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Pharmacological Basis for the Medicinal Use of Ginger in Gastrointestinal Disorders

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Ginger (rhizome of *Zingiber officinale*) has been widely used for centuries in gastrointestinal disorders, particularly dyspepsia, but its precise mode of action has yet to be elucidated. This study was undertaken to study the prokinetic action of ginger and its possible mechanism of action. Prokinetic activity of ginger extract (Zo.Cr) was confirmed in an in vivo test when it enhanced the intestinal travel of charcoal meal in mice. This propulsive effect of the extract, similar to that of carbachol, was blocked in atropine-pretreated mice, a standard cholinergic antagonist. Likewise, Zo.Cr showed an atropine-sensitive dose-dependent spasmogenic effect in vitro as well as in isolated rat and mouse stomach fundus tissues. In atropinized tissue, it showed spasmolytic activity as shown by the inhibition of 5-HT- and K^+-induced contractions. A spasmolytic effect was also observed in other gut preparations either as noncompetitive inhibition of agonist dose–response curves, inhibition of high K^+(80 mM)-induced contractions, or displacement of Ca^{2+} dose–response curves to the right, indicating a calcium antagonist effect. Phytochemical analysis revealed the presence of saponins, flavonoids, and alkaloids in the crude extract. These data indicate that Zo.Cr contains a cholinergic, spasmogenic component evident in stomach fundus preparations which provides a sound mechanistic insight for the prokinetic action of ginger. In addition, the presence of a spasmolytic constituent(s) of the calcium antagonist type may explain its use in hyperactive states of gut like colic and diarrhea.

KEY WORDS: *Zingiber officinale*; ginger; prokinetic; cholinergic; calcium antagonist.

The rhizome of the plant *Zingiber officinale* Roscoe, commonly known as ginger, has been commonly used as a food additive and spice as well as a phytomedicine since ancient times. The typical use of ginger in the kitchens as a condiment began in the 13th century, which enhanced the importance of this rhizome in European markets (1). In addition to its flavoring effects, ginger is also considered an essential component of the kitchen pharmacy and is particularly used in combination with foods which cause delayed gastric emptying or flatulence such as beans, certain pulses, and vegetables like radish and cauliflower (2).

Ginger has been widely studied for its pharmacological activities and has been reported to exhibit anti-inflammatory, antipyretic, antimicrobial, hypoglycemic, antimigraine, antischistosomal, antioxidant, hepatoprotective, diuretic, hypocholesterolemic (1, 3), and antihypertensive activities (4). Phytochemical studies show the presence of pungent principles, such as gingerol, shogaol, zingerone, and paradol (5), while the main aroma defining component is zingiberol (6).

Ginger finds immense use in many of the world's different medicinal systems (2, 7). More commonly, ginger has been traditionally used in disorders of the gastrointestinal tract, as a stomachic, laxative, sialogogue, gastric emptying enhancer, appetizer, antiemetic, and antidyspepsic and, at the same time, as an antidiarrheal and anticolic agent (2, 7). Several studies have been conducted in both animals (8, 9) and humans (10–13) showing its prokinetic action, however, the precise mechanism of action is not yet clear. On the contrary, some studies also reported the inability of ginger to impart any stimulant effect on the bowel (14, 15), while others showed that ginger exhibits

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a spasmolytic action but the precise mode of action remains to be elucidated. However, there is no single study showing the presence of a combination of stimulatory and inhibitory activities in ginger. In this study we confirmed the prokinetic action of ginger extract and showed the presence of a unique combination of spasmogenic and spasmolytic activities mediated through cholinergic and calcium antagonist mechanisms, respectively, which may explain some of the medicinal uses of ginger.

MATERIALS AND METHODS

Chemicals. The following reference chemicals were obtained from the sources specified: acetylcholine chloride (ACh), atropine sulfate, carbamylcholine chloride (carbachol, CCh), hexamethonium chloride, histamine dihydrochloride, 5-hydroxytryptamine hydrochloride (5-HT), nicotine hemisulfate, and verapamil hydrochloride (Sigma Chemical Company, St. Louis, MO). The chemicals used for the charcoal meal transit test were acacia powder, hydrolyzed starch, and vegetable charcoal (BDH Laboratory Supplies, Poole, England). All chemicals used were of the highest purity grade. Stock solutions of all chemicals were made in distilled water and the dilutions were made fresh in normal saline on the day of the experiment.

