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Research Article

Gastroprotective Efficacy of Coenzyme Q10 in Indomethacin-Induced Gastropathy: Other Potential Mechanisms

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Though recently the mitochondrial bioenergetic coenzyme (Co)Q10 has been shown to protect against indomethacin-induced gastric ulceration, yet the full mechanistic cassettes have not been investigated. Therefore, the current investigation assessed further gastroprotective mechanisms of CoQ10 using the indomethacin-induced gastropathy model. While CoQ10 was administered at 3 dose levels to male Wistar rats, the proton pump inhibitor, pantoprazole, was given at 4 dose levels ahead of pyloric ligation and indomethacin administration. Indomethacin evoked gastric ulcerations that were associated by decreased gastric mucosal nitric oxide and glutathione levels. The NSAID reduced gastric volume and mucin content, but increased titratable acidity, acid output, and peptic activity. CoQ10, especially at the higher dose levels, as well as pantoprazole pretreatments reverted almost all diversions induced by the NSAID to different extends. Moreover, preadministration with the nonselective nitric oxide synthase inhibitor, L-NAME, boosted ulcer formation that was associated by suppression of gastric mucosal nitric oxide in CoQ10 and pantoprazole-treated groups. The current investigation shows that CoQ10 guards against gastric ulceration via its partial inhibition of titratable acidity and peptic activity, as well as enhancement of mucin secretion due to both gastric mucosal nitric oxide and glutathione replenishment, especially at the higher dose levels.

1. Introduction

Ubiquinone Q10, 2, 3 dimethoxy-5 methyl-6-decaprenyl benzoquinone, or simply coenzyme (Co) Q10, is an indispensible cofactor in complexes I to III of the mitochondrial electron-transport chain [1] acting either as an electron acceptor or donor [2]. Empowered by its lipid solubility, CoQ10 is found in virtually all cell membranes, as well as lipoproteins [2]. Its reduced form, ubiquinol, is produced in the GIT or by mitochondrial flavoenzymes [1, 3, 4] that is a potent free radical scavenger [2, 5]. The maximal antioxidative power of the ubiquinol is credited to its electron donating properties that neutralizes free radicals [6] and its ability to replenish other valuable endogenous antioxidants [2, 7]. Besides, the study of Papucci et al. [8] demonstrated that CoQ10-mediated antiapoptotic activity might be an essential mechanism in its powerful actions.

The role of CoQ10 in protection against neurodegenerative diseases, aging, as well as other ailments such as diabetes and cardiovascular impairments is well established [9–12]. However, limited literature exists about its efficacy in combating gastric mucosal injury. The study by Kohli et al. [13] was the first to report that supplementation with CoQ10 in the diet aids healing of chronic acetic acid gastric ulcers in rats via hampering hypoxia. More recently, El-Abhar [14] has renewed the interest in evaluating the potential effectiveness of CoQ10 against gastropathy induced by NSAIDs using the indomethacin acute gastric ulcer model. The author endowed its antiulcerogenic effect to CoQ10's well-documented antioxidant capacity, besides replenishment of prostaglandin E_2 and nitric oxide in the gastric mucosa; characters that endorse its potential usefulness against gastric damage. Nevertheless, the potential role of CoQ10 on gastric acid, pepsin, and mucin secretion that participate in the

indomethacin-induced gastric ulceration has to be unveiled; this was the goal of the current investigation using pyloric ligated rats and the proton pump inhibitor pantoprazole as a reference antiulcer drug.

2. Materials and Methods

2.1. Animals. Adult male Wistar rats, weighing 150–200 g, purchased from the Research Institute of Ophthalmology (Giza, Egypt) were kept in controlled environment, at a constant temperature ($23 \pm 2^{\circ}$C), humidity ($60 \pm 10\%$), and light/dark (12/12 h) cycle. Rats were acclimatized for one week prior to beginning of experimental study and were allowed free access to standard rat chow and tap water *ad libitum*. Experimental protocols were approved by the Research Ethical Committee of the Faculty of Pharmacy, Cairo University (Cairo, Egypt) and comply with the Guide for the Care and Use of Laboratory Animals (ILAR) [15].

