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ORIGINAL ARTICLE

Mangiferin, a natural xanthone, accelerates gastrointestinal transit in mice involving cholinergic mechanism

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Abstract

AIM: To investigate the effects of mangiferin on gastrointestinal transit (GIT) in normal and constipated mice, together with the possible mechanism.

METHODS: Intragastrically-administered charcoal meal was used to measure GIT in overnight starved Swiss mice. In the first experiments, mangiferin (3 mg/kg, 10 mg/kg, 30 mg/kg, and 100 mg/kg, *po*) or tegaserod (1 mg/kg, *ip*) were administered 30 min before the charcoal meal to study their effects on normal transit. In the second series, mangiferin (30 mg/kg) was tested on delayed GIT induced by several different pharmacological agonists (morphine, clonidine, capsaicin) or antagonists (ondansetron, verapamil, and atropine) whereas in the third series, mangiferin (30 mg/kg, 100 mg/kg and 300 mg/kg) or tegaserod (1 mg/kg) were tested on 6 h fecal pellets outputted by freely fed mice. The ratio of wet to dry weight was calculated and used as a marker of fecal water content.

RESULTS: Mangiferin administered orally significantly ($P < 0.05$) accelerated GIT at 30 mg/kg and 100 mg/kg (89% and 93%, respectively), similarly to 5-hydroxytryptamine$_4$ (5-HT$_4$) agonist tegaserod (81%) when compared to vehicle-treated control (63%). Co-administered mangiferin (30 mg/kg) totally reversed the inhibitory effect of opioid agonist morphine, 5-HT$_3$-receptor antagonist ondansetron and transient receptor potential vanilloid-1 receptor agonist capsaicin on GIT, but only to a partial extent with the GIT-delay induced by α_2-adrenoceptor agonist clonidine, and calcium antagonist verapamil. However, co-administered atropine completely blocked the stimulant effect of mangiferin on GIT, suggesting the involvement of muscarinic acetylcholine receptor activation. Although mangiferin significantly enhanced the 6 h fecal output at higher doses (245.5 ± 10.43 mg *vs* 161.9 ± 10.82 mg and 227.1 ± 20.11 mg *vs* 161.9 ± 10.82 mg of vehicle-treated control, at 30 and 100 mg/kg, $P < 0.05$, respectively), the effect of tegaserod was more potent (297.4 ± 7.42 mg *vs* 161.9 ± 10.82 mg of vehicle-treated control, $P < 0.05$). Unlike tegaserod, which showed an enhanced water content in fecal pellets (59.20% ± 1.09% *vs* 51.44% ± 1.19% of control, $P < 0.05$), mangiferin evidenced no such effect, indi-

cating that it has only a motor and not a secretomotor effect.

CONCLUSION: Our data indicate the prokinetic action of mangiferin. It can stimulate the normal GIT and also overcome the drug-induced transit delay, *via* a cholinergic physiological mechanism.

Key words: Mangiferin; Glucosylxanthone; Gastrointestinal transit; Prokinetic action; Cholinergic mechanism

Peer reviewer: Mauro Bortolotti, Professor, Internal Medicine and Gastroenterology, University of Bologna, via Massarenti 48, 40138 Bologna, Italy

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INTRODUCTION

Dyspepsia and constipation are common gastrointestinal disorders of ageing populations, irritable bowel syndrome, and in chronic users of narcotic and non-narcotic analgesics[1-5]. The high prevalence, economic consequences and decrement in health-related quality of life make these disorders a major public issue. Constipation remains a major gastrointestinal ailment with multiple symptoms and a diverse etiology. To get relief from chronic constipation, conventional treatments include the use of fiber supplements and laxatives, but the clinical data do not support the efficacy of these therapies[6]. Even recently introduced drugs such as tegaserod [a 5-hydroxytryptamine$_4$ (5-HT$_4$) partial agonist] and lubiprostone (a chloride channel activator approved by the Food and Drug Administration) were not found to be clinically useful, due to intolerable side effects[7,8]. Erythromycin, a non-peptide motilin receptor agonist, has been shown to induce phase 3 of the migrating motor complex in the antro-duodenum and cause an improvement in clinical symptoms of constipation[9], but there was a report that it lacks colon prokinetic effect in children with chronic constipation[10]. Although advances have been made in understanding gastrointestinal motility, visceral pain, mucosal inflammation, and tissue repair, the major gastrointestinal disorders like constipation remain significant therapeutic challenges[11]. Therefore, there is a need for intense research to develop newer, well-tolerated and effective drugs to cure or to alleviate the symptoms of chronic constipation.

Dyspepsia is a highly prevalent condition characterized by symptoms originating in the gastroduodenal region. Patients experience postprandial fullness, early satiation, epigastric pain, or burning in the absence of causative structural disease. These symptoms may coexist with irritable bowel syndrome, in which patients frequently complain of occasional bowel movement disorders, associated with abdominal pain or discomfort, but they are rarely due to an underlying organ involvement[12]. Treatment options that may be beneficial for functional dyspepsia include histamine H$_2$ blockers, proton pump inhibitors, and prokinetic agents. However, most of the available treatments have only limited efficacy[13,14]. Recent reports described the prokinetic and laxative effects of *Lepidium sativum* (garden cress) and *Aquilaria sinensis* (agarwood) in mice, which were partially mediated through a cholinergic pathway[15,16]. Developing drugs from natural sources (plant extracts or plant-derived substances) may be a treatment option to combat symptoms associated with dyspepsia and constipation.

