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Original Communication

Exploratory Effects of a Bovine Colostrum-Based Supplement on Salivary sIgA, Leukocyte Profiles, and Health Status in Middle-Aged and Older Adults

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Abstract

Objective: The rapid aging of the population is becoming a serious public health issue. This study aimed to evaluate the effects of a bovine colostrum (BC)-based multi-nutrient supplement on secretory immunoglobulin A (sIgA) levels and health status in middle-aged and older adults. **Methods:** A total of 188 participants aged 50–85 years were enrolled in a 90-day, double-anonymized trial and randomized to an intervention group or a positive control group. The intervention group received 1.12 g of BC powder daily, containing ≥1×10^8 CFU/g of *Bifidobacterium animalis subsp. lactis Bb-12*, while the positive control group received regular milk powder. The primary outcome was the change in salivary sIgA concentration. **Results:** A total of 171 participants completed the trial. After the intervention, the sIgA concentration was notably increased in both groups ($p < 0.01$). The sIgA concentration was increased from 66.3 (43.9, 113) μg/mL to 77.8 (51.5, 137) μg/mL in the intervention group and from 77.8 (48.8, 115) μg/mL to 85.5 (53.3, 133) μg/mL in the control group, with no significant difference between the two groups after intervention. Among participants aged ≥65 years, the intervention group had a greater increase in the sIgA concentration ($p = 0.020$). Additionally, the intervention group had lower leukocyte and neutrophil counts and a significantly lower incidence of oral ulcers, fatigue, and the common cold ($p < 0.05$). Sleep quality improved in both groups ($p < 0.05$). **Conclusion:** In the overall study population, no significant between-group difference was observed in the primary outcome (salivary sIgA); therefore, these findings should be interpreted as exploratory. However, potential signals of benefit were observed in older participants (≥65 years), which warrant confirmation in future studies. **ChiCTR-ID:** ChiCTR2400079567 (https://www.chictr.org.cn/showproj.html?proj=198323).

Keywords: bovine colostrum; immune; secretory immunoglobulin A; randomized controlled trial; health status

1. Introduction

Global aging trends show significant acceleration, with the population aged ≥60 years expected to increase from 1.0 billion to 1.4 billion between 2020 and 2030 [1]. With advancing age, immune function gradually declines due to reductions in both the number and functionality of immune cells. This process, collectively referred to as immunosenescence, results in diminished resistance to pathogens [2]. These changes may compromise the health and well-being of middle-aged and older adults, increasing the vulnerability of these age groups to various ailments, including respiratory infections, digestive disorders, sleep disturbances, and oral mucosal lesions [3]. Thus, enhancing immune function in older adults has emerged as a critical priority for promoting healthy aging and requires comprehensive improvements in nutrition and health across middle-aged and older populations.

Nutritional supplements containing vitamins, minerals, proteins, and bioactive compounds may serve as a practical adjunct to alleviate nutritional deficiencies and support health and immune function in aging populations [4]. Bovine colostrum (BC), the first mammary secretion produced postpartum in cows, has a long history of human consumption [4]. The distinctive composition of BC, which includes essential nutrients, immunomodulators, and prebiotic oligosaccharides, confers multiple health benefits. Indeed, compared with mature milk, BC contains higher levels of casein, whey proteins (including immunoglobulins and lactoferrin), and other proteins, as well as greater amounts of fat, ash, vitamins, and minerals. It also contains hormones, growth factors, cytokines, nucleotides, and

lower lactose levels [5,6,7]. Evidence suggests that BC ingestion may influence immune function beyond the gastrointestinal tract. BC supplementation has been shown to reduce the incidence of influenza-like episodes [8] and to decrease the frequency of upper respiratory tract infections (URTIs) and diarrhea in children [9,10]. BC-derived IgG exhibits binding and neutralizing activity against human respiratory syncytial virus [11]. Furthermore, a meta-analysis indicated that BC supplementation exerts a significant positive effect on urinary tract infection symptoms in trained athletes, who are at increased risk of such infections. A meta-analysis indicated that bovine colostrum supplementation may be effective in preventing the incidence of upper respiratory symptoms days and episodes in adults engaged in exercise training [12].

Secretory IgA (sIgA) functions as a key immunological barrier, providing mucosal protection against pathogenic microbes [13,14]. IgA supports mucosal immune homeostasis by regulating commensal microbiota and preventing pathogenic invasion [15]. Meanwhile, in a clinical trial involving 35 long-distance runners, BC supplementation significantly enhanced IgA levels [16]. Another study of 66 older adults examined the effects of colostrum milk supplementation in this population, but did not assess sIgA levels [17]. Research specifically examining the effects of BC powder on sIgA and immune function in aging populations remains limited [18]. Collectively, these studies suggest that BC can modulate immune function and enhance mucosal immunity, effects that are attributed to the unique composition of BC, including immunoglobulins, lactoferrin, and other bioactive components. The present study investigated the effects of BC supplementation on selected immune-related markers, particularly salivary sIgA and circulating leukocyte counts.

2. Participants and Methods

2.1 Study Design

This study employed a parallel-group, randomized, double-anonymized design with two arms. The program received full approval (SZEFYIEC-KYPJ-2023013). The research protocol was approved by the Ethics Committee of Xi'an Jiaotong University Health Science Center, in accordance with the 1964 Declaration of Helsinki, and was registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn; ChiCTR-ID: ChiCTR2400079567). To protect participant welfare, the research team obtained study insurance for all participants through Sunshine Insurance Group (Policy No.: 101691372023000006). Written informed consent was obtained from all participants.

