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Papaya preparation (Caricol®) in digestive disorders

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Abstract

Papaya (*Carica papaya* L.) is used as a natural remedy in abnormal digestion in tropical and industrialized countries. Besides this wide distribution little evidence has been produced with reference to its physiological effect in humans and the proof of efficacy. Former clinical observations had revealed positive effects for patients with constipation, heartburn, and symptoms of irritable bowel syndrome (IBS) after eating papaya preparations. In line with these former positive clinical observations, we studied the clinical effects of the papaya preparation Caricol® in a double blind placebo controlled study design.

In this study the participants were volunteers, with chronic (prevailing) indigestions and dysfunctions in the gastrointestinal tract. During the trial the intake of the substance of intent and placebo was 20 ml daily for 40 days. The endpoints were the frequency of 22 symptoms recorded before and after the documented intake recorded by questionnaire. The symptoms "Constipation", "Bloating", and "Heartburn" were defined as primary and frequency of „painful (straining) bowel movements" as secondary endpo-

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int. The participation ended after the intake period within two days ("early returnees"). Wash out effects were observed in "late returnees", who returned with a delay of 8.6 (±5.95 days). In the verum group early returnees revealed statistically significant improvements of the symptoms "constipation" and "bloating". The analysis of "heartburn" felt short of significant improvement because of the small number of included cases with this criteria (N=13, p=0.114). None of the significant benefits were observed after the washout phase. We conclude from these results, that the papaya preparation (Caricol®) contributes to the maintenance of digestive tract physiology. It ameliorates various functional disturbances, like symptoms of IBS. The mechanism of this digestive tract physiology support is discussed.

INTRODUCTION

Mild dysfunctions of the digestive system are very common among young people and adults. Ingredients of the papaya fruit (*Carica papaya L.*) and the processed fruit have been associated with beneficial impact on digestion or diseases (Aruoma *et al.* 2010; Marotta *et al.* 2011; Forstner 1971; Ghoti *et al.* 2011; Somanah *et al.* 2012; Scolapio *et al.*1999). The fruit is considered a traditional remedy for gastrointestinal functional disorders in countries with papaya plants. Caricol® is a preparation from organically cultivated papaya. Clinical observations revealed positive effects on symptoms of irritable bowel syndrome in patients with constipation, loose stools, and heartburn. This clinical study aimed to test the treatment efficiency in functional digestive tract disorders under randomized controlled conditions.

Papaya contains an abundance of bioactive substances in the peel, seeds, and fruit pulp (Brocklehurst *et al.* 1985). The richness of enzymes in papaya juice has been known since 1878 (Witmann 1878). In Papaya-producing countries the fruit is used as the drug for the treatment of parasitosis (Stepek *et al.* 2007) and infected skin lesions (Starley *et al.* 1999). Osato *et al.* investigated the antimicrobial and antioxidant capacity and found a bacteriostatic effect against various enteropathogens, such as Bacillus subtilis, Enterobacter Cloacae, Escherichia coli, Salmonella typhi, Staphylococcus aureus, Proteus vulgaris, Pseudomonas aeruginosa and Klebsiella pneumonia (Osato *et al.* 1993). Thereby a modulating effect on the physiological gut flora can be anticipated as an possible effect of the substance. The ingredients of papaya react with oxygen free radicals in gastrointestinal diseases, implying an antioxidant mechanism.

The most important enzyme – papain – was characterized in 1968 (Drenth *et al.* 1968). The enzymes chymopapain and papaya protease III were characterized in the 80s of the last century (Zucker *et al.* 1985; Jacquet *et al.* 1989). In addition to the known proteases, papaya contains lipases (Dominguez *et al.* 2006) and a number of not yet identified other enzymes (El Moussaoui *et al.* 2001).

