Neuroendocrinology Letters Volume 39 No. 1 2018
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Supplementation of Caricol®-Gastro reduces chronic gastritis disease associated pain

Friedrich-Anton Weiser [1], Michael Fangl [2], Wilhelm Mosgoeller [3]

1 Gruppenpraxis Medico Chirurgicum, Anton-Baumgartner-Straße 44, 1230 Wien, Austria
2 Endozent - Ordination für Innere Medizin, Speisingerstrasse 57-61 / 4 / 67, 1130 Wien, Austria
3 Inst. of Cancer Research, Clinic Internal Medicine-I, Med Univ. Vienna, 1090 Wien, Austria

Correspondence to: Wilhelm Mosgoeller, MD.
Inst. of Cancer Research
CIM-I, Borschkegasse 8a, 1090 Wien, Austria.
TEL: +43 664 28 48 324 ; E-MAIL: wilhelm.mosgoeller@meduniwien.ac.at

Submitted: 2017-01-08 Accepted: 2017-01-22 Published online: 2018-03-28

Key words: **papaya; oats; nutritional supplement; inflammation; randomized placebo controlled prospective clinical study; gastritis; abdominal pain; symptom relieve**

Neuroendocrinol Lett 2018; **39**(1):19–25 **PMID:** 29604620 NEL390118A02

Abstract

OBJECTIVE: Papaya and oats are natural food and used in traditional medicine in many parts of the world. Papaya has a high content of enzymes supporting digestive function. Oats are a source of minerals, beta-glucan fibres, immunmodulatory and antiinflammatory probiotic substances. Caricol®-Gastro combines both constituents, it was designed as vegan organic preparation for intestinal inflammatory diseases. We performed a randomized, double blind placebo controlled clinical trial to investigate the potential of Caricol®-Gastro as add on therapy in patients with diagnosed chronic gastritis.

METHODS: 60 Patients with endoscopically confirmed mild chronic disease were recruited. A structured interview documented the baseline data. Then the patients were allocated to the verum or placebo group by handing out a numbered study package with the study substance for the daily intake at home. A single dose was 20 g, taken twice per day. After 30 days the participants were interviewed again.

RESULTS: After the intake phase the disease related symptoms were found improved in both groups, indicating a strong placebo effect. However, the pain load reduction in the Caricol®-Gastro group was significantly larger (p=0.048).

DISCUSSION: Due to the inherent biological activities of ingredients of papaya and of oats and their known effects (anti-inflammatory, epithelial integrity), the observed beneficial effects may be owed to the constituents synergisms to reduce chronic inflammation. We conclude, that the regular intake is a safe add on therapeutic option for patients with chronic gastritis to support standard medical care.

INTRODUCTION

Gastritis

Gastritis is an inflammatory disease of the stomach mucosa, which occur in two major forms. Acute gastritis may arise as response to exaggerated stress, nikotin or alcohol intoxication, then the symptoms occur timely close to the stressor or environmental trigger. Typical symptoms are pain, nausea, loss of appetite, reflux-oesophagits , feeling of bad taste in mouth, etc.

In contrast, patients with chronic gastritis develop their symptoms more gradually, typically over months. Characteristically the patients are over 50 years old. Among the elderly it is estimated that every second person has at least a mild form of chromic gastritis and symptoms like bloating, nausea, pressure, pain in the upper abdomen, diarrhea, dislike of specific foods. Chronic gastritis is associated with atrophic changes in the mucosa, sometomes associated with a helicobacter pylori triggered inflammation. While acute forms appear dramatic, it is typical for the chronic form to show only few inflammatory signs. A leading symptom is pain in the upper abdomen. The preliminary diagnoses is based on the patient`s history and physical examination, the final diagnosis is confirmed by gastroscopy and biopsy. Therefore, the increasing incidence in the last years of gastritis has been paralleled by an increase in upper endoscopic examinations.