2.2 Study Population

This study recruited 260 participants from five communities and institutions through extensive outreach at community residential sites, free medical clinics, nursing home lectures, and recruitment posters. Inclusion criteria were as follows: (1) permanent residents who had been continuously living in the project area for ≥2 years; (2) aged 50–85 years; (3) signed informed consent form; (4) willingness to adhere to the study protocol. Exclusion criteria were as follows: (1) active autoimmune disorders; (2) diagnosed lactose intolerance or an IgE-confirmed allergy to cow's milk; (3) current or previous history of cancer, prior chemotherapy, or history of organ transplantation; (4) use of medications affecting immune function (e.g., corticosteroids, thiopurines, methotrexate, anti-TNF agents) during the follow-up period. Following eligibility screening based on these criteria, 188 participants were enrolled. During the screening visit, the researchers explained the study purpose, procedures, and the informed consent form in detail. After written informed consent was obtained, investigators administered questionnaires, performed physical assessments, and collected biological specimens (saliva and blood) from all participants.

2.3 Randomization and Intervention

A simple randomization design was employed in this study. Excel-generated random numbers were assigned to participants, ordered by serial number. Each serial number received a random value, which was then rank-ordered and split into two groups at the median. Numbered envelopes containing serial number-random number pairs were prepared by the trial designer, who was not involved in data collection or field implementation. Participants were randomized to receive either BC powder supplementation (n = 94) or regular milk powder (n = 94) as the control. The trial procedures are illustrated in Fig. 1.

Table 1 provides a detailed description of the BC composition. This research was performed as a double-anonymized study. The milk powder was packaged in identical white boxes labeled only with usage instructions and a code number (“1” or “2”). The inner packaging consisted of uniform silver sachets, with 16 sachets per box. Each sachet contained 28 g of powder, sufficient for an 8-day supply. In practice, participants were required to visit the designated community center every 8 days to collect a new batch of the product, for a total of 11 collections ($8 \times 11 = 88$ days), plus an additional 2-day buffer period. At each visit, the participant returned the empty sachets, and adherence was recorded. Participants were instructed to consume one sachet twice daily. Both the project staff and participants were blinded to the identity of the powders corresponding to codes 1 and 2. The study designer unblinded the allocation after the trial concluded. The trial spanned approximately 90 days. To assess compliance, participants were asked to retain and submit all empty sachets. The BC powder used in this study contained 2000 mg of BC powder per 100 g, 75 mg of lactoferrin, 1000 mg of whey protein hydrolysate, and *Bifidobacterium animalis subsp. lactis Bb-12* at a minimum concentration of 1×10^8 CFU/g.

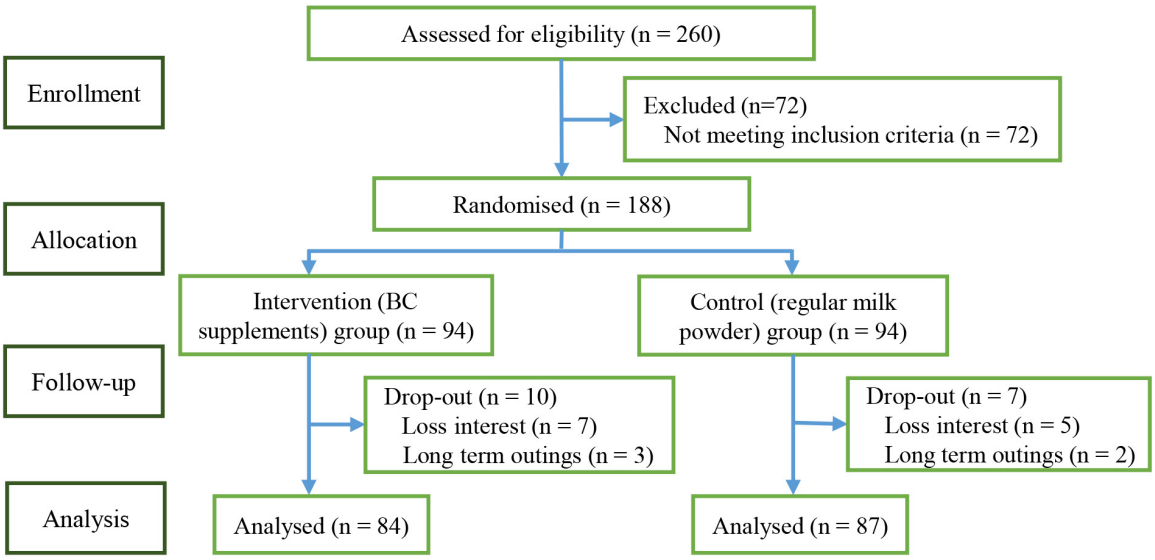

Fig. 1. CONSORT study flowchart. BC, bovine colostrum.

During each of the three follow-up visits, empty sachets were collected and counted. Each participant was expected to consume two sachets per day. Adherence was calculated as: (number of empty sachets/number of sachets that should have been consumed) × 100%. Compliance ≥85% was defined as high, 75%–85% as moderate, and <75% as low.

At baseline (day 0), participants underwent assessments at the research center. Trained staff collected 5 mL of blood and 1 mL of saliva. Participants were required to fast overnight from 10:00 PM, and samples were collected the following morning at 8:00 AM while fasting. Despite complex field conditions, sample collection was generally completed before 9:00 AM. Before saliva collection, participants rinsed their mouths three times with purified water. Saliva (1–2 mL) was collected using saliva collection tubes. All samples were immediately placed in a transport box with ice packs and transferred to the laboratory. Saliva samples were centrifuged at 4 °C (3000 rpm for 15 min), and the supernatants were aliquoted into Eppendorf (EP) tubes and stored at –80 °C. If precipitation occurred during storage, samples were recentrifuged. Blood samples were transported at 4 °C to a professional testing agency for analysis. After sample collection, participants underwent physical examinations and completed questionnaires, then began the 90-day supplementation/vehicle intervention. Participants received intervention diaries to record illnesses and supplement consumption throughout the trial.

