

サチャインチオイル摂取による血流依存性血管拡張反応

機能性食品のヒト血管に対する非侵襲的評価法

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著者名	南,和広 櫻村,修生 前崎,祐二 清柳,典子 丹羽,光一 相根,義昌 渡部,俊弘
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Flow-mediated Vasodilation Response to Ingestion of Omega-3-rich Sacha-inchi Oil: A Noninvasive Evaluation of a Functional Food for Human Vascular

MINAMI Kazuhiro^{*1§}, KASHIMURA Osamu^{*2}, MAEZAKI Yuji^{*3}, KIYOYANAGI Noriko^{*4},
NIWA Koichi^{*1}, SAGANE Yoshimasa^{*1} and WATANABE Toshihiro^{*1}

* 1 Department of Food and Cosmetic Science, Faculty of Bioindustry, Tokyo University of Agriculture,
196 Yasaka, Abashiri, Hokkaido 099-2493

* 2 Faculty of International Agriculture and Food Studies, Tokyo University of Agriculture,
1-1-1 Sakuragaoka, Setagaya-ku, Tokyo 156-8502

* 3 Nippon Kayaku Food Techno Co., Ltd., 219 Iwahana-cho, Takasaki, Gunma 370-1208

* 4 Nippon Kayaku Co. Ltd., 1-1, Marunouchi 2-chome, Chiyoda-ku, Tokyo 100-0005

In this study, we designed a noninvasive method to evaluate functional foods for improvements in endothelial function. Omega-3 fatty acids are known to exert cardio-protective effects, including improvement of endothelial function. Endothelial dysfunction is an early event in hypertension and arteriosclerosis, and can lead to blood pressure increases and formation of plaques that block blood flow. The flow-mediated vasodilation (FMD) response is considered to represent endothelial function. Oil from the seeds of Sacha-inchi (*Plukenetia volubilis* L.) contains 45.5% α -linolenic acid (ω 3) of total fatty acid content, while canola oil contains only 9.7% α -linolenic acid. Twenty healthy subjects (10 males and 10 females; age 21.6 ± 0.83 years) were given a single dose of 350 mg Sacha-inchi oil or canola oil. FMD of the subjects was $11.2 \pm 2.53\%$ at baseline. Three hours after ingesting Sacha-inchi oil, the FMD of the subjects increased to $17.2 \pm 1.82\%$. Ingesting canola oil resulted in an FMD increase to only $11.7 \pm 2.05\%$. These findings suggest that Sacha-inchi oil can improve endothelial function. We suggest that FMD-based evaluation of functional foods is a viable tool for assessing their efficacy in promoting human vascular health.

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Key words : Flow-mediated vasodilation, endothelial function, Sacha inchi, functional food, omega-3 fatty acid
血流依存性血管拡張反応, 血管内皮機能, サチャインチ, 機能性食品, ω 3脂肪酸

To date, multiple studies have characterized functional foods that can affect hypertension, arteriosclerosis, and coronary artery disease. However, most of these studies were based on data from animal and cell culture assays, and only a small number employed human-based tests. In the latter, evaluations relied mainly on measuring blood pressure changes and pulse-wave velocity^{1)~4)}. This assessment provides indirect information on vasomotor tone, an important indicator of vascular endothelial function^{5)~8)}. Vasomotor tone is the amount of tension in the smooth muscle inside blood vessel walls, particularly in arteries. Many factors control vasomotor tone, including vasoactive substances, structural shift of the vascular wall, desensitization of the vascular nerve system, and

changes in the susceptibility of the receptor for vasoactive substrates^{9)~13)}.

Cardiovascular disease (CVD) is the leading cause of death in the USA and accounts for 32% of all deaths¹⁴⁾. In Japan, CVD is the second-leading cause of death and the most prevalent disease, based on national medical care expenditure data^{15), 16)}. The prevalence of short-term risk factors for CVD, such as smoking, high blood pressure, and high cholesterol levels, has recently decreased gradually owing to clinical and public health efforts and education¹⁷⁾. However, many adults who are at low risk for CVD in the short term are nonetheless at high risk over their lifespan^{18), 19)}. Therefore, daily diet appears to be an important factor in reducing lifetime risk for developing CVD.

