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Brief Report

Anti-Wrinkle Effect of BB-1000: A Double-Blind, Randomized Controlled Study

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Abstract: Skin aging usually results from intrinsic or extrinsic stress. Photodamage promotes skin damage and stimulates the skin, manifesting as wrinkles, dryness, roughness, and loss of elasticity. We have previously found that blackberry (*Rubus fruticosus* B) fermented by *Lactobacillus plantarum* JBMI F5, designated BB-1000, showed an in vitro and in vivo anti-skin-aging activity. In the present study, we have further evaluated the anti-aging effect of BB-1000 via a randomized, double-blind, and placebo-controlled clinical trial. The trial included 102 volunteers aged 35 to 59 years who have dry skin and wrinkles. Subjects took BB-1000 or a placebo orally at 800 mg/day for 12 weeks. Skin hydration and degree of wrinkles around the eyes were measured at weeks 6 and 12. Skin hydration had no significant effect in both groups at weeks 6 and 12. Otherwise, volunteers in the BB-1000 group had a significant reduction in eye wrinkle grade at week 12. These findings suggest that BB-1000 may be considered a candidate anti-aging agent for preventing skin wrinkles as a nutricosmetic agent.

Keywords: skin aging; clinical study; randomized; double-blind; probiotics

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1. Introduction

The skin is one of the largest and most complex organs in the body. It is composed of several cells and layers to provide a structural barrier that separates the internal and external environments of the body [1]. Skin aging is a phenomenon caused by structural and functional changes in skin cells and tissues. In the skin, moisture retention and wrinkles occur due to intrinsic and extrinsic aging [2].

As the lifespan of the population and incomes increase, interest in anti-aging products is growing. With the spread of this trend, the demand for skin health functional foods is also increasing.

To improve skin aging, AHAs (alpha hydroxy acids), antioxidants, moisturizers, retinoids, sunscreens, botulinum toxin injection or filler therapy, and dermabrasion such as chemical, physical, and laser peeling are used [3]. Physicochemical methods may have side effects such as irritation, contact dermatitis, and reduced effectiveness, and in addition, the phenomenon of exaggerated wrinkles other than the treatment site, bruising at the injection site, difficulty in pronunciation, paresthesia, infection, tissue necrosis, and swelling at the treatment site. It requires a recovery period, and due to side effects such as the risk of complications, there is a growing interest in suppressing skin aging through the intake of safe materials [3]. Therefore, many studies have been reported on functional food and cosmetic materials with fewer side effects [4–7].

Blackberry is a plant belonging to the genus *Rubus idaeus* of the Rosaceae family [8]. It contains flavonoids, phenols, anthocyanins, etc., and has been confirmed to have excellent antioxidant activity. It has been reported to have anticancer, antiallergic, anti-obesity, and antibacterial properties because it contains triterpenes [9–11].

Lactic acid bacteria have been reported to have antibacterial, immune, and antioxidant activity [12,13]. Studies have been reported demonstrating beneficial effects of lactic acid bacteria on skin aging in animal models and in human clinical trials [14,15].

Our previous animal experiments showed that BB-1000, which is blackberry fermented with *Lactobacillus (L.) Plantarum* JMBI-F5, showed inhibited UV-induced skin wrinkles, an increase in epidermal thickness, and collagen fiber accumulation in the skin [16]. Based on these effects, this clinical study evaluated the wrinkle improvement of BB-1000 for Korean participants aged 35 to 60 years with wrinkles and dry skin.

2. Methods

This clinical trial was designed as a randomized, double-blind, placebo-controlled, and parallel study. This clinical trial was reviewed and approved by the Independent Institutional Bioethics Committee (IRB) for the human application protocol, and informed consent was obtained prior to the study. This study was approved by the Global Medical Research Center (GMRC) and was performed in accordance with the standard operating procedures of the ICH GCP (Approval number: GIRB-20928-BE, Protocol number: CBG-BB-1000). The clinical trial was planned for 12 months from the date of approval. Subjects were screened on 30 November 2020, enrolled on 14 December 2020, and the final subjects completed the study on 28 April 2021.

2.1. Preparation of BB-1000

For the purpose of the study, a test product based on BB-1000 (500 mg/capsule) and a placebo were prepared. The formulation was composed of ingredients including flavor, dextrin, dextrose, stevia, magnesium stearate, silicon dioxide, and synthetic pigments (Table 1).