A pilot pre-experiment demonstrated that a 1:10,000 dilution placed most samples within the linear range of the ELISA standard curve and was consistent with the manufacturer's recommendations. Secretory IgA (sIgA) concentration was measured using a human IgA ELISA kit (AB195215, Abcam, Cambridge Biomedical Campus, Cambridge, CB2 0AX, United Kingdom). Per the manufacturer's guidelines, this kit shows no cross-reactivity with samples from rats, hamsters, donkeys, sheep, mice, rabbits, or guinea pigs, indicating high specificity. Unlike human colostrum, BC contains very low levels of sIgA; therefore, it is highly unlikely that the ELISA results were influenced by bovine sIgA. All ELISA procedures, including reagent preparation, sample loading, incubation, washing, and detection, were performed strictly according to the kit instructions. Peripheral blood samples were analyzed for complete blood counts at a certified diagnostic laboratory. Saliva was selected for sIgA measurement because saliva directly reflects mucosal immune function, which is critical for evaluating immune responses to BC-based multi-nutrient supplementation. Additionally, saliva collection is non-invasive, making this process more practical for repeated measurements in a large cohort. All collected blood and saliva samples were utilized in the present analysis. Any remaining samples were stored for potential future studies to investigate additional biomarkers and immune markers.

Physical activity was evaluated across four domains (work, household, transportation, and leisure) using the Chinese version of the long form of the International Physical Activity Questionnaire – Long Form (IPAQ-LF). Prior research has validated the IPAQ as a reliable tool for assessing physical activity in adults, including older individuals [19,20,21]. Physical activity intensity was expressed in metabolic equivalents (METs), calculated as the ratio of activity metabolic rate to resting metabolic rate. Weekly MET-minutes (MET-min/week) were calculated as: MET value × frequency (days/week) × duration (min/day). Based on IPAQ criteria, physical activity levels were classified as low, moderate, or high.

Dietary intake was assessed using a Food Frequency Questionnaire (FFQ), which collects data on the frequency and amount of various foods consumed over a specified pe-

Table 1. Nutritional components.

Project	Unit	Per 100 g	Reference intake of nutrients (%)
Energy	kJ	1846.0	22%
Protein	g	23.0	38%
Fat	g	14.5	24%
Carbohydrates	g	54.0	18%
Sodium	mg	350.0	18%
Vitamin A	μg RE	450.0	56%
Vitamin D	μg	8.0	160%
Vitamin E	mg α-TE	12.0	86%
Vitamin B2	mg	0.6	43%
Vitamin C	mg	40.0	40%
Folic acid	μg DFE	425.0	106%
Calcium	mg	1300.0	163%
Iron	mg	7.8	52%
Zinc	mg	4.5	30%
Lactoferrin	mg	75.0	—

Note: Raw cow's milk, skimmed milk powder, lactose, oligoisomaltose, bovine colostrum (BC) powder, hydrolyzed whey protein powder, lactoferrin, vitamin A, vitamin D, vitamin E, vitamin C, folic acid, calcium carbonate, ferrous sulfate, zinc sulfate, *Bifidobacterium animalis subsp. lactis Bb-12* (the number of viable bacteria at the time of production was $\geq 1 \times 10^8$ CFU/g). Food allergen alert: This product contains milk and dairy products. RE, Retinol Equivalent; α-TE, Alpha-Tocopherol Equivalent; DFE, Dietary Folate Equivalent.

The additional amount of oligoisomaltose was 8 g per 100 g of BC supplement powder.

The additional amount of BC powder was 2000 mg per 100 g of BC supplement powder.

The additional amount of hydrolyzed whey protein powder was 1000 mg per 100 g of BC supplement powder.

Each time, use one small bag (about 28 g) and mix the contents with 180 mL of warm, boiled water (about 50 ℃). Stir until fully dissolved, then drink. It is recommended to consume 2 servings per day. This product is not suitable for infants or young children.

riod (typically the past month or year) [22]. The questionnaire comprises three core components: a food list, consumption frequency, and portion size. Average daily nutrient intake was calculated as daily consumption frequency × portion size × nutrient content, and the results were summed across all foods to obtain total daily nutrient intake. The FFQ was administered at baseline and at the 90-day follow-up visit to assess dietary intake over the previous month. Both study products were milk-based powders provided in identical packaging and dosing schedules.

2.4 Outcomes

The primary outcome was the change in secretory IgA levels from baseline to day 90. Secondary outcomes included changes in immune cell counts and proportions in blood tests. Additional endpoints were health status measures assessed by questionnaires and self-reports, covering oral ulcers (painful lesions with a yellow pseudomembrane and red halo), sleep quality (measured by the Pittsburgh Sleep Quality Index (PSQI) [23], with higher scores indicating poorer sleep), colds (viral upper respiratory infections with symptoms such as nasal congestion), fatigue (general weakness), and diarrhea (more than three watery stools per day exceeding 200 g/day). These measures provided a comprehensive evaluation of the effects of the intervention on selected immune-related markers, particularly salivary sIgA and circulating leukocyte counts. Oral ulcers [24] were defined as painful oral mucosal lesions with a yellow pseudomembrane and erythematous halo. Fatigue was defined as subjective generalized weakness. Colds were defined as self-reported symptoms of viral upper respiratory infection (e.g., nasal congestion, sore throat). Sleep quality was assessed using PSQI.

2.5 Quality Control

This study implemented several quality control measures. A randomized controlled design was used to minimize confounding factors and balance intergroup differences, ensuring double-anonymized randomization. Staff members received regular training in volunteer recruitment, sample collection, and questionnaire administration to standardize procedures and facilitate smooth coordination. Before the trial, WeChat groups were created to maintain communication with participants, provide daily reminders for formula intake, and monitor compliance by counting returned empty packages during follow-up visits.

2.6 Sample Size Estimation

Sample size determination was conducted using PASS software (version 2026, NCSS, LLC, 329 North 1000 East, Kaysville, UT 84037, USA), utilizing published data on immune markers (including NK cells and IgA levels) from prior research [16]. This investigation maintained 90% statistical power with $\alpha = 0.05$. A mean intergroup sIgA difference of 0.26 yielded a minimum required sample size of 164 participants. For NK cell values ($\delta = 2.07$), the calculated minimum was 98 participants. The larger sample size of 164 was selected within this range. Accounting for a 10% dropout rate, a total of 180 participants were required, with 90 participants allocated to each group. In China, the menopausal transition in women typically occurs around 50 years of age, and a significant decline in hormone levels is also observed in men within a similar age range. Therefore, the target age range was set at 50–85 years.

