PMA – Zeolite (Clinoptilolite) in the Management of Irritable Bowel Syndrome – a Non-Interventional Study

Zum Einsatz von PMA – Zeolith (Klinoptilolith) bei Patienten mit Reizdarmsyndrom – eine nicht-interventionelle Studie

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ABSTRACT

In clinical practice, the treatment of patients with irritable bowel syndrome (IBS) can be very challenging. The aims of the present non-interventional study (NIS) were to investigate the tolerability and efficacy of PMA-zeolite under everyday conditions in patients with diarrheic IBS type (IBS-D) or constipated type (IBS-C) or mixed type (IBS-M).

Methods To document prospective data on tolerability and symptom frequency in the frame of a nationwide NIS, we recruited 204 IBS patients. The study focused on the IBS-related quality of life (measured by the SF-36 questionnaire) and improvements of IBS-related symptoms according to specific ROM-III criteria and stool consistency (Bristol stool scale). The participants documented their abdominal pain, bloating, number of bowel movements, and stool consistency through a web-based internet platform (initial and exit questionnaires) and daily diary entries over the period of intake (8 weeks).

Results A total of 82.2 % of the recruited patients had filled in the questionnaires before and after the 8-week treatment with PMA-zeolite. Seven of the eight subscales of the SF-36 improved significantly ($p < 0{,}001$); the reduction in abdominal pain was especially significant ($p < 0{,}001$). The diary entries confirmed the reduction in abdominal pain and revealed a significant reduction in days with bloating ($p < 0{,}001$). The Bristol-stool-scale analysis showed improvements; particularly, patients with IBS-D benefited from the treatment ($p < 0{,}001$).

Conclusion The treatment duration of 8 weeks was well tolerated by most patients. Under everyday life conditions, PMA-zeolite alleviated the global IBS-related symptoms and raised the quality of life (QOL). The PMA-zeolite, thus, may represent a good adjuvant therapeutic option for patients with irritable bowel syndrome.

ZUSAMMENFASSUNG

Die medizinische Betreuung von Patienten mit Reizdarmsyndrom (RDS) kann sehr herausfordernd sein. Die Ziele der vorliegenden Nicht-Interventionellen-Studie (NIS) waren die Dokumentation der Verträglichkeit und Wirksamkeit des PMA-Zeoliths unter Alltagsbedingungen bei Patienten mit durchfallartigem RDS-Typ (RDS-D) oder Obstipationstyp (RDS-C) oder Mischtyp (RDS-M).

Methoden Im Rahmen einer bundesweiten NIS wurden 204 Patienten mit RDS rekrutiert, um Daten zu Verträglichkeit, Lebensqualität, und Symptomfrequenz zu gewinnen. Die Studie

konzentrierte sich auf die RDS-bezogene Lebensqualität (gemessen mit dem SF-36-Fragebogen) und Verbesserungen der RDS-bezogenen Symptome gemäß der RDS-spezifischen ROM-III-Kriterien, sowie der Stuhlkonsistenz (gemessen per Bristol-Stuhlformen-Skala). Die Teilnehmer dokumentierten ihre Symptome wie Bauchschmerzen und Blähungen, sowie die Anzahl der Stuhlgänge und die Stuhlkonsistenz über eine webbasierte Internetplattform (Anfangs- und Ausstiegsfragebögen) und führten ein Tagebuch über den Einnahmezeitraum von 8 Wochen.

Ergebnisse 82,2 % der rekrutierten Patienten hatten die Fragebögen vor und nach der 8-wöchigen Behandlung mit PMA-Zeolith ausgefüllt. Sieben der acht Subskalen des SF-36 verbesserten sich signifikant ($p < 0{,}001$), die Reduktion der Bauchschmerzen war ebenfalls signifikant ($p < 0{,}001$). Die Analysen der Tagebucheinträge bestätigten die Verringerung der Bauchschmerzen und zeigten eine deutliche Abnahme der Tage mit Blähungen. Die Bristol-Stuhlformen Analyse zeigte Verbesserungen. Besonders Patienten mit RDS-D profitierten von der Behandlung ($p < 0{,}001$).