Mangiferin is a naturally occurring glucosylxanthone commonly encountered in several traditionally used medicinal plants[17] that has been shown to exhibit multiple pharmacological effects that include antioxidant, anti-inflammatory[18-20], and immunomodulatory activities[21]. Diminutions in glutamate-induced neurotoxicity and memory enhancement effects of mangiferin have also been reported[22,23]. Mango fruit is rich in mangiferin[24] and, according to Nadkarni[25], the ripe fruit is very wholesome, nourishing, and useful in nervous and atonic dyspepsia and constipation. We previously demonstrated that mangiferin affords gastroprotection against absolute ethanol or indomethacin-induced gastric ulceration through an antioxidant mechanism[26]. Mangiferin also attenuated acidified ethanol-induced gastric damage in mice and this gastroprotective effect was accompanied by enhanced gastric emptying (unpublished observations from our laboratory) suggesting a likely prokinetic effect. In the light of these observations, the present study was aimed to verify a possible prokinetic effect of mangiferin on normal and delayed gastrointestinal transit, evoked by several different pharmacological agents in mice, and to analyze the underlying mechanism.

MATERIALS AND METHODS

Plant material and isolation of mangiferin

Mangiferin (Figure 1) used in this study was extracted and isolated from the bark of *Mangifera indica L.* (Anacardiaceae) as per procedures reported earlier[26]. A voucher specimen (No. 32628) of the plant material authenticated by Dr. Francisco Edson de Paula has been deposited at the Herbário Prisco Bezerra of the Federal University of Ceará. The isolated mangiferin (MGF) was approximately of 95% purity[20] having the molecular weight 422.5 and melting point (mp) 27 ℃.

Animals and animal procedures

Swiss albino male mice (20-25 g) obtained from the Central Animal House of the Federal University of Ceará

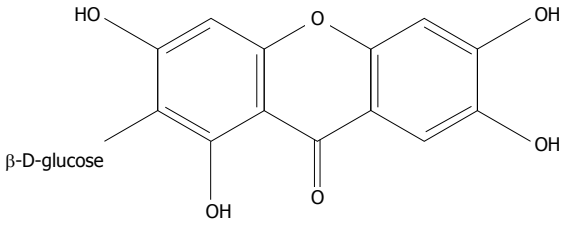

Figure 1 Chemical structure of mangiferin.

were used. They were housed in environmentally-controlled conditions (23 ℃ ± 2 ℃, 12-h light-dark cycle), with free access to a standard diet (Purina Chow) and water *ad libitum*. They were kept in wire-mesh cages to prevent coprophagy. Mice were fasted for 15 h prior to the experiments, but allowed free access to water.

The experimental protocols were approved by the Animal Care and Use Committee of the Federal University of Ceará in accordance with the ethical guidelines of the International Association for the Study of Pain.

Chemicals

Capsazepine (Calbiochem, San Diego, California, United States), indomethacin, capsaicin, clonidine hydrochloride (Sigma Aldrich Co., St. Louis, MO, United States), and morphine (Cristália, Brazil) were used. All other chemicals used were of analytical grade. MGF was dissolved in 2% dimethylsulfoxide (DMSO) and further dilutions were made in distilled water. Drug concentrations were adjusted for treatment to give a volume of 10 mL/kg.

Gastrointestinal transit in mice

Gastrointestinal transit was measured using the charcoal propulsion test[27]. In the first series of experiments, overnight fasted mice were used to establish the dose-response of mangiferin on gastrointestinal transit (GIT). These animals were distributed into 6 groups (eight in each): group 1 received 10 mL/kg vehicle (the diluent of mangiferin, 2% DMSO in distilled water) whereas groups 2, 3, 4 and 5 were treated orally with mangiferin in doses of 3 mg/kg, 10 mg/kg, 30 mg/kg or 100 mg/kg. The 6th group served as the positive control and was treated with tegaserod (1 mg/kg, *ip*). Thirty minutes following the treatments, each mouse was orally given 0.1 mL of charcoal meal (5% activated charcoal suspended in 10% aqueous gum Arabic). The animals were killed 20 min later by cervical dislocation, and the intestines were removed from the pylorus through the ileocecal junction. The extent of charcoal propulsion in the small intestine was measured (distance travelled by the charcoal (from pylorus to the most distal part of the small intestine) and expressed as follows:

Gastrointestinal transit (%) = distance travelled by the charcoal/total length of the small intestine × 100.

In the second series of experiments, mice in groups (eight/group) were used to study the effect of mangiferin (30 mg/kg, *po*) on gastrointestinal transit delay caused by the opioid agonist morphine (2.5 mg/kg, *sc*), 5-HT$_3$-receptor antagonist ondansetron (3 mg/kg, *ip*), transient receptor potential vanilloid 1 (TRPV1) agonist capsaicin (0.3 mg/kg, *po*), α_2-adrenoceptor agonist clonidine (0.1 mg/kg, *ip*), calcium antagonist verapamil (5 mg/kg, *ip*), and cholinergic muscarinic antagonist atropine (3 mg/kg, *sc*). The effects of these drugs on GIT (administered 30 min before the charcoal meal test) alone, or their co-administration with mangiferin were established. To verify the specificity of the above drugs that cause transit delay, the effects of their corresponding agonists (serotonin 3 mg/kg, *sc*; calcium chloride 50 mg/kg, *ip*; and bethanechol 3 mg/kg, *ip*) or antagonists (naloxone 1 mg/kg, *ip*; yohimbine 2 mg/kg, *sc*; and capsazepine 5 mg/kg, *ip*) alone or in their combination (administered 15 min before) were observed on GIT. The dose selection of test drugs was based on our pilot studies and literature reports.