2.7 Blinding

Until the statistical analysis was completed, the participants, outcome assessors, and statisticians remained anonymized to group allocations.

Table 2. Baseline demographic characteristics.

Parameter	Total (n = 188)	Intervention (n = 94)	Control (n = 94)	t/χ^2	p-value
Age (years)	65.3 ± 6.46	65.6 ± 5.54	64.9 ± 7.27	0.801	0.424
Sex				0.024	0.877
Male	63 (33.5%)	32 (34.0%)	31 (33.0%)		
Female	125 (66.5%)	62 (66.0%)	63 (67.0%)		
Nation					1.000#
Han	187 (99.5%)	93 (98.9%)	94 (100%)		
Mongolian	1 (0.5%)	1 (1.1%)	0		
Marital status					1.000#
Divorce	1 (0.5%)	1 (1.1%)	0		
Widowed	5 (2.7%)	2 (2.1%)	3 (3.2%)		
Spinster	1 (0.5%)	1 (1.1%)	0		
Married	181 (96.3%)	90 (95.7%)	91 (96.8%)		
Educational level				1.788	0.409
College or above	59 (31.4%)	29 (30.9%)	30 (31.9%)		
Secondary school	101 (53.7%)	54 (57.4%)	47 (50.0%)		
Primary and lower	28 (14.9%)	11 (11.7%)	17 (18.1%)		
Living condition				4.491	0.106##
Live alone	7 (3.7%)	1 (1.1%)	6 (6.4%)		
Nursing home	17 (9.0%)	7 (7.4%)	10 (10.6%)		
Live with family	164 (87.2%)	86 (91.5%)	78 (83.0%)		
Living environment				1.155	0.607##
One-story house	9 (4.8%)	4 (4.3%)	5 (5.3%)		
Walk-up building	18 (9.6%)	7 (7.4%)	11 (11.7%)		
Elevator building	161 (85.6%)	83 (88.3%)	78 (83.0%)		

Continuous variables are presented as the mean ± SD; categorical variables are presented as n (%). The superscript # represents the p-value from Fisher's exact test. The superscript ## represents the p-value by Monte Carlo simulation from Chi-squared test. SD, standard deviation.

2.8 Statistical Analysis

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed with the Kolmogorov–Smirnov test. Categorical variables are presented as frequencies (%) and compared using χ^2 or Fisher's exact tests. For R×C contingency tables in which >20% of cells had expected frequencies <5 or any expected frequency <1, a Monte Carlo version of the Pearson chi square test (based on 3000 replicates) was employed. For 2 × 2 tables, the choice of test followed standard criteria: Pearson chi square (all expected ≥5 and N ≥ 40), Yates continuity corrected chi square (1 ≤ expected <5 and N ≥ 40), or Fisher's exact test (expected <1, N < 40, or a zero cell count). Non-normally distributed continuous variables are reported as median (interquartile range (IQR); Q1–Q3), whereas normally distributed variables are expressed as the mean ± standard deviation (SD). Intragroup differences (versus baseline) were analyzed using paired t-tests or Wilcoxon signed-rank tests, and between-group differences were evaluated using the analysis of covariance (ANCOVA). Group effect, time effect, and group × time interaction were analyzed using generalized estimating equations (GEEs), with adjustments for age and gender. Statistical significance was defined as $p < 0.05$.

Participants with missing outcome data at day 90 were excluded from the corresponding analyses. No imputation was performed; all analyses used available-case data, and the number of participants included in each analysis is reported accordingly. Age-stratified analyses using a 65-year cutoff, based on commonly accepted geriatric thresholds, were performed post hoc and considered exploratory. No adjustment for multiplicity was made; therefore, these findings should be interpreted with caution.

3. Results

3.1 Baseline Characteristics of the Study Population

The 188 participants had a mean age of 65.3 ± 6.46 years, and 33.5% were male. Educational attainment was as follows: 31.4% had a college degree or higher, 53.7% had completed secondary/technical school, and 14.9% had a primary school education or lower. Most participants lived with family members (87.2%). There were no significant differences in baseline demographic characteristics between groups (Table 2).

3.2 Analysis of Intervention Compliance

The proportion of participants with high compliance exceeded 86% in both groups at all three time points, with

Table 3. sIgA concentrations of participants grouped by age (M, (Q1, Q3)).

Subgroup		Total	Control	Intervention	[a]*p*-value	[b]*p*-value		
						Time	Group	Time × group
Total	Day 0	75.0 (47.0, 113)	77.8 (48.8, 115)	66.3 (43.9, 113)	0.495	<0.001	0.816	0.238
	Day 90	80.9 (52.3, 134)	85.5 (53.3, 133)	77.8 (51.5, 137)	0.274			
	Growth rate (%)	16.2 (4.84, 31.6)	15.1 (2.23, 30.5)	16.7 (6.03, 36.0)	0.337			
	[c]*p*-value	<0.001	<0.001	<0.001				
<65	Day 0	82.5 (49.9, 117)	85.8 (54.9, 117)	79.5 (45.8, 120)	0.399	<0.001	0.540	0.502
	Day 90	91.6 (51.5, 145)	97.0 (61.2, 147)	91.4 (50.7, 142)	0.581			
	Growth rate (%)	12.9 (4.68, 27.8)	11.4 (4.78, 23.3)	15.1 (2.43, 30.3)	0.691			
	[c]*p*-value	<0.001	0.001	<0.001				
≥65	Day 0	71.1 (42.5, 108)	75.1 (41.2, 108)	65.4 (42.3, 105)	0.672	<0.001	0.941	0.020
	Day 90	75.8 (50.2, 131)	76.2 (47.9, 131)	77.4 (53.7, 135)	0.044			
	Growth rate (%)	19.8 (5.24, 35.4)	14.9 (1.30, 31.4)	22.0 (7.72, 42.4)	0.057			
	[c]*p*-value	<0.001	0.001	<0.001				

Data are presented as median (IQR, Q1–Q3).

