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Effects of Food Containing Pine Bark Extract on Capillary Blood Flow: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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Abstract

Background: Capillary blood flow supplies oxygen and nutrients to tissues throughout the body and removes metabolic waste; however, it declines with unhealthy lifestyles and aging. Therefore, maintaining adequate capillary blood flow is important. In this study, we aimed to evaluate the effects of consuming food containing pine bark extract on capillary blood flow in healthy adults. **Methods:** A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the effect of pine bark extract on capillary blood flow in healthy participants. Fifty healthy women aged 40 - 59 years who were troubled by cold sensitivity were enrolled and randomly assigned to two groups. The active food group consumed food containing pine bark extract (2.4 mg/day as procyanidins B1 and B3) for 8 weeks, whereas the placebo food group consumed food without pine bark extract for the same period. The primary outcome was capillary blood flow velocity. The secondary outcome was capillary congestion, which was evaluated by a physician using a visual analog scale (VAS) based on capillary images. **Results:** After 8 weeks, compared with the placebo food group, the active food group showed a significant increase in capillary blood flow velocity and a significant decrease in capillary congestion. No adverse events related to the test food were observed. **Conclusions:** Intake of food containing pine bark extract may improve capillary blood flow in healthy women troubled by cold sensitivity.

Keywords

Pine Bark Extract, Procyanidin B1, Procyanidin B3, Capillary

1. Introduction

The vasculature consists of arteries, veins, and capillaries distributed throughout the body. Capillaries supply oxygen and nutrients to tissues and collect metabolic waste [1].

Unhealthy dietary habits, smoking, sleep deprivation, aging, and obesity have been associated with reduced capillary blood flow velocity and volume [2] [3]. A decline in capillary blood flow reduces cellular metabolism and adversely affects tissue function [3] [4]. Furthermore, when the transport of heat produced in deep body sites to peripheral regions is hindered by reduced blood flow, skin temperature is not maintained, resulting in cold extremities [5]. Cold extremities cause neck and shoulder stiffness, fatigue, and impaired sleep quality [6] [7], thereby reducing quality of life (QOL). In Japan, many adult women across all age groups report awareness of cold extremities [8]. Therefore, maintaining normal capillary blood flow through lifestyle improvements is considered important for preserving QOL and overall health.

Pine bark extract has been reported to be rich in polyphenols, particularly oligomeric proanthocyanidins [9]. The main polyphenols in pine bark extract are procyanidins B1 and B3 [10]. Various physiological effects of pine bark extract have been reported, including antioxidant activity [11], cholesterol reduction [12], improvement of vascular endothelial function [13], and inhibition of platelet aggregation [14]. In our exploratory open-label study, 8-week consumption of pine bark extract by healthy Japanese women aged 40 - 59 years with cold sensitivity significantly improved capillary blood flow velocity at the nailfold [15]. Therefore, in the present study, we aimed to confirm these findings using a randomized, double-blind, placebo-controlled, parallel-group design in healthy Japanese women with cold sensitivity to confirm whether consumption of pine bark extract improves capillary blood flow.

2. Materials and Methods

2.1. Study Design

This study was conducted as a randomized, double-blind, placebo-controlled, parallel-group trial with an allocation ratio of 1:1 over an 8-week intake period. No methodological changes were made after study initiation.

2.2. Study Participants and Setting

Paid volunteers were recruited for this study. Healthy adults who met the inclusion criteria and did not meet any of the exclusion criteria were eligible to participate. Before study initiation, prospective participants received a full explanation of the study and provided written informed consent.

The inclusion criteria were as follows: 1) Healthy females aged 40 to 59 years-old.; 2) Subjects who aware of coldness.; 3) Subjects who can make self-judgment and are voluntarily giving written informed consent.

