the TNF α level were significantly decrease in all gastric ulcer treated groups as compared to the gastric ulcer group exposed to exercise. It was noticed that the ADMA level and the TNF α level were significantly lower in dexilent treated group with exercise and both quercetin and dexilent treated group as compared to dexilent treated group. However, the ADMA levels and the TNF α level were significantly higher in quercetin treated group and quercetin treated group with exercise as compared to dexilent treated group.

As regard to quercetin treated group, the ADMA level and the TNF α levels showed significant decrease in dexilent treated group with exercise, quercetin treated group with exercise and both quercetin and dexilent treated group. It was observed that the ADMA levels and the TNF α level were significantly higher in quercetin treated group with exercise as compared to dexilent treated group with exercise.. However, the ADMA level and the TNF α level were significantly lower in both quercetin and dexilent treated group as compared to dexilent treated group with exercise. At the end, as compared to quercetin treated group with exercise the ADMA level was significantly lower in group treated with both quercetin and dexilent (Table 3).

Table (3): Asymmetric Dimethyle Arganine (µmol/L) and Tumor Necrotic Factor α (pg/mg protein) in all studied groups

Parameters	Control Group I	Gastric ulcer Group II	Gastric ulcer with exercise Group III	Dexilant treated Group IV	Quercetin treated gastric Group V	Dexilant treated with exercise Group VI	Quercetin treated with exercise Group VII	Quercetin and dexilant treated group VIII
ADMA(µmol /L)	1.41±0.14	4.96±0.40 [a]	4.09±0.24 [a,b]	2.43±0.16 [a,b,c]	3.57±0.32 [a,b,c,d]	1.98±0.21 [a,b,c,d,e]	2.9±0.47 [a,b,c,d,e,f]	1.49±0.18 [b,c,d,e,f,g]
TNF α (pg/mg protein)	30.99±3.08	88.05±10.05 [a]	79.78±4.8 [a,b]	48.61±2.03 [a,b,c]	63.12±3.34 [a,b,c,d]	40.42±4.91 [a,b,c,d,e]	55.8±3.9 [a,b,c,e,f]	32.48±2.49 [b,c,d,e,f,g]

ADMA: Asymmetric Dimethyle Arganine, TNF α: Tumor Necrotic Factor α
a b c d e f g denotes statistical significance at p≤ 0.05. [a] shows significance as compared to group I, [b] shows significance as compared to group II , [c] shows significance as compared to group III, [d] shows significance as compared to group IV, [e] shows significance as compared to group V, [f] shows significance as compared to group VI, [g] shows significance as compared to group VII

The histopathological analysis of the gastric tissue in the present work revealed the following (Figure 1)**:**

Control group exhibited normal architecture of the gastric tissue. While, Gastric ulcer group displayed disruption of the surface epithelium and necrotic lesions penetrate deeply into. There was extensive edema of submucosa layer hemorrhage and leucocyte infiltration. Gastric ulcer with exercise group showed disruption of the surface epithelium, there was edema of sub-mucosal layer, hemorrhage and leucocyte infiltration. Dexilant treated group revealed slight improvement of the surface epithelium, there was mild edema of submucosa layer and mild leucocyte infiltration. In addition, quercetin treated group displayed slight disruption of the surface epithelium, there was edema of submucosa layer, hemorrhage and leucocyte infiltration.

Dexilant treated with exercise group exhibited mild disruption of the surface epithelium, there was mild edema of submucosal layer and mild leucocyte infiltration. Also, quercetin treated with exercise group revealed slight disruption of the surface epithelium, there was mild edema of submucosal layer, and leucocyte infiltration. While, quercetin and dexilant treated group showed restoration of normal architecture of gastric tissue with disappearance of edema, hemorrhage and leucocyte infiltration.

Immunohistochemical expression of Bcl-2 with quantitative changes of its positive cells of gastric mucosa in all albino rats groups:

Figure (2) displayed normal immunohistochemical expression of Bcl-2 in gastric tissue of the control group and revealed reduction of Bcl-2 expression in gastric ulcer group. The immunohistochemical expression of Bcl-2 showed mild increase in gastric tissue of gastric ulcer with exercise group. On the other hand, expression of Bcl-2 showed prominent increase in all other gastric ulcer-treated groups (Figures 2).