[a] The *p*-value indicates between-group comparisons at baseline (Wilcoxon rank-sum test).

[b] The *p*-value indicates group effect, time effect, and group × time interaction derived from generalized estimating equations (GEEs) models adjusted for age (when not stratified) and sex.

[c] The *p*-value indicates within-group changes from baseline to day 90 (Wilcoxon signed-rank test).

Growth rate (%) = (day 90 – day 0) / day 0 × 100%. sIgA, Secretory IgA; IQR, interquartile range.

no significant differences between the two groups (p = 0.618, 0.454, and 0.752, respectively).

3.3 Changes in Salivary sIgA Concentration

No significant baseline differences in salivary sIgA levels were observed between the intervention and control groups (p = 0.495). By day 90, both groups showed significant increases in sIgA: intervention group (66.3→77.8 μg/mL) and control group (77.8→85.5 μg/mL; $p < 0.001$). However, no significant intergroup difference was observed post-intervention (p = 0.274). Stratified analysis revealed that among participants aged ≥65 years, the intervention group demonstrated significantly higher sIgA levels than controls (p = 0.044), with a marginally significant increase rate (p = 0.057). GEE analysis indicated a significant time-by-group interaction (p = 0.020; Table 3). Effect sizes are presented as median changes and percentage growth rates to complement p-values.

3.4 Comparison of White Blood Cell and Neutrophil Counts

The intervention and control groups showed no significant baseline differences. The intervention group demonstrated significantly lower white blood cell and neutrophil counts than controls on day 90 ($p < 0.05$; Table 4). These findings warrant additional investigation to elucidate the underlying biological mechanisms. Importantly, all leukocyte and neutrophil values remained within established adult reference ranges throughout the study, indicating physiological modulation rather than pathological suppression.

3.5 Comparison of Health Outcomes and Symptom Improvement

Self-reported health status did not differ significantly between the intervention and control groups at baseline or on day 56. However, by day 90, a higher proportion of participants in the intervention group reported "never feeling fatigued" in the previous 6 weeks (p = 0.049). The number of common cold episodes increased over the trial period in the control group (p = 0.004); however, these episodes remained unchanged in the intervention group ($p > 0.05$), resulting in a significant intergroup difference (p = 0.049). Furthermore, the intervention group showed a significantly reduced incidence of oral ulcers on day 90 compared with days 0 and 56 (p = 0.016), whereas the control group showed no change ($p > 0.05$). This between-group difference was also statistically significant on day 90 (p = 0.025; Table 5).

3.6 Comparison of Nutrient Intake and Physical Activity

FFQ-assessed daily nutrient intake revealed no significant between-group differences in key nutrients (protein, fat, vitamins A/C/D/E, minerals, folate) ($p > 0.05$). IPAQ-LF measurements likewise showed no significant differences in physical activity levels between groups at baseline or post-intervention. Baseline MET-min/week values were comparable in the intervention and control groups (5166 vs. 5097; p = 0.239). After the intervention, the intervention group reported 4935 MET-min/week compared with 4473 MET-min/week in the control group (p = 0.796). Physical activity levels did not significantly affect salivary sIgA concentration ($p > 0.05$). Overall, FFQ-assessed daily intake of major macronutrients (protein, fat) and selected micronutri-

Table 4. The effects of 90 days of supplementation on immune cell levels among participants.

Parameters	Control (n = 86)	Intervention (n = 84)	[a]*p*-value	[b]*p*-value		
				Time	Group	Time × group
Leukocyte (10^9/L)						
Day 0	5.28 (4.46, 6.11)	5.22 (4.41, 5.77)	0.635	0.005	0.109	0.083
Day 90	5.74 (4.82, 6.57)	5.24 (4.67, 6.03)	0.034			
[c]*p*-value	0.005	0.090				
Neutrophil (10^9/L)						
Day 0	3.05 (2.45, 4.04)	2.90 (2.41, 3.56)	0.346	0.331	0.018	0.086
Day 90	3.28 (2.74, 4.12)	2.99 (2.56, 3.48)	0.006			
[c]*p*-value	0.067	0.774				
Lymphocyte (10^9/L)						
Day 0	1.77 (1.41, 2.18)	1.69 (1.42, 2.13)	0.836	0.002	0.577	0.822
Day 90	1.78 (1.44, 2.23)	1.80 (1.54, 2.22)	0.770			
[c]*p*-value	0.059	0.010				
Erythrocyte (10^{12}/L)						
Day 0	4.60 (4.36, 4.88)	4.62 (4.37, 4.93)	0.491	<0.001	0.968	0.401
Day 90	4.53 (4.22, 4.86)	4.52 (4.28, 4.78)	0.434			
[c]*p*-value	0.001	<0.001				
Monocyte (10^9/L)						
Day 0	0.32 (0.26, 0.37)	0.32 (0.26, 0.39)	0.924	<0.001	0.300	0.159
Day 90	0.36 (0.28, 0.47)	0.35 (0.29, 0.43)	0.117			
[c]*p*-value	<0.001	<0.001				
Eosinophil (10^9/L)						
Day 0	0.09 (0.05, 0.14)	0.08 (0.06, 0.12)	0.985	0.098	0.087	0.263
Day 90	0.11 (0.06, 0.18)	0.09 (0.06, 0.13)	0.252			
[c]*p*-value	0.027	0.085				
Basophil (10^9/L)						
Day 0	0.02 (0.01, 0.03)	0.02 (0.01, 0.02)	0.094	0.639	0.174	0.405
Day 90	0.02 (0.01, 0.03)	0.01 (0.01, 0.02)	0.995			
[c]*p*-value	0.357	0.693				
Hemoglobin (g/L)						
Day 0	141 (133, 147)	141 (133, 147)	0.576	<0.001	0.673	0.548
Day 90	137 (131, 146)	138 (130, 148)	0.494			
[c]*p*-value	0.001	<0.001				
Platelet (10^9/L)						
Day 0	208 (165, 237)	216 (175, 248)	0.922	<0.001	0.893	0.905
Day 90	217 (184, 262)	219 (186, 262)	0.934			
[c]*p*-value	<0.001	<0.001				

