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Comparative Study on The Possible Protective Effect of Boswellic Acids and /or Co-Enzyme Q10 Against Stress-Induced Peptic Ulcer in Normally Fed and Protein Malnourished Rats

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Abstract: Peptic ulcer (PU) is one of the common diseases affecting mankind. 'It kills few but troubles many'. Available therapeutic drugs for peptic ulcers have failed to meet pharmacological expectations due to their drawbacks e.g., proton pump inhibitors. The current study was conducted to study the possible protective role of Boswellic acids (BA) and/or Co-enzyme Q_{10} (Co Q_{10}) against stress induced PU in the rats under the conditions of protein malnutrition (PM)& normally fed (NF), besides a possible involved mechanistic pathway. 2major groups were randomly divided; ("NF"&"PM" rats) each major group was classified into 5subgroups (6 rats each) using doses of 250 mg/kg for BA and 200 mg/kg for Co-Q_{10} orally 1hr before stress as following: 1unstressed(NF-control), 2unstressed(PM-control), 3(control ulcer-NF), 4(control ulcer-PM), 5(BA-NF), 6(BA-PM), 7(Co Q10-NF), 8(Co Q_{10}-PM), 9combination of the BA and Co-Q_{10}-NF), 10combination of BA and Co Q_{10}-PM), 10combination of BA and Co Q_{10}-PM). After 21days from PM, rats were stressed (electric shock for 3hours at 30volts). Parameters were; Ulcer and preventive index, Nonprotein sulfa hydrate (NPSH) compounds, Lipid peroxidase, Super oxide dismutase (SOD)activity, Glutathione S transferase (GST) activity, DT diaphorase activity [NAD(p)H oxidoreductase], Serum albumin, Serum immunoglobulin (IgA), Autophagy factor; Beclin using Western Blot, Endoplasmic reticulum factor; Bax using PCR. Ulcer Index was an evidence of PU. PM as; Body weight loss and decreased Serum albumin. BA&Co-Q_{10} had Preventive Index and decreased inflammatory and stress biomarkers; (NPSH), Lipid peroxidase, (SOD), [NAD (p) H], (IgA). Pathway cascade products was through; Autophagy factor and Endoplasmic reticulum factor. BA and Co-Q_{10} can be introduced as protective agents against peptic ulcer due to its anti-inflammatory and antioxidant effects.

Keywords: Peptic-Ulcer; Stress; Boswellic-acids; Co-enzyme-Q_{10}; Protein-malnutrition; Beclin; Bax.

1. INTRODUCTION

Peptic ulcer is one of the common diseases affecting mankind 'It kills few but troubles many',[1] still, prognosis of peptic ulcer is unclear, in turn, the mechanism of available treatment. Gastric mucosa is able to resist autodigestion yet it is exposed to several 'insults' like; hydrochloric acid, pepsin, reflux of bile, spicy food, microorganisms and at times alcohol and ulcerogenic medications. In turn, it is known that the integrity of the gastric mucosa is preserved via protection mechanisms against these 'aggressive' insulting influences. [2]

Occurrence was approximately 3-10%, still 'as a result of excessive advertising of antacids the public has come to believe that man is fighting a against acidity'.[3]

Still, PU prognosis and treatment is not clearly understood. Stomach lining can stand against being self-digested never the less, it is endangered by plenty of aggressive factors like gastric juice, pepsin and bile acids and spicy food, germs and acid-based drugs and ethanol. In turns, solidity of stomach lining is kept intact via protection versus aggressive causes.[4] Gastritis leads to PU to deteriorates into 4th grade ulcer, which is 10%–40% fatal. [5] [6] [7]

Frequently, PU prognosis can be; hemorrhage, puncture, and occlusion. [8] Hemorrhage due to PU is a common problem with 10% fatality rate, besides many comorbidities.[9] Although perforated PU incidence is fewer frequent than hemorrhage, it is the most frequent fatal complication by 30%; categorized as a medical crisis which necessitates operation as soon as possible, since it decreases indisposition. [10]

Signs and symptoms of PU are presented as longwinded serious and abrupt stark stomachache of reverberation soreness in comorbidity with peritoneal inflammation, elevated body temperature and elevated white blood cell count are linked to puncture triplet of; high heart rate, gastric ache, and stiffness.[11]

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PU including stomach and duodenum sores which in turn are most frequent digestive organ diseases in medical field.[12] Thus, trails classify this as outbreak disaster of the era. [13]

In addition, PU is considered as a common cause of digestive tract surgical intervention, moreover, of bad prognosis and of high fatality rate.[14] PU occurrence probability is growing high in the current era of time. Upcoming time shows a reduction in PU. Still, changes around the world in addition to bigger geriatric presence in population lead to multiple co-diseases and multiple medication prescriptions in turn higher rate of PU impediments. Egypt recorded 245 patients (18%) of PU, 206 (15%) ulcerated duodenums and 57 (4%) gastric sores.[15] Growing rate of disease is directly related to aggressive causes present such as; ethanol overuse, imbalanced diet, cigarette overuse, and anxiety all together lead to outbreak with worldwide apprehension, smoking, and stress has made this disease a major health problem of global concern. [16 17 18]

