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Mechanisms involved in the gastro-protective effect of STW 5 (Iberogast®) and its components against ulcers and rebound acidity

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Abstract

The protective effect of a commercial preparation (STW 5, Iberogast®), containing the extracts of bitter candy tuft, lemon balm leaf, chamomile flower, caraway fruit, peppermint leaf, liquorice root, Angelica root, milk thistle fruit and greater celandine herb, against the development of gastric ulcers was previously reported in an earlier publication (Khayyal et al., 2001). All extracts produced a dose dependent anti-ulcerogenic effect associated with a reduced acid output, an increased mucin secretion, an increase in prostaglandin E_2 release and a decrease in leukotrienes. The effect on pepsin content was not uniform and did not seem to bear a relationship with the anti-ulcerogenic activity. The best effects were observed with the combined formulation, STW 5. Furthermore, the effect of the latter in protecting against the development of rebound gastric acidity was examined experimentally in rats and compared with the effect of some commercial antacid preparations (Rennie®, Talcid® and Maaloxan®). A model of testing rebound acidity was developed by inducing a marginal increase in gastric acidity through the administration of indomethacin, in such a way that it could be easily neutralized, allowing any eventual secondary increase in acidity to be measured within a few hours of administration. In addition, the serum gastrin level was measured after drug treatment to establish any correlation between it and any rebound acidity. The results obtained demonstrated that STW 5 did not only lower the gastric acidity as effectively as the commercial antacid, but it was more effective in inhibiting the secondary hyperacidity. Moreover, STW 5 was capable of inhibiting the serum gastrin level in rats, an effect which ran parallel to its lowering effect on gastric acid production.

Keywords: STW 5; Iberogast; Iberis amara; Gastric ulcer; Indomethacin; Gastric mucosa; Mucin; Prostaglandin E2; Leukotriene D4; Gastrin; Acid rebound; Rebound acidity

Introduction

Initially, the potential anti-ulcerogenic effect of STW 5 and its individual components were studied (Khayyal et al., 2001). The pathogenesis of peptic ulcer involves a disturbance of the natural balance between aggressive factors in the stomach, e.g. the production of acid and pepsin, and defensive mechanisms involving the elaboration of mucus and bicarbonate as well as mucosal turnover (Piper and Stiel, 1986). The primary endogenous mediators of gastric acid secretion are mainly acetylcholine, gastrin and histamine, the roles of which

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are intricately interrelated (Hayward et al., 1991). The protective mechanisms of mucus and bicarbonate secretion depend to a large extent on prostaglandin E_1 and E_2 secretion, and these in turn depend on the activity of the cyclooxygenase enzyme system. Gastric mucosal injury could be produced by a variety of agents which disturb that balance, including alcohol, nonsteroidal anti-inflammatory drugs, parasympathomimetics, and drugs with histamine-like properties.

Some plant constituents and their combination in the form of a commercial preparation (STW 5) have been studied to determine their usefulness as anti-ulcerogenic agents. STW 5 (Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) consists of a fixed combination of plant extracts namely bitter candytuft (*Iberis amara*), Melissa leaf (*Melissa officinalis*), Matricaria flower (*Matricaria recutita*), caraway fruit (*Carum carvi*), peppermint leaf (*Mentha* × *piperita*), Angelica root (*Angelica archangelica*), milk thistle (*Silybum marianum*), elan-dine herb (*Chelidonium majus*), in addition to liquorice root (*Glycyrrhiza glabra*). The anti-ulcerogenic effect of the individual plant extracts as well as their combination was determined using indomethacin as a standard ulcerogen and cimetidine as a reference anti-ulcerogenic agent. Further experiments were then carried out to investigate possible mechanisms involved in their anti-ulcerogenic action. Parameters such as free acidity, mucin and pepsin concentrations in the gastric juice, as well as prostaglandin and leukotriene levels in the gastric mucosa were measured.

Many agents that reduce gastric acidity often have a tendency to induce a secondary rise in acidity within a short time of administration. These include H_2-receptor blockers, proton pump inhibitors (Nwokolo et al., 1991) and many antacid preparations. Rebound acid hypersecretion may contribute to the high ulcer relapse rate after discontinuation of H_2-receptor antagonists (Nwokolo et al., 1991; Wilder-Smith et al., 1991). A variety of factors have been proposed to explain the earlier ulcer relapse rate, including secondary hypergastrinemia with rebound acid hypersecretion after discontinuation of the drug. Secondary hypergastrinemia may also lead to tolerance to prolonged courses of H_2 antagonists associated with decreased acid inhibition (McQuaid, 1991). Similarly, many antacids containing calcium, as carbonate or other salts, cause an increase in gastric acid secretion which might be explained, at least in part, to direct stimulation by the calcium ions. Other antacids, notably magnesium hydroxide and aluminum hydroxide may also cause acid rebound, possibly, through antral alkalinization with subsequent gastrin release (Hade and Spiro, 1992). Gastrin secretion is a function of the gastric antral mucosa and is highly dependent upon gastric intraluminal pH. It is inhibited significantly by a pH of less than 3.0 (McQuaid, 1991). Courses of standard therapy with antisecretory agents such as H_2 blockers or H^+/K^+/ATPase inhibitors cause a significant rise in the 24 h plasma gastrin levels. Since STW 5 was found to exert some beneficial properties on gastric acidity, it was therefore of interest to investigate whether it causes rebound hyperacidity or not. The effect of this agent was compared in rats with conventional antacid trade preparations. Since acid production is associated with gastrin secretion, among other factors, serum gastrin level of rats was estimated during the phase of the rebound hyperacidity to illustrate the possible mode of action of the selected drugs.

