Journal of Ethnopharmacology 158 (2014) 25–32

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Research Paper

Efficacy and safety of Korean red ginseng for cold hypersensitivity in the hands and feet: A randomized, double-blind, placebo-controlled trial

Kyoung-Sun Park [a], Kang-In Park [a], Jin-Woo Kim [a], Young-Jin Yun [a], Se-Hwa Kim [a], Chang-Hoon Lee [a], Jae-Woo Park [b], Jin-Moo Lee [a,*]

[a] Department of Korean Medicine Obstetrics & Gynecology, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Republic of Korea
[b] Department of Internal Medicine, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Republic of Korea

ARTICLE INFO

Article history:
Received 9 May 2014
Received in revised form
19 August 2014
Accepted 16 September 2014
Available online 8 October 2014

Keywords:
Cold hypersensitivity in the hands and feet
Korean red ginseng
Infrared thermography
Cold stress test
Distal–dorsal difference

ABSTRACT

Ethnopharmacological relevance: In Korean medicine, the steamed root of *Panax ginseng* C.A. Meyer, known as Korean red ginseng (KRG), is used to invigorate the body, enhance *qi*, and improve blood flow. It is a potential treatment for cold hypersensitivity in the hands and feet (CHHF), a common complaint among Asians, especially women. However, few studies of its efficacy and safety for CHHF have been conducted.

Materials and methods: This randomized, double-blind, placebo-controlled trial included 80 female patients with CHHF at Kyung Hee University Hospital at Gangdong, Seoul, Korea. The participants took six capsules of 500-mg KRG powder or placebo twice daily for 8 weeks and were followed up for 4 weeks. The primary outcome measure was change in skin temperature of the hands. The secondary outcome measures included change in skin temperature of the feet, visual analog scale (VAS) scores of CHHF severity, recovered temperature (RT) of the hands after cold stress test, distal–dorsal difference (DDD) in temperature of the hands, power variables of heart rate variability (HRV), and 36-item Short-Form Health Survey (SF-36) scores.

Results: The KRG group had significantly higher skin temperature of the hands and feet, lower VAS scores, higher RT of the right 5th finger, and less parasympathetic activity than the placebo group at 8 weeks. No significant differences were noted in DDD of the hands and SF-36 scores. No serious adverse events were reported during the study.

Conclusions: Peripheral vasodilation by KRG may alleviate CHHF. Further controlled studies are required to elucidate the effects of KRG on the autonomic nervous system.

1. Introduction

Cold hypersensitivity in the hands and feet (CHHF) is a condition in which affected individuals feel excessively cold at low temperatures because of spastic peripheral vasoconstriction. It is significantly more prevalent among women than men in the Korean population (Hur et al., 2012). CHHF can disturb employers in cold climates, and lower the quality of life by interfering with daily activities. Various neurovascular, psychosocial, cultural, environmental, and medical factors might contribute to CHHF (Traynor and MacDermid, 2008). However, few studies have been performed to elucidate its etiology (Hur et al., 2012). Further, satisfactory treatments for this condition are not available; the current treatment approaches often involve behavioral modification (Craigen et al., 1999). Therefore, identification of an effective therapeutic modality for CHHF is essential.

Abbreviations: BMI, body mass index; BP, bodily pain; BP, blood pressure; CHHF, cold hypersensitivity in the hands and feet; CST, cold stress test; DDD, distal–dorsal difference; GH, general health perception; HF, high frequency; HF norm, high-frequency power normalized unit; HRV, heart rate variability; KRG, Korean red ginseng; LF, low-frequency; LF/HF ratio, low-frequency to high-frequency power ratio; LF norm, low-frequency power normalized unit; lnHF, logarithmic high-frequency power; lnLF, logarithmic low-frequency power; MH, mental health; NO, nitric oxide; PF, physical function; RE, role limitations owing to emotional problems; RP, role limitations owing to physical health problems; RT, recovered temperature; SF, social function; SF-36, the 36-item Short Form Health Survey; T_0, skin temperature immediately after cold stress; T_6, skin temperature 6 min after cold stress; VAS, visual analog scale; VT, energy and vitality

* Corresponding author. Tel.: +82 2 440 7129; fax: +82 2 440 7143.
E-mail addresses: lovepks82@naver.com (K.-S. Park), shinysmile714@gmail.com (K.-I. Park), shampoo1211@naver.com (J.-W. Kim), khclinic@empas.com (Y.-J. Yun), nimaru@hanmail.net (S.-H. Kim), lchgdsl@hanmail.net (C.-H. Lee), pjw2907@hanmail.net (J.-W. Park), hanbang9597@hanmail.net (J.-M. Lee).

http://dx.doi.org/10.1016/j.jep.2014.09.028
0378-8741/

Korean red ginseng (KRG) is the steamed root of *Panax ginseng* C.A. Meyer. It acquires additional physiological properties through chemical transformation of its active components, including ginsenosides, polysaccharides, peptides, and polyacetylenic alcohols (Park, 1996). Steamed ginseng, containing ginsenosides Rg3 and Rg5, has more potent endothelium-dependent vasodilator and radical-scavenging effects than raw ginseng (Kim et al., 2000). In Korean medicine, KRG is considered to have a warm quality: it is used as a tonic to invigorate the body, enhance *qi*, and improve blood flow (Kwan, 1999). However, its efficacy for treating CHHF has rarely been investigated. Only one clinical trial of subjective tolerance to cold stress has been conducted (Kaneko and Nakanishi, 2004).

This randomized, double-blind, placebo-controlled trial was aimed at evaluating the efficacy and safety of KRG comprehensively.

2. Materials and methods

2.1. Ethical approval

The study protocol adhered to the guidelines of the amended Declaration of Helsinki and was approved by the institutional review board and ethics committee of Kyung Hee University Hospital at Gangdong (approval number KHNMC-OH-IRB 2012-004). The trial is registered under identification number NCT01664156 (ClinicalTrials.gov). Written informed consent was obtained from all participants before enrollment, and patients were given adequate time to declare whether they wished to participate.