In animals the local application of papaya latex and papain reduced histamine mediated gastric acid secretion (Cho & Han 1984). A five-minute digestion with papain (10mg/ml) triggers the release of intestinal surface membrane glycoproteins in the intestinal mucosa (Forstner 1971). The membrane-bound enzymes on the mucosal surface are resistant to trypsin and chymotrypsin, but can be released by papain exposure. The majority of the released enzymes is functional, thus the main function the enzmes is to increase the efficiency of the body's own digestive enzymes.

In view of these former results from traditional and medical experience and from open label studies, we performed a placebo-controlled randomized double-blind study with Caricol® to evaluate effects of this substance on symptoms in the digestive tract.

MATERIALS AND METHODS

The study substance (Caricol®) was a preparation from papaya manufactured based on an ethno-traditional recipe. The production resulted in an approximately 30-percent weight reduction, and increased the papain activity by 3.75-fold (report from the Institute of Food and Environmental LEFO Arensburg research, findings from May 21, 2004).

A placebo was used as control substance matching the test substance in taste, smell, texture, color and appearance. No ingredients with known digestive effects were used (Table 1). The study protocol was developed according to the guidelines for GCP (Good Clinical Practice) by a research-consulting firm (SCIgenia, Vienna, Austria, www.scigenia.com).

The study was performed as a prospective, placebo-controlled, double-blind randomized study notified to the ethics committee and focusing on functional digestive disturbances. Assessments were recorded before and after the ingestion of active treatment with the test substance Caricol® and "placebo" in the cohort. Volunteering participants were recruited by after advertisement. An interview with a medical doctor preselected suitability for participation

Table 1. Placebo production (ingredients).

Ingredients	Gramm
Water	229.33
Lemon juice	1.00
Modified starch	4.18
Xanthan	1.20
Sugar	14.00
Aroma Papaya	
Aroma Lemmon	0.02
Aroma mixture	0.11
Color	0.16
Total of Additives	20.67
Total Mixture	250.00

according to in- and exclusion criteria (Table 2 and 3). Participants received a medical laboratory blood test (cholesterol, CRP – C-Reactive Protein, blood count, etc.) as incentive to participate and to exclude any preexisting severe disease. These standardized tests were performed prior to the inclusion of the participants at the Endler Medical Laboratories, Vienna. From 160 volunteers 139 participants were selected according to the predefined in- and exclusion criteria.

Data were recorded by a modified questionnaire based on ROME III criteria (Table 4; 15 of 22 questionnaire items). Items were categorized as rarely-never (Score: 0), sometimes (1), often (2), most of the time (3), always (4). Statistical analysis was based on score differences before and after the consumption of the test substance.

Three functional disturbances were defined primary endpoints:
- Constipation
- Flatulence
- Heartburn

Because a reduction of constipation is typically associated with a reduction of perceived pain during bowel movements we defined the frequency reduction of "painful bowel movement" as secondary endpoint.

Prior to the actual study we selected the optimal dose in a pilot investigation in five arms, with different doses and papaya preparations. Here the

Table 2. Inclusion criteria for the participants.

	Symptoms
1	Age between 18 to 75 years
2	Complaints since more than 6 months
3	Recurrent abdominal pains or discomfort
4	Improvement of symptoms "after"
5	straining, imperative urge to defecate
6	Feeling of incomplete emptying
7	Mucous stool
8	Bloating
9	Too hard stool
10	Too soft stools
11	Heartburn

Participants were recruited if criteria 1, 2, and two additional criteria (3-11) applied.

Table 3. Exclusion criteria for the participants.

