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Real-world evidence for XBIOTIX postbiotics in gastrointestinal health: A two-study observational program in Bulgaria

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ABSTRACT

Background & Aims: Microbiome health is increasingly considered a pivotal component of overall health. There is evidence that postbiotics may affect diversity of gut microbiota, have an antimicrobial effect, and improve general wellbeing. Our observational studies aim to assess general wellbeing and gastrointestinal symptom outcomes of (1) taking postbiotics alongside antibiotic therapy, compared to probiotics and antibiotics alone, and (2) taking postbiotics for 30 days in the context of already existing gastrointestinal symptomatology.

Methods: In study 1, 610 patients with acute infections were prescribed antibiotic monotherapy or antibiotics paired with either probiotics or postbiotics. In study 2, 187 patients with gastrointestinal symptomatology were prescribed a 30-day course of postbiotics for their condition. At the follow-up appointment, on the last day of their prescribed therapy, the patients in both studies were given surveys to recall and rate general wellbeing and gastrointestinal outcomes. In study 1, the survey inquired about patient status during the prescribed therapy. In study 2, the survey inquired about patient status at day 0 (baseline), day 10, and their current day-30 status.

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Results: In study 1, postbiotics were associated with significantly lower diarrhea and abdominal distention symptom frequency scores than probiotics, as well as a greater proportion of symptom-free patients. Postbiotic and probiotic groups had significantly comparable symptom scores for abdominal pain and overall comfort, both higher than antibiotic monotherapy. In study 2, the proportion of patients rating their overall comfort as good or excellent rose from 10% on Day 0–91% by Day 30. Patients reporting none/mild abdominal pain and abdominal distention rose from 21% to 88% and 9%–79%, respectively.
Conclusions: Postbiotics were associated with higher general wellbeing and lower gastrointestinal symptom burden in both the antibiotic context and as a standalone therapy. Randomized controlled trials should further investigate these observational findings and confirm postbiotics' therapeutic role.

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Introduction

A growing body of scientific evidence demonstrates that microbiome health is one of the most important determinants of overall health. Dysbiosis can increase risk of colonization by opportunistic pathogens, alter intestinal permeability, and be accompanied by an array of gastrointestinal symptoms like abdominal distention, nausea, and abdominal discomfort [1]. It is also posited to produce downstream effects in the “microbiota-gut-brain axis”, with mood, sleep, and energy levels implicated.

One of the most common causes of microbiome disruption is antibiotic therapy, provoking antibiotic-associated diarrhea (AAD, defined as 3 or more loose stools in 24 hours) in 5–30% of patients [2,3]. Beyond antibiotic origins, a broad range of factors including poor dietary habits, chronic medication use, autoimmune conditions, chronic stress, and other environmental exposures can trigger gut dysbiosis and functional gastrointestinal complaints, which are prevalent across the general population [4].

Considering this significant epidemiological burden, it is important to investigate interventions that support, restore, or maintain a healthy intestinal microbiome across diverse clinical contexts. Postbiotics are one such therapy, but their real-world clinical data remains sparse compared to the evidence base for probiotics – a gap worth addressing, especially given the mechanistic advantages of postbiotics. As “preparation(s) of inanimate microorganisms and/or their components that confer a health benefit on the host” [5], postbiotics may deliver the beneficial effects of microbiome modulation without the constraints associated with live organisms: no requirement for preservation at certain temperatures, no vulnerability to oxygen exposure during packaging, and no dependence on successful gut colonization - often slow, unreliable, or ineffective, especially in states of active inflammation or dysbiosis [6,7].

Studies combining postbiotics with antibiotics also show antimicrobial effects against typical nosocomial pathogens in vitro [8], antimicrobial effects against H. pylori in vivo [9], and significantly higher fecal bacterial diversity with reduced numbers of pathogenic species compared to a placebo [10]. There is evidence that postbiotic metabolites are effective for inhibition and bactericidal activity [11].

XBIOTIX, a yeast-derived postbiotic, contains Saccharomyces cerevisiae fermentates, within a gastro-resistant capsule for targeted intestinal release. There is in vitro evidence supporting S. cerevisiae's gut microbiome-modulating and anti-inflammatory properties [12–14] and in vivo reports on immune [15,16], respiratory [17], and allergy symptom improvement [18–20]. In controlled trials, this type of postbiotic demonstrated improvement of gastrointestinal discomfort and constipation via

microbiome modulation [21]. However, real-world observational data in a large clinical population in both antibiotic-context and standalone maintenance use remains absent from the literature.

To address this gap, XBIOTIX was evaluated across two complementary observational studies - in the context of antibiotic co-administration and as a standalone intervention. Together, these studies aimed to assess the impact of XBIOTIX on gastrointestinal and general wellbeing outcomes across both acute and maintenance use cases.