2.2. Patients

The inclusion criteria were as follows: (1) female patients aged 16–60 years; (2) complaint of CHHF; and (3) over 0.3 °C difference between the palm and the arm. We excluded patients who reported any of the following conditions: (1) skin ailments, radiculopathy, thrombophlebitis, and injuries affecting infrared imaging; (2) alcohol abuse or alcoholism; (3) history of cancer within the past 5 years; (4) severe cardiac, pulmonary, hepatic, or renal diseases; (5) severe depression or mental illness; (6) use of antihypertensive, antidiabetic, or thrombolytic agents; (7) pregnancy or breastfeeding; (8) allergy to KRG or ginseng; (9) ingestion of herbal medicines or nutritional supplements within a week before participation; and (10) participation in another clinical trial within the past 3 months.

Participants were recruited by sending text messages to patients with CHHF at Kyung Hee University Hospital at Gangdong. Advertisements were placed in the local newspaper and on the hospital homepage. In addition, posters, brochures, and banners were placed inside the hospital.

2.3. Randomization and blinding

Group allocation was performed by an independent statistician using a randomization program. The participants were randomly and equally assigned to the KRG or placebo group and were not stratified. The investigator was subsequently notified of the number assigned to each participant, and the participants were given a random number at their second visit. The allocation table of participants was kept by an independent statistician until the end of the study.

The participants, the investigator, and the clinical pharmacist were blinded to the treatment and only the independent statistician was aware of the randomization. Blinding was assessed at the end of the study.

2.4. Intervention

KRG was manufactured by Korea Ginseng Corporation (Seoul, Korea) from the root of 6-year-old *Panax ginseng* C.A. Meyer (Araliaceae) harvested in Korea. Fresh ginseng was steamed at 90–100 °C for 3 h and dried at 50–80 °C. Capsules containing KRG powder (KRG capsule; 500 mg/capsule) were prepared from hydroxypropyl methylcellulose, pectin, purified water, sucrose fatty acid ester, glycerin, calcium gluconate, and glacial acetic acid. The following ginsenosides were identified by high-performance liquid chromatography: Rb1, 5.61 mg/g; Rb2, 2.03 mg/g; Rc, 2.20 mg/g; Rd, 0.39 mg/g; Re, 1.88 mg/g; Rf, 0.89 mg/g; Rg1, 3.06 mg/g; Rg2(s), 0.15 mg/g; Rg3(r), 0.08 mg/g; Rg3(s), 0.17 mg/g; Rh1, 0.30 mg/g; and minor ginsenosides. Voucher specimens are kept at Korea Ginseng Corporation.

Each participant in the KRG group took six KRG capsules twice daily (1 h after breakfast and dinner), totaling 6 g of KRG per day, for 8 weeks. The dosage was determined on the basis of the total amount of Rb1 and Rg1 (6 mg/g), according to the Korean Food Standards Codex. Participants in the placebo group took placebo capsules similar in color, flavor, and smell to the KRG capsules for the same duration. The placebo was composed of cornstarch, natural color (Brown CG-11771; Jey's F.I., Inc., Seongnam, Korea), brown caramel color (Bolak Co., Seoul, Korea), and red ginseng flavor (C80509; French Korean Aromatics Co., Yongin, Korea). Every participant was asked to annotate a diary after taking the capsules to check compliance with the study protocol. Those with over 70% compliance were included in the per-protocol analysis.

The participants were prohibited from undergoing therapies that might affect symptoms of CHHF, including herbal therapy, acupuncture, moxibustion, cupping, and infrared treatment. They were also prohibited from taking antihypertensive, antidiabetic, or thrombolytic agents. However, medications that would not affect CHHF, such as those for common cold, stomachache, diarrhea, and menstrual pain, were allowed.

2.5. Outcomes measures

The primary outcome measure was change in skin temperature of the hands. The secondary outcome measures included change in skin temperature of the feet, visual analog scale (VAS) scores of CHHF severity, recovered temperature (RT) of the hands, distal–dorsal difference (DDD) of the hands, power variables of heart rate variability (HRV), and 36-item Short-Form Health Survey (SF-36) scores.

2.5.1. Infrared thermography

Skin temperature was measured by infrared thermography (IRCT 510; Dongseo Co., Seoul, Korea). The participants were asked to avoid hot showers, hot packs, smoking, exercise, acupuncture, and stimulants such as caffeine for 2 h before the examination. Each participant was acclimatized to room temperature (25 ± 1 °C) for 15 min and seated comfortably on a chair without physiological or psychological stress. The participant stood in the anatomical posture during thermal imaging of the limbs. Then, the average temperatures in 5-mm squares on the arm (LU4), palm (PC8), anterior thigh (ST32), and dorsum of the foot (LR3) were calculated (Fig. 1). Finally, thermal differences between the arm and the palm and between the anterior thigh and the dorsum of the foot were measured on both sides and the bilateral measurements were averaged as follows:

$\Delta T_{\text{right hand}}$ = skin temperature of the right arm − skin temperature of the right palm;

$\Delta T_{\text{left hand}}$ = skin temperature of the left arm − skin temperature of the left palm;