Fecal pellets output and water content

The third series of experiments were performed to determine whether the prokinetic action of mangiferin or 5-HT$_4$ agonist tegaserod was capable of propagating a prokinetic signal along the entire length of the gastrointestinal tract. With this aim, the treatment effects of mangiferin or tegaserod were verified on 6 h fecal pellets output and fluidity (water content) as per the method described earlier, with little modification[28]. Briefly, mice in groups (eight in each) were treated with vehicle, mangiferin at oral doses of 30 mg/kg, 100 mg/kg and 300 mg/kg or tegaserod (1 mg/kg, *ip*) and then transferred to individual cages (19 cm × 31 cm, lined with bright non-absorbent white paper) and monitored constantly over six hours. To prevent water absorption, no bedding was included in the observation cages; also, to minimize the risk of water evaporation and coprophagia, fecal pellets were collected at 1 h intervals. Fecal pellets were then weighed (wet weight, in mg), desiccated in an oven (50 ℃, 6 h), and weighed again (dry weight, in mg). Fecal water content was calculated according to the equation:

Water content (%) = 100 (wet weight - dry weight)/ wet weight.

Statistical analysis

Statistical analysis was performed by analysis of variance followed by Student Newman Keuls as *post-hoc* tests using GraphPadPrisma 4.0 (GraphPad Software, San Diego, CA, United States). The parametric data was expressed as mean ± SEM. Differences were considered to be statistically significant when $P < 0.05$.

RESULTS

Effect of mangiferin on gastrointestinal transit

Mangiferin significantly ($P < 0.05$) accelerated GIT at oral doses of 30 mg/kg and 100 mg/kg by 89% and 93%, respectively, compared with the vehicle control which showed 63% GIT (Figure 2). However, mangiferin response was not dose-related. On the other hand, tegas-

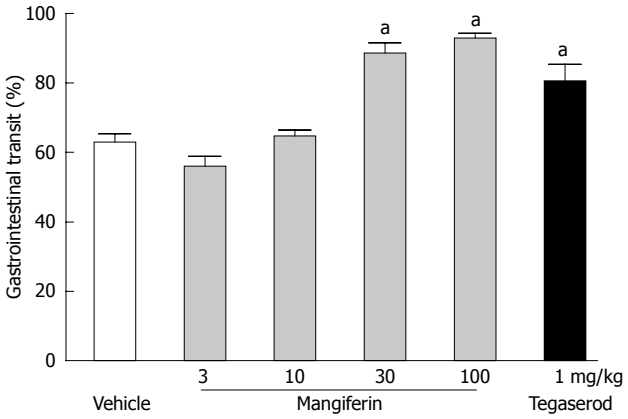

Figure 2 Effects of mangiferin and tegaserod on normal gastrointestinal transit. Each column represents mean ± SEM (n = 8). $^{a}P < 0.05$ *vs* vehicle control group.

erod, a known prokinetic included in the study as a positive control, stimulated GIT by 81%. We observed from pilot experiments that the vehicle (2% DMSO, 10 mL/kg, *po*) itself does not influence the GIT. Therefore, test drug responses on GIT were compared with the vehicle-treated control.

Effect of mangiferin on drug-induced gastrointestinal transit-delay

The opioid agonist morphine (2.5 mg/kg, *sc*), α_2-adrenoceptor agonist clonidine (0.1 mg/kg, *ip*), 5-HT_3-receptor antagonist ondansetron (3 mg/kg, *ip*), calcium antagonist verapamil (5 mg/kg, *ip*), TRPV1 agonist capsaicin (0.3 mg/kg, *po*), and cholinergic muscarinic antagonist atropine (3 mg/kg, *sc*), all significantly ($P < 0.05$) delayed GIT by 42.4%, 63.2%, 32.9%, 50.7%, 28.7%, and 31%, respectively, when compared to corresponding vehicle-treated control transit values (Figures 3 and 4). These delayed transits were found to be effectively reversed in mice pretreated with respective antagonists (naloxone 1 mg/kg, *ip*; yohimbine 2 mg/kg, *sc*; and capsazepine 5 mg/kg, *ip*) or agonists (serotonin 3 mg/kg, *sc*; calcium chloride 50 mg/kg, *ip*; and bethanechol 3 mg/kg, *ip*). While co-administered mangiferin totally reversed the inhibitory effects of morphine, ondansetron and capsaicin on GIT, the transit delays caused by clonidine and verapamil were only partially reversed. However, co-administered atropine completely blocked the stimulant effect of mangiferin on GIT (Figure 5), suggesting the involvement of muscarinic acetylcholine receptor activation.