Table 1. Formulation of BB-1000 and placebo.

Component	Placebo (% of *w*/*w*)	BB-1000 (% of *w*/*w*)
Cellulose	4.6030	-
BB-1000	-	26.6668
Citric acid anhydrous	3.0000	-
Chefmaster® Burgundy Wine Pigment	0.0720	-
Chefmaster® Buckeye Brown Pigment	0.0770	-
Grape Flavor Powder	1.8000	1.8000
Dextrin	37.4480	29.0000
Dextrose	47.0000	36.5332
Stevia	3.0000	3.0000
Magnesium stearate	1.0000	1.0000
Silicon dioxide	2.0000	2.0000

2.2. Study Design

The research was conducted in accordance with the functional cosmetic efficacy evaluation guidelines of the Korean Ministry of Food and Drug Safety (KFDA 11-1470000-000863-01). According to the photographic evaluation criteria of wrinkles, the degree of wrinkles in the corners of the eyes (Crow's feet) was evaluated in 10 grades (0, none; 2, none/fine; 2, fine; 3, fine/mild; 4, mild; 5, mild/moderate; 6, moderate; 7, moderate/severe; 8, severe; 9, very severe). The volunteers were Korean males and females between the ages of 35 and 60 with grade 3 or higher for both the left and right eye wrinkles. Informed consent was obtained from all subjects involved in the study. Volunteers who consented to the clinical trial were enrolled as eligible subjects by evaluating demographic characteristics, lifestyle, cosmetics, medical history and drug administration, blood pressure, pulse rate, clinical pathology, pregnancy response, skin wrinkles, and skin moisture content (Supplementary Tables S1 and S2). The criteria for selection were grade 3 or higher for both left and right eye wrinkles. The number of total volunteers in this study was 100 Koreans,

and considering the exclusion rate (25%), 74 volunteers were tested because 26 dropped out (Table 2).

Table 2. Number of volunteers for clinical trials.

	Placebo	BB-1000	Sum of Columns
Enrolled volunteers	37	37	74
Total volunteers *	50	50	100

* Number of cases considered for dropout (25%).

At visit 2 (randomization visit, week 0), all human subjects who met the selection/exclusion criteria were assigned to each group according to the assignment code of the randomization method. For double-blinding, the coded information of each group was kept sealed until the end of the clinical trial. For balanced randomization between groups, the number of subjects in each group was equally assigned. Volunteers randomized to either the BB-1000 or placebo groups received the product for oral intake at a dose of 800 mg/kg/day for 12 weeks (Figure 1). At visits 1, 3, and 4, volunteers washed away skin waste or debris, and rested for 30 min at 20~24 °C, 40~60% RH.

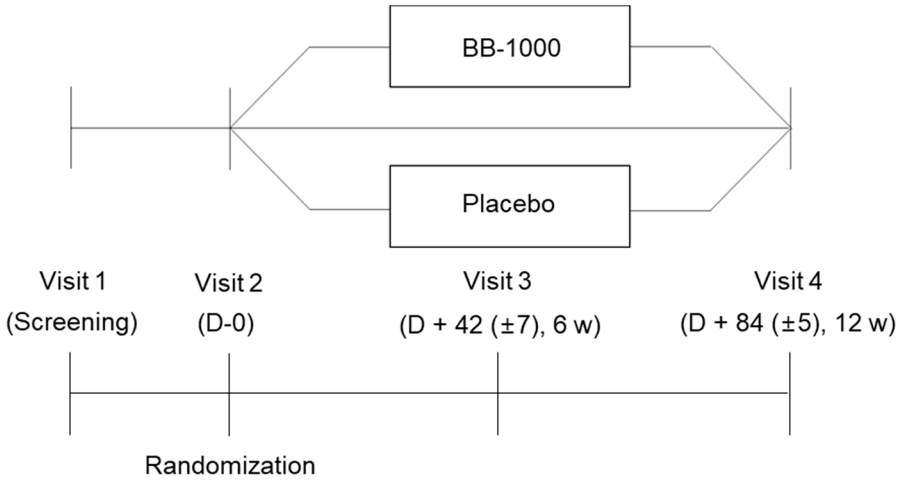

Figure 1. Schematic protocol for clinical trials.

