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Anti-Ulcerative Potential of Egyptian Propolis against Oxidative Gastric Injury Induced by Indomethacin in Rats

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ABSTRACT: The anti-ulcerative and antioxidant potentials of Egyptian propolis alcoholic extract as well as its total phenolic and flavonoid contents were evaluated. The content of total phenols and flavonoids of propolis extract were determined by spectrophotometric methods with an FC reagent and by the complexation reaction with aluminium chloride, respectively. The antioxidant activity was examined with 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and superoxide anion radicals scavenging assays. Indomethacin-induced ulcer with or without pylorus ligation was used as the gastric ulcer model in rats. Oxidative stress was evaluated by measuring stomach homogenate levels of GSH, MDA and NO. The effects of the extract on gastric juice volume and acid output were evaluated. The total phenolic and flavonoid contents of propolis extract was 87.65 ± 0.5 mg GAE/g and 113.14 ± 0.86 mg QE/g extract respectively. The in vitro antioxidant activity was demonstrated by its ability to quench free radicals generated by DPPH and superoxide anion radicals, with the IC50 9.97 ± 0.45 and 11.29 ± 0.65 µg/ ml, respectively. Animals pretreated with propolis extract (200 and 400 mg/kg, b.w.) before indomethacin-induced ulcer model resulted in significant decrease in gastric ulcers and improved oxidative balance in gastric mucosal tissues. These findings indicate that Egyptian propolis possesses potent anti-ulcerative and antioxidant activities, corroborating the folk use of propolis preparations, and contributing for its pharmacological validation.

Key words: Propolis, Anti-ulcer, Gastric ulcer, Indomethacin, Pylorus ligation, Antioxidant, total phenolic and flavonoid contents

ORIGINAL ARTICLE

INTRODUCTIN

Peptic ulcer is erosion in the lining of the stomach or duodenum occurring at a site where the mucosal epithelium is exposed to acid and pepsin. Smoking, stress, nutritional deficiencies and ingestion of nonsteroidal-anti-inflammatory drugs increase gastric ulcer incidence (Belaiche et al., 2002).

The current medical treatment of peptic ulcer is generally based on the inhibition of gastric acid secretion by H2-antagonists, such as omeprazole and antimuscarinics, as well as the acid-independent therapy like that provided by sucralfate and bismuth (Bighetti et al., 2005). However, one of the major problems in gastro-duodenal ulcer treatment is that, despite of the healing rate of 80–100% after 4–8 weeks of therapy with H2-antagonists and proton pump inhibitors, the rate of ulcer recurrence within one year after stopping treatment is between 40 and 80% (Miller and Faragher, 1989). Besides, most of these drugs produce several adverse reactions (Ariyphisi et al., 1986).

Therefore, it is important to search for new anti-ulcer agents. In the last years, there has been an increased interest in the search for gastroprotective agents from natural sources. Propolis is a resinous hive product collected by honeybees from plants (Sforcina and Bankova, 2011). It has gained popularity as either an alternative medicine or dietary supplement for health amelioration and disease prevention in various parts of the world, including United States of America, European Union and Japan (Teixeira et al., 2006). Its use was recommended because it displays antibacterial, antifungal, antiviral, hepatoprotective, anti-inflammatory and immunomodulatory properties (Reis et al., 2000; Castaldo and Capasso, 2002; Abd El Hady et al.,2007). Analysis of propolis chemical composition allowed the identification of at least 300 compounds (De Castro, 2001), mainly terpenoids, flavonoids and phenolic compounds (Abd El Hady and Hegazi, 2002; Abd El Hady et al., 2007). The antiulcerogenic properties of Brazilian green propolis was described (Barros et al. 2007, 2008).

However, so far there is no work earlier reported on the antiulcer activity of Egyptian propolis. The present investigation was undertaken to demonstrate its pharmacological potential. The efficacy of the extract was compared to that of a reference drug.

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METHODS AND MATERIALS

Propolis:

Egyptian propolis was collected from Gharbia province of east area of Nile Delta, Egypt.