The exclusion criteria were as follows: 1) Subjects who were diagnosed with serious disease (e.g., diabetes, liver disease, kidney disease, digestive disease, heart disease, respiratory disease and/or peripheral vascular disease); 2) Subjects who had a gastrointestinal surgery; 3) Subjects with strange finger conditions at measurement points (like inflammation or injury); 4) Subjects with a disease currently under treatment; 5) Subjects with food allergies; 6) Subjects with anemic; 7) Women who are/might be pregnant or lactating during the current study periods; 8) Subjects who play high intensity sports and/or are on a diet; 9) Subjects who have an extremely irregular eating habit, are shiftworker and/or midnight-shift worker; 10) Subjects who can't stop using functional foods (including Food for Specified Health Uses or Foods with Function Claims) and/or Specified quasi-drugs during the current study periods; 11) Subjects who are under treatment with medications (including OTC and/or pre-scribed medications); 12) Subjects who have excessive alcohol intake more than approximately 60 g/day of pure alcohol equivalent, habit of drinking not less than 5 days a week, or can't stop drinking from the days before each measurement; 13) Subjects who smoke 21 or more cigarettes a day, or cannot quit smoking during from waking to inspection completed; 14) Subjects who can't stop their manicure or false nail during the current study periods; 15) Subjects who are participating in other studies or planning to participate at the start of the current study; 16) Subjects who are judged as unsuitable for the current study by the investigator for other reasons.

This study was approved by "The Ethics Committee of Miura Clinic, Medical Corporation Kanonkai" (Chair: Masaaki Nishi) (approval date: January 30, 2025) and was conducted in accordance with the "Declaration of Helsinki" (amended October 2013) and "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" (partially revised March 27, 2023). The study was performed under physician supervision at the Miura Clinic. The study protocol was registered with the clinical trial registry operated by the University Hospital Medical Information Network (UMIN000057143; trial name: "A Study on the Effect of Food Containing Plant Extract on Capillary Blood Flow-A Randomized, Double-blind, Placebo controlled, Parallel-group Study-").

2.3. Intervention

During the study, the intervention consisted of continuous intake of the test food for 8 weeks. The active food was prepared by tableting a mixture of pine bark extract (Toyo Shinyaku Co., Ltd.), powdered reduced maltitol, microcrystalline cellulose, sucrose fatty acid ester, and silicon dioxide. For the placebo food, the pine bark extract in the active formulation was replaced with caramel coloring to ensure indistinguishable appearance from the active food.

The daily intake of both the active food and placebo food was two tablets (250 mg × 2 tablets). During the intake period, participants consumed two tablets of the assigned test food once daily with water or lukewarm water. The caloric and nutrient compositions per recommended daily intake are shown in **Table 1**. The

amounts of pine bark-derived procyanidins B1 and B3 in the active food were 2.4 mg per day.

Table 1. Analysis of nutrient composition values of test food.

	Placebo food (2 tablets)	Active food (2 tablets)
Energy (kcal)[a]	2	2
Protein (g)[b]	0	0
Fat (g)	0.02	0.02
Carbohydrate (g)	0.5	0.5
Sodium (g)	0.004	0.0002
Pine Bark-Derived Procyanidins B1 and B3 (mg)	0.000	2.4

a. Calorie conversion factors: protein, 4; fat, 9; carbohydrates, 4. b. Nitrogen protein conversion factor: 6.25.

2.4. Test Items

The primary outcome was capillary blood flow velocity, and the secondary outcome was capillary congestion. These parameters were evaluated at three time points: before intake (baseline), after 4 weeks, and after 8 weeks. No changes to the outcome measures were made after study initiation. Capillary blood flow velocity was measured at the nailfold of the ring finger on the non-dominant hand in the seated position after a rest period, using a capillary imaging device (GOKO Bscan-ZD; GOKO Imaging Devices Co., Ltd.). Image analyses were performed using analysis software (GOKO-VIP and GOKO Measure Plus; GOKO Imaging Devices Co., Ltd.). Capillary congestion was evaluated by a physician using a 100-mm visual analog scale (VAS) based on capillary images, with the left end labeled "not congested at all" and the right end labeled "very congested." The VAS score was quantified as the distance from the left end.

Participants were provided with a diary and instructed to record daily throughout the intake period the following information: (1) test food intake status; (2) physical condition; (3) intake of medicines and health foods; and (4) alcohol consumption, exercise, and smoking status.

2.5. Number of Cases

The target sample size was determined based on a previous report in which continuous intake of pine bark extract for 8 weeks (2.4 mg/day as pine bark-derived procyanidins B1 and B3) improved skin elasticity through improved blood flow as the mechanism of action because no randomized controlled trials (RCTs) existed evaluating capillary blood flow in healthy adults after administration of pine bark extract at the typical intake levels found in Japanese functional foods. The calculation used the change in skin elasticity from baseline (placebo food group: −0.073 ± 0.015; active food group: −0.003 ± 0.011) [16], with a significance level of 0.05 and statistical power of 80%. To account for potential dropouts and dis-

continuations, the sample size was set at 25 participants per group (50 participants in total).