Effect of mangiferin on 6 h fecal pellets weight and water content

Table 1 shows the 6 h fecal pellets output and water content from freely fed mice treated with vehicle, mangiferin (30 mg/kg, 100 mg/kg and 300 mg/kg) or tegaserod (1 mg/kg). Six hours cumulative measurement of fecal mass output and water content in the vehicle-treated group was not significantly different from the normal control group.

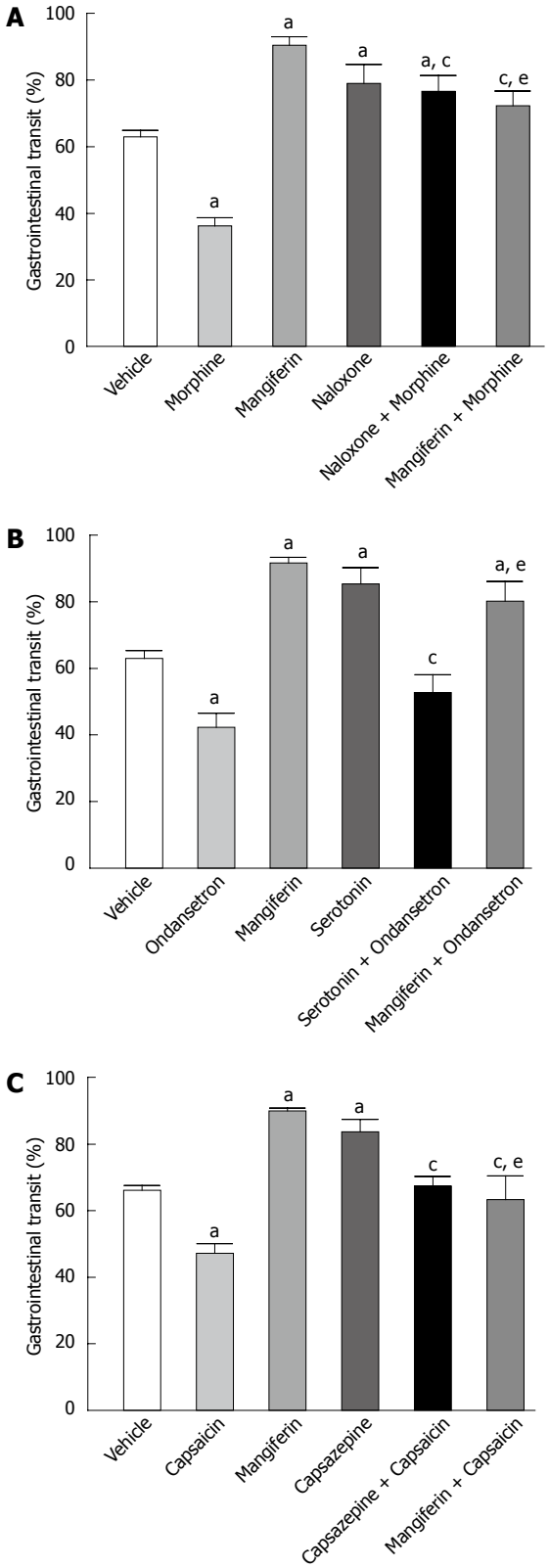

Figure 3 Effect of co-administered mangiferin on delayed gastrointestinal transit induced by morphine, ondansetron, and capsaicin in mice. A: Morphine (2.5 mg/kg, *sc*); B: Ondansetron (3 mg/kg, *ip*); C: Capsaicin (0.3 mg/kg, *po*) induced gastrointestinal transit-delay. Each column represents mean ± SEM (n = 8). $^{a}P < 0.05$ *vs* vehicle control group; $^{c}P < 0.05$ *vs* respective morphine/ondansetron/capsaicin; $^{e}P < 0.05$ *vs* mangiferin alone group.