Animals. Experiments performed complied with the rulings of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (16). Balb-C mice (20–25 g), Sprague–Dawley rats (170–200 g), local rabbits (around 1 kg), and guinea pigs (500–700 g) of either sex used in the study were housed in the animal house of The Aga Khan University under a controlled environment (23–25°C). Animals were fasted for 24 hr before the experiment and given tap water ad libitum and a standard diet consisting of (g/kg): flour, 380; fiber, 380; molasses, 12; NaCl, 5.8; nutrivet L, 2.5; potassium meta bisulfate, 1.2; vegetable oil, 38; fish meal, 170; and powdered milk, 150. Sacrificing was done by cervical dislocation.

Plant Material and Extraction Procedure. A total of 1 kg of fresh ginger was bought from the central vegetable market in Karachi, Pakistan. A sample was deposited at the Herbarium of the Department of Biological and Biomedical Sciences, The Aga Khan University, Karachi, with the voucher number ZO-RH-06-02-46. Ginger was washed for any contaminants and then sliced to expose the inner part. It was then soaked in 2 L of 70% aqueous methanol and kept for a total of 3 days, thrice. The combined filtrate was concentrated in a rotary evaporator to obtain a thick extract with a yield of 4.2%.

Preliminary Phytochemical Analysis. The crude extract was screened for the presence of saponins, flavonoids, tannins, phenols, coumarins, sterols, terpenes, alkaloids, and anthraquinones using standard analytical methods (17).

Charcoal Meal Gastrointestinal Transit Test. The method of Croci *et al.* (18) was used, with slight modifications. Mice were divided into groups of six. Two of the groups, serving as the test groups, were then treated orally with two increasing doses of the extract (30 and 100 mg/kg). One group, treated with saline (10 mL/kg, p.o.), served as the blank or negative control; and the last group, used as the positive control, was administered CCh (1 mg/kg, p.o.), a standard cholinergic agent and gastrointestinal stimulant. After 15 min, the animals were given 0.3 mL of charcoal meal (distilled water suspension containing 10% gum acacia, 10% vegetable charcoal, and 20% starch). After 30 min, the mice were sacrificed and the abdomens immediately opened to excise the whole small intestine. The length of the small intestine and the distance between the pylorus region and the front of the charcoal meal were measured for obtaining the charcoal transport ratio or percentage. To test for an ACh-like involvement in the prokinetic effects of the extract and CCh, separate sets of mice were pretreated with atropine (10 mg/kg, p.o.) 15 min before the administration of the extract or CCh.

Rat and Mouse Stomach Fundus. Experiments on isolated tissues were carried out as previously described (19). Animals were sacrificed by cervical dislocation and stomach fundal longitudinal strips 2 mm wide and 15 mm long were mounted in 10-mL tissue baths with Kreb's solution at 37°C and aerated with a mixture of 95% oxygen and 5% carbon dioxide (carbogen). The composition of Kreb's solution was (mM): NaCl, 118.2; $NaHCO_3$, 25.0; $CaCl_2$, 2.5; KCl, 4.7; KH_2PO_4, 1.3; $MgSO_4$, 1.2; and glucose, 11.7 (pH 7.4). Basal tension of 1 g for rat and 0.5 g for mouse stomach fundus was applied, and the responses were recorded following an equilibrium period of 60 min. Submaximal doses (0.3 μM) of CCh were tested repeatedly to stabilize the preparation and the responses were recorded through isotonic Harvard Transducers coupled with Harvard Student Oscillographs.

Rabbit Jejunum. Segments 2 cm long were mounted in 10-mL tissue baths containing Tyrode's solution at 37°C and aerated with carbogen gas. The composition of Tyrode's solution (mM) was: KCl, 2.7; NaCl, 136.9; $MgCl_2$, 1.1; $NaHCO_3$, 11.9; NaH_2PO_4, 0.4; glucose, 5.6; and $CaCl_2$, 1.8 (pH 7.4). A preload of 1 g was applied to each tissue and the tissues kept undisturbed for an equilibrium period of 30 min, after which responses to ACh (0.3 μM) were obtained. The tissues were presumed stable only after the reproducibility of the said responses. This preparation is known to exhibit spontaneous rhythmic contractions and thus allows studying spasmolytic activity without using any agonist (20). The ginger extract was examined later for activity.

Rat, Mouse, and Guinea Pig Ileum. Segments 2 cm long were mounted in a 10-mL tissue bath containing Tyrode's solution, aerated with carbogen, and maintained at 37°C as described previously (21). Isotonic responses were recorded on Harvard Student Oscillographs. Under these conditions, ileum behaves as a quiescent preparation. A preload of 1 g was applied to each tissue and kept constant throughout the experiment. Following an equilibration period of 30 min, isotonic contractions to ACh (0.3 μM) were repeated to stabilize the preparation. An agonist contact time of 20 sec was used, together with a 3-min interval between doses.