1	Acute Diarrhea in the last four weeks
2	Regular use of laxatives
3	Use of Probiotics in the last 4 weeks
4	Fever in the last four weeks
5	Antibiotics in the last four weeks
6	Colon carcinoma or other tumor
7	Radiation, Chemotherapy in the last three months
8	Chronic inflammatory bowel disease (Colitis Ulcerosa, Morbus Crohn)
9	Acute oral cortisone intake
10	Type 1 diabetes, other severe metabolic disease
11	Chronic liver or kidney disease
12	Known allergy to papaya
13	Known severe fructose intolerance
14	Caricol® consumption in last four weeks
15	Narcotic drugs, alcohol abuse
16	Participation in any other medical trial

Volunteers were excluded if one of the above items (Table 3) applied.

single original dose of 20 ml Caricol® indicated therapeutic efficacy. A higher Caricol® dose and raw papaya puree discontinued from further investigation.

This report is on two arms:
Daily, single dose only (20 ml) active test supplement (Caricol®)

Table 4. Questionnaire items (self reporting).

Item Nr.	Rome III module	Question
1	FAP5, CM1, IBS1	How often did you have discomfort or pain anywhere in your abdomen?
2	---	Pain cramps?
3	FAP8	How often did the pain limit or restrict your daily activities?
4	IBS5	Did you have more frequent bowel movements?
5	IBS6	Did you have less frequent bowel movements?
6	IBS8, CM8	Did you have hard stools?
7	IBS10, CM10	Did you have lumpy stools?
8	IBS7/9, FBD16	When this discomfort or pain started, were your stools (bowel movements) looser?
9	FBD16/CM17, IBS10	Did you have loose, mushy or watery stools?
10	CM9	Did you have fewer than three bowel movements (0-2) a week?
11	CM11, FBD11	Did you strain during bowel movements?
12	FBD19	Did you have bloating or distension?
13	CM12, FBD12	Did you have a feeling of incomplete emptying after bowel movements?
14	IBS4	Did this discomfort or pain get better or stop after you had a bowel movement?
15	FBD21	Did you feel uncomfortably full after a regular-sized meal?
16	------	Nausea
17	------	Stomachache
18	FAP2	Heartburn
19	------	Mucous stools
20	------	Loss of appetite
21	------	Feeling hungry
22	------	Bad taste

FAP5 Rome-III, Functional abdominal pain module, question 5
CM1 Rome-III, Constipation module, question 1
IBS1 Rome-III, Irritable bowel syndrome, question 1
FBD16 Rome-III, Functional bowel disorder, question 16
------ Additional question contributed by the principal investigator

Daily single dose (20 ml) placebo supplement.

Both test substances (placebo, verum) were packed undistinguishable; to conform to a double blinded protocol. The double blinded randomization was done with Rancode V. 3.6 (IDV-Data Analysis and Design of Experiments, Kreiling, Germany).

The following study documents were employed:

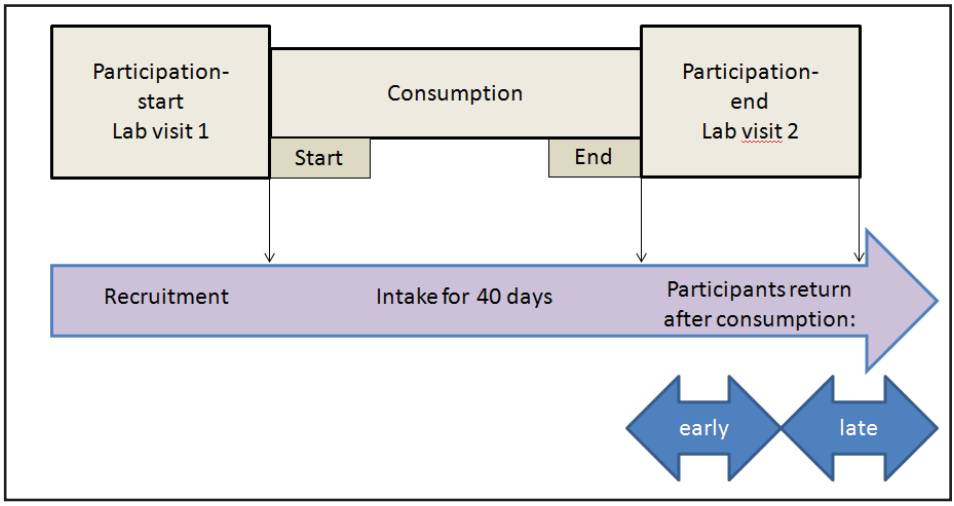

Figure 1. Scheme of participation for each volunteer: After recruitment the participation started in the study centre with a health check and the first evaluation, followed by a 40 day consumption period. Participants were divided into groups of "early" (within two days) or "late" (after 3 days and longer) returnees according revisiting the lab after the test period.

