World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
wjgpt@wjgnet.com
doi:10.4292/wjgpt.v4.i1.9

World J Gastrointest Pharmacol Ther 2013 February 6; 4(1): 9-15
ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Tibetan herbal formula Padma Digestin modulates gastrointestinal motility *in vitro*

Bruno M Balsiger, Magali Krayer, Andreas Rickenbacher, Beatrice Flogerzi, Cecile Vennos, Juergen M Gschossmann

Bruno M Balsiger, Juergen M Gschossmann, Department of Clinical Research, University of Berne, 3001 Bern, Switzerland
Bruno M Balsiger, Clinic for Gastroenterology, Lindenhofspital (Hochhaus), 3001 Bern, Switzerland
Magali Krayer, Beatrice Flogerzi, Juergen M Gschossmann, Department of Gastroenterology, University of Berne, 3001 Bern, Switzerland
Andreas Rickenbacher, Department of Visceral and Transplant Surgery, University of Zürich, 8006 Zürich, Switzerland
Cecile Vennos, Scientific Division, Padma Inc., 8340 Hinwil, Switzerland
Juergen M Gschossmann, Department of Internal Medicine, Klinikum Forchheim/Friedrich-Alexander Universität Erlangen-Nürnberg, 91301 Forchheim, Germany
Author contributions: Balsiger BM and Gschossmann JM designed the study; Krayer M performed the experiments; Balsiger BM supervised the experiments; Vennos C contributed the test substance; Balsiger BM, Krayer M, Flogerzi B and Rickenbacher A analyzed the data; Krayer M, Vennos C and Gschossmann JM wrote the paper; all the authors contributed equally to this work.
Supported by The Research Grant from Padma Inc., Switzerland, to Vennos C
Correspondence to: Juergen M Gschossmann, MD, Department of Internal Medicine, Klinikum Forchheim/Friedrich-Alexander Universität Erlangen-Nürnberg, Krankenhausstrasse 10, 91301 Forchheim, Germany. juergen.gschossmann@klinikum-forchheim.de
Telephone: +49-919-1610205 Fax: +49-919-1610205
Received: June 8, 2012 Revised: November 28, 2012
Accepted: December 20, 2012
Published online: February 6, 2013

Abstract

AIM: To examine the effects of Padma Digestin on the smooth muscle motility of different gastrointestinal segments *in vitro*.

METHODS: The effects of the ethanolic extract of Padma Digestin (at 8.16 mg/mL or 81.6 mg/mL) on the contractility and susceptibility to acetylcholine (ACh) of muscle strips from the cardia, antrum, pylorus, duodenum, jejunum, ileum and colon of male Wistar rats were analyzed.

RESULTS: Compared with the control treatment, the Padma Digestin extract had a procontractile effect on the antral smooth muscle strips. Padma Digestin decreased ACh sensitivity in cardia muscle strips and increased it in those from the antrum and pylorus. In the intestinal segments, spontaneous contractility was inhibited in both the duodenal and jejunal strips, whereas reactivity to ACh was inhibited in the jejunal strips only. In the colonic samples, Padma Digestin inhibited spontaneous and ACh-stimulated contractility at a low dose but seems to have increasing effects at a high dose.

CONCLUSION: Padma Digestin extract has region-specific effects on the contractility and excitability of gastrointestinal smooth muscle. Our results support the traditional use of Padma Digestin for maldigestion and functional gastrointestinal disorders.

Key words: Tibetan Medicine System; Herbal; Gastrointestinal motility; Smooth muscle; Padma Digestin

Balsiger BM, Krayer M, Rickenbacher A, Flogerzi B, Vennos C, Gschossmann JM. Tibetan herbal formula Padma Digestin modulates gastrointestinal motility *in vitro*. *World J Gastrointest Pharmacol Ther* 2013; 4(1): 9-15 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i1/9.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i1.9

INTRODUCTION

Functional gastrointestinal disorders (FGDs) are characterized by various symptoms without underlying identifiable structural lesions or biochemical abnormalities[1]. Symptoms such as abdominal pain and discomfort, bloating, flatulence, changes in stool consistency, and postprandial fullness are very common and have a great impact on

the quality of life of affected patients[2,3]. The pathogenesis of FGDs is still unclear; however, different factors such as disturbed gastrointestinal motility, accommodation and hypersensitivity, side effects of pharmaceuticals, psychosocial status, changes in inflammatory status and helicobacter pylori infection are likely to be involved[2,4-8].

In general practice, unspecific dyspeptic complaints are often addressed using symptom-based approaches such as proton pump inhibitor treatment, Helicobacter pylori eradication and dietary modifications[8,9]. Given the high prevalence of FGDs, their impact on patient quality of life, and their socio-economic importance, safe and effective treatment options are urgently needed[2,10,11]. Phytotherapeutics contain a wide variety of chemical substances in very small doses. They are known to act as so called multi-target drugs, which target and affect multiple different pathophysiological pathways simultaneously[12-14].

Network models show that partial inhibition of multiple targets by synergistically acting agents can be more effective than complete inhibition of a single target[12,15]. In herbal preparations, each chemical is usually present at a very low dose. The synergistic action of these chemicals allows them to be clinically effective, as well as minimizes the risk for side effects[13,14]. Due to the joint activity of multiple herbal compounds, the resulting mechanism of action cannot be deduced from the known effects of each individual ingredient. Even though one might be able to predict which molecular pathways would be affected, the sum of these changes may not reflect the resulting effect of the mixture.

