Zeitschrift für
Phytotherapie

2024
Volume 45
Page 54–60

Sonderdruck

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ISSN 0722-348X

Thieme

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Results of a Prospective Online Survey on Effects of Self-treatment

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Keywords
Gastrointestinal symptoms, dyspepsia, IBS, grapefruit, online-survey, herbal

Bibliography
Zeitschrift für Phytotherapie 2024; 45: 54–60
DOI 10.1055/a-2194-2206
ISSN 0722-348X

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ABSTRACT

In this explorative longitudinal survey, self-reported data was collected from persons suffering from chronic gastrointestinal symptoms, who were seeking relief employing self-medication with a grapefruit seed extract (GKE). This is not a clinical trial nor a non-interventional study, but an explorative longitudinal survey with self-reports. The data was collected online and there were no personal contacts with a physician or a study nurse. Participants followed their own decision to use GKE and to provide their data to a data retrieval system, following informed consent according to existing national regulations on data protection. The test product was provided by the sponsor to make sure that the correct product was used for the intended observation period.

Drop in criteria were chronic gastrointestinal symptoms, including those of functional dyspepsia (FD, resp. non-ulcer dyspepsia NUD) and/or irritable bowel syndrome (IBS) for more than 4 weeks, resulting in a score of an expanded Nepean Index ('total gastrointestinal score') higher than 20. Symptoms were documented 4–12 days (VA) prior to GKE use on day 1 and then on day 1, days 28, 42 and 56 of continuous oral use. New symptoms, predominating symptoms, stool habits, amount of oral intake and global status was retrieved every day during the observation period. On day 56 some global assessments were additionally recorded.

The evaluation cohort was intended to be at least 100, and within the survey cohort we were able to evaluate 100 subjects (15 m and 85 f). Total gastrointestinal symptom score decreased from a mean (± SD) of 78.7 ± 36.9 points by 26.4 % on day 14, by 53.1 % on day 28, by 58.7 % on day 42, and by 49.9 % on day 56, when compared to day 1. Upper gastrointestinal symptoms like heartburn improved better compared to lower GI symptoms (by 57.9 % versus 47.3 % on day 56). Overall complaints were rated as "very strongly improved" by 30 %, "strongly improved" by 42 %, "somewhat improved" or "unchanged" by 20 % and as "deteriorated" by 1 %. GKE was tolerated well. Minor adverse events reported were judged as most probably unrelated by the authors. More than half of the participants rated the intake as "very pleasant" or "pleasant" and intended to continue GKE beyond the observation period.

In this prospective uncontrolled survey, GKE seemed to improve GI-symptoms, based on users reports. These results need to be confirmed in controlled clinical trials proofing efficacy and tolerance of GKE in functional GI-diseases. Data collected from participants without any personal contact bear a high risk of bias. Evaluation of self-treatment as presented here is clearly restricted to marketed products and may report interesting details of self-treatment outside prescription settings.

Introduction

The broad spectrum of gastrointestinal symptoms such as pain, heartburn, nausea, emesis, abdominal distension, flatulence, and diarrhea may be related to various etiologies, ranging from acute infections to chronic dysfunctions, as well as functional gastrointestinal disorders (FGID) or food intolerances.

Roughly 30 % of the general population in western societies suffer from chronic gastrointestinal symptoms. Many patients with functional dyspepsia (FD) or IBS seek relief by using herbal remedies, including self-treatments of their own choice.