Determination of phenolic compounds:

The total phenolic content in propolis extract was measured using Folin-Ciocalteu (FC) reagent based on procedure described by Singleton et al. (1999) with some modifications. Briefly, 0.5 ml of extract (1mg/ml) was mixed with 1.5 ml (1:10 v/v diluted with distilled water) Folin-Ciocalteau's reagent and allowed to stand for 22°C for 5 min. Then 2 ml of sodium carbonate (Na_2CO_3, 7.5%, w/v) was added and the mixture allowed to stand for another 90 min and kept in the dark with intermittent shaking. Then the absorbance of the blue color that developed was measured at 725 nm using spectrophotometer (HITACHI U-1900 spectrophotometer 200V). The experiment was carried out in triplicates. Gallic acid was used for constructing the standard curve (20 to 100 µg/ml; $y = 0.0058x - 0.0025$, $R^2 = 0.9979$ (Figure 1) and the total phenolic content concentration in the extract was expressed as milligrams of gallic acid equivalent per gram of dry weight (mg GAE/g) of extract.

Total flavonoid contents:

Aluminium chloride colorimetric method was used for flavonoids determination. Quercetin was used for constructing the standard curve (20 to 100 µg/ml; $y = 0.007x - 0.012$, $R^2 = 0.999$) (Figure 2) and the total flavonoid compounds concentration in the propolis extract was expressed as milligrams of quercetin equivalent per gram of dry weight (mg QE /g) of extract. Propolis extract (0.5 ml of 100:1000 µg /ml) in methanol was separately introduced into test tubes and mixed with 1.5 ml of methanol, 0.1 ml of 10% aluminium chloride, 0.1 ml of 1 M potassium acetate and 2.8 ml of distilled water. The tubes were covered with parafilm and it remained at room temperature for 30 min; the absorbance of the reaction mixture was measured at 415 nm (Pourmorad et al., 2006). The experiment was carried out in triplicates.

Antioxidant activities:

DPPH radical scavenging activity: DPPH radical scavenging activity of propolis extract was analyzed according to a modified procedure of Matsushige et al.(1996). 1 ml of methanolic solution of varying concentration sample (1, 5, 10 and 25 µg/ml) was added to 1 ml of methanol solution of DPPH (60µM). The prepared solutions were mixed and left for 30 min at room temperature. The optical density was measured at 520 nm using a spectrophotometer (UV-1650PC Shimadzu, Japan). Mean of three measurements for each compound was calculated. The activity was expressed as the concentration of sample necessary to give a 50% reduction in the sample absorbance (IC50).

Superoxide anion scavenging activity:

Superoxide anion scavenging activity was determined according to a modified method of Matsushige et al. (1996). Reaction mixtures containing 1.4 mL of 50 mM Na2CO3 (pH 10.2), 100 µL of 3 mM xanthine, 100 µL of 3 mM EDTA, 100 µL of BSA (1.5 mg/mL), 100 µL of 75 mM Nitro blue tetrazonium, and 50 µL of varying concentrations of the propolis sample (1, 5, 10 and 25 µg/ml) were preincubated at 30 °C for 10 min, and 50 µL of xanthine oxidase (0.3 unit/mL) was added. After incubation at 30 °C for 20 min, 200 µL of 6 mM CuCl2 was added to stop the reactions and the absorbance was measured at 560 nm. The activity was expressed as the sample concentration necessary to give a 50% reduction in the sample absorbance (IC50).

Pharmacological studies:

Preparation of propolis extract: Propolis ethanol extract (PEE) was freshly prepared, solvent evaporated under reduced pressure then the crude extract suspended in vehicle (1% Tween 80 in distilled water).

Experimental animals: Male albino rats (laboratory animal house, National Research Center, Cairo, Egypt) weighing 150 - 200 g were used in this study. The animals were housed in groups of six in stainless steel community cages at 22 ± 2 °C with a 12 h light/dark cycle and allowed to acclimatize for a period of 15 days prior to experimental use. Throughout the experiment, the rats were allowed free access feed (rats dietary pellets prepared by Cairo Company of Oil & Soap, Egypt) and water.