Immunohistochemical expression of NF-κB with quantitative changes of its positive cells of gastric mucosa in all albino rats groups:

Figure (3) displayed normal immunohistochemical expression of NF-κB in gastric tissue of the control group and revealed prominent increase of NF-κB expression in gastric tissue of gastric ulcer group. The immunohistochemical expression of NF-κB showed reduction in gastric tissue of in all other gastric ulcer-treated groups (Figures 3).

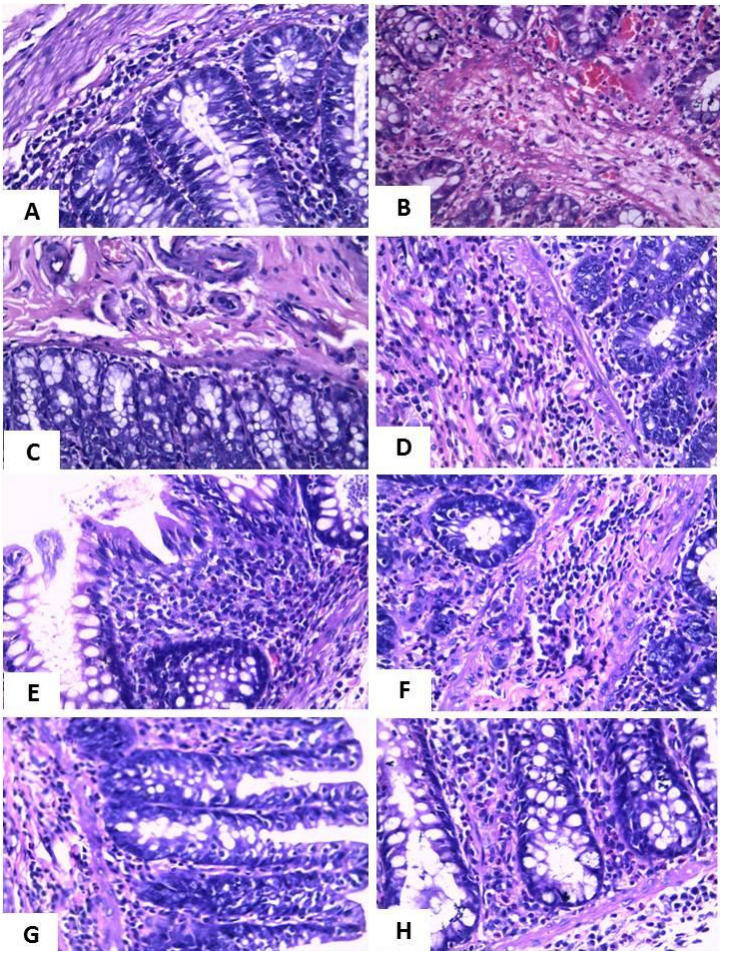

Figure (1): Histopathological examination of gastric tissue of (A): control group. (B): gastric ulcer group. (C): gastric ulcer with exercise group. (D): dexilant treated group. (E): quercetin treated group. (F): dexilant treated with exercise group. (G): quercetin treated with exercise group. (H): quercetin and dexilant treated group.