Materials and methods

Plant extracts and drugs

STW 5 (Iberogast®), and its individual components: bitter candytuft (*Iberis amara*), melissa leaf (*Melissa officinalis*), Matricaria flower (*Matricaria recutita*), caraway fruit (*Carum carvi*), peppermint leaf (*Mentha* × *piperita*), Angelica root (*Angelica archangelica*), milk thistle (*Silybum marianum*), elan-dine herb (*Chelidonium majus*), and liquorice root (*Glycyrrhiza glabra*) were obtained either as 30% alcoholic extracts or as lyophilized extract from Steigerwald Arzneimittelwerk, GmbH, Darmstadt, Germany.

The commercial antacid products used were Rennie® (Roche Nicholas, Eppstein-Bremthal, Germany), Talcid® (Bayer, Leverkusen, Germany) and Maaloxan® (Rhône-Poulenc-Rorer Casella-med, GmbH&Co. KG, Köln, Germany). They were used as the powdered form of the commercial product.

Magnesium carbonate, indomethacin and cimetidine were obtained from Sigma Chemical Co. (St. Louis, MO, USA).

Animals

Male Wistar rats weighing 120–150 g each were used for this study. Animals were obtained from the National Research Centre, Dokki, Cairo, and were fed on a standard pellet diet. They were housed at the animal facility at the Faculty of Pharmacy, Cairo University at a temperature of 25 ± 1 °C and humidity of 60 ± 5%. The study was conducted according to the guidelines for animal experiments set by the Faculty of Pharmacy, Cairo University in accordance with international guidelines. The rats were randomly divided into groups of 8–10 animals each for the experiments described below.

Induction of ulcers and assessment of anti-ulcerogenic effect of extracts

Thirty-six hours before subjecting the rats to experimentation, they were subdivided into groups of ten.

Feed was withdrawn from them, allowing them free access to water only, then the latter was also withdrawn one hour before the experiment (Meshali et al., 1983; Bhargava et al., 1973).

Ulcers were induced acutely by giving the animals indomethacin orally in a dose of 10 mg/kg (Shay et al., 1954). Five hours later the rats were killed by decapitation. The stomachs were removed, opened along their greater curvature, and gently rinsed with cold normal saline and pinned on a paraffin and plastic polymer plate, before being examined under an illuminated magnifying glass. The mucosal layer was carefully inspected for the occurrence of ulcers and their numbers counted. The severity of ulcers was given an arbitrary score from 0 to 4 according to the extent of ulceration, 0 indicating a normal mucosa with no ulcers, 1–4 signifying the presence of lesions varying in intensity from 1 mm to perforation.

The alcoholic extracts were administered at three dose levels of 2.5, 5 and 10 ml/kg body weight orally one hour before the oral administration of indomethacin to groups of 10 rats each in order to assess the dose-dependent nature of their anti-ulcerogenic effect and to be able to choose the most appropriate dose of each extract for the experiments to follow. Five hours later, the extract-treated animals were killed and their stomachs were examined and assessed for ulcers. Another group of rats was given cimetidine orally in a dose of 100 mg/kg one hour before indomethacin administration and served as reference standard. The ulcer index for each group was calculated according to the following formula (Robert et al., 1967):

% Incidence of animals with ulcers	+ mean severity on arbitary scale	+ mean number of ulcers /stomach
10	(0–4)	

The protective anti-ulcerogenic effect of the extracts was taken as the percentage change in the ulcer index as compared to the indomethacin treated group.

Assessment of antisecretory and cytoprotective parameters

For the assessment of the antisecretory and cytoprotective activities of STW 5, the lyophilized extracts were reconstituted with water before use to give the same concentration as in the original alcoholic extracts. In this way, the possible interfering effect of alcohol in the original alcoholic extracts was obviated. The extracts were given orally to groups of 8 rats each, in the dose regarded from the above experiment as showing good anti-ulcerogenic activity. Accordingly, the reconstituted aqueous extracts were administered in the following doses: 10 ml/kg for STW 5, *Matricaria recutita*, *Angelica archangelica* and *Silybum marianum*, 5 ml/kg for *Glycerrhiza glabrata* and *Melissa officinalis*, 2.5 ml/kg for *Mentha* × *piperita*, *Carum carvi* and *Iberis amara*.

Forty-eight hours before starting the experiment, each animal was then housed singly in a cage with a raised bottom of wide mesh to allow passage of faeces and prevent caprophagia. The feed, but not water, was withheld from the animals before subjecting them to the procedure of pyloric ligation (Shay et al., 1954). At the end of the starvation period, the extracts were administered orally in the above doses. One hour later, the rats were lightly anaesthetized with ether, and a nearly 2 cm mid-line incision was made extending from the xiphoid downwards to expose the stomach. The junction between the pylorus and the duodenum was picked up and pyloric ligation was carried out by passing a silk thread below the pylorus and then tying the thread in such a way to close the pylorus without crushing its wall. The abdominal wall was then closed with Michel's clips, the abdominal wound cleansed thoroughly with physiological saline, dried, and covered with a solution of collodion. At this point, indomethacin was given intraperitoneally in a dose of 10 mg/kg and the animals were then allowed to recover, placed in their individual cages, and received neither food nor water during the rest of the experiment.

Four hours later, the animals were again anaesthetized with ether, the abdomen was opened and a ligature was placed at the oesophageal-cardiac junction. The stomach was then removed, washed in physiological saline, and blotted dry before sacrificing the animals. An opening was made along the greater curvature and gastric contents drained through a funnel into a graduated centrifuge tube. The stomach was then slit open along the entire greater curvature and the mucosa was scrubbed off and weighed.

The gastric contents of each animal were then centrifuged and the following parameters were assessed in the supernatant:

(a) *Free acidity and acid output*: Free acid concentration was determined by direct titration of 100 µl of gastric juice against 0.005 N sodium hydroxide using phenol red as indicator and expressed as mEq/l. The acid output/hour was calculated by multiplying the free acidity by the gastric juice volume and dividing by 4, as 4 h had elapsed between ligation and sampling. The acid output was expressed as µEq/h.