2.2. Treatments and Experimental Groups. Animals were singly housed and fasted for 36 h in wide mesh bottom cages, allowed free access to water except for the last hour before treatment/N^G-Nitro-L-arginine methyl ester (L-NAME) administration. Two subsets of experiments were performed; in the first subset of experiments, animals were randomly allocated into 9 groups ($n = 6$–9). The first group received vehicle (1% Tween 80) and served as the control, while the second one represented the ulcerated group, where rats were injected intraperitoneally by indomethacin (20 mg/kg; Sigma-Aldrich, MO, USA) [16]. The following three cohorts were administered 40, 200, and 400 mg/kg of CoQ10 (Kaneka Corporation, Osaka, Japan), whereas the 4 dose levels of pantoprazole sodium (Wyeth, Madison, NJ, USA); namely, 3, 10, 20, and 30 mg/kg, were administered to the last 4 groups. Treatments were given orally 1 h before indomethacin injection; and both indomethacin and CoQ10 were suspended in the vehicle. For evaluation of the involvement of nitric oxide synthase (NOS) enzyme in the gastroprotective efficacy of CoQ10 and pantoprazole, another subset of experiments ($n = 6$–10 rats) ultilizing L-NAME (Sigma-Aldrich, MO, USA; 50 mg/kg, i.p.) [17] were performed. The nonselective NOS inhibitor was administered to rats 30 min before either CoQ10 (200 mg/kg) or pantaprazole (20 mg/kg) treatments, 1 h prior to ulcer induction by indomethacin. Another group served as the corresponding control. Gastric ulcer number and indices, as well as gastric mucosal nitric oxide levels, were determined in these groups.

2.3. Indomethacin-Induced Gastric Ulceration, Pyloric Ligation, and Gastric Juice Collection. One hour after treatment administration, pyloric ligation was carried out according to the method of Shay et al. [18] for the collection of gastric juice. Immediately thereafter, indomethacin was injected and rats were euthanized under deep ether anesthesia 4 h later. Following ligature of the oesophagocardiac junction, stomachs were excised and gastric juice was collected after an incision at the greater curvature. Following gastric ulcer assessment, gastric mucosal homogenates were prepared in saline.

2.4. Assessment of Gross Mucosal Damage. The number and the length (mm) of individual lesions in the mucosa were measured in a double-blinded fashion, where the sum of lengths of all lesions in each stomach was regarded as the ulcer index [19].

2.5. Gastric Volume, Titratable Acidity, and Acid Output Determination. The collected gastric juice was centrifuged at 1000 g for 10 min and gastric volume (mL/4 h) was recorded after removal of solid debris; however, samples having solid mass volumes more than 0.6 mL were discarded [18]. Titratable acidity was carried out according to the method of Grossman [20] by titrating gastric juice against sodium hydroxide (0.01 N) using phenol red as an indicator. Acid output was calculated as the rate of the of gastric juice production [21].

2.6. Peptic Activity Determination. The peptic activity of the gastric juice was determined according to the method described by Sanyal et al. [22]. In brief, bovine serum albumin (2%) was added to diluted gastric juice in hydrochlo-ric acid (0.01 N), then incubated at 37°C for 10 min. Trichloroacetic acid (0.3 M) was used to stop the enzymatic activity and mixtures were boiled for 5 min, followed by centrifugation (5 min at 1000 g) and filtration. To the filtrate, NaOH (0.5 N) and Folin reagent were added, and the absorbance was read at 680 nm after 20 min of color development.

2.7. Mucin Content Determination. The mucin content of the gastric juice was determined according to the method described by Winzler [23]. Briefly, to diluted samples orcinol (1.6%) and sulphuric acid (60%) were added, vortexed, and boiled for 10 min. Mixtures were cooled in ice-cold water to stop the reaction and the absorbance was measured at 425 nm.

2.8. Glutathione Estimation. The method for the assessment of glutathione in the gastric mucosa was based on that of Beutler et al. [24]. Gastric mucosal homogenates were deproteinated with 5-sulfuosalicylic acid (10%) for 30 min at 4°C and then centrifuged at 3000 g for 15 min at 4°C. An aliquot of the acid-soluble supernatant was diluted with phosphate buffer (0.3 M, pH 7.7) and 5,5′-dithiobis-2-nitrobenzoic acid (1 mM) was added to the samples. The optical density was determined at 412 nm.