In Mansoura, Egypt, elevated anxiety occurrence nervousness tension and misery are; 40.2%, 46.6% and 27.9%, correspondingly. Unspectacularly academic youth were of 4.6 anxious and curriculum burden represent common anxious reasons. In retrogression study anxious causes and worldwide disease key grade guided anxiousness grade. [19] Cystic fibrosis mechanism is multifactorial, still, there are many causes suggested, oxidative stress is one of them. [20]

Imbalanced diet causes poor treatment outcome among inpatients for decades. By halve 30' it was linked. [21] PU prevalence with above 20% decrease in physique mass, consequently ten times fatality than fewer mass loss. [22 23] Imbalanced diet causes decrease in body function and bad prognosis for inpatients. [24]

Presence of imbalanced diet encourages stress free radicals because of diminished SOD, GSH, and catalase. In addition, GSH reduction is due to poor diet.[25] Malfunctioned kidney patients suffer inequality of oxidative stress elements and protection mechanisms eventually lead to cellular destruction. [26]

In Egypt, *Helicobacter pylori* is 90% incidence. Clinical trial demonstrated that seroprevalence of Helicobacter *pylori* demography is 60% in Cairo, 88% in Alexandria, 87% urban Assiut and 40% rural Assiut. [27]

Besides, current treatment agents of PU have drawbacks and side effects such as; arrhythmia, gynecomastia, hypersensitivity, impotence, and hematopoietic alteration of medications, in; anticholinergics, H-receptor antagonists, and proton pump inhibitors. [28 29]

Many published researches in the Middle East showed metronidazole resistance as approximately 60-80%. [30 31 32] Cultures showed worldwide elevated resistance to metronidazole, while other antimicrobial agents' resistance to other tested antimicrobial agents was less common (4% for clarithromycin, erythromycin, and azithromycin resistance against 2% for ciprofloxacin and ampicillin resistance). Metronidazole use in *H. pylori* infection in Egypt is almost useless.[33] Leptin heals PU caused by nervousness and anxiety.[34]

Gastric inflammation is an inflammatory reflex mechanism in case of stomach mucosal damage via inflammatory mediators flooding such as; lymphocytes and plasma cells. Process includes basic layer of mucosal lining and glands leading to massive corruption of glands, shrinking and metaplasia. Different causative agents end up in stomach inflammation such as drugs, immunity and gene factors and also microorganisms. [35 36] Researches on reactive oxygen species showed that scavenging enzymes are attenuated by *H. pylori* presence and gastric carcinoma in gastric inflammation. [37 38]

Autophagy is essential in cellular intuitive and decease is unclear. [39] Nevertheless, autophagy is a reflex mechanism in supplying nourishment and power in case of nervousness.[40] Knockout of autophagy genome or process disturbance by medications leads to cellular decease.[41] In-vivo research proved that autophagy genome is fundamental in power balance in intracellular early-stage neonate favism. [42] Contradictory, long time or too much autophagy processing favors cellular decease. Autophagy is a step-in cascade reaction of type-2 automated cellular decease or autophagy cellular decease.[43]

Bcl-2 (B-cell lymphoma) amino-acids group responsible for apoptosis and autophagy. Primary basic element Bcl-2, suggested to have 4 subtypes preserved Bcl-2 homology domains (BH1–4), inhibited apoptosis via homogenization and repossession of pre-apoptotic amino acid groups; Bax and Bak.[44] Bax and Bak have the ability to oligomerize into proteolipid holes and permit outmost mitochondrial membrane, in turn, cytochrome c production in addition to, intermembrane elements in cytosol starting cascade apoptotic series.[45] [46] Autophagy stimulated by favism. [47]

Phyto chemists and internal medicine specialists favor herbal medicine around the world to stop and treat many diseases. Trials proved multiple herbs ability to heal PU besides researches showed exact pathway of herbal healing process. [48 49]

Boswellia serrata, family Boswellia genus called frankincense.[50] B. serrata used in healing and power regain in inpatients. According to literature, B.

serrata important in asthma healing, gastrointestinal disturbances, orthopedics disorders and melanoma.[51] Boswellic acids, a pentacyclic triterpene compounds of herbs essential for healing of many disorders.[52]

B. serrata is famous for healing or quickening healing process. Anciently, B. serrata was an asthma treatment, gastrointestinal disorders, arthritis, and cancer. [53] Boswellic acids, consists of pentacyclic triterpene molecules which is formed by plants family Boswellia, anciently used in many diseases healing. [54]

Boswellic acids have been recognized by reduce human leukocyte elastase, a serine protease, accordingly originates cells insult subsequently, aggravates inflammatory reaction pathway. [55 56] Anti-inflammatory action of boswellic acids in paw edema in rats and mice, have been proved. [57] Besides, in 2007, it was proved that B. serrata pure extraction showed an anti-inflammatory property in human peripheral blood mononuclear cells and mouse macrophages via inhibiting tumor necrosis factor-α (TNF-α), IL-1β, nitric oxide, and mitogen-activated protein kinases. [58] Besides, multiple clinical trials highlighted the value of boswellic acid for its powerful anti-inflammatory treatment. [59 60 61 62]