- Information and invitation to participate for medical practices and medical laboratories
- Inclusion checklist (Table 2), exclusion checklist (Table 3),
- informed consent form
- Questionnaire with 22 specific items (Table 4)
- Badge for the documentation of the daily intake
- Monitor log for documentation of contacts with the participants during the intake phase

In total 139 participants were recruited and divided evenly between all arms of the study. 126 participants completed their participation according to the protocol; they returned the "questionnaire before" and "questionnaire after" (return rate 90.65%).

The allocation of the participants to the study group placebo (N=42) and verum (N=42) was balanced. There were 4 drop outs in each group.

Figure 1 illustrates the sequence of events for each participant. Successfully recruited participants were referred to the study center for a medical check. The investigational data were obtained by self-assessment on the symptoms via questionnaire (Table 4). Included participants were allocated to one of the study groups at random, and then received the appropriate substance (active

treatment, or placebo) for 40 days. The compliance was monitored according to GCP by SCIgenia.

After the test period the same self-assessment was performed again to obtain the data on the items "after". Depending on the time the participants returned after the 40 day ingestion period the participants were stratified in "early" and "late" returnees. "Early" returnees appeared in the study center within two days (mean: 0.1 ± 1.62 days) after the end of the consumption period, late returnees completed their participation between three to sixteen days (8.6 ± 5.95) after the consumption period.

Documents were collected in the I-GAP study center, controlled for completeness by SCIgenia, and questionnaire scores were transferred to an electronic database. Not reported items were left blank in the database. To minimize transfer errors we applied the so called double entry method. After the data transfer was completed, the database entries from two different teams were subtracted. A checksum different from 0 indicated a typing error, which was re-checked against the original documents and corrected. The subtraction of the two corresponding scores "before" and "after" consumption revealed the variables for the statistical analyses after the electronic file was closed. We included those variables, where the symptoms were present at the initial examination in varying degrees. At participation start typical symptom frequencies were "sometimes 1", "2-often" or "3-mostly." The highest frequency score 4 (always) was given in 7.3% of the cases only.

The subtraction resulted in the variables for descriptive and analytical statistical analysis. A positive difference indicated that the symptom frequency decreased during the ingestion phase. A negative variable indicated that the symptom frequency "increased" during the ingestions phase.

In order to detect possible washout effects after regular consumption, data from "early" and "late" returnees were analyzed separately.

The statistical analysis was performed using the computer program SPSS V. 17. In each group (verum, placebo), the variables indicating a benefit (symptom reduction) were counted and compared to the number of variables indicating no benefit (frequencies unchanged or increased). The counts to indicate benefits and no benefits per study arm (verum, placebo) were compared by means of the Mann-Whitney U test. The significance level for the difference between active treatment and placebo was set at $p<0.05$.

Because in various investigations it was described that papaya ameliorates ulcer or reduces gastric acid production, we determined the content of histamine and histamine receptor binding capacity. Caricol® was extracted in 20% (w/w) ethanol in a ratio from drug to solvent of 1:1. After sonication for five minutes the extraction mix was steered at room temperature for one hour on a magnetic stirrer. The insoluble fraction was removed by centrifugation (3 500 × g, five minutes). The supernatant was aliquoted and stored at 4 °C.