In clinical settings, after exclusion of organic disorders like GERD, gastritis, and others employing standard work-up including endoscopy, such chronic symptoms may be differentiated into non-ulcer dyspepsia (NUD) [1] or irritable bowel syndrome (IBS), when meeting the criteria of functional gastrointestinal disorders established by the Rome Foundation. Comorbidities with other disorders and overlap between the major functional gastrointestinal disorders are frequent [2, 3]. Therefore, the exact attribution in daily practice may be challenging due to variability and overlap of symptoms [4]. Symptoms of functional gastrointestinal diseases include acid-related symptoms due to gastro-duodenitis and/ or gastroesophageal reflux disease (GERD). Pathophysiological concepts of acid-related diseases include malfunction of motility in the upper and lower gastrointestinal (GI) tract. The overlap of malfunctions of upper and lower GI tract and the broad range of symptoms may explain why PPIs do not provide full symptom resolution in numerous patients diagnosed with GERD [5]. PPIs may also cause or deteriorate certain gastrointestinal symptoms, especially when ending the treatment [6]. In primary care in Germany the most frequent prescribed drugs for the treatment of FD symptoms are herbal medicinal products (88.2 %) [7].

Herbal remedies exert a broad spectrum of pharmacological actions (multi-target approach) combined with proven good tolerability [8]. Some herbal compounds exert prokinetic or anti-inflammatory actions; volatile essential oils like peppermint oil [9] or caraway oil have strong carminative effects due to defoaming and spasmolytic activities [10]. Other herbal compounds seem to influence the microbiome by antibacterial and antifungal effects. Combinations of herbal compounds were shown to act synergistically [11].

The antibacterial effect of grapefruit kernels was discovered by an observation that these kernels would not rot in compost. Later it was shown that grapefruit kernel extract (GKE) extract exerts antibacterial [12, 13] – including *Helicobacter pylori* [14] – and antifungal [15] effects. GKE contains high amounts of flavonoids, e. g., hesperidin, naringin, rutin and quercetin [16]. Since certain pesticides accumulate in the seeds, it is important to use materials of controlled organic quality [17]. GKE claims to improve cardiovascular health, metabolic syndrome, immune functions, as well as to prevent infections. There are encouraging experiences with GKE in the treatment of GI symptoms such as heartburn, acute and chronic dyspeptic symptoms, as well as acute and chronic diarrhea. GI microbiome plays a central role in various GI malfunctions and syndromes, but there are still plenty unknowns.

In naturopathic settings, therapies are often used as self-treatment without any involvement of a physician. Therefore, a conventional clinical trial may not meet real life conditions and may not necessarily be the first step in discovering potential beneficial effects on patients' symptoms. Studies without meeting patients in person, have been performed successfully and are labelled as "study by correspondence" [18, 19]. A special designed platform for performing studies in persons or patients was developed by the startup company Clinical Evidence Evaluations (Clinev2.de) with special emphasis on stringent data protection of the participants.

Our prospective survey was intended to collect data by internet on people with chronic gastroenterological symptoms who intended a self-treatment with GKE and were willing to report their symptoms during a defined period of time.

Methods

Study design

This evaluation is a longitudinal prospective cohort survey in persons suffering from chronic gastrointestinal symptoms, who intend a self-treatment with a GKE. Persons reported their answers on a daily basis using an online platform with an electronic case report form. Formally, this is a survey and not a clinical trial, since there is no clinical setting, and participants had no contact to a physician. Under these conditions, German regulations do not require an ethic vote.

A short information about data pull was to be read on the internet page of the tested product and more detailed information was provided on the internet pages of the online research organization.

Participants decided on the self-treatment and the participation on data retrieval on their own. After they had given informed consent about their data protection, pre-study data was retrieved. Those participants, who seemed real persons and met the drop in criteria received GKE for a eight-week self-treatment period. Participants physical addresses were never linked to other personal data in the evaluation system and addresses were deleted after shipment of GKE.

Participants

We included adult male and female persons (18 to 75 y) planning to perform self-treatment of their gastrointestinal symptoms with GKE and willing to be honest participants of the survey. Drop in criteria were gastrointestinal symptoms for more than 4 weeks which were defined as symptoms resulting in a total gastrointestinal symptom score (see below) above 20. We did not include subjects who reported diagnoses or conditions, which may interfere with gastrointestinal functions, which suggest an unclear clinical situation, acute symptoms, or alarm signs of any acute disease. Those applicants got a recline and a recommendation to seek advice from a physician. We also excluded persons from analysis reporting recent or intended changes in any concomitant drug use which could have an impact on gastrointestinal functions or symptoms.