However, mangiferin at doses of 100 mg/kg and 300

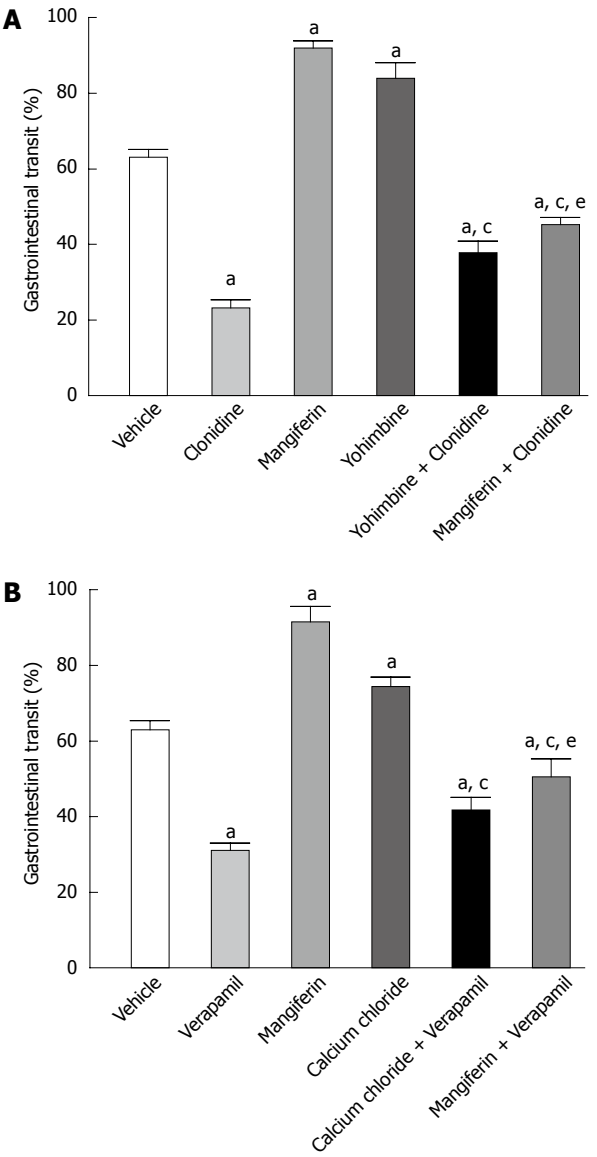

Figure 4 Effect of co-administered mangiferin on d[e]layed gastrointestinal transit induced by clonidine and verapamil in mice. A: Clonidine (0.1 mg/kg, ip); B: Verapamil (5 mg/kg, ip) induced gastrointestinal transit-delay. Each column represents mean ± SEM (n = 8). [a]P < 0.05 *vs* vehicle control group; [c]P < 0.05 *vs* respective clonidine/verapamil group; [e]P < 0.05 *vs* mangiferin alone group.

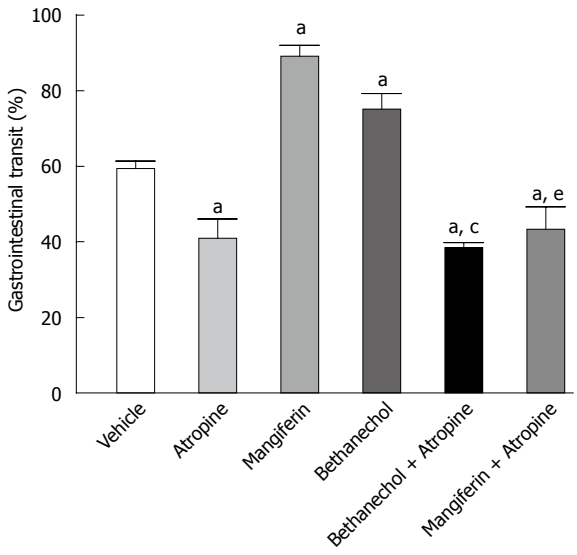

Figure 5 Effect of co-administered mangiferin on atropine-induced delayed gastrointestinal transit in mice. Each column represents mean ± SEM (n = 8). [a]P < 0.05 *vs* vehicle control group; [c]P < 0.05 *vs* bethanechol alone group; [e]P < 0.05 *vs* mangiferin alone group.

Table 1 Effects of mangiferin and tegaserod on 6 h cumulative fecal pellet wet weight and water content in freely fed mice

Group	Dose	Fecal pellets wet weight (mg)	Water content (%)
Control (normal)	-	156.8 ± 20.98	50.46 ± 2.28
Control (vehicle)	-	161.9 ± 10.82	51.44 ± 1.19
Mangiferin	30 mg/kg, *po*	205.7 ± 12.69	50.31 ± 1.61
	100 mg/kg, *po*	245.5 ± 10.43[a,c]	49.76 ± 3.25
	300 mg/kg, *po*	227.1 ± 20.11[a,c]	49.11 ± 3.01
Tegaserod	1 mg/kg, *ip*	297.4 ± 7.42[a,c]	59.20 ± 1.09[a,c]

The results are expressed as mean ± SEM of 8 animals per group. Statistical comparison was performed using analysis of variance followed by Student Newman Keuls test. [a]P < 0.05 *vs* control (normal) group; [c]P < 0.05 *vs* control (vehicle) group.

mg/kg, and tegaserod at 1 mg/kg significantly (P < 0.05) enhanced the fecal pellets output by 52%, 40%, and 80%, respectively, when compared to fecal output in vehicle-treated mice (161.9 mg). Fecal mass analysis from different treatment groups revealed that only the tegaserod-treated group evidenced significantly (P < 0.05) elevated water content (59%) relative to the vehicle-treated control (51%), suggesting that, unlike mangiferin, tegaserod possibly promotes ionic secretion.

DISCUSSION

In this study, we demonstrated the stimulant effect of mangiferin, a glucosylxanthone on GIT in mice using the charcoal meal test, a suitable preclinical model for quantification of changes in GIT and to analyze the effects of test drugs on gastro-intestinal motility[28,29]. However, the present experiment is not completely suitable to demonstrate the effect on constipation, because the charcoal test measures gastric emptying and small intestinal transit, rather than the colonic transit, that is important for constipation. Mangiferin accelerated normal GIT and showed an oral efficacy at doses of 30 mg/kg and 100 mg/kg. Our principal aim in this study was to verify whether mangiferin can exert a prokinetic action that could help to alleviate constipation, a major gastrointestinal functional disorder affecting 12%-17% of the general population in North America and elsewhere[30,31]. Prokinetic drugs share the common characteristic of accelerating GI motility and they appear to be more effective than a placebo in the treatment of functional dyspepsia[32], wherein constipation is a common feature.