Schlussfolgerung Unter Alltagsbedingungen linderte PMA-Zeolith die globalen RDS-bedingten Symptome und verbesserte die Stuhlkonsistenz und krankheitsassoziierte Lebensqualität.

Introduction

The everyday lifestyle with irritable bowel syndrome (IBS) can be very challenging. IBS patients suffer from malfunction, especially of the large intestine, without any observable morphological changes. Often, the symptoms prevail or recur for many years. Typically, the search for patho-anatomical changes (endoscopy, X-ray, and MRI) reveals no explanation for the complaints [1]. IBS can be considered as a disorder of the gut–brain axis. Enterochromaffin (EC) and neuroendocrine cells of the gastrointestinal tract might play a key role in the pathogenesis of IBS. However, the aetiology remains under discussion. Possible risk factors are genetic, post-infectious changes, chronic viral and bacterial infections, medication side effects, disturbances in the intestinal microbiome, low-grade mucosal inflammation, immune activation, or altered mucosal permeability [2, 3]. Approximately 80 % of irritable bowel syndrome (IBS) patients report that their symptoms are triggered after ingesting one or more specific food groups [4].

IBS can occur in all age groups; it is more common in women, and in the second and third decade of life, women outweigh men by a ratio of 2:1. However, this relationship is much less evident in older ages [5]. Treatment regimens include dietary restrictions, targeting of global symptoms, focusing on the psychological status, and treating abdominal pain [6]. IBS can be associated with changes in microbiota and immune functions [7]. Probiotics can reduce the visceral hypersensitivity associated with micro-inflammation and psychological stress, improve flatulence and abdominal distension, and reduce IBS symptom scores [8]. Due to possible synergistic effects, a combination of dietary fibre and selected probiotics may be tried in the treatment of IBS [5].

Another important treatment approach for IBS might be the mineral zeolite-clinoptilolite (ZC). Recently, the effects of PMA (Panaceo micro-activation)-zeolite-clinoptilolite (ZC) were investigated in a small, randomised, placebo-controlled trial where we described the positive effects in IBS patients [9] that can be explained because ZC is an excellent detoxifying, anti-oxidative, and anti-inflammatory agent [10].

Zeolites-clinoptilolites are microporous and crystalline silicate minerals of natural or synthetic origin with characteristic interconnected cavities [11]. The material consists of two negatively charged compounds ([AlO4] and [SiO4] tetrahedrons), which attract alkali (Na, K, etc.) and/or earth alkali (Mg, Ca, etc.) cations. The loosely attached ions can be easily exchanged for other positively charged and also larger molecules [12]. The large internal surface increases the selective ion-exchange capacity [13, 14, 15] and vindicates their use in human medicine [10, 16]. In any case, it is always essential to use accordingly approved products for oral application in humans [17].

ZC can bind and inactivate living bacteria [18, 19, 20]. ZC in dog food impacts enteral microbiota [21]. Disruption of the physiologic symbiotic relationship (eubiosis) between the human host and the microbiota may contribute to IBS [7]. Preclinical studies revealed positive effects on microbial intestinal populations [17]. Taken at larger doses zeolites may modulate specific microbiome species [20]. In chicken fed with natural ZC, a significant reduction in *Escherichia coli* ($p < 0.05$) [22] and a significant increase in *Lactobacillus acidophilus*[23] were observed. In laying hens, the supplementation with a natural ZC caused a significant reduction in Enterobacteriaceae, a pathogen-rich family, while symbiotic bacteria were found intact [20].

The medical device PMA-ZC is a natural clinoptilolite processed with a specific micronisation technology (Panaceo micro-activation – PMA, patent WO2018/100178A1). The micronisation enhances biophysical properties related to the particle's surface beyond the ion exchange and binding properties of conventionally powdered clinoptilolite materials. PMA-ZC increases the tolerance towards chemotherapy in patients treated for colorectal cancer [24] and can reduce or even eliminate post-therapeutic effects when given during or after aggressive therapies [25]. Only natural ZC with a high silica content are chemically stable in gastric acid [26]. Consequently, not every ZC variant is *a priori* safe for human use; adequate testing and certification is mandatory. For our study, we opted for PMA-ZC as the study substance, mainly because it is stable in the intestine, e. g., no lead is released in the intestinal juice [17].