For Histamine detection the supernatant was subjected to HPLTC analysis (High Performance Thin Layer Chromatography). The reference substances were histamine base and (L)- histidin. The supernatant and the reference substances were loaded on silica gel F254 (Merck, Germany). The mobile phase was CHCL3/methanol/NH3aq 2/2/1 (V/V). The derivatisation was 300 mg ninhydrin reagent in 100 ml Buthanol. Then the plate was dried for 1 min at 100 °C. The plates were inspected visually.

In addition to the determination of histamine the competing binding and nonspecific binding of Caricol® to Histamine H1 receptors was investigated using ^{3}H-Pyrilamine and the filtration method.

RESULTS

The reduction of symptoms of the "early returnees" for both (verum vs. placebo) is listed under Table 5. Items 1 through 4 revealed no significant difference between placebo and active treatment. Considering constipation (Questionnaire item # 5) 82% of evaluable participants in the verum group benefited from regular use. In the placebo group, the proportion was significantly lower (p<0.031). Considering item # 11 (painful, strenuous bowel movements) 93% of participants in the verum group had a benefit from regular Caricol® intake (Figure 2). Compared to placebo the benefit was statistically significant (p=0.016).

Considering item #12 (flatulence), in the Caricol® group 78% of the participants had a benefit, the difference from the placebo group was significant (p=0.017, Table 5).

Considering item #18 (heartburn) 85% of only 13 evaluable participants improved after regular Caricol-intake, compared with 55% from 11 participants in the placebo group. In this small sample size, statistical analysis revealed no significant result, but showed a trend towards superiority of Caricol® (p=0.114).

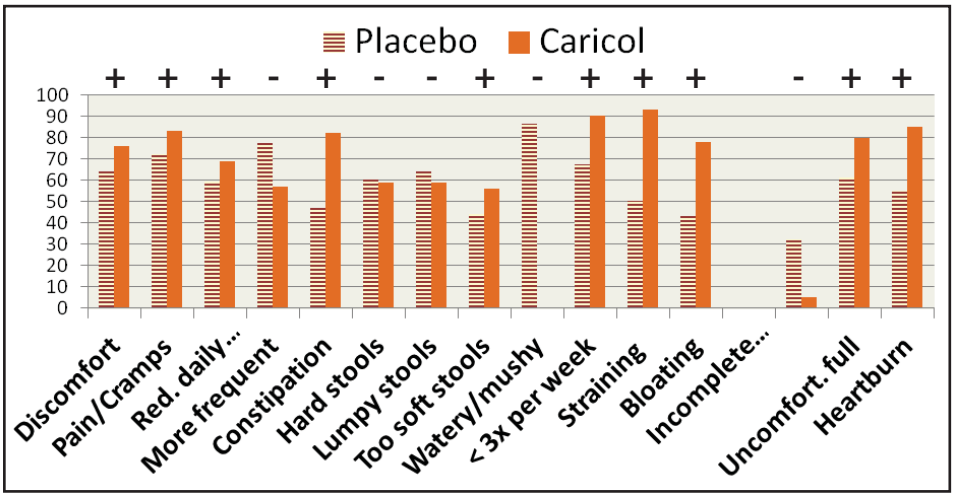

Figure 2. Comparison of the results between placebo and Caricol®; the majority of Rome-III items - indicated by "+" revealed more benefit in the Caricol® group than in the placebo group. Note that the symptom "Watery/mushy stool" was not present in the carcol group) In the Caricol® group "constipation" was found ameliorated in over 80% of the cases. Because amelioration of constipation leads to the increase of less severe symptoms, we conclude that the amelioration of hard and lumpy stool was compensated by a participant shift towards these symptoms caused by the reduction of constipation. This conclusion is further supported by the observation, that over 90% reported the benefit of reduced "straing" during bowel movements.

In the comparison between the groups of those participants who returned several days after the end of the ingestion phase the effect vanished (Table 6). A weak trend showed beneficial effects. More persons in the active treatment group had benefits compared to the placebo group.