(b) *Mucin concentration*: Mucin was determined according to the spectrophotometric method described by Winzler (1955), based on the determination of hexose component of mucin.

(c) *Pepsin concentration*: Pepsin was determined according to the spectrophotometric method described by Sanyal et al. (1971) depending on the digestion of serum albumin by the peptic activity of the gastric juice, using tyrosine as a standard.

(d) *Analysis of prostaglandins and leukotrienes in the mucosal contents*: The collected mucosa was divided into two portions which were processed as follows:
One portion was accurately weighed, acidified with 3 N hydrochloric acid, homogenized, and then extracted twice with diethyl ether. The ether was evaporated to dryness and the residue was kept for the assay of prostaglandins as PGE_2 using an ELISA kit (Neogen corporation, USA).
The other portion was treated with 2.5 ml absolute ethanol, homogenized, and centrifuged. The supernatant was evaporated to dryness and the residue was used for assaying leukotrienes as LTD_4 using an ELISA kit (Neogen corporation, USA).

Effect of STW 5 and some commercial antacids on gastric acid rebound

Effect on gastric acidity

The principle for establishing a method for testing rebound acidity was to find a suitable dose of indomethacin to induce a measurable degree of acidity in the stomach that would wane off within about 5 h of drug administration. Giving a drug in a dose that could just counteract the increased acidity at its initial stages of development would then allow any rebound acidity to be detected 4–5 h later. From pilot experiments, indomethacin in an oral dose of 1 mg/kg was found to be suitable for that purpose.

Animals were randomly divided into several groups, each of 10 rats. The animals were fasted for 18 h before the experiment, and each rat was kept singly as previously described. One group served as control and received only saline. Indomethacin was given orally in a dose of 1 mg/kg to three groups of animals, and gastric acidity was determined at time intervals of 1, 2, and 5 h, respectively after administration. STW 5 (2.5 ml/kg) and the commercial antacids (magnesium carbonate, 250 mg/kg; Rennie, a dose corresponding to 250 mg magnesium carbonate/kg; Talcid, 332.5 mg hydrotalcit/kg; and Maaloxan in a dose equivalent to 26.5 mg $Al(OH)_3 + 43.5$ mg $Mg(OH)_2$/kg) were given orally each to a group of 10 animals, 1 h after indomethacin administration and the gastric acidity was determined as described above after 2 and 5 h of indomethacin administration. These doses were selected after initial pilot experiments to find the smallest dose necessary to neutralize the indomethacin-induced acidity within 1 h of administration and ensuring that the effect wears off shortly, allowing for any rebound acidity to be detected within 5 h of indomethacin administration.

Effect on serum gastrin level

In another set of experiments, animals were divided into six groups, each of 6 rats, to determine the serum gastrin level. Animals were fasted for 18 h before subjecting them to experimentation. One group of rats was kept as control, and the others were injected intraperitoneally with 10 mg/kg indomethacin. One hour later, the rats were given the drugs mentioned above in the pre-selected doses. Blood was collected from the retro-orbital plexus of each animal using fine heparinized capillary tubes, 2 and 5 h after indomethacin administration. The collected blood was centrifuged and the serum was separated and kept frozen until assayed for gastrin using a Gamma Dab Gastrin ^{125}I radioimmunoassay kit (DiaSorin Stillwater, Minnesota, USA).

Statistical analysis

Statistical analysis was carried out using one way analysis of variance (ANOVA) followed by the least significant difference (LSD) test. Values are given as means $\pm$ S.D. and $p < 0.05$ was considered to be statistically significant.

Results

Effect on indomethacin-induced gastric ulcers

STW 5 and its individual plant extracts produced a dose-dependent protection against the ulcerogenic effect induced by indomethacin (Fig. 1). STW 5 in the doses used showed good anti-ulcerogenic effect particularly with the highest dose of 10 ml/kg amounting to nearly 60%, an effect nevertheless less than that produced by cimetidine (100 mg/kg).

With respect to the free acidity, STW 5 given 1 h before indomethacin prevented the marked rise in gastric acidity and acid output induced by the latter. Similar effects were obtained with the other plant extracts, especially those of matricaria leaf, caraway fruit and bitter candytuft, which were effective even in reducing the acidity below normal values, their effect approaching that of cimetidine (Figs. 2 and 3).

Gastric mucin, which was significantly reduced by indomethacin, was not only preserved by STW 5, but its level was even increased two-fold. All the individual plant extracts, with the exception of that of peppermint leaf, also showed an increase in the mucin content, thus providing protection against the gastric ulceration. The most significant effects were observed with the extracts of liquorice root, matricaria flower and caraway fruit (Fig. 4).