In regard of our own clinical and preclinical findings [9] on the therapeutic potential, we now investigated the tolerability and the effect of supplementation of the medical device PMA-ZC under everyday life conditions in a larger number of IBS patients and focused on QOL (quality of life) aspects and gastrointestinal symptom amelioration.

▶ **Tab. 1** Likert scale with 5 ordinal steps to compare IBS-related symptoms “before” and “after” the intake. For the lead symptom, “abdominal pain”, the resolution was higher (7 ordinal steps).

Never or rarely	Sometimes	Often	Almost everyday	Everyday
1	2	3	4	5

Material and Methods

NIS – Non-interventional study

Study type

The study type was non-interventional (NIS), a typical design for PMS studies (post-market surveillance). Our research was approved by the competent ethical commission of the Health Council of the city of Vienna (EK17–171–1017). A study homepage served as a communication platform between study team and participants. We installed a hotline for troubleshooting and to increase compliance. Patients could visit the website for extensive information, ask any questions, and register at their own pace.

Recruitment procedures and participation criteria

Patients suffering from IBS between the age of 18 and 90 years were primarily informed by their physician. The physician provided access codes to suitable patients to unlock the baseline questionnaire on the described web platform.

After written acceptance of the study conditions and registration, the patients filled in the baseline IBS-related questionnaire and completed the quality-of-life (SF-36) questionnaire.

Intake phase

Eligible and recruited patients received the study substance for an administration of 8 weeks via conventional mail. The substance came with a diary to daily document both 1) the intake of the PMA-ZC (morning/noon/evening) and 2) IBS-related symptoms (abdominal pain, bloating and frequency of bowel movements, and stool-consistency according to the Bristol stool scale). The recruitment lasted for over two years (28 months) to include all four seasons of the year, avoiding season-related bias.

Towards the end of their participation, the patients received a reminder and access code to fill in the web-based exit questionnaires and forward the completed diary. Participants who finished the study after 8 weeks (“per protocol”) and filled the diary in over 80 % of the days received a body cream and a bath additive; the value was about 45 euro. The platform entries “Before” and “After” the intake phase were compared by means of descriptive and inferential statistics. The daily entries over the 8 weeks were split into 3 equally long phases: 1) beginning, 2) middle, and 3) towards the end.

Endpoints

Quality of Life, SF-36

The health-related quality of life (QOL) was documented with the Short Form Health Survey (SF)-36 research tool; we compared the eight test subscales [27] before and after intake. Those subscales were:

1. Physical functioning,
2. Physical role functioning,
3. Bodily pain,
4. General perception of health,
5. Vitality,
6. Social functioning,
7. Emotional role functioning,
8. Mental health.

Specific IBS-related symptoms,

The subjective symptom load, like abdominal pain, “too high/low bowel movement frequency”, “frequency of too soft”/too hard stools”, was documented by the participants via a Likert scale (▶ **Tab. 1**).