2.3. Eye Wrinkle Changes Measurement

Wrinkle changes after taking BB-1000 were compared by photographic evaluation. Skin imaging was measured using MARK Vu (PSI PLUS, Suwon, Korea). In the normal light (NL) mode of the LED continuous light source, the images were taken by dividing into the front, face, and left and right sides. The eye wrinkle volume was measured by measuring the skin volume excluding the wrinkle area among the skin surfaces of the eye corners (Crow's feet), and this was used as data to judge the effect of wrinkle improvement. Wrinkles in the corners of the eyes (Crow's feet) were measured using PRIMOS lite (GFM, Germany), and average roughness (Ra), maximum peak-to-valley (Rmax), maximum peak height (Rp), maximum valley depth (Rv), and maximum average roughness (Rz) parameters were analyzed.

2.4. Skin Hydration Analysis

Skin moisture content was measured using a Corneometer® CM 825 (Courage & Khazaka, Courage & Khazaka, Cologne, Germany). The Corneometer® CM 825 is a device that measures the moisture content of the skin layer 30~40 μm below the stratum corneum of the skin without interference from cosmetics and dermatological drugs. The average value of at least three measurements at the orthogonal intersection between the corner of the eye and the tip of the nose was used.

2.5. Safety Test

The safety of BB-1000 was evaluated by volunteers' adverse reactions, blood and biochemical analysis, and urinalysis after clinical trials.

2.6. Statistical Analysis

Statistical analysis was performed using SAS® (Version 9.4, SAS Institute, Cary, NC, USA). Changes between groups were analyzed by the paired t-test or Wilcoxon signed rank test. The significance was considered for the levels of $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***).

3. Results

3.1. Effect of BB-1000 on Eye Wrinkle Improvement

We previously reported the significant efficacy of BB-1000 for wrinkle improvement in in vitro and in vivo models [16]. To validate these findings, this study attempted to explore the effects of oral ingestion of BB-1000 in the human body.

Representative parameters of wrinkles were considered as photographic wrinkle grades, mean average roughness (Ra), maximum peak-to-valley (Rmax), maximum peak height (Rp), maximum valley depth (Rv), and maximum average roughness (Rz) parameters. These parameters were measured under relaxed conditions. The degree of wrinkles in the corners of the eyes (Crow's feet) was photographically evaluated as the scores of wrinkle grades according to the KFDA standard guideline. Figure 2a shows the representative wrinkle reductions after 12 weeks of BB-1000 intake. The effect of BB-1000 did not show a wrinkle reduction after 6 weeks, but it was significantly reduced to 0.22 ± 0.47 from the baseline at 12 weeks (Figure 2b). As shown in Figure 2c, eye wrinkle volume was analyzed by measuring the corners of the eyes (Crow's feet) with PRIMOS lite.