Intervention – Test product

The tested grapefruit seed extract (CitroBiotic®) is a food supplement (NEM) provided as a fluid extract of grapefruit seeds and peels. Only organic grown grapefruits from Southern Europe are used in the production process. Secondary plant compounds, mainly bioflavonoids, are extracted in a multistage process employing glycerol. Depending on the grapefruit batch used, the extract contains a total flavonoid concentration of 4,000–5,000 µg/ml. HPLC analyses show a broad spectrum of flavonoids, the lead substance is naringin. Vitamin C concentration is at least 30 mg/ml, and the pH value ranges from 2.6 and 2.9. The recommended daily intake is 15 drops t.i.d. After opting in, the test product (2 bottles, each 100 ml) was sent to participants free of charge.

Evaluation Parameters

Primary outcome was the change in total gastrointestinal symptom score on day 56 compared to baseline. Total gastrointestinal symptom score is the sum of a well-established, validated upper abdominal symptom score and an established lower abdominal symptom score [20–22]. The upper abdominal score (part I of the validated Nepean Dyspepsia Index developed by Talley et al. [23, 24] comprised 15 questions related to symptoms of the upper abdomen (typical for NUD). Each symptom was evaluated by intensity (0–5), frequency (0–4), and impact on quality of life (0–4) during the previous two weeks and was then summed up. The 15 symptoms related to upper abdomen were: pain, discomfort, burning, heartburn, cramps, pain in chest region, early satiety, acid upcoming, postprandial fullness, tension, bloating, nausea, belching, vomiting and bad breath. In addition, participants were asked 10 questions related to symptoms of the lower abdomen, typical for IBS: pain in the colonic region, spasms, spasms before, during or after defecation, anal pain, diarrhea, obstipation, lower abdominal tension and bloating in lower abdomen, using the same evaluation scoring as for the upper evaluation. This not-validated part is not influencing the validated upper GI score. Scores were calculated separately as sum of symptoms for upper and lower gastrointestinal scores. Total scores of < 20 was found in persons not meeting criteria for gastrointestinal malfunction, while patients with diagnoses of functional gastrointestinal diseases like non-ulcer-dyspepsia or irritable bowel syndrome typically report total scores between 50 and 100 [20–22]. A relative improvement of at least 30 % was considered clinically relevant based on the established use of the combined upper and lower GI score [20–22].

The total gastrointestinal score was documented prior to inclusion (VA) and again on day 1 prior to the first intake and following intake on days 14, 28, 42 and 56.

On daily basis participants documented: new symptoms, predominant symptom and its severity, intake (dosage), stool habits, changes in lifestyle and global mental/psychological status. For safety aspects, we checked the new symptoms reported each day for UEs in all persons with reports after intake.

At the end of the survey period the participants were asked additional questions on their global assessments of efficacy, usability, and tolerability of GKE. The participants were also asked about their intention on further treatment with GKE.

Statistical Analysis

The course of total gastrointestinal symptom score (expanded Nepean Dyspepsia Index) was analyzed as primary outcome: changes at day 56 were compared to baseline. There were two baseline data retrievals of extended total gastrointestinal score, before and after shipment of test-product named VA and day 1. Participants showing inconsistence in their answers and those with extreme changes pre and after run-in were excluded from analysis, comparable to the procedure for placebo-responses in clinical studies using a placebo run-in phase.