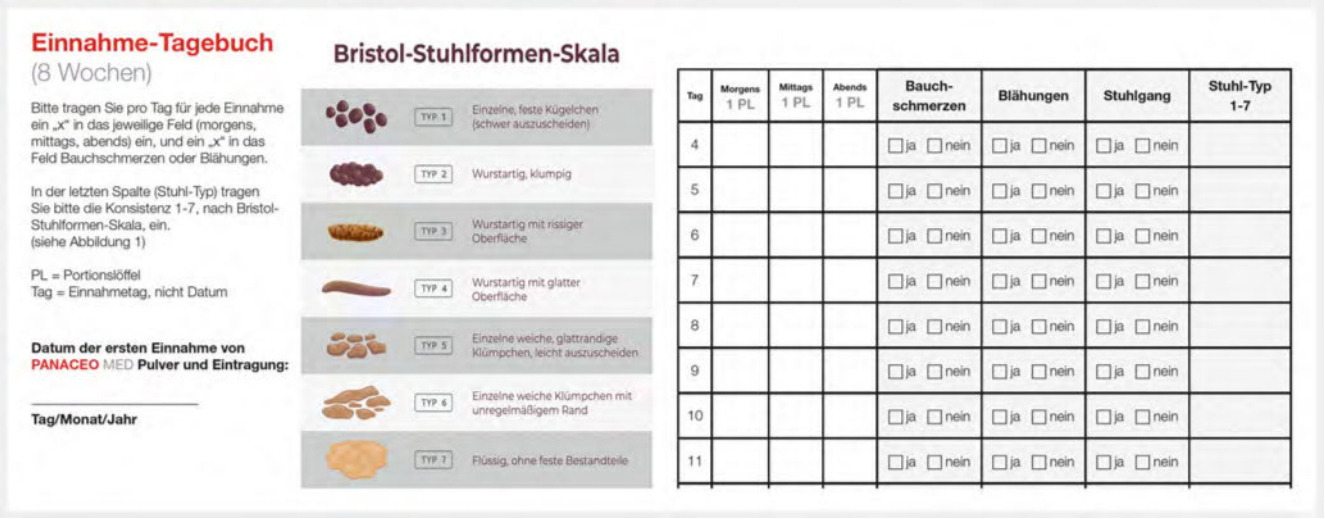
Diary

Together with the study substance (PMA-ZC), the participants received a diary for daily documentation of the oral intake and their IBS-related symptoms. The participants were instructed to enter an “X” in the diary every day for any ingestion of the study substance. Additional entries for each specific day were to concern “abdominal pain”, “bloating”, days with bowel movements, and count of bowel movements on this day. Participants documented stool consistency according the Bristol stool scale (▶ **Abb. 1**).

The entries for the first three days were discarded; they served the participants’ habituation and training, but were not included in the analyses. The complete intake duration for the analyses of the diary entries was split into three equal stages: 1) beginning stage (days 4–20, t1); 2) middle stage (days 21–37, t2); and 3) end stage (days 38–54, t3). From the daily entries per stage, we calculated and statistically analysed the average number of events per week.

Test substance and intake

The test substance was the PMA-ZC, a zeolite manufactured by Panaceo International GmbH (Gödersdorf, Austria), a registered medical device licensed under the respective EU regulations and marketed under the supervision of the competent Austrian Medical Authority BASG. Typically, NIS (non-interventional studies)



▶ **Abb. 1** first page of three pages from the participants diary to document one line per day: substance intake, stomachache, bloating, stool (yes/no), and in case of stool: consistency according to the Bristol-stool-scale.

▶ **Tab. 2** Gender and age of the participants.

Participants	N	Min. age	Max. age	Mean	Std
total	202	18	92	45.73	± 15.194
male	60	18	88	50.00	± 14.710
female	142	20	92	43.92	± 15.083

with medical devices are pragmatic studies, obligatory for PMS (post-market surveillance); they contribute to the medical use.

The dose for a single intake was around 3 grams. In addition to the written instructions for intake, the participants could watch a video on the online web platform on how to stir up the powder in a glass of water and drink it swiftly. During the first 3 days, the instruction was to increase the intake of PMA-ZC gradually (e. g., start with half a spoon in the morning and half a spoon in the evening). After that, one level scoop should be taken two times a day with meals and a glass of water (100 ml). In case of new symptoms, patients were instructed to contact their physicians or document their daily experience in the diary.

Data Processing and Statistics

We compared the baseline values with the middle stage or end stage (diaries) or with the "after intake" values (questionnaires). To include the questionnaires or the diary for the final evaluation, 80 % of the entries were the required minimum. For each parameter, the respective number of cases are given in the respective table legends.

The software package SPSS (V.27, IBM) and the statistical program BIAS (Version 11.12, epsilon Verlag, Frankfurt, Germany) were used for analyses. In addition to descriptive analyses, for comparisons between different time points, *t*-tests for paired samples or the general linear model (GLM) for repeated measures were applied. Bonferroni correction for the alpha error was carried out in case of multiple testing.

