ISSN 2150-5349 (online)

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2013 February 6; 4(1): 1-15

Baishideng Publishing Group
www.wjgnet.com

WJGPT

World Journal of Gastrointestinal Pharmacology and Therapeutics

A peer-reviewed, online, open-access journal of gastrointestinal pharmacology and therapeutics

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2011-2015

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World Journal of Gastrointestinal Pharmacology and Therapeutics

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Quarterly Volume 4 Number 1 February 6, 2013

World Journal of Gastrointestinal Pharmacology and Therapeutics
Volume 4 Number 1 February 6, 2013

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NAME OF JOURNAL
World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN
ISSN 2150-5349 (online)

LAUNCH DATE
February 6, 2010

FREQUENCY
Quarterly

World Journal of Gastrointestinal Pharmacology and Therapeutics
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
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PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
February 6, 2013

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2150-5349/g_info_20100315084234.htm

ONLINE SUBMISSION
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World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
wjgpt@wjgnet.com
doi:10.4292/wjgpt.v4.i1.1

World J Gastrointest Pharmacol Ther 2013 February 6; 4(1): 1-3
ISSN 2150-5349 (online)

FIELD OF VISION

Continuous quality improvement of colorectal cancer screening

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Received: October 29, 2012 Revised: January 21, 2013
Accepted: February 2, 2013
Published online: February 6, 2013

Abstract

Quality assurance is a key issue in colorectal cancer screening, because effective screening is able to improve primary prevention of the cancer. The quality measure may be described in terms: how well the screening test tells who truly has a disease (sensitivity) and who truly does not have a disease (specificity). This paper raises concerns about identification of the optimal screening test for colorectal cancer. Colonoscopy *vs* flexible sigmoidoscopy in colorectal cancer screening has been a source of ongoing debate. A multicentre randomised controlled trial comparing flexible sigmoidoscopy with usual care showed that flexible sigmoidoscopy screening is able to diminish the incidence of distal and proximal colorectal cancer, and also mortality related to the distal colorectal cancer. However, colonoscopy provides a more complete examination and remains the more sensitive exam than flexible sigmoidoscopy. Moreover, colonoscopy with polypectomy significantly reduces colorectal cancer incidence and colorectal cancer-related mortality in the general population. The article considers the relative merits of both methods and stresses an ethical aspect of patient's involvement in decision-making. Patients should be informed not only about tests tolerability and risk of endoscopy complications, but also that different screening tests for bowel cancer have different strength to exclude colonic cancer and polyps. The authorities calculate effectiveness and costs of the screening tests, but patients may not be interested in statistics regarding flexible sigmoidoscopy screening and from an ethical point of view, they have the right to chose colonoscopy, which is able to exclude a cancer and precancerous lesions in the whole large bowel.

Key words: Colorectal cancer; Cancer screening; Sigmoidoscopy; Colonoscopy; Standard of care; Ethical aspects; Clinical competence

Madalinski M. Continuous quality improvement of colorectal cancer screening. *World J Gastrointest Pharmacol Ther* 2013; 4(1): 1-3 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i1/1.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i1.1

COMMENTARY ON HOT TOPICS

Colorectal cancer (CC) is a common cause of morbidity and mortality in which early detection is vital. From the United States comes a multicentre randomized study of colorectal screening with flexible sigmoidoscopy (FS)[1]. The results of this study raise a number of important questions regarding the assessment of quality in screening tests and ethical issues.

A total of 77 445 participants of Schoen *et al*[1] were randomly assigned to be screened for CC, and 77 455 to usual care (from 1993 to 2001). Participants in the intervention group were offered FS at baseline and at 3 or at 5 years. They were referred to their primary care physicians for decisions regarding diagnostic follow-up. A screening-detected cancer was defined as a CC diagnosed within 1 year after a positive FS and was considered to be posi-

tive, if a polyp or mass was detected. Cancers located in the rectum through the splenic flexure were defined as distal, and those in the transverse colon through the caecum were defined as proximal. Death from CC was the primary end point. Secondary end points included CC incidence, cancer stage, survival, harms of screening, and all-cause mortality. Participants in the control group only received endoscopy (FS or colonoscopy), if they asked for it, or if their physician recommended it.