2.9. Nitric Oxide Estimation. Nitric oxide was assayed according to the method of Miranda et al. [25], where gastric mucosal homogenates were deproteinated with absolute ethanol for 48 h at 4°C, and then centrifuged at 12000 g for 15 min at 4°C. To an aliquot of the supernatant, vanadium trichloride (0.8% in 1 M HCl) was added for the reduction of nitrate to nitrite, followed by the rapid addition of Griess reagent consisting of N-(1-Naphthyl) ethylenediamine dihydrochloride (0.1%) and sulfanilamide (2% in 5% HCl), incubated for 30 min at 37°C, cooled, and the absorbance at 540 nm was measured.

Table 1: Effect of 40, 200, and 400 mg/kg coenzyme Q10 (CoQ10-40, -200, and -400; p.o.) as well as 3, 10, 20, and 30 mg/kg pantoprazole (PANTO-3, -10, -20, and -30; p.o.) on ulcer number, ulcer index, and gastric mucosal nitric oxide (NO) content in indomethacin- (INDO-; 20 mg/kg, i.p.) induced gastric injury.

Groups	Parameters		
	Ulcer number (Median (minimum-maximum))	Ulcer index (mm)	Gastric mucosal NO (μM/g tissue)
CONT (vehicle)	0.0 (0-0)	0.0 ± 0.00	894.9 ± 31.05
INDO	8.0* (5-10)	11.3*@ ± 1.17	704.8* ± 24.75
PANTO-3	4.5*• (3-6)	6.3*@#• ± 0.42	807.9*@ ± 27.36
PANTO-10	3.5* (3-4)	5.2*@#• ± 0.40	829.3@ ± 29.18
PANTO-20	2.5@ (2-3)	2.7*@• ± 0.33	871.2@ ± 20.34
PANTO-30	0.0@ (0-1)	0.1*@ ± 0.09	893.8@ ± 31.12
CoQ10-40	6.0*‡ (5-7)	7.2*@†‡ ± 0.48	754.4 ± 28.20
CoQ10-200	3.0@ (2-4)	3.3*@‡ ± 0.33	817.7@ ± 26.58
CoQ10-400	1.0@ (1-2)	1.00*@ ± 0.09	831.0@ ± 18.84

For ulcer number, values are median of 6–9 rats and statistical analysis was performed using Kruskal-Wallis test (nonparametric ANOVA) followed by Dunn's Multiple Comparisons Test, $P < 0.05$. For ulcer index and gastric mucosal NO, values are means ± S.E.M. of 6–9 rats; comparisons were carried out using one-way ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test, $P < 0.05$. As compared to control (CONT) (*), INDO (@), PANTO-20 (#), PANTO-30 (•), CoQ10-200 (†), and CoQ10-400 (‡).

2.10. Statistical Analysis. Parametric data were expressed as mean of 6–10 experiments ± S.E.M. and statistical comparisons were carried out using one-way analysis of variance (ANOVA) followed by Student-Newman-Keuls multiple comparisons test. Statistical comparisons for nonparametric data for gastric ulcer number were analyzed using Kruskal-Wallis nonparametric ANOVA test followed by Dunn's multiple comparisons test. All analysis utilized SPSS 16.0 statistical package for Windows (SPSS Inc., Chicago, L, USA). The minimal level of significance was identified at $P < 0.05$.