In case of an infectious aetiology (e.g. helicobacter pylori) the therapy is straight forward, specific antibiotic therapies eradicate the germs. The therapy of non infectious chronic gastritis remains a challenge. For the pain symptoms nonsteroidal antiinflammatory drugs are commonly used, however a side-effect of this drug family is damage of the gastro duodenal mucosa (Graham & Smith 1988). Newer generations of the nonsteroidal antiinflammatory drugs are not safer than the old ones, as far as gastrointestinal side-effects are concerned. Therefore these drugs should be avoided when analgesia is the main treatment goal. Graham & Smith (1988) recommend that – if these drugs are applied – to use the lowest possible dose. Alternative strategies and approaches especially in pain-dominated forms of chronic gastritis are desired.

The substance of investigation in this clinical study was designed as supplementary medication for patients with chronic gastritis. Caricol®-Gastro is a combination of natural ingrediencies like papaya pulp and an oats preparation. Both, papaya and oats are used in the traditional medicine in various cultures.

Papaya, a traditional rememdy

Papaya is a tropical fruit with an abundance of bioactive enzymes like papain, chymopapain, lysozyme, in the shell, the seed, and the pulp (Brocklehurst *et al.* 1985). The enzyme activity in the juice was already described in 1878 (cited in (Witmann 1878)). In the meat industry papaya enzymes are used as softeners. Epidemiological studies describe that regular papaya consumption has a beneficial nutritive effect due to its anti-oxidative capacity and enzyme activity (Lohsoonthorn & Danvivat 1995; Pandey & Shukla 2002). The vitamin C content can be above that of oranges. In addition to antioxidants, the papaya contains β-carotene and bioflavonoids in high concentration, as well as minerals such as potassium, magnesium and calcium.

The structure of papain has long been known (Drenth *et al.* 1968). The enzymes chymopapain and papaya proteinase III were defined biochemically in the 1980s (Zucker *et al.* 1985; Jacquet *et al.* 1989). In addition to the known cysteine proteinases (papain, chymopapain, caricain) and glycyl endopeptidase, papaya is a rich source of other enzymes (El Moussaoui *et al.* 2001). In the 1980s, proteinase omega (Dubois *et al.* 1988) and papaya proteinase IV (Ritonja *et al.* 1989) were biochemically characterized. More recently, the potential of Caricapapaya lipase as an acylating agent (Dominguez de Maria *et al.* 2006; Abdelkafi *et al.* 2011) has become the focus of systematic research. This plant lipase proved to be a promising biocatalyst for the dissolution of alcohols and carboxylic acids (Miyazawa *et al.* 2008). Only in 2009, a so-called GDSL motif Carboxylesterhydrolase from papaya latex was isolated and biochemically characterized (Abdelkafi *et al.* 2009). It is expected that various other bioactive substances are found in the papaya fruit to explain nutritive effects and effects on male and female hormone production (Gopalakrishnan & Rajasekharasetty 1978).

A short incubation of only 5 minutes with 10 microgram per milliliter papain liberates proteins from the inner surface of the rat gastrointestinal mucosa (Forstner 1971). Enzymes of the human intestinal epithelium on the brush border membrane are resistant to trypsin and chymotrypsin, but can be solubilized by papain. Most of the enzymes dissolved by papain retain their activity and support intestinal digestion (Maestracci 1976). In patients with gastrointestinal disease papaya is known to interfere with reactive oxygen species (Osato *et al.* 1993). Papaya latex and cristallin papain (3.2 mg/kg) reduces the histamin triggered secretion of gastric acid (Cho & Han 1984).

In view of above-mentioned clinical observations in small studies, Caricol® was studied in a double-blind, placebo-controlled, clinical trial in over 100 "healthy" volunteers with IBS symptoms. The test dose was 20 ml daily for 40 days. Endpoints included the frequency of symptoms "constipation," "painful bowel movements," "flatulence," and "heartburn" (Muss *et al.* 2013).

Oats (AVENA SATIVA L.)

Avena Sativa L. is known for the high content of fatty acids, vitamins, minerals and fibers and mucous promoting and therefore epithelium protecting substances. A plethora of clinical studies described the positive influence on serum cholesterol, glucose metabolism, and general gastrointestinal function (Rasane *et al.* 2015).

Oats provide valuable fatty acids, vitamins, minerals and fiber, healing mucilage and have a positive effect on cholesterol, blood sugar and intestinal health.