Guinea Pig Colon. A 10-cm-long portion of the colon 5 cm distal to the ileocecal junction was dissected out of the abdominal cavity of guinea pigs. Segments about 1–2 cm long were mounted in 10-mL tissue baths containing Kreb's solution at 37°C and aerated with carbogen gas. A tension of 2 g was applied to each tissue and kept constant through the experiment. Following an equilibrium period of 30 min, submaximal doses of CCh (0.3 μM) were administered until reproducible responses were obtained and then the ginger extract was tested for any activity. Responses were recorded via a Harvard Isotonic Transducer coupled with a Harvard Student Oscillograph.

Acute Toxicity Study. Animals were divided into groups of five mice each. The test was performed using increasing doses of the plant extract (1, 2.5, and 5 g/kg), given orally, in a 10-mL/kg

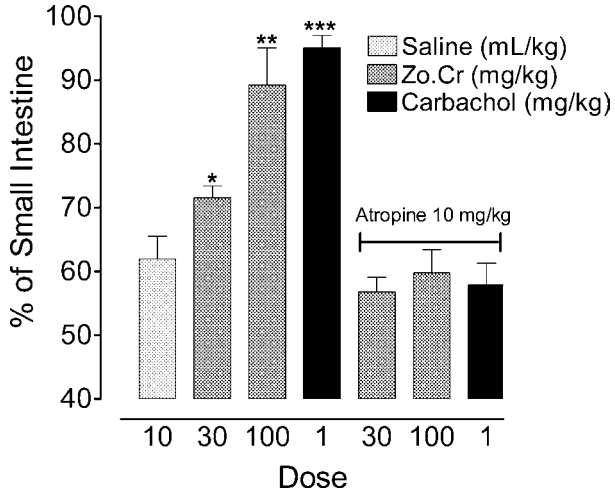

Fig 1. Effect of ginger crude extract (Zo.Cr) and carbachol on charcoal meal intestinal transit in the absence and presence of atropine in mice. $*P < 0.05$, $**P < 0.01$, and $**P < 0.001$ vs. saline control, Student's t-test. $n = 6$.

volume to different groups serving as test groups. Another group of mice was administered saline (10 mL/kg, p.o.) and used as the negative control. The mice were allowed food ad libitum during a 24-hr test and kept under regular observation for mortality and behavioral changes.

Statistical Analysis. All data are expressed mean ± standard error of mean (SE; n = number of experiments) and the median effective concentrations (EC_{50} values) with 95% confidence intervals (CI). The statistical parameter applied is Student's t-test, with $P < 0.05$ noted as significantly different.

RESULTS

Phytochemical Analysis. Zo.Cr showed the presence of saponins, flavonoids, and alkaloids. None of the other classes of compounds tested positive in the crude extract.

Effect on Gastrointestinal Transit. The prokinetic effect of the extract was studied in mice. The extract dose dependently propelled the charcoal meal travel through the small intestine (Figure 1). The distance traveled by the vehicle control (saline) was 61.9 ± 3.5%. The plant extract at the doses of 30 and 100 mg/kg moved the charcoal meal to 71.5 ± 1.9 ($P < 0.05$) and 89.2 ± 5.9% ($P < 0.01$ vs. saline control). CCh (1 mg/kg) moved the charcoal meal to 95.1 ± 1.9% ($P < 0.001$) of the small intestinal length. This enhancement seen in the traverse of charcoal meal in comparison to the control mice by the extract (30 and 100 mg/kg) and CCh (1 mg/kg) was completely blocked in the atropine (10 mg/kg)-pretreated mice (Figure 1).

Effect on Rat and Mouse Stomach Fundus. In rat stomach fundus strips, Zo.Cr produced a dose-dependent contractility from 0.01 to 5.0 mg/mL (Figure 2), with an EC_{50} value of 0.18 mg/mL (0.05–0.32, 95% CI; $n = 5$). Pretreatment of the tissue with atropine (0.1 μM), but not hexamethonium (0.3 mM), completely abolished the stimulatory effect of the extract, similar to that of CCh, while the stimulant effect of 5-HT remained unaltered, suggesting specific blockade of muscarinic receptors. However, when 5-HT was tested in the presence of ginger extract in the atropinized tissue, the stimulant effect of 5-HT was partially blocked, suggestive of the presence of some relaxant component (Figure 2). The spasmolytic effect of Zo.Cr was further studied to explore the possible mechanism involved. When tested against high K^+ (80 mM)-induced contractions in the absence of atropine, Zo.Cr showed dose-dependent (0.3 to 3.0 mg/mL) inhibition (Figure 3B), with an EC_{50} of 0.93 mg/mL (0.81–1.04, 95% CI; $n = 4$). Similarly, verapamil also inhibited the K^+-induced contractions (Figure 3C). Likewise in the mouse stomach fundus, the extract exhibited contractility with an