Data are presented as median (IQR (Q1, Q3)). [a]Wilcoxon rank-sum test was used to analyze differences between groups on day 0. ANCOVA was used to compare group differences at day 90, adjusting for baseline measurements. [b]GEE was used to evaluate the group effect, time effect, and group × time interaction effect, and the analyses were adjusted for age and gender. [c]Wilcoxon signed-rank test was used to analyze changes in each parameter over time across different groups. All leukocyte and neutrophil values remained within established adult reference ranges throughout the study period.

Note: In the control group, one participant yielded an insufficient blood sample volume. Repeat collection was attempted; however, the participant declined further blood draws for personal reasons.

ents (vitamins A, C, D, E, minerals, and folate) showed no significant between-group differences at baseline or after 90 days, indicating comparable background dietary nutrient exposure in the intervention and control groups.

3.7 Comparison of Improvement in Sleep Quality

Baseline PSQI scores did not differ significantly between groups (intervention: 8.1 ± 2.9; control: 8.4 ± 3.2; $p = 0.502$). At 90 days, PSQI scores decreased to 5.0 ± 2.8 in the intervention group and 5.3 ± 2.9 in the control group ($p = 0.500$). Sleep quality improved significantly from baseline in both groups ($p < 0.05$; Fig. 2).

4. Discussion

This randomized controlled trial examined the effects of BC supplementation on salivary sIgA levels, immuno-

Table 5. Self-reported changes within 90 days (%).

Group/parameter	Intervention (n = 82)	Control (n = 83)	χ^2	[b]*p*-value
Oral ulcers				
Day 0			0.321	0.867 [##]
Never	67 (80.7%)	65 (79.3%)		
Sometimes	12 (14.5%)	14 (17.1%)		
Frequently	4 (4.8%)	3 (3.7%)		
Day 56			2.725	0.332 [##]
Never	69 (83.1%)	72 (87.8%)		
Sometimes	12 (14.5%)	6 (7.3%)		
Frequently	2 (2.4%)	4 (4.9%)		
Day 90			6.657	0.025 [##]
Never	70 (84.3%)	78 (95.1%)		
Sometimes	11 (13.3%)	2 (2.4%)		
Frequently	2 (2.4%)	2 (2.4%)		
χ^2	1.125	12.030		
[a]*p*-value	0.910[##]	0.016[##]		
Bitter taste				
Day 0			0.710	0.700 [##]
Never	57 (68.7%)	52 (63.4%)		
Sometimes	22 (26.5%)	24 (29.3%)		
Frequently	4 (4.8%)	6 (7.3%)		
Day 56			1.673	0.433
Never	61 (73.5%)	53 (64.6%)		
Sometimes	14 (16.9%)	20 (24.4%)		
Frequently	8 (9.6%)	9 (11.0%)		
Day 90			3.391	0.183
Never	51 (61.4%)	51 (62.2%)		
Sometimes	19 (22.9%)	25 (30.5%)		
Frequently	13 (15.7%)	6 (7.3%)		
χ^2	7.561	1.504		
[a]*p*-value	0.109[##]	0.826		
Fatigue				
Day 0			0.357	0.837
Never	60 (72.3%)	57 (69.5%)		
Sometimes	17 (20.5%)	17 (20.7%)		
Frequently	6 (7.2%)	8 (9.8%)		
Day 56			1.892	0.388
Never	67 (80.7%)	59 (72.0%)		
Sometimes	12 (14.5%)	16 (19.5%)		
Frequently	4 (4.8%)	7 (8.5%)		
Day 90			6.310	0.049 [##]
Never	68 (81.9%)	53 (64.6%)		
Sometimes	13 (15.7%)	25 (30.5%)		
Frequently	2 (2.4%)	4 (4.9%)		
χ^2	3.585	4.217		
[a]*p*-value	0.489 [##]	0.377 [##]		
Cold				
Day 0			0.074	0.786
Never	74 (89.2%)	72 (87.8%)		
≥ once a month	9 (10.8%)	10 (12.2%)		
Day 56			1.069	0.301
Never	70 (84.3%)	64 (78.0%)		
≥ once a month	13 (15.7%)	18 (22.0%)		

Table 5. Continued.

Group/parameter	Intervention (n = 82)	Control (n = 83)	χ^2	[b]*p*-value
Day 90			3.883	0.049
Never	66 (79.5%)	54 (65.9%)		
≥ once a month	17 (20.5%)	28 (34.1%)		
χ^2	2.219	11.283		
[a]*p*-value	0.232	0.004		
Diarrhea				
Day 0			1.302	0.254
Never	78 (94.0%)	73 (89.0%)		
≥ once a month	5 (6.0%)	9 (11.0%)		
Day 56			0.074	0.786
Never	74 (89.2%)	72 (87.8%)		
≥ once a month	9 (10.8%)	10 (12.2%)		
Day 90			0.701	0.403
Never	77 (92.8%)	73 (89.0%)		
≥ once a month	6 (7.2%)	9 (11.0%)		
χ^2	1.414	0.081		
[a]*p*-value	0.493	0.961		
Frequency of bowel movements				
Day 0			0.529	0.713 ##
3–5 times/day	2 (2.4%)	3 (3.7%)		
1–2 times/day	73 (88.0%)	69 (84.1%)		
2–3 days/time	8 (9.6%)	10 (12.2%)		
Day 56			1.196	0.606 ##
3–5 times/day	1 (1.2%)	2 (2.4%)		
1–2 times/day	70 (84.3%)	73 (88.0%)		
2–3 days/time	12 (14.5%)	8 (9.6%)		
Day 90			3.191	0.363
3–5 times/day	1 (1.2%)	2 (2.4%)		
1–2 times/day	69 (83.1%)	72 (87.8%)		
2–3 days/time	13 (15.7%)	8 (9.8%)		
χ^2	1.895	0.574		
[a]*p*-value	0.810 ##	0.966 ##		