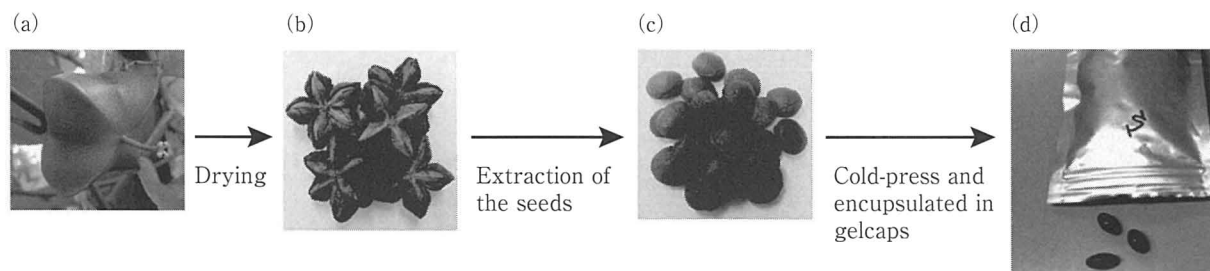


Fig. 1 Sacha-inchi and Sacha-inchi oil capsules

(a) Sacha-inchi fruit. (b) Dried Sacha-inchi fruits. (c) Sacha-inchi seeds. (d) Sacha-inchi oil encapsulated in gelcaps.

One of the factors responsible for vasomotor tone, flow-mediated vasodilation (FMD), which is the dilation response of the artery to the shear stress of blood flow, has been utilized in clinical medicine for a noninvasive method to examine endothelial function^{20, 21)}. Vascular endothelial cells produce nitric oxide (NO) in response to the shear stress from increased blood flow. NO acts as a trigger for smooth-muscle action to dilate vessel diameter. Measuring the FMD has been established as a diagnostic method in which blood flow is arrested using cuff inflation and released when the cuff is deflated. This increases blood flow, which results in FMD induction. FMD can be detected by diagnostic ultrasound imaging as a dynamic image of the expanding vessel diameter. Currently, FMD is used to diagnose the initial symptoms of hypertension and arteriosclerosis in humans.

In this study, we designed a noninvasive method to evaluate the effects of functional foods using an FMD-based strategy termed FMD-based Evaluation of Functional Food for Vascular Health (FEFF-VH), in which FMD measurement is conducted under conditions of dietary restriction. To assess this strategy as an evaluation method, we focused on omega-3 fatty acids, because multiple studies, including primary and secondary prevention clinical trials, and some studies which measured FMD, concluded that the consumption of omega-3 fatty acids is an effective dietary strategy to reduce the risk factors of CVD^{22)~24)}. We selected Sacha-inchi oil as an omega-3-rich food, rather than individual fatty acids, because our focus is on establishing the evaluation procedure in functional foods. Additionally, the oil from the seeds of the Inca peanut or Sacha-inchi (*Plukenetia volubilis* L.) contains high levels of omega-3 fatty acids in the form of α -linolenic acid^{25), 26)}.