3. Results

Indomethacin-induced gastric ulceration in the glandular portion of the stomach in all rats (Table 1) was significantly reduced by pretreatment with pantoprazole or CoQ10 in a dose-dependent manner. In Shay rats, indomethacin markedly decreased the gastric volume (80%) but increased the titratable acidity (272.5%), as well as the acid output (218.4%), as compared to control values (Figures 1(a)–1(c)). Compared to the indomethacin-treated group, the lowest dose of CoQ10 was the only one that elevated gastric volume by 14%. On the other hand, all doses of the coenzyme ameliorated partially the titratable acidity by almost 10%; however, none of them affected the acid output. Contrariwise, pantoprazole dose dependently reduced titratable acidity and acid output below that of both normal and indomethacin-treated rats, effects that were most prominent at the 30 mg/kg dose level. However, the gastric volume was only reduced by the highest dose of pantoprazole. As depicted in Figure 2, indomethacin increased peptic activity (143%) that was antagonized only by the 400 mg/kg CoQ10 dose. Meanwhile, all doses of pantoprazole reduced peptic activity by 12.9, 20.3, 27.7, and 30.7%, respectively, as compared to indomethacin-treated group. Indomethacin, as shown in Figure 3, leveled off mucin concentration in the gastric juice by 55.7%, while CoQ10 (200 and 400 mg/kg), as well as pantoprazole (10–30 mg/kg) dose dependently elevated it. Indomethacin (Figure 4) markedly depleted the glutathione mucosal content to half its level, as compared to the normal values. CoQ10 (200 and 400 mg/kg) stalled its depletion by 61.9 and 77.9%, respectively, as compared to the indomethacin-treated rats, effects that were slightly above pantoprazole (20 and 30 mg/kg) treatments. Furthermore, indomethacin (Table 1) significantly decreased the nitric oxide mucosal content by 21.2%, as compared to the control animals. CoQ10 (200 and 400 mg/kg) in indomethacin-treated animals markedly prevented the NSAID-induced depletion of gastric mucosal nitric oxide contents that reached 91.4 and 92.8%, respectively, as compared to control values. Likewise, pantoprazole (20 and 30 mg/kg) restored the gastric mucosal nitric oxide content to normal values, effects that mounted to 123.6 and 126.8%, respectively, as compared to indomethacin-treated rats. Finally, ulcer indices were elevated after CoQ10/pantoprazole pretreatment with L-NAME that were accompanied by further reductions in gastric mucosal nitric oxide levels by 19.2 and 13.7%, respectively, as compared to their single administration in indomethacin-treated animals. Nonetheless, these effects were not reflected on the ulcer number in the L-NAME-CoQ10/pantoprazole-treated groups, pointing thus to increased severity of ulcerations (Table 2).

4. Discussion

The current study supports the gastroprotective effect of CoQ10 and further extents the findings of El-Abhar [14], showing a dose-dependent effect in an indomethacin gastropathy model, being most potent at higher dose levels. CoQ10 boosted mucin secretion in the gastric juice at both higher dose levels, showing a dose-dependent increment. Enhancement of mucin secretion was associated by increased

Table 2: Effect of L-NAME (50 mg/kg; i.p.) on gastroprotection by 200 mg/kg coenzyme Q10 (CoQ10-200; p.o.) and 20 mg/kg pantoprazole (PANTO-20; p.o.) on ulcer number, ulcer index, and gastric mucosal nitric oxide (NO) content in indomethacin (INDO; 20 mg/kg, i.p.) induced gastric injury.

Groups	Parameters		
	Ulcer number (Median (minimum-maximum))	Ulcer index (mm)	Gastric mucosal NO (μM/g tissue)
CONT (vehicle)	0.0 (0-0)	0.0 ± 0	862.7 ± 28.38
INDO	7.5* (5-9)	10.3* ± 1.50	704.2* ± 35.19
PANTO-20	2.5 (2-3)	2.7*@ ± 0.33	877.2@ ± 29.42@
L-NAME + PANTO-20 + INDO	4.0* (3-6)	5.0*@ ± 0.37	703.9*# ± 7.74
CoQ10-200	2.5 (2-3)	3.3*@ ± 0.33	812.7@ ± 29.18
L-NAME + CoQ10-200 + INDO	3.5* (3-4)	4*@ ± 0.26	701.1*† ± 5.63

For ulcer number, values are median of 6–10 rats and statistical analysis was performed using Kruskal-Wallis test (nonparametric ANOVA) followed by Dunn's Multiple Comparisons Test, $P < 0.05$. For ulcer index and gastric mucosal NO, values are means ± S.E.M. of 6–10 rats; comparisons were carried out using one-way ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test, $P < 0.05$. As compared to control (CONT) (*), INDO (@), PANTO-20 (#), and CoQ10-200 (†).

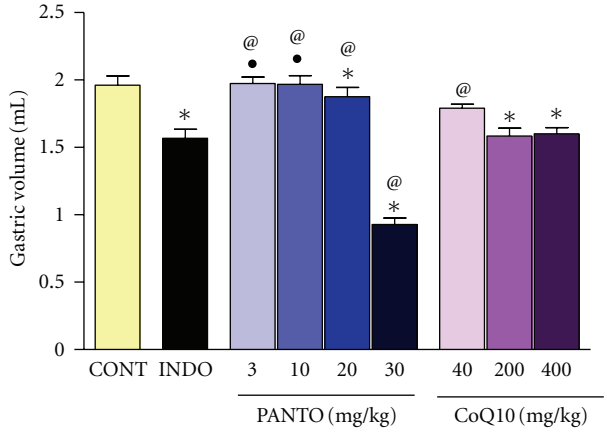
glutathione and constitutive enhancement of nitric oxide levels in the gastric mucosa. Moreover, the current investigation depicted additive gastroprotective mechanisms for CoQ10 via reduction of titratable acidity, with a corollary inhibition in peptic activity at the 400 mg/kg dose level. To the authors' knowledge, the effect of CoQ10 on the gastric juice has not been studied before.

