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Note of invitation to the 55th meeting of the Vitamin Society of Japan

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Introduction

Research on vitamins has advanced in the process of fight against vitamin deficiency which had raised fear as a disease with unknown etiology. In the present days when we have entered the 21st century, in parallel with increasingly greater attention paid to the means of correcting imbalance between the intake and consumption of energy as well as to the safety of foodstuffs, great expectations and needs have grown for the beneficial effects of supplements as a source of vitamins with an eye toward health maintenance and disease prevention in industrialized society supported by highly advanced technologies, giving vitamin research similarly important or more important roles as compared with those played by past research which had been pursued to combat vitamin deficiency. It is hoped that the holding of this meeting will facilitate the contribution of vitamin research to the promotion of health and longevity in this aging society as well as to the advances of research in the field of life science.

The 55th Meeting of the Vitamin Society of Japan is going to be held on Thursday, May 29 and Friday, May 30 of 2003 at the WelCity Shimane hall (Izumo Welfare Pension-funded Hall) and Izumo City Hall in Izumo City, Shimane Prefecture. During the two days, presentations of the report of the reports on 114 general topics will be made, and general meeting of the Vitamin Society of Japan as well as a symposium will be held, and memorial lectures by the recipients of the Vitamin Society Award and special lectures will be delivered.

The memorial lectures by the recipients of the Vitamin Society Award of this year are going to be given by Professor Katsuyuki Tanizawa at the Institute of Scientific and Industrial Research, Osaka University under the title of "Discovery of new built-in peptide quinone coenzymes and their production mechanisms" as well as by Professor Itaru Yamamoto at the Faculty of Pharmaceutical Sciences, Okayama University under the title of "Study on the molecular modification of vitamin C and its properties." In addition, the memorial lecture by the recipients of the Incentive Award will be delivered by Takanori Yokota, an instructor at the Faculty of Medicine, Tokyo Medical and Dental University under the title of "Discovery of, Elucidation of the Developmental Mechanism of, and Establishment of Treatment Methods for, Familial Idiopathic Vitamin E Deficiency."

Recently, research on the mechanisms underlying biological reactions in the body in which NAD (nicotinamide adenine dinucleotide) is involved has made amazing advances. For example, functions of NAD have become widely known not only as coenzymes involved in redox reactions but also as the substrate for ADP ribosylation, a post-translational protein modification reaction, as well as for cyclic ADP-ribose production, second messenger regulating calcium mobilization, and a very wide diversity of ADP-ribosylation reactions have also become revealed. On the other hand, research on NAD has shown continuing progress and has produced new findings, for example, that NAD functions as the acetyl group acceptor in histone deacetylation and, via the regulation of chromatin structure, determines the life span of yeast, etc. as well as that channels exist opening of which is induced by NAD. The coming special lectures and symposium are planned to focus on such a wide variety of NAD functions.

More specifically, in the special lectures, Dr. Takashi Sugimura, an honorary president of the National Cancer Center, and Dr. Danesh Moazed at Harvard University are going to talk about ADP-ribosyl transferase of cabbage butterfly as well as about NAD and aging. In the symposium, lectures will be delivered by Professor Taisei Mori at the Center for Integrative Biosciences, Okazaki National Research Institute, Professor Masanao Miwa at the School of Medicine, University of Tsukuba, and Dr. Masaharu Terashima at the Faculty of Medicine, Shimane Medical University, about the NAD-mediated regulation of calcium channel activity, regulation of cellular functions through poly ADP-ribosylation as well as mono ADP-ribosylation in vertebrates. These lectures will get you more deeply interested in a wide variety of in vivo functions of vitamins.