2.6. Research Methods

Paid volunteers were recruited, and participants were enrolled by the principal investigator according to the inclusion and exclusion criteria. A statistical analyst used computer-generated random numbers to allocate participants by block randomization (block size of four), with age, body mass index (BMI), and capillary blood flow velocity used as adjustment factors. An allocation manager who was not directly involved in the study assigned the randomized participants to the active food group or placebo food group. The allocation manager prepared and sealed a key code table listing the allocation results and kept it sealed until the analysis population was determined, thereby ensuring blinding of all study personnel except the allocation manager. Test food were individually packaged as two-tablet sachets in plain aluminum bags and distributed to ensure blinding of both participants and intervention providers.

During the study, participants were instructed to avoid substantial changes in lifestyle habits, including diet, alcohol consumption, exercise, bedtime, and smoking; refrain from excessive exercise and extreme dieting or overeating; and, in principle, avoid the use of medicines (including OTC and prescription medicines), designated quasi-drugs, and health foods (including Foods for Specified Health Uses and Foods with Function Claims). Participants were also instructed, in principle, to avoid topical medicines and to consult the testing institution in advance if unavoidable intake was necessary due to poor physical condition. Participants were required to abstain from alcohol consumption and excessive exercise from the day before until completion of each visit; to finish eating by 22:00 on the day before each visit and fast until the end of the visit (water or lukewarm water permitted); to avoid pungent and stimulatory foods (e.g., curry, chili pepper, ginger, and Tabasco) at dinner on the day before each visit; to refrain from smoking from waking until the end of testing on visit days; and not to take the test food on visit days before coming to the clinic. In addition, participants were instructed to record the amount of water consumed from waking on visit days and consume a similar amount at subsequent visits, as well as to avoid bathing (including showers), devices that could excessively warm or cool the body, and massages before clinic visits. Except in emergency situations, participants were permitted to use medicines only with approval from the principal investigator or sub-investigator.

2.7. Statistical Analysis

The population analyzed was a Per-Protocol Set (PPS). Repeated-measures analysis of variance was performed to assess group-by-time interactions. Between-group comparisons at each visit were conducted using two-tailed unpaired t-tests for both measured values and changes from baseline, and end-of-intake results were evaluated. The significance level was set at 5% for all tests. Statistical analyses

were performed using IBM SPSS Statistics version 28. Participant background characteristics are presented as mean ± standard deviation, whereas other data are presented as mean ± standard error. No additional analyses were conducted.

3. Results

3.1. Analysis Participants

A total of fifty participants were enrolled. No dropouts occurred after randomization, and the allocated interventions were implemented in 25 participants per group. During the study period, one participant in the active food group discontinued participation for personal reasons unrelated to the test food, resulting in 49 completers. After completion of the study, five participants met the rejection criteria, leaving 44 participants for analysis. The reasons for rejection were violations of study precautions during the study period (active food group, n = 1; placebo food group, n = 4). Analyses were performed according to the original group allocation.

Recruitment through completion of follow-up was conducted from March 2025 to July 2025, and the study was terminated after all participants completed follow-up. The baseline characteristics of the analysis population are presented in Table 2, and the flow of participants from enrollment to analysis is shown in Figure 1.