Coenzyme Q_{10} molecule similar to vitamins aids aerobic process in cellular mitochondria also in energy-source; ATP. Coenzyme Q_{10} a scavenger in reactive oxygen species. Coenzyme Q_{10} possesses inflammation cyto protection ability via decreasing IL-6 biomarker in cardiovascular diseases.[63] Similarly, it was proven that coenzyme Q_{10} enhances endothelial properties in cardiovascular disorders.[64] Coenzyme Q_{10} is proposed in melanoma healing, since in a clinical trial on Chinese females there was a correlation between decreased levels in serum coenzyme Q_{10} and breast cancer risk.[65] Coenzyme Q_{10} creatine kinase action in addition psychological stability in old age bipolar sadness.[66]

Coenzyme Q10 (CoQ10), also known as ubiquinone-10, a crucial lipid-soluble substance, occurring in the inner mitochondrial layer. Acting as hydrogen carrier in the respiratory chain, exerting a crucial physiological function. Acting as an enzymes activator and inducing immunity. As an antioxidant, it is considered as key factor sequestering free radicals, guarding cell membrane stability, DNA from free radicals which cause oxidative damage and aids reusing of vitamin E and keep normal energy levels. It is also important in the formation of cellular adenosine triphosphate, in turn, supplies modulating antioxidants defense system. Researches proved that antioxidants are outstandingly distinctive from each other and each have a particular role. Magnetizing consideration and the range of clinical researches which is greatly increasing. [67 68 69]

Hence, the current research was intended to study the protective role of Boswellic acids and Co-enzyme Q_{10} on stress induced peptic ulcer in protein malnourished and normally fed rats together with signaling pathway involved in process; Beclin and Bax as autophagy and endoplasmic reticulum via mitochondrial oxidative stress reflex mechanism under malnutrition (Hospitalized patient psychological consequences).

2. METHODS

In a comparative study, using a randomly grouped male rats, possible protective effects of both drugs were studied.

2.1. Materials

2.1.1. Animals

The used experimental animals were adult Sprague-Dawley male rats their weight are 150-200 grams, 60 rats were randomly divided into two major groups; normally fed group and protein malnourished group divided as following:

1. 30 rats were divided to 5 subgroups of normally fed rats for protection experiments.

2. 30 rats were divided to 5 subgroups for induction experiments (induction of PM) and protection experiments.

All rats were obtained from National American Marine Research Unit (NAMRu) Abasia, Cairo. The rats were housed (3 /cage) in stainless steel wire bottom cage in a conditioned atmosphere at 22 ±2° C. Animals were fed on standard pellet diet for 1 week for adaptation of animal house purpose. All animals were fasted over night before exposure to stress (electric shock).

Experimental animals were fed a standard diet [70]. They were allowed food and water ad-Libitum. Two types of diet were utilized depending on the amount of casein.

First type; Standard diet: (20% casein as Protein control diet) for normally – fed groups.

Second type; Low-protein diet: (5% Casein) for protein - malnourished groups.

Everything in animals' techniques was done according to the Ethics Committee of the faculty of Pharmacy AL-Azhar University, Egypt (permit number: 81/2016). Unnecessary disturbance of animals, pressure and tough maneuver was avoided.

2.1.2. Chemicals

Boswellic acids (Sigma, Aldrich MO, China); Co enzyme Q_{10} (Mepaco, Egypt); Sodium chloride (El-Nasr, C. Abozohbal, Egypt); Thiobarbituric acid (TBA) (Sigma, Aldrich MO, USA); Trichloroacetic acid (TCA) (10%) (Sigma Aldrich MO, USA); Tris-HCl (Merck) [Tris (hydroxymethyl) aminomethone hydrochloride]; Phenol indophenol (Sigma, Aldrich

MO, USA); 2,6-dichlorophenol-indophenol sodium salt hydrate; Catalase (Sigma, Aldrich MO, USA).

2.1.2. Experimental Design

Two major groups were randomly divided; (30 normally - fed rats and 30 protein malnourished rats) each major group was classified into 5 subgroups (6 rats each) as following:

1st subgroup is unstressed group (normally fed rats control).

2nd subgroup is unstressed group (protein malnourished rats' control).

3rd subgroup is exposed to electric current or shock for 3 hours at 30 volts (control ulcer group-normally fed).

4th subgroup is exposed to electric current or shock for 3 hours at 30 volts (control ulcer group-protein malnourished).

5th subgroup is exposed to electric current or shock for 3 hours at 30 volts and given Boswellic acids (250 mg/kg orally 1 hour once before stress) (normally fed rats).

6th subgroup is exposed to electric current or shock for 3 hours at 30 volts and given Boswellic acids (250 mg/kg orally 1 hour once before stress) (protein malnourished rats).

7th subgroup is given Co-Enzyme Q_{10} and exposed to electric current or shock for 3 hours at 30 volts (200 mg/kg orally 1 hour once before stress) (normally fed rats).

8th subgroup is given Co-Enzyme Q_{10} and exposed to electric current or shock for 3 hours at 30 volts (200 mg/kg orally 1 hour once before stress) (protein malnourished rats).

9th subgroup is given a combination of the Boswellic acids and Co-Enzyme Q_{10} (250 and 200 mg/kg respectively orally 1 hour once before stress) and exposed to electric current or shock for 3 hours at 30 volts (normally fed rats).

10th subgroup is given a combination of Boswellic acids and Co-Enzyme Q_{10} (250 and 200 mg/kg respectively orally 1 hour once before stress) and exposed to electric current or shock for 3 hours at 30 volts (protein malnourished rats).

