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Effect of Nilitis® SR on Knee Pain in Japanese Adults: A Double-Blind, Randomized, Placebo-Controlled Study

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Abstract:

Objectives: The mitigation of knee pain leads to improved quality of life (QOL). NiLitis® SR is a dietary supplement containing Boswellin® Super (Boswellia serrata extract), Curcumin C3 Complex® (turmeric extract) and ginger extract, which is hypothesized to have an anti-inflammatory effect. This study examined the effect of NiLitis® SR on knee pain in healthy Japanese adults.

Methods: This was a double-blind, randomized placebo-controlled trial, comparing the ingestion of NiLitis® SR as against placebo over an 8-week period. In-hospital inspections were carried out three times, i.e., at 0 week, 4 weeks and 8 weeks. The primary outcome measure was the Japanese Knee Osteoarthritis Measure (JKOM). Secondary outcome measures were Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), serum hyaluronic acid (sero-HA), serum high sensitivity C-reactive protein (hs-CRP) and questionnaires (using Likert scale for Quality of Life).

Results: In the NiLitis® SR group, VAS, JKOM total score and WOMAC total score significantly decreased at the end of 8 weeks. Compared with the placebo group, subjects in the NiLitis® group showed significantly lower values in VAS and sero- hyaluronic acid.

Conclusion: Intake of NiLitis® SR relieves knee pain and may control hyaluronic acid outflow into the bloodstream.

Keywords: ***QOL, JKOM, WOMAC, Boswellia serrata, turmeric, ginger.***

Introduction

Quality of life (QOL) is a measure of a person's overall health and well-being[1]. Knee pain has been shown to reduce QOL[2]. This applies to not only patients suffering from a disease such as knee osteoarthritis (OA) or rheumatoid arthritis (RA) but to healthy individuals as well. This study aimed to evaluate the effectiveness of NiLitis® SR in reducing knee pain in individuals who are not particularly affected by OA and RA.

NiLitis® SR is a dietary supplement containing Boswellin® Super, Curcumin C3 Complex® and ginger extract. Boswellin® Super is a standardized *Boswellia serrata* extract (*B.Serrata*) and contains boswellic acids as its major bioactive component. The anti-inflammatory activity of Boswellic acids is reported to be its potential to control the production of

inflammatory leukotrienes (LTs) by selectively inhibiting 5-lipoxygenase activity[3, 4, 5, 6]. This anti-inflammatory activity of *B. serrata* extract may prevent the degeneration of connective tissues caused by inflammatory arthritis. In addition, boswellic acids decrease the levels of glutamic–pyruvic transaminase, glycohydrolase, and β-glucuronidase, which otherwise increase during joint pain[7, 8]. Patients with inflammatory arthritis also display high levels of hyaluronidase activity. Hyaluronidase is a glycohydrolase enzyme that catabolizes hyaluronic acid (HA) polymer[9]. Hyaluronic acid prevents friction between cartilages in the synovial fluid[10]. Therefore, *B. serrata* extract alleviates knee pain by controlling the catabolism of HA. However, whether intake of *B. serrata* enhances knee joint function in healthy individuals has not been scientifically studied to date, and additional clinical trials are required to confirm the effects of *B. serrata* on the knee joint[11,12].

Turmeric extract contains curcuminoids as its major bioactive component. Curcumin C3 Complex® is an extract from the rhizomes of *Curcuma longa*, standardized to contain not less than 95% Curcuminoids. Curcumin suppresses the formation of thromboxane B_2 and leukotriene B4 (LTB_4) and the activities of lipoxygenase, cyclooxygenase and hyaluronidase[13, 14, 15, 16, 6]. In this manner, Curcumin shows a similar mechanism of action to that of boswellic acids; therefore, it may also play a role in alleviating knee pain. Clinical studies elaborating the role of Curcuminoids to offer relief to subjects suffering from osteoarthritis has been clearly demonstrated in the past as well [17, 18].

Ginger extract contains gingerols, namely 6-, 8- and 10-gingerols, as its major component. Its mechanism of action is similar to that of Boswellic acids and Curcumin, in that it inhibits the biosynthesis of LT[19]. However, ginger extract may reduce RA symptom because of its potential role in reducing prostaglandin and thromboxane as well as inhibition of thrombocyte production[20, 21]. However, despite these studies, there is not enough evidence showing that ginger extract can improve knee pain.