This will be the first meeting of the Vitamin Society of Japan held in the Sanin region, which can be said to be, in a sense, a place where medicine was first introduced in Japan in light of a Japanese myth of white rabbit in Inaba (old name of eastern part of Tottori Prefecture) contained in "Kojiki" (one of the oldest books in Japan containing legendary stories of old Japan). According to "Kojiki," Ookuninushi-no-mikoto (the god of marriage and good luck) gave a wounded (skinned) rabbit of Inaba a tip for healing the wound. In the Izumo Taisha shrine dedicated to Ookuninushi-no-Mikoto (a Shinto deity), remnants have been found of a sacred central pillar (which is called shin-no-mihashira in Japanese, and is presumed to have been made up of three component pillars) to support the original building of Main Hall which, according to currently existing documents, had been a gigantic edifice reaching a height of as much as 48 meters. Moreover, many of you may remember the news of the excavation of as many as 358 copper swords in the Koujindani remains as well as the discovery of 39 bell-shaped bronze vessels (called "Doutaku" in Japanese, which are supposed to have been put to some ceremonial use) in the Kamoiwakura remains. In commemoration of the holding of the meeting of the Vitamin Society of Japan in the Izumo area, which is the motherland of ancient Japanese culture and myths, a cultural lecture under the title of "The Romance of Ancient Izumo" is planned to be delivered on the first day of the meeting by Mr. Yasutaka Hayami who is a scholar of ancient history. In addition, in the social gathering following the lecture, attractions with specificity to the birthplace of myths are to be offered. Please don't miss them. Furthermore, after the meeting has finished, you will be able to enjoy visiting areas mentioned in ancient myths to conjure up images of the remote past as well as taking a walk around the Izumo area rich in verdure to commune with the beauty of nature in early summer. Such pleasures accompanying a meeting of the Vitamin Society of Japan can be experienced only when such a meeting is held in such a region with a profound history as the Izumo region.

We would be delighted to see many of you participate in the coming meeting for the presentation of the latest results of vitamin research and discussion in the Izumo region, which is a birthplace of Japanese myths.

The Latest Results of, and Trend in, Research on Catechins

-From the 18th Lecture Meeting of the Tea Scientific Research Group of Japan-

Isao Tomita
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Prof.Isao Tomita

In recent years, tea catechins (flavan-3-ol derivatives) have attracted people's attention. This is because reports have been successively made that catechins, especially (-)-epigallocatechin gallate (EGCG; for its chemical structure, see Figure 1), exhibit potent free-radical scavenging and reactive oxygen scavenging effects at least in in-vitro experimental systems and that results of experiments using a wide variety of animal models of lifestyle-related diseases such as cancer and arteriosclerosis have indicated that catechins may have prophylactic effects on such diseases, in addition to antibacterial and deodorant effects. A wide range of beneficial effects of catechins in terms of sanitation/hygiene in daily life and disease prevention have been reported so far and are summarized in Table 1.

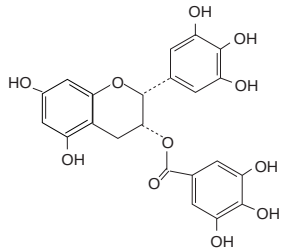


Figure 1. Chemical structure of catechin (EGCG)

Table 1. Effects of catechins

antioxidative effect, antimutagenic effect, anticancer effect, serum cholesterol lowering effect, antihypertensive effect, hypoglycemic effect, antithrombotic effect, anti-arteriosclerotic effect, antibacterial effect, deodorant effect, anti-caries effect, antiviral effect, intestinal microbial balance improving effect, and antiallergic effect

The Tea Scientific Research Group of Japan has called an annual meeting in March. This year, the 18th meeting was held on March 13 at the Bouquet Tokai hall. In the part of general lectures, reports was made on the deodorant, antibacterial and antifungal effects of catechins in their application to refrigerators (cooling fans) and air-conditioners (filter, fans, etc.) (Hunayama et al., Hitachi Home & Life Solutions, Inc.; Takimoto et al., Taiyo Co., Ltd.) and the mechanisms underlying such effects, as well as on the sustained release of catechins when they are mixed with ceramics (to form catechin-ceramic hybrids) and further with L-ascorbic acid 2-phosphate magnesium (Hatayama et al.; Chisso Corporation). While beneficial effects of catechins have been confirmed in both of these cases, in the application to air-conditioners in particular, catechins have been reported not only to exert deodorant effect on the odor of ammonia, etc. but also to effectively remove gaseous formaldehyde, which is deemed to be a chemical causing sick house syndrome.