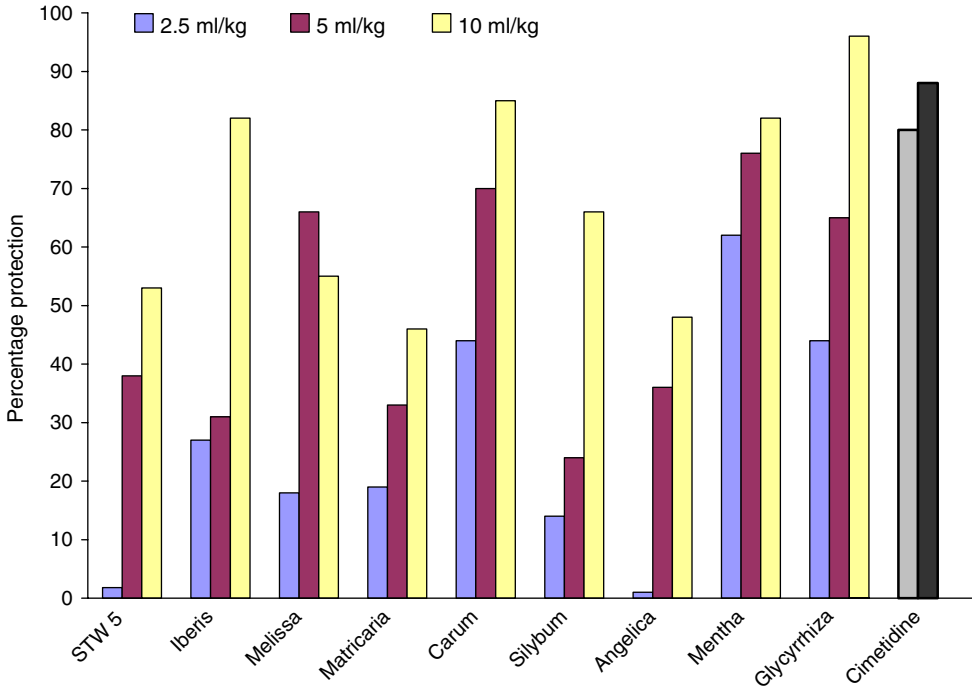

Fig. 1. Protective effect of the different plant extracts against indomethacin-induced ulcers. Columns represent the change in ulcer index of the extract treated groups ($n = 10$) as a percentage of the indomethacin-treated rats.

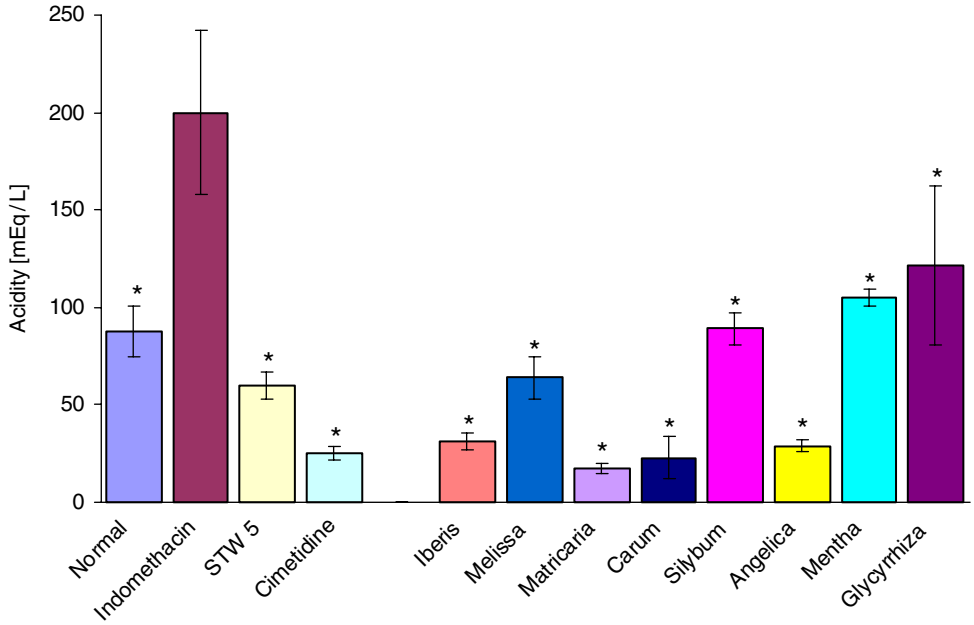

Fig. 2. Effect of treatment with different extracts (doses mentioned in text) on acidity of the gastric juice of pyloric ligated rats. Values are given as means ± s.e.m. of eight observations. *Significantly different from the indomethacin-treated group at $p < 0.05$ [ANOVA followed b LSD test].

Indomethacin tended to lower the gastric pepsin content to a small but statistically significant extent, but the effect of the individual extracts was rather variable. STW 5 and some extracts, like *Matricaria* and *Silybum*, tended to raise it, while others, like *Angelica*, tended to lower it, and some, like peppermint and liquorice, hardly affected it (Fig. 5).

Some of the above effects could possibly be associated with effects on prostanoid levels. The prostaglandin content of the gastric mucosa dropped from 696 ng/g in

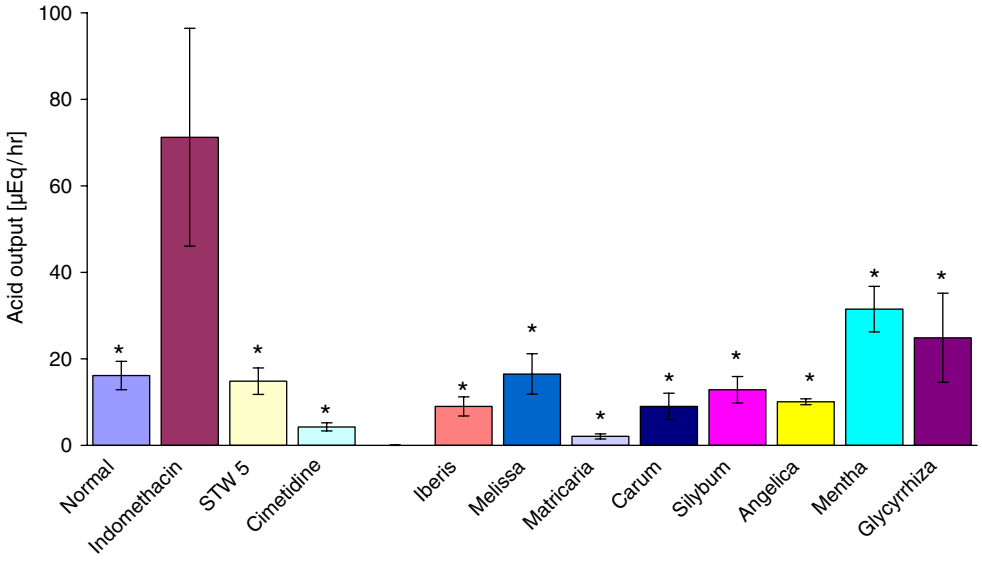

Fig. 3. Effect of treatment with different extracts (doses given in text) on acid output of the gastric juice of pyloric ligated rats. Values are given as means ± s.e.m. of 8 observations. *Significantly different from the indomethacin-treated group at $p < 0.05$ [ANOVA followed b LSD test].