As knee pain severely reduces QOL even in the absence of disease, identifying a new natural supplement and substantiating its application through clinical trials for use in management of healthy knee joint is warranted. As mentioned above, NiLitis® SR containing *B. serrata* extract, turmeric extract and ginger extract would relieve knee pain. Therefore, we examined the effect of NiLitis® SR on knee pain in healthy Japanese adults who were experiencing knee pain.

I Subjects and Methods

1 Trial design:

This study was conducted as a double-blind, randomized placebo-controlled trial. It compared the NiLitis® SR group with the placebo group to verify the efficacy of NiLitis® SR. The ratio of assignment was 1:1. The ingestion period was set at 8 weeks, and in-hospital inspections were conducted three times (0week, 4 weeks and 8 weeks) during this duration in the Seishin-kai Medical Association Inc., Takara Medical Clinic (Shinagawa-ku, Tokyo).

2 Ethical Considerations:

This study was conducted according to the Declaration of Helsinki and was approved by the ethics committees in the Seishin-kai Medical Association Inc., Takara Medical Clinic (Shinagawa-ku, Tokyo). All subjects provided written informed consent before the commencement of the study. This study has been registered on UMIN-CTR (UMIN000014324).

3 Subjects:

The study subjects were recruited from individuals who registered in the monitor recruitment site (http://www.monitor-touroku.jp/index.html), which was run by ORTHOMEDICO Inc. (Bunkyo-ku, Tokyo). Through this process, forty eight (48) subjects were recruited for the study.

Healthy Japanese adults who were experiencing knee pain were registered in this trial. Subjects aged in their 60s were preferentially recruited, followed by subjects in their 50s, 40s, 30s, and then 20s, until the required number of subjects was achieved. Patients were excluded if they met the following criteria: (a) at least one previous medical history of malignant tumor, heart failure or myocardial infarction, (b) currently under treatment for either atrial fibrillation, cardiac arrhythmia, hepatic disorder, renal disorder, cerebrovascular disorder, rheumatism, diabetes mellitus, dyslipidemia, hypertension, or other chronic disease, (c) currently taking medicines, herbal

medicines, or dietary supplements, (d) allergic to medicines or foods related to the test material of this trial, (e) pregnant, lactating, or planning to get pregnant during the trial period, (f) enrolled into other clinical trials within the last 3 months before agreeing to participate in this trial, and (g) judged unsuitable for participating in this trial by the physician.

4 Sample size & study procedures:

Total forty eight (48) subjects were equally distributed between two groups (NiLitis® and Placebo).The study was a double-blind trial. The subjects, the principal investigators and the analysts were all blinded to trial information. The staff of ORTHOMEDICO Inc. (Bunkyo-ku, Tokyo) provided computer-generated random numbers using the Statlight#11Ver.2.10 software (Yukms Co., Ltd., Kawasaki-shi, Kanagawa). Inclusion criterion was a relatively high score in the visual analogue scale (VAS) included in the Japanese Knee Osteoarthritis Measure (JKOM). Thus, a total of 48 subjects were incorporated in this study. The allocation number was decided based on age with VAS in JKOM as a layout adjustment factor, and randomizations were assigned with one given to each study participant following a completely randomized design (24 subjects/ group).

5 Interventions:

NiLitis® SR and placebo were provided by the Sabinsa Japan Corporation (Toshima-ku, Tokyo). Table 1 shows the ingredients of each intervention. In addition, subjects were instructed to ingest their allocated study medication with water after breakfast once a day.

Table 1 Nutritional information of NiLitis® SR and the placebo

Ingredients	Unit	NiLitis® S	Placebo
Boswellin® Super			
– *Boswellia serrata* extract	mg	33.34	-
– starch syrup of reduced malt sugar	mg	20.00	127.50
– crystalline cellulose	mg	43.16	165.00
– Calcium stearate	mg	3.00	6.00
– Micro silicon dioxide	mg	0.50	1.50
Curcumin C3 Complex® - Turmeric extract	mg	100.00	-
Ginger extract	mg	40.00	-
Hydroxyl propyl methyl cellulose	mg	28.00	-
Carboxy methyl-cellulose sodium	mg	6.00	-
Microcrystalline cellulose	mg	170.00	-
Magnesium stearate	mg	4.00	-
Propylene glycol	mg	1.00	-
Total	mg	449.00	300.00