In fresh raw tea leaves treated anaerobically, increase in gamma amino butylic acid (GABA) is seen, and by utilizing this phenomenon, so-called "Gabaron-Cha" (tea rich in gamma amino butylic acid) is manufactured. Tsuru et al. reported about the production of a tea drink having sweet floral aroma by utilizing L. brevis-fermented tea extract. Moreover, reports have been made about the antiproliferative effects of extracts of Goishi cha (a kind of fermented tea) and Awa Bancha (a kind of anaerobically fermented tea), which have been traditionally produced in the Shikoku region, on human leukemia cells (U937) (Sazuka et al.; Kochi University of technology) as well as about the in-vivo kinetics of a catechin (epigallocatechin gallate: EGCG) following its oral administration to humans (D. Raederstorff et al.; Roche Vitamins Ltd., Basel, Switzerland). The group of Dr. Raederstorff in particular reported detailed data on change over time in blood concentration of EGCG in volunteers receiving the single (EGCG 50-1,600 mg) or repeated (EGCG 200-800 mg; 10 days) oral administration of a capsule containing 94% EGCG prepared from tea extract. Their report revealed that blood EGCG concentration increased dose-dependently to reach a maximum within 1-2 hours after the administration and that its elimination half life is 4-5 hours, indicating good tolerability and low risk of accumulation.

The Tea Scientific Research Group of Japan invites applications from those who would like to obtain research grants (In the last fiscal year, applications were invited during the period from June 1 to July 31). Out of 17 applicants of the last fiscal year, 5 had been accepted and reported the results of their research in the previous meeting lecture meeting. The names of the lecturers and the themes of their lectures are as follows: All of these lectures dealt with up-to-date and interesting information.

1. Development of Methods for distinguishing the varieties of commercially available tea (Mr. Ujihara; National Institute of Vegetable and Tea Science [NIVTS], National Agricultural Research Organization [NARO])
2. Confirmation of Fundamental Chemical Properties of Tea Catechins Affecting Their Functionality (Mr. Tanaka; Graduate School of Biomedical Sciences, Nagasaki University)
3. Elucidation of Environmental Factors Affecting Oxalic Acid Synthesis in Tea Leaves and the Development of Tea with Low Oxalic Acid Content (Mr. Morita; Faculty of Agriculture, Shizuoka University)
4. Research on the Inhibitory Effects of Theanine, a Component of Tea, on Glutamic Acid-induced Cell Death of neurons in the cerebral cortex and on Molecular Mechanisms Underling the Effects
(Mr. Nagasawa; Kyoto Pharmaceutical University)
5. How are the floral aroma of oolong tea and black tea formed?--Elucidation of the Mechanisms Underlying Tea Aroma Formation Mediated by Beta-primeverosidase--
(Mr. Mizutani; Institute for Chemical Research, Kyoto University)

In addition to these lectures, two special lectures, the highlights of the meeting, were given under the following titles:

1. Cell Growth Regulation and Long-term Storage of Organic Tissues at Room Temperature with the Use of Green Tea Polyphenols (Mr. Gen; Institute for Frontier Medical Sciences, Kyoto University)
2. Inhibitory Effects of Tea Catechins on Oxidative DNA Damage (Mr. Kaneko; Tokyo Metropolitan Institute of Gerontology)

Due to limitations of space, the details of these lectures will be omitted here. Briefly, findings reported in these lectures in general seemed to have reflected the physical properties of catechins (solubility in both water and oil) which are distinguishable from those of vitamins E and C. Needless to say, catechins are not vitamins directly involved in the maintenance of life, but are "health factors" deeply influencing the maintenance of human health. In recent years, green tea prepared from the leaves of

varieties of tea containing epigallocatechin-3-(3"-O-methyl) gallate, i.e., so-called methylcatechin, including Benifuki (originally bred for black tea and semi-fermented tea), has been reported to have anti-allergic effects and has gained the spotlight (About this, Mr. Banri Yamamoto has already talked in detail in the 17th meeting of the Tea Research Group of Japan). Interestingly, the content of methylcatechin considerably varies with the variety of tea. Recent research revealed that, other varieties than Benifuku, including Benifuji, Benihomare, Yamakai and Okumidori contain about 0.4-1.3 g of methylcatechin per 100 g of dried leaves, while the Yabukita variety, which is the most popular tea variety for green tea, contains no methylcatechin (RYOKUCHA Vol. 6, p.39-40, 2003).