The HPLTC chromatogram of the test samples did not detect any Histamine, while the reference substances were detected according to expectations. In the Caricol® sample neither histamine nor a histidine band could be observed in the plates (data not shown).

The extract preparation inhibited the binding of the ligand to histamine H1 receptor in a dose dependent manner with an IC 50 of 840 µg/ml. The confidence interval ranges from 371 µg/ml to 1897 µg/ml.

DISCUSSION

Our data proved beneficial clinical effects of the test substance (Caricol®) under double-blind, placebo-controlled, randomized conditions. This trial was performed with participants without particular illnesses; therefore we

Table 5. Symptom reduction in early returnees.

Symptom	Placebo		Verum		More improv.	Placebo vs. Caricol®	Remarks
	N	% reduction	N	% reduction	P/V		
01	22	64	17	76	V	0.395	n.s.
02	18	72	12	83	V	0.488	n.s.
03	17	59	13	69	V	0.564	n.s.
04	13	77	7	57	P	0.370	n.s.
05	19	47	17	82	V	0.031	significantly more participants improved with the papaya preparation Caricol® than placebo
06	20	60	17	59	P	0.943	n.s.
07	14	64	17	59	P	0.760	n.s.
08	18	44	18	56	V	0.623	n.s.
09	7	86	2	00	P	0.033	Statistically significant by chance (Type 1 error) no reliable Data, because placebo: N=7, Caricol®: N=2
10	9	67	10	90	V	0.225	n.s.
11	12	50	14	93	V	0.016	significantly more participants improved with the papaya preparation Caricol® than placebo
12	23	43	23	78	V	0.017	significantly more participants improved with the papaya preparation Caricol® than placebo
13	20	00	19	00	=	1.000	n.s.
14	22	32	19	05	V	0.035	significantly more participants improved with the papaya preparation than placebo Note that this symptom's frequency increased
15	18	61	20	80	V	0.206	n.s.
16	12	83	13	62	P	0.235	n.s.
17	18	61	17	82	V	0.171	n.s.
18	11	55	13	85	V	0.114	Improvement, not stat. sign.
19	8	100	7	43	P	0.016	Statistically significant but no reliable Data, because placebo: N=8, Caricol®: N=7
20	8	75	11	64	P	0.609	n.s.
21	19	58	18	83	V	0.095	Trend: towards specific effect of Caricol®
22	13	77	10	80	V	0.862	n.s.

Comparison of Placebo versus Caricol® by means of Mann-Whitney U test, (two sided) Note that in early returnees, the majority of parameters reveled a stronger effect of Caricol. This was statistically significant for the symptoms 5 (constipation), 11 (Painful bowel movement), 12 (bloating).

Table 6. Symptom reduction late returnees.

Symptom	Placebo		Verum		More improvement P / V	MWU-Test Placebo vs. Caricol®
	N	%	N	%		
01	12	83	12	50	P	0.090
02	5	40	8	88	V	0.083
03	9	56	8	75	V	0.417
04	6	83	6	83	=	1.000
05	8	88	9	67	P	0.327
06	8	75	11	82	V	0.726
07	7	71	11	82	V	0.615
08	11	36	13	54	V	0.402
09	3	67	7	86	V	0.513
10	5	60	6	83	V	0.409
11	7	86	10	50	P	0.141
12	13	77	13	69	P	0.665
13	11	00	11	00	=	1.000
14	12	50	12	42	V	0.688
15	11	73	13	69	P	0.854
16	4	50	6	100	V	0.066
17	11	82	7	100	V	0.245
18	5	40	7	71	V	0.297
19	4	75	5	80	V	0.866
20	1	00	4	25	V	0.617
21	12	50	10	70	V	0.353
22	4	50	6	100	V	0.066

Comparison of Placebo versus Caricol® by means of Mann-Whitney U test, (two sided) Note that in late returnees (after the washout phase), there were trends towards a beneficial effect of Caricol, however no variables remained statistically significant.

could not anticipate any strong clinical effects. Yet this study design was appropriate enough to observe the clinical benefit of regular consumption of the papaya preparation Caricol® to reduce symptomatic dysfunctions of the intestinal tract. The highest benefit among our participants was related to symptoms such as abdominal pain and dyscomfort, constipation, painful (straining) bowel movements, heartburn.