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6 Outcomes:

i) Primary outcome: Subjects were investigated for their QOL related to knee pain using JKOM. The endpoints with JKOM were the VAS and the total JKOM score. The 0-100 mm VAS was used to evaluate present pain intensity, with a score of "0" indicating "no pain at all" and a score of "100" indicating "very severe pain." The overall JKOM total score was calculated based on answers to 25 questions about "knee pain and stiffness," "state of daily life," "regular activity" and "condition of health," with "0" being "the mildest" and "4" being "the most severe."[22]

ii) Secondary outcomes:

(1) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): 23 Subjects were investigated for their QOL relating to knee pain using WOMAC scores. WOMAC score was calculated based on the answers to 24 questions about "pain," "stiffness," and "difficulty to perform the daily activity," with "0" being "the mildest" and "4" being "the most severe."

(2) Inflammatory markers - Blood samples (15 mL of venous blood) were collected from each subject and serum hyaluronic acid (sero-HA) and high sensitivity C-reactive protein (hs-CRP) were evaluated. Blood collection took place at Seishin-kai Medical Association Inc., Takara Medical Clinic, and serum analyses were entrusted to LSI Medience Corporation (Chiyoda-ku, Tokyo).

(3) Questionnaires (Likert scale) - All patients responded to the questionnaire using a Likert scale ("1: does not fit me at all," "2: hardly fits me," "3: really does not fit me," "4: slightly fits me," "5: somewhat fits me," or "6: almost completely fits me"). The questions were as follows: "My hands feel cold," "My feet feel cold," "My body feels cold," "I have pain in my stomach," "I feel stressed," "My range of activities is smaller," "I feel physical fatigue," "I feel troubled about life," "I have constipation," "I have stiffness in my body," "My skin condition is bad," "My quality of sleep is bad," "I have a stuffy nose," "I have fits of coughing," and "I cannot concentrate on things."

iii) Safety evaluation

Body measurement, physical examination, urine analysis, peripheral blood analysis, and medical interview were performed to evaluate the safety of study medication and the overall health status of subjects at 0 and 8 weeks. Body measurement, physical examination, urine analysis, drawing of blood and medical interviews were carried out at Seishin-kai Medical Association Inc., Takara Medical Clinic. Peripheral blood analysis was entrusted to LSI Medience Corporation.

(a) Body measurement and physical examination

Height, body weight, body mass index, body fat percentage, systolic blood pressure, diastolic pressure, and heart rate were recorded.

(b) Urine analysis

Urine (approximately 25 mL) was collected from each subject and analyzed for protein, glucose, urobilinogen, bilirubin, ketone body, pH, occult blood, specific gravity, nitrite and leukocytes.

(c) Peripheral blood chemical analysis

The peripheral blood chemical analysis included the following: white cell count, red cell count, hemoglobin, hematocrit, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocyte differential count, aspartate aminotransferase/glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/glutamate pyruvate transaminase (ALT/SGPT), γ-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), leucine amino peptidase (LAP), total bilirubin, direct bilirubin, indirect bilirubin, cholinesterase, zinc turbidity test (ZTT), total protein, urea nitrogen, creatinine, uric acid, creatine kinase (CK), sodium, potassium, chloride, calcium, inorganic phosphorus, serum iron, serum amylase, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, free fatty acids, glucose, hemoglobin A1c (HbA1c; National Glyco hemoglobin Standardization Program), and glycoalbumin. The blood samples were used in this analysis in a manner similar to that used for monitoring inflammatory markers.

(d) Medical interview

Subjects were interviewed with regard to lack of sleep, state of defecation, shape of defecation, sense of defecation, headache, dizziness, stomachache,

anorexia, nausea, menstrual cycle (women), and other subjective symptoms.

(e) Statistical methods

Within-group comparisons compared the measured values at 4 and 8 weeks with those of 0 week by the Dunnett's test. Between-group comparisons included the measured values at baseline (0 weeks) by analysis of variance (ANOVA) and the measured values at 4 or 8 weeks by analysis of covariance (ANCOVA). During analysis of VAS, JKOM total score and WOMAC total score, baseline and baseline of sero-HA were set as covariates. In addition, for analyzing inflammatory markers, baseline and baseline of VAS were used as covariates. On the other hand, the covariates of questionnaires were only set at baseline. Effect size (*d*) was calculated from the difference of the mean and standard deviation.