Animal experimental studies were conducted according to the guidelines of institutional animal ethical committee.

Acute toxicity testing and LD50 determination: Median lethal dose was estimated following the method described by Lorke (1983). Briefly, on first day mice were starved for 24 hours prior to drug administration. They were divided into two groups (test and negative control) of five mice each. A single dose of between 500-5000 mg/kg/day was administered orally on second day. Five different dosing levels were used. The animals were given food and water four hours post drug administration. On second and third day, they were observed for signs of toxicity. The number of death that occurred within 48 hours was recorded.

Pharmacological assays:

Indomethacin-induced ulcer in pyloric ligated rats: Pyloric ligated rats were carried out according to the

method described by Shay et al.(1945). Rats were starved for 18 h but allowed free access to drinking water. A midline ventral incision starting from the xiphoid cartilage downwards was made to expose the stomach and the duodenum. The pylorus was ligated and the abdominal wall was sutured. Propolis extract was administered immediately after pyloric ligation followed by oral administration of indomethacin (30 mg/kg). Four hours later, animals were sacrificed by cervical dislocation, the abdominal cavity was opened and a ligature was placed at the oesophagocardiac junction and the stomach was removed. An opening was then made along the greater curvature and the volume of gastric juice was measured. The mucosa was examined (Mózsik et al., 1982) and the total lesion number was counted and the severity of lesions was calculated based on the following score:0 = no ulcer, 1 = lesion ≤ than 1 mm, 2 = lesion of size 1-2 mm , 3 = lesion of size 2-3 mm, 4 = lesion of size 3-4 mm, 5 = lesion of size > 4 mm. The gastric volume was determined according to the method of Shay et al. (1945). Titratable acidity was determined according to the method described by Grossman (1963). A fixed amount of the supernatant of gastric secretion was titrated with 0.01 N sodium hydroxide using phenolphthalein as indicator. Results were expressed as mEq/l and the titratable acidity was calculated as follows: Titratable acidity (mEq/l) = V1 X 1000/V2 X 100; Where: V1 = volume of 0.01 N NaOH used for titration (ml). V2 = volume of gastric juice taken for titration (ml).

Acid output was calculated as microequivalnts per 4 h according to the method described by Brodie and Hooke (1971), by multiplying the volume of the gastric secretion by the titratable acidity in mEq/l. Acid Output (µEq/4h) = T X V; where: T = titratable acidity (mEq/l). V = volume of gastric juice (ml).

Indomethacin-induced ulcer: We investigated the anti-ulcerative effect of propolis using an indomethacin-induced ulcer model in rats. To the first and second group 1 ml of vehicle was given (1% Tween-80 aqueous solution), the third, fourth and fifth groups were treated orally with Egyptian propolis extract 200 mg/kg, 400 mg/kg and ranitidine 50 mg/kg respectively to 24 h fasted rats. Immediately, 30 mg/kg indomethacin was given to each rat in all groups except the normal group. An identical volume of distilled water was given to the normal group. Six hours after the indomethacin administration, all groups were sacrificed and stomachs of the rats were removed, and ulcerous regions were examined macroscopically. Stomachs were homogenized and reduced glutathione (GSH), malondialdehyde (MDA) and nitric oxide (NO) were measured in the stomach homogenates.

Statistical analysis: The data were analyzed using one way ANOVA followed by post hoc Sheffe's Test using SPSS computer software Version 16. Data were expressed as mean ± SD, level of significance was measured at $p< 0.05$ and 0.01.

Data were reported as mean ± standard error of the mean (S.E.M.) of 6 rats and were compared using one-way analysis of variance (ANOVA), followed by Tukey test. Statistical analysis of ulcer scores was carried out using Kruskal-Wallis non parametric one way.

RESULTS

Total phenolic and flavonoid contents: The present study revealed that the total phenolic and flavonoid contents of propolis extract in terms of mg gallic acid equivalent/g and quercetin equivalent/g extract was 87.65 ± 0.5 mg GAE/g and 113.14 ± 0.86 mg QE/g extract (Figure1- 3).