A total of 86.6% of participants (67 071) underwent at least one FS screening, and 50.9% (39 440) underwent two screenings; at least one screening was positive for a polyp or mass in 28.5% of participants (22 083)[1].

The study showed a reduction in the incidence of distal CC in the intervention group for each cancer stage, ranging from 19.8% for stage I cancers (50 fewer cases diagnosed) to 61.7% for stage Ⅳ cancers (66 fewer cases diagnosed). Mortality related to distal CC was also reduced for each stage, by 21.4% for stage I cancers (3 fewer deaths) to 60.7% for stage Ⅳ cancers (51 fewer deaths)[1]. The number needed to screen with FS to prevent 1 death from CC was 871 and to invite to FS screening to prevent 1 CC was 282[1].

Also the incidence of proximal CC was reduced by 14.4% to 20.7% in the intervention group for stages Ⅰ, Ⅱ, and Ⅲ cancers (22, 34, and 25 fewer cases, respectively), but by only 2.0% (2 fewer cases) for stage Ⅳ disease[1].

The study described by Schoen *et al*[1] showed a reduction in the incidence of proximal CC, but FS was not success in identifying and removing all precursor lesions destined to develop into cancer in the whole colon and the authors did not show a reduction in mortality related to proximal CC[1]. Although the study revealed that FS as compared with usual care may result in overall CC mortality, but much of the benefit in reducing CC in mortality from screening derived from its reduction in stage IV the disease, which has a much higher mortality than lower stages[1].

Using colonoscopy as the screening method, Schoen *et al*[1] calculated that they could increase the number of screening-detected cancers by approximately 16 percentage points (from < 25% to approximately 40% of CC diagnosed in participants assigned to FS). There is also evidence that colonoscopy with adenomas removal reduces incidence of CC[2]. Moreover, it has an impact on the reduction of mortality from CC[3-6], and in the first 10 years after polypectomy, reduces the risk to a level similar to that in a control group of patients with no adenomas[3].

In the Schoen *et al*[1] study, 28.5% of participants (22 083) underwent at least one positive endoscopy screening test for a polyp or mass. However, the authors did not mention, whether the second FS revealed only polyps? If this was the case and the second FS revealed a CC or large polyps then it is possible that the endoscopists' skills or bowel preparation may have an impact on the study results.

A high-quality examination ensures the detection of "all" neoplastic lesions - it may be related to an endoscopist's speciality[5-7]. Patients who underwent colonoscopy performed by a gastroenterologist had the greatest reduction in risk for CC mortality[5,6]. Also a reduction in death from proximal CC may be probably related to colonoscopy performed by a gastroenterologist[5,6].

It could be argued that colonoscopy screening is more expensive than FS, but 50.9% participants (39 440) of the Schoen *et al*[1] study, underwent two screenings FS (in 3-5 years). Moreover, there are no studies directly assessing the optimal interval for FS screening[8], but there is a strongly and significantly lower risk of CC within 10 year after negative colonoscopy[9]. Although, the ratio of the cost of FS screening to colonoscopy screening is unknown[10], but diagnostic colonoscopy and diagnostic FS may cost £555 and £441 respectively (figures derive from the Trust's Service Line Reporting information April-September 2012 in The Pennine Acute Hospitals NHS Trust, United Kingdom). I think therefore a model-based economic analysis may easily find colonoscopy screening as less costly than FS screening.

Although colonoscopy has a slightly higher incidence of perforation than FS[11], but the most common site of perforation during colonoscopy used to be the left colon[11,12]. Schoen *et al*[1] reported 0.0028% perforation for screening with FS (2.8 per 100 000 examinations), and nearly 40 times more perforations on repeat screening 0.1075% (107.5 per 100 000 examinations). The incidence of colonoscopic perforation could be very low 0.004% in diagnostic colonoscopy and could be as high as 0.02% in therapeutic colonoscopies, with individual series rates ranging from 0% to 0.86%[13]. The national colonoscopy audit performed in the United Kingdom, reported rate 0.04% perforations (1:2511 procedures)[14]. Nonetheless, the audited adult patients who underwent diagnostic or therapeutic colonoscopy could have an even higher risk of complications than screening individuals, because they were symptomatic patients (two perforations occurred in patients with inflammatory bowel disease)[14].