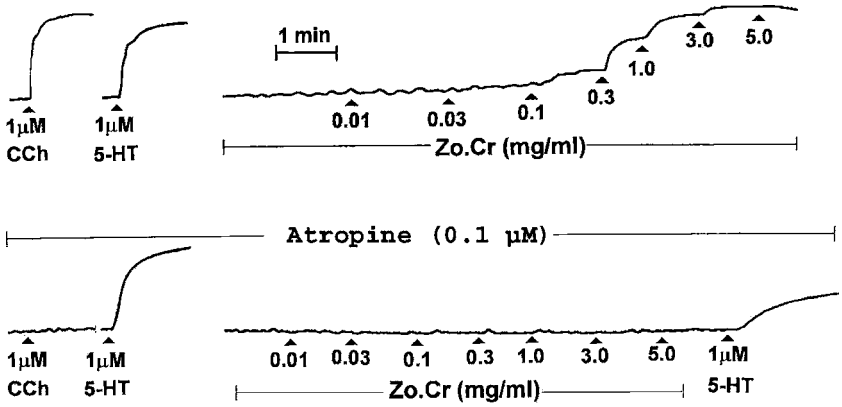

Fig 2. Typical tracing showing the stimulant effect of ginger crude extract (Zo.Cr) in comparison to carbachol (CCh) and 5-hydroxytryptamine (5-HT) in the absence and presence of atropine in isolated rat stomach fundus preparation. The last response of 5-HT was taken while the extract was still present in the bath to show the inhibitory effect of Zo.Cr.

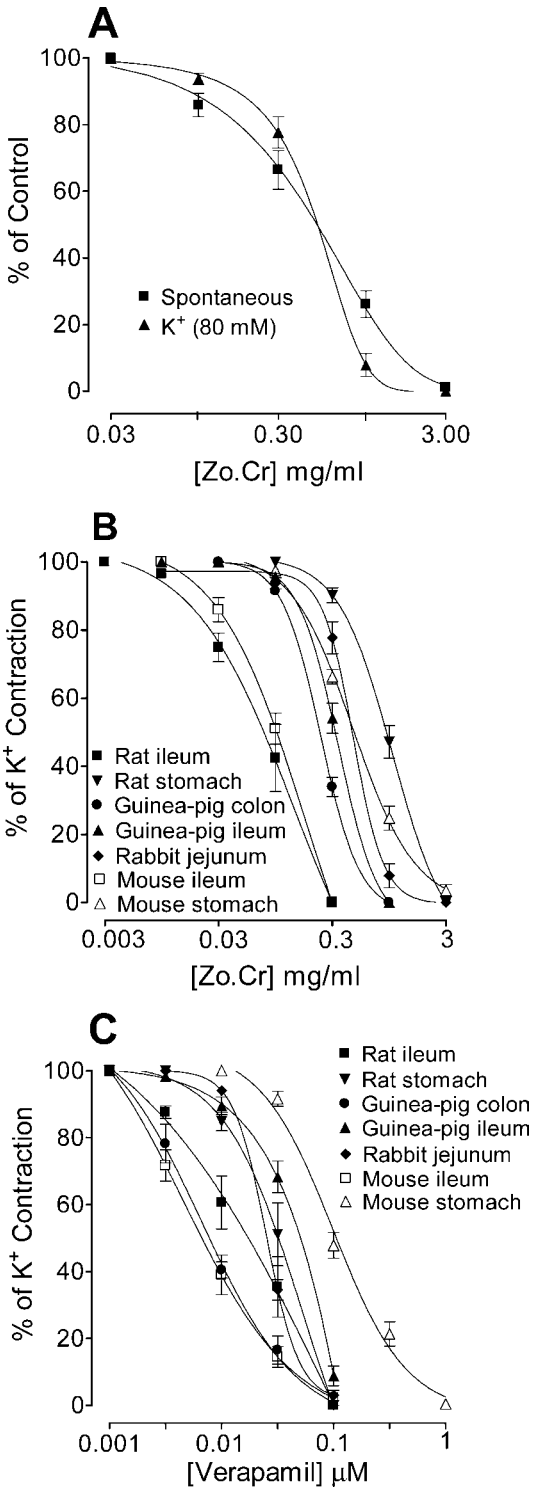

Fig 3. Inhibitory effect of ginger crude extract (Zo.Cr) on spontaneous and K^+-induced contractions in isolated rabbit jejunum (**A**). Lower panels show comparison of the inhibitory effect of (**B**) Zo.Cr and (**C**) verapamil against K^+-induced contractions, in the absence of atropine, in different gut preparations. Values shown are the mean ± SE of three to six determinations.