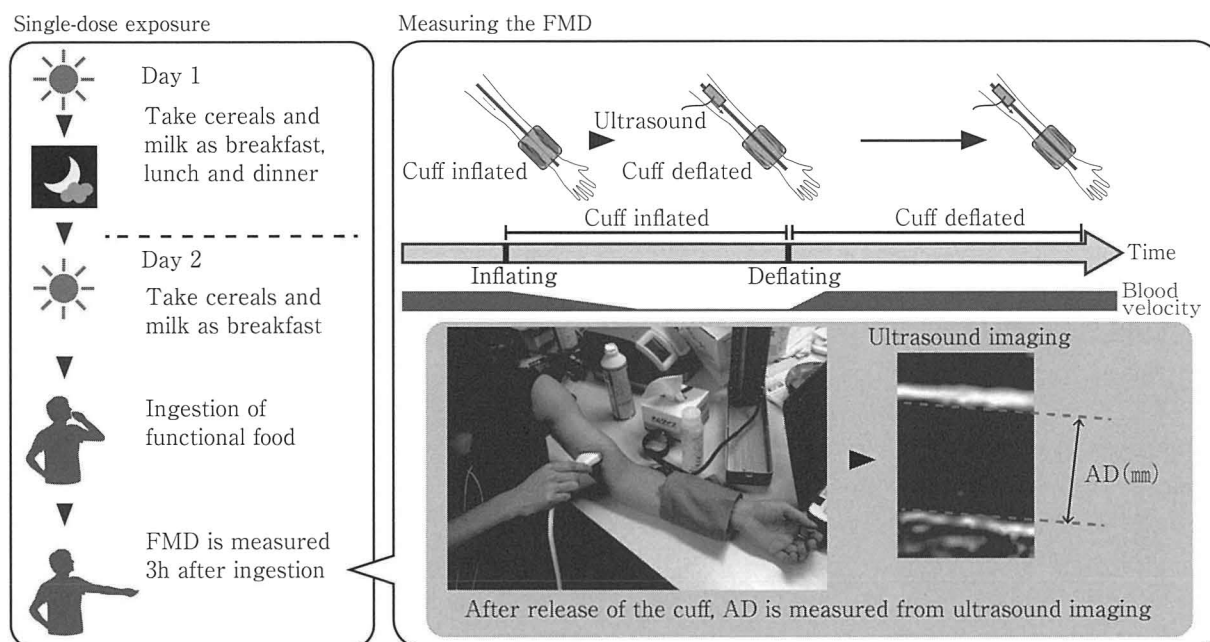
Materials and Methods

1. Materials

Sacha-inchi seeds from Peru (Fig. 1) were cold-pressed to release the oil. The oil was left to stand for 24 h, and the precipitation was removed. The supernatant was used as Sacha-inchi oil. The oil was encapsulated into 350-mg soft capsules made of gelatin containing caramel pigment.

2. Fatty acid contents

The fatty acids in the oil were esterified as follows. Oil samples (40-60 mg) and 6 mg of heptadecanoic acid (as internal standard) were dissolved in 2 mL of hexane in test tubes with screw caps. After the hexane was evaporated by nitrogen gas, the samples were dissolved with 0.5 M NaCl/methanol and then sealed after purging with nitrogen gas. The samples were heated at 100°C for 9 min with periodic shaking. After chilling on ice, a boron trifluoride-methanol reagent was added to the samples, which were then sealed after purging with nitrogen gas. The samples were heated at 100°C for 7 min with periodic shaking and then chilled on ice. Next, the samples were mixed with 3 mL of hexane, and 5 mL of saturated saline solution were added. The mixture was centrifuged at 1,500 rpm for 10 min, and the hexane layer was collected for gas chromatography (GC) with flame ionization detection (FID). The separation was achieved using an InertCap Pure-WAX column, 30 m $\times$ 0.25 mm $\times$ 0.25 μ m (GL Sciences, Tokyo, Japan). The split ratio was 1 : 80 and the carrier gas was helium at 100 kPa. The injection volume was 1.0 μ L. The injector and detector temperature were 250°C and 260°C, respectively. The oven temperature was held at 150°C for 5 min and then increased to 250°C at a rate of 10°C/min; the temperature was held for 20 min.



FEFF-VH method

(FMD-based evaluation of functional food for vascular health)

Fig. 2 FMD-based Evaluation of Functional Food for Vascular Health (FEFF-VH) method

In this method, a single dose of the functional food to be evaluated is administered under conditions of dietary restriction to avoid confounding (left). Flow-mediated dilation (FMD) is then measured (right). Following food restriction, the subjects were given a capsule containing the Sacha-inchi oil or a placebo. After 3h, the FMD response was measured. After avascularization with a cuff for 5 min, blood flow is released by deflating the cuff. Monitoring of the brachial artery by ultrasound imaging is initiated concurrently with cuff deflation. Arterial diameter (AD) is measured from the ultrasound imaging. The FMD is calculated as $(AD_{\max} - AD_{\text{at rest}}) / AD_{\text{at rest}}$.