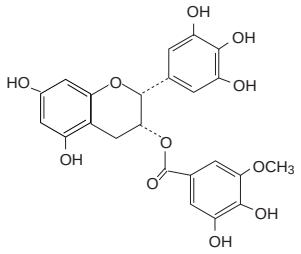


Figure 2. Chemical structure of Methylcatechin（EGC3"MeG)

We have entered the days where tea production with an eye toward body-modulating functions as well as aroma and taste, which have been thought much of in the processes of tea cultivation and development of tea products, is sought. Furthermore, studies on polyphenols, which have been performed mainly on catechins (EGCG in particular) and have produced excellent results, will make further progress by assimilating the achievements produced in related research fields, and polyphenols, on the back of vitamins, will come to universally accepted as "health factors" in the near future.

In closing, I want to mention the individuals who had taken the initiative in scientific research on tea for many years and received an honorary award for efforts yet to be widely recognized from the Tea Scientific Research Group of Japan on the day of the meeting. The names of the three recipients are as follows: Mr. Masayuki Nakagawa (advisor to the Japan Tea Manufacturing Technology Society and former director general of the National Institute of Vegetable and Tea Science, Ministry of Agriculture, Forestry and Fisheries), Mr. Shigeki Konishi (professor emeritus at Shizuoka University), and Mr. Syuuichi Takeo, Central Research Institute, Itoen, Ltd. (former director of the Department of Tea, National Institute of Vegetable and Tea Science, Ministry of Agriculture, Forestry and Fisheries.

EGCG the most abundant catechin in green tea: Pharmacokinetic parameters in humans

Currently, epidemiologic studies on the preventive effects of green tea on heart diseases and cancer are in progress. In addition, anti-obesity effect of green tea has also captured attention recently. Such beneficial effects of green tea are thought to derive from catechins, especially EGCG, that are contained in tea leaves. It has been suggested that EGCG, which is most abundantly found in green tea extract, exerts various beneficial effects including antioxidative, anticancer and antihypertensive effects. In spite of the fact that findings indicative of beneficial effects of catechins have been obtained, concerning the kinetics of EGCG in humans, only limited data have been obtained and studies focusing on other tea catechins than EGCG (such as (-)-epicatechin [EC], (-)epigallocatechin [EGC] and (-)epicatechin gallate [ECG]) have been mainly performed. In the 18th lecture meeting of the Tea Scientific Research Group of Japan, however, a group of Roche Vitamins Ltd. (D. Raederstorff et al.; Roche Vitamins Ltd., Basel, Switzerland) reported the results of a study focusing on the kinetics of EGCG in humans. The details of the report will be discussed below.

In the meeting, data on change over time in plasma EGCG concentration in healthy volunteers receiving the oral administration of "TEAVIGO™" containing EGCG with a purity of 94% on average, which has become successfully extracted from green tea leaves by using patented and innovative technology of Roche Vitamins Ltd.

Materials and Methods

Single oral administration

Subjects: 60 healthy white male volunteers aged 18-44 years

Dose levels and dosing regimen: Single doses of 50 mg, 100 mg, 200 mg, 400 mg, 800 mg and 1,600 mg of TeavigoTM were orally administered following 10-hour fasting

Rsult

Data on the profile of plasma concentration of free and total EGCG (free plus conjugated EGCG) are given in Tables 1 and 2, and data on changes over time in plasma concentration following administration are shown in Figure.