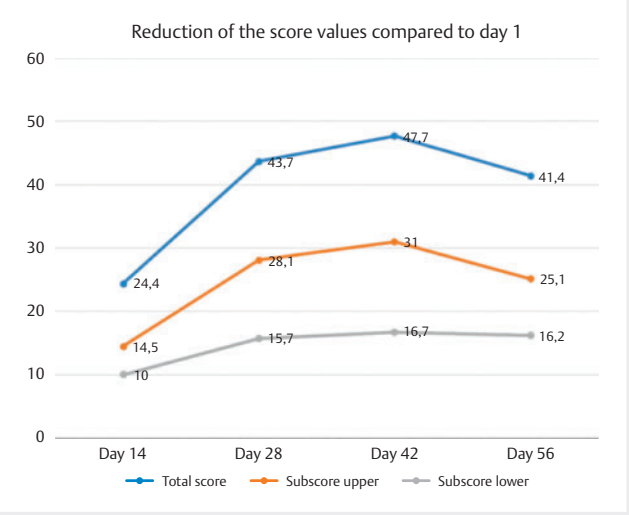
The original outline intended to take the mean of VA and day 1 as a combined baseline. When we realized that after exclusion of extreme run-in-responders there was still a clear improvement of symptoms between VA and day1 evaluation outcome, we used a conservative approach, using the day 1 values as baseline. All data were evaluated in a descriptive manner.

Subscales for upper abdominal and lower abdominal symptoms were compared to discriminate differential effects on symptoms related to upper or lower gastrointestinal tract.

▶ **Table 1** Means ± SD of absolute scores at the upper lines and means of individual relative changes compared to day 1 below.

	Day 1*	Day 14	Day 28	Day 42	Day 56**
Total score	78.7 ± 36.9	54.2 ± 32.7	35.0 ± 26.6	31.6 ± 24.6	37.6 ± 30.0
Subscore upper	44.8 ± 24.4	30.3 ± 21.3	16.7 ± 14.7	13.8 ± 13.6	19.9 ± 17.3
Subscore lower	33.9 ± 19.9	23.9 ± 17.2	18.3 ± 14.5	17.5 ± 14.6	17.8 ± 15.7
Relative decrease to day 1					
Total score	%	26.4 ± 40.8	53.1 ± 31.3	58.7 ± 29.3	49.9 ± 36.2
Subscore upper	%	25.2 ± 47.8	60.9 ± 34.6	68.0 ± 28.9	57.9 ± 38.7
Subscore lower	%	29.9 ± 43.2	43.9 ± 39.7	47.3 ± 46.7	47.3 ± 50.2

*First day of intake; **Last day of intake



▶ **Fig. 1** Absolute improvements of total score (= sum of subscores for upper GI-tract and lower GI-tract): Reductions of mean scores = differences compared to day 1 during treatment for 56 consecutive days of self-treatment with GKE.

New daily symptoms, predominating symptoms, stool habits, amount of oral intake and global were listed or evaluated. New symptoms were listed as possible UEs, then assessed by the authors for relation to the test product.

Final global assessment on changes of general health, gastrointestinal symptoms, tolerability, intake, intention of further use, and tolerability were analyzed descriptively.

All data are presented as means ± SD (standard deviation). Changes in sum scores over time were analyzed using the two-tailed paired t-test compared to baseline (V1).

We intended to end with at least 100 participants with full documentation for the entire observation period (VA – day 56), in order to establish a basis suitable to show significant changes of scores; this number would also allow detection of differences between subgroups with different symptom patterns. To facilitate a number of 100 full respondents, we allowed a larger number to opt in, accounting for potential drop out or loss of interest. Bivariate and multivariate analysis were used to investigate possible influencing factors like gender, age, symptom score at beginning, duration of symptoms, and symptom patterns.