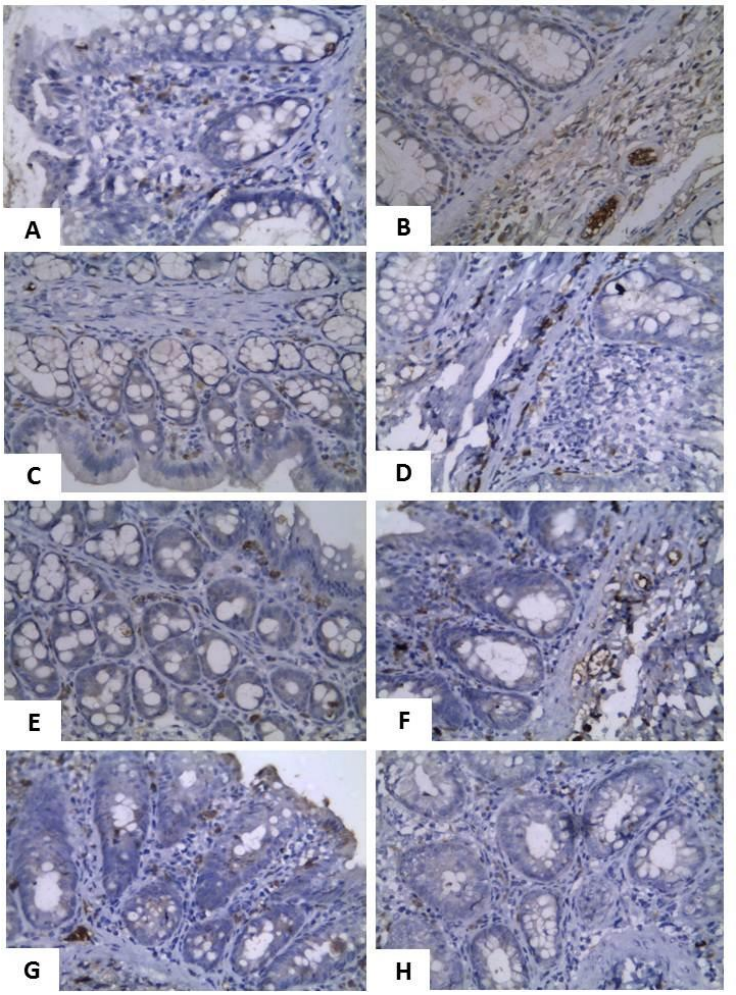

Figure (2): Immunohistochemical analysis of (A): control group. (B): gastric ulcer group. (C): gastric ulcer with exercise group. (D): dexilant treated group. (E): quercetin treated group. (F): dexilant treated with exercise group. (G): quercetin treated with exercise group. (H): quercetin and dexilant treated group.

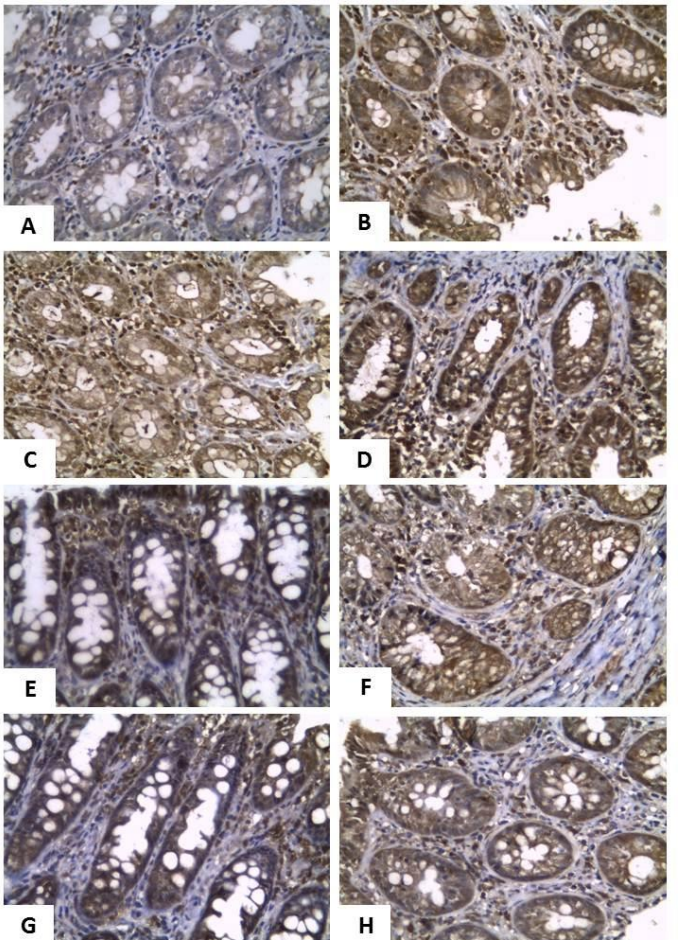

Figure (3): Immunohistochemical analysis of NF-κB in gastric tissue of (A): control group. (B): gastric ulcer group. (C): gastric ulcer with exercise group. (D): dexilant treated group. (E): quercetin treated group. (F): dexilant treated with exercise group. (G): quercetin treated with exercise group. (H): quercetin and dexilant treated group.