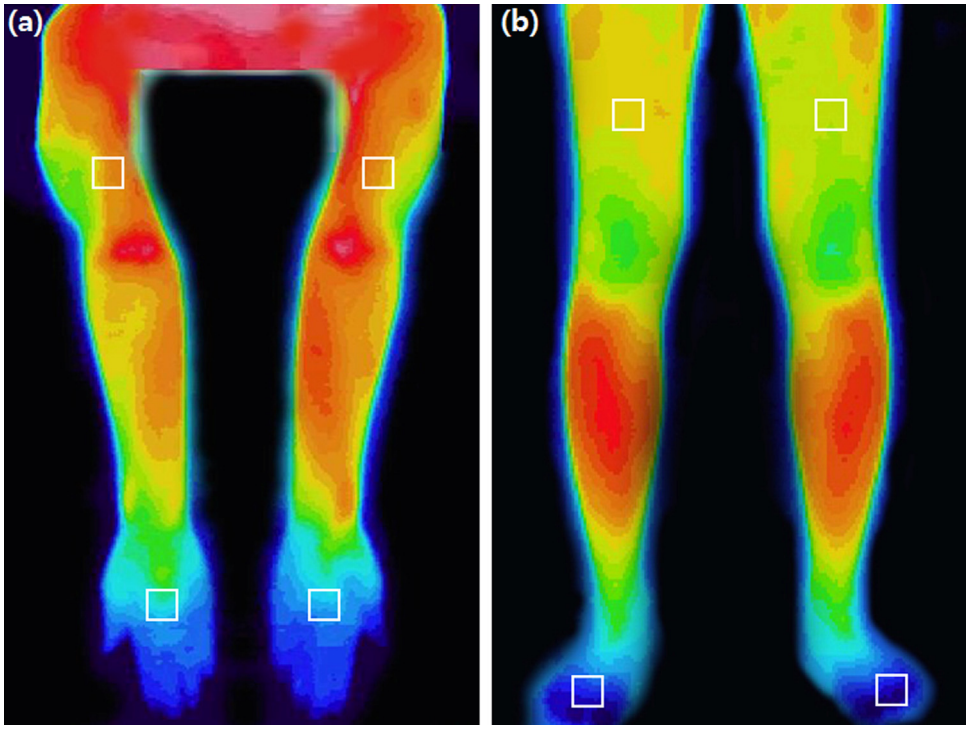

Fig. 1. Measurement of skin temperature by infrared thermography. Thermal images show the paired measurement areas (squares) on the (a) upper and (b) lower limbs.

$\Delta T_{hands} = (\Delta T_{right\ hand} + \Delta T_{left\ hand})/2$;
$\Delta T_{right\ foot}$ = skin temperature of the right anterior thigh − skin temperature of the right dorsum of the foot;
$\Delta T_{left\ foot}$ = skin temperature of the left anterior thigh − skin temperature of the left dorsum of the foot;
$\Delta T_{feet} = (\Delta T_{right\ foot} + \Delta T_{left\ foot})/2$.

2.5.2. VAS

A 100-mm VAS was used to assess severity of CHHF. The scores ranged from 0 (no discomfort) to 100 (most intense discomfort) and were rounded to the nearest integer in millimeters.

2.5.3. Cold stress test

The cold stress test was used to examine recovery after cold stress. The participant was acclimatized to room temperature (25 ± 1 °C) for 15 min and seated comfortably on a chair. Both hands were submerged in cold water (20 °C) for 1 min and carefully dried with a towel. Thermal images of the dorsum of both hands were obtained immediately and 6 min after immersion. The average temperatures of the dorsum and each finger were measured. RT was calculated as $T_6 - T_0$, where T_6 and T_0 are the skin temperatures 6 min and immediately after cold stress, respectively.

2.5.4. DDD assessment

DDD is the difference in temperature between a finger and the dorsum of the hand (Anderson et al., 2007). It has a positive value if the finger is colder than the dorsum, and a high DDD indicates severe cold hypersensitivity in the fingers. After the hands were equilibrated at room temperature (25 ± 1 °C), their thermal images were obtained. Then, the average temperatures of the dorsum and fingers were measured. Thermal images of both hands were also obtained 6 min after cold stress, performed as previously described. DDD was calculated by subtracting the temperature of each finger from that of the dorsum. Finally, the maximum DDD and number of fingers with DDD of > 1 °C were determined.

2.5.5. HRV analysis

For this examination, the participant was seated in a comfortable chair in a quiet room and asked to relax for 10 min. Clip-type electrocardiogram leads of an HRV analyzer (SA-3000P; Medicore Co., Seoul, Korea) were attached to the wrist and left ankle. The analyzer detected signals at 500 Hz and automatically calculated the frequency-domain parameters including low-frequency power (LF; 0.04–0.15 Hz) and high-frequency power (HF; 0.15–0.4 Hz). The parameters were log-transformed to obtain a normal distribution.

2.5.6. SF-36

The SF-36 is a generic instrument to measure health-related quality of life and is widely used to survey physical and emotional health. The validated Korean version used in this study was obtained from the Health Assessment Laboratory (Boston, MA, USA). It consisted of 36 questions grouped into eight dimensions: physical function (10 items), role limitations owing to physical health problems (four items), bodily pain (two items), general health perception (six items), energy and vitality (four items), social function (two items), role limitations owing to emotional problems (three items), and mental health (five items). The number of response options per question was either two (yes or no) or six (none, very mild, mild, moderate, severe, or very severe). Each dimension score was expressed as a value between 0 and 100, with higher scores representing better health status (Ware and Sherbourne, 1992).

2.6. Assessment of safety

Complete blood count, erythrocyte sedimentation rate, and liver and renal functions were examined to determine the safety of the treatment. The laboratory data were recorded in a case report form by the investigator. The participants were asked to record any adverse events in their diaries throughout the study. All adverse events were later described in the case report form.

2.7. Sample size calculation

This study had a pilot characteristic to evaluate the efficacy of KRG for CHHF by using infrared thermography. Although there was no previous study with a similar design, we calculated the sample size based on a study that used similar variables. The previous study measured the tolerance time to cold stress to assess the efficacy of KRG for CHHF using a 2-sided test, yielding a 5% significance level (Kaneko and Nakanishi, 2004). The formula for estimating the sample size was as follows:

$$n_t = n_c = \{(Z_{\alpha/2}+Z_{\beta})^2\sigma^2(\lambda+1)\}/(\mu_t-\mu_c)^2$$

In the previous study, the tolerance time to cold stress was prolonged 0.35 min in the KRG group compared with the control group ($\mu_t-\mu_c$), and the mean standard deviation (σ) was 0.84. In our study, the ratio (λ) of KRG to placebo was 1:1. With an 80% power ($1-\beta$) and a 5% significance level (α), assuming $\mu_t-\mu_c=0.35$ and $\sigma=0.84$, a sample size of $n_t=n_c=32$ participants per group was needed (n_t, number of participants in the KRG group; n_c, number of participants in the placebo group). Anticipating a drop-out rate of approximately 20%, the total sample size was calculated as more than 80 women.

2.8. Statistical analysis

Efficacy was assessed by intention-to-treat analysis using the method of last observation carried forward. Baseline characteristics of the groups were compared by independent *t*-test or chi-square test. Baseline and 8-week data were compared in each group by paired *t*-test and between the groups by independent *t*-test. Blinding was assessed by chi-square test. An independent statistician performed the statistical analyses by using SPSS version 17.0 (SPSS, Inc., Chicago, IL). $P<0.05$ represents statistical significance.

3. Results

3.1. Study participants

Of 115 eligible patients, 80 participants were randomly allocated to the KRG or placebo group between October 2012 and May 2013. Seventy-four participants completed the 12-week protocol (Fig. 2).