Results

Patients

▶ **Tab. 2** shows the gender and age distribution of the recruited patients. The ratio between female and male participants was within the expected range: 71.2 % to 28.8 %, respectively. Of the 204 recruited patients, 166 (82.2 %) finished their participation by completing the exit questionnaire after termination of the 8-week intake. Two participants (1 %) dropped out because they felt no benefit; the total dropout rate was 17.8 %.

QOL, Health-related quality of life

▶ **Tab. 3** summarises the results of the SF-36 quality-of-life documentation. After Bonferroni correction, seven of the eight subscales improved significantly. Both physical and mental summary scales improved significantly ($p < 0.001$).

IBS-related symptoms

We observed intake-associated effects reported via the web questionnaire. The frequency of "abdominal pain" decreased significantly ($p < 0.001$). The experience of "pain relief after bowel mo-

▶ **Tab. 3** IBS-related QOL (quality of life, SF-36); SF-36 subscales, mean scores and standard deviation (STD), intake related score changes, number of patients (N) that provided baseline and after intake ratings. Student's *t*-test and Bonferroni correction for multiple testing; except for the subscale 01 (physical function), all subscales improved significantly.

	SF-36 Subscale	Baseline score ± STD	Score improvement	N	Significance p =
01	Physical function	82.4 ± 22.74	4.1	165	0.015
02	Role physical	52.9 ± 40.42	19.1	162	< 0.001
03	Bodily pain	57.0 ± 19.79	14.6	165	< 0.001
04	General health perception	56.6 ± 18.83	6.1	166	< 0.001
05	Vitality	41.2 ± 18.72	12.2	164	< 0.001
06	Social functions	54.1 ± 20.56	18.8	162	< 0.001
07	Role emotional	50.9 ± 41.13	23.1	163	< 0.001
08	Mental health	55.8 ± 16.95	11.9	165	< 0.001
09	Physical summary scale	62.1 ± 20.18	11.1	161	< 0.001
10	Mental summary scale	49.9 ± 20.75	16.8	158	< 0.001

▶ **Tab. 4** IBS-related symptom frequency as reported at baseline and after two months. The significance (p) was determined by means of Student's *t*-test for paired observations.

Frequency of IBS-related symptoms		Baseline score ± STD	Score after 2 months	Symptom frequency	N	p =	Significance
Abdominal pain		5.46 ± 1.39	–0.92	decrease	166	< 0.001	Significant
Pain relief after defecation		2.54 ± 1.12	0.18	increase	166	0.100	Not sig.
Bowel movement	Too high	2.53 ± 1.15	–0.20	decrease	163	0.052	Tendency
	Too low	1.82 ± 0.99	–0.05	decrease	148	0.553	Not sig.
Stool consistency	Too soft	3.01 ± 1.21	–0.50	decrease	162	< 0.001	Significant
	Too hard	1.74 ± 0.94	0.27	increase	155	0.005	Significant

vement" increased slightly but not to the extent of significance (p = 0.100). ▶ **Tab. 4** reports baseline and subjective changes of the frequency of "bowel movements" and "stools consistency".

Diary

From the 127 returned diaries, those of two participants were excluded from analyses because less than 80 % of the days were documented; 125 diaries were analysed, and none of them contained a safety concern.

IBS-related symptoms

▶ **Tab. 5** summarises the days per week with IBS-related symptoms as documented by the participants day by day. Days with abdominal pain and bloating became less (p < 0.001), while the days with bowel movements did not change. The number of bowel movements decreased with borderline significance; the average Bristol score (stool consistency) decreased continuously; the reduction was statistically significant.

Stool consistency

Because the cohort of IBS patients was a mix of patients with IBS-D (diarrheic type) and IBS-C (constipation type), we analysed the IBS subgroups separately. ▶ **Tab. 6** summarises the subjective global ratings of the respective participants after the intake phase. Most patients with initially too hard, too soft, or mixed stools benefitted from the intake. From the 21 patients who initially rated their stool consistency as "about right", only 10 (48 %) patients improved, and 11 patients did not experience any difference attributable to the intake.