2.1.3. Parameters investigated

Ulcer Index:

After exposure to electric shock, rats were killed by cervical dislocation. Abdomens were opened and the stomachs were exposed, excised and opened from greater curvature, rinsed with saline and pinned flat on a cork board to be exposed to gross lesions evaluation the gastric lesions were evaluated according to the method described. [71]

The gastric lesions were scored according to their severity between 0 (non-visible) and 4 (deep lesions with diameter greater than 8mm) in each stomach. The scores of each lesion were then summed up and the results referred to the measure lesion score ± SE of the mean the ulcer indices were assayed and calculated and the gastric walls are prepared for the histopathological examination by using suitable dyes.

Oxidative stress markers:

In total gastric tissue homogenate; Nonprotein protein sulfa hydrate (NPSH) compounds, lipid peroxidase.

In stomach systolic fraction; Super oxide dismutase (SOD) activity, Glutathione S transferase (GST) activity, DT diaphorase activity [NAD (p) H oxidoreductase].

In blood; Serum albumin

Test for immunological parameters; serum immunoglobulin (IgA) as stress marker.

Immunoturbidimetric procedure using cobas integra system for quantitative immunological determination of immunoglobulin A in serum. [72]

Principle: Rat IgA forms a precipitate with a specific antiserum which is determined turbidimetrically at 340 nm.

Using 2 reagents;

Reagent 1: anti-IgA antiserum in phosphate buffer stabilized with 0.09% sodium azide in vial B. (liquid).

Reagent 2: reagent for antigen excess check IgA in diluted serum stabilized with 0.09% sodium azide in vial C. (liquid).

Pathway cascade products:

Autophagy factor; Beclin (using Western Blot)

Endoplasmic reticulum factor; Bax (using real time PCR)

Histopathological tissue structure.

2.1.4. Statistical analysis

Data were stated as means ± S.E.M. Comparisons among means were done using One-Way ANOVA. Statistical analysis was accomplished using Graph Pad Prism software (version 9.0.1); a probability level of less than 0.05 was believed to be statistically significant.

3. RESULTS

3.1. Induction Experiments:

3.1.1. Induction of Ulcer

Ulcer Index was recorded for stomach of untreated rats and severity was recorded as shown in **Figure 1**.

3.1.2. Induction of Protein malnutrition

3.1.2.1. Body weight loss

5% casein caused significant weight loss in PM rat groups (even groups; 2,4,6,8,10). However, 20% casein caused significant weight gain in NF rat groups (odd groups; 1,3,5,7,9) as shown in **Figure 2**.

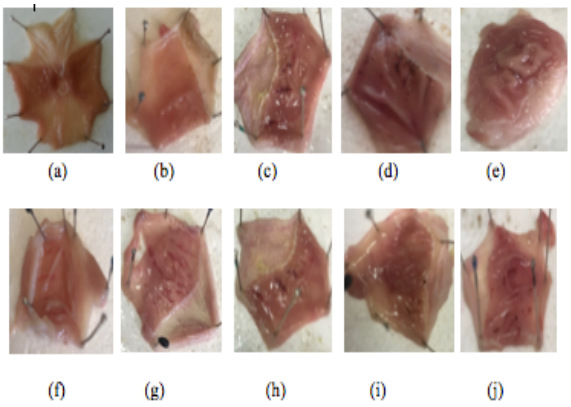


Figure 1. Influence of stress-induced peptic ulcer (30 volts for 3 hours) on (**a**) unstressed normal stomach (NF-control); (**b**) unstressed normal stomach (PM-control); (**c**) untreated ulcerated stomach (control ulcer-NF); (**d**) untreated ulcerated stomach (control ulcer-PM); (**e**) mild inflamed stomach (250 mg/kg BA-NF); (**f**) mild inflamed stomach 250 mg/kg (BA-PM); (**g**) moderate inflamed stomach 200 mg/kg (Co Q_{10}-NF); (**h**) Moderate inflamed stomach 200 mg/kg (Co Q_{10}-PM); (**i**) slightly inflamed stomach 250 mg/kg and 200 mg/kg of combination of the BA and Co-Q_{10} respectively (NF); (**j**) Mild inflamed stomach 250 mg/kg and 200 mg/kg combination of BA and Co Q_{10} respectively (PM). Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$).

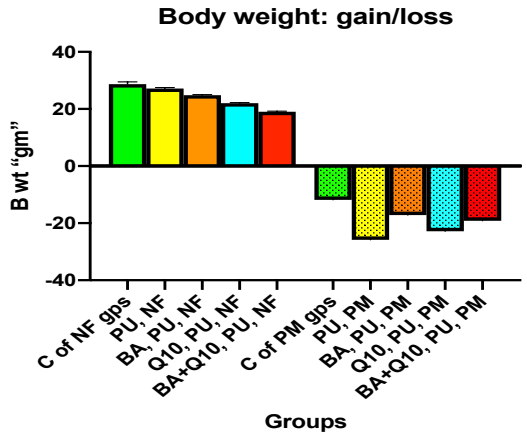


Figure 2: Influence of 5% casein (PM) diet versus 20% casein (NF) diet on body weight. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$).
C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress (30 volts for 3 hours). BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). PM: Protein Malnourished. NF: Normally Fed.

3.1.2.2. Serum Albumin

5% casein caused significant serum albumin reduction in PM rat groups as shown in **Figure 3**.

