Effects of Winter Savory (*Satureja montana* L.) on Peripheral Body Temperature of People Who Experience a ‘Feeling of Cold’ (*Hie-Sho*)

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The objective of this study was to evaluate the effect of winter savory (*Satureja montana* L.) on the peripheral body temperature of people who experience a ‘feeling of cold’ (*hie-sho*). We conducted a clinical trial with a double-blind, randomized, placebo-controlled, single-ingestion crossover design. First, under cold-water loading conditions, the ingestion of powdered winter savory extract (WSE) was found to accelerate the recovery rate of the medial middle-finger temperature. Next, under daily living conditions, the peripheral temperature of the wrist, medial and dorsal middle finger, and middle toe after WSE ingestion was found to be higher than that after the placebo ingestion. In addition, the blood flow and thermal sensation data agreed with the changes in the peripheral body temperature observed by WSE ingestion. This is the first report to demonstrate that WSE ingestion has a warming effect on the peripheral body temperature of people who experience a ‘feeling of cold’.

Keywords: winter savory, peripheral body temperature, feeling of cold, human, warming, thermoception

Introduction

The ‘feeling of cold’ (*hie-sho*) occurs at epidemic proportions among Japanese women and causes a variety of troubling symptoms. These symptoms include: shoulder stiffness, headache, swelling, sleeplessness, frequent urination, peripheral numbness, limb pain, chilblains, and purple fingernails (Miura *et al.*, 2001; Yamato and Aomine, 2002). These symptoms are not limited to menopausal women, as they are also observed in young women (Miyamoto *et al.*, 1995); therefore, it is worth studying methods of alleviating these symptoms.

The feeling of cold is thought to be caused by sympathetic hypertonia, which causes disturbances in peripheral circulation induced by contraction of peripheral vessels (Takatori *et al.*, 1990; Ushiroyama, 2005). Therefore, improving peripheral circulation is important for alleviating the symptoms of feeling of cold.

Endothelial nitric oxide (NO), which is synthesized by

the activation of nitric oxide synthase (NOS), was reported to participate in locally mediated vasodilation, followed by an increase in peripheral skin temperature (Kellogg *et al.*, 1999 and 2008). The activity of NOS is affected by dietary factors (Wu and Meininger, 2002), and a variety of polyphenolic compounds have been demonstrated to induce the activation of NOS (Grande *et al.*, 2004; Duarte *et al.*, 1993; Herrera *et al.*, 1996; Andriambeloson *et al.*, 1998; Flesch *et al.*, 1998; Burns *et al.*, 2000; Karim *et al.*, 2000; Mullen *et al.*, 2002; Pérez-Vizcaino *et al.*, 2002). Therefore, the ingestion of these compounds might improve peripheral circulation, followed by alleviation of the symptoms of feeling of cold.

Winter savory (*Satureja montana* L.), which belongs to the Lamiaceae family and has been used as a food condiment for hundreds of years, contains a variety of active components, such as essential oil (Piccaglia and Marotti, 1993; Grosso *et al.*, 2010) and phenolic compounds (Tomás-Barberán *et al.*, 1990; Darbour *et al.*, 1996; Četković *et al.*, 2007; Gíão *et al.*, 2009). The polyphenolic components in winter savory, such as naringenin, eriodictyol, and luteolin, were reported to induce vasodilation in an *in vitro* study us-

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ing rat aorta (Sánchez de Rojas *et al.*, 1996a; Sánchez de Rojas *et al.*, 1996b; Sánchez de Rojas *et al.*, 1999). Therefore, the ingestion of winter savory should produce a peripheral vasodilation effect, followed by alleviation of the symptoms of the feeling of cold.

In the present study, we investigated whether the ingestion of winter savory could improve the feeling of cold in young women. To assess the feeling of cold, we used a cold-water loading test (in Exp. 1) that has been proven to be a reproducible method for distinguishing between participants with and without the feeling of cold (Yamada *et al.*, 2007). We also measured changes in the time-course of peripheral body temperature, as well as changes in bodily thermoception under daily living conditions (in Exp. 2).

Materials and Methods

Selection of subjects experiencing the feeling of cold

We selected the subjects from 20 females using a questionnaire about the symptoms of the feeling of cold as reported by Takumi *et al.* (2010). Thirteen females that have experienced the feeling of cold were selected as the subjects. In order to avoid fluctuations in basal body temperature, each subject participated in the experiments within 2 weeks after menstruation. Taking these conditions into account, the test was eventually carried out on 7 females.