Discussion

The findings of this study showed that aspirin-induced peptic ulcer in rats resulted in significant damage to gastric tissue, as evidenced by a significant drop in pH, an increase in total stomach acidity parameters, an increase in UI, and a decrease in CR. as compared to the normal control group. These results are in accordance with previous reports (Cryer and Mahaffey, 2014; and Saha et al., 2016).

The present work showed that aspirin could cause gastric hyperacidity by antagonizing the effect of histamine on H2 receptors within the parietal cell membranes, which results from the stimulatory G protein acting via protein kinases to increase the intracellular concentration of cyclic AMP, which in turn causes an increase in H2 transport into the gastric lumen by H+K+ ATPase (Chan

et al., 2017). Another mechanism of aspirin is the systemic blocking of COX-1 enzyme, which is responsible for PG production, so when decrease PG level leads to increasing H2 transport and increase HCl formation with subsequent decrease of gastric pH, increase its total gastric acidity and increase of UI with decrease CI (Ornelas et al., 2017).

COX-1 suppression by aspirin contributed to a considerable release of endothelin-1 (ET-1) which is a powerful vasoconstrictor that has been demonstrated to produce mucosal damage (Gunaydin and Bilge, 2018). In addition to irreversible inhibition of COX-1 enzyme by aspirin results in a deficiency in neutrophil activation, resulting in the generation of ROS, which in turn causes the gastrointestinal damage (Diaz-Gonzalez and Sanchez-Madrid, 2015).

In addition, aspirin also inhibits thromboxane A2 on platelets, inhibiting platelet aggregation, and therefore increasing ulcer bleeding (Orlando et al., 2014). Aspirin induced decrease in blood flow, mucus-bicarbonate discharges, impairment of platelet aggregation, loss of epithelial cell renewal, and an increase in leukocyte adherence that are contributing for pathogenesis of ulceration (Handa et al., 2014). The results of the present work are in line with those previously outcomes reported by Motamed et al., (2015) who found that moderate physical exercise has improved gastric pH and the accompanied gastric total acidity in rats.

The mechanism by which moderate physical exercise might be due to improvement of gastric pH and decline total gastric acidity levels was not well definite, but it might be related to antioxidant, anti-inflammatory and anti-apoptotic effects of moderate exercise as revealed in our results. The mechanism by which moderate exercise significantly decrease UI with concomitant significant increase of CI have not been reported but it is possible that physical activity may affect peptic ulcer disease through various biologic mechanisms, including improving the immune system's ability to neutralize the effects of aspirin and improving a person's ability to deal with stressful situations. (Lee et al., 2019).

The decrease in acid secretion is another proposed mechanism by which physical exercise might influence the development of ulcer disease. Regular physical activity (walking, gardening, or swimming) has been associated with a decreased risk for severe GIT hemorrhage due to improvement of the blood supply (Jones et al., 2015).

Dexilent's antioxidant, anti-inflammatory, and anti-apoptotic properties may be responsible for the considerable rise in stomach pH and reduction in overall gastric acidity levels as shown in the results of the present work. In addition, another explaining mechanism is that dexilent is a modified PPI. These PPI medications irreversibly block hydrogen-potassium adenosine triphosphatase on the luminal side of the parietal cell, thus preventing secretion of hydrogen ions into the gastric lumen (Kitay et al., 2019).

The reduction of UI with concomitant significant increase of CI might be explained by that was dexilent inhibits stomach acid output for up to 36 hours, aiding in the repair of ulcers and erosions, stabilizing thrombi, and minimizing GIT

bleeding bleeding in patients on low dose aspirin (Ali Khan and Howden, 2018). Additionally, dexilent promotes mucosal cell renewal by promoting gene expression of prosurvival proliferating cell nuclear antigen, survivin, epidermal growth factor, and basic fibroblast growth factor (Rantanen et al., 2014).