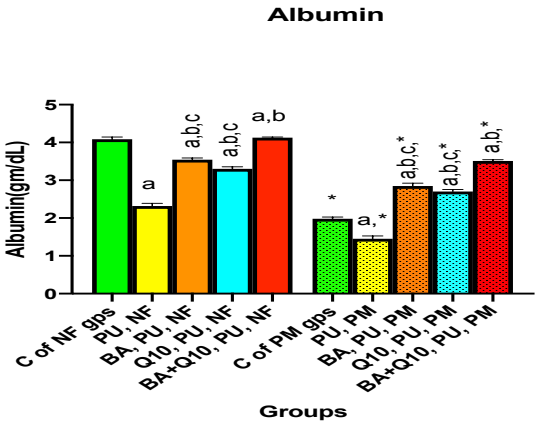


Figure 3: Influence of 5% casein (PM) diet versus 20% casein (NF) diet on serum albumin. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group.*: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

3.2. Protection Experiments:

3.2.1. Preventive Ulcer Index

Administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant prevention of ulcer in rat stomach in both; normally fed and protein malnourished groups as shown in **Figure 4**.

3.3. Oxidative Stress Markers:

3.3.1. In total gastric tissue homogenate

3.3.1.1. Nonprotein sulfa hydrate (NPSH) compounds:

Administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of NPSH compounds in gastric tissue homogenate in both; normally fed and protein malnourished groups as shown in **Figure 5**.

3.3.1.2. Lipid Peroxidase:

Administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of lipid peroxidase level in gastric tissue

homogenate in both; normally fed and protein malnourished groups as shown in **Figure 6**.

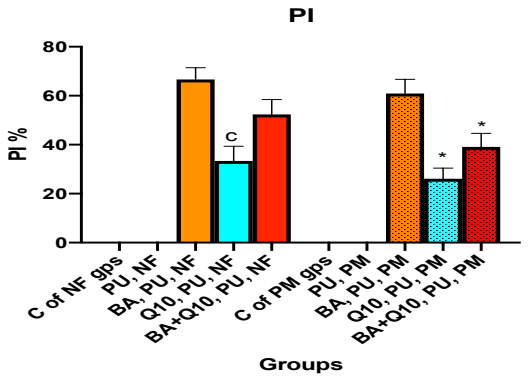


Figure 4: Preventive index of oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 administered 1hr prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet on rat stomach. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$).
C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished. *: Significant from the corresponding NF group. c: Significant from Corresponding Combination group.

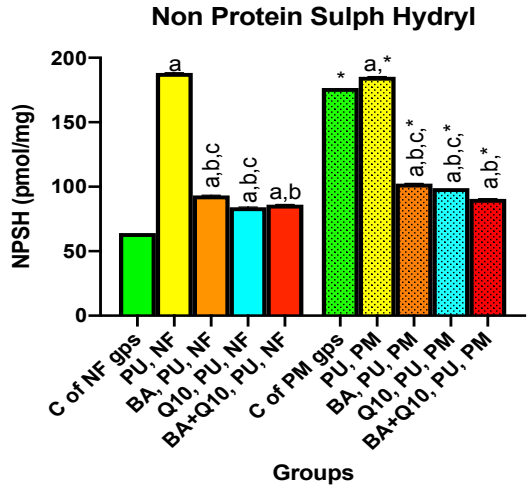


Figure 5: NPSH level in gastric tissue homogenate following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

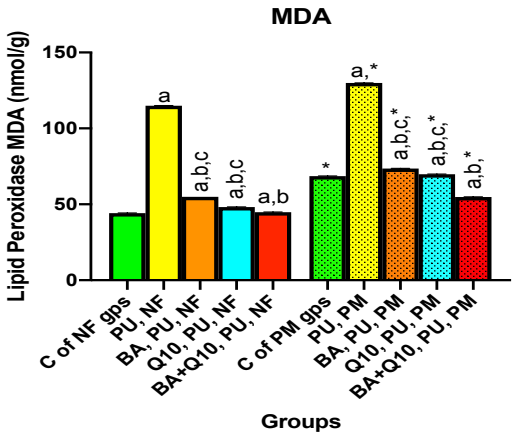


Figure 6: Lipid peroxidase level in gastric tissue homogenate following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

3.3.2. In stomach systolic fraction

3.3.2.1. Super oxide dismutase (SOD) activity:

Administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of SOD levels in stomach systolic fraction in both; normally fed and protein malnourished groups as shown in **figure 7.**

3.3.2.1. Super oxide dismutase (SOD) activity:

Pretreatment with 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of SOD levels in stomach systolic fraction in both; normally fed and protein malnourished groups as shown in **Figure 8**.

3.3.2.2. Glutathione S transferase (GST) activity:

Administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of GST levels in stomach systolic fraction in both; normally fed and protein malnourished groups as shown in **Figure 9**.