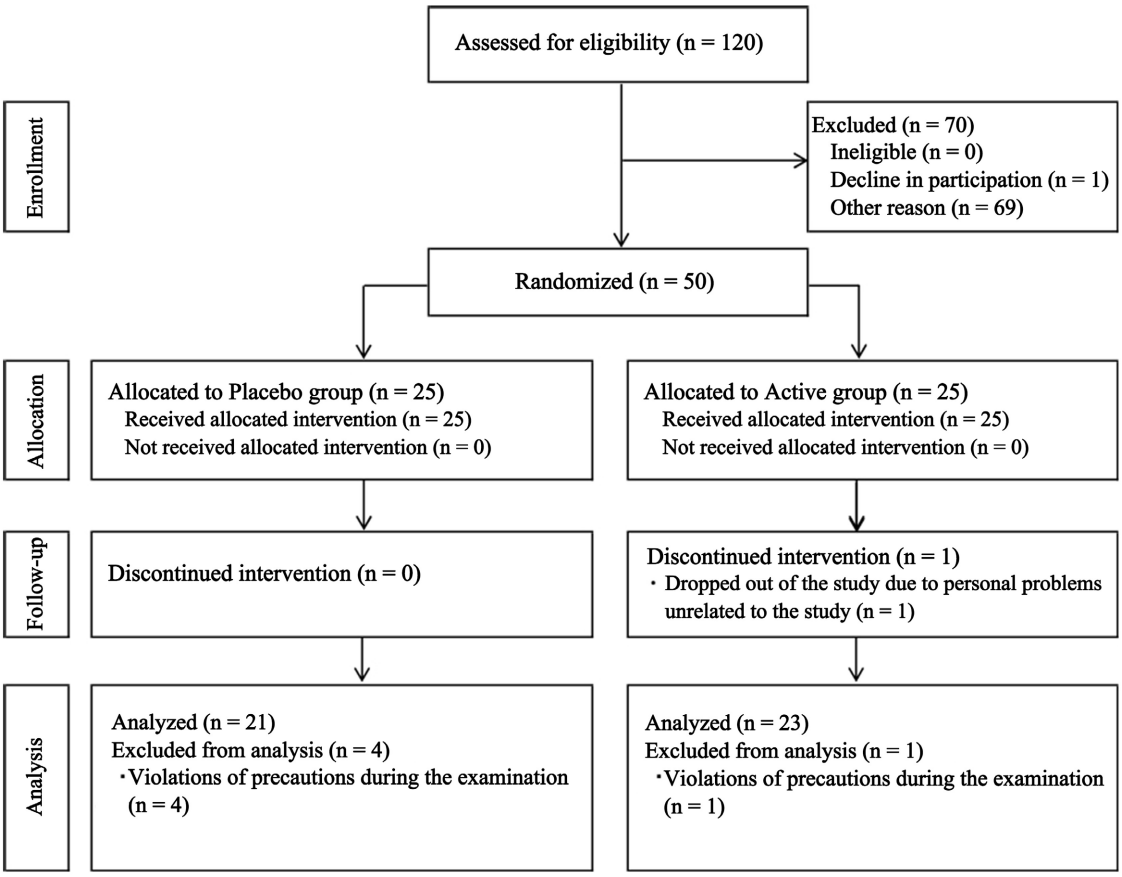

Figure 1. Flow diagram of progress through phases of randomized, double-blind, placebo-controlled, parallel-group study.

Table 2. Participant characteristics.

Parameter	Placebo food group (n = 21)	Active food group (n = 23)
Age (years old)	51.1 ± 5.3	51.1 ± 5.6
Height (cm)	158.6 ± 6.5	158.6 ± 5.0
Body weight (kg)	51.2 ± 9.6	53.0 ± 10.8
BMI	20.3± 3.5	21.1 ± 3.9
Capillary blood flow velocity (μm/s)	263.92 ± 188.87	230.27 ± 126.99

Values are expressed as means ± SDs. No significant difference was observed.

3.2. Analysis Results

Capillary blood flow velocities are presented in Table 3. A significant group-by-time interaction was observed. Between-group comparisons of both the measured values and changes from baseline showed that, at 8 weeks, the measured value and change from baseline were significantly higher in the active food group than in the placebo food group (measured value, $P = 0.040$; change from baseline, $P = 0.011$).

Table 3. Test results for capillary blood flow velocity.

Domain	Group		Baseline	4 Weeks	8 Weeks	*P*-value (Interactions between Groups and Time Points)
Capillary blood flow velocity (μm/s)	Placebo food (n = 21)	Measured	263.92 ± 41.21	270.77 ± 41.16	249.89 ± 34.92	$P = 0.026$
		Changes from baseline		6.84 ± 46.53	−14.04 ± 41.68	
	Active food (n = 23)	Measured	230.27 ± 26.48	359.18 ± 43.38	376.32 ± 47.36*	
		Changes from baseline		128.90 ± 44.72	146.05 ± 43.39*	

Values are expressed as means ± SEs. *Significantly different from the placebo food group ($P < 0.05$).

Capillary congestion results are presented in Table 4. A significant group-by-time interaction was also observed. Between-group comparisons indicated that, at 8 weeks, the change from baseline was significantly lower in the active food group than in the placebo food group ($P = 0.025$).

Table 4. Test results for capillary congestion.