Materials and methods

Two observational studies were conducted from January to May 2026 to evaluate survey data from 797 patients meeting the inclusion and exclusion criteria, with 610 patients in study 1 and 187 patients in study 2. The patients were invited to participate by a total of 84 healthcare professionals across 17 regions in Bulgaria, including general practitioners, ENT specialists, gastroenterologists, and dental specialists. All prescribed therapies follow standard clinical practice and treating physicians decided on exact therapies based on their own clinical judgement, independent of the study. All participants taking the supplement received the same commercially available formulation (XBIOTIX, Fudivitta, Bulgaria, batch/lot unknown): one gastro-resistant capsule containing 500 mg dry Saccharomyces cerevisiae fermentate, taken once daily. Antibiotics and probiotics were prescribed with varying dosages, administration frequencies, formulations, and compositions, according to the specific clinical needs of the patients as well as the standard dosage regimen of the selected product. Surveys (Fig. 1) were distributed to patients at their follow-up appointments on the last day of antibiotic intake in study 1 and on day 30 in study 2. Investigator-developed scales, using the five-point format standard for patient-experience measurement, were used instead of a single validated instrument to keep the questionnaires brief and suited to descriptive data rather than diagnostic use

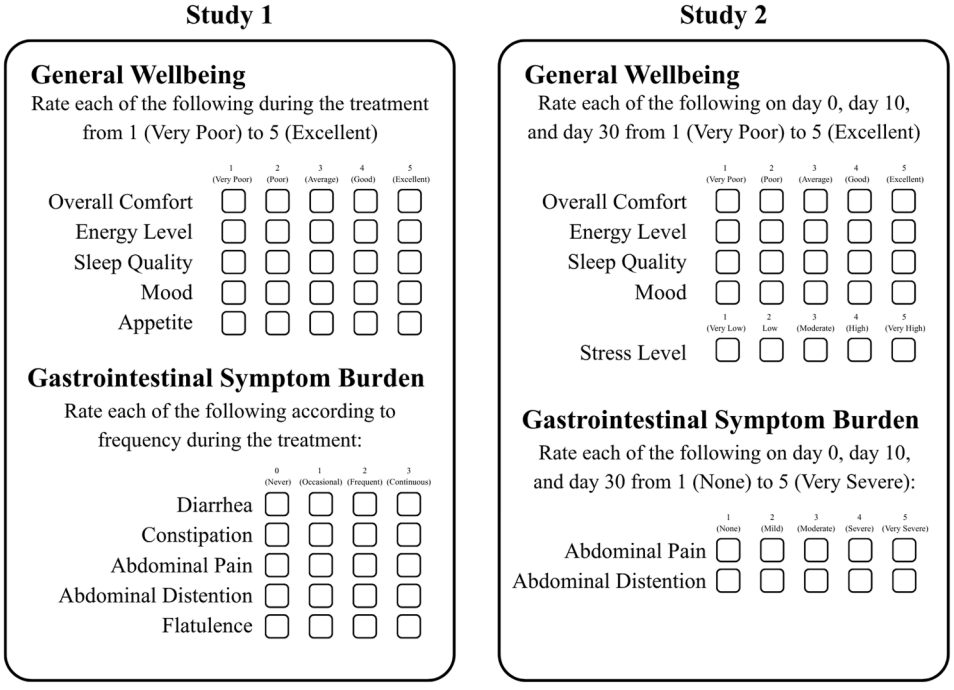


Fig. 1. General Wellbeing & GI Symptom Burden Questionnaires for Study 1 and Study 2.

(Fig. 1). These surveys were not independently psychometrically validated for this study population, which is noted as a limitation. Item non-response was left as missing with no imputation, and the number of observations available for each comparison is reported in Tables 2 and 3. Participants were not aware of the study hypothesis.

Study 1

The 610 included patients were prescribed antibiotics of the penicillin or cephalosporin classes for an acute bacterial infection by their treating specialist: general practitioners managed mixed infection types, ENT specialists treated upper respiratory tract infections, and dental specialists treated odontogenic infections. Prescription of an adjunct microbiome-modulating supplement, either postbiotics or probiotics, was determined by the treating physician's clinical judgement.

361 patients were prescribed XBIOTIX and 193 patients were prescribed probiotics alongside the antibiotic therapy, while 56 patients received the antibiotic alone without adjunct supplementation.

Eligible patients were adults (at least 18 and at most 65 years old), with a confirmed or suspected bacterial infection for which an antibiotic in tablet or sachet form was prescribed. Participants were excluded if they had severe immunodeficiency, had any known allergic reactions to the prescribed antibiotics, postbiotics, or probiotics, were pregnant or nursing, were participating in any other clinical study at the moment of this study, or were related professionally or personally to the prescribing physician or any other doctor at the treating physician's healthcare facility.