Colorectal cancer is the third most common in incidence and the fourth most common cause of cancer death worldwide[15]. An effective screening programme plays a key role to cope with the growing problem of CC. So far, the United Kingdom study has been the only study to show a significant 31% reduction in CC mortality from one-time screening with FS[16]. It also found a significant reduction in the CC incidence (by 23%)[16]. Another study performed in Italy showed an 18% reduction in incidence of CC, but FS in this study did not cause significant reduction in mortality[17]. In Schoen's study comparing FS with usual care, after an average of nearly 12 years, participants in the screening group had a 21% reduction in the incidence of CC and a 26% lower rate of CC mortality than participants in the usual care group. Also a reduction of mortality by 50% and incidence by 29% related to distal CC was noticed.

Despite this great result, the doctors and health authorities are in an ethical dilemma over the optimal screening for CC. Colonoscopy provides a more complete examina-

tion than FS and a patient may not be interested in statistics regarding FS, and ask, if it is better for him to have FS or a complete colonoscopy.

When the patients will be totally informed about the limitations and benefits of FS and colonoscopy, they may be interested to make a decision themselves and choose a more sensitive endoscopy test which is able to exclude a cancer and precancerous lesions in the whole large bowel. Very experienced doctors do not need much more time to complete colonoscopy in most cases, when the top of the endoscope is in the area of splenic flexure. Furthermore, colonoscopy without sedation is common in many European countries and Asia[18,19]. Therefore the cost of colonoscopy and FS may not differ widely, if endoscopists offer really good skills. In the future, every individual may be involved in the decision-making, and the doctors should be interested in the patient's preference regarding the screening test, because patients have the right to make their own choice[20].

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P- Reviewers Angelo Z, Gibson RJ, Pimanov SI **S- Editor** Jiang L **L- Editor** A **E- Editor** Li JY

World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
wjgpt@wjgnet.com
doi:10.4292/wjgpt.v4.i1.4

World J Gastrointest Pharmacol Ther 2013 February 6; 4(1): 4-8
ISSN 2150-5349 (online)

FIELD OF VISION

Inhibition of apoptosis in the management of nonalcoholic fatty liver disease

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Received: September 19, 2012 Revised: December 26, 2012
Accepted: January 11, 2013
Published online: February 6, 2013

Abstract

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the developed world. The pathogenesis of NAFLD is multifactorial, involving obesity, insulin resistance, inflammation and oxidative stress. Accordingly, several treatments targeting these pathways have been evaluated in patients with NAFLD but have either shown limited efficacy or an unfavorable safety profile. On the other hand, increased hepatocyte apoptosis also appears to be implicated in the development and progression of NAFLD and recent pilot studies suggest that inhibition of apoptosis might represent a useful approach in this disease. However, several issues pertaining both to the efficacy and safety of this new class of agents remain unresolved and larger studies are required to clarify the role of this therapeutic modality in the management of NAFLD.

Key words: Apoptosis; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Fatty liver; Carcinogenesis; Cirrhosis; Caspase

Bouziana SD, Tziomalos K. Inhibition of apoptosis in the management of nonalcoholic fatty liver disease. *World J Gastrointest Pharmacol Ther* 2013; 4(1): 4-8 Available from: URL: http://www.wjgnet.com/2150-5349/full/v4/i1/4.htm DOI: http://dx.doi.org/10.4292/wjgpt.v4.i1.4

COMMENTARY ON HOT TOPICS

Nonalcoholic fatty liver disease (NAFLD) is a burgeoning health problem and is recognized as the main cause of chronic liver disease in the developed world[1,2]. It affects approximately 34%-46% of the general adult population in Western countries[3,4]. Moreover, the prevalence of NAFLD is substantially higher in obese and diabetic patients, reaching 70%[5-7]. Given the worldwide growing epidemics of obesity and type 2 diabetes mellitus, the prevalence of NAFLD is expected to rise further in the following years[1,5]. NAFLD covers a wide spectrum of histological abnormalities ranging from steatosis to the coexistence of steatosis with inflammation and a variable degree of fibrosis [nonalcoholic steatohepatitis (NASH)], to cirrhosis and even to hepatocellular carcinoma[1,8]. Patients with NAFLD, particularly those with NASH, have increased all-cause mortality compared with the general population, with cardiovascular disease and liver-related disease being the leading causes of death[9-11].