EC_{50} value of 0.59 mg/mL (0.28–0.89, 95% CI; $n = 3$). Pretreatment of the tissue with atropine (0.1 μM), but not hexamethonium (0.3 mM), completely abolished the stimulatory effect of the extract. Zo.Cr was also able to relax the high K^+ (80 mM)-induced contractions (Figure 3B) in the absence of atropine, with an EC_{50} of 0.51 mg/mL (0.32–0.70, 95% CI; $n = 3$). Similarly, verapamil also inhibited the K^+-induced contractions in mouse stomach fundus (Figure 3C).

Effect on Rabbit Jejunum. When tested on the spontaneous movements of rabbit jejunum, Zo.Cr was found to be devoid of any stimulant effect and instead caused a dose-dependent (0.1 to 3.0 mg/mL) spasmolytic effect (Figure 3A), with an EC_{50} of 0.51 mg/mL (0.36–0.66, 95% CI; $n = 6$). On the high K^+ (80 mM)-induced contractions, the extract exhibited dose-dependent (0.1 to 3.0 mg/mL) relaxation (Figures 3A and B),with an EC_{50} of 0.5 mg/mL (0.4–0.6, 95% CI; $n = 4$), similar to that of verapamil (Figure 3C). The interaction with calcium channels was further studied in jejunum, which is known to be quick in responding to spasmolytic activity (20). Zo.Cr dose dependently (0.1–1.0 mg/mL; $n = 7$) shifted the Ca^{2+} dose–response curves to the right (Figure 4A), similar to that produced by verapamil (0.1–1.0 μM; $n = 7$; Figure 4B).

Effect on Rat, Mouse, and Guinea Pig Ileum. Zo.Cr tested on the resting baseline of rat, mouse, and guinea pig ileum did not show any effect up to 10 mg/mL, thus ruling out the possibility of a stimulant effect in these preparations. To see if the extract has any relaxant effect, contraction was induced with high K^+(80 mM), which produced sustained contraction, allowing acquisition of inhibitory dose–response data. The cumulative addition of Zo.Cr to the tissue bath relaxed this induced contraction in the rat, mouse, and guinea pig ileum (Figure 3B), with EC_{50} values of 0.08 mg/mL (0.02–0.14, 95% CI; $n = 5$), 0.09 mg/mL (0.07–0.13, 95% CI; $n = 3$), and 0.30 mg/mL (0.27–0.33, 95% CI; $n = 5$), respectively. Verapamil also relaxed the induced contractions in all of these tissues (Figure 3C).

Zo.Cr was also studied for its interaction with ACh, 5-HT, and histamine dose–response curves in guinea pig ileum. It dose dependently (0.1–0.3 mg/mL) shifted the ACh, 5-HT, and histamine dose–response curves to the right in a nonparallel manner, with suppression of the maximal response ($P < 0.05$; Figure 5).

Effect on Guinea Pig Colon. The crude extract was also tested on a large intestine preparation. Zo.Cr was again found to be devoid of any stimulant effect when tested on the resting baseline of guinea pig colon. As in the ileum of rat, mouse, and guinea pig, when tested on K^+(80 mM)-induced contractions, Zo.Cr relaxed this