Due to their complex mechanism of action and overall favorable safety profile, herbal preparations seem to be especially well-suited for the treatment of multifactorial diseases. Various plants as well as herbal combination preparations have produced favorable outcomes in FGDs[14,16-20]. The polyherbal preparation Padma® Lax has been shown to be effective in the treatment of dominant irritable bowel syndrome[19,20], and the multimodal effects on intestinal motility have been identified as the mode of action of this formula[21].

Padma Digestin® is a polyherbal formula produced in Switzerland according to the international pharmaceutical guidelines. The preparation is licensed as a drug (Swissmedic No. 59375) and is available under the same name in various European countries. It is a modern representation of a formula from Traditional Tibetan Medicine (Tibetan name: Se'bru 5). Padma Digestin consists of five herbs, which have been used in this composition in the Himalayas for hundreds of years. In Europe, the formula has been used for more than 20 years for disturbed digestion with dyspeptic symptoms such as epigastric pressure, postprandial fullness, bloating, and flatulence as well as for lack of appetite, *e.g.*, in convalescence or old age. Traditionally, the formula has also been used for ailments of the lower abdomen and lower back including sexual dysfunction, recurrent cystitis or lower back pain. Some of the plants or chemical constituents that comprise Padma Digestin have previously been shown to influence gastrointestinal motility[22-24]. Despite the information on the individual ingredients, to our knowledge, there are no reports on the effects of the multicompound formulation as a whole.

Therefore, the aim of the present study was to investigate the effects of Padma Digestin ethanolic extracts on different gastrointestinal segments regarding spontaneous contractile activity and susceptibility to acetylcholine (ACh) *in vitro*.

MATERIALS AND METHODS

Animals

After an overnight fast with free access to drinking water, 21 male Wistar rats (in-house breeding, Central Animal Facilities, University Hospital Berne, Switzerland) weighing 160 to 275 g were anesthetized with a mixture of ketamine and xylazine in a ratio of 1:1 (1 mL per kg body weight) (Dr. E Gräub AG, Berne, Switzerland). All of the procedures and subsequent animal care were in accordance with the guidelines of the Department of Agriculture of Berne, Switzerland, which provided the approval for this study.

Tissue preparation

Several gastrointestinal segments were analyzed: cardial, antral, pyloric, duodenal, jejunal, ileal and colonic. Tissue samples were rapidly harvested and placed in cold modified Krebs-Ringer's bicarbonate buffer (118.3 mmol/L NaCl, 4.7 mmol/L KCl, 1.2 mmol/L $MgSO_4$, 1.2 mmol/L KH_2PO_4, 2.5 mmol/L $CaCl_2$, 25 mmol/L $NaCHO_3$, 0.026 mmol/L CaEDTA and 11.1 mmol/L glucose) (Sigma Chemicals, Buchs, Switzerland) saturated with carbogen (95% O_2 + 5% CO_2) (Carbagas, Berne, Switzerland). Different gut segments were excised from the same location in each animal and prepared as follows: circular muscle strips from cardial (n = 12) and pyloric tissue (n = 9), muscle strips from the antrum (n = 44) in the circular axis and muscle strips from the duodenum (n = 22), jejunum (n = 24), ileum (n = 24) and colon (n = 36) in the longitudinal axis. The muscle strips were placed in organ bath chambers (5 mL) (Radonit Glass Technology Inc., Monrovia, CA, United States) filled with modified Krebs-Ringer's bicarbonate buffer maintained at 37.5 ℃ and aerated with carbogen.

Test substance

Padma Digestin is a multicomponent herbal preparation based on a classical formula composed of five herbs that originates from Tibetan Medicine. One capsule contains 204 mg pomegranate seeds (*Punica granatum* L.), 102 mg lesser galangal rhizome (*Alpinia officinarum* Hance), 25.5 mg long pepper fruit (*Piper longum* L./*Piper retrofractum* Vahl.), 12.75 mg cardamom seeds (*Elettaria cardamomum* Maton var. Miniscula Burkill), and 12.75 mg cassia bark (*Cinnamomum aromaticum* Nees). Padma Digestin was produced and supplied by Padma Inc., Hinwil, Switzerland. The mixture was extracted with 70% (v/v) ethanol

(EtOH) (B. Braun, Emmenbrücke, Switzerland). 250 mg/mL of the test substance was shaken for 30 min at 37 ℃ and centrifuged at 5000 *g*. Then, the supernatant was lyophilized with a yield of 20.4% (w/w). Just before use, the lyophilized extract was dissolved in 70% EtOH. One milliliter of this solution corresponded to the extract of 2126 mg Padma Digestin powder.

Study design

In the first set of experiments (9 animals), the *in vitro* effects of the ethanolic extract of Padma Digestin on the contractility and susceptibility to ACh (Sigma Chemicals, Buchs, Switzerland) were analyzed in colonic muscle strips, and EtOH was used as a control. Cardial, antral, pyloric, duodenal, jejunal and ileal tissue strips were collected from the same rats and used in preliminary experiments to assess the recording patterns and reproducibility of the *in vitro* contractile activity of different segments of the upper gastrointestinal tract (data not shown). In a second set of experiments (12 animals), the *in vitro* effect of the Padma Digestin ethanolic extract on the contractility and susceptibility to ACh was studied in cardial, antral, pyloric, duodenal, jejunal, ileal and colonic muscle strips and compared with EtOH, which was used as a control.