In light of the considerable prevalence of NAFLD and its associated increased mortality, there is a pressing need for identifying effective treatments for this disease. The pathogenesis of NAFLD is multifactorial, involving obesity, insulin resistance, inflammation, oxidative stress and increased hepatocyte apoptosis[8,12]. Accordingly, several treatments have been evaluated in this population, including lifestyle changes and pharmacological agents targeting the underlying pathogenetic mechanisms, including insulin-sensitizing, weight-reducing, antioxidant and antiinflammatory agents[1,12,13]. However, the evalu-

ated agents have either shown limited efficacy or have been associated with an unfavorable safety profile[1,12,13]. Accordingly, current therapeutic approaches propose lifestyle modifications including diet and exercise as first line treatment in patients with NAFLD[1]. However, diet and exercise are of limited efficacy and are characterized by low long-term adherence rates[1].

In this context, novel agents targeting hepatocyte apoptosis might represent a useful tool in the management of NAFLD. Apoptosis is a physiological, highly organized and genetically programmed form of cell death which contributes to body homeostasis by removing aged and damaged cells. Thus, apoptosis represents a major protective defense mechanism against a number of harmful factors including viral attacks and carcinogens[14]. However, aberrant hepatocyte apoptosis may induce hepatic injury and disease progression *via* up-regulation of inflammation and fibrosis[14-16]. Indeed, hepatocyte apoptosis is increased in NAFLD and correlates with the severity of inflammation and fibrosis[14-16]. Moreover, apoptosis is a main feature of NASH differentiating it from isolated steatosis and may also contribute to the progression from NASH to cirrhosis[16-18]. In experimental models, increased apoptosis appears to contribute to progression to hepatocellular carcinoma (HCC) independently from other carcinogens (*e.g.*, inflammation)[19]. It has been suggested that damaged hepatocytes become resistant to apoptotic death in more advanced NAFLD because of downregulation of proapoptotic molecules and upregulation of antiapoptotic mediators[19-21]. As a result, damaged cells escape apoptosis and high proliferation rates are observed leading to HCC[19-21].

Given the important role of apoptosis in NAFLD, a recently reported pilot study by Ratziu *et al*[22] evaluated the safety and efficacy of inhibition of hepatocyte apoptosis in this disease. This phase Ⅱ, randomized, double-blind, placebo-controlled, multicenter clinical trial evaluated GS-9450, an irreversible selective inhibitor of caspases 1, 8 and 9, in patients with NAFLD[22]. Caspases are intracellular proteolytic enzymes that are key effectors of the apoptotic process[14]. The study included 124 patients 18 to 75 years-old with biopsy-proven NASH and serum alanine aminotransferase (ALT) levels > 60 IU/L[22]. Exclusion criteria included histological findings of cirrhosis, HCC, platelets < 75 000/mm^3, neutrophils < 1500/mm^3, hemoglobin < 11.0 g/dL, creatinine clearance < 70 mL/min (estimated with the Cockcroft-Gault equation), weight lose > 4% within 8 wk before screening, daily alcohol consumption > 30 g in males and > 20 g in females, drug-induced fatty liver and liver damage attributed to other liver diseases (*e.g.*, viral hepatitis, autoimmune hepatitis and hemochromatosis). Patients with type 2 diabetes mellitus were eligible for inclusion in the study if they were not insulin-dependent, they were not under treatment with glitazones for at least 6 mo before screening, the onset of diabetes was within the last 10 years and there were no signs of peripheral diabetic neuropathy or gastroparesis. Patients were randomly assigned to receive GS-9450 1, 5, 10 or 40 mg or placebo once a day for 4 wk. All patients were required to follow a balanced lifestyle during the study. A follow-up of 4 wk followed the treatment period. The main efficacy endpoints were the change in serum ALT, aspartate aminotransferase (AST) and cytokeratin (CK)-18 fragment levels during the treatment period. CK-18 is a major cytoplasmic filament protein of the hepatocellular cytoskeleton that is cleaved mainly by caspase-3 during the apoptotic process leading to formation of CK-18 fragments[15]. Thus, CK-18 fragment levels reflect the extent of hepatocyte apoptosis[15].