Nutritive ingredients of oats are:

- Ca. 7% fat with a favorable ratio of monounsaturated oleic acids to polyunsaturated linoleic acids
- Omega-6 fatty acids
- Protein content 12–20%
- avenanthramides – effective polyphenols with anti-oxidative and anti-inflammatory action (histamine receptor blocker, reduction of secretion of pro-inflammatory cytokines IL-6 and IL-8)
- Proteoglycan – protective mucus for mucosas
- Polyphenols: anti-inflammatory anti-oxidants, support wound healing, re-epithelialization, and skin barrier funtion
- High content of B vitamins (important for metabolic processes) and Vit E (radical scavenger, strengthens the immune system, anti-inflammatory)
- Calcium, iron, manganese, copper and zinc
- β-glucan, and
- Saponin

If oats is heated the insoluble fibers together with xylan and araban produce a mucous mass which protects the inner lining of the gastrointestinal tract. Many oat fibers function as probiotic substance and contribute to the lowering of the blood cholesterol (Othman *et al.* 2011; Ho *et al.* 2016), the fiber content also reduces the sharp increase of blood sugar after a meal and therefore reduces the risk for insuline resistancy and hunger attacks (Tan *et al.* 2017). Epidemiological studies suggest that regular oat intake reduces the risk to develop a gastro-intestinal cancer.

Beta-glucans contained in the oats bind free bile acids in the intestine, which has a positive effect on the blood cholesterol level (Othman *et al.* 2011). The water-soluble beta-glucans are also very swellable and form a viscous mass with water (McRorie & Chey 2016), to delay the passage of the stomach and food components such as sugar are digested and absorbed more slowly. After an oat meal, the blood sugar rises slowly, which has a positive effect on the insulin secretion (Tan *et al.* 2017). Food cravings are mitigated.

Summing up, Caricol®-Gastro was designed to support the medical therapy of gastrointestinal diseases like gastritis. Based on our knowledge on the ingredients and what we know about the pathology of gastritis the anti-inflammatory, anti-oxidative, and mucosa-protective properties of the study substance may contribute to the amelioration of gastritis symptoms. More specifically it may reduce stomache pain and pain in the gastro-intestinal region by stabilizing the inner lining and regeneration support of the epithelial cells in the the gastric mucosa.

In patients with chronical gastritis inflammation associated pain is a leading symptom, therefore we focussed on pain parameters as primary endpoints for this study.

MATERIAL AND METHODS

We realised a prospective randomized placebo controlled clinical trial in patients with verified chronic gastritis, and documented the gastritis associated pain and symptom load before and after the regular intake of the study substances.

Study Center

The study protocol was according to international standards for clinical research. We performed no specific invasive interventions, therefore no ethical committee was involved.

The two study centers were a physicians' office, specialized in the treatment of gastrointestinal diseases. Patients with an endoscopically verified diagnosis of chronic gastritis were invited to participate. The verification of the diagnosis by gastroscopy and biopsy was not part of the study, it was an inclusion criterium. The study was not advertised in any media, all invited patients were patients of the investigators since long.

The study substance

The verum substance was Caricol®-Gastro, it consists of (weight %) organic papaya pulp 39.44%, organic wholemeal outs flour 6.25%, organic apple juice concentrate 10.5%, natural aroma 0.08%, water 43.73%. It is free of genetically modified organisms, and free of preservatives and dyes. It contains no added sugar, modified starch, lactose, and soy products. The packaging was carried out in Vienna in accordance with current EC regulations for the manufacture and packaging of foodstuffs.

The controll substanze contained (weight %): water 81.25%; tri-sodiumcitrat; Resistamyl 310 0.85%; Palsgard 5304 0.20%; Sugar 5%; pulpiz 7.24%; Lemmon juice concentrate 1.3%; Caramell light 1.32%; Caramell dark 0.24%; Colour; aroma (Plum, Mango).

Both substances (placebo and verum) were provided by the study sponsor, the placebo was matched in colour and consistency, and was packed in servings with identical look, compared to the verum substance. One serving contained 20 g, the participants were advised to take two servings per day, before a main meal, i.e. lunch or supper.