In addition to the subjective global rating (▶ **Tab. 6**), we analysed the daily documented Bristol scores. ▶ **Abb. 2** shows the Bristol scores in the beginning, middle, and end stage of the respective subgroups. The subgroups were established on the basis of the participants' initial ratings: 1) too hard, 2) too soft, and 3) about right. At the beginning, the average ± SEM Bristol stool scores were 2.9 ± 0.21, 4.9 ± 0.19, and 3.6 ± 0.11, respectively. While it stayed relatively the same in the subgroup "about right" (p = 0.793), after about 4 and 8 weeks, in the sub-group "too

▶ **Tab. 5** Diary entries at the beginning (t1), middle (t2), and end stage of participation (t3); ANOVA with Bonferroni p-value correction for multiple testing. The days per week with abdominal pain and bloating became fewer as the intake continued from the beginning to the participation end phase. The number of days with bowel movements remained roughly the same. Stool frequency was lowered slightly, stool consistency – as indicated by the Bristol score – decreased continuously.

	Stage / N	Beginning t1	Middle t2	End t3	Total	t1:t2	t2:t3	t1:t3
		Mean ± STD			p	p	p	p
Days with abdominal pain	116	1.66 ± 1.63	1.27 ± 1.60	1.04 ± 1.46	< 0.001	0.001	0.076	< 0.001
Days with bloating	118	3.80 ± 2.22	3.10 ± 2.30	2.76 ± 2.19	< 0.001	< 0.001	0.029	< 0.001
Days with bowel movements	119	6.38 ± 0.92	6.25 ± 1.14	6.33 ± 1.11	0.542	0.304	1.000	1.000
Stool frequency. N bowel movements	119	9.53 ± 4.49	9.07 ± 4.01	9.13 ± 4.00	0.037	0.023	0.112	1.000
Stool consistency (Bristol score)	119	4.26 ± 1.07	4.13 ± 1.00	4.08 ± 0.90	0.003	0.035	1.000	0.010

▶ **Tab. 6** Stool consistency, participant's rating at baseline, and subjective changes after about 8 weeks of regular intake. Note that the majority of patients benefitted from the therapy, irrespective of "too hard" or "too soft" at baseline.

Effect on stool consistency, subjective rating				
After intake / Baseline	**Improved N (%)**	**Worse N (%)**	**About the same N (%)**	**Total N 100 %**
Too hard	12 (67 %)	0 (0 %)	6 (33 %)	18
Hard & soft mixed	6 (86 %)	0 (0 %)	1 (14 %)	7
Too soft	38 (76 %)	1 (2 %)	11 (22 %)	50
About right	10 (48 %)	0 (0 %)	11 (52 %)	21
Total	66 (69 %)	1 (1 %)	29 (30 %)	96

hard", it improved (not significantly), and in the sub-group "too soft", it improved significantly ($p < 0.001$, ANOVA).

Report of adverse or side effects

To document possible side effects, the diary contained the question, "Did you experience any changes?" (yes/no), and an open field for about 20 words was provided to explain the answer. ▶ **Tab. 7** summarises this documentation.

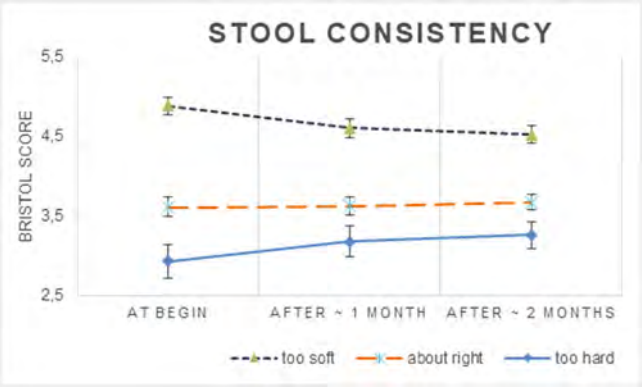
Discussion

Many patients experienced benefits from the intake of PMA-ZC after 4 weeks; after 8 weeks, it was 84.1 % (▶ **Tab. 7**). We observed no noticeable changes of stool consistency in participants who at baseline rated their stool frequency and stool consistency as "about right". Observed ameliorations were more marked in IBS-D patients compared to patients with IBS-C. No reports of treatment-related events and no safety concerns were raised, which corroborates the results of a recent clinical trial [9].