Treatment with GS-9450 induced a significant, dose-dependent reduction in serum ALT levels whereas ALT levels did not change in the placebo group[22]. This reduction occurred as early as the third day of treatment. In the group that received 40 mg GS-9450, at week 4, only 2 patients (8%) were nonresponders (*i.e.*, had a decrease in ALT levels of < 10% relative to baseline) whereas 35% of patients showed normalization of ALT values. A dose-dependent reduction was also observed in serum AST levels in patients who received GS-9450. Among patients who received the highest GS-9450 dose, the percent of patients who had normal AST levels increased from 20% at baseline to 48% at the end of the treatment period. Serum CK-18 fragments decreased only in patients who were treated with 10 and 40 mg GS-9450 but this decrease did not differ from the change in the placebo group[22].

At 4 wk after treatment discontinuation, serum ALT levels returned to baseline levels in the groups that received 1, 5 and 10 mg GS-9450 but where lower than baseline in the 40 mg group[22]. This rebound effect was apparent from the first week of the follow-up period[22]. Serum AST levels increased within 1 wk of discontinuation of GS-9450 in all groups to modestly above baseline levels[22].

There was no change in markers of insulin resistance (serum glucose and insulin levels, homeostasis model of insulin resistance), serum γ-glutamyl transpeptidase levels, lipids or weight during treatment with GS-9450[22].

Regarding the safety of GS-9450, the majority of the adverse events recorded in patients treated with this agent were of mild to moderate severity and most were not attributed to GS-9450[22]. No serious adverse events were recorded during treatment with GS-9450. Moreover, there were no notable differences in the frequency of adverse events between the groups assigned GS-9450 and placebo[22].

Overall, the study of Ratziu *et al*[22] suggests that GS-9450 dose-dependently lowers serum ALT levels and is well-tolerated in patients with NAFLD. Previous studies evaluating this agent have also reported promising results. In a phase I clinical trial, GS-9450 was well-tolerated when administered to healthy individuals[23]. In a double-blind, placebo-controlled phase Ⅱa trial in patients with chronic hepatitis C, a disease also characterized by increased hepatocellular apoptosis, GS-9450 reduced serum

ALT levels[24]. Moreover, in a substudy of the latter trial, GS-9450 induced a moderate reduction in caspase-8 expression and a strong reduction in caspase-3 expression in peripheral T-lymphocytes[25].

Besides GS-9450, a wide range of pan-caspase inhibitors has been evaluated in pilot studies yielding encouraging results. IDN-6556, an irreversible, broad-spectrum caspase inhibitor, attenuated hepatocellular apoptosis and hepatic inflammation and fibrosis in animal models[26,27]. In humans, IDN-6556 was well-tolerated in a phase Ⅱ clinical trial by both normal volunteers and patients with elevated transaminase levels and lowered transaminase levels in the latter[28]. Moreover, in a phase I and Ⅱ clinical trial, IDN-6556 reduced aminotransferase levels in patients with chronic hepatitis C or NASH[29,30]. Another irreversible pan-caspase inhibitor, VX-166, reduced hepatocellular apoptosis, inflammation and fibrosis in experimental models but had a modest effect on ALT levels and markers of oxidative stress in animal models with established steatosis/steatohepatitis[31,32].