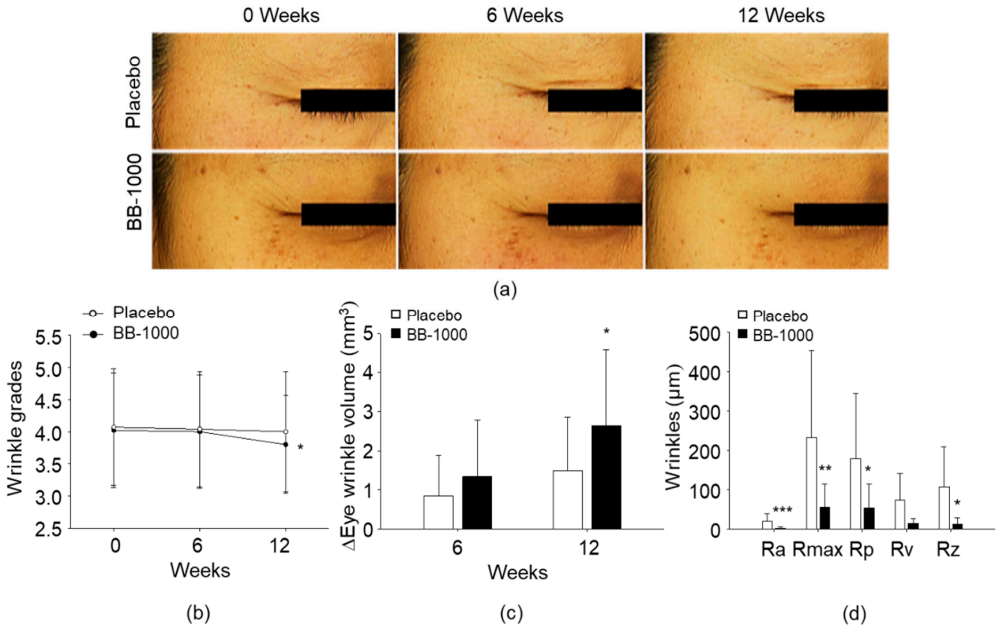

Figure 2. Effects of BB-1000 on eye wrinkle changes: (**a**) Representative photographs of participants with wrinkles after oral ingestion of placebo and BB-100 for 0, 6, and 12 weeks. (**b**) Photographic periorbital wrinkle grades at weeks 0, 6, and 12. (**c**) The effect of placebo and BB-1000 on skin wrinkle volume at 6 and 12 weeks. The eye wrinkle volume change is the difference in values after 6 and 12 weeks from the baseline (week 0). (**d**) Changes in skin wrinkle parameters after 12 weeks. Ra, average roughness; Rmax, maximum peak-to-valley; Rp, maximum peak height; Rv, maximum valley depth; Rz, maximum average roughness (Rz). Data are mean ± SD. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ versus placebo.

Changes in eye wrinkle volume were calculated by subtracting the time zero value from the absolute value after intake of placebo or BB-1000. After 6 weeks, the skin wrinkle volumes of BB-1000 and the placebo group increased by 1.34 ± 1.45 and 0.85 ± 1.04 mm^3, respectively, but there was no significant difference between the groups. On the other hand, at 12 weeks, the BB-1000 group increased by 2.65 ± 1.94 mm^3, compared to the placebo group (1.49 ± 1.36 mm^3), which was statistically significant between the groups ($p < 0.05$). To clarify the above results, various R-type parameters were analyzed. Most parameters of the BB-1000 group were significantly improved at week 12 compared to the placebo group (Figure 2d). Although maximum average roughness (Rv) was not statistically significant, it appeared to be effective compared to the placebo. These results suggest that BB-1000 has a remarkable effect on wrinkle improvement.

3.2. Effect of BB-1000 on Eye Skin Hydration

The skin moisture content was measured three times at the right angle to the tail and nose tip with Corneometer® CM 825, and the average value was calculated. Figure 3a shows the skin moisture content measured at 0, 6, and 12 weeks of BB-1000 and placebo administration. There was no difference in water content between groups in both the BB-1000 and placebo groups. Additionally, changes in skin moisture content were compared and are presented in Figure 3b. After 6 weeks, the contents of placebo and BB-1000 groups increased by 2.17 ± 1.33 AU ($p < 0.0001$) and 2.08 ± 1.22 AU ($p < 0.0001$), respectively, but there was no statistically significant difference between groups. After 12 weeks, although the skin moisture content of the placebo and the BB-1000 groups increased to 4.20 ± 1.70 AU ($p < 0.0001$) and 4.77 ± 1.78 AU ($p < 0.0001$), there was also no statistical significance between the groups.

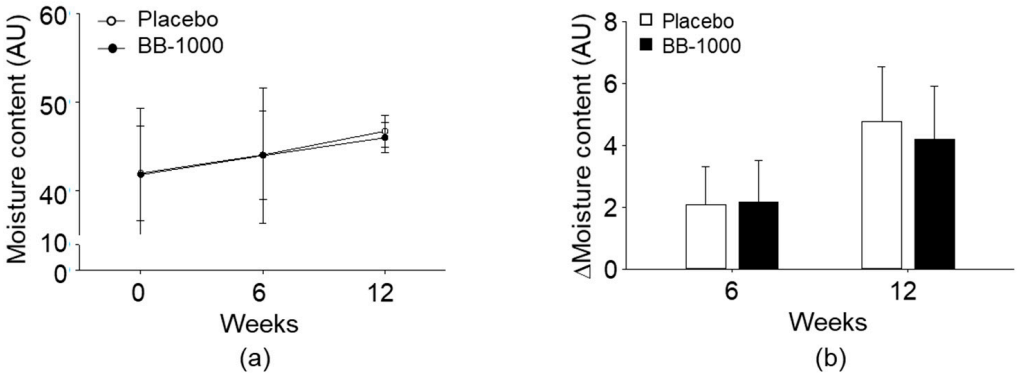

Figure 3. Effects of BB-1000 on skin moisture content: (**a**) Skin moisture content around the eyes at weeks 0, 6, and 12 of placebo and BB-1000 groups. (**b**) Changes in skin moisture content around the eyes from baseline after 6 and 12 weeks. Data are mean ± SD.