Study design

The study design and outcome focused on the patients' perspectives. Because NIS are prone to bias, we considered methods to reduce bias, like minimising the possible influences of physicians and using a web platform for self-recruitment. The role of medical physicians was only to inform suitable patients about the study; they were not involved in data collection or patient follow-up.

Bias associated with non-random allocation is inherent to pragmatic NIS and could lead to consistent over- or underestimations of treatment effects [28]. This concerns 1.) the existing evidence of bias, 2.) the content of the quality assessment tools, and 3.) the ways that study quality have been assessed and identified and the tools that could be used to assess non-randomised studies [28]. In our study, we therefore made use of case-mix scenarios and analysed, e. g., the increased, decreased, and normal parameters



▶ **Abb. 2** Bristol-score development in the three subgroups (too soft, about right, too hard). While there was no particular change in participants that started with a stool consistency "about right". It improved not significantly with "too hard" stools (N = 19; p = 0,229), and improved highly significantly in the group "too soft stool" (N = 64; p < 0,001).

within our cohort. Our strategy of recruiting patients with IBS-D and IBS-C, as well as mixed types, does not guarantee removal of bias but mirrors everyday practice and is informative when it comes to judging the contribution of a placebo effect to the overall result [28].

The participants were instructed to make a daily entry in the diary (substance intake and IBS-related symptoms). This can reduce placebo effects simply because the obtained data are rather based on day-to-day factual entries and less on subjective global estimates after some time, i. e., the end of participation. Furthermore, we encouraged self-observation by asking for the daily documentation of IBS-related symptoms and stool consistency. While a global statement is prone to bias from placebo-like effects, a daily fact-based entry throughout the participation period can reduce this bias.

Interpretation of the results

Even with a space in their diary reserved for reporting any noticeable experiences, the participants documented no adverse events, and no safety concerns were raised. Therefore, one outcome of this observational study corroborates the safety-related findings from a recent clinical trial with PMA-ZC [9].

Quality of life (QOL)

IBS can be considered a disorder of the gut–brain axis [5, 29]. Psychological factors can contribute to the manifestation of IBS and can have a significant impact on mental health and social well-being and social situations [30, 31]. The SF-36 is a validated questionnaire to also measure mental-health-related QOL; it is well accepted in clinical research. The analyses revealed a statistically significant improvement of seven subcategories and the physical and mental summary scales (▶ **Tab. 3**). We conclude from the SF-36 scores that the study participation increased the QOL. As the PMA-ZC shows a positive impact on the QOL, its use can be beneficial for IBS patients.

IBS-related symptoms

Abdominal pain is a key symptom IBS patients suffer from. The comparison of the patient's perspective at the beginning and after the end of participation revealed a significant improvement (▶ **Tab. 4**). To obtain a more objective view than just a global estimation, we analysed the diary entries. Parameters like "days with abdominal pain" and "days with bloating" declined after 4 weeks and decreased further towards the end of observation (▶ **Tab. 5**).

The observed improvements from the beginning towards the end of the participation constitute a therapeutic effect. Without controls, this improvement might contain a placebo effect of unknown size. Alternatively – because the substance is not absorbed like pharmaceutical agents – the improvements indicate a specific effect of the PMA-ZC in the lumen of the stomach and small and/or large intestines. To estimate the placebo allotment, it is interesting to note that the days with bowel movements per week were not affected by the treatment (▶ **Tab. 5**), which corroborates the assumption that the daily documentation increases the objectivity of the observations reported via diaries.

Our cohort was composed of patients with 1) the diarrheic type (IBS-D), 2) predominantly constipated type (IBS-C), or 3) patients with a mix of days with diarrhoea and constipation (IBS-M). The comparison of these subgroups can reveal hints on the ameliorating mechanisms. We assembled the subgroups on the basis of the participants' rating of their predominant stool consistency at participation start (too hard – constipated, too soft – diarrheic type, etc.). ▶ **Tab. 6** documents the participants' subjective outcome ratings. In the group that rated their stool consistency as "about right", only 48 % improved, which is in the range of placebo effects. In the other groups, the portion of participants who described a benefit was 67 % with hard stools, and it was 70 % with "soft stools" or even higher in mixed-type patients (▶ **Tab. 6**).