Prokinetics exert their physiological actions through effects on a variety of neurotransmitter receptors in-

cluding acetylcholine, dopamine, motilin and serotonin. Therefore, to characterize mangiferin as a prokinetic, we tested its ability to revert the delayed GIT induced by several pharmacological agents which act by different action mechanisms. The results show that mangiferin accelerates normal GIT as well as the delayed GIT promoted by different pharmacological agents, indicating its prokinetic action *in vivo*. Co-administered mangiferin (30 mg/kg) effectively suppressed the GIT-delay induced by opioid receptor agonist morphine, 5-HT$_3$-receptor antagonist ondansetron, or TRPV1-receptor agonist capsaicin. This implies that mangiferin's action is non-specific and likely to combat constipation associated with therapeutic or surgical interventions. Patients with chronic pain during daily opioid therapy are frequently burdened with symptoms of constipation[5]. It is estimated that up to 81% of patients still report constipation despite regular use of laxatives. Studies by Iwata *et al*[33] reveal that morphine inhibits small intestinal transit, causing tonic contraction of the ileal circular muscle *via* inhibition of the nitrergic pathway in mice in a naloxone reversible manner. Also, mangiferin administered orally at a similar dose (30 mg/kg) significantly prevented morphine-induced delay in gastric emptying in Wistar rats (unpublished observations from our laboratory).

In the present study we found that systemic administration of clonidine in mice inhibits GIT in mice, consistent with earlier reports[34,35]. This inhibitory effect of clonidine was significantly inhibited by pre-administration of yohimbine, an α_2-adrenoceptor antagonist, or by co-administration of mangiferin. However, the reversal of clonidine's effect on GIT delay was incomplete and did not attain the levels of normal transit. Clonidine by its central sedative effect might have contributed to greater depression of GIT.

Prokinetic drugs either directly or indirectly stimulate smooth muscle function, activating intrinsic primary afferent neurons (IPANs) located in the myenteric plexus that play important roles in controlling gastric emptying and small- and large-intestinal transit[36]. The release of acetylcholine from these neurons is amplified by presynaptic serotonin 5-HT$_4$ receptor activation or blockade of 5-HT$_3$ receptors[37]. Thus, prokinetic drugs like cisapride, mosapride and tegaserod, which have dual action (i.e., induce both 5-HT$_4$ receptor agonistic and 5-HT$_3$ receptor blockade effects), have gained clinical importance for the treatment of functional dyspepsia and chronic constipation[38]. Although the greatest interest has been focused on the development of serotonergic drugs as prokinetics[39], conflicting data currently exists on the efficacy of mixed 5-HT$_4$ agonist and 5-HT$_3$ antagonist drugs, like cisapride, mosapride and tegaserod, for the treatment of constipation[7], attention has been now been drawn to discover alternatives for the treatment of constipation. Interestingly, mangiferin was able to overcome the delayed GIT induced by several pharmacological agents suggesting an action similar to mosapride, a commonly used prokinetic drug and recently described prokinetic, and the laxative effects of lepidium sativum in mice, which act *via* a mechanism that facilitates cholinergic neurotransmission[40].

In rodents, the cholinergic stimulant bethanechol acts not only in the enterocytes, but also in submucosal nerves[41], and since the effects on ion transport were nerve-dependent we decided to investigate the GIT stimulating effect of mangiferin in comparison with bethanechol in atropinized animals. The results show that atropine, the cholinergic antagonist, blocks the stimulatory effects of both mangiferin and bethanechol suggesting that these drugs, by specifically activating cholinergic muscarinic receptors, could induce Ca^{2+} mobilization in the submucosal neurons, thereby stimulating gut motility and secretion. The part played by calcium in mangiferin's effect is further supported by our results with verapamil, a calcium channel blocker that could also produce an effective blockade. In this study, while atropine totally blocked the prokinetic action of mangiferin, only a partial blockade was observed with clonidine, an alpha$_2$-adrenoceptor agonist, and verapamil, a voltage dependent calcium channel blocker, suggesting that participation of muscarinic cholinergic receptors could play a major role in the stimulant effect of mangiferin on GIT.

Interestingly, mangiferin, besides accelerating GIT in normal as well as in constipated mice, could enhance the fecal output (but not the water content) in fecal mass. In contrast, fecal pellets produced by tegaserod-treated mice had higher water content than vehicle- or mangiferin-treated mice, presumably due to its greater secretomotor action on the colon. The increase in water content is indicative of augmented secretory activity, which might be the reason for its diarrhea-inducing side effect when used to control constipation[42]. Thus mangiferin appears to have a safer prokinetic profile than tegaserod, since it has no diarrhea inducing effect.

In conclusion, this study has shown that mangiferin, a glucosyl xanthone ameliorate, delayed gastrointestinal transit induced by several pharmacologic agents *via* cholinergic mechanism, an action similar to that of some prokinetic drugs. Our study suggests that mangiferin could be an alternative to available prokinetic drugs for the treatment of functional gastrointestinal disturbances such as dyspepsia and postoperative ileus.

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COMMENTS

Background

Dyspepsia and constipation are functional gastrointestinal ailments with diverse etiology and symptoms which adversely influence the health-related quality of life. Treatment modalities include the use of fiber supplements, laxatives and prokinetic agents, but the clinical data do not support the efficacy of these therapies. Therefore, there is a need for intense research to develop newer well-tolerated and effective drugs for a cure or symptom-alleviation for dyspepsia

and constipation.

