Effects of a Standardized Oligomerized-Polyphenol from Litchi chinensis Fruit Extract and Mixed Plant Extract Supplementation on Peripheral Circulation and Cold Sensitivity

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Summary Certain individuals tend to suffer from a cold sensation—particularly in the lower extremities—despite most people not suffering from the same sensation. In Japan, this phenomenon is called “hie-sho” and reduces quality of life for several people, particularly women. A previous study has shown that a standardized oligomerized-polyphenol from Litchi chinensis fruit extract (OPLFE) reportedly causes a significant increase in body surface temperature. The present study aimed to investigate whether supplementation with OPLFE affected peripheral circulation and cold sensitivity. This randomized, double-blind, placebo-controlled trial was performed including 25 participants (age, 45.0±10.4 y; 3 males and 22 females) who were assigned to consume OPLFE, mixed plant extract with OPLFE, or placebo capsules for 14 d. Participants were instructed to relax for 60 min in a temperature-controlled room prior to obtaining measurements. Changes in skin temperature and peripheral blood flow of the middle finger were assessed immediately before and 1, 5, 10, 20, and 30 min after immersion in cold water (10˚C). Participants’ height, weight, skin temperature, and blood flow in peripheral tissue were measured; furthermore, their “hie-sho” was measured using the Visual Analog Scale (VAS). Skin temperature and blood flow in peripheral tissue increased in the OPLFE and mixed plant extract with OPLFE groups on day 14 compared with those on day 1. In addition, cold sensitivity in these two groups significantly improved between day 1 and day 14. These findings suggest that OPLFE improves “hie-sho” by increasing peripheral blood flow and skin temperature.

Key Words hie-sho, skin temperature, cold water load, lower extremities, placebo

A cool environment can cause a cold sensation on the skin, and this feeling of coldness differs between individuals. In Japan, women often suffer from a cold sensation—particularly in the lower extremities—when others are not cold. This unusual feeling of a cold sensation is called “hie-sho” in Japanese and is more common in females than in males (1–6). “Hie-sho” is a phenomenon that makes a person feel extremely cold in certain parts of the body, especially peripheral parts like limbs and lumbar region, compared with that in other parts of the body (1). In a study of 1,020 people, “hie-sho” has been found to be related to malaise, such as insomnia, fatigue, and swelling of lower limbs (7). Therefore, “hie-sho” is linked to reduced quality of life. However, the term “hie-sho” does not exist in Western medicine. Although “hie-sho” is a part of daily life for many people, most physicians do not consider it requires active treatment because no objective diagnostic method has yet been established. As a result, several individuals resort to Chinese medicine and supplements for treating “hie-sho.”

Several reports have explored the cause of “hie-sho.” The skin temperature of peripheral body parts greatly decreases during cold exposure (8), which is believed to be caused by decreased peripheral circulation (9). In an experiment involving rats, it was found that vasodilation is slower in females than males during cold exposure. This result supports the findings of an epidemiological study that “hie-sho” is more common in women (10).

A standardized oligomerized-polyphenol from Litchi chinensis fruit extract (OPLFE) (Amino Up Co., Ltd., Sapporo, Japan) has been approved as a dietary ingredient by the US Food and Drug Administration in 2007, and it has been recognized as safe since 2014. OPLFE has been the subject of several clinical trials and has been shown to offer numerous health benefits, including protection against oxidative stress (11), prevention and treatment of hyperuricemia (12), reduction in fatigue (13, 14), reduction of visceral fat (15), and increase in body surface temperature (16). Moreover, OPLFE has been shown to inhibit inflammatory markers following exercise (17, 18). Currently, a mixed plant extract containing OPLFE and 11 other ingredients is available on the Japanese market. Previous studies have reported...
that ginseng extract improves blood flow (19). In addition, ginkgo can induce arterial and venous vasoactive changes associated with increases in tissue perfusion, peripheral and cerebral blood flow, ocular blood flow, and microcirculation (20). The present study aimed to investigate the clinical effects of supplementation with OPLFE or mixed plant extract with OPLFE on peripheral circulation and cold sensitivity.

MATERIALS AND METHODS

Study participants. Overall, 25 participants were recruited for the present study and were divided into the following three groups: the OPLFE group: mean age, 48.1±5.5 y (two males and six females); the mixed plant extract with OPLFE group: mean age, 39.8±11.7 y (nine females); and the placebo group, age 49.1±12.1 y (one male and seven females.) The inclusion criteria were as follows: participants feel extremely cold in certain parts of the body, especially peripheral parts like limbs and lumbar region, compared with that in other parts of the body (Fig. 1). The exclusion criteria were as follows: 1) participants receiving outpatient care or taking medication for an underlying disease, 2) participants with an allergy to lychee, 3) participants in poor physical condition during the test period, and 4) participants with a result of >50 mm of “cold sensitivity” on the Visual Analog Scale (VAS). This clinical trial was approved by the ethical committee of Teikyo Heisei University, Tokyo, Japan (reference no. 29-094) and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN: R00035322). Informed consent was obtained from each participant in accordance with the provisions of the Declaration of Helsinki.