Domain	Group		Baseline	4 Weeks	8 Weeks	*P*-value (Interactions between Groups and Time Points)
Capillary congestion (mm)	Placebo food (n = 21)	Measured	51.78 ± 4.86	49.99 ± 4.39	50.16 ± 4.60	$P = 0.037$
		Changes from baseline		−1.79 ± 2.11	−1.62 ± 1.50	
	Active food (n = 23)	Measured	56.85 ± 4.78	47.21 ± 4.28	46.86 ± 4.68	
		Changes from baseline		−9.64 ± 3.30	−9.98 ± 3.16*	

Values are expressed as means ± SEs. *Significantly different from the placebo food group ($P < 0.05$).

3.3. Adverse Events

During the study period, adverse events such as sore throat, rhinorrhea, and cold-like symptoms were reported. All events were judged by the principal investigator to be unrelated to the test food. No serious adverse events were observed.

4. Discussion

In this randomized, double-blind, placebo-controlled, parallel-group study of healthy women aged 40 - 59 years with cold sensitivity, an 8-week intake of food containing pine bark extract significantly increases capillary blood flow velocity compared with the placebo food group and significantly improves capillary congestion. Congestion, defined as stagnation of blood flow, refers to a state in which blood flow within capillaries or veins is impeded by factors such as thrombosis or microvascular dysfunction, resulting in increased residual blood volume at the affected site. When congestion occurs, normal blood flow is hindered, leading to an insufficient supply of oxygen and nutrients to tissues [17]. Therefore, improvements in capillary congestion support enhanced capillary blood flow. The observed improvements in capillary blood flow velocity and congestion indicate that pine bark extract improves capillary blood flow.

As blood moves from arteries to veins, it passes through the capillary network to deliver oxygen and nutrients to tissues. Blood flow depends on vascular characteristics such as capillary diameter and density, blood viscosity, and vasoactive factors, including endothelial nitric oxide [1] [18]. Blood flow velocity and volume are known to decrease with aging, obesity, and unhealthy lifestyle habits [2] [3]. The mechanisms underlying the observed improvement in capillary blood flow following pine bark extract intake can be considered in light of existing knowledge.

The low-density lipoprotein (LDL)-lowering and antioxidant effects on LDL provide one plausible explanation. LDL transports cholesterol in the blood; excessive LDL increases blood viscosity and impairs blood fluidity or accumulates in vessel walls to cause stenosis, thereby reducing blood flow [19]. Elevated LDL levels also increase oxidative stress, such as reactive oxygen species (ROS), which oxidize LDL and increase circulating oxidized LDL levels. In rats, intravenous administration of oxidized LDL reduces microcirculatory blood flow [20] [21]. Human studies on pine bark extract report LDL-lowering and antioxidant effects [12] [22]. Therefore, pine bark extract may improve capillary blood flow through LDL reduction, suppression of oxidized LDL, and antioxidant effects on LDL.

Another plausible mechanism involves improvement in platelet aggregation. Platelet aggregation, defined as the adhesive and aggregative function of platelets, is a determinant of blood fluidity and consequently influences blood flow velocity [23]. Pine bark extract improves platelet aggregation in healthy adults with high baseline platelet aggregation [14]. Thus, improvement of platelet aggregation may contribute to the observed enhancement of capillary blood flow.

Improvements in vascular endothelial function also provide a plausible expla-

nation. The endothelium regulates vascular structure and maintains the balance between vasoconstriction and vasodilation [3] [24], thereby modulating blood flow velocity and volume to ensure efficient delivery of oxygen and nutrients to peripheral tissues. Pine bark extract improves vascular endothelial function in healthy adults [13]. Therefore, enhancement of endothelial function may contribute to the observed improvement in capillary blood flow.

Taken together, pine bark extract appears to improve capillary blood flow through LDL reduction, suppression of oxidized LDL, antioxidant effects on LDL, and improvements in platelet aggregation and endothelial function.

The safety of pine bark extract is also confirmed. No adverse events attributable to the intake of food containing pine bark extract were observed, suggesting that long-term intake does not raise safety concerns.

This study has several limitations. The study targets healthy women aged 40 - 59 years with cold sensitivity; therefore, the effects in younger and older populations remain unclear. Future studies should include broader populations to further confirm the effects of pine bark extract on capillary blood flow. Furthermore, since this study did not concurrently perform biomarkers tests or biochemical blood analyses—specifically blood tests measuring LDL levels, platelet aggregation capacity and vascular endothelial function—nor vascular function tests, the proposed mechanisms of action are speculative.