3.3. Safety of BB-1000

Clinical pathology tests for the safety evaluation of BB-1000 in this clinical study were divided into hematological, biochemical, and urinalysis at visits 1 and 4. As shown in Table 3, there were no statistically significant differences between the groups after 12 weeks of the hematological and biochemical analysis. Urinary factors, such as specific gravity, pH, protein, glucose, ketone, bilirubin, red blood cells (erythrocytes), urobilinogen, nitrites, and white blood cells (leukocytes), were analyzed at visits 1 and 4 in placebo and BB-1000 groups. Consistent with blood analysis results, there were also no significant changes in placebo nor BB-1000. These results suggest that BB-1000 can be used as a safe functional food.

Table 3. Results of hematology and biochemical analysis in placebo and BB-1000 groups.

	Placebo		BB-1000	
	Visit 1	**Visit 4**	**Visit 1**	**Visit 4**
WBC ($10^3/\mu L$)	5.35 ± 1.15	5.44 ± 1.39	5.20 ± 1.33	5.38 ± 1.44
RBC ($10^6/\mu L$)	4.29 ± 0.31	4.32 ± 0.36	4.33 ± 0.33	4.35 ± 0.39
Hb (g/dL)	13.04 ± 1.24	13.01 ± 1.35	13.40 ± 0.92	13.40 ± 1.06
Hct (%)	38.68 ± 3.13	39.16 ± 3.69	39.93 ± 2.96	39.16 ± 3.69
Platelet ($10^3/\mu L$)	262.00 ± 69.81	260.53 ± 69.95	243.12 ± 62.71	242.98 ± 58.59
Neutrophil (%)	57.62 ± 6.25	55.67 ± 8.73	53.99 ± 6.60	54.17 ± 6.39
Lymphocyte (%)	32.48 ± 6.02	34.41 ± 8.28	36.08 ± 6.20	35.73 ± 6.04
Monocyte (%)	6.97 ± 1.48	7.13 ± 1.45	6.97 ± 1.53	7.14 ± 1.34
Eosinophil (%)	2.21 ± 1.70	2.06 ± 1.38	2.17 ± 1.65	2.32 ± 1.62
Basophil (%)	0.72 ± 0.36	0.74 ± 0.35	0.79 ± 0.39	0.64 ± 0.26
Glucose (mg/dL)	91.63 ± 7.85	91.91 ± 10.32	91.60 ± 14.18	92.69 ± 12.97
Protein (g/dL)	7.08 ± 0.35	7.24 ± 0.38	7.09 ± 0.33	7.17 ± 0.38
Albumin (g/dL)	4.22 ± 0.22	4.33 ± 0.26	4.29 ± 0.19	4.34 ± 0.23
T Bil (mg/dL)	0.64 ± 0.20	0.69 ± 0.24	0.64 ± 0.28	0.67 ± 0.25
BUN (mg/dL)	12.31 ± 2.99	13.06 ± 2.33	13.04 ± 3.17	13.60 ± 2.78
AST (U/L)	22.06 ± 11.43	22.26 ± 6.34	22.06 ± 8.36	22.64 ± 8.10
ALT (U/L)	18.44 ± 19.17	18.36 ± 15.76	18.72 ± 10.12	20.60 ± 16.80
γ-GTP (U/L)	21.54 ± 16.34	20.85 ± 18.62	25.80 ± 20.49	25.76 ± 27.91
Creatinine (mg/dL)	0.64 ± 0.10	0.64 ± 0.09	0.64 ± 0.12	0.63 ± 0.12
TC (mg/dL)	201.31 ± 35.60	210.72 ± 33.01	203.06 ± 32.94	200.67 ± 27.31
HDL-C (mg/dL)	57.44 ± 13.61	60.77 ± 14.05	56.20 ± 10.57	57.36 ± 12.02
LDL-C (mg/dL)	119.60 ± 32.44	125.49 ± 31.02	122.24 ± 26.74	121.18 ± 24.05
TG (mg/dL)	99.02 ± 50.62	98.72 ± 44.26	103.30 ± 55.75	102.51 ± 61.07

WBC, white blood cells (leukocytes); RBC, red blood cells (leukocytes); Hb, hemoglobin; Hct, hematocrit; T Bil, total bilirubin; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride. Data are mean ± SD.