Patients

Patients at the study center were informed about the opportunity to participate in the study through a notice in the wating area. Patients who expressed their interest and matched the inclusion criteria, were handed out the detailed study information and informed consent form.

The Inclusion criteria were:

- Diagnosis confirmed by gastroscopy and biopsy
- Exclusion of ulcer and cancer
- Negative Breath test for Campylobacter
- Age between 18–75 years old
- Complaints since longer than 3 months

The exclusion criteria focussed on serious illnesses, of which the course and medical treatment could interfere with the study results. More specifically, we excluded patients with:

- Colon cancer
- Known papaya allergy
- Blood in the stool
- Known gluten intolerance
- Patients with severe fructose intolerance
- Patients already taking Caricol® (in the last 4 weeks)
- Radiation / chemotherapy (in the last 3 months)
- Patients with Type I diabetes or severe metabolic disorder

The eligible patients signed the informed consent form, then received a structured interview by a senior gastroenterologist to document the baseline parameters. The documentation was kept at the investigators office for the next interview. The recruited and fully documented patients left the study center with a study package and a date for the exit visit. The package contained 60 servings of the study substance (placebo or verum) and detailed information about the study, and the intake and documentation rules for the next 30 days.

Study roll out

Randomization. Neither the participant nor any investigators' team member knew, which of the study packages contain the verum or placebo substance. The randomization between the two goups (verum, placebo) was carried out with the study planning software Randlist V 1.2 (Datinf, Tübingen, Germany). To fulfill the criterium "double blind", the prepared and sealed study packages were number coded and then brought to the study centre for distribution to the recruited patients.
Participation. The intake of the study substance at the participants home was integrated in the participants routine life. To improve the participants' compliance they were actively contacted via telephone at least once during the 30 day intake phase. In addition, a study hotline for questions of any kind was installed.
Measured parameters and Endpoints. We documented 11 endpoints related to the quality of life and possible gastritis associated symptoms. Primary endpoints were pain sensations, like stomache pain, pain in the upper abdomen, and the subjective severity of the pains. A pragmatic endpoint was the the impact of the disease related symptoms on every day life. These main endpoints were embedded in the questionnaire to document:

- Sudden strong stomach ache
- Pain in the upper abdomen
- Pain related to food intake
- Nausea
- Vomiting
- Bloating
- Furred tongue
- Halitosis
- Cravings for food
- Impact on daily routine.
- Severity of the pain

Data processing and statistics

After the patients returned and provided the relevant data in a second interview, the recorded pre- and post intake data were transferred to an electronic spreadsheet (Microsoft Excel). The data transfer was done twice, then the first entry was subtracted from the second entry. The subtraction results was „0" if both entries were identical. Deviations from zero indicated a wrong entry which were corrected according to the original source document. The controlled and verified data were subjected to statistical analysis using descriptive and non-parametric tests. The respective statistical test is indicated in the respective result section.

Because different scales were used in collecting the frequency parameters (e.g. epigastric pain, scores from 1 to 4) and pain intensity, scores from 1 to 10), the pain intensity scores were divided by 2.5 to normalize the data to the scale size of the other parameters.

Because our patients presented with an individual mix of pain related parameters we analysed typical combinations of pain site and pain intensity. When harmonic means for a bifactorial ANCOVA way were not given, we used the bifaktorial rank-variance analysis (Kubinger 1986; Conover 1999; Bortz *et al.* 2008) to investigate the combined effect of pain site, intensity scores, and impact on everyday life of our patients with chronic gastritis.

RESULTS AND DISCUSSION

Participants

We recruited 60 patients diagnosed with mild chronic gastritis. The recruited patients were randomly allocated to the verum or control group. Table 1 provides an overview on the gender distribution in the recruited patients.

35 patients received a package with the verum substance, of these 6 patients dropped out (2 for unknown reason, 4 claimed to have sensed no effect and therefore

Tab. 1. Gender of recruited participants.