On the last day of their antibiotic course, patients completed a structured questionnaire. It was developed by the investigators to capture subjective patient self-assessment of general wellbeing and gastrointestinal symptom burden during antibiotic treatment. General wellbeing items were structured around five single-item domains (overall comfort, energy level, sleep quality, mood, and appetite), drawing on the Quality of Life in Reflux and Dyspepsia (QOLRAD)'s five domains (emotional distress, sleep disturbance, food/drink problems, physical/social functioning, vitality) [22]. Response format followed a 5-point quality-anchored scale (“very poor” to “excellent”), rather than QOLRAD's native 7-point frequency scale, as the focus of this section was subjective wellbeing. Gastrointestinal symptom items (diarrhea, constipation, abdominal pain, abdominal distention, and flatulence) were conceptually derived from the symptom domains of the Gastrointestinal Symptom Rating Scale (GSRS) [23] and assessed using a 4-point frequency scale (“never” to “continuous”), consistent with the scale range of the original GSRS instrument.

Statistical considerations

Between-group differences were analyzed using the Kruskal-Wallis test, with pairwise comparisons performed via Bonferroni-corrected Mann-Whitney U tests ($\alpha = 0.0167$ across three pairs), using the R software environment for statistical computing and Python matplotlib for graphics.

Study 2

In this study, a total of 187 patients with at least one gastrointestinal complaint were prescribed the standard dose of postbiotic therapy for 30 days, following a gastroenterology consultation.

Eligible patients were adults (at least 18 and at most 65 years old). Participants were excluded if they anticipated dietary or medication changes during the observation period, had any known allergic reactions to the prescribed postbiotics, were pregnant or nursing, were participating in any other clinical study at the moment of this study, or were related professionally or personally to the prescribing physician or any other doctor at the treating physician's healthcare facility.

On the last day of the 30-day postbiotic course, patients completed an investigator-developed questionnaire to capture subjective patient self-assessment of general wellbeing and GI symptom burden during standalone postbiotic treatment. They described their baseline complaints and retrospectively rated their general wellbeing and GI symptom burden at Day 0, Day 10, and Day 30, with Day 0 serving as each patient's baseline. General wellbeing items (overall comfort, energy level,

sleep quality, mood, and stress level) were developed as in Study 1, rated on the same 5-point scale ("very poor" to "excellent"), but with the substitution of stress level for appetite, rated on an analogous 5-point scale ("very low" to "very high"). Gastrointestinal symptom burden items (abdominal pain and abdominal distention) were rated on a parallel 5-point severity scale ("none" to "very severe"), consistent with the response format of the PROMIS Global Health-10 [24].

Statistical considerations

Wilcoxon signed-rank test for paired comparisons (Day 0 vs. Day 10 and Day 0 vs. Day 30) using the R software environment and Python matplotlib for graphics.

Ethical statement

All procedures were performed in compliance with relevant laws and institutional guidelines. Both studies were non-interventional, post-marketing observational surveys of a food supplement. All treatment decisions — choice of antibiotics, postbiotics, or probiotics — were made independently by treating physicians according to standard clinical practice, without any study-directed protocol or intervention. These observational studies of food supplements fall outside the scope of Bulgaria's Medicinal Products in Human Medicine Act and do not meet Art. 197 (2) of the Bulgarian Health Act's definition of "medical scientific research". Thus, they fall outside the scope of the associated formal ethics committee frameworks. All patients were informed that their anonymized responses would be used for research purposes and provided informed consent to their treating physician prior to participation. Patient records, including identifying information, were retained locally by treating physicians and were never accessed by the study sponsor or authors; only fully anonymized, aggregated survey data were transferred for analysis, in compliance with the EU General Data Protection Regulation (GDPR).

Results

Demographics

A total of 853 patients completed the surveys for both studies. Of these, 56 were excluded, due to age outside the inclusion criteria, leaving a total of 797 valid participant surveys. Baseline demographic and clinical characteristics for both studies are summarized in Table 1.

In study 1, all patients had an acute infection, of which 361 patients were prescribed XBIOTIX and 193 patients were prescribed probiotics alongside the antibiotic therapy, while 56 patients received the antibiotic alone without adjunct supplementation. The average antibiotic course duration was 7.4 days, with a range of 2–16 days.

In study 2, all patients reported at least one gastrointestinal complaint before treatment, with 50% of patients reporting abdominal distention, 40% reporting abdominal pain, 18% reporting diarrhea, and 12% reporting general GI discomfort.

Outcomes

Patients who took XBIOTIX along with their antibiotic therapy reported greater general wellbeing and less frequent gastrointestinal symptoms compared to patients who took probiotics with antibiotics or just antibiotics. XBIOTIX had the most favorable median scores across all Study 1 parameters (Table 2). Patients to whom a 30-day course of XBIOTIX postbiotics was administered as a standalone treatment for gastrointestinal complaints reported improved outcomes in all 7 parameters on Day 30 and Day 10 as compared to Day 0, with large within-subject effect sizes ($r \geq 0.90$ for all parameters; Table 3). Comparisons (Day 0 vs Day 10 and Day 0 vs Day 30) of all parameters were statistically significant (exact *P*-values in Table 3). Given the retrospective, self-reported, single-arm design of Study 2, these findings are best interpreted as a consistent within-subject association.