Antioxidative Activity of propolis extract: Propolis had significant scavenging effects on the DPPH and superoxide anion radicals which increased with increasing concentration in the 1-25µg/ml range (Figures 4, 5). Concentration of propolis sample necessary to decrease initial concentration of DPPH and superoxide anion radicals by 50% (IC50) under the experimental condition was determined as 9.97 ± 0.45 and 11.29 ± 0.65 µg/ ml, respectively. The lower value of IC50 indicates a higher antioxidant activity.

Anti-ulcerative effect of propolis: The Egyptian propolis ethanol extract (PEE) was found to produce a decrease in ulcer number and severity in both doses in indomethacin-induced ulcer in pyloric ligated rats. In the indomethacin-induced gastric ulcer in the pyloric ligated model, (Table 1) treatment with propolis extract (200 and 400 mg/kg) respectively, significantly reduced the acid output and hence, raised gastric pH significantly ($P<0.01$) in comparison with control group (Table 1) and it was comparable to ranitidine 50 mg/kg. In addition, propolis extract in its two doses significantly decreased ulcer number and severity.In addition, administration of Egyptian propolis extract (200 and 400 mg/kg) respectively, as well as ranitidine 50 mg/kg, in indomethacin-induced gastric model (without pylorus ligation) significantly reduced gastric ulcer ($P<0.01$) (Table 2).Indomethacin 30 mg/kg significantly depleted reduced glutathione and nitric oxide levels in the stomach homogenates, and elevated malondialdehyde levels indicating lipid peroxidation ($P<0.05$) (Table 3) and (Figures 6-8).Egyptian propolis extract, in its two doses, elevated the reduced glutathione as well as the nitric oxide levels. On the other hand, only Egyptian propolis 400 mg/kg depleted the elevated malondialdehyde levels in the stomach homogenates ($P< 0.05$) (Table 3) and (Figures 6-8). These findings reflect the beneficial effects of Egyptian propolis on the oxidative stress in the stomach.

Table 1. Effect of administration of Egyptian propolis extract on gastric mucosa in indomethacin-induced ulcer in pyloric ligated rats

Drugs	Ulcer number	Ulcer severity	Titratable acid (mEq/l)	Acid output (µEq/4h)
Pyloric ligated group	0.33 ± 0.2	0.05 ± 0.34	126.66 ± 12.87	577.91 ± 56.45
Indomethacin 30 mg/kg	5.16 ± 3.8[b]	12.5 ± 4.5[b]	108.83 ± 94.06	1034.91 ± 152.65[b]
Propolis 200 mg/kg	-	-	105.00 ± 21.83	435.16 ± 109.81[*]
Propolis 400 mg/kg	-	-	107.00 ± 15.08	535.00 ± 80.74 [*]
Ranitidine 50 mg/kg	-	-	112.25 ± 10.23	498.66 ± 35.62[*]

Each value represents the mean of 6 rats ± SE of the mean. Statistical analysis was carried out using Kruskal-Wallis non parametric one way ANOVA for ulcer number and severity, and One way ANOVA followed by Tukey test for titratable acidity and acid output. [b]Statistically significant from the normal. *Statistically significant from the control (P<0.01).

Table 2. Effect of administration of Egyptian propolis extract on gastric mucosa in indomethacin-induced gastric ulcer

Drugs	Ulcer number	Ulcer severity
Pyloric ligated group	-	-
Indomethacin 30 mg/kg	5.500 ± 0.562[b]	10.170 ± 0.703[b]
Propolis 200 mg/kg	1.000 ± 0.019[*]	1.167 ± 0.091[*]
Propolis 400 mg/kg	-	-
Ranitidine 50 mg/kg	-	-

Each value represents the mean of 6 rats ± SE of the mean. Statistical analysis was carried out using Kruskal-Wallis non parametric one way ANOVA. [b]Statistically significant from the normal. *Statistically significant from the control (P<0.01).