Research frontiers

Mangiferin is a natural polyphenolic compound found in several traditional medicinal plants, including *Mangifera indica* (mango). The mango fruit contains mangiferin and is very wholesome, nourishing and useful in nervous and atonic dyspepsia and constipation. Mangiferin may be a treatment option to combat symptoms associated with dyspepsia and mild to moderate constipation.

Innovations and breakthroughs

In the present study, the authors showed that mangiferin is remarkably effective as a prokinetic agent *via* a cholinergic mechanism in the upper gastrointestinal tract. Mangiferin could enhance gastrointestinal transit and also increase fecal output in normal and physiological situations.

Applications

The study results suggest that mangiferin is a promising lead compound for the treatment of functional gastrointestinal disturbances such as dyspepsia and light to moderate constipation.

Terminology

Dyspepsia: a functional gastrointestinal disorder wherein patients experience postprandial fullness, early satiation, epigastric pain, or burning in the absence of causative structural disease; Constipation: a functional problem of the gastrointestinal tract, with symptoms including hard stools, straining during defecation, and a sense of incomplete evacuation. Treatment options include use of fiber supplements, and prokinetics/laxatives to relieve these functional disorders; Prokinetics: an important class of medicinal products for the treatment of all clinical forms of dyspepsia/moderate constipation that promote gastric emptying and intestinal transit; Mangiferin: a naturally-occurring xanthone glucoside present in many medicinal plants, which has antioxidant and anti-inflammatory actions.

Peer review

The authors performed an experimental study aimed at evaluating the effects of mangiferin in comparison with tegaserod on normal and pharmacologically constipated mice, along with investigating the possible mechanism, and found that mangiferin has a prokinetic action *via* a cholinergic mechanism. This paper is sufficiently well done and most interesting.

REFERENCES

1 **DiJoseph JF**, Taylor JA, Mir GN. Alpha-2 receptors in the gastrointestinal system: a new therapeutic approach. *Life Sci* 1984; **35**: 1031-1042
2 **Firth M**, Prather CM. Gastrointestinal motility problems in the elderly patient. *Gastroenterology* 2002; **122**: 1688-1700
3 **Camilleri M**, Tack JF. Current medical treatments of dyspepsia and irritable bowel syndrome. *Gastroenterol Clin North Am* 2010; **39**: 481-493
4 **Chang HY**, Kelly EC, Lembo AJ. Current gut-directed therapies for irritable bowel syndrome. *Curr Treat Options Gastroenterol* 2006; **9**: 314-323
5 **Walters JB**, Montagnini M. Current concepts in the management of opioid-induced constipation. *J Opioid Manag* 2010; **6**: 435-444
6 **Johanson JF**, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther* 2007; **25**: 599-608
7 **Kinoshita Y**, Hashimoto T, Kawamura A, Yuki M, Amano K, Sato H, Adachi K, Sato S, Oshima N, Takashima T, Kitajima N, Abe K, Suetsugu H. Effects of famotidine, mosapride and tandospirone for treatment of functional dyspepsia. *Aliment Pharmacol Ther* 2005; **21** Suppl 2: 37-41
8 **Saad R**, Chey WD. Lubiprostone for chronic idiopathic constipation and irritable bowel syndrome with constipation. *Expert Rev Gastroenterol Hepatol* 2008; **2**: 497-508
9 **Peeters TL**, Vantrappen G, Janssens J. Fasting plasma motilin levels are related to the interdigestive motility complex. *Gastroenterology* 1980; **79**: 716-719
10 **Venkatasubramani N**, Rudolph CD, Sood MR. Erythromycin lacks colon prokinetic effect in children with functional gastrointestinal disorders: a retrospective study. *BMC Gastroenterol* 2008; **8**: 38
11 **Wallace JL**, Ferraz JG. New pharmacologic therapies in gastrointestinal disease. *Gastroenterol Clin North Am* 2010; **39**: 709-720
12 **Loyd RA**, McClellan DA. Update on the evaluation and management of functional dyspepsia. *Am Fam Physician* 2011; **83**: 547-552
13 **Ford AC**, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, Moayyedi P. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ* 2008; **337**: a2313
14 **Chey WD**, Howden CW, Tack J, Ligozio G, Earnest DL. Long-term tegaserod treatment for dysmotility-like functional dyspepsia: results of two identical 1-year cohort studies. *Dig Dis Sci* 2010; **55**: 684-697
15 **Attaluri A**, Donahoe R, Valestin J, Brown K, Rao SS. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. *Aliment Pharmacol Ther* 2011; **33**: 822-828
16 **Kakino M**, Izuta H, Ito T, Tsuruma K, Araki Y, Shimazawa M, Oyama M, Iinuma M, Hara H. Agarwood induced laxative effects via acetylcholine receptors on loperamide-induced constipation in mice. *Biosci Biotechnol Biochem* 2010; **74**: 1550-1555
17 **El-Seedi HR**, El-Barbary MA, El-Ghorab DM, Bohlin L, Borg-Karlson AK, Göransson U, Verpoorte R. Recent insights into the biosynthesis and biological activities of natural xanthones. *Curr Med Chem* 2010; **17**: 854-901
18 **Amazzal L**, Lapôtre A, Quignon F, Bagrel D. Mangiferin protects against 1-methyl-4-phenylpyridinium toxicity mediated by oxidative stress in N2A cells. *Neurosci Lett* 2007; **418**: 159-164
19 **Márquez L**, García-Bueno B, Madrigal JL, Leza JC. Mangiferin decreases inflammation and oxidative damage in rat brain after stress. *Eur J Nutr* 2011; Epub ahead of print
20 **Barreto JC**, Trevisan MT, Hull WE, Erben G, de Brito ES, Pfundstein B, Würtele G, Spiegelhalder B, Owen RW. Characterization and quantitation of polyphenolic compounds in bark, kernel, leaves, and peel of mango (Mangifera indica L.). *J Agric Food Chem* 2008; **56**: 5599-5610
21 **Leiro J**, Arranz JA, Yáñez M, Ubeira FM, Sanmartín ML, Orallo F. Expression profiles of genes involved in the mouse nuclear factor-kappa B signal transduction pathway are modulated by mangiferin. *Int Immunopharmacol* 2004; **4**: 763-778
22 **Lemus-Molina Y**, Sánchez-Gómez MV, Delgado-Hernández R, Matute C. Mangifera indica L. extract attenuates glutamate-induced neurotoxicity on rat cortical neurons. *Neurotoxicology* 2009; **30**: 1053-1058
23 **Pardo Andreu GL**, Maurmann N, Reolon GK, de Farias CB, Schwartsmann G, Delgado R, Roesler R. Mangiferin, a naturally occurring glucoxilxanthone improves long-term object recognition memory in rats. *Eur J Pharmacol* 2010; **635**: 124-128
24 **Canuto KM**, de Souza Neto MA, Garruti DS, Colho de Lima MA. Evaluation of the use of ethylene inhibitors on production of volatile compounds and mangiferin in mango fruit. *Quim Nova* 2010; **33**: 1535-1540
25 **Nadkarni KM**. Indian Materia Medica. Vol. 1. Mumbai: Popular Prakashan, 1993: 805-806
26 **Carvalho AC**, Guedes MM, de Souza AL, Trevisan MT, Lima AF, Santos FA, Rao VS. Gastroprotective effect of mangiferin, a xanthonoid from Mangifera indica, against gastric injury induced by ethanol and indomethacin in rodents. *Planta Med* 2007; **73**: 1372-1376
27 **Capasso F**, De Ruggiero G, Di Rosa M, Sorrentino L. [Pharmacological research on a deethylate metabolite of 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide (metoclopramide)]. *Boll Chim Farm* 1976; **115**: 649-657
28 **Izzo AA**, Mascolo N, Borrelli F, Capasso F. Defaecation,