Table 1
Baseline demographic and clinical characteristics of participants.

A. Participants in study 1, study 2, and total

Characteristic	Study 1 (n=610)	Study 2 (n=187)	Total (n=797)
Sex (Female/Male)	379 (62%)/231 (38%)	109 (58%)/78 (42%)	488 (61%)/309 (39%)
Age, mean ± SD	39.4 ± 12.4 years	41.8 ± 11.7 years	40.0 ± 12.3 years
Age 18-30	167 (27%) patients	45 (24%) patients	212 (27%) patients
Age 31-45	239 (39%) patients	69 (37%) patients	308 (39%) patients
Age 46-65	204 (33%) patients	73 (39%) patients	277 (35%) patients
Cities/Towns of Residence	82 cities/towns	45 cities/towns	110 cities/towns (17 overlap)
Chronic Health Conditions[a]	78 patients	5 patients	83 patients
Referring specialist	GP: 248 (41%) patients ENT: 221 (36%) patients Dental: 138 (22.5%) patients Gastro: 3 (0.5%) patients	Gastro: 187 patients	GP: 248 (31.1%) patients ENT: 221 (27.7%) patients Dental: 138 (17.3%) patients Gastro: 190 (23.8%) patients

B. Study 1 participants by treatment arm

Characteristic	XBIOTIX + antibiotic (n=361)	Probiotic + antibiotic (n=193)	Antibiotic alone (n=56)	*P*
Sex (Female/Male)	224 (62.0%)/137 (38.0%)	128 (66.3%)/65 (33.7%)	27 (48.2%)/29 (51.8%)	0.049
Age, median [IQR]	39 [31–49]	36 [29–50]	36 [27–49]	0.207
Age 18-30	87 (24.1%) patients	59 (30.6%) patients	21 (37.5%) patients	
Age 31-45	147 (40.7%) patients	77 (39.9%) patients	14 (25.0%) patients	
Age 46-65	126 (34.9%) patients	57 (29.5%) patients	21 (37.5%) patients	
Chronic Health Conditions	48 (13.3%) patients	24 (12.4%) patients	6 (10.7%) patients	0.852
Referring specialist	GP: 150 (41.6%) patients ENT: 121 (33.5%) patients Dental: 89 (24.7%) patients Gastro: 1 (0.3%) patients	GP: 77 (39.9%) patients ENT: 75 (38.9%) patients Dental: 40 (20.7%) patients Gastro: 1 (0.5%) patients	GP: 21 (37.5%) patients ENT: 25 (44.6%) patients Dental: 9 (16.1%) patients Gastro: 1 (1.8%) patients	0.349

(A) Participants in Study 1, Study 2, and Total; (B) Study 1 Participants by Treatment Arm;
[a] Study 2's 5 patients with diagnosed chronic GI disease (ulcerative colitis n=2, IBS n=1, GERD n=1, gastritis n=1) were pooled into the general analysis due to low n.

Study 1 outcomes: general wellbeing

There was a statistically significant difference in overall comfort, appetite, and mood between postbiotic co-administration and antibiotic only groups (Table 2). The probiotic group, when compared to standalone antibiotic therapy, saw statistically significantly higher overall comfort only. The postbiotic group had a significantly higher appetite score than the probiotic group but differences in overall comfort, mood, sleep quality, and energy level were insignificant. There were no significant findings in sleep quality and energy level across the three arms.

Study 1 outcomes: gastrointestinal symptom burden

Compared to the antibiotic-only group, the postbiotic group showed a statistically significant lower symptom burden (measured by frequency) across four of the five GI outcomes (Table 2) and a greater percentage of patients who never or occasionally experienced the symtpoms (Fig. 2). The symptom-free rate was 28.0 percentage points higher for diarrhea, 28.1 points higher for abdominal pain, 18.1 points higher for abdominal distention, and 17.9 points higher for constipation. The probiotic group, on the other hand, only had a statistically significant lower abdominal pain frequency when compared to the standalone antibiotic therapy control group, with a 22.0-percentage-point higher symptom-free rate. There was no significant difference found in diarrhea, abdominal distention, or constipation between the probiotic and antibiotic-only groups.

Comparing the two supplements directly, postbiotics were associated with significantly lower diarrhea and abdominal distention frequency ratings, with 21.7 percentage points higher diarrhea-free rate and 13.8 percentage points higher abdominal distention-free rate. Abdominal pain and constipation did not differ significantly between the two groups.

Statistically non-significant results were seen across the board for flatulence.

Table 2
Study 1 - general wellbeing & GI symptom burden during antibiotic therapy with XBIOTIX postbiotics, with probiotic, or alone.