Subjects The subjects included 7 healthy Japanese female volunteers (18–22 years old, height: 156.1 ± 0.6 cm, body weight: 47.6 ± 1.7 kg, BMI: 19.5 ± 0.6 , values are mean $\pm$ SD, respectively). The study was conducted with the approval of the ethics committee of the University of Shiga Prefecture in accordance with the recommendations of the Helsinki Declaration, and written consent was obtained from the subjects after a full explanation of the contents.

Test samples Two hard capsules were prepared from gelatin (Capsules, Matsuya Co. Ltd., Osaka, Japan); one contained powdered winter savory extract (WSE, 300 mg) and the other contained powdered sugar (300 mg) as placebo. The composition of the WSE is listed in Table 1. The dose of WSE was chosen to be within the amount that could be taken daily as herbal tea. The WSE was prepared as follows: water (200 g) was added to dried winter savory leaves (100 g, Albania) and refluxed for 1 hour. After cooling, the solu-

tion was filtered to remove the particulates and the filtrate was concentrated and freeze dried, resulting in 25 g of WSE being obtained. To ensure that the test was properly blinded, each capsule was confirmed to have no odor.

A blinded third party generated the treatment sequence and allocated a capsule randomly to each subject. Each subject ingested one of two capsules on the first day and the other capsule on the second day with warm water (60 mL, 37°C). The order of ingestion was randomized. To exclude the effect of the first sample, a washout period of at least one day between treatments was used. The washout period was determined according to the absorption, metabolism, and urinary excretion of Laminacea family extracts in humans (Baba *et al.*, 2005). All the subjects were in good health throughout the study period, with none complaining of discomfort after the ingestion of any of the capsules.

Measurements Peripheral body temperature was measured with a thermometer (BTH-601 Bio Research Center Co., Nagoya, Japan) and blood flow on the tip of the middle finger was measured with an ALF 21D laser Doppler flowmeter (Advance Co., Tokyo, Japan). The visual analog scale (VAS) method is used in behavioral science to measure a variety of subjective phenomena (Wewers and Lowe, 1990). We used the VAS to measure changes in bodily thermoception. The VAS is a horizontal line anchored by word descriptors about bodily thermoception on the left (cool) and right (warm) sides of the midpoint. The subjects indicated their perception of the current state of their hand, foot, and body temperature on the VAS. The sensation score was determined by measuring the length from the midpoint of the line to the point that the subjects marked.

Testing protocol Measurements were carried out in a quiet, air-controlled room ($25 \pm 0.5^\circ\text{C}$) with $\approx 50\%$ humidity. This study was conducted using a double-blind, randomized, placebo-controlled, single-ingestion crossover design. Each measurement was taken between 9:00 and 13:00 to avoid the influence of diurnal variations in body temperature. The subjects were not allowed to eat, and drank only water after awakening on the experiment day. The ingestion of alcohol and irritating foods, such as spices, were prohibited on the day prior to testing. Each subject wore the same clothing (jersey and socks) for all measurements to remove the influence of clothing on body surface temperature. The subjects rested in the sitting position for more than 30 min ($25 \pm 0.5^\circ\text{C}$) prior to sample ingestion. The tests were carried out following a single ingestion to examine the fast-acting effect of WSE.

In Exp. 1, the temporal changes in the recovery rate of peripheral body temperature under the cold-water loading conditions were measured as follows. Thermoprobes were

Table 1. Composition of WSE (300 mg).

Energy (kcal)	0.9
Protein (mg)	12
Lipid (mg)	0
Carbohydrate (mg)	216
Sodium (mg)	0.1

fixed on the medial middle-finger tip with surgical tape. The finger was soaked in water (15°C, 5 min) 60 min after the ingestion of capsules containing either WSE (300 mg) or placebo (powdered sugar, 300 mg) with 37°C water (60 mL). The start time of soaking (60 min) was established according to the expected plasma concentration of rosmarinic acid, which is a main polyphenolic compound of WSE (Baba *et al.*, 2005). The temperature of the medial middle finger and blood flow were measured every minute for 20 min. Recovery rate (%) = [(current temperature – minimum temperature during soaking) / (pre-soaking temperature – minimum temperature during soaking)] × 100.