Recruited with verified diagnosis "Gastritis"	N= 60, (25 Placebo, 35 Verum)
Male	22
Female	38

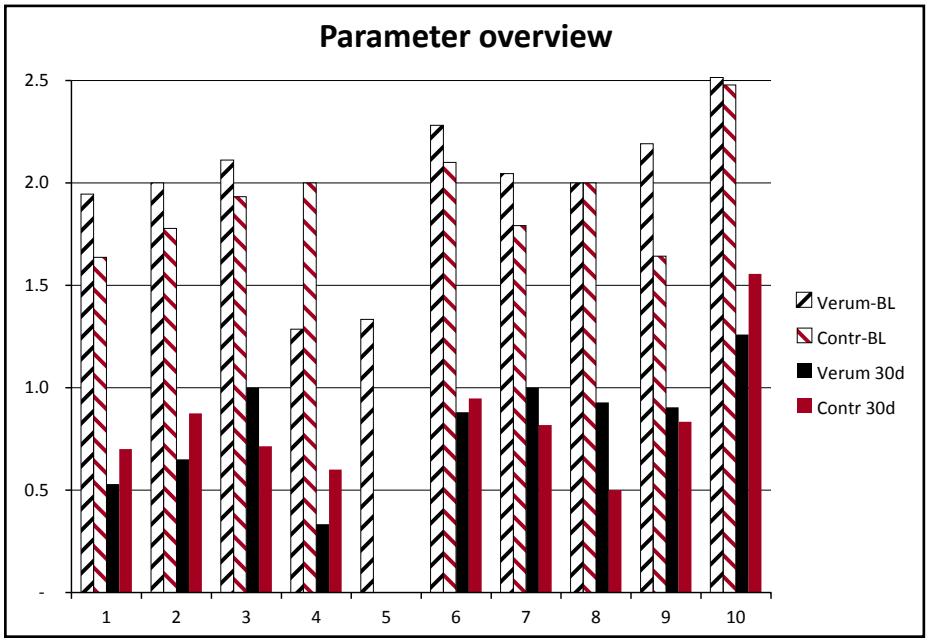

Fig. 1. Overview of Symptom change after 30 days intake; bars with stripes "before intake" (baseline data, BL); full bars: "after intake" Control). Syptoms are: 1) Sudden stomach ache; 2) Pain in the upper abdomen; 3) Pain associated with food intake; 4) Nausea; 5) Vomiting; 6) Bloating; 7) Furred tongue; 8) Halitosis; 9) Craving for food; 10) Impact on daily routine. The respective number of participants that provided the symptom is given in Table 2. Note that in both groups all parameters were reduced after the intake phase, which indicates a strong placebo effect. However, for the acute stomach ache (Symptom 1), or Symptom 2 "pain in upper abdomen", and 10) "impact on daily routine"), the verum intake lead to notably better improvements, than placebo.

terminated their participation early), 29 patients in the verum group completed their participation according to protocol. Twenty five patients were allocated to the control group, of these 3 patients dropped out preterm, 22 patients completed the study according to protocol.

A few patients tried to reduce their anti-acidic treatment during the intake phase, but went back to the original medication regime. The number was too small to further evaluate this issue. None of the participants reported sideffects of the medication, not during the exit visit at the study center, and not during the telephone contacts.

In our cohorts with mild chronic gastrits, the patients reported their individual symptom mix, many individual symptoms scored "0". Because a not existing symptom cannot possibly be improved and therefore their inclusion in the analysis would skew the outcome and bias the analysis of positively reported complaints, the symptoms with "0" scores in the baseline data were removed from the data set before the statistical analyses. All patients data indicating positive symptoms at baseline and completion of the full term from 51 patients were included into the statistical analysis.

Overview on all Symptoms

When comparing the means before and after the intake phase, all endpoints in both groups (verum and placebo) revealed a remarkable improvement. Figure 1 provides an overview of the changes of the positvely report symptoms under treatment.

Table 2 gives the detailed symptom frequency data before and after intake.