Parameter	XBIOTIX + antibiotic	Probiotic + antibiotic	Antibiotic alone	Kruskal– Wallis *P*	XBIOTIX vs probiotic	XBIOTIX vs AB-only	Probiotic vs AB-only
A. General Wellbeing							
	Median [IQR] [a]				Effect size r [a] [95% CI]; **MW-U *P* ($\alpha = 0.0167$)** [b]		
Overall comfort	5 [4.0–5.0]	5 [4.0–5.0]	4 [3.0–5.0]	**0.0024**	r = +0.01 [-0.08, +0.09]; *P* = 0.8956	**r = -0.25 [-0.41, -0.08]; *P* < 0.001**	**r = -0.24 [-0.40, -0.08]; *P* = 0.0018**
Energy level	4 [4.0–5.0]	5 [4.0–5.0]	4 [3.0–5.0]	0.2234	r = +0.01 [-0.09, +0.10]; *P* = 0.8665	r = -0.13 [-0.33, +0.04]; *P* = 0.0843	r = -0.12 [-0.29, +0.05]; *P* = 0.1296
Sleep quality	5 [4.0–5.0]	5 [4.0–5.0]	5 [3.0–5.0]	0.0984	r = -0.07 [-0.16, +0.02]; *P* = 0.1239	r = -0.13 [-0.29, +0.03]; *P* = 0.0705	r = -0.07 [-0.23, +0.10]; *P* = 0.4034
Mood	5 [4.0–5.0]	5 [4.0–5.0]	5 [3.0–5.0]	**0.0144**	r = -0.10 [-0.18, -0.01]; *P* = 0.0376	**r = -0.18 [-0.34, -0.02]; *P* = 0.0147**	r = -0.10 [-0.27, +0.07]; *P* = 0.2298
Appetite	5 [4.0–5.0]	4 [3.0–5.0]	4 [3.0–5.0]	**< 0.001**	**r = -0.14 [-0.23, -0.04]; *P* = 0.0027**	**r = -0.32 [-0.48, -0.16]; *P* < 0.001**	r = -0.18 [-0.34, -0.01]; *P* = 0.0306
B. Gastrointestinal Symptom Burden							
	Median [IQR] [a] (% never) [c]				Effect size r [a] [95% CI]; **MW-U *P* ($\alpha = 0.0167$)** [b]		
Diarrhea	0 [0.0–0.0] (83.4%)	0 [0.0–1.0] (61.7%)	0 [0.0–1.0] (55.4%)	**< 0.001**	**r = +0.22 [+0.14, +0.30]; *P* < 0.001**	**r = +0.28 [+0.15, +0.42]; *P* < 0.001**	r = +0.07 [-0.08, +0.21]; *P* = 0.3796
Abdominal pain	0 [0.0–1.0] (74.5%)	0 [0.0–1.0] (68.4%)	1 [0.0–1.0] (46.4%)	**< 0.001**	r = +0.07 [-0.02, +0.15]; *P* = 0.0961	**r = +0.30 [+0.16, +0.45]; *P* < 0.001**	**r = +0.23 [+0.09, +0.38]; *P* = 0.0017**
Abdominal distention	0 [0.0–1.0] (57.3%)	1 [0.0–1.0] (43.5%)	1 [0.0–1.0] (39.3%)	**0.0003**	**r = +0.16 [+0.07, +0.25]; *P* < 0.001**	**r = +0.21 [+0.07, +0.36]; *P* = 0.0034**	r = +0.06 [-0.10, +0.22]; *P* = 0.4568
Constipation	0 [0.0–0.0] (83.9%)	0 [0.0–0.0] (77.2%)	0 [0.0–1.0] (66.1%)	**0.0031**	r = +0.06 [-0.01, +0.13]; *P* = 0.0694	**r = +0.18 [+0.05, +0.32]; *P* = 0.0011**	r = +0.13 [-0.02, +0.28]; *P* = 0.0541
Flatulence	0 [0.0–1.0] (51.8%)	1 [0.0–1.0] (46.6%)	1 [0.0–1.0] (44.6%)	0.0853	r = +0.08 [-0.02, +0.16]; *P* = 0.0971	r = +0.13 [-0.03, +0.29]; *P* = 0.0714	r = +0.06 [-0.10, +0.22]; *P* = 0.4481

[a] Median [IQR] and effect size (Mann-Whitney rank-biserial correlation r, with bootstrap 95% CI) are reported because both scales are ordinal (4- and 5-point).
[b] Bold values are significant at Bonferroni-corrected threshold ($\alpha = 0.0167$).
[c] "% never" values represent the portion of included patients who did not report experiencing the symptom at all during the treatment period.

Table 3
Study 2 - longitudinal outcomes of standalone XBIOTIX intake.