In Exp. 2, temporal changes in peripheral body temperature at a constant room temperature, i.e., under the daily living conditions, were measured as follows. Thermoprobes were attached to a variety of peripheral body parts (wrist, medial middle finger, dorsal middle finger, middle toe, and neck) with surgical tape. Temperature and blood flow were measured every minute for 59 min immediately following ingestion of a capsule containing either WSE (300 mg) or placebo (powdered sugar, 300 mg) with 37°C water (60 mL).

Measurement of rosmarinic acid An Agilent 1100 Series HPLC system, equipped with a diode array detector (Agilent Technologies, Palo Alto, CA) and a Capcell Pak C18 MG column (250 mm × 4.6 mm i.d.; particle size, 5µm; Shiseido, Tokyo, Japan), was used to measure rosmarinic acid. The operating conditions were as follows: column oven temperature, 40°C; mobile phase, a linear gradient from 100% solvent A (10% acetonitrile, pH 2.5 adjusted with phosphoric acid) to 100% solvent B (acetonitrile) over 25 min, and maintained at 100% B for 2 min; flow rate, 1 mL/min; and injection volume, 20 µL. All samples were filtered through a 0.45-µm PTFE membrane filter (DISMIC-13HP, Toyo Roshi, Tokyo, Japan) prior to injection. The UV spectra (wavelengths from 200 to 400 nm) plus retention time were used for the identification of rosmarinic acid, and a wavelength of 280 nm was used for quantification.

Measurement of carvacrol Gas chromatography-mass spectrometry (GC-MS) was performed using a Hewlett-Packard 5890 SERIES II gas chromatograph equipped with an HP-5972 mass-selective detector and a DB-1 fused silica capillary column (60 m × 0.25 mm i.d.; film thickness of 0.25 µm; J&W Scientific). The operating conditions were as follows: injector temperature, 250°C; helium carrier gas flow rate, 1 mL/min; oven temperature program, 60°C, raised at 3°C/min to 210°C (40 min); injection volume, 1 µL, using a split ratio of 1:50; ionization voltage, 70 eV; ion source temperature, 140°C.

Statistical analysis Results are expressed as the mean ± SEM. The time-course data were evaluated by repeated

ANOVA. Comparisons between treatment groups at specific time-points were evaluated by two-tailed paired *t*-test. Statistical values were calculated using the commercially available software package GraphPad Prism version 5 (GraphPad Software, Inc., CA, USA). Probability values *p* < 0.05 were regarded as significant.

Results

Changes in middle-finger temperature and blood flow in experiment 1 Fig. 1 shows the temporal changes in the recovery rate of middle-finger temperature in Exp. 1. After cold-water loading (15°C, 5 min), the recovery rate of the medial middle-finger temperature in the WSE-ingestion group was higher than in the placebo-ingestion group (*p* < 0.05 by two-way repeated measures ANOVA).

Fig. 2 shows the temporal changes in blood flow cold-water loading was higher in the WSE-ingestion group than in the placebo-ingestion group (*p* < 0.05 by two-way repeated measures ANOVA).

Fig. 1. Time-Course Changes in Recovery Rate of Temperature under the Cold-Water Loading Conditions (Exp.1).

Recovery rate (%) = [(temperature at the time – the lowest temperature during soaking) / (temperature just before soaking – the lowest temperature during soaking)] × 100. Each value is expressed as a mean ± SEM. *n* = 7. Time versus treatment effect, *p* < 0.05 (two-way repeated measures ANOVA).

Fig. 2. Time-Course Changes in Blood Flow under the Cold-Water Loading Conditions (Exp.1).

Each value is expressed in terms of the difference from the mean blood flow rate as a mean ± SEM. *n* = 7. Time versus treatment effect, *p* < 0.05 (two-way repeated measures ANOVA).