By lowering the number of mast cells and antagonizing histamine's activities, quercetin has been discovered to enhance stomach pH and lower overall acidity levels (Jafarinia et al., 2020). Quercetin has been shown to decrease H+K+-ATPase activity by up to 33% as a secondary mechanism for lowering overall acidity and raising gastric pH (Carvalho et al., 2018). Also, quercetin has antioxidant, anti-inflammatory and anti-apoptotic as exhibited in our results with subsequent improvement of gastric ulcer. In addition, quercetin controls the activity of COX and NOS. Also, Quercetin enhanced nuclear translocation of the nuclear factor related to erythroid 2 (Nrf_2) which plays a significant role in protecting the digestive tract from oxidative damage. Hemoxigenase-1 (HO-1) and other antioxidant defense proteins, as well as NF-kappaB activation and intercellular adhesion molecule-1 (ICAM-1) and P-selectin expression, are all negatively regulated by Nrf2 and so suppress pro-inflammatory signaling as well as increase the activities of GPx **(**Habtemariam, 2019).

The combination of exercise with either dexilent or quercetin dramatically elevated gastric pH and decreased both total gastric acidity and UI with concurrent enhancement of CI. Also, combination of both dexilent and quercetin exhibited greater improvement of these parameters as compared to the ulcer or other treated groups. The combination of these treatment gave rise to greater improvement of gastric ulcer which might be related to the combination of their mechanisms.

In the present work, the results exhibited that the gastric HSP70 level was dramatically elevated in the ulcer group as compared to the control group. The mechanism for increasing the gastric HSP70 level in the ulcer group by aspirin was that Hsp70 is a group of highly conserved stress proteins which are critical for the body's capacity to maintain its own stability, cellular stress tolerance, normal physiological function, and increased defense and adaptation of cells to lethal stimulus. The aspirin-induced oxidative stress may be countered in rats by overexpression of the heat shock protein 70 gene (HSP70) (Stetler et al., 2010). HSP70 overexpression enhances ulcer healing by enhancing stomach mucosal blood flow and cell proliferation. Expression of HSP70 can also be caused by long term administration of aspirin to increase the adaptive cellular protection-tolerances through modulation of the denatured and unfolded proteins (Liu et al., 2011).

In the current work, the results showed that the gastric HSP70 level was remarkably increased in the exercise treated group as compared to the ulcer group. For the exercise-treated group, HSP70 levels increased as a consequence of hypoxia, increased temperature, and generation of free radicals (Lollo et al., 2013). The level of plasma HSP70 during exercise is increased due to numerous release of HSP70 from lymphocytes during high-load exercise (Lawler et al., 2016). The mechanism for decline of the gastric HSP70 level in the dexilent treated group was that dexilent reduces stomach acid output, suppresses the

production of oxidative stress indicators like MDA, and reverses the expression of proinflammatory markers like TNF, thereby relieving the stress state (Ruiz-Hurtado et al., 2021).

The results of the present work demonstrated that the gastric level of HSP70 decreased in the quercetin treated group as compared to the ulcer group. These results were in accordance with several studies (Yang et al., 2016). The mechanism for decline of the gastric HSP70 level in the quercetin treated group was that A number of kinases, including creatine kinase2 (CK2), which has been demonstrated to promote HSP70 production via the phosphorylation of heat shock factor 1 (HSF1) threonine 142, were inhibited by quercetin. Thereby, quercetin may decrease HSP70 induction by preventing CK2 phosphorylation of HSF1 and thus inhibiting HSP70 induction (Zorz et al., 2011). The findings of this research showed a considerable increase in HSP70 activity in the dexilent exercise group. The mechanism for increasing the gastric HSP70 level in dexilent with exercise group was due to the exercise effect which increase the gastric HSP70 level.

The combination of exercise with either dexilent or quercetin significantly increased the gastric HSP70 activity as compared to either dexilent or quercetin groups. The combination of these treatment gave rise to greater improvement of the gastric HSP70 which might be related to the combination of their mechanisms. The results of the present work showed that the ADMA activity considerably higher in the ulcer group as compared to the normal group.