Experimental design. In the present randomized, double-blind, placebo-controlled trial, participants were randomly assigned to the OPLFE, mixed plant extract with OPLFE, or placebo group. All participants were instructed to ingest three capsules of the allocated substance prior to dinner every day for 14 d. Throughout the study period, participants were instructed to maintain a daily diary recording their intake of the assigned substance, any adverse events observed, and any medication used. Participants were instructed to maintain their usual lifestyle habits, such as diet, alcohol intake, and exercise, as much as possible. Participants whose intake of the allocated substance was ≤90% were considered non-compliant with the test protocol and excluded from analysis.

Experiments were performed on days 1 and 14. Participants were asked to refrain from consuming alcohol the day before the experiment and caffeinated drinks (e.g.,...
Oligonol Supplementation for Curbing “Hie-Sho”

There is growing evidence that OPLFE, an optimized phenolic product mixture obtained from lychee fruit polyphenols (LFP) containing catechin type monomers and lower oligomers of proanthocyanidin (21), can elicit physiological and biochemical alterations in vitro and in vivo (14, 22, 23). OPLFE used in this study contained 21.9% polyphenol monomer ((-)-catechin and (−)-epicatechin etc.) and 13.3% polyphenol dimer (procyanidin B2 etc.), while LFP contains 6.4% polyphenol monomer and 9.9% polyphenol dimer (24). The safety profile of OPLFE has been documented in numerous clinical and toxicological studies (21, 25). OPLFE attained “generally recognized as safe” status in 2009. The OPLFE capsules contained 50 mg OPLFE plus 260 mg dextrin. The mixed plant extract with OPLFE capsules contained 50 mg OPLFE, butcher’s broom extract, ginkgo biloba extract, vinca minor extract, zinc yeast, passion flower extract, ginseng extract, Myrciaria dubia fruit juice, black cohosh extract, guarana, enzyme-treated asparagus extract, and calcium stearate (total 310 mg). The placebo capsules contained 310 mg dextrin.

Evaluation items.

1) Height, weight, body mass index (BMI), and blood pressure: We recorded body height (HM200P; Charder Electronic Co., Ltd., Taichung, Taiwan), weight (BC-760; TANITA Corporation, Tokyo, Japan), and blood pressure (HEM-6310F; OMRON Corporation, Kyoto, Japan). BMI was calculated for all participants.

2) Cold sensitivity: Feelings of cold sensitivity were recorded using VAS from none (0) to severe (100) (26).

3) Skin temperature: Skin temperature was measured at the palm side of the right middle finger using thermistors (LT-ST08-12; Nikkiso-Therm Co., Ltd.) that were secured using micropore tape. All thermistors were connected to a data collection device (LT-8A; Gram Corporation, Saitama, Japan).

4) Blood flow in peripheral tissue: A probe (type C; ADVANCE Co., Ltd., Tokyo, Japan) of a laser Doppler blood flowmeter (ALF21; ADVANCE Co., Ltd.) was placed in contact with the palm side of the right middle finger to measure blood flow in peripheral tissue.

Statistical analysis. All data were expressed as mean±standard deviation (mean±SD). The equality of variance was evaluated using Levene’s test. Height, weight, and BMI data were analyzed using one-way analysis of variance (ANOVA) with three between-group factors. Cold sensitivity, skin temperature, and blood flow data were analyzed using two-way ANOVA with three between-group factors and time factors. Tukey’s honest significant difference post hoc test was used for multiple comparisons. When a significant difference was observed in Levene’s test, Wilcoxon signed-rank and Kruskal-Wallis tests were performed. *p<0.05.

Table 1. Participants’ height, weight, and BMI.

|                  | OPLFE (n=8) | Mixed product (n=9) | Placebo (n=8) | p value |
|------------------|-------------|---------------------|--------------|---------|
| Height (cm)      | 162.5±8.6   | 165.4±4.5           | 161.6±9.7    | 0.588   |
| Weight (kg)      | 58.7±16.1   | 61.8±10.9           | 54.6±8.8     | 0.523   |
| BMI (kg/m²)      | 21.9±4.3    | 22.5±3.5            | 20.8±2.4     | 0.630   |

Fig. 3. Serial measurements of VAS for cold sensitivity in the OPLFE (black bar), mixed plant extract with OPLFE (gray bar), and placebo (white bar) groups. Data are presented as mean±SD. When a significant difference was observed in Levene’s test, Wilcoxon signed-rank and Kruskal-Wallis tests were performed. *p<0.05.
RESULTS

Height, weight, and BMI

There were no significant baseline differences among the OPLFE, mixed plant extract with OPLFE, and placebo groups in any participant characteristics, including height, weight, and BMI (Table 1).