Experimental protocol

The proximal end of the muscle strip was fixed to a glass rod. The distal end was connected to a noncompliant force transducer system (Kulite Semiconductors Products Inc, NJ, United States) for continuous recording of the contractile activity. The muscle strips were stretched stepwise to their optimal point of tension-length relationship and allowed to equilibrate for a period of 60 to 90 min in the organ bath chamber with repetitive changes of buffer (Figure 1). First, the baseline contractility without Padma Digestin or EtOH was measured starting at the recording of spontaneous contractile activity. Then, the muscarinic receptor agonist ACh was added in increasing concentrations every six minutes. Preliminary experiments (data not shown) indicated that muscle strips from the stomach and the small intestine were less responsive to ACh than the colonic strips in this experimental setting. Therefore, colonic strips were treated at the concentrations of 20 mmol/L, 200 mmol/L and 2 μmol/L; however, two additional concentrations of 20 μmol/L and 200 μmol/L were used for all the other gastrointestinal segments. The muscle strips were then washed several times with Krebs-Ringer's modified solution until the spontaneous activity returned to stable. Next, 19.2 μL of the resuspended Padma Digestin extract was added to the organ chambers, resulting in a chamber concentration corresponding to 8.16 mg of the original raw powder per mL (low dose). This final concentration was chosen because it corresponds to 816 mg of active ingredients in 100 mL of water, which is the recommended single dose of Padma Digestin. At the same time 19.2 μL of 70% EtOH was added to the control muscle strips as a solvent control. After a superfusion time of 15 min, spontaneous contractility and excitability by ACh were recorded as described above. The strips were washed again thoroughly with Krebs-Ringer's solution to rinse away the test substances. Once the spontaneous activity returned to stable, 192 μL of resuspended Padma Digestin extract corresponding to a final chamber concentration of 81.6 mg/mL raw powder (high dose) or 192 μL of 70% EtOH (control) was added. The high dose corresponds to 10 times the recommended single dose of Padma Digestin. The recordings were repeated as described above. At the end of the experiment, the length of each muscle strip was measured, and the tissue was blotted dry and weighed to determine the cross sectional area (CSA).

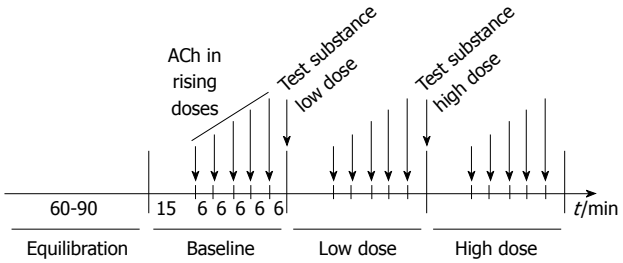

Figure 1 Experimental protocol. ACh: Acetylcholine.

Statistical analysis

Spontaneous contractile activity was checked visually. Muscle strips without useable recordings were excluded from the study. Contractile activity was calculated as the total area under the curve (integrated contractile activity) using the AcqKnowledge software (Biopac Systems, Inc, Goleta, CA, United States). For each reading, 5-min intervals were analyzed.The contractile activity values were normalized to CSA, which was calculated using the following formula: CSA (mm^2) = [tissue wet weight (mg)]/{[tissue length (mm)] × [tissue density (mg/mm^3)]}. The value for smooth muscle tissue density was taken from the literature[25] as 1.05 mg/mm^3. The results were expressed as % CSA ± SE and related to baseline activity. Student's *t* test was used to compare the effects of Padma Digestin and EtOH. *P* values < 0.05 were considered significant.

RESULTS

Gastric segments

Neither EtOH nor the Padma Digestin extract had an effect on the spontaneous contractile activity of the circular cardial strips (Figure 2A). In the antral strips, EtOH treatment reduced spontaneous contractility to 88% ± 2% and 83% ± 2% of the native control at the low and high doses, respectively. This inhibition was almost completely mitigated by the Padma Digestin extract (95% ± 2% and 99% ± 2% of the native control). A similar effect was observed in the pyloric strips; however, the increase in spontaneous contractility compared with the solvent control did not reach statistical significance (Figure 2A).

The ACh-stimulated contractile response in the circular cardial strips was reduced by EtOH, and this re-