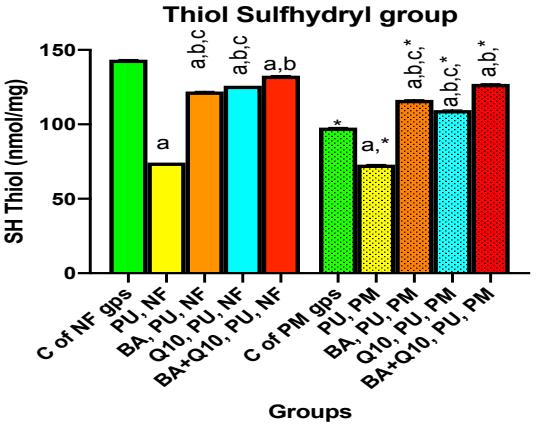


Figure 7: Thiol sulfhydryl group levels in gastric tissue homogenate following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

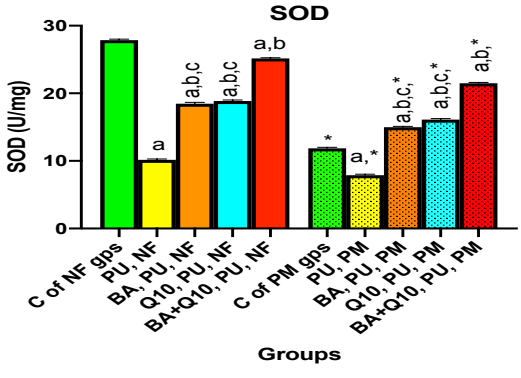


Figure 8: SOD levels in stomach systolic fraction following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg).PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

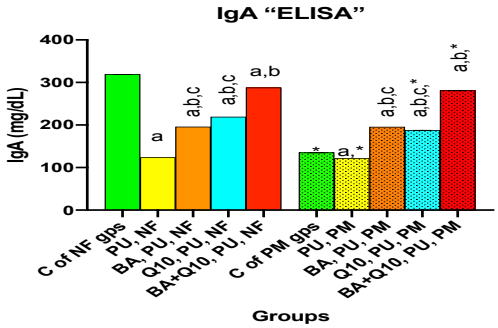


Figure 9: GST levels in stomach systolic fraction following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

3.3. Immunological Parameters; Serum Immunoglobulin (IgA) as stress marker:

Administration of 250 mg/kg of Boswellic acids caused statistically significant reduction of IgA levels in serum of both; normally fed and protein malnourished groups. While Co-Enzyme Q_{10} and combination of BA and Co-Q_{10} have failed to show reduction of Ig A serum level in both; normally fed and protein malnourished groups as shown in **Figure 10**.

3.4. Pathway cascade products:

3.4.1. Endoplasmic reticulum factor; Bax (using real time PCR):

Bax (gene primer sequence: F:5′CGGCGAATTGGAGATGAACTGG3′ R:5′CTAGCAAAGTAGAAGAGGGCAACC3′) was significantly decreased levels following oral administration of 250 mg/kg of Boswellic acids and

200 mg/kg Co-Enzyme Q 10 1 hour prior to stress induced ulcer as shown in **Figure 11**.

3.4.2. Autophagy factor; Beclin (using Western Blot):

PM groups showed significantly higher Beclin than NF groups following oral administration of 250 mg/kg of Boswellic acids and 200 mg/kg Co-Enzyme Q_{10} 1 hour prior to stress induced ulcer as shown in **Figure 12.**

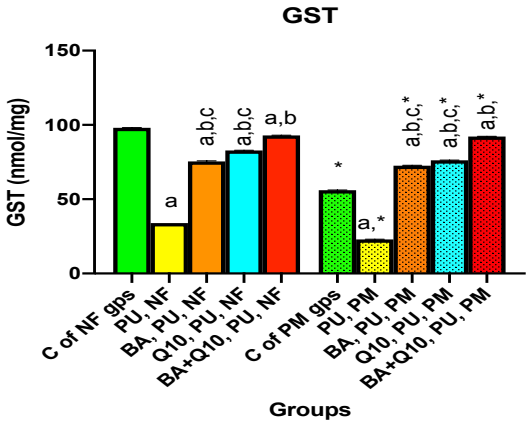


Figure 10: Serum IgA levels following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

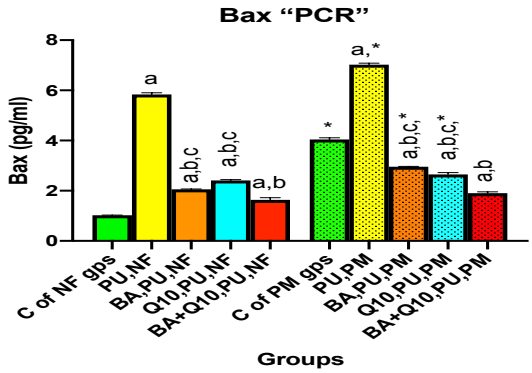
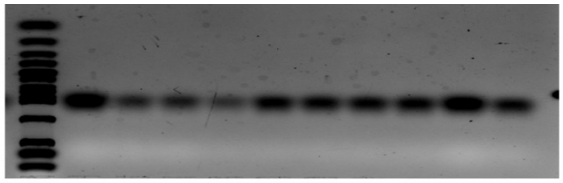
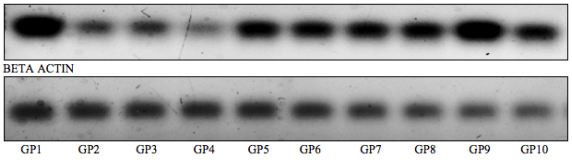