3. Subjects

In September 2016, 20 healthy students (10 male and 10 female) at Tokyo University of Agriculture aged 19 to 21 years were recruited for the study. We selected healthy subjects without a history of hypertension, diabetes mellitus, or dyslipidemia, to avoid potential influence on endothelial function. The study protocol was approved by the Tokyo University of Agriculture Committee of Human Subject Research Ethics. Informed consent for participation in the study was obtained from all subjects.

4. FEFV-VH, a combined method of food restriction and FMD measurement

To evaluate the improvement capacity of vascular endothelial function, we conducted a combined method of food restriction and FMD measurement (Fig. 2). The study was performed at the Okhotsk Campus of Tokyo University of Agriculture between September 2016 and January 2017. Each subject was randomly administered a single dose of the Sacha inchi oil or canola oil (as placebo) as a soft capsule in a cross-over manner. The second dose was administered more than a week later.

Subjects were asked not to take any nutritional supplements on the day before the test or on the morning of the test, except for 90-130 g/meal of cereal (Flugra, Calbee, Tokyo, Japan) and 600-800 ml/day of milk. The purpose of the dietary restriction was to avoid the intake of omega-3 fatty acids. Subjects were given a capsule containing 350 mg of either the test oil or placebo oil, which was prepared at Nippon Kayaku Food Techno Co., Ltd. (Takasaki, Japan), and FMD was measured 3 h after the oil was administered. Before measuring FMD, subjects' blood pressure was measured using an electronic sphygmomanometer (ES-P2000, Terumo, Tokyo, Japan). To arrest the blood flow in the brachial artery, pressure (blood pressure plus 40 mmHg) was applied to the antebrachial region using the cuff of a mercurial sphygmomanometer (Yamasu, Japan) for 5 min. The pressure was released by deflating the cuff, and the brachial artery was monitored concurrently by ultrasonic diagnostic equipment (LOGIQ P6, GE Healthcare, Little Chalfont, UK). The arterial diameter (AD) was measured using the FMDscope software (Media Cross Co. Ltd, Japan). Based on the AD

measurement, the expansion rate of the FMD (% FMD) was calculated.

5. Serum measurement

High-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels of the subjects were determined using an Alere Afinion AS100 Analyzer (Alere Inc., Waltham, MA, USA).

6. Statistical analysis

The values are expressed as the mean $\pm$ standard deviation. The differences in mean values were assessed with one-way ANOVA followed by the Bonferroni multiple comparisons test. $p < 0.01$ was considered statistically significant.

Results

1. Fatty acid contents in Sacha-inchi oil

The fatty acid contents in the oil were analyzed by GC (Table 1). The most abundant fatty acid was α -linolenic acid (45.5%), an omega-3 fatty acid, followed by linoleic acid (35.5%), an omega-6 fatty acid. The fatty acid contents in the canola oil placebo were also analyzed. The most abundant fatty acid in the canola oil was oleic acid (57.6%) (Table 1). α -linolenic acid comprised only 9.7% of the total fatty acids. Fatty acid contents in Sacha-inchi oil have been previously analyzed^{26), 27)}; these reports also characterized the oil as omega-3-rich.

Table 1 Fatty acid contents in the Sacha-inchi oil and canola oil used as a placebo

Fatty acids (%)	Sacha-inchi oil	Canola oil
α -Linolenic acid	45.53	9.7
Linoleic acid	35.5	20.69
Oleic acid	10.49	57.56
Palmitic acid	4.61	4.73
Stearic acid	3.23	1.91
Others	0.64	5.41

2. Evaluation of Sacha-inchi oil by the FEFV-HV method

To assess the oil's capacity to improve vascular endothelial function, we used the noninvasive FEFV-HV evaluation method (Fig. 2). The characteristics of the subjects are shown in Table 2. Whole-day food restriction was used to prevent the effects of diet on vascular endothelial function. Fig. 3 (a) shows the typical AD dilation response to ingestion of Sacha-inchi oil. The FMD response reached maximal value 60 sec post-cuff release. Based on the maximum AD (AD_{max}) and baseline AD (AD at rest; AD immediately before arresting the blood flow by cuff), the expansion rate of the FMD was calculated as $(AD_{max} - AD_{at\ rest}) / AD_{at\ rest}$ (Fig. 3 (b)).