We further investigated the effect on stool consistency in an additional analysis of the Bristol scores documented in the diaries. In patients with initially "too hard" stools, the stool consistency (Bristol score) started to normalise after 4 weeks and improved further after 8 weeks (Abb. 2). In patients with initially "too soft" stools, the stool consistency (Bristol score) tended towards "about right" after 4 weeks and improved further after 8 weeks, which again is an improvement for these specific patients. The common mechanism to explain these superficially controversial reactions could be an effect related to the substance intake, which includes a possible placebo effect. However, in the subgroup who rated their stools "about right", we observed no changes (Abb. 2), which clearly implies that the patients with deviating stool consistencies (too soft or too hard) can benefit from an 8-week intake phase.

Mechanism of action

The aetiology of IBS is still a matter of debate, but silent inflammation is among the signs associated with IBS. ZC was described as a detoxifying, anti-oxidative, and anti-inflammatory agent, which – considering the respective aetiologic aspects of IBS – could explain an ameliorating effect [10]. Ground ZC are particles with interconnected cavities that increase the surface [11] to attract and bind cations, like NH_4 groups, contained in other positively charged and also larger molecules [12].

▶ **Tab. 7** Summary of subjective descriptions in the diary; positive and negative opinions.

Did the intake make a change?	N	% after 4 weeks	% after 8 weeks	Positive comments	Negative verbal comments, Side effects
Yes	69	55.2	84.1	69	0
No	10	8.0	12.2	0	0
Yes & No	3	2.4	3.7	3	3
No Answer	43	34.4	–	0	0
Total	125	100.0	100.0		

We hypothesise an anti-inflammatory effect or impact of the microbiome of the ZC on the intestinal mucosa, which contributes to the alleviation of cramps and the sensation of pain. ZC can bind and inactivate living bacteria [18, 19, 20]. ZC in dog food impacts enteral microbiota [21]. As the disruption of the symbiotic relationship between the human host and the intestinal microbiota may contribute to IBS [7], the positive effect of ZC may occur indirectly via modification of the microbiome. Preclinical studies revealed positive effects on microbial intestinal populations [17]. It is known that ZC can modulate specific microbiome species [20, 32], e. g., a significant reduction in *Escherichia coli* [22] and a significant increase in *Lactobacillus acidophilus* [23].

Limitations

We did not include any laboratory parameters like microbiome analyses, which theoretically could have further underlined the results achieved. In this pragmatic study – realised across the country – and considering the heterogeneity of underlying mechanisms and/or IBS types, laboratory parameters would have added very little. However, the outcome of our study corroborates the results of a prospective placebo-controlled trial with laboratory parameters as endpoints [9].

With the observed positive effects in IBS, PMA-ZC may also gain further importance for adjunctive treatment in metabolic diseases associated with a disruption of the intestinal mucosal barrier [33, 34]. Due to the micronisation of the PMA-ZC used in this study, the results should not be extrapolated to other conventionally ground ZC powders.

Conclusions

Various clinoptilolites are advertised with “scientifically unproven” effects. Typically, they are marketed as “food supplement”, “raw material”, or other designations, out of the control of medical authorities. Typically, materials from natural sources are poorly standardised, which hampers suitable medical research. In contrast, the clinoptilolite-based study substance used in our NIS has been approved by competent authorities and is standardised.

The intake improved the patients’ quality of life significantly and reduced the frequency of IBS-related symptoms. These NIS results corroborate earlier findings, like that PMA-ZC can reduce abdominal pain and bloating. The intake over 8 weeks improved the patients’ stool consistencies (diarrheic or too hard) towards normal.

Fördermittel

Panaceo International GmbH

Interessenkonflikt

We declare in the manuscript, about on coauthor: SE is employed by Panaceo International GmbH, the company who sponsored the study substance. The sponsor had no influence on the project roll out, data analyses, or presentation. HV received honoraria for lectures from Panaceo. CM, WM, and RJ have no conflict of interest to declare.

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