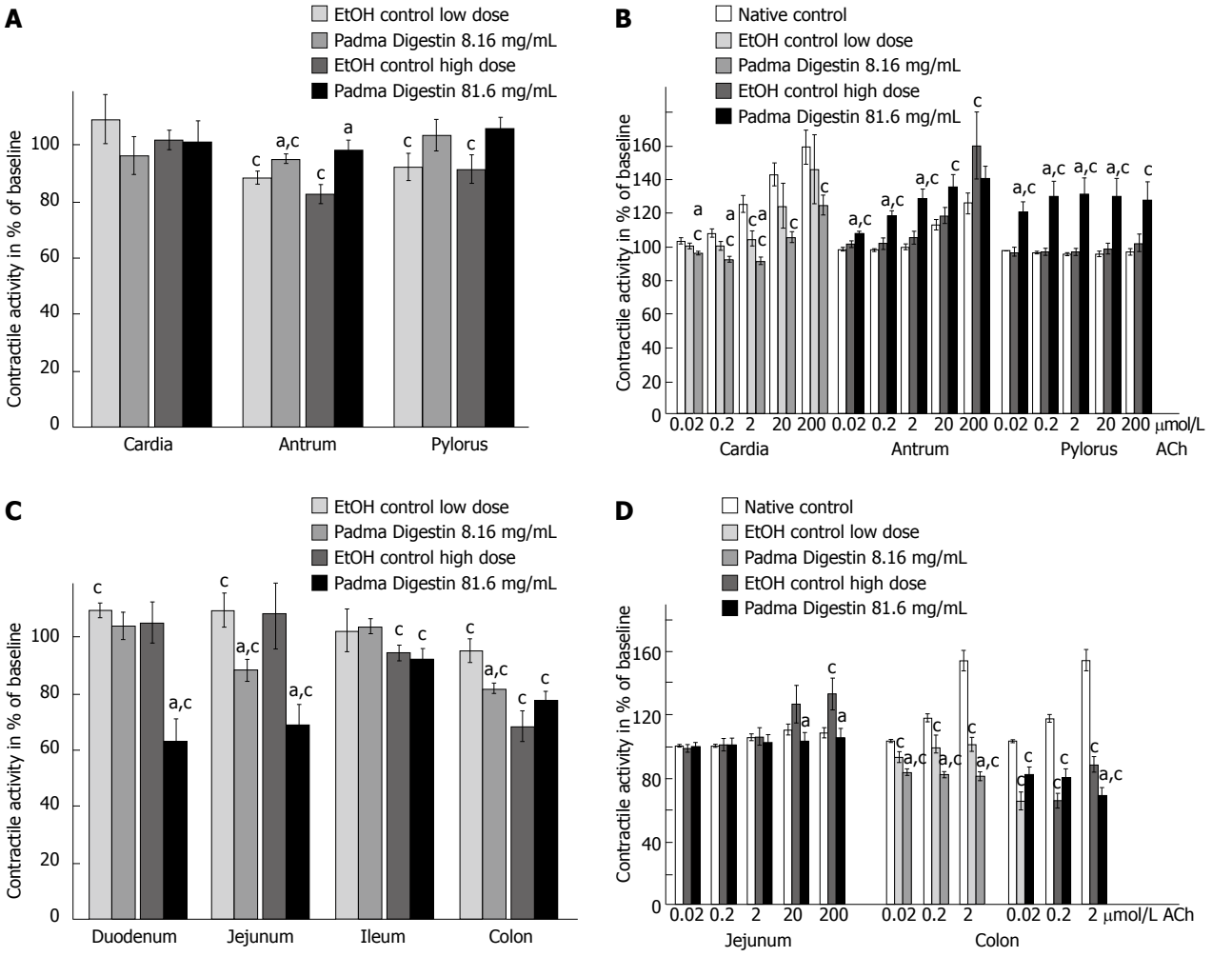

Figure 2 Effect of the Padma Digestin extract. A: Spontaneous contractility of gastric smooth muscle strips; B: Contractility of stomach smooth muscle strips stimulated by acetylcholine; C: Spontaneous contractility of intestinal smooth muscle strips; D: Contractility of intestinal smooth muscle strips stimulated by acetylcholine. EtOH: Ethanol, $^{a}P < 0.05$ *vs* EtOH control; $^{c}P < 0.05$ *vs* baseline.

duction was statistically significant at 2 µmol/L and 20 µmol/L ACh in the high dose and at 2 µmol/L ACh in the low dose (Figure 2B). The Padma Digestin extract further decreased succeptibility to ACh and this effect was statistically significant in 20 mmol/L and 200 mmol/L as well as in 2 µmol/L ACh in the low dose. In the antral and pyloric strips, EtOH increased the contractile response but only at a few concentrations of ACh (Figure 2B, low dose not shown). Compared with the EtOH control, the Padma Digestin extract enhanced the ACh-stimulated procontractile activity of the antral and pyloric strips (Figure 2B).

Intestinal segments

Low dose EtOH enhanced the spontaneous contractile activity of the duodenal and jejunal muscle strips; while in the ileal (high dose EtOH) and colonic (low and high dose EtOH) strips, the spontaneous contractility was reduced (Figure 2C). Compared with EtOH treatment, superfusion with the Padma Digestin extract strongly inhibited the spontaneous contractile activity in the duodenal (high dose), jejunal (low and high dose) and colonic strips (low dose) (Figure 2C). The procontractile activity of ACh in the duodenal strips was inhibited by the solvent EtOH and more so by the Padma Digestin extract, albeit without reaching statistical significance (data not shown). In the jejunal strips, EtOH increased ACh susceptibility at the high dose and with 20 and 200 µmol/L of ACh. This increase was abolished by the Padma Digestin extract (Figure 2D). Neither EtOH nor the Padma Digestin extract had an effect on the ileal strips (data not shown).

In the colonic strips, the pro-contractile effect of ACh was significantly inhibited by EtOH and was even further inhibited by the Padma Digestin extract at the low (all ACh concentrations) and the high (2 µmol/L ACh) dose. With 0.02 µmol/L and 2 µmol/L ACh, the high dose of the preparation increased the contractility compared to solvent alone; however, this effect was not statistically significant (Figure 2D).