Results

Participants

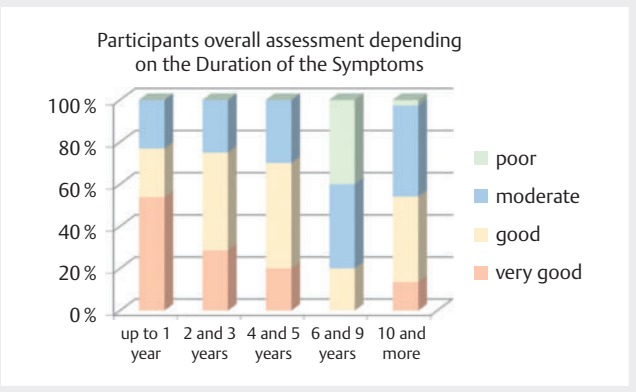
We received interest to participate from 234 interested persons. 5 of these withdraw their consent to use their data, so we collected data on VA from 229 interested persons. 146 interested persons responded for day 1 after having been sent the test product and were considered being participants. These 146 participants were analyzed for safety.

122 persons responded during the entire 56 days. We included 5 persons with shorter reporting but showing no or nearly no symptoms prior to their termination of reporting. We excluded 27 persons with extreme changes during run-in (score decreased by > 50 % (24 persons) or increased by > 100 % (3 persons). Finally, we achieved a collection on 100 participants with complete and consistent documentation for statistical evaluation. There was a mean score improvement of 11 % in this full participation cohort during study-run-in. For further analysis day 1 analysis was used as baseline for day 56 comparison.

Participant characteristics

The sample consisted of 85 female and 15 male participants. Mean age (± SD) was 51.0 ± 10.8 y, height 169.5 ± 7.1 cm, weight 70.3 ± 18.1 kg and BMI 24.4 ± 6.0 kg/m^2. 65 persons did not report any previous disease. An evaluation of their GI-symptoms by a physician in the past was reported by 40 participants. The most frequent gastrointestinal diagnoses were IBS (n = 17), NUD (n = 7), food intolerances (n = 5), reflux disease (n = 2). A few participants reported more than one diagnosis, then showing a frequent association of IBS and NUD (n = 4).

All participants reported one or several symptoms: flatulence (n = 73), constipation (n = 35), abdominal pain (n = 32), diarrhea (n = 30), abdominal spasms (n = 16), fullness (n = 11), reflux and heartburn (n = 10) and other symptoms in their free-text documentations.



▶ **Fig. 2** Overall assessments in participants presented on the basis of duration of the GI-symptoms.

Mean duration of symptoms was 9.1 ± 9.9 y.

81 participants did not take any concomitant medication for their symptoms at inclusion. Current therapy (> 4 weeks) was reported (and continued unchanged): probiotics n = 4, butylscopolamine n = 3, healing earth n = 1, zeolites n = 1, psyllium n = 1, a multi-component herbal drug (Iberogast®) n = 1, magaldrate n = 1, macrogol n = 1, inulin n = 1, macrogol + electrolytes (Laxatan®) n = 1.

Outcome of gastrointestinal scores (main parameter)

Total gastrointestinal score showed significant improvements from a mean (± SD) of 78.7 ± 36.9 points by 26.4 % after 14 days, by 53.1% after 28 days, by 58.7 % after 42 days, and by 49.9 % after 56 days to 37.6 ± 30.0 on day 56. The subscores for upper and lower GI-tract were 44.8 points and 33.9 points at day 1 and improved to a range of 14–20 and 17–18 on days 28–56 (see ▶ **Table 1**). Absolute changes (reductions) on day 56 as compared to day 1 are 41.4 points (total GI score) and 25.1 and 16.2 for upper and lower GI-score, resp. (▶ **Fig. 1**). The upper GI tract score shows higher relative reductions, being highest on day 28 and day 42. On day 56 we found a minor deterioration compared to day 42 (see lower part in ▶ **Table 1**).

Looking at the course of each single symptom in the questionnaire, we had to restrict our analysis to those symptoms that were present on day 1 in enough participants (some symptoms e. g. nausea were only present in a very small number of participants). The following symptoms showed highest values of improvement: heartburn, abdominal spasms, and gastric pain.