Categorical variables are presented as counts (%). [a]The *p*-value indicates within-group comparison across three time points. [b]The *p*-value indicates between-group comparison at the corresponding time point. Categorical variables are presented as n (%). Note: Six participants withdrew from the 90-day follow-up visit for personal reasons. After excluding missing values, 165 participants provided complete data across all three surveys: 82 in the intervention group and 83 in the control group. The superscript ## represents the *p*-value by Monte Carlo simulation from Chi-squared test.

logical parameters, and health status in older adults. Our results indicated that BC supplementation did not significantly increase salivary sIgA levels or alter most baseline immune parameters in the overall sample. However, a potentially beneficial effect on salivary sIgA was observed in the subgroup aged ≥65 years. Additionally, the intervention group demonstrated better clinical outcomes, including a lower incidence of common colds and oral ulcers.

As the primary immunological barrier, mucosal immunity serves a critical role in defending against exogenous infections. The absence of mucosal surface antibodies may increase vulnerability to viral and bacterial infections. The sIgA functions as the principal mucosal antibody and a frontline defense against respiratory infections such as pneumonia and influenza [25]. The overall increase in salivary sIgA concentration observed in this study is a positive indicator, potentially reflecting a beneficial effect of nutritional intervention on the immune status of middle-aged and older individuals. This study also revealed that the effects of nutritional intervention may vary by age. Specifically, among participants aged 65 years and older, the nutritional benefits of BC supplementation were more pro-

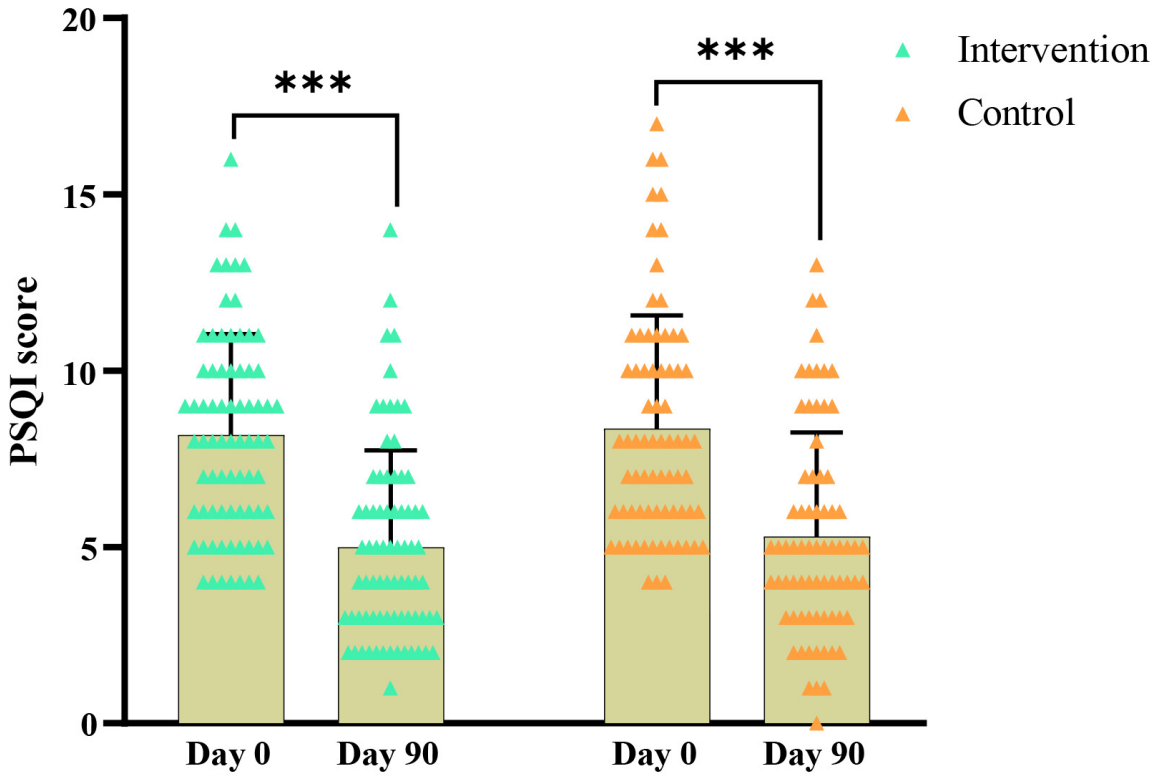

Fig. 2. PSQI scores in the two groups (n = 94 per group at baseline; n = 82 in the intervention group and n = 83 in the control group at day 90). PSQI scores in the intervention and control groups at baseline and after 90 days of supplementation. Bars represent mean PSQI scores, and error bars represent the standard deviation. At 90 days, PSQI scores declined to 5.0 ± 2.8 (intervention) and 5.3 ± 2.9 (control) (***$p < 0.001$). PSQI, Pittsburgh Sleep Quality Index.

nounced than those of regular milk powder. These findings suggest that BC supplementation may offer greater immune-enhancing potential in older populations and offer new perspectives for future research. Studies have indicated that many older adults do not adequately adjust their dietary intake, leading to suboptimal nutritional status and increased risks of infection and other health problems [26]. Concurrently, a selective decline in gastrointestinal function occurs with aging, manifested as reduced taste sensitivity, slower metabolism, decreased appetite, and diminished absorptive capacity, all of which may impair effective nutrient absorption and utilization [27]. Therefore, exploring methods to improve nutrient absorption efficiency in older people or to develop more readily absorbable nutritional supplements warrants further investigation. Prior studies in athletes have reported significant increases in sIgA after BC supplementation. Differences in baseline immune status, physical stress exposure, and population characteristics may partly explain why no overall between-group difference was observed in our cohort.