Cold sensitivity (VAS)

As illustrated in Fig. 3, "cold sensitivity" in the OPLFE and mixed plant extract with OPLFE groups improved significantly between day 1 and day 14 ($r=0.74$; $p<0.05$ and $r=0.83$; $p<0.05$, respectively). No significant change was observed in the placebo group. In addition, there were no significant differences among the OPLFE, mixed plant extract with OPLFE, and placebo groups.
Skin temperature

As shown in Fig. 4, skin temperature was significantly different among the OPLFE, mixed plant extract with OPLFE, and placebo groups ($\tau^2=0.08; p<0.05$). Skin temperature was significantly higher in the OPLFE group on day 14 than in the OPLFE and mixed plant extract with OPLFE groups on day 1 as well as placebo group on days 1 and 14 ($p<0.05$). Furthermore, it was significantly higher in the mixed plant extract with OPLFE group on day 14 than on day 1 ($p<0.05$).

Blood flow in peripheral tissue

As shown in Fig. 5, blood flow was significantly different among the OPLFE, mixed plant extract with OPLFE, and placebo groups ($\tau^2=0.11; p<0.05$). It was significantly higher in the OPLFE group on day 14 than in the OPLFE and placebo groups on day 1 ($p<0.05$). Furthermore, it was significantly higher in the mixed plant extract with OPLFE group on day 14 than on day 1 ($p=0.059$) and significantly higher in this group on day 14 than in the OPLFE group on day 1 and placebo group on days 1 and 14 ($p<0.05$).

DISCUSSION

The present study aimed to examine the effect of OPLFE and mixed plant extract with OPLFE product on skin temperature, blood flow in peripheral tissue, and cold sensitivity. Our results demonstrated significant improvements in these measures from day 1 to day 14 in participants taking OPLFE and mixed plant extract with OPLFE.

OPLFE Oligonol was obtained by oligomerizing the polyphenol polymers in LFP using a modification of a patented technology previously described. The process involves mixing proanthocyanidins with tea extract but not with l-cysteine and purifying the mixture using a column. Oligonol contains 15.7% polyphenol monomer and 13.3% polyphenol dimer, while LFP contains 6.4% polyphenol monomer and 9.9% polyphenol dimer (24). It is reported that the serum polyphenol concentration continued a high values for 6 h after the intake of OPLA (100 mg) (27). Kitadate et al. have previously assessed the effects of OPLFE on body temperature and found a significant increase in body surface temperature between thermographs of the palms of participants in the OPLFE group before and after supplementation, suggesting peripheral blood flow improvement in healthy people (16). Blood flow increases due to polyphenols are attributed to improvements in cardiovascular health and brain function (28). Because OPLFE is a highly bioavailable source of low molecular weight LFPs, the potential benefits of OPLFE are greater than those of the original lychee fruit polyphenol. Previous studies have indicated that polyphenols might regulate nitric oxide (NO) production via the protein kinase C-dependent nicotinamide adenine dinucleotide phosphate oxidase activation pathway (29). Moreover, a NO-dependent mechanism is supported by the previous finding that OPLFE enhanced NO production by regulating phosphorylation and dephosphorylation of endothelial NO synthase (eNOS) (30). Therefore, it is posited that OPLFE improved “hie-sho” by increasing peripheral blood flow in the present study. Moreover, improvement in “hie-sho” was observed in participants taking mixed plant extract with OPLFE, which included OPLFE and 11 other plant extracts that may also influence circulation. A previous study has reported that ginseng extract improved blood flow (19). When it is metabolized, the arginyl-fructosyl-glucose in Korai ginseng extract causes NO to be produced, which is considered to act as a vasodilatation factor (19). Ginkgo may also exert arterial and venous vasoreactive changes associated with increases in tissue perfusion, peripheral and cerebral blood flow, ocular blood flow, and microcirculation (20, 31). A study has reported that females with low BMI have poor circulation (32). However, consistent findings have not been reported taking age and menstrual cycle into consideration (32–34). Because abnormality and a genetic factor of female sex hormones are involved in causing poor circulation, it will be necessary to consider various factors in future (34). Finally, the present study is subject to several limitations, including the sample size and intake amount. We suggest that additional studies with a larger sample size are needed to further investigate dose response.

Authorship

Research conception and design: HW and TH; experiments: HW, TS, and KU; statistical analysis of the data: HW; interpretation of the data: HW, TS, KU, and TH; writing of the manuscript: HW, TS and TH.

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