However, there are some concerns regarding the safety of GS-9450 and caspase inhibitors in general. There is a potential risk of carcinogenesis when apoptotic mechanisms are inhibited given the key role of apoptosis in protecting against tumor development[19,21]. The existing data regarding this possible association is meagre and controversial[21]. GS-9450 might theoretically be safer than pan-caspase inhibitors since it acts primarily on hepatocytes and blocks the activity of specific caspases. However, most information about the safety of caspase-inhibitors is from experimental models and therefore it is difficult to reach definite conclusions about their safety in humans[21]. The existing clinical studies are small and short in duration[22,24,28-30]; accordingly, larger and long-term studies are required to evaluate the carcinogenic potential, if any, of caspase inhibitors.

Another concern regarding the safety of caspase inhibitors is ALT overshoot, *i.e.,* elevation of ALT levels three times the baseline value after discontinuation of treatment, which could result in acute hepatic failure[29,30]. This adverse effect was observed in patients with chronic hepatitis C who were treated with the pan-caspase inhibitor IDN-6556 and could be due to massive apoptosis of hepatocytes, which escaped apoptosis during treatment, after the abrupt withdrawal of the drug[30]. In the study by Ratziu *et al*[22], although ALT values increased after discontinuation of GS-9450 and in some patients exceeded baseline levels, they did not reach three times the initial values. Therefore, GS-9450 might be safer than pan-caspase inhibitors but this has to be further evaluated in larger studies. It has been suggested that the risk of ALT overshoot might be reduced by the gradual instead of sudden removal of the caspase inhibitor but this remains to be evaluated in future studies[30]. On the other hand, the relapse of ALT levels after discontinuation of GS-9450 treatment suggests that long-term treatment will be necessary[22], limiting the clinical significance of ALT overshoot.

In addition to these safety concerns, there are some limitations regarding the evaluation of the efficacy of GS-9450 in the study by Ratziu *et al*[22]. In this study, the change in serum ALT and CK-18 fragment levels was used to assess the efficacy of GS-9450[22]. It is well established that both ALT and CK-18 fragment levels correlate with NAFLD severity[1,10,15,33]. However, more than 60% of patients with NAFLD have normal ALT levels, implying that normal ALT levels do not exclude the presence of the disease[1,4,33,34]. Moreover, the reduction in serum ALT levels correlates with the improvement in liver steatosis and inflammation but not fibrosis[1,35]. On the other hand, liver biopsy is the gold standard for the diagnosis, staging, monitoring and evaluation of drug response in NAFLD[1,3]. Given the short follow-up (4 wk), a second liver biopsy was not performed in the study by Ratziu *et al*[22]. Therefore, long-term studies that will evaluate the effects of GS-9450 on liver histology are needed before reaching definite conclusions on the efficacy of this agent.

In conclusion, despite its limitations, the pilot study by Ratziu *et al*[22] provides additional evidence that the inhibition of apoptosis might have a role in the management of NAFLD. Therefore, the efficacy and safety of this approach merits further evaluation in larger and longer-term studies. On the other hand, given that NAFLD has a multifactorial pathogenesis, a combination of agents targeting the multiple implicated mechanisms, including increased apoptosis, should be another focus of future studies. Finally, on the grounds of the strong genetic impact on NAFLD development and progression[36,37], investigating related genes and polymorphisms might allow the identification of patients who are at higher risk for progression of NAFLD and/or who might experience greater benefits from the different therapeutic approaches.

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World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
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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*

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Supported by The Research Grant from Padma Inc., Switzerland, to Vennos C
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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).

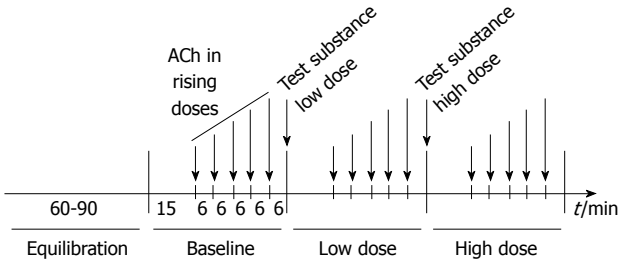

Figure 1 Experimental protocol. ACh: Acetylcholine.