Gastritis pain intensity and impact on everyday life

Among the symptoms, which after Verum intake, revealed more benefits than the placebo effect was the "acute stomache pain" (Symptom 1 in Figure 1) and "pain frequency in the upper abdomen" (Symptom 2 in Figure 1). Because pain is the lead symptom of patients suffering from chronic gastritis, we analyzed the overall impact of pain in our patients. Figure 2, shows the changes in overall pain intensity and impact on the daily routine. Again, there was a considerable placebo effect, however, in both categories the patients reported a larger benefit in the Verum group. By means of the Mann Whitney U-test, at baseline the groups were comparable (pain severity – p=0.644; impacted daily routine – p=0.993). After the intake phase we observed

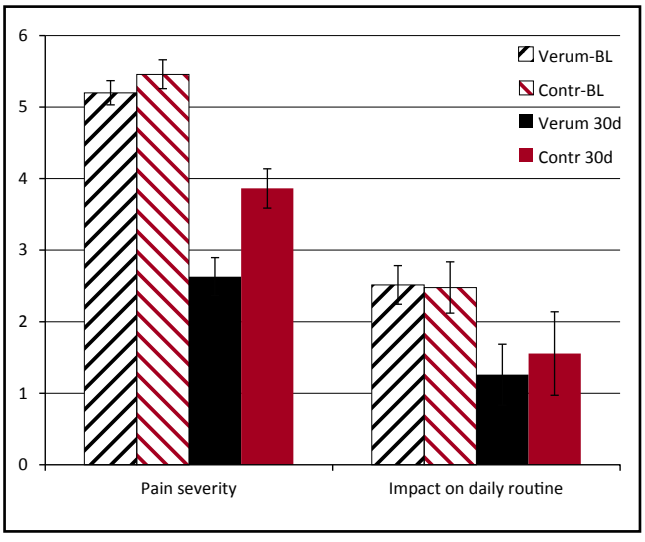

Fig. 2. Average severity of pain (original scale from 1 to 10) and average frequency of a disrupted daily routine (scale 1 to 4) at baseline (BL) and after the intake phase (30d), in the verum and control group. While the two groups were similar at baseline, after the intake phase the patients in the verum group improved beyond the placebo effect in both categories.

Tab. 2. Symptom frequency at baseline and after the intake phase. As most patients contributed only few symptoms to the study, and because we removed those scoring "0", the count of analysable symptom scores varies between the respective symptoms.
At baseline the two groups revealed similar means. No pair of means revealed significant group differences according to the Mann Whitney-U test (MWU). This implies that the randomization created two fairly comparable groups. After the intake phase most means of pain related symptom scores were lower in the Verum group indicating a benefit on the pain load attributable to the Verum-intake. However, at the level of single symptom frequencies, no significant differences were observed.

			1	2	3	4	5	6	7	8	9	10
			acute gastric pain	Epigastric pain	Pain w. food intake	Nausea	Vomiting	Bloating	tongue	halitosis	Craving	Impacton routine
Baseline	Control	Mean	1.64	1.78	1.93	2.00		2.10	1.79	2.00	1.64	2.48
		N	11	18	15	6		20	12	5	14	23
		SEM	0.19	0.17	0.27	0.47		0.17	0.22	0.49	0.24	0.20
	Verum	Mean	1.94	2.00	2.11	1.29	1.33	2.28	2.05	2.00	2.19	2.51
		N	18	23	18	14	3	32	22	14	21	35
		SEM	0.21	0.20	0.22	0.21	0.27	0.19	0.25	0.29	0.20	0.17
Control / Verum		MWU *p*=	0.431	0.593	0.481	0.104	0.687	0.747	0.960	0.061	0.644	0.993
After intake	Control	Mean	0.70	0.88	0.71	0.60		0.95	0.82	0.50	0.83	1.56
		N	10	16	14	5		19	11	4	12	18
		SEM	0.32	0.26	0.26	0.36		0.20	0.22	0.25	0.33	0.27
	Verum	Mean	0.53	0.65	1.00	0.33		0.88	1.00	0.93	0.90	1.26
		N	17	20	15	12		25	21	14	21	27
		SEM	0.25	0.20	0.31	0.14		0.24	0.26	0.28	0.23	0.26
Control / Verum		MWU *p*=	0.568	0.463	0.613	0.616		1.000	0.566	0.731	0.122	0.309

more benefits in the verum group compared to placebo. Again, considering an individual parameter only, the difference between Placebo and Verum were not statistically significant (pain severity, p=0.122; impacted daily routine, p=0.309).