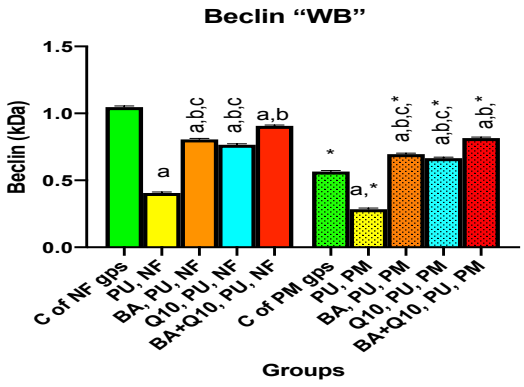
Figure 11: Endoplasmic Reticulum factor; Bax levels following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). C: control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200 mg/kg). PU: Peptic Ulcer due to stress. NF: Normally Fed. PM: Protein Malnourished. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). a: Significant from corresponding C group. b: Significant from corresponding PU group.c: Significant from Corresponding Combination group.*: Significant from the Corresponding NF group.



(a) Beclin



(b) Beta actin



(c)

Figure 12. (a), (b), (c) levels of Beclin following oral administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 1 hour prior to stress on 5% casein (PM) diet versus 20% casein (NF) diet. Data are expressed as the mean values ± S.E.M. (n=6). Data were analyzed by one-way ANOVA. Significance ($p<0.05$). a: Significant from corresponding control group. b: Significant from corresponding PU group. c: Significant from Corresponding Combination group. *: Significant from the corresponding NF group. C: Control (untreated and unstressed). BA: Boswellic Acids (250 mg/kg). Q10: Co-enzymeQ10 (200

mg/kg). PU: Peptic Ulcer due to stress. BA+Q10: Combination of BA and Q10 (250 mg/kg and 200 mg/kg respectively). NF: Normally Fed. PM: Protein Malnourished.

3.5. Histopathological Tissue structure

Administration of 250 mg/kg of Boswellic acids 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} showed significant protection against inflammatory infiltration and edema of both; normally fed and protein malnourished groups in H & E-stained gastric tissues as shown in **Figure 13**.

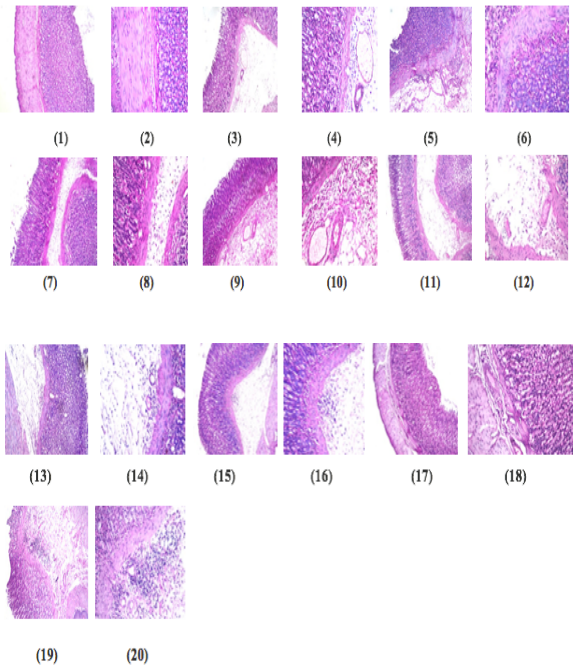


Figure 13. Histopathological tissue structure of: on (group1) unstressed untreated (NF-control); there was no histopathological alteration and the normal histological structure of the mucosa , submucosa , muscularis and serosa were scored 0 as recorded in (Fig.1&2); (group2) unstressed untreated (PM-control); there was no histopathological alteration and the normal histological structure of the mucosa , submucosa , muscularis scored 0 (Fig.3&4); (group3) stressed untreated (control ulcer-NF); sever oedema with few inflammatory cells infiltration were recorded and there was focal inflammatory cells infiltration as well as focal aggregation and oedema in the submucosa scored 3 (Fig.5&6); (group4) stressed untreated (control ulcer-PM); sever oedema with few inflammatory cells infiltration were recorded and diffuse inflammatory cells infiltration and oedema were detected in submucosa scored 4 (Fig.7&8); (group5) 250 mg/kg (BA-NF); the submucosa showed oedema , focal inflammatory cells infiltration and dilated blood vessels in submucosa scored 1 (Fig.9&10); (group6) 250 mg/kg (BA-PM); oedema with few inflammatory cells infiltration were detected in submucosa scored 2 (Fig.11&12); (group7) 200 mg/kg (Co Q_{10}-NF); the submucosa showed oedema and inflammatory cells infiltration scored 2 (Fig.12&13); (group8) 200 mg/kg (Co Q_{10}-PM); oedema with few focal inflammatory cells infiltration were observed in submucosa scored 3 (Fig.13&14); (group9) 250 mg/kg and 200 mg/kg of combination of the BA and Co-Q_{10} respectively (NF); there was no histopathological alteration scored 1 as recorded in (Fig.15&16); (group10) 250 mg/kg and 200 mg/kg combination of BA and Co Q_{10} respectively (PM); oedema with focal as well as diffuse inflammatory cells infiltration were noticed in the submucosa scored 2 (Fig.19&20).