II Results

1 Participant flow

Figure 1 shows the flow chart of subjects in this study. All subjects (n =24/group) in both the NiLitis® SR and placebo groups completed all examinations. The total number of subjects included in the analyses in each of the groups was 24 (NiLitis® SR group, 5 males and 19 females) (placebo group, 8 males and 16 females). The mean ages (±standard deviation) in the NiLitis® SR and placebo groups were 49.0 ±10.5 and 49.0 ±9.8 years, respectively (Table 2).

Figure 1Flow chart of subjects

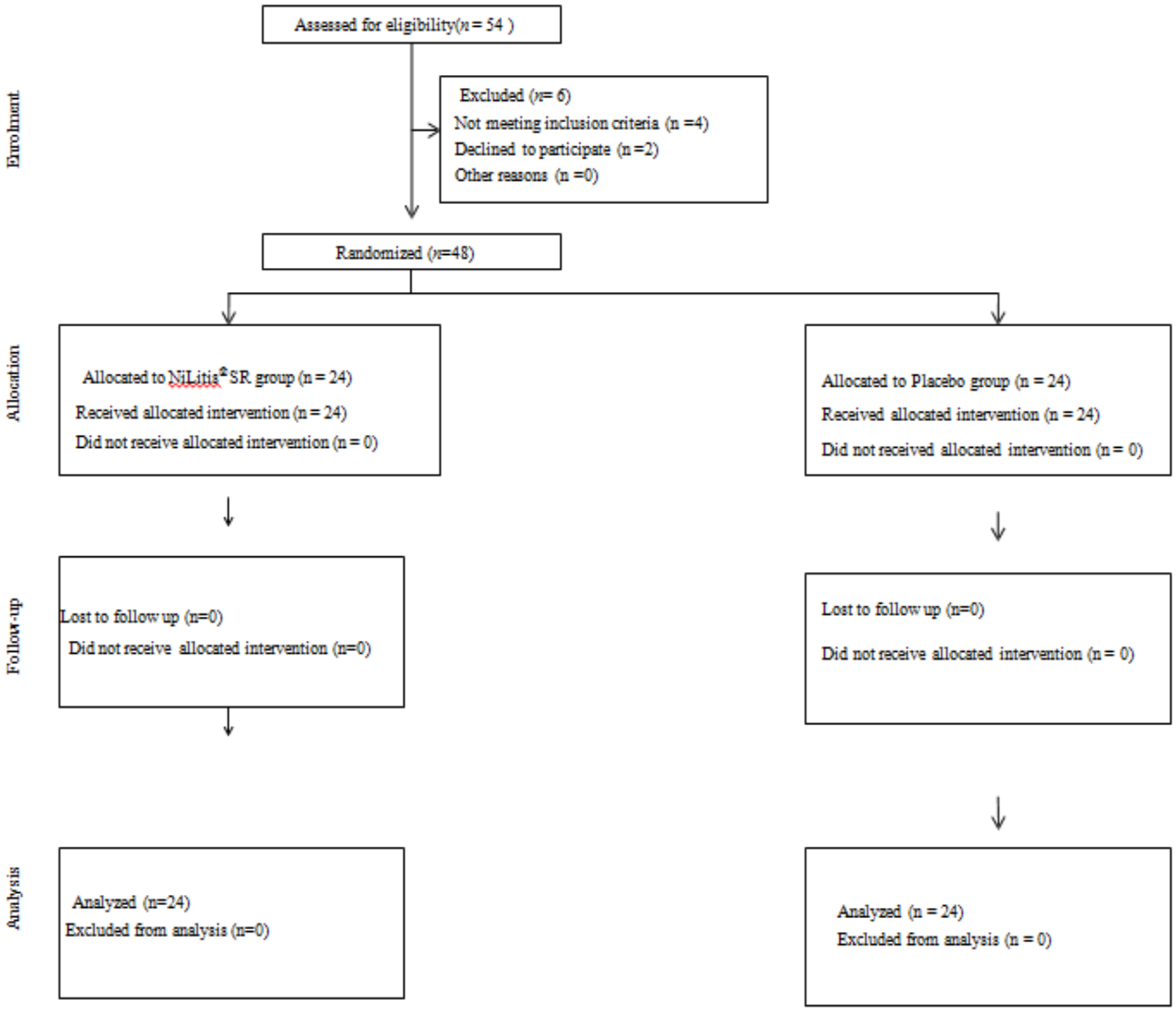

Table 2 Demographics of the included subjects

Item	Unit	NiLitis® SR		Placebo	
N (male/female)	people	24(5/19)		24 (8/16)	
Age	years	49.0	(10.5)	49.0	(9.8)
Height	Cm	160.1	(6.7)	162.1	(9.3)
Weight	kg	53.0	(8.5)	60.9	(10.1)
BMI	kg/m^2	20.6	(2.9)	23.4	(3.3)
Body fat rate	%	23.5	(6.7)	26.3	(7.2)

Mean (standard deviation)

2) JKOM, WOMAC, Inflammatory marker

Table 3 shows the measured values from subjects belonging to the NiLitis® SR and placebo groups in this study. In the NiLitis® SR group, VAS, JKOM total score and WOMAC total score decreased compared with those at baseline (0week; Table 3). Compared with the placebo group, NiLitis ® SR intake lowered values in VAS and sero-HA (Table3).

Table 3. Measured values of JKOM total score, WOMAC total score and blood tests

Item	Unit	Group	Week 0	Week 4	Week 8