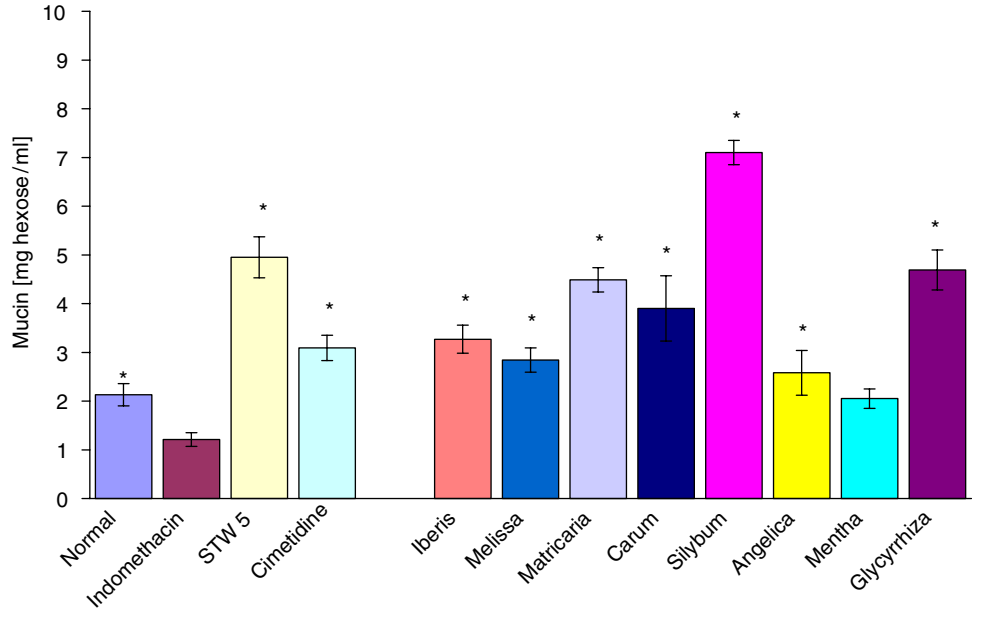

Fig. 4. Effect of treatment with different extracts (doses in text) on mucin content of the gastric juice of pyloric ligated rats. Values are given as means ± s.e.m. of 8 observations. *Significantly different from the indomethacin-treated group at $p < 0.05$ [ANOVA followed b LSD test].

normal animals to nearly 48 ng/g under the influence of indomethacin, while the leukotriene levels rose from nanogram levels in normal rats to 1.8 µg/g. The changes in PG and LT levels were prevented to a large extent by cimetidine, which was used as a reference anti-ulcerogenic agent (Figs. 6 and 7). STW 5 and its individual components produced similar effects to cimetidine, where they tended to normalize the values of the mucosal contents of both prostaglandins and leukotrienes.

Effect on gastric rebound and serum gastrin levels

In normal rats, the total acidity after 1 h of giving indomethacin, increased to more than twice the normal

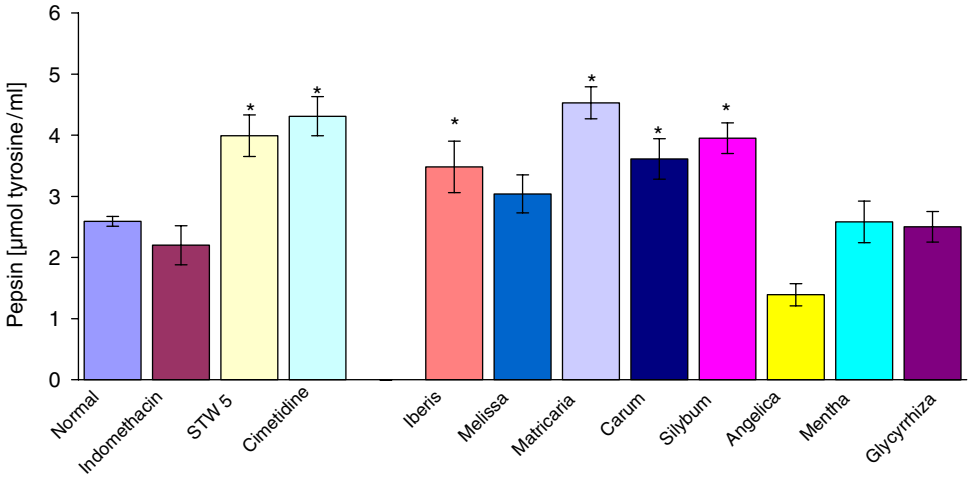

Fig. 5. Effect of treatment with different extracts (doses in text) on pepsin content of the gastric juice of pyloric ligated rats. Values are given as means ± s.e.m. of 8 observations. *Significantly different from the indomethacin-treated group at $p < 0.05$ [ANOVA followed b LSD test].