intestinal fluid accumulation and motility in rodents: implications of cannabinoid CB1 receptors. *Naunyn Schmiedebergs Arch Pharmacol* 1999; **359**: 65-70
29 **Suchitra AD**, Dkhar SA, Shewade DG, Shashindran CH. Relative efficacy of some prokinetic drugs in morphine-induced gastrointestinal transit delay in mice. *World J Gastroenterol* 2003; **9**: 779-783
30 **Zarate N**, Spencer NJ. Chronic constipation: lessons from animal studies. *Best Pract Res Clin Gastroenterol* 2011; **25**: 59-71
31 **Higgins PD**, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004; **99**: 750-759
32 **Moayyedi P**, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2004; **18**: CD001960
33 **Iwata H**, Tsuchiya S, Nakamura T, Yano S. Morphine leads to contraction of the ileal circular muscle via inhibition of the nitrergic pathway in mice. *Eur J Pharmacol* 2007; **574**: 66-70
34 **Ruwart MJ**, Klepper MS, Rush BD. Clonidine delays small intestinal transit in the rat. *J Pharmacol Exp Ther* 1980; **212**: 487-490
35 **Umezawa T**, Guo S, Jiao Y, Hisamitsu T. Effect of clonidine on colonic motility in rats. *Auton Neurosci* 2003; **107**: 32-36
36 **Furness JB**. The enteric nervous system: normal functions and enteric neuropathies. *Neurogastroenterol Motil* 2008; **20** Suppl 1: 32-38
37 **Gershon MD**, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology* 2007; **132**: 397-414
38 **Mizuta Y**, Shikuwa S, Isomoto H, Mishima R, Akazawa Y, Masuda J, Omagari K, Takeshima F, Kohno S. Recent insights into digestive motility in functional dyspepsia. *J Gastroenterol* 2006; **41**: 1025-1040
39 **Fayyaz M**, Lackner JM. Serotonin receptor modulators in the treatment of irritable bowel syndrome. *Ther Clin Risk Manag* 2008; **4**: 41-48
40 **Yoshida N**, Omoya H, Kato S, Ito T. Pharmacological effects of the new gastroprokinetic agent mosapride citrate and its metabolites in experimental animals. *Arzneimittelforschung* 1993; **43**: 1078-1083
41 **Hirota CL**, McKay DM. Cholinergic regulation of epithelial ion transport in the mammalian intestine. *Br J Pharmacol* 2006; **149**: 463-479
42 **Stephens DP**, Thomas JH, Collins SJ, Goldrick PB, Fowler S. A clinical audit of the efficacy of tegaserod as a prokinetic agent in the intensive care unit. *Crit Care Resusc* 2008; **10**: 71

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