3.2. Baseline characteristics

General characteristics of the participants are presented in Table 1. No significant differences were observed between the two groups in the baseline demographic characteristics, ΔT_{hands}, ΔT_{feet}, and VAS scores of CHHF. The difference in alcohol use was nearly significant: a higher proportion of participants drank in the placebo group. We excluded patients with a history of alcohol abuse or alcoholism, which can affect CHHF, during screening. Moreover, the average alcohol consumption per person in the KRG group was 2.40 glasses/week compared with 3.08 glasses/week in the placebo group, which hardly affected the outcome.

3.3. Outcomes

3.3.1. Change in skin temperature

ΔT_{hands} significantly decreased in the KRG group compared with the placebo group over 8 weeks (1.30 ± 2.16 °C vs. 0.37 ± 1.45 °C; $P=0.027$). No significant intergroup difference in

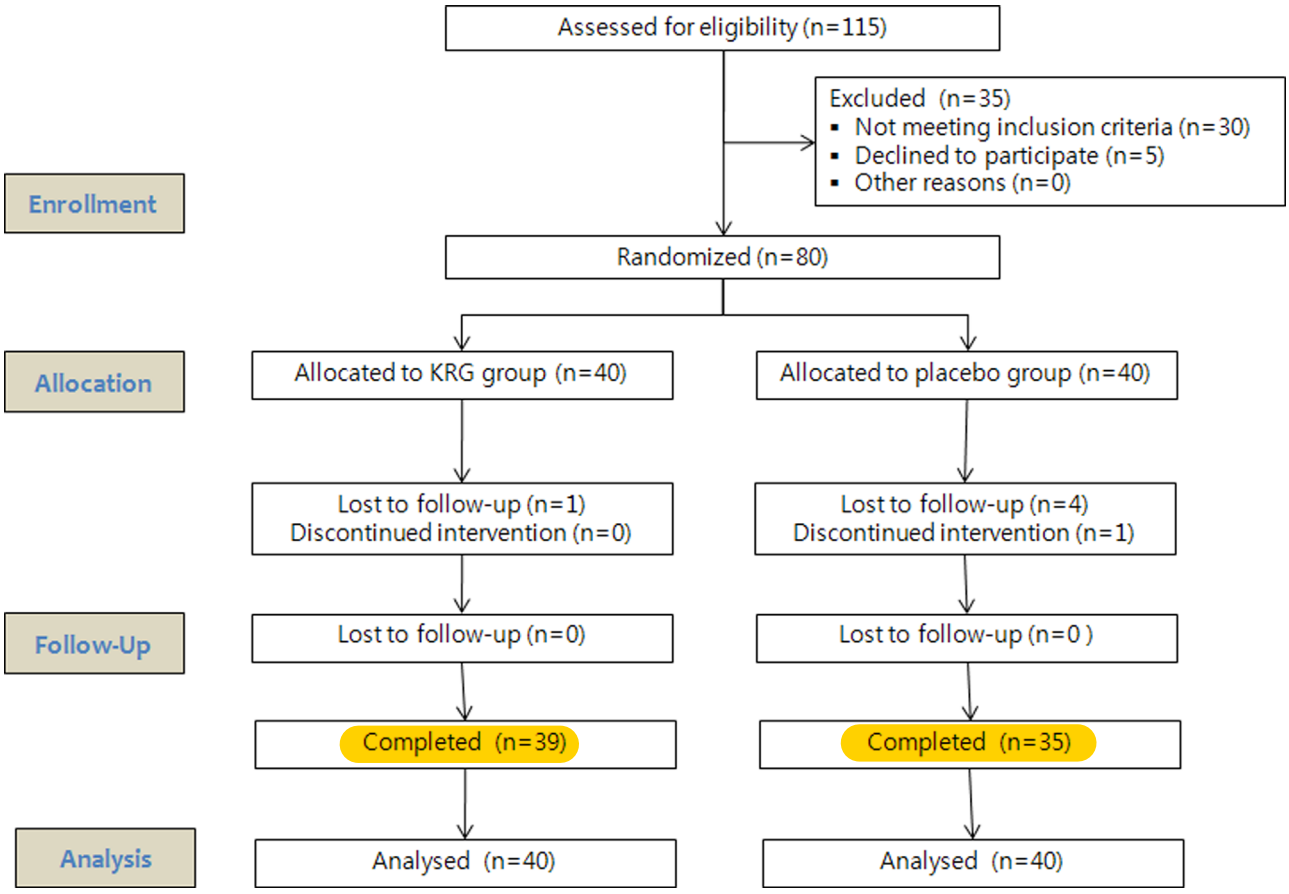

Fig. 2. Flow chart of the trial. *Abbreviation*: KRG, Korean red ginseng.

ΔT_{feet} (1.23 ± 2.53 °C vs. 0.29 ± 2.10 °C; $P=0.076$) was noted (Table 2 and Fig. 3a).

3.3.2. VAS scores of CHHF

VAS scores of the hands significantly decreased in both the KRG (reduction of 20.65 ± 17.69) and the placebo (reduction of 8.80 ± 12.35) groups and showed a significant difference between the groups ($P=0.001$). Those of the feet also significantly decreased by 18.78 ± 26.65 and 7.85 ± 16.81, respectively (intergroup $P=0.032$; Table 2 and Fig. 3b).

Table 1
Baseline characteristics of the participants.

	KRG group ($n=40$)	Placebo group ($n=40$)	P
Age (years)	40.35 ± 12.67	38.05 ± 11.63	0.400
Height (cm)	160.99 ± 5.01	161.89 ± 4.82	0.413
Body weight (kg)	52.79 ± 5.00	55.00 ± 6.82	0.103
BMI (kg/m^2)	20.37 ± 1.80	21.01 ± 2.79	0.225
BP systolic (mmHg)	119.83 ± 11.57	118.00 ± 14.04	0.528
BP diastolic (mmHg)	75.15 ± 8.53	71.98 ± 9.24	0.114
Pulse rate (/min)	76.83 ± 9.62	78.83 ± 8.88	0.337
Body temperature (°C)	36.22 ± 0.35	36.22 ± 0.34	0.974
Exercise (yes/no)	23/17	20/20	0.501
Smoking (yes/no)	2/38	0/40	0.152
Alcohol (yes/no)	8/32	16/24	0.051
ΔT_{hands} (°C)	1.77 ± 2.02	1.28 ± 1.43	0.219
ΔT_{feet} (°C)	3.25 ± 2.19	3.00 ± 2.22	0.615
Hand VAS score	77.60 ± 12.62	74.75 ± 13.79	0.338
Foot VAS score	80.20 ± 17.93	76.23 ± 15.15	0.287

Abbreviations: KRG, Korean red ginseng; BMI, body mass index; BP, blood pressure; ΔT_{hands}, averaged thermal difference between the arm and the palm; ΔT_{feet}, averaged thermal difference between the anterior thigh and the dorsum of the foot; VAS, visual analog scale.
Values are mean ± SD or count.