Significant benefits beyond the placebo effect and the active treatment group was found for the symptoms 5 (constipation) and 11 (painful defecation) (Table 5, Figure 2). Because quite frequently people who suffer from constipation experience bowel movements as painful, the significant reduction of this

symptom confirms the significant improvement of constipation. This is in concordance with other observations on benefits from papaya enzyme preparations in patients with chronic pancreatitis (Isaksson & Ihse 1983).

Among the early returnees regular Carcol® intake improved "flatulence" significantly (beyond the observed placebo effect). It is known that papain supports the physiological digestion via enzymatic activity. Because it can ameliorate symptoms associated with maldigestion (Cho & Han 1984), (Forstner 1971), the high papain content of Caricol® can contribute to the observed reduction of this beneficial effect on flatulence.

Chen *et al.* investigated the effects of papaya on ulcer and histamine induced acid secretion in rats. The authors compared the efficacy of papaya latex treatment with the intravenous application of papain and concluded that papain is the active principle to exert the ulcer-protective effect (Chen *et al.* 1981). These results were confirmed only 3 years later. Cho and Han stimulated the gastric acid secretion in rats and fed papain. After a single dose they observed a significant reduction of gastric acid secretion for 48 hours. Because intraperitoneal papain injection had no effect, this underlines the mechanism of papain as local acting bioactive enzyme to convey the reported gastric acid reduction (Cho & Han 1984). The antiulcer activity of papaya was also observed in mice (Ezike *et al.* 2009).

A positive, however, not significant tendency was shown in our trial also concerning the improvement of heartburn. In the active treatment group the benefit was evident, however because of the small number of participants (Table 5) the difference between benefits in the active treatment group and placebo failed to reach statistical significance (p= 0,114). Heartburn may be – among other reasons – attributed to gastric acidity which in turn can be triggered by factors such as histamine and other paracrine stimuli (Schubert 2011).

We searched for histamine and histidine as possible Caricol® ingredient, no detectable amounts were found, but Caricol® bound to, and therefore blocked the histamine H1 receptors. In view of the observed clinical improvement of the symptom heartburn (Table 5) we postulate that the histamine mediated gastric acid production is reduced by a Caricol® ingredient.

This agrees with Cho and Han, who demonstrated that papain reduces gastric acid secretion induced by histamine in animal trials (Cho & Han 1984). Our observation that regular intake of Caricol® reduces heartburn in humans maybe plausibly explained by the papaya ingredients.

Papaya is known to convey anti-acid and anti ulcer effects. Chen *et al.* investigated the effects of papaya on ulcer and histamine induced acid secretion in rats. The authors compared the efficacy of papaya latex treatment with the intravenous application of papain and concluded that papain is the active principle to exert the ulcer-protective effect (Chen *et al.* 1981). These results were confirmed only 3 years later. Cho and Han stimulated the gastric acid secretion in rats and fed papain. After a single dose they observed a significant reduction of gastric acid secretion for 48 hours. The effect weaned within 96 hours. Because intraperitoneal papain injection had no effect, this underlines the mechanism of papain as local acting bioactive enzyme to convey the reported gastric acid reduction (Cho & Han 1984). The antiulcer activity of papaya was also observed in mice (Ezike *et al.* 2009).