In aspirin induced peptic ulcer, there is an observed drop in DDAH-1 gene expression with subsequent increase of ADMA level in damaged mucosa due to decreasing ADMA metabolism. Lowering DDAH gene expression might be related to the imbalance oxidative status associated with gastric injury caused by aspirin. A direct link has been shown between the production of ROS and ADMA, according to this theory (Shahin et al., 2018).

The results of the current study revealed that exercise treated group effectively attenuated the rise of gastric ADMA level as compared to the gastric ulcer group. Mechanism by which moderate physical activity reduced increased levels of gastric ADMA via its antioxidant, anti-inflammation, and anti-apoptotic properties (Semeraro et al., 2022). In addition to increase HSP70 (Nakhjavani et al., 2012) as shown in our results. The results of the current study exhibited that the gastric ADMA level remarkably reduced in dexilent group as compared the ulcer group. These results were in line with other previous reports (Hu et al., 2017).

An anti-inflammatory and antioxidant activity of dexilent that may directly affect inflammatory cells such endothelial cells, neutrophils, and monocytes to modulate the expression of adhesion molecules was hypothesized to be a mechanism for lowering stomach ADMA levels in the dexilent treated group. This prevents the activation of Nf K-B, the production of inflammatory cytokines, and the chemotaxis of neutrophils. Also, blocking the release of pro-inflammatory cytokines, increasing the endogenous anti-oxidant defense mechanism and maintaining the integrity of the internal structure of damaged tissue, so dexilent

balances the oxidative stress and decreases ADMA level (Alfahad et al., 2021) as shown in our results.

The results of the present work demonstrated that the gastric level of ADMA decreased in the quercetin treated group as compared to ulcer group. The mechanism for decline the gastric ADMA level in the quercetin treated group was that Antioxidant quercetin scavenges free radicals, reducing their production, and quercetin also possesses anti-inflammatory and anti-apoptotic properties (Ranganathan et al., 2015). Inhibiting lipid peroxidation by catalysing the breakdown of H2O2 and GPx reduces ADMA levels in the stomach by lowering gastric ulcer pathogenesis (Zhang et al., 2020). The combination of exercise with either dexilent or quercetin significantly increased gastric HSP70 activity. Also, combination of both dexilent and quercetin exhibited greater improvement of this parameter as compared to the ulcer or other treated groups.

The combination of these treatment gave rise to greater improvement of gastric HSP70 which might be related to the combination of their mechanisms. In the present work, our findings revealed that TNFα significantly increased in the ulcer group as compared to the control group. The mechanism for increase of the gastric TNFα level in aspirin induced gastric ulcer was that aspirin causes inflammation by stimulating macrophages to produce cytokines as TNFα that then enhance infiltration of neutrophils (Sugimoto et al., 2016). One purposed mechanism for decreased the gastric TNFα by moderate exercise was that regular exercise performed at a moderate intensity prevented neutrophil infiltration and reduced lipid peroxidation, which resulted in the down regulation of pro-inflammatory cytokines like TNF (Manna and Jain, 2015).

Also, it appears that a systemic physiological adaptation occurs as a consequence of exercise-induced oxidative challenge and improves the resistance to further oxidative stress by increasing antioxidant and housekeeping enzyme activities while decreasing neutrophil-dependent inflammation (Arabacı Tamer et al., 2020). When compared to the ulcer group, the dexilent group showed significant reductions in stomach TNF levels. According to prior studies, these results were consistent with these findings (Ruiz-Hurtado et al., 2021).

The purposed mechanism for reduction of the gastric TNFα after the dexilent treatment was that dexilent has direct anti-inflammatory effects by reducing the expression of TNF-α at both transcription and protein levels. Dexilent suppresses the monocytic cell line's generation of TNF (Ruiz-Hurtado et al., 2021). The results of the present work demonstrated that the gastric level of TNFα decreased in the quercetin treated group. These results were in accordance with earlier studies (Alkushi and Elsawy, 2017; Zhang et al., 2020). There are several reasons why quercetin reduces gastric TNF-a, but the most common one is that quercetin regulates myeloperoxidase (MPO), a biomarker of neutrophil infiltration that has pro-inflammatory and pro-oxidative qualities, in peptic ulcers (Zhang et al., 2020). Quercetin has been shown to decrease MPO levels with subsequent suppression of neutrophil activity. Hence, it decrease the TNFα level (Farzaei et al., 2015).