3.3.3. RT of the hands after cold stress

RT of the right 5th finger increased by 1.07 ± 2.79 °C in the KRG group but decreased by 0.25 ± 2.84 °C in the placebo group. A significant difference between the groups was noted in this variable ($P=0.040$; Table 3).

3.3.4. The DDD of the hands

The maximum DDD immediately after cold stress decreased by 0.49 ± 1.52 °C in the KRG group and 0.62 ± 1.95 °C in the placebo group. The maximum DDD at 6 min after cold stress decreased by 0.60 ± 1.84 °C after KRG intake and increased by 0.15 ± 2.06 °C after placebo intake. The number of fingers with DDD > 1 °C at 6 min after cold stress decreased by 1.73 ± 5.35 in the KRG group and increased by 0.25 ± 5.54 in the placebo group. However, no significant differences in these variables were found between the groups (Table 4).

3.3.5. Power variables of HRV

The KRG group showed significantly decreased logarithmic LF (0.34 ± 1.02) and HF (0.38 ± 1.06). Contrarily, the placebo group showed increased logarithmic LF (0.06 ± 0.93) and HF (0.13 ± 0.85). The groups showed a significant difference in logarithmic HF ($P=0.019$; Table 5).

Table 2
Comparison of ΔT_{hands}, ΔT_{feet}, and VAS scores.

	KRG group ($n=40$)			Placebo group ($n=40$)			P^b
	Baseline	8 weeks	P^a	Baseline	8 weeks	P^a	
ΔT_{hands} (°C)	1.77 ± 2.02	0.47 ± 1.71	0.000	1.28 ± 1.43	0.91 ± 1.41	0.113	0.027
ΔT_{feet} (°C)	3.25 ± 2.19	2.02 ± 2.29	0.004	3.00 ± 2.22	2.71 ± 2.11	0.387	0.076
Hand VAS score	77.60 ± 12.62	56.95 ± 23.95	0.000	74.75 ± 13.79	65.95 ± 16.33	0.000	0.001
Foot VAS score	80.20 ± 17.93	61.43 ± 24.29	0.000	76.23 ± 15.15	68.38 ± 18.77	0.005	0.032

Abbreviations: KRG, Korean red ginseng; ΔT_{hands}, averaged thermal difference between the arm and the palm; ΔT_{feet}, averaged thermal difference between the anterior thigh and the dorsum of the foot; VAS, visual analog scale.
Values are mean ± SD.
[a] Paired *t*-test.
[b] Independent *t*-test.

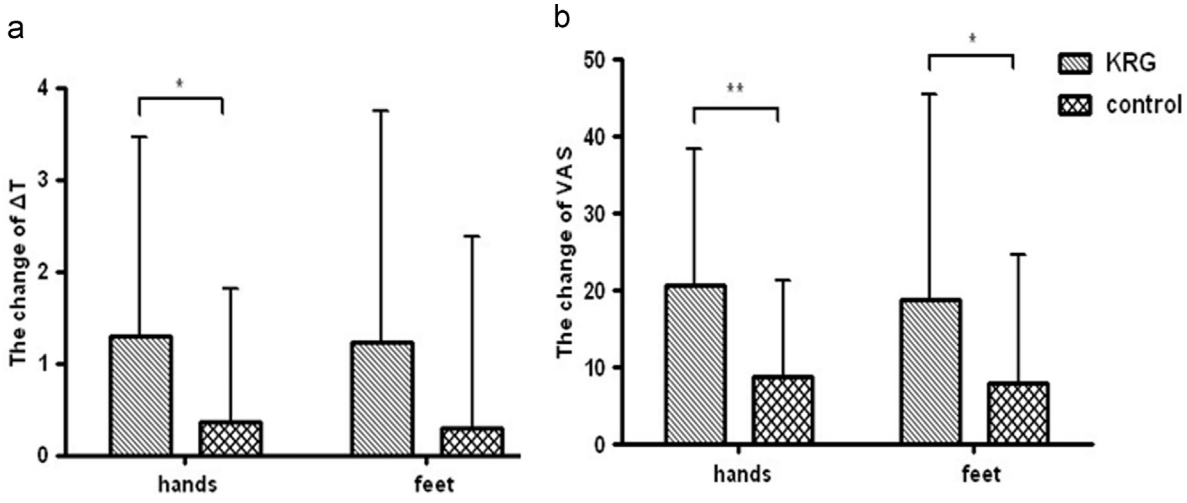

Fig. 3. Changes in skin temperature and VAS scores. (a) ΔT_{hands} and ΔT_{feet}. (b) VAS scores. *Abbreviations*: KRG, Korean red ginseng; ΔT, averaged thermal difference; VAS, visual analog scale. *$P<0.05$ and **$P<0.01$ by independent *t*-test.

Table 3
Comparison of RT (°C).