5. Conclusion

Food containing pine bark extract improves capillary blood flow in healthy women aged 40 - 59 years who are troubled by cold sensitivity.

Author's Contributions

Conceptualization, T.K. and K.T.; Methodology, N.K.; Validation, A.Y.; Formal analysis, K.O. and A.Y; Investigation, N.K. and K.O.; Writing—Original Draft Preparation, K.O; Supervision, K.T. and N.M.; Writing-Review & Editing, T.M. and S.T.; Visualization, K.O. and A.Y.; Project Administration, S.T. and T.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by The Ethics Committee of Miura Clinic, Medical Corporation Kanonkai (approval date: 30 January 2025; approval number: R2404).

Informed Consent Statement

Informed consent was obtained from all participants involved in the study.

Data Availability Statement

The data used in this manuscript are not publicly available because of commercial restriction, but are available on reasonable request.

Conflicts of Interest

The test food used in this study was provided by Toyo Shinyaku Co., Ltd. This study was commissioned to Oneness support Co., Ltd. by Toyo Shinyaku Co., Ltd. Seven of the authors (K.O., N.K., A.Y., T.M., S.T., T.K., and K.T.) are employees of and receive their salaries from Toyo Shinyaku Co., Ltd. N.M., a physician affiliated with Miura Clinic, Medical Corporation Kanonkai, conducted this study as the principal investigator under contract with Oneness support Co., Ltd.

References

[1] Godwin, L., Tariq, M.A. and Crane, J.S. (2023) Histology, Capillary. StatPearls. https://europepmc.org/article/nbk/nbk546578#__NBK546578_dtls__

[2] Komai, M., Takeno, D., Fujii, C., Nakano, J., Ohsaki, Y. and Shirakawa, H. (2024) Nailfold Capillaroscopy: A Comprehensive Review on Its Usefulness in Both Clinical Diagnosis and Improving Unhealthy Dietary Lifestyles. *Nutrients*, **16**, Article 1914. https://doi.org/10.3390/nu16121914

[3] Jin, K. (2019) A Microcirculatory Theory of Aging. *Aging and disease*, **10**, 676-683. https://doi.org/10.14336/ad.2019.0315

[4] Østergaard, L. (2020) Blood Flow, Capillary Transit Times, and Tissue Oxygenation: The Centennial of Capillary Recruitment. *Journal of Applied Physiology*, **129**, 1413-1421. https://doi.org/10.1152/japplphysiol.00537.2020

[5] Young, A.J., Sawka, M.N. and Pandolf, K.B. (1996) 7 Physiology of Cold Exposure. In: Marriott B.M. and Carlson S.J., Eds., *Nutritional Needs in Cold and in High-Altitude Environments*: *Applications for Military Personnel in Field Operations*, National Academies Press, 127-148.

[6] Tsuboi, S., Mine, T., Tomioka, Y., Shiraishi, S., Fukushima, F. and Ikaga, T. (2019) Are Cold Extremities an Issue in Women's Health? Epidemiological Evaluation of Cold Extremities among Japanese Women. *International Journal of Women's Health*, **11**, 31-39. https://doi.org/10.2147/ijwh.s190414

[7] Bae, K., Go, H., Park, K., Ahn, I., Yoon, Y. and Lee, S. (2018) The Association between Cold Hypersensitivity in the Hands and Feet and Chronic Disease: Results of a Multicentre Study. *BMC Complementary and Alternative Medicine*, **18**, Article No. 40. https://doi.org/10.1186/s12906-018-2082-3

[8] Imai, M., Akasofu, K. and Fukunishi, H. (2007) Subjective Chills and Their Related Factors in Adult Women. *Ishikawa Journal of Nursing*, **4**, 55-64.

[9] Ikeguchi, M., Tsubata, M., Tabata, A. and Takagaki, K. (2006) Effects of Pine Bark Extract on Lipid Metabolism in Rats. *Nippon Eiyo Shokuryo Gakkaishi*, **59**, 89-95. https://doi.org/10.4327/jsnfs.59.89

[10] Samejima, M. and Yoshimoto, T. (1982) Accumulation and Structural Changes of Flavanols in the Barks of Cryptomeria Japonica D. Don and Pinus Densiflora Sieb. and Zucc. *Bulletin*, *Tokyo University Forests*, **72**, 17-29.