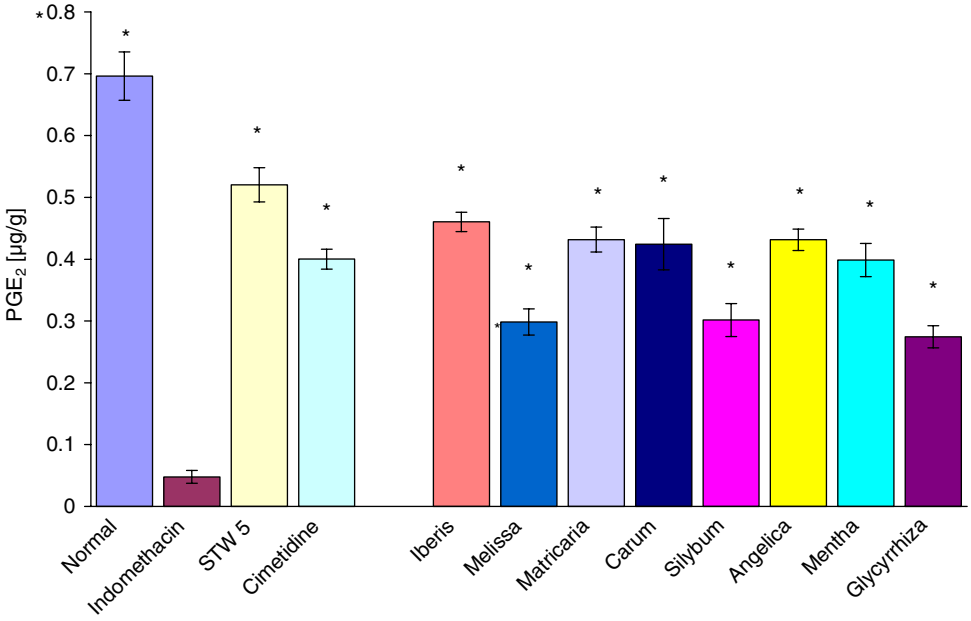

Fig. 6. Effect of treatment with different extracts (doses in text) on prostaglandin E_2 content of the gastric juice of pyloric ligated rats. Values are given as means ± s.e.m. of 8 observations. *Significantly different from the indomethacin-treated group at $p < 0.05$ [ANOVA followed b LSD test].

value and increased further to 3.5 times after 2 h, but then started to decline reaching nearly normal values after 5 h.

Treatment of rats with STW 5 in a dose of 2.5 ml/kg, p.o., brought the total acidity back to normal values after 2 h of indomethacin administration. There was also a decrease in gastric acidity produced by the selected antacids (magnesium carbonate, Rennie, Maaloxan and Talcid) where the total gastric acidity recorded was either normalized or even fell below normal values (Fig. 8).

However, treatment of rats with these antacids tended to increase the total gastric acidity when measured 5 h after indomethacin administration. This increase was highest in the group treated with Rennie and Talcid, and was lowest with groups treated with either STW 5 or magnesium carbonate (Fig. 9).

Serum gastrin level of normal rats could not be detected before or even 2 h after indomethacin treatment, as it was below the level of the sensitivity of the assay method used. However, 5 h after indomethacin administration, the serum gastrin level of rats was found

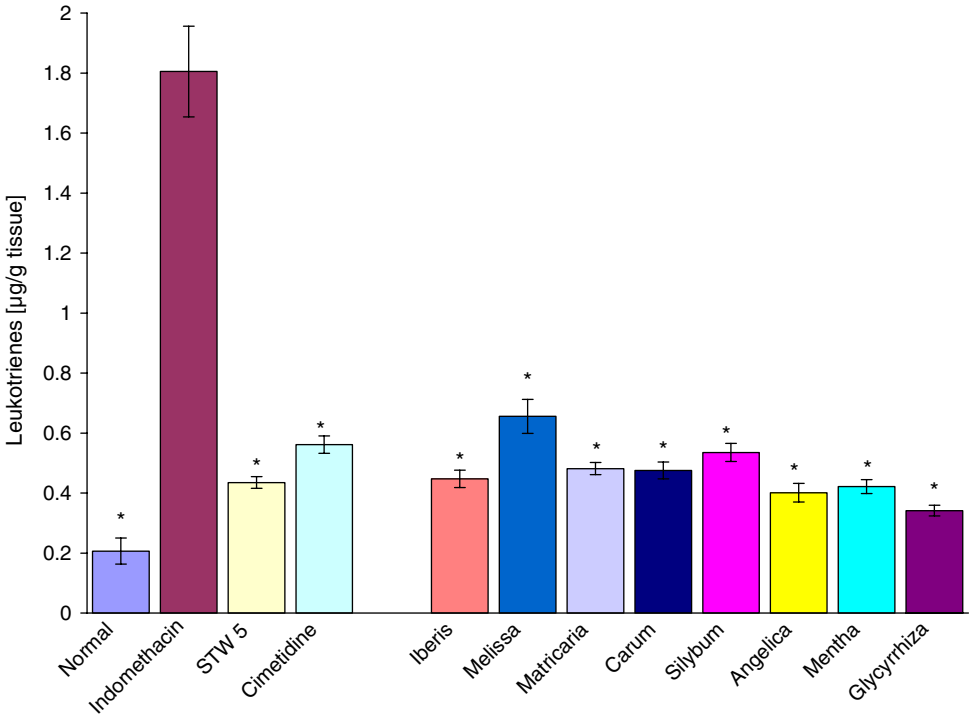

Fig. 7. Effect of treatment with different extracts (doses in text) on leukotriene content of the gastric juice of pyloric ligated rats. Values are given as means ± s.e.m. of 8 observations. *Significantly different from the indomethacin-treated group at $p < 0.05$ [ANOVA followed b LSD test].