		KRG group (n=40)			Placebo group (n=40)			P^b
		Baseline	8 weeks	P^a	Baseline	8 weeks	P^a	
Left	Dorsum	2.32 ± 1.31	2.68 ± 1.15	0.130	2.32 ± 1.39	2.57 ± 1.09	0.336	0.783
	1st finger	3.26 ± 2.31	3.95 ± 1.98	0.082	3.31 ± 2.27	3.40 ± 1.88	0.832	0.299
	2nd finger	3.03 ± 2.41	3.73 ± 2.34	0.087	3.38 ± 2.39	3.11 ± 2.13	0.565	0.115
	3rd finger	2.95 ± 2.72	3.83 ± 2.41	0.054	3.26 ± 2.54	3.11 ± 2.24	0.762	0.123
	4th finger	3.26 ± 2.85	4.01 ± 2.54	0.123	3.63 ± 2.69	3.29 ± 2.53	0.526	0.130
	5th finger	3.32 ± 2.65	3.82 ± 2.88	0.356	3.51 ± 2.71	3.36 ± 2.45	0.759	0.375
Right	Dorsum	2.28 ± 0.94	2.74 ± 1.04	0.024	2.27 ± 1.12	2.59 ± 1.00	0.127	0.615
	1st finger	3.15 ± 2.14	3.99 ± 1.94	0.033	3.53 ± 2.09	3.51 ± 1.94	0.956	0.104
	2nd finger	2.99 ± 2.35	3.92 ± 2.07	0.023	3.12 ± 2.35	3.30 ± 2.08	0.660	0.181
	3rd finger	2.88 ± 2.43	3.78 ± 2.16	0.032	2.88 ± 2.38	3.04 ± 2.21	0.701	0.200
	4th finger	3.01 ± 2.50	4.03 ± 2.38	0.026	3.11 ± 2.56	3.13 ± 2.22	0.963	0.107
	5th finger	3.03 ± 2.39	4.10 ± 2.32	0.020	3.28 ± 2.45	3.03 ± 2.34	0.582	0.040

Abbreviations: RT, recovered temperature; KRG, Korean red ginseng.
Values are mean ± SD.
[a] Paired *t*-test.
[b] Independent *t*-test.

Table 4
Comparison of DDD.

	KRG group (n=40)			Placebo group (n=40)			P^b
	Baseline	8 weeks	P^a	Baseline	8 weeks	P^a	
Maximum DDD (T_0; °C)	1.31 ± 1.33	0.82 ± 1.43	0.050	1.70 ± 1.56	1.08 ± 1.34	0.051	0.735
Number of fingers with DDD > 1 °C (T_0)	3.68 ± 4.09	2.30 ± 3.71	0.059	4.33 ± 4.43	3.18 ± 4.08	0.168	0.836
Maximum DDD (T_6; °C)	1.66 ± 1.64	1.06 ± 1.79	0.047	1.84 ± 1.81	1.85 ± 1.75	0.964	0.166
Number of fingers with DDD > 1 °C (T_6)	4.85 ± 4.67	3.13 ± 4.24	0.048	4.45 ± 4.25	4.48 ± 4.24	0.977	0.155

Abbreviations: KRG, Korean red ginseng; DDD, distal–dorsal difference; T_0, skin temperature immediately after cold stress; T_6, skin temperature 6 min after cold stress.
Values are mean ± SD.
[a] Paired *t*-test.
[b] Independent *t*-test.

Table 5
Comparison of power variables of HRV.

	KRG group (n=40)			Placebo group (n=40)			P^b
	Baseline	8 weeks	P^a	Baseline	8 weeks	P^a	
lnLF	5.47 ± 0.95	5.13 ± 1.03	0.045	5.17 ± 1.06	5.22 ± 1.20	0.694	0.076
lnHF	5.40 ± 1.02	5.02 ± 1.19	0.028	5.37 ± 1.14	5.51 ± 1.11	0.325	0.019
LF norm	51.08 ± 20.50	52.33 ± 20.44	0.697	45.83 ± 21.15	43.77 ± 19.06	0.556	0.484
HF norm	49.17 ± 20.82	46.42 ± 20.93	0.431	55.07 ± 20.19	56.23 ± 19.06	0.726	0.415
LF/HF	1.62 ± 1.57	1.76 ± 1.92	0.627	1.35 ± 1.83	1.11 ± 1.14	0.416	0.357

Abbreviations: KRG, Korean red ginseng; lnLF, logarithmic low frequency power; lnHF, logarithmic high frequency power; LF norm, LF power normalized unit; HF norm, HF power normalized unit; LF/HF, LF to HF ratio.
Values are mean ± SD.
[a] Paired *t*-test.
[b] Independent *t*-test.

3.3.6. SF-36 scores

The score for energy and vitality decreased by 4.63 ± 13.70 in the KRG group comparing to the reduction of 0.25 ± 9.74 in the placebo group, which failed to show a significant difference between the two groups (P=0.104). The scores for other dimension and total scores were not significantly different between the groups (Table 6).

3.4. Safety and adverse events

One adverse event was reported in the KRG group: the patient complained of itching, but the symptom was slight and disappeared within a few days. No serious adverse events were reported during the study. Besides, there were no safety issues in our study.

3.5. Assessment of blinding

In the KRG group, 26 of 39 participants assumed that they had received the active intervention while 13 believed that they had received the placebo. Fourteen of 35 participants in the placebo group assumed that they had received the active intervention, and 21 guessed that they had received the placebo (P=0.035; Table 7).

Table 6
Comparison of SF-36 scores.

	KRG group ($n=40$)			Placebo group ($n=40$)			P^b
	Baseline	8 weeks	P^a	Baseline	8 weeks	P^a	
PF	86.00 ± 11.67	86.25 ± 12.02	0.888	87.75 ± 13.15	88.38 ± 11.12	0.614	0.816
RP	79.38 ± 34.38	82.50 ± 29.53	0.323	92.50 ± 18.08	88.75 ± 21.15	0.110	0.080
BP	78.00 ± 23.19	77.13 ± 23.55	0.784	74.75 ± 20.73	80.88 ± 20.69	0.062	0.122
GH	55.25 ± 16.91	57.25 ± 15.73	0.310	53.25 ± 19.33	54.63 ± 19.69	0.462	0.779
VT	49.38 ± 17.77	44.75 ± 15.69	0.039	48.75 ± 17.68	48.38 ± 15.54	0.812	0.104
SF	77.08 ± 19.88	81.13 ± 15.18	0.250	82.00 ± 18.97	81.45 ± 17.61	0.848	0.299
RE	83.35 ± 32.91	84.23 ± 27.19	0.866	85.88 ± 24.91	90.05 ± 21.57	0.323	0.616
MH	33.20 ± 14.83	33.10 ± 14.38	0.962	34.10 ± 14.32	34.00 ± 14.32	0.952	0.970
Total	541.45 ± 93.66	546.03 ± 78.74	0.685	558.78 ± 67.55	566.28 ± 58.48	0.413	0.840

Abbreviations: PF, physical function; RP, role limitations owing to physical health problems; BP, bodily pain; GH, general health perception; VT, energy and vitality; SF, social function; RE, role limitations owing to emotional problems; MH, mental health.
Values are mean ± SD.