Fig. 4 shows the mean expansion rate in subjects (stratified by gender) at baseline and following ingestion of Sacha-inchi oil or placebo. At baseline, the subjects' AD expansion rate was $9.7 \pm 2.49\%$ (males), $12.4 \pm 1.94\%$ (females), and $11.2 \pm 2.53\%$

Table 2 Baseline characteristics of study participants ($\pm$ standard deviation)

Parameter	Male (n=10)	Female (n=10)	Total (n=20)
Age (years)	21.6 $\pm$ 0.97	21.5 $\pm$ 0.71	21.6 $\pm$ 0.83
Height (cm)	171.8 $\pm$ 6.16	162.3 $\pm$ 4.00	167.1 $\pm$ 7.02
Weight (kg)	67.0 $\pm$ 6.16	51.1 $\pm$ 3.30	59.0 $\pm$ 9.47
Systolic blood pressure (mmHg)			
At baseline	129.6 $\pm$ 13.01	116.5 $\pm$ 12.97	123.1 $\pm$ 14.32
After ingesting placebo	128.7 $\pm$ 8.94	115.3 $\pm$ 12.64	122 $\pm$ 12.68
After ingesting Sacha-inchi oil	125.9 $\pm$ 9.65	111.9 $\pm$ 10.15	118.9 $\pm$ 12.02
Diastolic blood pressure (mmHg)			
At baseline	66.1 $\pm$ 5.24	59.3 $\pm$ 12.68	62.7 $\pm$ 10.06
After ingesting placebo	70.9 $\pm$ 11.79	72.7 $\pm$ 8.14	70.9 $\pm$ 9.90
After ingesting Sacha-inchi oil	75.1 $\pm$ 14.07	66.6 $\pm$ 6.98	70.9 $\pm$ 11.65
High-density lipoprotein (HDL) cholesterol (mg/dl)			
After ingesting placebo	66.4 $\pm$ 12.82	75.2 $\pm$ 21.28	68.3 $\pm$ 16.83
After ingesting Sacha-inchi oil	66.0 $\pm$ 16.2	73.5 $\pm$ 21.48	67.5 $\pm$ 18.71
Low-density lipoprotein (LDL) cholesterol (mg/dl)			
After ingesting placebo	85.3 $\pm$ 18.71	71.0 $\pm$ 10.07	78.2 $\pm$ 16.65
After ingesting Sacha-inchi oil	82.8 $\pm$ 22.42	72.8 $\pm$ 5.30	77.8 $\pm$ 17.04

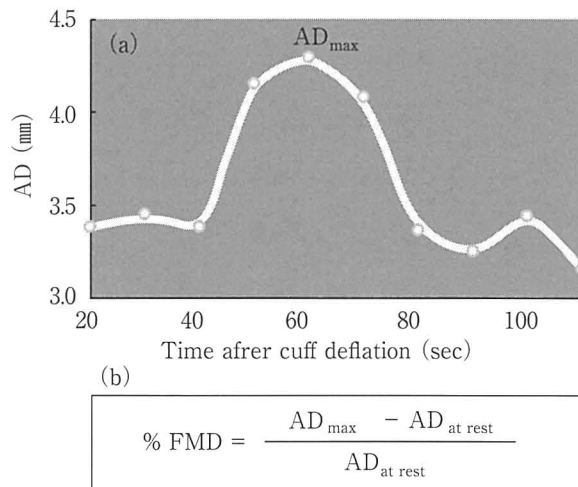


Fig. 3 A representative measurement of the flow-mediated dilation (FMD) response in a subject who ingested Sacha-inchi oil

- (a) A representative line graph recording the arterial dilation (AD) mediated by the increase in blood flow. The AD was measured by the method illustrated in Fig. 3.
- (b) Formula for calculating the expansion rate of the FMD. AD_{max} is defined as the maximum AD reduced by an increase in blood flow, and $AD_{at\ rest}$ is defined as the AD at baseline.