The combination of exercise with either dexilent or quercetin significantly reduced gastric TNFα. Also, combination of both dexilent and quercetin exhibited greater

improvement of gastric TNFα as compared to the ulcer or other treated groups. The combination of these treatment gave rise to greater enhancement of gastric TNFα which might be related to the combination of their mechanisms. This histopathological impairment in aspirin-induced ulcers may be attributable to the increased production of NO in the stomach mucosa as a result of the overexpression of iNOS. Aspirin induces inflammation and neutrophil infiltration, as well as an increase in TNF- production, which in turn increases the production of superoxide by neutrophils (Mahmoud and Abd El-Ghffar, 2019).

While, the results of this study revealed that in all treated groups the histopathological changes of gastric tissue induced by aspirin was attenuated. It was noted that these changes were remarkably improved with combination of dexilent and quercetin as compared with other treated groups. The mechanism by which all treatments improved the histopathological changes might be reflected to their antioxidant, anti-inflammatory and anti-apoptotic effects of exercise, dexilent and quercetin (Xu et al., 2019; Paz et al., 2020) as shown in our results.
The mechanism by which aspirin decreased Bcl-2 was that Bcl-2 mRNA and protein expressions and the Bcl-2/Bax ratio were lowered by aspirin because aspirin increased Bax mRNA and protein expressions and decreased Bcl-2 mRNA and protein expressions (Alarifi et al., 2017).

The aspirin mechanism which increased NF-KB was that aspirin increase inflammatory factors by which NF-kB is activated like IL-8 during the development of peptic ulcer through inhibitory factor κB-α (IkB) kinase complex phosphorylates IkB, and then degradation of IkB (Marta et al., 2020). The mechanism by which moderate regular exercise decrease immunehistochemical expression of NF-KB was that the phosphorylation of NF-B and IB was lowered dramatically by moderate frequent exercise as a method for reducing NF-KB immunohistochemical expression. Moderate exercise training and inhibition of macrophage markers at the mRNA level reduced the expression of inflammatory genes, including IL-6 and TNF (Liu and Chang, 2018).

The results of the current study exhibited that the immunehistochemical expression of Bcl-2 remarkably increased in contrast to the decreased NF-KB level in dexilent group as compared to the ulcer group. These results were in line with other previous reports (Lu et al., 2019). In order to preserve the usual proapoptotic/antiapoptotic ratio, dexilent suppresses aspirin-induced up-regulation of Bax and down-regulation of Bcl-2, therefore raising Bcl-2 levels (Rantanen et al., 2014). The results of the current study exhibited that the immunehistochemical expression of Bcl-2 significantly increased in contrast to the decreased NF-KB level in quercetin group as compared to the ulcer group. These results were in line with Serafim et al., 2020.

The mechanism for increasing Bcl-2 level was that quercetin has an antiapoptotic impact against aspirin-induced apoptosis in gastric tissue that was mediated through inhibiting the c-Jun N-terminal kinases (JNK) and ERK-mediated apoptotic pathways (Abdel-Tawab et al., 2020). The mechanism for decreasing NF-kB level was that the NF-kB pathway, which is involved in the generation of pro-inflammatory cytokines including tumour necrosis factor- (TNF-), interleukin-6

(IL-6), and interleukin-1 (IL-1), is suppressed by quercetin, which suppresses inflammation via neutrophil infiltration (Cheng et al., 2019).

The combination of exercise with either dexilent or quercetin significantly increased BcL-2 and decreased NFκB. Also, combination of both dexilent and quercetin exhibited greater improvement of these parameters as compared to the ulcer or other treated groups. The combination of these treatment gave rise to greater improvement of BcL-2 and NFκB which might be related to the combination of their mechanisms.

Conclusion

We concluded that combination of quercetin and dexilent could improve gastric ulcer induced by aspirin via their anti-apoptotic, anti-inflammatory and antioxidant effects.

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