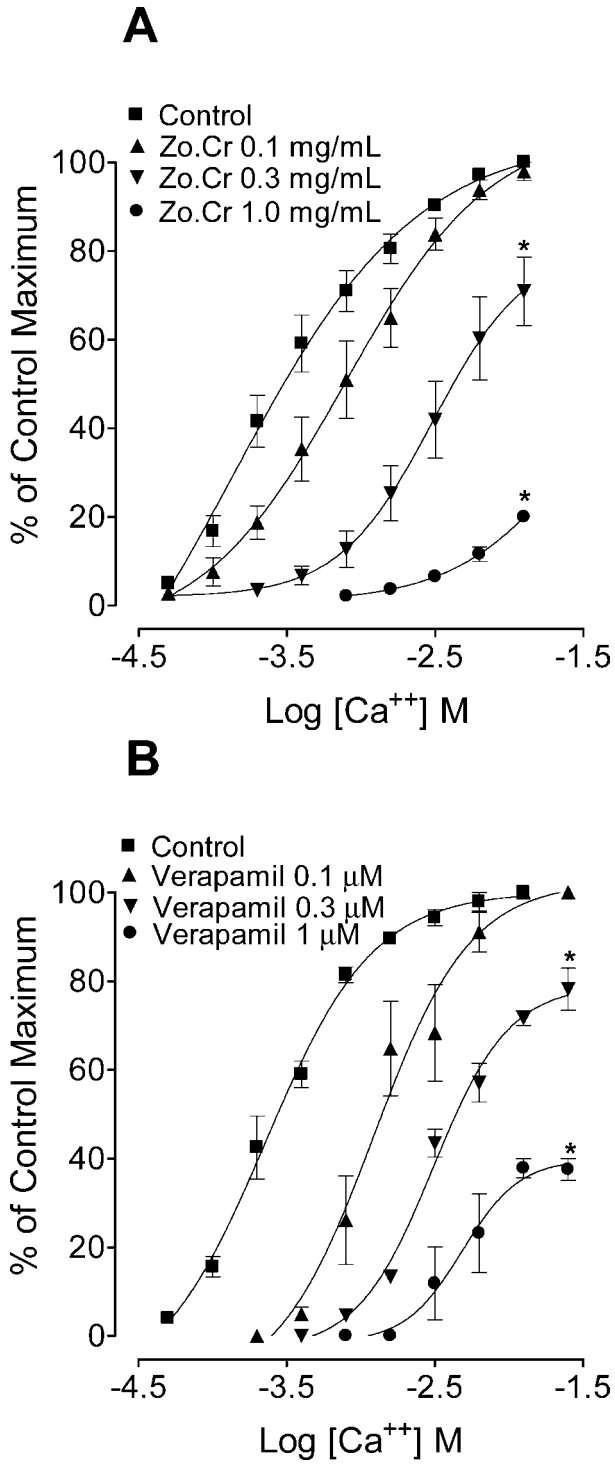

Fig 4. Dose–response curves showing the effect of increasing doses of (**A**) ginger crude extract (Zo.Cr) and (**B**) verapamil on Ca^{2+} dose–response curves constructed in a Ca^{2+}-free medium in isolated rabbit jejunum. $*P < 0.01$ vs. control curve values. All values shown are the mean ± SE of seven determinations).

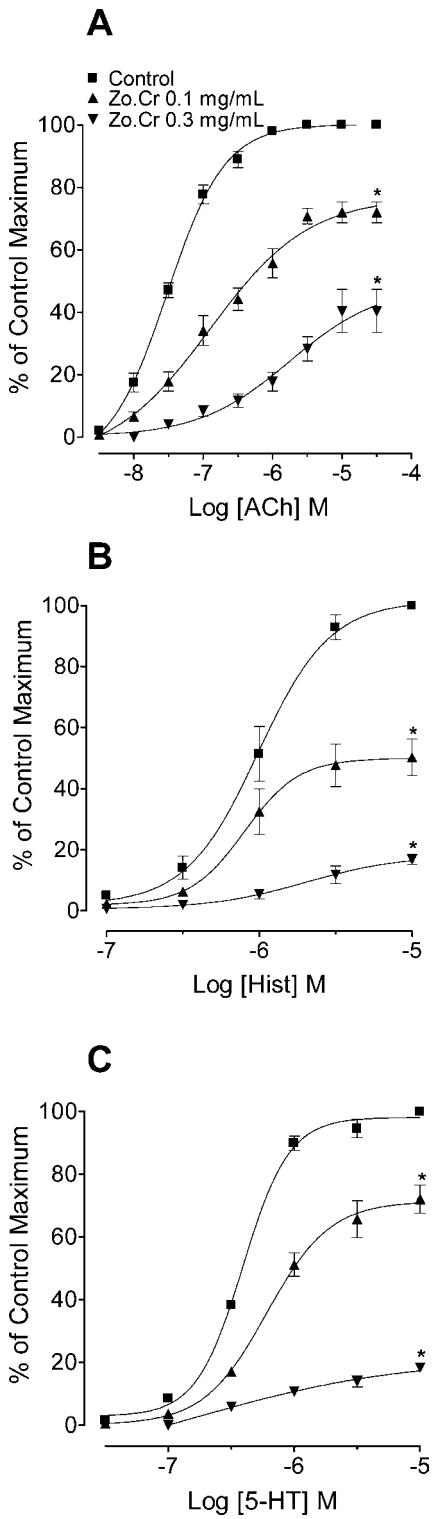

Fig 5. Dose–response curves of (**A**) acetylcholine (ACh), (**B**) histamine (Hist), and (**C**) 5-hydroxytryptamine (5-HT) in the absence and presence of increasing doses of ginger crude extract (Zo.Cr) in isolated guinea pig ileum. $*P < 0.001$ vs. control curve values. All values shown are the mean ± SE of four determinations.

contraction in guinea pig colon (Figure 3B), with an EC_{50} value of 0.24 mg/mL (0.21–0.27, 95% CI; $n = 4$). Verapamil also relaxed the K^+-induced contraction in the tissue preparation.