Table 3. Effect of administration of Egyptian propolis extract on GSH, MDA and NO in indomethacin-induced gastric ulcer

Drugs	GSH	MDA	NO
Pyloric ligated group	10.52 ± 0.728	183.3 ± 8.308	46.20 ± 3.265
Indomethacin 30 mg/kg	5.499 ± 0.395[a]	289.4 ± 8.725[a]	8.914 ± 0.956[a]
Propolis 200 mg/kg	11.79 ± 1.465[*]	230.2 ± 20.236	79.02 ± 8.863
Propolis 400 mg/kg	14.28 ± 1.696[*]	195.9 ± 13.46[*]	64.16 ± 4.236
Ranitidine 50 mg/kg	15.00 ± 1.323[a*]	179.9 ± 7.114[*]	60.10 ± 5.874

Each value represents the mean of 6 rats ± SE of the mean. Statistical analysis was carried out using One way ANOVA followed by Tukey test. [a]Statistically significant from the normal. *Statistically significant from the control (P<0.05).

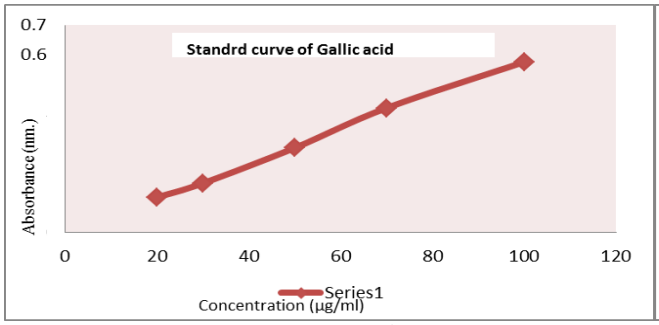

Figure 1: Standard curve of Gallic acid

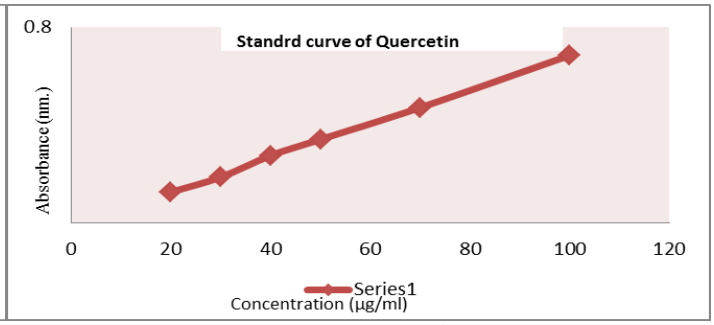

Figure 2: Standard curve of Quercetin

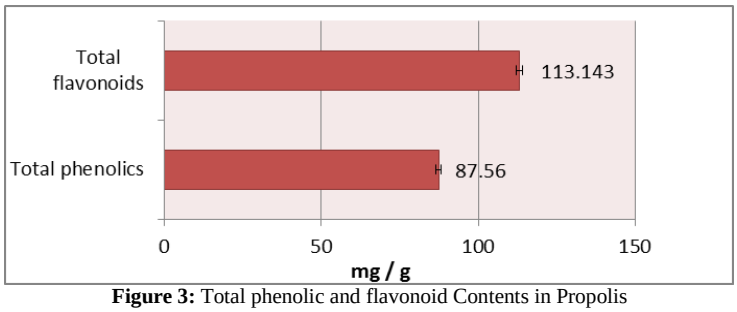

Figure 3: Total phenolic and flavonoid Contents in Propolis

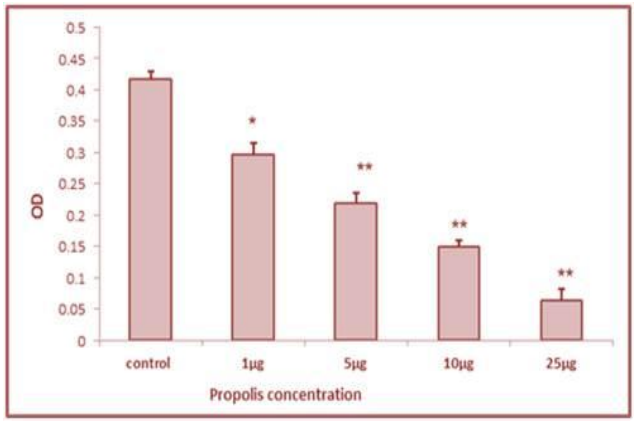

Figure 4. Free radical scavenging activity in different concentrations of propolis in the DPPH radical assay.
Significantly different from control group (*p < 0.05, **p < 0.01). Values are mean ±SD.