Others had shown the beneficial effect of papaya preparations by contributing to an antioxidative support (Aruoma *et al.* 2010; Ghoti *et al.* 2011). As described earlier some symptoms related to Irritable Bowel syndrome may occur because of silent inflammation in the gut (Muss 2005). This assumption is further corroborated by the observation of an inflammatory histamine secretion in the gut (Raithel *et al.* 1999). Under the hypothesis of an antioxidant and antiinflamtory impact of papain (Aruoma *et al.* 2010; Marotta *et al.* 2011) the abundance of phytochemicals in papaya may also mediate an antioxidative effect of Caricol® in the digestive system.

To our surprise in the active treatment group 83% of the participants reported a reduction of "hunger", compared to only 58% in the placebo group (Table 5). This beneficiary effect felt just short of the level of significance (p=0.095) in a small study group.

In Table 5, the symptoms number 9 and 19 revealed a pseudo-significant difference between placebo and active treatment. For both items the symptom frequency at participation start was too low (Table 5) to allow comprehensible conclusions. Therefore we consider the computed significance a possible statistical type one error (false positive finding).

The few drop outs resulted in a low attrition rate under 10%, therefore the results are representative for the study population. Our study may be of particular interest to gastroenterologists, because our investigational endpoints were taken from the Rome III consensus criteria which are under consistent review by the American Society of Gastroenterology (http://www.gastro.org). The majority of questionnaire items (fifteen out of the 22) were taken from

the Rom-III standard diagnostic modules and applied in a change-sensitive context.

The health status of participants was checked for appropriate inclusion and exclusion criteria with additional confirmation via a blood test.

Caricol® contains a plethora of bioactive ingredients. To test for a possible washout of beneficial bioactice substances, we divided the participants into two groups according to the time between last consumption and return for the second and final evaluation. The stratification was between "early" and "late" returnees. In contrast to our early returnees, the group of late returnees' didn´t show any significant improvement of tested items. We therefore conclude that the observed positive effects of our test substance Caricol® are substance mediated. The benefits vanished after some washout time, as expected from a neutraceutical preparation. The finding that none of the positive effects seen in the early returnees was observed also in the late returnees, underlines, that the proposed pharmaceutical effect is conveyed by Caricol® ingredients. In agreement to the observation by Cho and Han (1984) – the papain mediated effects disappeared after about three days – we observed no significant differences between placebo and active treatment after the washout time (Table 6).

Our data underlines the efficiency of clinical investigations in a study setting, which, according to the European Food Safety Authority (EFSA) is pivotal for health claims associated with food for healthy persons. To arrange for a study population representative for the general population, a high number of volunteers had to be recruited because only few participants under observation suffered from the specific symptom. On account of our study design many participants did not report the presence of every specific symptom in the list with 22 items. This contributed to the fact that many (non prevalent) items didn´t reveal any change. To exclude any bias by asymptomatic participants, we focused on the analysis on those cases with prevailing symptoms at the participation start, and could successfully demonstrate beneficial effects for common symptoms

SUMMARY

In this study we tested the efficiency of the papaya preparation Caricol® for the treatment of different intestinal dysfunctions (e.g. ROME III criteria, Irritable bowel syndrome). Our data proved beneficial clinical effects of the test substance under double-blind, placebo-controlled, randomized condi-

tions. The finding that regular intake of Caricol® significantly contributes to the amelioration of constipation was confirmed by the observed reduction of painful bowel movements.

We could not detect histamine and histidine, but we detected that a Caricol® ingredient bound to histamine H1 receptors. In view of the clinical improvement of the symptom "heartburn" we conclude that a Caricol® ingredient reduced the gastric acid production via Histamine H1 receptor blocking.

Because all significant symptoms disappeared in the late returnees this underlines that a nutraceutical effect (ingredient mediated) may be responsible for the observed benefits. The significant reduction of "bloating" and "flatulence" can be explained by the high papain content, which supports physiological digestion and reduces symptoms associated with maldigestion.

Summing up, the randomized placebo controlled double blinded study confirmed earlier reports on beneficial effects of the papaya preparation Caricol® in humans.

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