DISCUSSION

Functional gastrointestinal disorders, characterized by various gastrointestinal symptoms without identifiable

structural lesions, are multi-factorial conditions, i.e. they can be caused by multiple factors. They are difficult to treat due to the broad spectrum of symptoms, as well as the complex and ill-understood etiology. Because current standard treatment strategies are yielding unsatisfactory results, there is a growing interest in complementary methods[26,27]. Previous studies have reported encouraging results on the use of phytotherapeutics for chronic functional gastrointestinal disorders[9,16,20], and the influence of several herbal preparations on gut motility[21,28-30].

The results of our *in vitro* study show that Padma Digestin can modulate gut motility in a region-specific manner. While in cardial segments, Padma Digestin extract inhibited ACh-stimulated contractility compared with EtOH, it had a procontractile effect on the spontaneous and ACh-stimulated contractility of the antral and pyloric segments. Antral and pyloric motility are essential for gastric emptying and are reduced by different factors such as EtOH consumption or psychogenic stress[31-34]. The Padma Digestin extract prevented EtOH-mediated motility suppression. Our results suggest that Padma Digestin could reduce epigastric pressure and postprandial fullness by improving gastric emptying.

In segments of the small bowel, the control solvent EtOH enhanced the spontaneous contractile activity in the duodenal and jejunal strips and inhibited the contractile activity in ileal strips at the high dose. This finding differs from the results reported in earlier studies[32,35], possibly because in contrast to the single dose administration used in the present study, Palasciano *et al*[32] analyzed the effect of chronic EtOH administration. We analyzed longitudinal muscle strips in our study, whereas Lu *et al*[35] studied circular smooth muscle preparations, which are known to show different contractility patterns and sensitivity to neurotransmitters or other substances.

Compared with the EtOH control, the Padma Digestin extract inhibited the spontaneous contractility of duodenal and jejunal strips with little effect on ACh susceptibility[36].

Different components of the Padma Digestin formula, such as pomegranate seeds[22], piperine[24,37], cardamom[23,38] and cassia cinnamon[39], are known to inhibit small bowel motility. This inhibition and especially the reduction in the susceptibility to ACh stimulation is thought to have spasmolytic effects[22,37-39], thus relieving the abdominal symptoms of FGD. The finding that there is reduced motility in the duodenum and jejunum leads to a prolonged contact of nutrients with the small intestinal mucosa. This might increase their luminal absorption[40] and is in line with the experiences and observations of Traditional Tibetan Medicine, where the formula is also used in malnutrition.

In the colonic strips, the inhibitory effect of EtOH on contractility is well-documented by earlier studies[21,41]. The results we obtained with the Padma Digestin extract suggest a biphasic effect on colonic smooth muscle. While the low dose inhibited the spontaneous as well as the ACh-stimulated contractility compared with the solvent control, the high dose seems to have had a positive effect on the spontaneous contractile activity and the contractility stimulated with 0.02 μmol/L and 0.2 μmol/L ACh, albeit without statistical significance.

Similar to Padma Digestin, different inhibitory and excitatory effects of other herbal substances have been shown in different parts of the stomach and intestine[30,42]. A possible molecular mechanism may be the interaction of Padma Digestin with transient receptor potential (TRP) channels, which are known to influence smooth muscle activity. Various substances contained in the ingredients of Padma Digestin act on different TRP channels. Cinnamaldehyde, a component of cassia bark, has procontractile effects on rat urinary bladders *in vitro*, acting *via* TRP ankyrin 1 (TRPA1)[43]. Pungent substances such as piperine and gingerols, contained in long pepper and lesser galangal, are known agonists of TRPA1[44,45], which is involved in colonic smooth muscle contractions[46]. Piperine may also exert contractile effects *via* TRP vanilloid 1 (TRPV1)[43,47]. On the other hand, piperine also seems to have inhibitory effects on upper gastrointestinal motility, which may be due to either desensitization after prolonged activation of TRPV1[48] or other receptors such as the cannabinoid 1 receptor[24]. Piperine has been shown to have opposing effects on gastrointestinal motility at low and high doses[49]. While lower doses lead to desensitization and seem to act *via* TRP channels, higher doses are thought to have nonspecific direct actions on the smooth muscle. Other TRP-influencing substances found in Padma Digestin plants are the flavonoid galangin[6,8,10] and gingerols contained in lesser galangal[50,51].

The effects of Padma Digestin shown in the present study are likely to occur *via* different mechanisms. Herbal medicines and especially polyherbal formulations are thought to act on multiple target pathways simultaneously[13,15]. This type of multicomponent mechanism of action is especially well suited for the treatment of multifactorial, chronic diseases[12] such as functional gastrointestinal disorders, where safe and effective treatment options are needed[10]. Padma Digestin might be one such option with its diverse effects on gastrointestinal motility. Further studies may elucidate its other modes of action that are clinically relevant, as well as molecular mechanisms of this complex phytotherapeutic compound.

In summary, the results demonstrated a region-specific effect of Padma Digestin on the motility of the rat gastrointestinal tract *in vitro*. Padma Digestin may have a positive effect on functional gastrointestinal disorders by facilitating gastric emptying and intestinal nutrient absorption and by relieving muscular spasms. Thus, our data are in favor of the traditionally prescribed use of Padma Digestin for maldigestion and suggest a potential benefit of this herbal preparation in the treatment of functional disorders of the upper gastrointestinal tract in particular.

ACKNOWLEDGMENTS

The authors thank Dr. Luis Tovar for performing the preliminary *in vitro* organ chamber experiments.