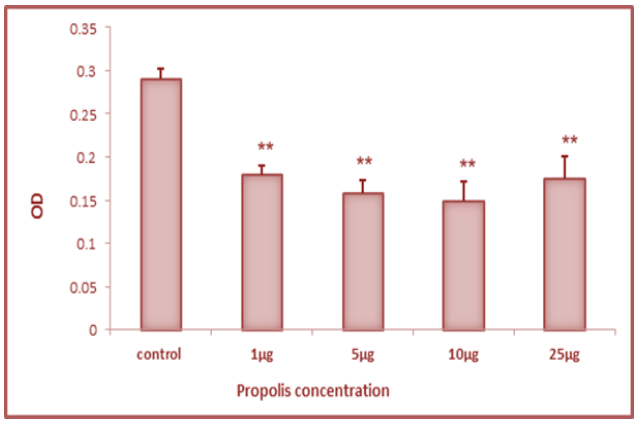

Figure 5. Free radical scavenging activity in different concentrations of propolis in the xanthine- XOD assay.
Significantly different from control group (** p < 0.01). Values are mean ±SD.

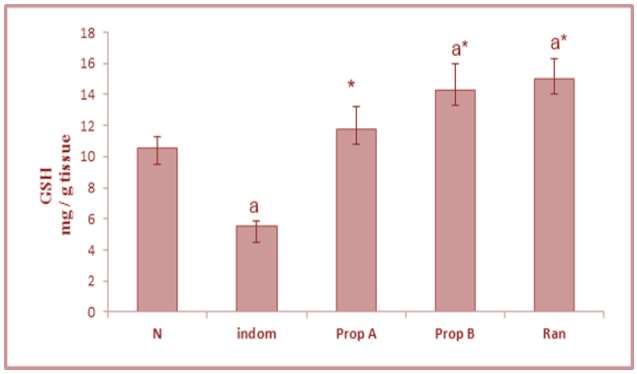

Figure 6: Effect of Egyptian propolis on reduced glutathione (GSH) in indomethacin-induced gastric ulcer in rats. Prop A (PEE, 200 mg/kg), Prop B (PEE, 400 mg/kg), Ran (ranitidine, 50 mg/kg), Indo (indomethacin, 30 mg/kg) and N (normal). Statistically significant from the normal (^{a}p < 0.05). Statistically significant from the control (*p < 0.05).

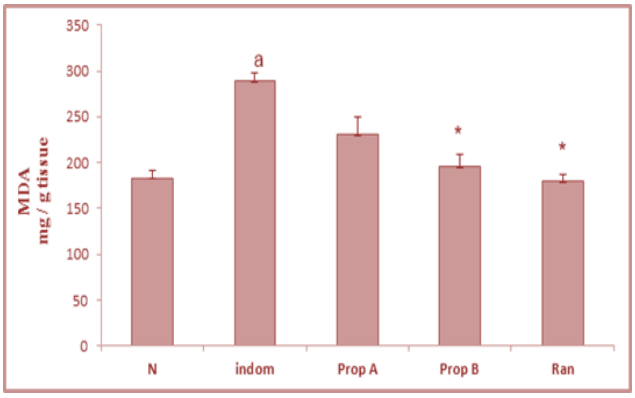

Figure 7: Effect of Egyptian propolis on malondialdehyde (MDA) in indomethacin-induced gastric ulcer in rats.
Prop A (PEE, 200 mg/kg), Prop B (PEE, 400 mg/kg) and Ran (ranitidine, 50 mg/kg), Indo (indomethacin, 30 mg/kg) and N(normal). Statistically significant from the normal (^{a}p < 0.05). Statistically significant from the control (*p < 0.05).