Changes in peripheral body temperature and blood flow in experiment 2 The temporal changes in peripheral body temperature in Exp. 2 are shown in Fig. 3. For all peripheral regions (wrist, medial middle finger, dorsal middle finger, and middle toe), the ingestion of WSE was more effective in preventing decreases in body temperature than the ingestion of placebo (wrist: $p < 0.05$ at 0-59 min by two-way repeated measures ANOVA; medial middle finger: $p < 0.05$ at 0-59 min by two-way repeated measures ANOVA, $p < 0.05$ at 36 min by paired t -test; dorsal middle finger: $p < 0.05$ at 0-59 min by two-way repeated measures ANOVA, $p < 0.05$ at 56 min by paired t -test; middle-toe: $p < 0.05$ at 0-59 min by two-way repeated measures ANOVA). Neck temperature was slightly elevated after ingestion of WSE and tended to be higher than after the ingestion of placebo ($p = 0.0773$ at 0-50 min by two-way repeated measures ANOVA, $p < 0.05$ at 14, 17, 19-24, 26, and 24-29 min by paired t -test). The temporal changes in the blood flow measured at the tip of the third finger are shown in Fig. 4. There is no significant difference in

blood flow between the WSE and placebo groups ($p = 0.208$: two-way repeated measures ANOVA).

Changes in bodily thermoception in experiment 2 Fig. 5 shows the temporal changes in bodily thermoception in Exp. 2. For the VAS method, positive and negative sensation-scores indicate the degree of heat and cold, respectively. The sensation score for the hand in the WSE-ingestion group was higher than in the placebo-ingestion group ($p < 0.05$ by two-way repeated measures ANOVA, $p < 0.05$ at 25-35 min by paired t -test). The sensation score for the foot and body in the WSE-ingestion group tended to be higher than in the placebo-ingestion group (foot: $p < 0.05$ at 0-35 min by two-way repeated measures ANOVA, $p < 0.05$ at 25 min and $p < 0.05$ at 35 min by paired t -test; body: $p < 0.05$ at 0-45 min by two-way repeated measures ANOVA; $p < 0.05$ at 15-45 min by paired t -test). A tendency for elevated sensation scores was observed at about 25-35 min after the ingestion. A similar tendency for changes in peripheral body temperature is shown in Fig. 3.

Fig. 3. Time-Course Changes in Temperature under the Daily Living Conditions (Exp. 2).

Each value is expressed in terms of the difference from the mean temperature before ingestion as means $\pm$ SEM. $n = 7$. Time versus treatment effect, $p < 0.05$ at 0-59 min (wrist (a), medial middle finger (b), dorsal middle finger (c), and middle toe (d), two-way repeated measures ANOVA), $p = 0.0773$ at 0-50 min (neck (e), two-way repeated measures ANOVA), * $p < 0.05$ (paired t -test).

Fig. 4. Time-Course Changes in Blood Flow under the Daily Living Conditions (Exp.2).

Each value is expressed in terms of the difference from the mean blood flow rate before ingestion as means $\pm$ SEM. $n = 7$. Time versus treatment effect, $p = 0.208$ (two-way repeated measures ANOVA).

Content of rosmarinic acid and carvacrol in WSE The rosmarinic acid content of WSE was found to be 38.6 mg/g. This is comparable to the rosmarinic acid content of powdered boiled-water extracts of oregano (*Origanum vulgare* L.) and sweet majoram (*Origanum majorana* L.), which have been found to contain 41.5 and 41.4 mg/g, respectively, as determined by the HPLC method described herein. Conversely, the content of carvacrol, which is the main aromatic component in winter savory, was found to be 0.32 mg/g in WSE, as determined by GC-MS.

Discussion

We demonstrated that WSE had a warming effect on the peripheral body temperature under cold-water loading conditions, as shown in Fig. 1. In order to avoid pain, so that peripheral body temperature can be altered, the temperature of the cold-water used in this test was set to 15°C (Yagi *et al.*, 2002, Kusumi and Emori, 2009). Next, we examined the effect of WSE at a constant room temperature, i.e., under the daily living condition. As shown in Fig. 3, WSE prevented decreases, or enhanced increases, in a variety of peripheral body temperatures (medial middle finger, dorsal middle finger, and middle-toe). Both in Exp. 1 and Exp. 2, the blood flow data was consistent with the observed changes in the peripheral body temperature (Fig. 2 and 4). These results suggest that the ingestion of WSE has a warming effect on the peripheral body temperature of those who have a feeling of cold. The thermal sensation score of the WSE-ingestion group tended to be higher than that of the placebo-ingestion group in Exp. 2 (Fig. 5). Those who have a feeling of cold suffer from peripheral cold sensations throughout the year. Therefore, improving the sensation of warmth is thought to be very important for alleviating the symptoms of the feeling of cold. In the present study, the ingestion of WSE seems to

Fig. 5. Time-Course Changes in Sensation in Body Temperature under the Daily Living Conditions (Exp.2).