Parameters	Day 0 (median [IQR])	Day 10 (median [IQR])	Day 30 (median [IQR])	Effect size r[a] (D0 vs D10) [95% CI]	Effect size r[a] (D0 vs D30) [95% CI]	Wilcoxon *P* D0 vs D10	Wilcoxon *P* D0 vs D30
A. General wellbeing							
Overall comfort	2 [2.0–3.0]	3 [3.0–4.0]	4 [4.0–5.0]	**r = -0.98 [-1.00, -0.94]**	**r = -0.98 [-1.00, -0.95]**	$P = 2.8\times10^{-25}$	$P = 3.5\times10^{-29}$
Energy level	3 [2.0–3.0]	3 [3.0–4.0]	4 [3.0–4.0]	**r = -0.96 [-1.00, -0.91]**	**r = -1.00 [-1.00, -1.00]**	$P = 5.2\times10^{-18}$	$P = 2.9\times10^{-23}$
Sleep quality	3 [2.0–3.0]	3 [3.0–4.0]	4 [3.0–4.0]	**r = -0.98 [-1.00, -0.93]**	**r = -1.00 [-1.00, -1.00]**	$P = 3.8\times10^{-18}$	$P = 1.9\times10^{-20}$
Mood	3 [3.0–4.0]	4 [3.0–4.0]	4 [4.0–5.0]	**r = -0.90 [-0.99, -0.78]**	**r = -0.98 [-1.00, -0.95]**	$P = 6.1\times10^{-18}$	$P = 1.7\times10^{-23}$
Stress level	3 [3.0–4.0]	3 [2.0–3.0]	2 [2.0–3.0]	**r = +0.97 [+0.91, +1.00]**	**r = +0.97 [+0.93, +1.00]**	$P = 9.4\times10^{-15}$	$P = 2.3\times10^{-17}$
B. Gastrointestinal symptom burden [b]							
Abdominal pain	3 [3.0–4.0]	2 [2.0–3.0]	1 [1.0–2.0]	**r = +0.97 [+0.93, +1.00]**	**r = +0.98 [+0.95, +0.99]**	$P = 3.3\times10^{-24}$	$P = 2.8\times10^{-25}$
Abdominal distention	4 [3.0–4.0]	3 [2.0–3.0]	2 [1.0–2.0]	**r = +0.94 [+0.88, +0.99]**	**r = +0.97 [+0.93, +0.99]**	$P = 5.5\times10^{-25}$	$P = 1.6\times10^{-27}$

[a] Matched-pairs rank-biserial r (Wilcoxon signed-rank), bootstrap 95% CI (2,000 resamples); asymptotic *P*-values; improvement is shown by r < 0 for wellbeing items and by r > 0 for stress, abdominal pain and distention (lower = better).

[b] Gastrointestinal Symptom Burden analysis restricted to patients reporting the symptom at baseline (Day 0 score > 1); abdominal pain (n = 161); abdominal distention (n = 187).

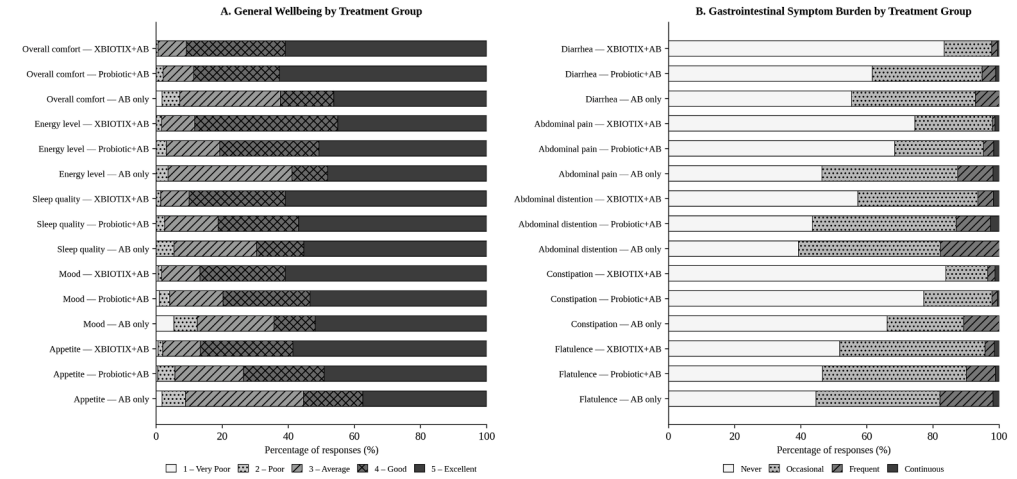


Fig. 2. Study 1 - Distribution of Responses by Treatment Group
(A) General wellbeing items (overall comfort, energy level, sleep quality, mood, appetite), rated 1 (very poor) to 5 (excellent). (B) Gastrointestinal symptom burden items, rated by frequency: 0 (never) to 3 (continuous). AB = antibiotic.

Study 2 outcomes: general wellbeing & gastrointestinal symptom burden

Standalone postbiotic therapy was associated with statistically significant individual improvement in all seven parameters by Day 10, sustained through Day 30 (Table 3). Overall comfort, energy level, sleep quality and mood scores increased, while stress level, abdominal pain, and abdominal distention scores decreased over the same period. Effect size (|r|) for all parameters was 0.90 or higher on Day 10 and 0.97 or higher on Day 30, compared to Day 0.

The full distribution of responses on Day 0, Day 10, ad Day 30 for each parameter of general wellbeing and gastrointestinal symptom burden is shown in Fig. 3. Across all parameters, the proportion of patients in the most favorable (top 2) categories increased from Day 0–30.