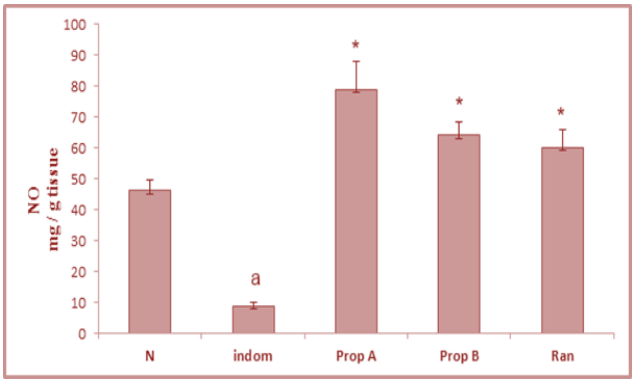

Figure 8: Effect of Egyptian propolis on nitric oxide (NO) in indomethacin-induced gastric ulcer in rats.
Prop A (PEE, 200 mg/kg), Prop B (PEE, 400 mg/kg) and Ran (ranitidine, 50 mg/kg), Indo (indomethacin, 30 mg/kg) and N(normal). Statistically significant from the normal (^{a}p < 0.05). Statistically significant from the control (*p < 0.05).

DISCUSSION

Phenolics present in propolis ethanol extract have received considerable attention because of their polarity. Flavonoids as one of the most diverse and wide spread group of natural compounds are probably the most important natural phenols. These compounds possess a broad spectrum of chemical and biological activities including radical scavenging properties (Patil et al., 2012). Our analyses of total phenolic and flavonoid contents, free radicals (DPPH, superoxide anion) scavenging activity showed that the propolis extract had a significant high antioxidant activity. Our data are in accordance with the use of the entire crude propolis extract in traditional medicine (De Castro, 2001).Although in most of the cases the etiology of the ulcers is unknown, it is generally accepted that they result from an imbalance between aggressive factors and the maintenance of mucosal

integrity through endogenous defense mechanisms (Piper and Stiel, 1986). The anti-ulcer activity of the propolis extract was evaluated by employing indomethacin/pylorus ligation and indomethacin induced ulcer models. These models represent some of the most common causes of gastric ulcer in humans. Many factors and mechanisms are implicated in the ulcerogenesis and gastric mucosal damage induced by different models employed in the present study involving, depletion of gastric wall, mucin mucosal damage induced by non-steroidal anti-inflammatory drugs and free radical production. To regain the balance, different therapeutic agents including natural products are used such as the propolis extract undertaken for the present study primarily to evaluate its anti-ulcerogenic potential. The number of lesions in the untreated ulcer group was quite high. The group pretreated with propolis had a dramatic decrease in the number of lesions. The number of lesions present on the gastric mucosa is indicative for the gastric damage (West, 1982). A significant reduction in the number of lesions in the pretreated propolis groups may be due to inhibiting gastric acid secretion, an important factor in ulcer. The volume and total acidity were significantly increased in the untreated ulcer group relative to the normal group. The increase in volume of the untreated ulcer rats is undoubtedly due to the increased production of HCl, as is evident from the total acidity of the gastric juice. The volume of gastric juice in indomethacin-induced ulcer rats was significantly reduced by propolis. There has been a considerable interest in finding natural antioxidants to replace synthetic ones for effective management of therapeutic drug toxicity such as peptic ulcer (Pratt, 1992). The volume of acid present in gastric secretion which encompasses HCl, pepsinogen, mucus, biocarbonates, intrinsic factor and protein reflects acid volume. Exposure of unprotected lumen of the stomach to accumulating acid could facilitate ulceration (Olsen, 1988), another major aggressive factor responsible for ulcers is the content of acid present in gastric juice. Over secretion of histamine contributes to increased secretion of gastric juice (Grossman, 1978). When the concentration of hydrogen ions in gastric juice decreases, it is reflective of high pH. The genesis of ulcer and gastric damage is facilitated by hydrogen ions which serve as another aggressive factor (Lüllmann et al., 2000).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is considered to be the major risk factor in gastric ulcers. The mechanisms suggested for the gastric damage caused by NSAIDs are inhibition of prostaglandin synthesis and inhibition of epithelial cell proliferation in the ulcer margin, which is critical for the re-epithelization of the ulcer (Levi et al., 1990).