The intervention group demonstrated significantly fewer oral ulcers than the control group, suggesting that BC supplementation may reduce oral inflammation and improve oral health. Oral ulcers are often associated with immune activity, and studies have shown elevated levels of inflammatory factors, such as IL-2, in individuals with oral ulcers [28]. Anti-inflammatory treatments can alleviate these symptoms, and other studies have indicated that BC can protect the oral mucosa and reduce the severity of oral mucositis. The improvement in oral ulcers following BC supplementation in this trial may stem from the modulatory effects of BC on the mucosal immune system, promoting a more balanced immune response [29,30,31,32]. When inflammation occurs, leukocytes, including neutrophils, are recruited to the inflamed site immediately [33,34]. After the intervention, lower leukocyte and neutrophil counts were observed in the intervention group, which may reflect modest changes in immune homeostasis rather than clinically significant anti-inflammatory effects [35]. Furthermore, the reduction in reported colds and fatigue in the intervention group suggests enhanced resistance to infection and overall health benefits. Sleep quality, as assessed by the PSQI score, improved significantly in both groups after the 90-day intervention, with a slightly greater improvement in the intervention group. Collectively, these findings highlight the potential of BC supplementation to modulate immune function, reduce inflammation, and enhance overall health, underscoring the need for further mechanistic studies. Since the intervention group received a combination of BC, whey protein, and probiotics, it is not possible to con-

clusively attribute the observed effects to BC alone. Therefore, future studies aim to disentangle the individual contributions of each component.

Nevertheless, the specific components of the BC-based milk powder responsible for the observed effects remain unclear. Both the BC supplement and the regular milk powder improved health status. The BC product contained BC, whey protein, and probiotics (Bb-12, $\geq 1 \times 10^8$ CFU/g), whereas the regular milk powder did not. Whey protein is easily digestible and may help maintain muscle mass in older adults and enhance mucosal immunity [36,37]. Probiotics such as Bb-12 have demonstrated immunomodulatory effects in diverse populations [38,39,40]. Essential micronutrients, including vitamins A, C, D, and E, as well as minerals, are crucial for immune function and overall health, especially in older adults [41,42,43,44]. Micronutrient complex supplementation may enhance immune cell diversity in older populations [45], and evidence indicates that multivitamin–mineral supplementation can influence immune function in healthy older adults [46,47,48]. While the BC supplement provided a comprehensive nutrient profile, further research is needed to identify the key components driving the observed health benefits. The present study evaluated health status using self-reported data and basic hematological markers. Future studies could benefit from including additional biomarkers, such as Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), glucose levels, and lipid profiles, to provide a more comprehensive assessment of the impact of BC-based multi-nutrient supplementation on overall health. BC provides immunoglobulins, lactoferrin, and growth factors that may enhance mucosal immunity; whey protein may support protein synthesis and gut barrier integrity; Bb-12 has documented immunomodulatory effects. Since these components were administered in combination, the associated independent contributions cannot be determined from this study.

This study has several limitations. First, although baseline demographic characteristics did not differ significantly between groups, interindividual variability in immune function and genetic factors may have contributed to heterogeneous responses to milk powder supplementation. When treated as a continuous variable, age did not differ significantly between groups; however, when age was categorized as 65 years or older, participants in the BC supplement group tended to be older. Although this difference was not statistically significant, age may still have influenced the outcomes. Additionally, the intervention period spanned seasonal transitions, and environmental factors associated with these changes may have affected health status. Finally, given the inherent complexity and uncertainty of intervention trials, potential confounding factors cannot be ruled out. While this study used peripheral blood leukocyte counts to evaluate immune function, future research could incorporate flow cytometry-based PBMC phenotyping to characterize T- and B-cell populations, as well as monocyte subsets, more precisely. Additionally, *ex vivo* mitogen stimulation assays could be incorporated to better reflect immune function and response. Future studies could also explore the role of changes in the gut microbiome and the potential influence of circulating metabolites to clarify the broader effects of BC-based multi-nutrient supplementation on immune health.

The observed sIgA differences in participants aged ≥65 years should be interpreted cautiously, as these analyses were exploratory and not pre-specified, and potentially subject to type I error due to multiple comparisons. Health-related symptoms were assessed via self-report and are, therefore, susceptible to recall and reporting biases; thus, these findings should be interpreted with caution and considered supportive rather than confirmatory. The subgroup analyses based on age (≥65 years) were exploratory and not adjusted for multiple comparisons, which may further increase the risk of type I error. Future trials should incorporate inflammatory cytokine profiling (e.g., IL-6, TNF-α), gut microbiota analyses, and PBMC phenotyping to elucidate underlying mechanisms.

5. Conclusion

In this exploratory randomized trial, supplementation with a BC-based multi-nutrient product did not demonstrate superiority over regular milk powder for the primary outcome of salivary sIgA in the overall population. Exploratory subgroup analyses suggested potential age-related differences, which should be interpreted cautiously and confirmed in adequately powered future studies.

Availability of Data and Materials

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

QW, XFW, XBZ, BX, RJX, and YFW designed the research study. QW, JLW, BX, XBZ, and YBZ performed the research. QW and JLW provided help and advice on the ELISA experiments. XMS, XL and TXZ analyzed the data. XFW, JLW, XRZ, TXC, and SDZ are involved in data collection and analysis, as well as drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical

standards. This study is approved by the Ethics Committee of The Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine (approval No. SZEFYIEC-KYPJ-2023013), written informed consent was obtained.

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Conflicts of Interest

The authors declare no conflicts of interest. China Feihe Co., Ltdhe supporting source had no such involvement or restrictions regarding publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR47306.

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