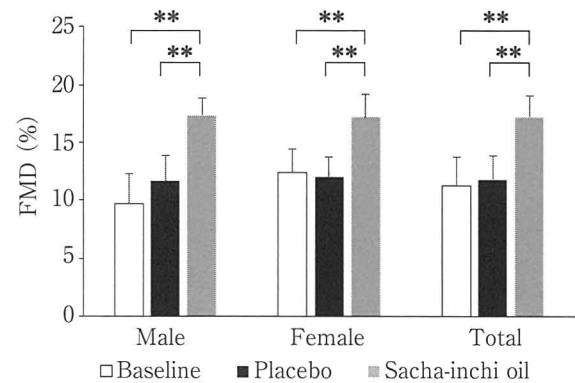


Fig. 4 Expansion rate of the FMD at baseline and after a single-dose administration of Sacha-inchi oil or placebo

Data represents the mean of all subjects, and the error bars indicate the standard deviation. **, $p < 0.01$.

(total). Normal endothelial functions are defined as an AD expansion rate greater than 6%, and rates lower than 6% are considered to indicate endothelial dysfunction (Fig. 5 (a))²⁸⁾. Thus, all subjects in this study exhibited normal FMD response. After ingestion of the Sacha-inchi oil, the AD expansion rate increased significantly to $17.3 \pm 1.54\%$ (males ; $p < 0.01$), $17.1 \pm 2.05\%$ (females ; $p < 0.01$), and $17.2 \pm 1.82\%$ (total ; $p < 0.01$). Since the significant increase of the expansion rate was not induced by

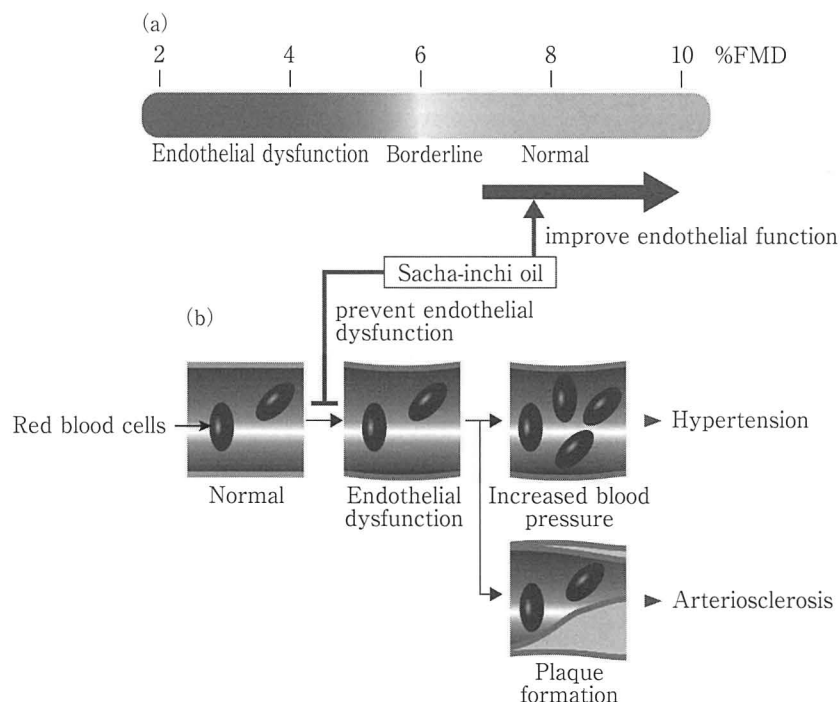


Fig. 5 Schematic model for the effect of the Sacha-inchi oil on vascular health

- (a) Normal endothelial functions are defined as an expansion rate (% flow-mediated dilation [FMD]) $> 6\%$. We found that consumption one-time dose of Sacha-inchi oil improves the expansion rate in healthy subjects.
- (b) Improving endothelial function would theoretically prevent cascade effects leading to cardiovascular disease.

ingestion of the placebo, the vessel dilation was induced by the Sacha-inchi oil rather than by other capsule components.