[a] Paired *t*-test.
[b] Independent *t*-test.

Table 7
Results of the blinding analysis.

		Participants' guess			*P*
		KRG, *n* (%)	Placebo, *n* (%)	Total, *n* (%)	
Allocation	KRG group	26 (66.7)	13 (33.3)	39 (52.7)	0.035
	Placebo group	14 (40.0)	21 (60.0)	35 (47.3)	
	Total, *n* (%)	40 (54.1)	34 (45.9)	74 (100.0)	

Abbreviations: KRG, Korean red ginseng.

4. Discussion

In this study, KRG intake significantly decreased ΔT_{hands}, ΔT_{feet}, and VAS scores compared with placebo intake. Further, RT of the right 5th finger increased and parasympathetic activity decreased after intake of KRG. No significant differences in DDD of the hands and SF-36 scores were noted. No safety issues were also identified.

Change in skin temperature was assessed by infrared thermography. This method may yield more information about the pattern of rewarming of the hand than monitoring of fingertip temperature (Coughlin et al., 2001). Subjective estimation of finger temperature is closely related to finger temperature measured by infrared thermography (Polunina et al., 2011). The absolute temperatures of the hands and feet vary considerably among individuals, so the temperatures of the palm and dorsum of the foot relative to those of the arm and anterior thigh, respectively, which remain consistent, were measured. In a previous study (Kim et al., 2001), when the criterion for thermal difference between the arm and the palm was set at over 0.3 °C, the sensitivity and specificity of infrared thermography were 94.0% and 90.0%, respectively. We therefore used this cut-off value for CHHF screening.

The cold stress test is a sensitive method to assess vascular thermoregulation (Voelter-Mahlknecht et al., 2006). Cold exposure causes peripheral vasoconstriction. The subsequent vasodilation is used for assessing physiological reactivity of blood vessels. Removal of the extremities from a cold environment results in prompt rewarming in healthy individuals, with over 80% temperature recovery within 5 min (Zaproudina et al., 2011). Therefore, we evaluated RT at 6 min following cold stress in this study. KRG administration increased RT of the right 5th finger after cold stress comparing with the placebo. KRG is thought to promote vasodilatation following vasoconstriction of the peripheral blood vessels after cold stress.

DDD, which shows the thermal gradient of the hands, is effective to assess CHHF, especially in the fingers. It has been used to evaluate the severity of vasoconstriction (Clark et al., 1999; Pauling et al., 2011). DDD of >1 °C in any finger at room temperature is considered a specific indicator of vascular disease (Anderson et al., 2007). Calculating the maximum DDD across all digits and the number of fingers with DDD >1 °C appeared to provide a greater discriminatory capacity than any other analysis that had been adopted in previous studies investigating DDD (Pauling et al., 2011). We did not find significant differences in these variables between the groups. Therefore, whether KRG reduces the thermal gradient between the dorsum of the hand and the fingers is not clear. KRG may have effectively increased the temperature of the hands rather than the fingertips.

No study has evaluated autonomic nervous activity after oral administration of KRG. The sympathetic nervous system plays a major role in regulating cutaneous blood flow (Abramson, 1972). Digital blood flow decreases after activation of the sympathetic nervous system and increases following its withdrawal. A previous study showed higher sympathetic nervous activity in subjects with slow temperature recovery after cold exposure than normal subjects (Brändström et al., 2012). Accordingly, we hypothesize that exaggerated sympathetic nervous activity contributes to CHHF. In our study, KRG intake lowered logarithmic HF as well as logarithmic LF, although not significantly, compared with placebo intake. KRG may reduce parasympathetic nervous activity to maintain LF/HF ratio in the normal range. Previously, the normal range for the LF/HF ratio was reported to be 1.5–2.0 (Camm et al., 1996). Controlled studies with more participants are needed to determine the effects of KRG on the autonomic nervous system in individuals with CHHF.

CHHF may lower quality of life by restricting daily activities in cold environments. Therefore, improving quality of life is an important goal of CHHF treatment. We did not find significant differences in SF-36 scores between the groups, probably because improvement in quality of life after KRG administration is detectable after 8 weeks. Comparison of SF-36 scores between normal and CHHF populations is needed. The SF-36 does not reflect the severity of CHHF because it is a generic instrument measuring health-related quality of life, so a specific tool to measure quality of life due to CHHF is also required.

Suggestions for the pathophysiology of CHHF include both vascular and neural etiologies. Previous studies have suggested that KRG and its ginsenosides have a vasodilating action on peripheral vessels and can increase the blood flow under cold stress in animal experiments (Kaneko and Nakanishi, 1984). The ginsenosides

isolated from KRG have been reported to cause vasodilatation in an endothelium-dependent and nitric oxide (NO)-mediated manner in a rabbit model (Chen, 1996). Especially, the ginsenoside Rg3 was proven to inhibit vascular contraction as a consequence of NO production in rats in vitro and in vivo (Kim et al., 2003). The vasodilating action of KRG is thought to contribute to the alleviation of CHHF, but the neural action of KRG cannot be determined from the results of this study. Moreover, the causal relationship between the vascular and neural actions of KRG needs to be examined.

Some results such as HRV outcomes may have been influenced by seasonal variation in the 8-week dosage period (Kristal-Boneh et al., 2000; Kristiansen et al., 2009). Our study was conducted between October 2012 and May 2013. Baseline values were mostly obtained in late fall or winter and participants were re-examined in spring. ΔT_{hands}, ΔT_{feet}, and VAS scores of patients with CHHF are higher in winter than during other seasons (Kim et al., 2012). In our study, the seasonal variation resulted in improvement for each variable in both groups. However, the statistically significant difference in the changed values of ΔT_{hands}, ΔT_{feet}, and VAS scores of CHHF between the groups proves the efficacy of KRG for CHHF.

Incomplete blinding is another limitation. Several participants had been exposed to KRG before the trial, so they were already aware of the flavor and smell of real KRG. Nonetheless, VAS scores, which are affected by participants' expectations, were significantly different between the groups. ΔT_{hands} and ΔT_{feet}, which are not affected by participants' expectations, were irrelevant to the success of blinding. Objective evaluation of CHHF by infrared thermography would be unaffected by incomplete blinding.