COMMENTS

Background

Functional gastrointestinal disorders are widely spread among Western populations. They are defined by symptoms such as abdominal pain and discomfort, bloating, flatulence, changes in stool consistency, and postprandial fullness without any identifiable organic or structural cause. Although not life threatening the condition has a great impact on quality of life in affected patients and thus, *e.g.*, by doctors visits or sick days from work, has also a socioeconomic relevance.

Research frontiers

Various factors are known to play a role in the development of functional gastrointestinal disorders. Because of the complex causes of the disease there is no accepted and effective standard therapy but treatment mostly follows a symptoms oriented trial and error method. Safe and effective treatment options are urgently needed. Some herbal medicines such as the formula Padma Digestin from Tibetan Medicine are traditionally used in functional dyspeptic symptoms but up to now their modes of actions are not known.

Innovations and breakthroughs

It was found that the herbal formula Padma Digestin has region-specific effects on contractility and sensitivity to stimulants of gastrointestinal smooth muscle. The effects shown here are known to promote gastric emptying and intestinal absorption and suggest a positive effect in functional dysmotility of the upper gastrointestinal tract. The results thus support the traditional use of Padma Digestin in maldigestion and functional gastrointestinal disorders.

Applications

The study suggests that by modulating stomach and gut smooth muscle motility the herbal formula Padma Digestin might be a much needed treatment option in functional gastrointestinal disorders.

Terminology

Padma Digestin is a classical herbal formula from the Tibetan Medicine System (Tibetan name: Se'bru 5). It is composed of five ingredients: pomegranate seeds, long pepper, cassia bark, cardamom seeds, and lesser galangal. The components of complex herbal formulas such as used in Tibetan Medicine achieve their effects synergistically and according to a multi-target mode of action.

Peer review

The investigation has profound pharmacological and therapeutic implications. The study is simple using the *in vitro* gastric tissue model and it has yielded convincing results. The authors have used "mixture" of phytochemicals. Further studies are needed to pin-point the exact molecular mechanisms for the observed effects on gastrointestinal motility.

REFERENCES

1 **Drossman DA**. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; **130**: 1377-1390 [PMID: 16678553]

2 **Sanger GJ**, Chang L, Bountra C, Houghton LA. Challenges and prospects for pharmacotherapy in functional gastrointestinal disorders. *Therap Adv Gastroenterol* 2010; **3**: 291-305 [PMID: 21180610 DOI: 10.1177/1756283X10369922]

3 **Mahadeva S**, Wee HL, Goh KL, Thumboo J. The EQ-5D (Euroqol) is a valid generic instrument for measuring quality of life in patients with dyspepsia. *BMC Gastroenterol* 2009; **9**: 20 [PMID: 19284606 DOI: 10.1186/1471-230X-9-20]

4 **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 [PMID: 17160514 DOI: 10.1007/s00535-006-1966-z]

5 **Levy RL**, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, Creed F. Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterology* 2006; **130**: 1447-1458 [PMID: 16678558 DOI: 10.1053/j.gastro.2005.11.057]

6 **Li X**, Chen H, Lu H, Li W, Chen X, Peng Y, Ge Z. The study on the role of inflammatory cells and mediators in post-infectious functional dyspepsia. *Scand J Gastroenterol* 2010; **45**: 573-581 [PMID: 20163288 DOI: 10.3109/00365521003632576]

7 **O'Morain C**. Role of Helicobacter pylori in functional dyspepsia. *World J Gastroenterol* 2006; **12**: 2677-2680 [PMID: 16718752]

8 **Summers A**, Khan Z. Managing dyspepsia in primary care. *Practitioner* 2009; **253**: 23-27 [PMID: 19938559]

9 **Talley NJ**, Vakil N. Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005; **100**: 2324-2337 [PMID: 16181387 DOI: 10.1111/j.1572-0241.2005.00225.x]

10 **De Giorgio R**, Barbara G, Furness JB, Tonini M. Novel therapeutic targets for enteric nervous system disorders. *Trends Pharmacol Sci* 2007; **28**: 473-481 [PMID: 17764756 DOI: 10.1016/j.tips.2007.08.003]

11 **Barkun A**, Crott R, Fallone C, Kennedy W, Lachaine J, Levinton C, Armstrong D, Chiba N, Thomson A, Veldhuyzen van Zanten S, Sinclair P, Escobedo S, Chakraborty B, Smyth S, White R, Kalra H, Nevin K. A one-year economic evaluation of six alternative strategies in the management of uninvestigated upper gastrointestinal symptoms in Canadian primary care. *Can J Gastroenterol* 2010; **24**: 489-498 [PMID: 20711528]

12 **Saller R**. [Tibetan remedies in chronic disease]. *Forsch Komplementmed* 2006; **13** Suppl 1: VII-VIII [PMID: 16582553 DOI: 10.1159/000091011]

13 **Schwabl H**, Vennos C. Der "multi-target"-Ansatz tibetischer Heilmittel: Wirkmechanismen von Padma 28 im entzündlichen Geschehen am Beispiel der Arteriosklerose. *Schweiz Z Ganzheitsmed* 2006; **18**: 213-218 [DOI: 10.1159/000282054]

14 **Wagner H**. Multitarget therapy--the future of treatment for more than just functional dyspepsia. *Phytomedicine* 2006; **13** Suppl 5: 122-129 [PMID: 16772111 DOI: 10.1016/j.phymed.2006.03.021]