Overall assessments

After 56 days the participants reported their overall assessment. The course of gastrointestinal complaints was assessed by 30 participants as “strongly improved”, by 42 as “somewhat improved”, by 20 as “unchanged” and in 1 as “deteriorated” (7 not reporting). There was a marked difference in assessment of general health with 13 reporting “strongly improved, 46 reporting “somewhat improved”, 34 reporting “unchanged” and 7 not reporting. There was a significant relation between the overall assessments and the prior duration of symptoms (▶ **Fig. 2**).

Intake was reported quite regular according to the daily documentation, mostly t.i.d., with few persons reporting b.i.d. – those stayed with b.i.d. over longer periods. On day 56 intake was assessed by 32 subjects as “very pleasant”, by 41 as “pleasant” and by 18 as “less pleasant”, 9 did not rate.

When asked about their intention regarding continuation of using GKE, 18 participants responded “yes, sure” 41 responded “yes, quite sure”, 25 reported “don’t know”, 6 responded “rather not”, 10 did not respond to this question.

The mean number of defecations per day was 1.7 on day 1 and remained unchanged.

New symptoms, UEs

We provided free text fields for reports on new symptoms or problems as first question each day. Some persons answered many gastrointestinal symptoms repeatedly – when the regarding symptoms were absent only for one or few days before. The number of such reports was rated as unremarkable.

There was no severe event, requiring immediate medical support or requiring termination of self-medication.

36 participants reported non-gastrointestinal symptoms: Headache (n = 13), infect of upper airways (n = 10), urinary tract infection (n = 5), herpes infection (n = 1). These and other reported unspecific symptoms or medical problems like menstruation, back pain and vertigo were considered by the authors as being not related to or caused by the intake of GKE. Skin irritation (n = 3), swelling of lymph-tissue (n = 1) or skin (n = 1) were reported as transient on few days, 3 times by participants with known intolerances. The remaining 2 reports may be interpreted as intolerance to GKE, but the continuation of intake by the participants does not support such an assumption.

Discussion

This cohort of people with gastrointestinal symptoms reported a relevant improvement of gastrointestinal symptom scores during self-treatment with GKE. The scores of both subscales for upper abdominal symptoms and for lower gastrointestinal symptoms improved within 14 to 42 days as well as their sum (total gastrointestinal symptom score). The relative mean reduction of score was even higher for upper gastrointestinal symptoms compared to IBS-related symptoms of lower abdomen (53 % reduction versus 47 % reduction), but it showed a small fallback in the last 14 days of treatment in the upper abdominal effects, while the mean of IBS-related score remained stable also in the last 14 days of treatment. Remarkably, GKE showed a strong relieve of acid-related reflux symptoms, mainly heartburn.

The adherent participants documented data showing quite accurate, detailed, and consistent responses. They seem to report their physical and psychological feelings in quite an open and realistic manner. Therefore, this study may be important to supplement previously published trials on patients suffering from gastrointestinal symptoms – especially from those who treat their complaints on their own and from those who do not involve a physician. The participants are not restricted to persons of younger age, who may be more familiar with online computer systems. Roughly 65 %

of participants were older than 50 years and 23 % older than 60 years.

Interestingly the extent of the reported effect is inversely related to the prior duration of symptoms. In this study we included participants with an average duration of symptoms of approx. 10 years, which is higher compared to previous studies using this questionnaire in the setting of observational studies in an academic center for natural healing [20–22].

A study on pharmacist-assisted self-medication in patients with very recent symptomatology, in contrast shows a different observation: the patients there might be addressed as more "acute" [25]. A better response in acute patients is regarded being "normal", since chronicity of functional disorders over years implies a selection of patients towards non-responders to many therapies.