Acute Toxicity. Zo.Cr was studied in mice at increasing doses (1, 2.5, and 5 g/kg) orally for 24 hr and was found to cause neither any significant behavioral change nor mortality in the animals when tested up to the dose of 5 g/kg.

DISCUSSION

We confirmed the gastric prokinetic activity of ginger reflected by the enhancement in the intestinal travel of charcoal in mice, similar to CCh, a cholinergic agonist and intestinal stimulant (22). This intestinal propulsive activity of the ginger extract was sensitive to atropine, a standard cholinergic antagonist (23, 24). To further study the possible mechanism of this prokinetic effect, we used isolated tissue preparations. Similar to the in vivo findings, the spasmogenic effect of ginger extract in the isolated rat and mouse stomach fundus was mediated through activation of cholinergic receptors as evident by its sensitivity to atropine. Atropine is also known to block the effect (not the receptors) of nicotine, as the end effect of nicotine in gut preparations is eventually due to release of ACh from myenteric plexus, which in turn activates muscarinic receptors at the end organ (25). To see whether the spasmogenic effect of the plant extract was mediated beyond the level of autonomic ganglia, the tissues were pretreated with hexamethonium (0.3 mM), a ganglion blocker (26). This treatment blocked the effect of nicotine (10 μM), but the effect of the ginger extract remained unaltered (data not shown), suggesting that the plant extract is devoid of any nicotinic effect and the spasmogenic effect observed is mediated through direct stimulation of muscarinic receptors.

The muscarinic receptors mediate human circular and longitudinal colonic smooth muscle contractions and so are important in controlling the gastrointestinal smooth muscle tone (27). They are present in the myenteric plexus, circular and longitudinal muscles, esophagus, stomach, ileum, and colon (28), maintaining the path and intensity of peristalsis (29). Ginger is traditionally used as a stomachic, laxative, prokinetic (7, 30), and digestive aid (31). All these folk uses seem to go in parallel with the findings of this study.

Phytochemical analysis of the extract revealed the presence of saponins, flavonoids, and alkaloids, of which saponins and some alkaloids are known gut stimulants (32).

Interestingly, when the spasmogenic effect in rat and mouse stomach fundus was blocked by atropine, a relaxant component was unmasked which was further studied in different isolated gut preparations such as rabbit jejunum, rat ileum, mouse ileum, and guinea pig ileum and colon. Surprisingly, the ginger extract was found to be devoid of a stimulant action in all the intestinal preparations studied, and only spasmolysis was observed. This spasmolytic effect was characterized in different ways:

1. obtaining cumulative dose–response curves with a direct relaxant effect against spontaneously contracting jejunum preparation,
2. constructing ACh, 5-HT, and histamine concentration–response curves in the absence and presence of increasing doses of extract,
3. obtaining cumulative dose–response curves for the inhibitory effect of ginger extract against high K^+-induced contractions, and
4. constructing Ca^{2+} concentration–response curves in the absence and presence of increasing doses of the extract in the Ca^{2+}-free medium.

In our earlier studies, it was observed that the relaxant effect present in plants is usually mediated through calcium channel blockade (20, 33). To see whether the spasmolytic effect of ginger extract was also mediated through a similar mechanism, the tissues were pretreated with high K^+ (80 mM), which opens voltage-operated Ca^{2+} channels to allow extracellular Ca^{2+} into the cytosol, and calcium channel blockers (CCB) inhibit these induced contractions (34). The ginger crude extract dose dependently relaxed this induced contraction, indicating a CCB-like effect not only in rat and mouse stomach fundus but also in rabbit jejunum, rat ileum, mouse ileum, and guinea pig ileum and colon. Verapamil, a standard CCB (35), also exhibited an inhibitory effect on the K^+-induced contractions in all tissues tested. However, a positive result in relaxing the K^+-induced contractions does not always indicate a CCB mode of action (36) but makes the substance eligible for further confirmation. Pretreatment of rabbit jejunum with the plant extract shifted the Ca^{2+} dose–response curves to the right, similarly to verapamil, thus confirming the CCB effect.