Gastric mucus acts as a protective barrier from the noxious effects of both gastric acidity and pepsin [26] and possesses free radical scavenging activity due to its natural composition [27], hence preventing gastric injury induced by a vast majority of insults. Though it was previously shown [14] that the 100 mg/kg CoQ10 dose failed to elevate gastric mucosal mucus content; however, in the current work, increasing the ubiquinone dose by two or four folds enhanced mucin secretion significantly in the gastric lumen. Evidence exists that escalating the levels of both prostaglandins E_2 [28] and nitric oxide [27] boosts gastric mucus formation and secretion. Indeed, the present study revealed a rise in mucosal nitric oxide content after CoQ10 treatment, an effect that goes in line with a previous one [14]. Oztay et al. [29] elucidated that an increment in endothelial NOS enhances nitric oxide levels after CoQ10 administration. Indeed, the current investigation supports this notion, where pretreatment with L-NAME further reduced nitric oxide level after indomethacin treatment and increased ulcer severity in CoQ10-treated animals. Moreover, it was previously [14] reported that the 100 mg/kg coenzyme administration raised gastric mucosal prostaglandin E_2 level partially in indomethacin-treated rats. Such a diverse effect on mucus formation and secretion between our report and that of El-Abhar's [14] reveals thus that a certain threshold of both mediators is needed to enhance mucus formation and secretion, pointing therefore to the importance of higher doses of CoQ10 as presented in the current work.

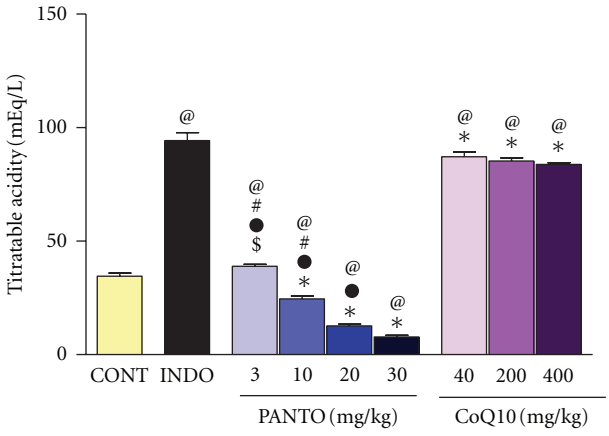
Another contributor in mucus synthesis is endogenous glutathione that stabilizes mucus composition by regulating the thiol/disulfide ratio [30]. In fact, CoQ10 in the current work replenished the major antioxidant molecule in the gastric mucosa that was depleted by indomethacin administration, an effect that is in line with a previous study [14], affording thus another explanation to increased mucin secretion in the current investigation. Moreover, this ubiquinone has been shown to replenish endogenous antioxidants [2, 7, 14], hence justifying the preservation of mucosal glutathione levels. Since mucus production, rapid gastric cell turnover, as well as complete barrier function repair are highly energy-dependent processes [13, 31], thus it is emphasized that adequate energy, besides an intact mitochondria [9] offered by the higher doses of CoQ10, are needed to combat gastric ulceration. In addition, CoQ10 possesses antiapoptotic activity [8] preserving thus gastric epithelial cells that secrete more mucus hampering gastric ulceration, as indomethacin gastropathy has been previously linked to programmed cell death [32].

The present work shows that CoQ10 administration reduced the titratable acidity without affecting acid output at all dose levels; however, only the lowest dose level was able to enhance gastric volume. As the acid output signifies the rate of acid formation, and it is affected by both gastric volume and titratable acidity, hence an increase in the former in the vicinity of a reduction of the latter might justify the overall unaltered levels of the acid output using CoQ10 in the present investigation. Since histamine plays a crucial role in stimulating acid secretion [33], therefore, the partial inhibitory effect of CoQ10 on titratable acidity may be related to its ability to suppress histamine release [34]. Another plausible explanation that validates its effect is the CoQ10-induced increment of prostaglandin E_2 [14], where this prostanoid is a humoral factor with prominent gastric acid secretion suppressive actions [33]. Meanwhile, the present suppression of acid secretion may be responsible for the current inhibition of peptic activity by the ubiquinone at 400 mg/kg dose level, where gastric acid is an essential factor for pepsinogen activation into pepsin [35].