This prospective survey has many limitations. Since there was no personal contact to the participants, theoretically the results may be biased by fake participants. Some participants may have exaggerated their symptoms in the beginning to get the tested product provided for free, though such persons would likely be the ones stopping their reporting at all after they got the product. On the other hand, there are only minor differences in the means of data, when looking at the course of scores in the more or less restricted groups of participants, the evaluated sample group of 100 persons gave very consistent, detailed and plausible reporting. Some of the observed effects may be explained by placebo effects and regression-to-mean effects. The better global assessment regarding gastrointestinal symptomatology in comparison to global health favors the assumption of a specific effect of GKE. It remains unresolved, whether placebo effects and verum effects of an oral treatment for chronic gastrointestinal symptoms would be higher, lower, or similar in controlled or uncontrolled clinical studies with the same product in a clinical setting.

The stronger relative effect in upper GI score supports the hypothesis, that in addition to beneficial influences on lower GI-function, e. g. by influences on gastrointestinal microbiota, there may be an additional effect on gastric function. One may speculate on the mode of action involved in the improvement of heartburn or gastric emptying. In contrast, a prokinetic effect of GKE in the lower GI tract seems not be involved, since there was no change in the number of spontaneous bowel movements per day. Finally, the mode of actions remain unclear and other studies are wanted to clarify this.

The onset of relief comes continuously within 14 to 28 days and remains stable over the observed period of 56 days – this is faster to other remedies, e. g. probiotic treatments [26].

Future clinical studies are wanted to further investigate the efficacy of GKE in controlled settings and other conditions. Furthermore, studies in specific models and patients with established diagnoses are urgently needed to evaluate the potential underlying modes of action. Presently, the German S3 guidelines for the treatment of irritable bowel syndrome state that various herbal medicinal products have proven effectiveness in symptom relief and may be used within a treatment concept (recommendation grade B, strong consensus) [27]. A European consensus paper also states that herbal remedies may be used for the treatment of functional dyspepsia [28].

Since there are limited therapeutic alternatives, GKE, a herbal remedy with good tolerability may be further developed as self-treatment or as probatory treatment in patients with mild symptoms meeting the criteria of functional gastrointestinal disorders.

Conclusion

This prospective survey in participants self-treating their chronic gastrointestinal symptoms with an oral intake supplement derived from grapefruit seeds showed a significant reduction of overarching 50 %, using established symptom scores. There is a continuous onset of action within 14–28 days, and the effect remains stable during the observation period of 56 days. Among the symptoms which improve we find heartburn and other symptoms, which are frequently reported in the context of GERD, NERD, FD (NUD), IBS, leaky gut, and intolerances.

This study retrieving data unfiltered from self-treating persons may help to establish effects that need to be confirmed in future randomized clinical trials. The up to now rarely investigated setting of self-treating persons, avoiding visits to doctors may be completely different from the more established setting of patients seeking diagnoses and treatments in a clinical setting. For further evaluation of GKE controlled clinical trials in well-diagnosed patients with gastrointestinal disorders are needed.

Contributors' Statement

BU: survey plan, plan for statistical evaluation, development of computer platform for data documentation, selection of collectives (sample), statistical analysis, writing of the manuscript. MS gave input to statistical evaluation and data interpretation and was involved in writing of the manuscript. MH: contribution to survey plan, plan for statistical evaluation, contribution to statistical analysis and text-writing.

Acknowledgement

We thank Jeffrey Sonntag and Finn Ziehe for technical development of the computer platform and technical service.

Conflict of Interest

BU is owner of the startup company, which organized this survey. The company received financial support for this project by Sanitas GmbH. He also received honorary for consulting and lectures by several pharmaceutical or health product companies Heilerde-Gesellschaft Luvos Just GmbH & Co. KG, Klostergarten GmbH, Aronia original Naturprodukte GmbH, Nutrin GmbH. MS received honoraria for lectures from Heilerde-Gesellschaft Luvos Just GmbH & Co. KG, Microbiotica GmbH, Bayer Vital GmbH, Dr. Willmar Schwabe GmbH & Co. KG. MH is owner of Sanitas GmbH. He was not involved in data selection and not in the process of assigning the PP-sample out of all data.

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