Recovery and adherence

In study 1, 97% of patients who took the postbiotic combination therapy reported feeling better post-treatment, compared to 95.9% who took the probiotic combination and 92.9% who took antibiotics only. Recovery time taking more than one week was less frequent in the postbiotic group (9.7%) compared to the probiotic group (10.4%) and the antibiotic monotherapy group (19.6%). 84.2% of the XBIOTIX group never needed additional medication during their combination therapy, while 76.7% of the probiotic group and 73.2% of the antibiotic-only group never made use of additional medication.

In study 2, adherence to prescribed postbiotic therapy was 97% and 95% of patients indicated they were satisfied with the treatment and that they would recommend it to others, respectively.

Discussion

Global antibiotic consumption reached approximately 34.3 billion defined daily doses (DDDs) in 2023 [25]. Antibiotics are known to disturb the proportions of beneficial and pathogenic bacterial gut populations, manifesting as gastrointestinal side effects - abdominal distention, abdominal pain, and AAD, which affects 5–30% of patients [2,3]. Their high prevalence means it is of both clinical and epidemiological importance to explore interventions that might mitigate these common antibiotic-associated gastrointestinal adverse events.

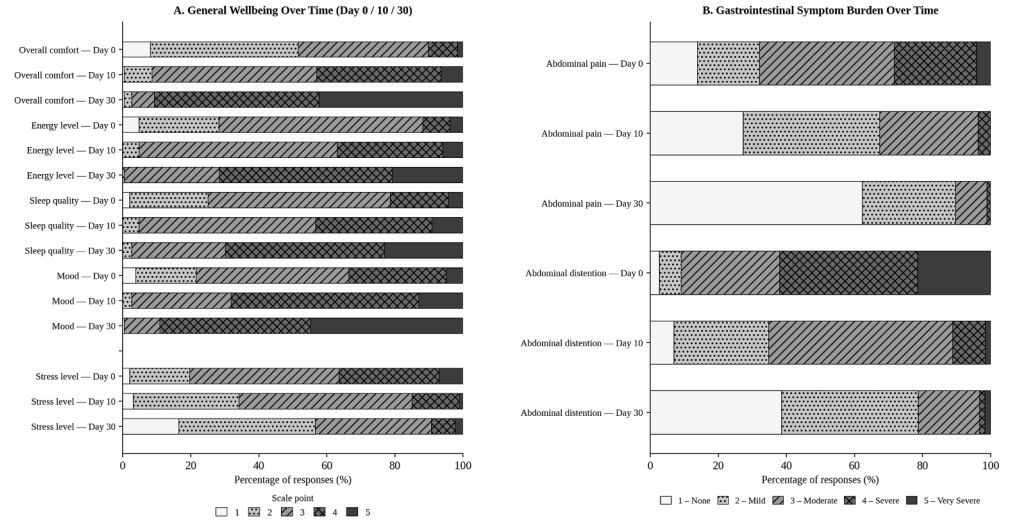


Fig. 3. Study 2 - Distribution of Responses Over Time (Day 0/Day 10/Day 30)
(A) General wellbeing over time. Overall comfort, energy level, sleep quality, and mood were rated 1 (very poor) to 5 (excellent). Stress level, shown separately below, used a different anchor: 1 (very low) to 5 (very high). Note that for stress level, a lower scale point is favorable, whereas for the other four items a higher scale point is favorable. (B) Gastrointestinal symptom burden over time. Abdominal pain and abdominal distention were rated 1 (none) to 5 (very severe).

Probiotics are routinely co-prescribed with antibiotics by physicians, especially to higher-risk patients and there is ample, albeit varying, research into the effectiveness of this approach [26–28]. Postbiotics, however, remain comparatively understudied despite being increasingly discussed in the scientific community as a safe and stable potential alternative agent or adjuvant to commonly used antibiotics due to their microbiome modulating characteristics [29]. The two studies presented here aim to address that gap: Study 1 compares postbiotic co-administration with antibiotics against probiotic co-administration and antibiotic-only therapy, while Study 2 examines general wellbeing and gastrointestinal outcomes associated with standalone postbiotic use in patients with functional gastrointestinal disturbances and gut dysbiosis. As neither study collected microbiome or biomarker data, the mechanistic explanations proposed below are drawn from the broader literature and should be considered hypothesis-generating rather than demonstrated by this dataset.

Study 1: postbiotic-antibiotic Co-administration

Postbiotic co-administration with antibiotics was associated with lower gastrointestinal symptom burden and higher general wellbeing than antibiotic monotherapy in most tested parameters. Compared with probiotics, postbiotics were associated with significantly lower diarrhea and abdominal distention frequency ratings, specifically, as well as higher preserved appetite but a similarly lower abdominal pain rating relative to the antibiotic-only group.