[11] Tubata, M., Takagaki, K. and Nakayama, J. (2013) The Powerful Antioxidant, Pine Bark Extract (FLAVANGENOL®) Suppresses Histamine Release from Mast Cell and

Moisturizes Skin Surface. *The Allergy in Practice*, **33**, 53-56.

[12] Nagamine, R., Takano, A., Hama, R., Suzuki, M., Kamiya, T. and Takagaki, K., *et al.* (2019) LDL-Cholesterol Lowering Effect of a Functional Food Containing Pine Bark Extract: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. *Japanese Pharmacology & Therapeutics*, **47**, 629-635.

[13] Fujiki, K., Takano, A., Tomozawa, H., Kamiya, T., Takagaki, K. and Tokushima, M. (2020) A Study on the Effect of Food Containing Pine Bark Extract on Vascular Endothelial Function—A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. *Japanese Pharmacology & Therapeutics*, **48**, 853-858.

[14] Fujiki, K., Takahashi, Y., Suzuki, M., Takano, A., Kamiya, T. and Takagaki, K., *et al.* (2021) The Effect of Food Containing Pine Bark Extract on Platelet Aggregation: A Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study. *Japanese Pharmacology & Therapeutics*, **49**, 1749-1755.

[15] Fujiki, K., Mashiki, S., Motooka, K., Takahashi, Y., Takano, A. and Takashima, S., *et al.* (2023) Effect of Pine Bark Extract on Capillary Blood Flow. *Japanese Pharmacology & Therapeutics*, **51**, 129-134.

[16] Chiken, Y., Matsuoka, N., Inoue, M., Takahashi, Y., Takano, A. and Takashima, S., *et al.* (2022) Effects of Food Supplementation with Pine Bark Extract on Skin Health Parameters: A Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study. *Japanese Pharmacology & Therapeutics*, **50**, 2257-2265.

[17] Haddadin, R., Aboujaoude, C. and Trad, G. (2024) Congestive Hepatopathy: A Review of the Literature. *Cureus*, **16**, e58766. https://doi.org/10.7759/cureus.58766

[18] Popel, A.S. and Johnson, P.C. (2005) Microcirculation and Hemorheology. *Annual Review of Fluid Mechanics*, **37**, 43-69. https://doi.org/10.1146/annurev.fluid.37.042604.133933

[19] Rubba, P., Iannuzzi, A., Postiglione, A., Scarpato, N., Montefusco, S., Gnasso, A., *et al.* (1990) Hemodynamic Changes in the Peripheral Circulation after Repeat Low Density Lipoprotein Apheresis in Familial Hypercholesterolemia. *Circulation*, **81**, 610-616. https://doi.org/10.1161/01.cir.81.2.610

[20] van der Zwan, L.P., Teerlink, T., Dekker, J.M., Henry, R.M.A., Stehouwer, C.D.A., Jakobs, C., *et al.* (2009) Circulating Oxidized LDL: Determinants and Association with Brachial Flow-Mediated Dilation. *Journal of Lipid Research*, **50**, 342-349. https://doi.org/10.1194/jlr.p800030-jlr200

[21] Shiraisi, A., Katayama, T., Kusanagi, Y., Matsubara, K., Ochi, H. and Ito, M. (2001) The Investigation of Ox-LDL-Induced Leukocyte Behavior in Pregnancy-Rat Microcirculation. *Japan Society for the Study of Toxemia of Pregnancy*, **9**, 169-170.

[22] Nakayama, S., Kishimoto, Y., Saita, E., Sugihara, N., Toyozaki, M., Taguchi, C., *et al.* (2015) Pine Bark Extract Prevents Low-Density Lipoprotein Oxidation and Regulates Monocytic Expression of Antioxidant Enzymes. *Nutrition Research*, **35**, 56-64. https://doi.org/10.1016/j.nutres.2014.10.010

[23] Ishikawa, S., Kubo, T., Fujiwara, H., Sunagawa, M., Tawaratsumida, Y., Ishino, T., *et al.* (2011) Influence to Blood Fluidity by Exercise in Rat: Influence of Training in High Temperature Environments. *Japanese Journal of Physical Fitness and Sports Medicine*, **60**, 475-482. https://doi.org/10.7600/jspfsm.60.475

[24] Durand, M.J. and Gutterman, D.D. (2013) Diversity in Mechanisms of Endothelium-dependent Vasodilation in Health and Disease. *Microcirculation*, **20**, 239-247. https://doi.org/10.1111/micc.12040