In view of the individual symptom pattern of our participants, we analyzed effect combinations by bifactorial rank-variance analysis (Kubinger 1986) and jointly considered "pain intensity" and the parameter "impact on daily routine". At baseline the two groups (verum, placebo) were comparable (H=0.654, df=1: p=0.418834), after the intake phase we observed a clear trend towards superiority of the verum over placebo (H=3.525, df=1: p=0.060).

Analysis of pain load and impact

For our patients with chronic gastritis recurrent and epigastric pain is more typical (Ammann 1984). Thus, the combined analyis of epigastric pain frequency and pain severity fairly reflect the disease related pain load in our patients. At baseline the non parametric bifactorial rank-variance analysis revealed the paramter-combination between the groups (verum, placebo) as similar (H=0.164, p=0.685), indicating a fair randomisation and group building. After the intake phase there was a clear trend towards beneficial effect of Caricol®-Gastro above the placebo effect (H=2.700, df=1, p=0.100). When including the "frequency of acute pain" into the test for pain load, at baseline the groups were fairly comparable (H=0.187, p=0.666), and after the intake the benefit in the verum group was significant (H=3.903, p=0.048), indicating an overall positive effect, which may be beneficial for patients with inflammation ruled alterations in the intestinal tract.

CONCLUSIONS

Our study showes that the pain load associated with chronic gastritis may be reduced by a regular intake of Caricol®-Gastro within 1 month.

The inherent biological activities of the ingredients of papaya and of oats and their known effects (anti-inflammatory, epithelial integrity), warrant to test Caricol®-Gastro in other diseases with underlying chronic inflammation.

Because Caricol®-Gastro has no known or expectable side effects, the regular intake is a safe therapeutic option for patients with chronic gastritis to support standard medical treatment.

REFERENCES

1 Abdelkafi S, Ogata H, Barouh N, Fouquet B, Lebrun R, Pina M, Scheirlinckx F, Villeneuve P, *et al.* (2009). Identification and biochemical characterization of a GDSL-motif carboxylester hydrolase from Carica papaya latex. Biochim Biophys Acta **1791**: 1048–1056.

2 Abdelkafi S, Barouh N, Fouquet B, Fendri I, Pina M, Scheirlinckx F, Villeneuve P, Carriere F (2011). Carica papaya lipase: a naturally immobilized enzyme with interesting biochemical properties. Plant Foods Hum Nutr **66**: 34–40.

3 Ammann R (1984) Schmerzen im Bereich des Abdomens p. 1–56. in Differentialdiagnose Innnerer Krankheiten, Ed. Siegenthaler W. Stuttgart, New York, Georg Thieme Verlag

4 Bortz J, Lienert GA, Boehnke K (2008). Analyse von Rangdaten p. in Verteilungsfreie Methoden in der Biostatistik, Ed. Boehnke K. Heidelberg, Springer Medizin Verlag.

5 Brocklehurst K, Salih E, Mckee R, Smith H (1985). Fresh non-fruit latex of Carica papaya contains papain, multiple forms of chymopapain A and papaya proteinase omega. Biochem J **228**: 525–527.

6 Cho CH, Han PW (1984). Papain reduces gastric acid secretion induced by histamine and other secretagogues in anesthetized rats. Proc Natl Sci Counc Repub China B **8**: 177–181.

7 Conover WJ (1999) Practical nonparamtreic statistics. New York: Wiley & sons.

8 Dominguez De Maria P, Sinisterra JV, Tsai SW, Alcantara AR (2006). Carica papaya lipase (CPL): an emerging and versatile biocatalyst. Biotechnol Adv **24**: 493–499.

9 Drenth J, Jansonius JN, Koekoek R, Swen HM, Wolthers BG (1968). Structure of papain. Nature **218**: 929–932.

10 Dubois T, Kleinschmidt T, Schnek AG, Looze Y, Braunitzer G (1988). The thiol proteinases from the latex of Carica papaya L. II. The primary structure of proteinase omega. Biol Chem Hoppe Seyler **369**: 741–754.