15 **Csermely P**, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci* 2005; **26**: 178-182 [PMID: 15808341 DOI: 10.1016/j.tips.2005.02.007]

16 **Tillisch K**. Complementary and alternative medicine for functional gastrointestinal disorders. *Gut* 2006; **55**: 593-596 [PMID: 16609129 DOI: 10.1136/gut.2005.078089]

17 **Tillisch K**. Complementary and alternative medicine for gastrointestinal disorders. *Clin Med* 2007; **7**: 224-227 [PMID: 17633940]

18 **Oikawa T**, Ito G, Koyama H, Hanawa T. Prokinetic effect of a Kampo medicine, Hange-koboku-to (Banxia-houpo-tang), on patients with functional dyspepsia. *Phytomedicine* 2005; **12**: 730-734 [PMID: 16323291 DOI: 10.1016/j.phymed.2005.03.001]

19 **Sallon S**, Ben-Arye E, Davidson R, Shapiro H, Ginsberg G, Ligumsky M. A novel treatment for constipation-predominant irritable bowel syndrome using Padma Lax, a Tibetan herbal formula. *Digestion* 2002; **65**: 161-171 [PMID: 12138321 DOI: 10.1159/000064936]

20 **Shi J**, Tong Y, Shen JG, Li HX. Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: a systematic review. *World J Gastroenterol* 2008; **14**: 454-462 [PMID: 18200670 DOI: 10.3748/wjg.14.454]

21 **Gschossmann JM**, Krayer M, Flogerzi B, Balsiger BM. Effects of the Tibetan herbal formula Padma Lax on visceral nociception and contractility of longitudinal smooth muscle in a rat model. *Neurogastroenterol Motil* 2010; **22**: 1036-1041, e269-270 [PMID: 20518857 DOI: 10.1111/j.1365-2982.2010.01512.x]

22 **Martel D**, Psychoyos A. Progesterone-induced oestrogen receptors in the rat uterus. *J Endocrinol* 1978; **76**: 145-154 [PMID: 0624879 DOI: 10.1016/S0378-8741(99)00102-6]

23 **Gilani AH**, Jabeen Q, Khan AU, Shah AJ. Gut modulatory, blood pressure lowering, diuretic and sedative activities of cardamom. *J Ethnopharmacol* 2008; **115**: 463-472 [PMID: 18037596 DOI: 10.1016/j.jep.2007.10.015]

24 **Izzo AA**, Capasso R, Pinto L, Di Carlo G, Mascolo N, Capasso F. Effect of vanilloid drugs on gastrointestinal transit