The current investigation goes in line with previous reports [36, 37] revealing a dose-dependent antisecetory efficacy of pantoprazole that was more prominent at higher dose



(a)



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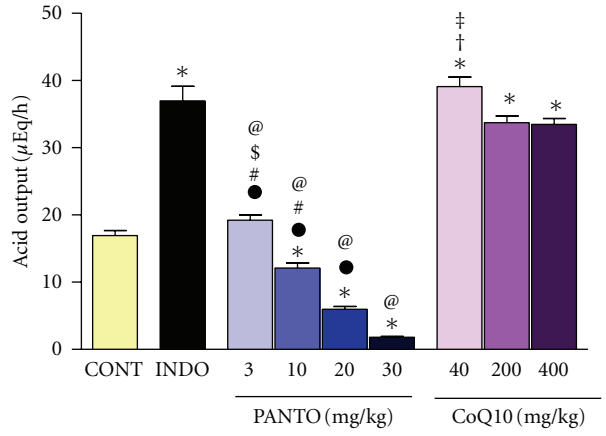

(c)

Figure 1: Effect of 40, 200, and 400 mg/kg coenzyme Q10 (CoQ10-40, -200, and -400; p.o.) as well as 3, 10, 20, and 30 mg/kg pantoprazole (PANTO-3, -10, -20, and -30; p.o.) on gastric volume (a), titratable acidity (b), and acid output (c) in indomethacin-induced (INDO; 20 mg/kg, i.p.) gastric injury. Values are means ± SEM of 6–9 rats; comparisons were carried out using one-way ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test, $P < 0.05$. As compared to control (CONT) (*); INDO ($^{@}$); PANTO-10 ($^{\$}$), -20 ($^{\#}$), and -30 ($^{\bullet}$); CoQ10-200 (†) and -400 (‡).

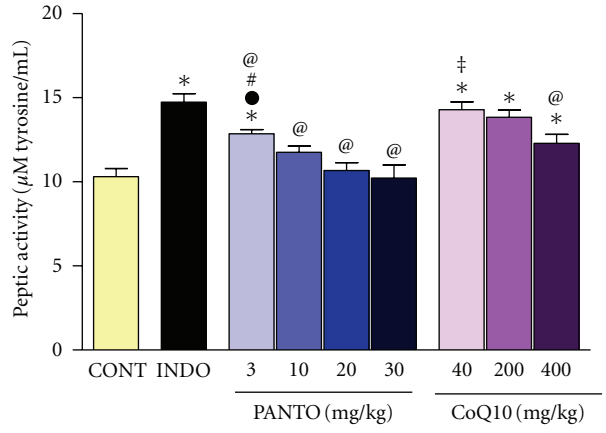

Figure 2: Effect of 40, 200, and 400 mg/kg coenzyme Q10 (CoQ10-40, -200, and -400; p.o.) as well as 3, 10, 20, and 30 mg/kg pantoprazole (PANTO-3, -10, -20, and -30; p.o.) on peptic activity in indomethacin-induced (INDO; 20 mg/kg, i.p.) gastric injury. Values are means ± SEM of 6–9 rats; comparisons were carried out using one-way ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test, $P < 0.05$. As compared to control (CONT) (*); INDO ($^{@}$); PANTO-20 ($^{\#}$) and -30 ($^{\bullet}$); CoQ10-400 (‡).