11 El Moussaoui A, Nijs M, Paul C, Wintjens R, Vincentelli J, Azarkan M, Looze Y (2001). Revisiting the enzymes stored in the laticifers of Carica papaya in the context of their possible participation in the plant defence mechanism. Cell Mol Life Sci **58**: 556–570.

12 Forstner GG (1971). Release of intestinal surface-membrane glycoproteins associated with enzyme activity by brief digestion with papain. Biochem J **121**: 781–789.

13 Gopalakrishnan M, Rajasekharasetty MR (1978). Effect of papaya (Carica papaya linn) on pregnancy and estrous cycle in albino rats of Wistar strain. Indian J Physiol Pharmacol **22**: 66–70.

14 Graham DY, Smith JL (1988). Gastroduodenal complications of chronic NSAID therapy. Am J Gastroenterol **83**: 1081–1084.

15 Ho HV, Sievenpiper JL, Zurbau A, Blanco Mejia S, Jovanovski E, Au-Yeung F, Jenkins AL, Vuksan V (2016). The effect of oat beta-glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: a systematic review and meta-analysis of randomised-controlled trials. Br J Nutr **116**: 1369–1382.

16 Jacquet A, Kleinschmidt T, Schnek AG, Looze Y, Braunitzer G (1989). The thiol proteinases from the latex of Carica papaya L. III. The primary structure of chymopapain. Biol Chem Hoppe Seyler **370**: 425–434.

17 Kubinger K (1986). A Note on Non-Parametric Tests for the Interaction in Two-Way Layouts. Biometrical Journal **28**: 67–72.

18 Lohsoonthorn P, Danvivat D (1995). Colorectal cancer risk factors: a case-control study in Bangkok. Asia Pac J Public Health **8**: 118–122.

19 Maestracci D (1976). Enzymic solubilization of the human intestinal brush border membrane enzymes. Biochim Biophys Acta **433**: 469–481.

20 Mcrorie JW, Chey WD (2016). Fermented Fiber Supplements Are No Better Than Placebo for a Laxative Effect. Dig Dis Sci **61**: 3140–3146.

21 Miyazawa T, Houhashi M, Inoue Y, Murashima T, Yamada T (2008). Resolution of secondary alcohols via Carica papaya lipase-catalyzed enantioselective acylation. Biotechnol Lett **30**: 1783–1787.

22 Muss C, Mosgoeller W, Endler T (2013). Papaya preparation (Caricol(R)) in digestive disorders. Neuro Endocrinol Lett **34**: 38–46.

23 Osato JA, Santiago LA, Remo GM, Cuadra MS, Mori A (1993). Antimicrobial and antioxidant activities of unripe papaya. Life Sci **53**: 1383–1389.

24 Othman RA, Moghadasian MH, Jones PJ (2011). Cholesterol-lowering effects of oat beta-glucan. Nutr Rev **69**: 299–309.

25 Pandey M, Shukla VK (2002). Diet and gallbladder cancer: a case-control study. Eur J Cancer Prev **11**: 365–368.

26 Rasane P, Jha A, Sabikhi L, Kumar A, Unnikrishnan VS (2015). Nutritional advantages of oats and opportunities for its processing as value added foods – a review. J Food Sci Technol **52**: 662–675.

27 Ritonja A, Buttle DJ, Rawlings ND, Turk V, Barrett AJ (1989). Papaya proteinase IV amino acid sequence. FEBS Lett **258**: 109–112.

28 Tan SY, Siow PC, Peh E, Henry CJ (2017). Influence of rice, pea and oat proteins in attenuating glycemic response of sugar-sweetened beverages. Eur J Nutr

29 Witmann H (1878). The fermentative action of the juice of the fruit of Carica papaya Pharm. J. Trans **9**: 449.

30 Zucker S, Buttle DJ, Nicklin MJ, Barrett AJ (1985). The proteolytic activities of chymopapain, papain, and papaya proteinase III. Biochim Biophys Acta **828**: 196–204.