3. Discussion

In this study, we designed an 'FMD-based noninvasive method to evaluate the effects of omega-3 fatty acid-rich Sacha-inchi oil on vascular health. The vascular endothelium is a tissue that responds to shear stress caused by varying blood flow and pressure, thereby maintaining appropriate vasomotor tone. Endothelial dysfunction is therefore one of the early signs of hypertension and arteriosclerosis, and is a factor in the pathogenesis of CVD. Hence, we focused on endothelial function in evaluating the oil. Endothelial dysfunction is closely related to the FMD response^{20), 21)}. Vessel dilation may be affected by consumables such as dairy products, curry, coffee, and polyphenols from cranberries and grape seeds^{29)~32)}. Therefore, in this study, we restricted food intake to exclude these confounders.

As shown in Fig. 5 (a), functionally normal endothelium exhibits an FMD > 6%, and lower expansion rates may indicate endothelial dysfunction. Since all subjects in our study had functionally normal vascular endothelium, we demonstrated that Sacha-inchi oil can increase the vasodilation capacity of the artery in healthy subjects. Additionally, the consumption of Sacha-inchi oil did not affect blood pressure at baseline without the induction of increased blood flow (Table 2). This indicates that the Sacha-inchi oil's effect on vasodilation depends on changes in blood flow, rather than simply increasing blood flow capacity. Ingestion of the placebo canola oil, which contained low levels of omega-3 fatty acid, did not result in FMD improvement, implying that a threshold level of omega-3 fatty acid is required for FMD improvement or it could imply that combination with omega-6 fatty acid is required for beneficial effects, although the function of the omega-6 fatty acid on the vascular function is remained unclear. Vascular endothelial dysfunction can lead to conditions such as hypertension and arteriosclerosis^{33), 34)} (Fig. 5 (b)). Therefore, improving vasodilatory capacity in response to changes in blood flow may reduce risk for CVD. Additionally, our FEFF-VH method is adaptable to individuals in pre-disease or disease stages, to assess the effects of functional foods on CVD.

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**サチャインチオイル摂取による血流依存性血管拡張反応：
機能性食品のヒト血管に対する非侵襲的評価法**

南 和広^{*1}・檜村修生^{*2}・前崎祐二^{*3}・清柳典子^{*4}

丹羽光一^{*1}・相根義昌^{*1}・渡部俊弘^{*1}

* 1 東京農業大学生物産業学部

(〒099-2493 北海道網走市八坂196)

* 2 東京農業大学国際食料情報学部

(〒156-8502 東京都世田谷区桜丘1-1-1)

* 3 日本化薬フードテクノ㈱

(〒370-1208 群馬県高崎市岩鼻町219)

* 4 日本化薬㈱

(〒100-0005 東京都千代田区丸の内2-1-1)

私たちは、血管機能を向上させる働きのある機能性食品を評価するための非侵襲的ヒト対象試験法を構築した。 ω 3脂肪酸は、血管機能を向上させる機能があることが知られている。そこで、本研究では、 ω 3脂肪酸を多く含むことで知られるサチャインチオイルを使用した。血管内皮機能障害は、高血圧や動脈硬化などの心血管疾患の初期症状である。近年、血管内皮機能は、血流依存性血管拡張反応 (FMD) の測定によって評価できることが明らかとなっている。本試験に使用したサチャインチオイルは、リノレン酸が、全脂肪酸の45.5%と高い ω 3脂肪酸含量を示した。サチャインチオイル (350mg) を健康な被験者 (男性10人・女性10人：平均年齢 21.6 ± 0.83 歳) に経口投与したところ、摂取3時間後のFMDが $11.2 \pm 2.53\%$ (通常時) から、 $17.2 \pm 1.82\%$ に上昇した。一方、プラセボとしてキャノーラオイル (9.7%リノレン酸含有) を投与してもFMDは、 $11.7 \pm 2.05\%$ への上昇にとどまった。以上の結果は、サチャインチオイルが、ヒトの血管内皮機能を向上させることを示している。私たちは、本研究の成果から、FMDを基礎とした本法を、ヒト血管機能を増進させる機能性食品の簡便で効果的な評価法として提案する。

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