VAS	Mm	NiLitis® SR Placebo	68.8 (12.1) 71.8 (10.3)	34.4 (23.8) 41.8 (24.2)	35.6 (22.3) 39.6 (27.3)
JKOM total score	Point	NiLitis® SR Placebo	48.3 (13.0) 48.5 (11.8)	39.4 (11.0) 39.5 (8.2)	38.8 (12.1) 36.4 (6.9)
WOMAC total score	Point	NiLitis® SR Placebo	23.7 (16.7) 24.0 (15.9)	14.3 (13.3) 14.6 (11.4)	12.7 (14.2) 9.8 (8.8)
Hyaluronic acid	ng/mL	NiLitis® SR Placebo	18.8 (14.3) 24.8 (24.8)	15.9 (6.4) 50.3 (101.4)	18.4 (8.9) 42.9 (66.8)
High sensitivity CRP	mg/dL	NiLitis® SR Placebo	0.03 (0.03) 0.09 (0.14)	0.05 (0.10) 0.04 (0.05)	0.04 (0.05) 0.05 (0.07)

3) Questionnaires (Likert scale)

Table 4 shows the questionnaire results at each analysis point in this trial. Marked differences in the scores of "my range of activities is smaller" and "I cannot concentrate on things" were observed between the NiLitis® and placebo groups at 0week (Table4). In the NiLitis® SR group, scores of "I feel troubled about life" (4 weeks) and "I have constipation" (8 weeks) decreased compared with those at baseline (Table 4). On the other hand, in the placebo group, scores of "my range of activities is smaller" (8 weeks) and "I feel troubled about life" (4 weeks; 8 weeks) increased after intake (Table 4).

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Table 4. Measured values for the questionnaire .Items were scored using a Likert scale of 1–5, with 1 indicating "strongly agree" and 5 indicating "Strongly disagree. Data expressed as Mean (SD)