4. DISCUSSION

This study supported Ulcer Index was proved through stress. Similarly, it was proved that mucosal damage via stress occurs due to reactive oxygen species production as a reflex mechanism to stress.[73] In the present study, 5% casein caused significant weight loss in PM rat groups. However, 20% casein caused significant weight gain in NF rat groups. In agreement, it was linked in a research that diet nature affects physique characteristics as well as psychological reflex.[74]

Present finding demonstrates that, 5% casein caused significant serum albumin reduction in PM rat groups. Likewise, it was postulated that cellular production of albumin is directly linked to the type of proper nutrition.[75] We suggest that, administration of 250 mg/kg of Boswellic acids caused statistically significant prevention of ulcer in rat stomach in both; normally fed and protein malnourished groups. This could be explained in due of exhibiting flavonoids and polyphenol groups, which act as free radical scavenging system.[76]

Similarly, Co-enzyme Q_{10} caused statistically significant prevention of ulcer in rat stomach in both; normally fed and protein malnourished groups. In parallel with our results, it was proved that Co-enzyme Q_{10} possessed gastroprotective properties.[77]

We found coordination between, administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of NPSH compounds in gastric tissue homogenate in both; normally fed and protein malnourished groups. In a trial to explain subcellular pathway, it was presented that liver mitochondrial synthesis is mainly responsible for the production.[78] In our study, administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of lipid peroxidase level in gastric tissue homogenate in both; normally fed and protein malnourished groups. The exact mechanism is via interleukin inhibition of production, thus, modulated production.[79]

We found a robust association between; administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of SOD levels in stomach systolic fraction in both; normally fed and protein malnourished groups. The exact mechanism is explained precisely that reactive oxygen species is involved in cascade of reaction to present ROS end product, which in turn interrupted using anti-oxidant properties of both plants.[80]

Administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 caused statistically significant reduction of lipid peroxidase level in gastric tissue homogenate in both; normally fed and protein malnourished groups. Similarly, it was proven that a mixture of Boswellic acids, coQ10, acts as a vehicle between the cytoplasm and mitochondria for long-chain fatty acids and permits beta-oxidation to occur in the mitochondria. In turn, produces energy and controls fatty acid accumulation. [81] Thus, may supply elevation in energy levels. [82]

Our results also revealed that, administration of 250 mg/kg of Boswellic acids and/or Co-enzyme Q_{10} caused statistically significant reduction of GST levels in stomach systolic fraction in both; normally fed and protein malnourished groups. In a support to the hypothesis, a decrease GST is due to the utilization by ROS. The present results showed that, administration of 250 mg/kg of Boswellic acids caused statistically significant reduction of IgA levels in serum of both; normally fed and protein malnourished groups.[83] While Co-Enzyme Q_{10} and combination of BA and Co-Q_{10} have failed to show reduction of Ig A serum level in both; normally fed and protein malnourished groups. The mechanism through which, immunomodulation process occurs in the gastric mucosal expression in response to stress.[84]

It was found that in PM groups showed significantly higher Beclin than NF groups following oral administration of 250 mg/kg of Boswellic acids and 200 mg/kg Co-Enzyme Q_{10} 1 hour prior to stress induced ulcer. In agreement, it have been postulated that elimination of oocyte in due of the pro-autophagic Beclin 1 protein indorses apoptosis synergistically. [85]

It was found that in PM groups showed significantly higher Beclin than NF groups following oral administration of 250 mg/kg of Boswellic acids and 200 mg/kg Co-Enzyme Q_{10} 1 hour prior to stress induced ulcer. In consistence, cross link between autophagy and stresses [86] is responsible for autophagy end element production. Our results demonstrate that Bax (gene primer sequence: F:5′CGGCGAATTGGAGATGAACTGG3′ R:5′CTAGCAAAGTAGAAGAGGGCAACC3′) was significantly decreased levels following oral administration of 250 mg/kg of Boswellic acids and 200 mg/kg Co-Enzyme Q_{10} 1 hour prior to stress induced ulcer. It's supported that Beclin and Bax are interacting to regulate apoptosis cascade of reaction, thus it's co-present as a product. [87]

Administration of 250 mg/kg of Boswellic acids 250 mg/kg of Boswellic acids and/or Co-enzyme Q10 showed significant protection against inflammatory infiltration and edema of both; normally fed and protein malnourished groups in H and E-stained gastric tissues. That's due to the abstract of B. serrata includes healing substances including; tannin, alkaloids, and different flavonoids, individually or together, efficiently decrease glucose and lipid profiles similarly to treat the wound. In turn, future researches required on each flavonoid to define the retrieval pathway. [88]

Authors recommend further studies to assess the ability of Boswellic acids and Co-enzyme Q_{10} in peptic ulcer healing in human.

5. CONCLUSIONS

Our results indicated that Boswellic acids and Co-enzyme Q_{10} played an important role in protection against stress-induced peptic ulcer in vivo; possibly by inhibiting mitochondrial reactive oxygen species (mtROS) production and autophagy Beclin as well as endoplasmic reticulum protein Bax. Therefore, this could be adapted by further research in ulcer healing process.

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Conflicts of Interest: "The authors declare no conflict of interest.".

Ethical Statement: Everything in animals' techniques was done according to the Ethics Committee of the faculty of Pharmacy AL-Azhar University, Egypt (permit number: 81/2016). Unnecessary disturbance of animals, pressure and tough maneuver was avoided.

Author Contribution: RE drafted the manuscript and made the practical work, KM, MM and AA supervised the practical work and manuscript writing.

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