in mice. *Br J Pharmacol* 2001; **132**: 1411-1416 [PMID: 11264233 DOI: 10.1038/sj.bjp.0703975]
25 **Gordon AR**, Siegman MJ. Mechanical properties of smooth muscle. I. Length-tension and force-velocity relations. *Am J Physiol* 1971; **221**: 1243-1249 [PMID: 5124267]
26 **Michelfelder AJ**, Lee KC, Bading EM. Integrative medicine and gastrointestinal disease. *Prim Care* 2010; **37**: 255-267 [PMID: 20493335 DOI: 10.1016/j.pop.2010.02.003]
27 **Mullin GE**, Clarke JO. Role of complementary and alternative medicine in managing gastrointestinal motility disorders. *Nutr Clin Pract* 2010; **25**: 85-87 [PMID: 20130161 DOI: 10.1177/0884533609358903]
28 **Borrelli F**, Capasso R, Pinto A, Izzo AA. Inhibitory effect of ginger (Zingiber officinale) on rat ileal motility in vitro. *Life Sci* 2004; **74**: 2889-2896 [PMID: 15050426 DOI: 10.1016/j.lfs.2003.10.023]
29 **Capasso R**, Savino F, Capasso F. Effects of the herbal formulation ColiMil on upper gastrointestinal transit in mice in vivo. *Phytother Res* 2007; **21**: 999-1101 [PMID: 17582592 DOI: 10.1002/ptr.2192]
30 **Schemann M**, Michel K, Zeller F, Hohenester B, Rühl A. Region-specific effects of STW 5 (Iberogast) and its components in gastric fundus, corpus and antrum. *Phytomedicine* 2006; **13** Suppl 5: 90-99 [PMID: 16765572 DOI: 10.1016/j.phymed.2006.03.020]
31 **Liu KJ**, Wang SL, Xie DP, Liu PY, Wang PS, Liu CY. Sexual differences of the inhibitory effect of ethanol on gastrointestinal motility: in vivo and in vitro studies. *Chin J Physiol* 2006; **49**: 199-203 [PMID: 17058452]
32 **Palasciano G**, Portincasa P, Di Ciaula A, Palmieri V. Prolonged consumption of moderate doses of alcohol and in vitro gastro-duodenal and ileal contractility in the rat. *Eur J Clin Invest* 1995; **25**: 171-175 [PMID: 7781663 DOI: 10.1111/j.1365-2362.1995.tb01544.x]
33 **Heinrich H**, Goetze O, Menne D, Iten PX, Fruehauf H, Vavricka SR, Schwizer W, Fried M, Fox M. Effect on gastric function and symptoms of drinking wine, black tea, or schnapps with a Swiss cheese fondue: randomised controlled crossover trial. *BMJ* 2010; **341**: c6731 [PMID: 21156747 DOI: 10.1136/bmj.c6731]
34 **Berezina TP**, Ovsyannikov VI. Mechanism for the inhibition of contractile activity of the gastric antrum and pylorus in rabbits during psychogenic stress. *Bull Exp Biol Med* 2009; **147**: 296-300 [PMID: 19529847 DOI: 10.1007/s10517-009-0495-1]
35 **Lu G**, Sarr MG, Szurszewski JH. Effects of ethyl alcohol on canine jejunal circular smooth muscle. *Dig Dis Sci* 1997; **42**: 2403-2410 [PMID: 9440612]
36 **Martinolle JP**, Garcia-Villar R, Fioramonti J, Bueno L. Altered contractility of circular and longitudinal muscle in TNBS-inflamed guinea pig ileum. *Am J Physiol* 1997; **272**: G1258-G1267 [PMID: 9176238]
37 **Mehmood MH**, Gilani AH. Pharmacological basis for the medicinal use of black pepper and piperine in gastrointestinal disorders. *J Med Food* 2010; **13**: 1086-1096 [PMID: 20828313 DOI: 10.1089/jmf.2010.1065]
38 **al-Zuhair H**, el-Sayeh B, Ameen HA, al-Shoora H. Pharmacological studies of cardamom oil in animals. *Pharmacol Res* 1996; **34**: 79-82 [PMID: 8981560 DOI: 10.1006/phrs.1996.0067]
39 **European Medicines Agency**, Committee on Herbal Medicinal Products. Assessment report on Cinnamomum verum J. S. Presl (Cinnamomum zeylanicum Nees), cortex and corticis aetheroleum. London: European Medicines Agency, 2010
40 **Bronner F**. Nutrient bioavailability, with special reference to calcium. *J Nutr* 1993; **123**: 797-802 [PMID: 8487089]
41 **Wang SL**, Xie DP, Liu KJ, Qin JF, Feng M, Kunze W, Liu CY. Nitric oxide mediates the inhibitory effect of ethanol on the motility of isolated longitudinal muscle of proximal colon in rats. *Neurogastroenterol Motil* 2007; **19**: 515-521 [PMID: 17564633 DOI: 10.1111/j.1365-2982.2007.00918.x]
42 **Zhang WW**, Li Y, Wang XQ, Tian F, Cao H, Wang MW, Sun QS. Effects of magnolol and honokiol derived from traditional Chinese herbal remedies on gastrointestinal movement. *World J Gastroenterol* 2005; **11**: 4414-4418 [PMID: 16038044]
43 **Andrade EL**, Ferreira J, André E, Calixto JB. Contractile mechanisms coupled to TRPA1 receptor activation in rat urinary bladder. *Biochem Pharmacol* 2006; **72**: 104-114 [PMID: 16725114 DOI: 10.1016/j.bcp.2006.04.003]
44 **Okumura Y**, Narukawa M, Iwasaki Y, Ishikawa A, Matsuda H, Yoshikawa M, Watanabe T. Activation of TRPV1 and TRPA1 by black pepper components. *Biosci Biotechnol Biochem* 2010; **74**: 1068-1072 [PMID: 20460725 DOI: 10.1271/bbb.90964]
45 **Mandadi S**, Roufogalis BD. ThermoTRP channels in nociceptors: taking a lead from capsaicin receptor TRPV1. *Curr Neuropharmacol* 2008; **6**: 21-38 [PMID: 19305786 DOI: 10.2174/157015908783769680]
46 **Dong Y**, Shi HL, Shi JR, Wu DZ. Transient receptor potential A1 is involved in cold-induced contraction in the isolated rat colon smooth muscle. *Shengli Xuebao* 2010; **62**: 349-356 [PMID: 20717636]
47 **Patacchini R**, Maggi CA, Meli A. Capsaicin-like activity of some natural pungent substances on peripheral endings of visceral primary afferents. *Naunyn Schmiedebergs Arch Pharmacol* 1990; **342**: 72-77 [PMID: 1698263 DOI: 10.1007/BF00178975]
48 **McNamara FN**, Randall A, Gunthorpe MJ. Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1). *Br J Pharmacol* 2005; **144**: 781-790 [PMID: 15685214 DOI: 10.1038/sj.bjp.0706040]
49 **Takaki M**, Jin JG, Lu YF, Nakayama S. Effects of piperine on the motility of the isolated guinea-pig ileum: comparison with capsaicin. *Eur J Pharmacol* 1990; **186**: 71-77 [PMID: 1704311 DOI: 10.1016/0014-2999(90)94061-2]
50 **Capasso R**, Mascolo N. Inhibitory effect of the plant flavonoid galangin on rat vas deferens in vitro. *Life Sci* 2003; **72**: 2993-3001 [PMID: 12706486 DOI: 10.1016/S0024-3205(03)00232-7]
51 **Iwasaki Y**, Morita A, Iwasawa T, Kobata K, Sekiwa Y, Morimitsu Y, Kubota K, Watanabe T. A nonpungent component of steamed ginger--[10]-shogaol--increases adrenaline secretion via the activation of TRPV1. *Nutr Neurosci* 2006; **9**: 169-178 [PMID: 17176640 DOI: 10.1080/10284150600955164]

P- Reviewer Parinandi NL **S- Editor** Zhai HH **L- Editor** A
E- Editor Li JY