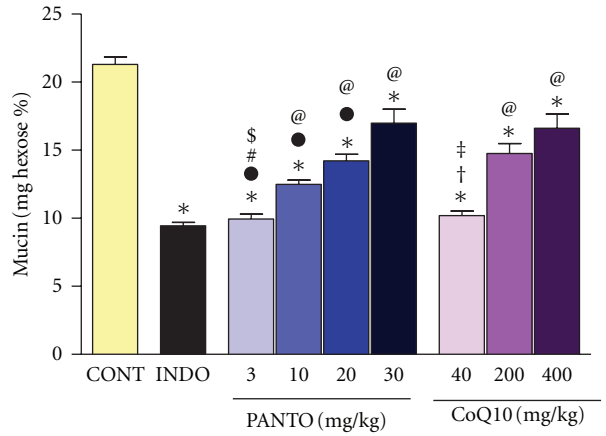

Figure 3: Effect of 40, 200, and 400 mg/kg coenzyme Q10 (CoQ10-40, -200, and -400; p.o.) as well as 3, 10, 20, and 30 mg/kg pantoprazole (PANTO-3, -10, -20, and -30; p.o.) on mucin secretion in indomethacin-induced (INDO; 20 mg/kg, i.p.) gastric injury. Values are means ± SEM of 6–9 rats; comparisons were carried out using one-way ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test, $P < 0.05$. As compared to control (CONT) (*); INDO ($^{@}$); PANTO-10 ($^{\$}$), -20 ($^{\#}$), and -30 ($^{\bullet}$); CoQ10-200 (†) and -400 (‡).

levels. Tough pantoprazole suppressed gastric acid section dose dependently, the gastric volume was only reduced by the 30 mg/kg regimen in the current work. The latter effect is supported by the study of Bigoniya et al. [38] in rats who reported that 40 mg/kg pantoprazole decreased gastric volume. Since a significant portion of gastric volume is a function of gastric acid secretion [39] and pantaprazole therapeutic activity relies on gastric acid secretion inhibition, via

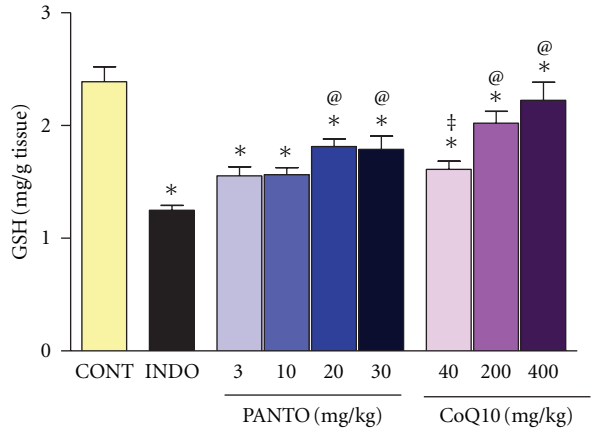

Figure 4: Effect of 40, 200, and 400 mg/kg coenzyme Q10 (CoQ10-40, -200, and -400; p.o.) as well as 3, 10, 20, and 30 mg/kg pantoprazole (PANTO-3, -10, -20, and -30; p.o.) on gastric mucosal glutathione (GSH) content in indomethacin-induced (INDO; 20 mg/kg, i.p.) gastric injury. Values are means ± SEM of 6–9 rats; comparisons were carried out using one-way ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test, $P < 0.05$. As compared to control (CONT) (*); INDO (@); CoQ10-400 (‡).

restraining proton pumps located on the apical membrane of the parietal cell [36, 37], hence it is accepted that a more potent antisecretory effect of the drug, as documented herein by the 30 mg/kg dose level, will possess more profound effects on gastric volume.

The antisecretory effect of pantoprazole effect might also clarify the current dose-dependent decrease in pepsin activity that is in harmony with the findings of Hatlebakk and Berstad [36]. Moreover, the mucin secretion was enhanced by the proton pump inhibitor, an effect that corroborates that of Blandizzi et al. [40]. These authors attributed such event to increased levels prostaglandins and increased availability of thiols, besides nitric oxide [41], both latter effects are confirmed in our work. Ulcer index was notably increased, while gastric mucosal nitric oxide content was significantly reduced after preadministration with the nonselective NOS inhibitor L-NAME. These results support the involvement of nitric oxide in the mucosal protection afforded by proton pump inhibitors as that reported by Murakami et al. [41], possibly via an increase in mucosal blood flow among other factors.

The current study supports and validates the antiulcerogenic efficacy of CoQ10 and provides other gastroprotective mechanisms via inhibition of titratable acidity with a subsequent decrease in peptic activity; in addition, the study confirmed that higher dose of CoQ10 is necessary to increase mucin secretion via enhancement of nitric oxide formed constitutively and glutathione production.

Conflict of Interests

The authors have no conflict of interests.

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