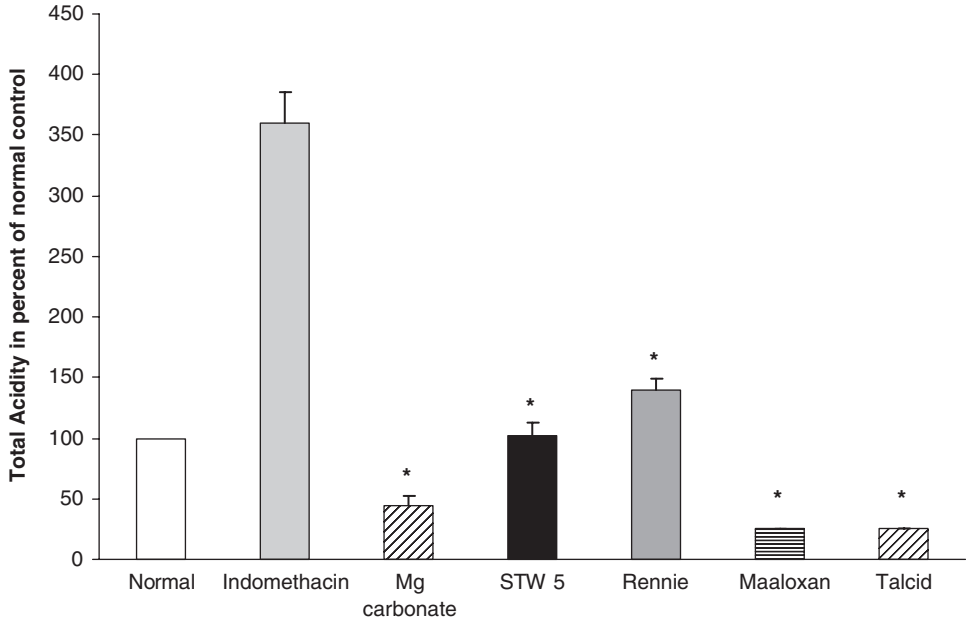

Fig. 8. Total gastric acidity after 2 h of indomethacin oral administration (1 mg/kg) in rats as percentage of control values and the effect of various agents given orally 1 h after indomethacin. Values are given as means ± s.e.m. Astersisks denote significant difference from indomethacin treated group at $p < 0.05$.

to be nearly 600 pg/ml. Treatment of rats with STW 5 showed a significant decrease in the serum gastrin level when measured 5 h after indomethacin treatment reaching a value of about 308 pg/ml. On the other hand, none of the other antacids could lower the serum gastrin level within the 5-h experimental period (Fig. 10).

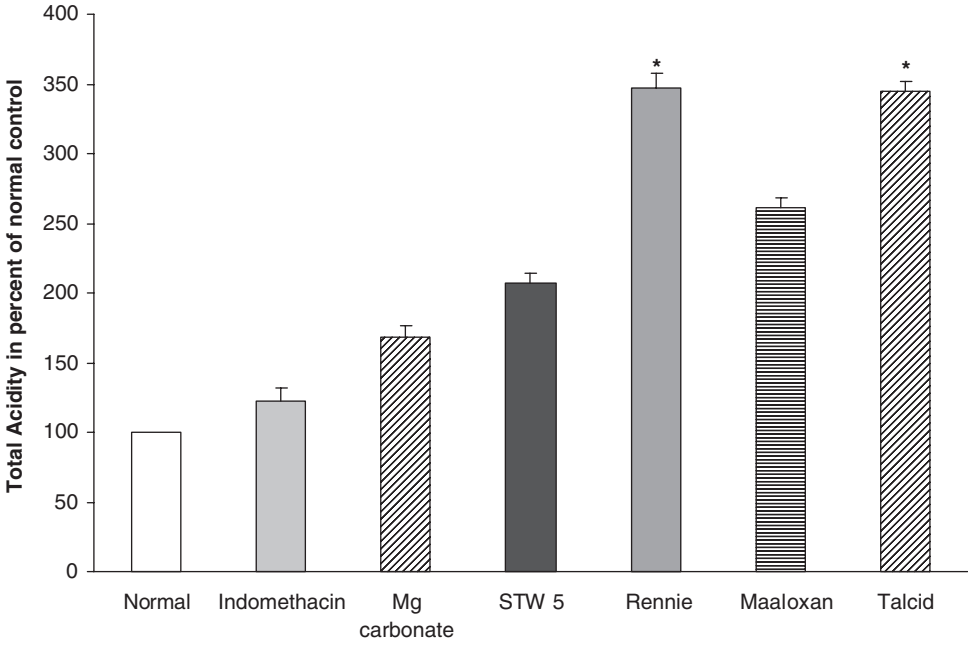

Fig. 9. Total gastric acidity after 5 h of indomethacin oral administration (1 mg/kg) in rats as percentage of control values and the effect of various agents given orally 1 h after indomethacin. Values are given as means ± s.e.m. Astersisks denote significant difference from indomethacin treated group at $p < 0.05$.