Table 1: Plasma-kinetic parameters of total EGCG in plasma

Dose (mg/day)		50		100		200		400		800		1600	
	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax (ng/mL)	8	130	43	180	134	332	108	624	244	1067	424	3392	877
Tmax (h)	8	1.4	0.6	2.2	1.4	1.4	0.3	1.4	0.7	1.8	0.7	1.3	0.5
t1/2z (h)	8	1.9	0.43	2.7	2.49	1.9	0.47	3.1	1.08	4.4	0.94	4.6	0.63

Table 2: Plasma-kinetic parameters of free EGCG in plasma

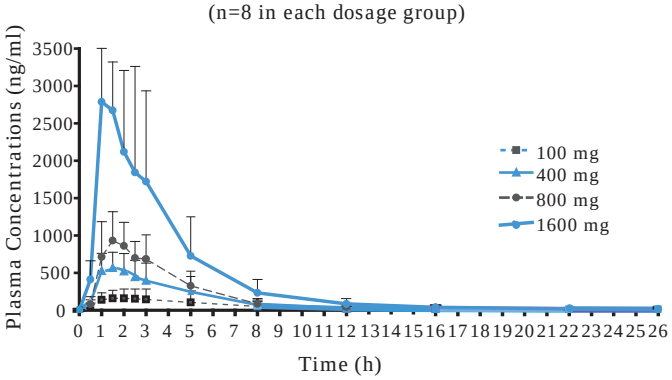
Dose (mg/day)		50		100		200		400		800		1600	
	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax (ng/mL)	8	120	29	190	137	310	141	568	221	964	327	2911	927
Tmax (h)	8	1.3	0.5	1.9	0.8	1.3	0.4	1.4	0.7	1.8	0.7	1.4	0.7
t1/2z (h)	8	1.8	0.4	3.3	4.4	2.3	0.8	2.9	0.7	3.6	1.2	4.9	0.5

Discussion

The results of this indicate show that EGCG exhibits good tolerability profile in humans even when administered in the amount (1,600 mg) that cannot be taken through usual use of green tea leaves and that EGCG has short elimination half-life, suggesting lower risk of its accumulation in the body.

In addition, in animal experiments, it has been confirmed that absorption of EGCG is delayed when it is taken with feed. Furthermore, it has also been shown that a large fraction of EGCG in the plasma is present in its free form, not as glucuronide or sulfate conjugates.

Fig. Mean Plasma Concentrations-Time Curves of EGCG as total form (n=8 in each dosage group)



Improvement in visual acuity in patients with age-related cataract through the ingestion of lutein

B.Olmedilla et al. Nutrition,19:21-24,2003

The prevalence of cataract increases with advancing age. The disease causes visual acuity deterioration and may lead to decreased activity of the elderly. The onset of cataract is presumed to be triggered by various factors related to progressive oxidative damages to the lens. Such oxidative damages to the lens may be prevented by the free-radical scavenging effect of antioxidants such as carotenoids and vitamin E. In fact, it has been suggested that long-term ingestion of vitamin C or E as well as ingestion of a large amount of vegetables with high lutein content, for example, may be associated with decrease in the risk of developing cataract.

Lutein and zeaxanthin are present in normal human retina, macula and crystalline lens, which enables explanation about the preventive effects of those carotenoids against cataract formation from biological point of view. As a matter of fact, macular pigment density decreases with advancing age. In addition, it has been suggested that dietary intake of lutein and zeaxanthin is positively correlated to, for example, serum concentrations of these carotenoids, macular pigment density, as well as visual function.

In this study, investigation was conducted into the effects of long-term ingestion of antioxidants (lutein and alpha-tocopherol) on their serum concentrations and visual function in patients with cataract.