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-

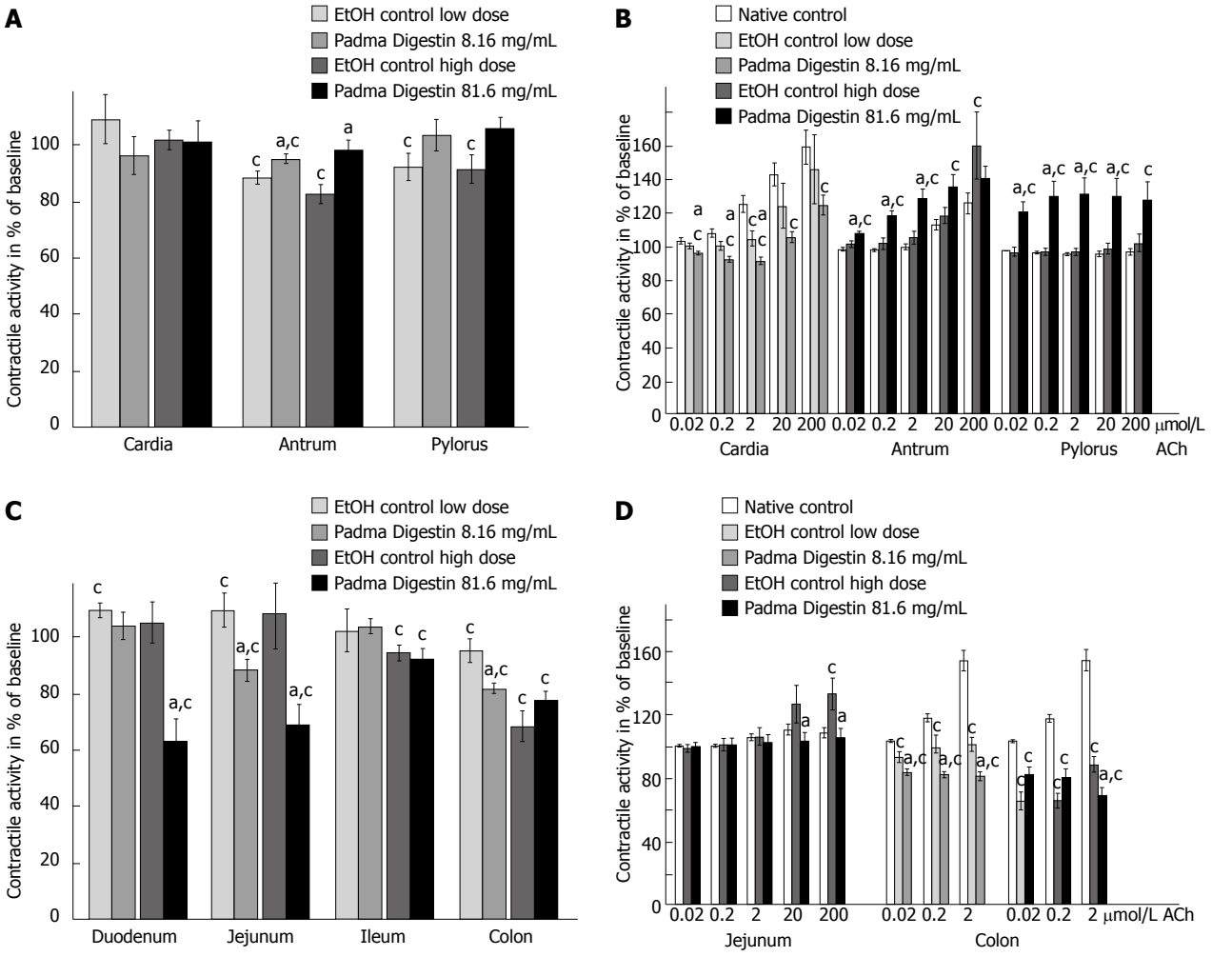

Figure 2 Effect of the Padma Digestin extract. A: Spontaneous contractility of gastric smooth muscle strips; B: Contractility of stomach smooth muscle strips stimulated by acetylcholine; C: Spontaneous contractility of intestinal smooth muscle strips; D: Contractility of intestinal smooth muscle strips 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.

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

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World Journal of Gastrointestinal Pharmacology and Therapeutics

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Volume with supplement

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Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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