Item	Group	Week 0	Week 4	Week 8
My hands feel cold	NiLitis® SR Placebo	2.2 (1.3) 2.1 (1.0)	2.3 (1.2) 1.9 (1.0)	2.5 (1.1) 2.3 (1.2)
My feet feel cold	NiLitis® SR Placebo	3.0 (1.4) 2.9 (1.5)	2.8 (1.3) 2.7 (1.3)	3.2 (1.4) 2.8 (1.4)
My body feels cold	NiLitis® SR Placebo	2.6 (1.1) 2.8 (1.3)	2.5 (1.2) 2.4 (1.1)	2.9 (1.1) 2.7 (1.1)
I have pain in my stomach	NiLitis® SR Placebo	3.7 (1.5) 3.4 (1.3)	3.2 (1.5) 3.5 (1.3)	3.2 (1.3) 3.4 (1.2)
I feel stressed	NiLitis® SR Placebo	3.1 (1.5) 3.1 (1.2)	3.0 (1.3) 3.3 (1.1)	3.1 (1.3) 3.1 (1.1)
My range of activities is smaller	NiLitis® SR Placebo	2.3 (1.1) 2.9 (1.1)	2.2 (1.0) 2.4 (1.1)	2.3 (1.1) 2.3 (1.0)
I feel physical fatigue	NiLitis® SR Placebo	3.0 (1.1) 3.3 (1.2)	2.8 (1.1) 3.3 (1.0)	3.1 (1.3) 3.1 (0.9)
I feel troubled about life	NiLitis® SR Placebo	2.9 (1.2) 2.8 (1.0)	2.3 (1.1) 2.3 (0.9)	2.4 (1.1) 2.4 (0.9)
I have constipation	NiLitis® SR Placebo	2.5 (1.3) 2.3 (1.2)	2.3 (1.3) 2.5 (1.1)	2.2 (1.3) 2.2 (1.2)
I have stiffness in my body	NiLitis® SR Placebo	3.9 (1.6) 4.2 (1.3)	3.8 (1.7) 4.3 (1.6)	3.8 (1.5) 4.0 (1.5)
My skin condition is bad	NiLitis® SR Placebo	3.0 (1.1) 3.1 (0.9)	2.8 (1.2) 2.8 (1.0)	2.9 (1.3) 2.8 (1.0)
My quality of sleep is bad	NiLitis® SR Placebo	3.0 (1.3) 3.2 (1.2)	2.9 (1.4) 3.2 (0.9)	3.0 (1.5) 3.0 (1.0)
I have stuffy nose	NiLitis® SR Placebo	2.1 (1.4) 2.0 (1.0)	1.9 (1.1) 2.1 (1.2)	2.0 (1.0) 1.9 (1.1)
I have fits of coughing	NiLitis® SR Placebo	1.7 (1.0) 2.0 (1.2)	1.9 (1.2) 1.8 (1.1)	1.9 (1.0) 1.8 (1.2)
I cannot concentrate on things	NiLitis® SR Placebo	1.9 (0.9) 2.6 (0.8)	2.2 (0.9) 2.5 (1.0)	2.2 (1.1) 2.3 (1.0)

4) Safety evaluation

Body measurement, physical examination, urine analysis, peripheral blood chemical analysis and medical tests were carried out to evaluate the safety and tolerance of NiLitis® SR . Based on safety evaluations, we found the following: (a) no health problems occurred at 0 weeks, 4 weeks and 8 weeks and (b) there were no medically significant changes accompanying test foods in any of the subjects (data not shown). In addition, the study participants did not report any adverse events.

III Discussion

This study examined the effect of NiLitis® SR on healthy Japanese adults experiencing knee joint pain. Knee pain was evaluated by their objective symptoms using JKOM and WOMAC. Blood analysis of sero-HA and hs-CRP were used for evaluation of subjective symptoms. Compared with baseline, the group that ingested NiLitis® SR showed significant decrease in VAS, JKOM, and WOMAC total score. In addition, the VAS score in the NiLitis® SR group was significantly

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lower than that in the placebo group. These results suggest that NiLitis® SR intake relieves knee pain in healthy individuals. The pain relief may be caused by a combined anti-inflammatory effect[6)19)] of the *B. serrata* extract, turmeric extract and ginger extract in NiLitis® SR.

Results showed that the sero-HA levels decreased compared with the placebo group in 8 weeks. The reduced sero-HA levels may be because of the inhibition of hyaluronidase activity by boswellic acids[9)] and/or suppression of Hyaluronic Acid catabolism by Curcumin and secretion of HA into the blood stream. It is important to note that we observed a difference in hs-CRP between the NiLitis® SR group and placebo at baseline. In future, a detailed examination of hs-CRP levels should be performed prior to allocating groups.

Conclusions

In conclusion, this study showed that successive intake of NiLitis® SR containing *B. serrata*, turmeric and ginger extracts help to relieve knee pain in healthy individuals. In addition, NiLitis® SR has the potential to inhibit efflux of hyaluronic acid into the blood stream. Thus, one NiLitis® SR per day for 8 weeks may be recommended for relieving knee pain.

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We would like to express our sincere gratitude towards the trial investigators, study personnel and the subjects who actively took part in this clinical trial. Further studies need to be conducted in a diverse population in large scale and for longer duration.

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