5. Conclusions

Peripheral vasodilation by KRG may alleviate CHHF. Examination of the effects on the autonomic nervous system under more controlled conditions is required to elucidate the neural mechanism of KRG in CHHF.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KSP, CHL, JWP, and JML obtained funding and designed the study. KIP, JWK, YJY, and SHK recruited the participants and conducted the trial. KSP and JWP analyzed the data and wrote the manuscript. All authors read and approved the manuscript.

Acknowledgments

This study was sponsored by the 2012 grant from the Korean Society of Ginseng funded by Korea Ginseng Corporation.

References

Abramson, D.I., 1972. Neural regulation of cutaneous circulation. Advances in Biology of Skin 12, 207–233.

Anderson, M., Moore, T., Lunt, M., Herrick, A., 2007. The 'distal–dorsal difference': a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. Rheumatology 46, 533–538.

Brändström, H., Wiklund, U., Karlsson, M., Ängquist, K.A., Grip, H., Haney, M., 2012. Autonomic nerve system responses for normal and slow rewarmers after hand cold provocation: effects of long-term cold climate training. International Archives of Occupational and Environmental Health 86, 357–365.

Camm, A., Malik, M., Bigger, J., Breithardt, G., Cerutti, S., Cohen, R., Coumel, P., Fallen, E., Kennedy, H., Kleiger, R., 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. European Heart Journal 17, 354–381.

Chen, X., 1996. Cardiovascular protection by ginsenosides and their nitric oxide releasing action. Clinical and Experimental Pharmacology and Physiology 23, 728–732.

Clark, S., Hollis, S., Campbell, F., Moore, T., Jayson, M., Herrick, A., 1999. The distal–dorsal difference as a possible predictor of secondary Raynaud's phenomenon. Journal of Rheumatology 26, 1125–1128.

Coughlin, P., Chetter, I., Kent, P., Kester, R., 2001. The analysis of sensitivity, specificity, positive predictive value and negative predictive value of cold provocation thermography in the objective diagnosis of the hand–arm vibration syndrome. Occupational Medicine 51, 75–80.

Craigen, M., Kleinert, J.M., Crain, G.M., McCabe, S.J., 1999. Patient and injury characteristics in the development of cold sensitivity of the hand: a prospective cohort study. The Journal of Hand Surgery 24, 8–15.

Hur, Y.M., Chae, J.H., Chung, K.W., Kim, J.J., Jeong, H.U., Kim, J.W., Seo, S.Y., Kim, K.S., 2012. Feeling of cold hands and feet is a highly heritable phenotype. Twin Research and Human Genetics 15, 166–169.

Kaneko, H., Nakanishi, K., 1984. Vasodilator action of ginsenosides. Clinic and Study 61, 2657–2662.

Kaneko, H., Nakanishi, K., 2004. Proof of the mysterious efficacy of ginseng: basic and clinical trials: clinical effects of medical ginseng, Korean red ginseng: specifically, its anti-stress action for prevention of disease. Journal of Pharmacological Sciences 95, 158–162.

Kim, D.H., Kim, Y.S., Lee, K.S., 2001. Standardization of diagnosis of cold hypersensitivity of hands and feet by infrared thermography. The Journal of Korean Gynecology 14, 129–134.

Kim, J.W., Park, K.S., Lee, C.H., Jang, J.B., Lee, K.S., Lee, J.M., 2012. Analysis of factors that can affect the assessment of cold hypersensitivity in hands and feet. The Journal of Korean Gynecology 25, 38–45.

Kim, N.D., Kim, E.M., Kang, K.W., Cho, M.K., Choi, S.Y., Kim, S.G., 2003. Ginsenoside Rg3 inhibits phenylephrine-induced vascular contraction through induction of nitric oxide synthase. British Journal of Pharmacology 140, 661–670.

Kim, W.Y., Kim, J.M., Han, S.B., Lee, S.K., Kim, N.D., Park, M.K., Kim, C.K., Park, J.H., 2000. Steaming of ginseng at high temperature enhances biological activity. Journal of Natural Products 63, 1702–1704.

Kristal-Boneh, E., Froom, P., Harari, G., Malik, M., Ribak, J., 2000. Summer–winter differences in 24 h variability of heart rate. Journal of Cardiovascular Risk 7, 141–146.

Kristiansen, J., Olsen, A., Skotte, J.H., Garde, A.H., 2009. Reproducibility and seasonal variation of ambulatory short-term heart rate variability in healthy subjects during a self-selected rest period and during sleep. Scandinavian Journal of Clinical & Laboratory Investigation 69, 651–661.

Kwan, C., 1999. The effects of different ginseng extracts on vascular contraction in vitro: evidence for Yin–Yang principle. Acta Phytotherapeutica 2, 73–77.

Park, J.D., 1996. Recent studies on the chemical constituents of Korean ginseng (*Panax ginseng* CA Meyer). Korean Journal Ginseng Science 20, 389–415.

Pauling, J.D., Flower, V., Shipley, J., Harris, N.D., McHugh, N.J., 2011. Influence of the cold challenge on the discriminatory capacity of the digital distal–dorsal difference in the thermographic assessment of Raynaud's phenomenon. Microvascular Research 82, 364–368.

Polunina, A., Gugleta, K., Kochkorov, A., Katamay, R., Flammer, J., Orgül, S., 2011. Relationship between peripheral blood flow in extremities and choroidal circulation. Klin Monatsbl Augenheilkd 228, 302–305.

Traynor, R., MacDermid, J.C., 2008. Immersion in cold-water evaluation (ICE) and self-reported cold intolerance are reliable but unrelated measures. Hand 3, 212–219.

Voelter-Mahlknecht, S., Krummenauer, F., Koulele, D., Mahlknecht, U., Pinzon, L.E., Dupuis, H., Letzel, S., 2006. First experiences with DIN ISO 14835-1 in the context of vibration-induced white finger disease. International Archives of Occupational and Environmental Health 79, 427–432.

Ware Jr., J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical Care 30, 473–483.

Zaproudina, N., Lipponen, J.A., Eskelinen, P., Tarvainen, M.P., Karjalainen, P.A., Närhi, M., 2011. Measurements of skin temperature responses to cold exposure of foot and face in healthy individuals: variability and influencing factors. Clinical Physiology and Functional Imaging 31, 307–314.