Study design: double-blind randomized study

Subjects: 15 patients given the diagnosis of age-related cataract

Dose levels : Lutein group (n=5):15mg
alpha-tocopherol group (n=5):100mg
Placebo group (n=5): corn oil 500mg
ingested three times per week

Study duration :two years

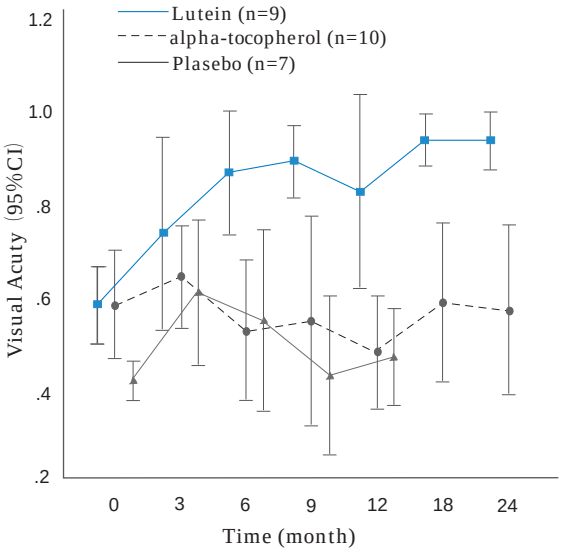


FIG. 1. Changes in visual acuity of patients with cataracts during the supplementation study (eyes were assessed individually). CI, confidence interval.

Results

In the lutein and alpha-tocopherol groups, increase in the serum concentration of respective antioxidants was observed. In those groups, serum concentrations of lutein and alpha-tocopherol reached the maximum levels 3-6 months after the initiation of ingestion, and remained at the level thereafter (Table 1). Serum biochemical examinations in the subjects did not reveal any adverse reactions. Although the planned duration of this study was 2-3 years, no improvement in visual function was noted especially in the placebo group, resulting in discontinuation of study participation by many subjects due to the necessity of cataract surgery.

After the ingestion of antioxidants in this study, visual acuity was improved only in the lutein group (Figure 1). In the lutein group, results of glare test (a test quantitatively evaluating the effects of stimulated glare on visual function) were also improved as compare with baseline (Table 2). During the study period, cataract progression was delayed in 4 out of 5 patients in the lutein group, 3 out of 5 patients in the alpha-tocopherol group, and 1 out of 5 patients in the placebo group.

Table2 Changes in Visual Function Parameters in Patients with Cataracts at Supplementation

	Initial	Final (12-24 mo)
Lutein group (n=9)		
Low	0.6-0.9	0.9-1.1
Medium	0.4-0.9	0.9-1.1
High	0.3-0.9	0.9-1.2
alpha-Tocopherol group (n=10)		
Low	0.3-0.7	0.3-0.8
Medium	0.3-0.7	0.2-0.8
High	0.3-0.6	0.4-0.8
Placebo group (n=7)		
Low	0.4-0.6	0.4-0.6
Medium	0.4-0.6	0.5
High	0.4-0.6	0.5

Low: 300 foot-candles, Medium: 2,500 foot-candles
High: 10,000 foot-candles, Data are ranges.

Table1 Changes in Serum Lutein and alpha-Tocopherol Concentrations with Supplementation in Patients with Cataracts

	Baseline	3 mo	6 mo	12 mo	18 mo	24 mo
Lutein group						
Lutein (mcM/L)	0.31±0.21	0.54±0.31*	0.65±0.32*	0.77±0.38*	0.51±0.25*	0.63±0.17*
alpha-tocopherol(mcM/L)	40.6±5.8	40.4±9.5	40.4±6.0	35.6±9.3	37.2±6.7	40.9±1.6
alpha-tocopherol group						
Lutein (mcM/L)	0.30±0.05	0.32±0.11	0.37±0.20	0.39±0.06	0.29±0.10	0.39±0.03
alpha-tocopherol(mcM/L)	36.2±6.0	44.6±7.7	41.8±6.5	41.8±6.3	40.0±4.2	50.4±2.8
Placebo group						
Lutein (mcM/L)	0.22±0.09	0.24±0.08	0.21±0.08	0.22±0.09		
alpha-tocopherol(mcM/L)	31.0±12.8	34.4±11.1	30.7±9.8	27.2±5.3		

* P<0.005