In addition to its traditional use as a gastric prokinetic, ginger is also used in diarrhea, dysentery, and colic (7) and the spasmolytic effect observed in this study also justifies the folk use of ginger to counter hypermotility states of the gut, as calcium antagonists are considered useful in such disorders (37).

Our phytochemical analysis has also shown the presence of flavonoids in the extract. Interestingly, flavonoids have been shown to exhibit a spasmolytic effect through blockade of calcium channels (38). Ginger and its

constituents have been reported to be spasmolytic in an earlier study (9), and the mode of action reported has only been speculated to be anticholinergic, antihistaminergic, or antiserotonergic. Huang *et al.* (39) demonstrated that galanolactone, a diterpinoid from ginger, has 5-HT_3 blocking activity when they reported the nonparallel rightward shift in the 5-HT dose–response curves constructed in guinea pig ileum with suppression of the maximum effect, under the influence of increasing doses of the compound. In this study we observed that the spasmolytic component(s) present in ginger is(are) of a nonspecific type, such as CCB. The ginger extract dose dependently shifted the ACh, 5-HT, and histamine dose–response curves to the right, in a nonparallel manner, with suppression of the maximum agonist response (Figure 5). CCBs are known to block the tissue contractile mechanisms irrespective of the receptor involved in the process of contraction, hence they would inhibit contractions induced by different agonists through a nonspecific action. Thus the earlier proposed mechanism through anticholinergic, antihistaminergic, or antiserotonergic action remains questionable, particularly in the absence of clear evidence or satisfaction of the criteria for competitive inhibition of the respective agonists (23).

The ginger extract exhibited a stimulant and then a spasmolytic effect in atropinized rat and mouse stomach fundus preparations while showing generalized spasmolysis in all other intestinal tissues tested. A simple explanation for such a selective spasmogenic effect in stomach fundus could be that the stomach fundus contains muscarinic receptor subtypes different from those located in intestinal preparations. However, this is unlikely because muscarinic receptors in all gut preparations are known to belong to the same receptor subtype (19, 24, 40). Thus, the other possible explanation which could be seen from the results (Figure 3B) is that the relaxation mediated by the extract in rat and mouse stomach fundus is weak compared with that in the other tissues, thus allowing the muscarinic-mediated stimulation to dominate over the CCB-type relaxant in the fundic preparation, while owing to the relaxant component being more potent in the other tissues, no muscarinic-mediated stimulant effect was seen. From the previous experiments performed in our lab, we have experienced that at least rat stomach fundus tends to be more responsive to spasmogenics than to spasmolytics, particularly when a combination of these stimulant and relaxant constituents coexists (41). There have also been reports in the literature on the specific spasmogenic activity of particular compounds in rat stomach fundus that had a spasmolytic effect in other tissues from rat and other species (42, 43). On the other hand, rat stomach fundus has been reported to be less responsive to spasmolytic activity (44, 45). Recently it has been reported that the contraction brought about by muscarinic agonists in rat stomach fundus is due to both calcium release from the intracellular Ca^{2+} pool and its influx via L-type Ca^{2+} channels in comparison to other gut tissues from rat and other species where the muscarinic-mediated effects are via the latter pathway only (46, 47).

Figure 3B shows that the relaxation exhibited by the ginger extract in rat and mouse ileum was mediated at much lower doses than in the other gut tissues, particularly compared with that in rat and mouse stomach fundus tissues. In contrast, verapamil was also tested on different gut preparations, where it was clearly devoid of a stimulant effect but caused relaxation in all the gut preparations studied with variable potencies, but no clear difference was observed between the stomach fundus and ileum of rat and mouse. It is not uncommon with CCBs to exhibit selectivity for any particular type of tissues (48). However, the possibility of the presence of some additional relaxant component(s) in ginger that might be more active in the rat or mouse ileum cannot be ruled out. Interestingly, in a more recent study (49) it was revealed that ginger exhibits an inhibitory effect in rat ileum through a combination of prejunctional (possibly through vanilloid receptors) and postjunctional effects, and we have confirmed here that the postjunctional inhibitory effect is through calcium antagonism.

This study showed the presence of a combination of spasmogenic (cholinergic) and spasmolytic (calcium antagonist) constituents in ginger. This has provided a scientific basis for the gastrointestinal prokinetic and relaxant activities of ginger by virtue of which ginger has found popular use for an array of digestive ailments. It has also provided evidence for diverse modes of action of ginger as an explanation for all the effects that had until now been undetermined.

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