These findings raise the question of what might mechanistically distinguish the two supplements and suggest that the parameters studied are reasonable candidate endpoints for a randomized trial. A plausible, literature-based rationalization for the more favorable scores observed is that postbiotics are unaffected by antibiotic action structurally and mechanistically, so they can be taken simultaneously with the antibiotic [6,7]. Probiotics, on the other hand, must be administered with a defined time buffer before or after antibiotic ingestion to prevent inactivation of the live organisms. In multimorbid, polypharmacy patients, this simplified same-time dosing regimen may meaningfully improve adherence and clinical outcomes. Postbiotics may also exert an antibacterial effect that targets the pathogenic bacterial growth seen in antibiotic dysbiosis and may alleviate associated GI

symptoms [18–21]. These mechanisms were not directly tested here but present an interesting avenue for further study.

Study 2: standalone postbiotic therapy

Standalone postbiotic therapy has a wide array of benefits across several patient populations. Studies report significant improvements in IBS symptom severity, abdominal pain, and quality of life [30], as well as decreased gastrointestinal symptomatology in patients with chronic diarrhea [31] and mild to moderate GI conditions [17], with significant stabilization of fecal calprotectin, a marker of intestinal inflammation, compared to placebo [32]. In these diverse patient populations, most authors confirm a significant increase in beneficial gut bacteria and decrease in pathogenic bacteria [31–33]. Inflammatory and metabolic effects have also been observed in varying populations taking postbiotics, though outcomes appear to depend on strain, extraction method, and dosage [33–37].

Our findings align with the broader literature. Statistically significant improvement was evident by Day 10 across all seven parameters and continued through Day 30 (Table 3). The observed pattern of concurrent improvement in gastrointestinal and systemic outcomes is compatible with the bidirectional interactions proposed by gut-brain-axis theory [38], though this study's design cannot test that mechanism directly. Our survey-based design cannot confirm a microbiome shift, but some researchers have observed systemic effects with postbiotic intake even without measurable shift in gut microbiota composition [39], suggesting that postbiotics may have systemic effects that occur independently of intestinal compositional change. Further research is needed to elucidate this relationship and its mechanisms or explore how the two may occur through independent pathways.

Conclusions

This real-world observational program offers one of the largest direct comparisons between postbiotic, probiotic, and antibiotic-only regimens for general wellbeing and gastrointestinal symptom burden in a cohort of this size. The findings show that postbiotics were associated with more favorable general wellbeing and GI symptom outcomes than probiotics when co-administered with antibiotics. Standalone postbiotic use was associated with rapid, sustained improvement in pre-existing GI symptoms, evident within days and maintained over a full month. This evidence base, taken together with the known mechanistic advantages of postbiotics as well as their hypothesized microbiome modulatory & gut-brain-axis effects in the literature, makes a compelling case for randomized controlled trials to confirm postbiotics' therapeutic role and define their place in clinical practice.

The strengths of our observational studies were the real-world diversity and setting of assigning therapy. Patients from 110 localities in 17 regions of Bulgaria were prescribed therapy by 84 healthcare professionals of varying specialties. Despite the potential prescribing bias between the arms in study 1, the selection of patients into each arm reflects actual physician prescribing behavior, since their clinical judgement was used instead of a prescribing algorithm.

The limitations of our studies arise from their observational, non-randomized design with self-reporting. The surveys were not independently psychometrically validated for this study population, instead conceptually modeled on the general wellbeing and GI symptom domains of validated instruments. They were given to the patients at the end of their prescribed therapy, which can introduce recall bias. This is especially significant in study 2, where patients recall and report data from day 0 and day 10 on day 30. No biomarker or microbiome data was collected, so mechanisms can only be inferred. Regarding control groups, study 1 had a relatively small antibiotic-monotherapy group with a lower proportion of female patients than the other two arms. Study 2 lacked a control group, and although this approach was intended to reduce inter-participant variability, a common concern when evaluating biotics, it cannot account for time-related confounding, regression to the mean, natural resolution of the underlying condition, placebo effects, increased clinical attention, or other concurrent factors. As a result, study 2 demonstrates a temporal association, not treatment efficacy. Additionally, the Bulgaria-only setting limits global generalizability and the lack of post-discontinuation follow-up means that whether effects persist after stopping postbiotics is unknown.

Future research should include RCT confirmation of these results to establish whether postbiotics have a genuine therapeutic role, and, if so, to inform prescription standards. Longer follow-up may be useful, as well as microbiome sequencing and analysis to elucidate the exact mechanisms by which postbiotics act on human health. Going further, postbiotic intake in healthy populations may be examined to assess it as a general wellness supplement in non-symptomatic populations.

Data availability

Anonymized survey data supporting the findings of this study are available from the corresponding author upon reasonable request.

Statement of authorship

Militsa Marinova: Conceptualization, Project administration. **Mariana Penkova-Radicheva**: Supervision, Formal Analysis. **Yoana Cholakova**: Investigation. Data curation. Writing - Original Draft. **Borislav Borissov**: Methodology, Validation, Writing - Review & Editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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