Each value is expressed in terms of the difference from the mean sensation in body temperature before ingestion as means $\pm$ SEM. $n = 7$. Time versus treatment effect, $p < 0.05$ (hand (a), two-way repeated measures ANOVA), $p < 0.05$ at 0-35 min (foot (b), two-way repeated measures ANOVA), $p < 0.05$ at 0-45 min (body (c), two-way repeated measures ANOVA), * $p < 0.05$ (paired *t*-test).

be effective in improving the sensation of warmth.

A recent study by Okuda *et al.* (1993) reported that the effective agents for subjects that suffered from a feeling of cold were classified into the following two groups: one group acts via endothelium-dependent peripheral vasodilation, and the other group acts via peripheral vasodilation by body heat production. The improvement in peripheral body temperature by a variety of antioxidants, such as anthocyanin in black currant extract and α -glucosylhesperidin, is considered to correspond to the former group (Takenami *et al.*, 2004; Takumi *et al.*, 2010). Pungent components, such as capsaicin in red pepper, gingerol and shogaol in ginger, and piperin in

black pepper, are thought to belong to the latter group (Watanabe *et al.*, 1987; Kobayashi *et al.*, 1998; Kawada *et al.*, 1986; Kawada 1987; Iwasaki *et al.*, 2006; Fujisawa *et al.*, 2005; Okumura *et al.*, 2010; McNamara *et al.*, 2005). Those components were reported to produce thermogenesis by enhancing energy metabolism via activation of the sympathetic nervous system and catecholamine secretion.

Spices of the Lamiaceae family are known to have a high antioxidant capacity compared to many other spices (Baño *et al.*, 2003; Fecka and Turek, 2007; Exarchou *et al.*, 2002; Fujie *et al.*, 2003). Rosmarinic acid, a common polyphenol antioxidant component of the Lamiaceae family, is found to improve endothelium-dependent vasodilation by the action of NO *in vitro* (Grande, *et al.*, 2004; Ersoy *et al.*, 2008). To examine the contribution of rosmarinic acid to the warming effect on the peripheral body temperature, we investigated the warming effect of powder of the boiled-water extract of other spices in the Lamiaceae family, i.e., oregano and sweet majoram, which contain rosmarinic acid content similar to WSE, as described in the results. However, we observed that these spices have no warming effect on peripheral body temperature (data not shown). These results indicate that not all spices containing rosmarinic acid have a warming effect on peripheral body temperature. Furthermore, we surmised that the participation of other active components besides rosmarinic acid could participate in the warming effect of winter savory, or that there were components that are antagonistic to rosmarinic acid in these spices. Further studies are needed to elucidate the contribution of rosmarinic acid to the warming effect of winter savory.

As described in the result, WSE has been found to contain carvacrol, which is a major aromatic component in the essential oil of winter savory (Piccaglia *et al.*, 1993). Carvacrol has been reported to activate TRPV3 (transient receptor potential vanilloid 3) and TRPA1 (transient receptor potential ankyrin 1) (Xu *et al.*, 2006). TRPA1 is a non-selective calcium permeable channel and considered to be involved in noxious cold sensations and neural transmissions related to pungency. Recent studies suggest that the activation of TRPA1 is involved not only in nociception and thermoception, but also in thermoregulation and energy metabolism (Iwasaki *et al.*, 2008; Masamoto *et al.*, 2009). In the present study, the ingestion of WSE not only prevented decreases in the peripheral body temperature, but also tended to elevate neck temperature. This might result from thermogenesis via TRP channel activation. Further studies are needed to elucidate the involvement of thermogenesis in the warming effect of winter savory.

In conclusion, we showed that the ingestion of winter savory under cold-water loading conditions and daily liv-

ing conditions was effective in alleviating decreases in the peripheral body temperature in those who have a feeling of cold. We also showed that the ingestion of winter savory improved one's warmth sensation. We suggest that the ingestion of winter savory might be effective in improving the feeling of cold in young women.

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