4. Discussion

Wrinkles are a major symptom of skin aging and are caused by several factors [17]. Typically, reactive oxygen species (ROS) is one of the important factors involved in the formation of wrinkles. Oxidative stress induced by ROS causes skin inflammation, and consequently activates MMP (matrix metalloproteinase) [18]. Activated MMP degrades collagen and promotes skin wrinkles [4,19]. Ultraviolet (UV) produces ROS, which regulate a variety of cellular functions, including inflammation, collagen degradation, and MMP activity [20].

We previously reported that blackberries fermented with *L. Plantarum* JMBI-F5 (BB-1000) were effective in improving skin wrinkles in hairless mice against UVB-induced skin aging [16]. BB-1000 improved skin wrinkles, suppressed the increase in epidermal thickness, and restored the decrease in collagen by UV irradiation. BB-1000 showed an antioxidant effect on UVB-induced oxidative stress by increasing the activity of GSH and SOD in serum and tissue. UV-induced reduction of type-I procollagen and increases of MMP-1, iNOS, and COX2 protein expression were inhibited by BB-1000. Phosphorylation of ERK1/2, JNK, p38, NFκB, and IκB proteins was also inhibited [16].

Therefore, we tried to confirm the effect of BB-1000 on the improvement of skin wrinkles in humans through a clinical trial. With dietary supplementation of BB-1000 for 12 weeks, the periorbital wrinkles showed marked improvements according to the photographic observation.

Lactic acid bacteria, including *Lactobacillus* and *Bifidobacterium*, play an important role in human intestinal microflora and are widely commercialized as probiotics [21]. Recently, reports of the effects of probiotics on skin health are increasing [6,22–24]. Nam et al. reported that *L. Plantarum* HY7714 reduced wrinkles via oral intake in a clinical study [23]. Such results are in agreement with our study. In addition, the natural products fermented with probiotics are effective for skin health and wrinkle improvement [5,16,25].

It has been reported that the anti-wrinkle effect of *Aloe arborescens* extract is enhanced by fermentation [5].

The results of this study are the first reports of the anti-wrinkle effect of BB-1000 through clinical trials. As shown in our study, eye wrinkles improved significantly after 12 weeks of BB-1000 ingestion. The results of this clinical trial are similar to a number of previous reports. However, it was found that BB-1000 had no effect on skin moisturizing enhancement. We reported in a previous study that BB-1000 had antioxidant properties and improved wrinkles by activating antioxidant mechanisms [16]. Dry skin is caused by damage to the skin barrier caused by oxidative stress, but it is known that there are various other factors [26,27]. It is known that the decrease in skin moisture can be controlled by water retention, maintenance of cell spacing, and adhesion and diffusion of cell growth factors and nutrients [27]. In addition, skin moisture retention is known to protect the skin from dryness by increasing water binding or hydrophilicity through physicochemical interactions with the lipid structure or protein of the stratum corneum [26].

Therefore, the specific mechanism of this clinical study on BB-1000 should be specified through further studies.

5. Conclusions

This study showed that oral intake of BB-1000 for 12 weeks could improve wrinkles in Korean men and women aged 35 to 60 years. The significance of this study is that the anti-wrinkle efficacy of BB-1000, a fermented blackberry product, was confirmed not only in previous animal experiments, but also in this clinical trial. In conclusion, as a result of clinical trials on skin wrinkle improvement and safety, BB-1000 is expected to be used with confidence as a health functional food that can improve skin wrinkles. Additionally, when BB-1000 is used with a moisturizer, the wrinkle improvement effect may be enhanced.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cosmetics9030050/s1, Table S1: Analysis of the subject's lifestyle; Table S2: Concomitant drugs administration.

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Institutional Review Board Statement: The study was conducted in accordance with the ICH GCP, and approved by the Institutional Review Board of the Global Medical Research Center (GMRC) (protocol code CBG_BB-1000 and date of approval 9 November 2020) for studies involving humans.

Informed Consent Statement: All participants in the study voluntarily provided informed consent.

Data Availability Statement: Not applicable. Data are not publicly available due to privacy reasons.

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Conflicts of Interest: The authors declare no conflict of interest.

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