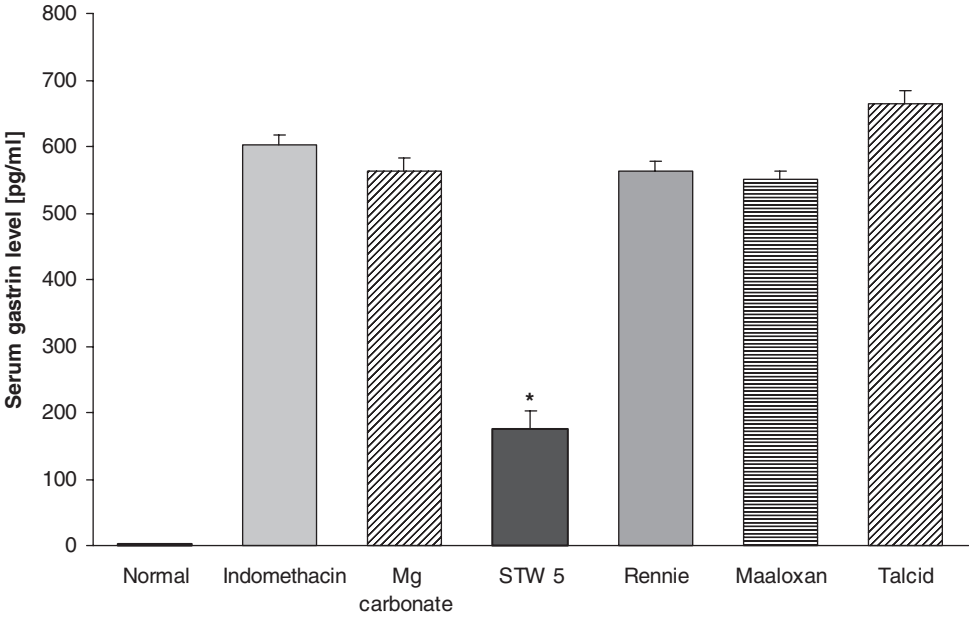

Fig. 10. Gastrin level in serum of rats 5 h after treatment with indomethacin together with STW 5 and some selected commercial antacids. Drugs were given 1 h after indomethacin administration. Asterisks denote significant difference from indomethacin treated group at $p < 0.05$.

Discussion

The anti-ulcerogenic effect of STW 5 and its components has been reported by Khayyal et al. (2001). The increased gastric acid secretion has been reported repeatedly for indomethacin, a finding which has been confirmed by the marked effect of indomethacin in increasing gastric acid secretion and the acid output of the tested rats.

The effect of indomethacin, like that of other non-steroidal anti-inflammatory drugs, is associated with cyclooxygenase inhibition, which has as a consequence,

diversion of arachidonic acid metabolism towards the lipooxygenase pathway, resulting in increased leukotriene synthesis (Pihan et al., 1988; Del Soldato et al., 1986). An increase in the leukotriene concentration was found in the present work together with a reduction in prostaglandin level after the administration of indomethacin. One of the relevant effects of prostaglandins on gastric mucosal function is to inhibit gastric acid and pepsin secretion (Robert et al., 1967; Classen et al., 1971). Leukotrienes have also been attributed an important role in the gastrointestinal ulceration (Wallace et al., 1990), possibly by enhancing mucosal injury through the release of oxygen radicals produced in this pathway (Del Soldato et al., 1986; Rainsford, 1987), or through an increase in vascular permeability in the gastric mucosa.

The results also showed that STW 5 and its individual components could protect the stomach against the ulcerative damage produced by the acute administration of indomethacin, as evidenced by their effect in reducing the number of ulcers produced by indomethacin. Other authors have also reported on the anti-ulcerative action of some plant extracts such as *Glycyrrhiza glabra* (Takagi and Ishii, 1967) and *Carum carvi* (Manonmani et al., 1994) which are included in the present study. Our findings therefore indicate that the extracts under investigation possess a cytoprotective effect, which might be mediated through lowering of the gastric acidity and the leukotriene content as well as elevating the concentration of mucin and prostaglandins. The extracts did not affect pepsin secretion indicating that they have a selective inhibitory action on the gastric acid secretion. The decrease in volume and the simultaneous decrease in the acidity may be one of the underlying factors of ulcer healing in the treated groups, since it has been reported that the acid inhibition accelerates ulcer healing (Inauen et al., 1988).

The initial effect of STW 5 on gastric acidity was essentially similar to that of the selected antacid drugs. However, gastric acidity increased with the different antacids when it was measured 5 h after indomethacin administration demonstrating a significant acid rebound effect, except for STW 5 and magnesium carbonate. The increased acid secretion after treatment with certain antisecretory drugs is probably due to hyperplasia of the enterochromaffin-like (ECL) cells (Waldum et al., 1996). It has been shown that the hyperplasia of the ECL cells together with hypergastrinemia secondary to profound acid inhibition are important factors participating in the rebound hypersecretion of acids (Waldum et al., 1996). Thus, post-treatment rebound acid hypersecretion can be understood as gastrin upregulating and/or stimulating growth of the ECL cell leading to increased amounts of releasable histamine (Sandvik et al., 1997). In addition, Nishida et al. (1995) showed that hypergastrinemia caused by long-term administration of antisecretory drugs increases the mucosal secretory response to pentagastrin through a gastrin/cholecystokinin B (CCK-B) receptor mediated pathway in rats. These findings are in accordance with the results of the present study where the serum gastrin level of rats after treatment with either indomethacin alone or together with the different antacids showed elevation of the serum gastrin level (since serum gastrin level of normal rats was beyond detection by the used technique). However, STW 5 was the only agent that lowered significantly the serum gastrin level. This might explain the protection produced by the plant extract against indomethacin-induced increase in gastric acidity as well as against the rebound hyperacidity. The mechanism by which STW 5 lowers serum gastrin still remains obscure. Whether or not the extract affects the gastrin/CCK-B receptor still has to be determined. It has been shown that antagonists of these receptors may exert biological activities appropriate for an anti-ulcer indication (Pendley et al., 1995) and to inhibit gastrointestinal damage in models of peptic ulcer disease by an antisecretory mechanism (Pendley et al., 1993). The antagonists of the CCK-B receptors have been suggested as novel anti-ulcer and antisecretory agents devoid of the disadvantages of secondary hyperacidity, hyperplasia and carcinoid (Miyata et al., 1995). It can be concluded however, that irrespective of a potential effect of STW 5 on the gastrin receptors, the combination of these plant extracts show a powerful reduction of the hypergastrinemia observed after indomethacin treatment, and may thus have a promising therapeutic value as an anti-ulcer agent that protects against the gastric damage without the risk of rebound hyperacidity. The gastroprotective effect of STW 5 might be attributed partly to inhibiting the release of aggressive factors involved in the pathogenesis of gastric ulcer and functional gastric diseases such as acid and leukotrienes and partly to promoting the production of defensive elements such as mucin and prostaglandins.

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