In the present study, indomethacin oral administration, a representative of NSAIDs family, caused a remarkably significant increase in ulcer number and severity, gastric juice, and total acidity. The ulceration induced by indomethacin is attributed mainly to various processes, including generation of reactive oxygen species, initiation of lipid peroxidation, infiltration of leukocytes, induction of apoptosis, and inhibition of prostaglandin synthesis (Bech et al., 2000). Decreased prostaglandin levels impair almost all aspects of gastro-protection and increases acid secretions which, in turn, aggravate the ulcer (Miller, 1983).Oral administration of propolis significantly reduced ulcer index, gastric juice acid output in indomethacin-induced ulcer in pylorus ligated rats. Gastric acid decrease is attributed to its ability to antagonize the binding of histamine to the H2 receptor on the parietal cells (Banji et al., 2010). Propolis can therefore counter the effect of indomethacin on acid secretion. Oral administration of propolis produced significant decrease in ulcerative index. Indomethacin is known to induce the reactive oxygen metabolites in animal models, which may contribute to mucosal injury (Chattopadhyay et al., 2006). Gastric damage depleted the GSH levels acting as the first line of cellular defense against oxidative injury. This might lead to aggravated tissue damage during stomach ulceration (El-Missiry et al., 2001), our experimental results are in line with these previous data (Mohafez et al., 2010). GSH and other antioxidant mechanisms (vitamins, melatonin, etc.) prevent tissue damage by keeping the ROS at low levels and at certain cellular concentrations (Ajaikumar et al., 2005). The oxidative stress in gastric tissue causes damage to key biomolecules such as lipids. This was apparent from the stimulated lipid oxidation leading to increased accumulation of MDA. As shown in the present results, propolis treatment significantly reverted the indomethacin-induced changes in MDA. This significant reduction in MDA levels suggest decreased lipid peroxidation and increased antioxidant activity of propolis. Ranitidine, an antisecretory drug, has often been reported to possess antioxidant and immunosuppressive actions, which might be responsible for its antiulcerogenic activity (Ardestani et al., 2004). Propolis provided a marked suppression of oxidative damage through excellent radical scavenging activity to DPPH and superoxide anion radicals. It brought MDA level closer to normal levels.Nitric oxide (NO) is an endogenous defensive factor for gastric cells and exhibits gastro-protective properties against different types of aggressive agents (Samini et al., 2002). It is involved in the maintenance of mucosal integrity through the regulation of mucus and alkaline secretion, gastric motility and microcirculation (Tsukimi and Okabe, 2001). NO is known to modulate acid levels, gastric mucus secretion, and blood flow in gastric tissues (Martín et al., 2001). NO has also been reported to prevent membrane lipid peroxidation (Hogg and Kalyanaraman, 1999), it may protect against NSAID damage by promotion of prostaglandin synthesis (Salvemini et al., 1993).

In the present study, indomethacin significantly reduced gastric mucosal NO level compared to control group. This finding was in accordance with Cadirci et al. (2007), who reported a decrease in NO level in stomach tissue damaged by indomethacin. Tripp and Tepperman (1995) also reported a decrease in NO biosynthesis, as a result of decreased nitric oxide synthase (NOS) activity that was associated with an increase in the extent of damage. Treatment with propolis significantly increased mucosal NO level when compared to indomethacin treated rats. In conclusion, Egyptian propolis can protect indomethacin induced-gastric ulceration due to its antioxidant properties. The mechanism of its gastro-protective activity may be attributed to reduction in gastric mucosal lipid peroxidation (MDA), elevation of gastric reduced glutathione and nitric oxide. Finally, propolis has a tremendous potential deserves a special attention of the scientific fraternity, due to its safety profile and can be a potent natural and safe alternative to conventional antiulcer treatment. However there is a shortage of clinical trial regarding its potency and efficacy.

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