GR

ORIGINAL SUBMISSION

000001

tokiwa
PHYTOCHEMICAL

GRN 000530

2014/06/30

The Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Pkwy
College Park, MD 20740

Dear Sir

We are submitting a GRAS exemption claim on the *Apocynum venetum* extract, VENETRON™ as a food ingredient.

Notified substance: VENETRON™ (*Apocynum venetum* extract)

Intended Use: As an ingredient in food at levels of up to 100 milligram per day

Basis: Scientific procedures

The data and information that are the basis for our GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at reasonable times at a specific address set out in the notice or will be sent to FDA upon request.

Best regards.

Jin Tatsuzaki

Jin Tatsuzaki
President
TOKIWA PHYTOCHEMICAL CO., LTD
158, KINOKO, SAKURA-SHI
CHIBA 285-0801
JAPAN
j-tatsuzaki@tokiwaph.co.jp

tokiwa
PHYTOCHEMICAL

Summary of Data Supporting the Status of TOKIWA's VENETRON™ as a GRAS Food Ingredient

Prepared by:
TOKIWA PHYTOCHEMICAL CO., LTD
158, KINOKO, SAKURA-SHI
CHIBA 285-0801
JAPAN

tokiwa
PHYTOCHEMICAL

EXPERT CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VENETRON™ (*APOCYNUM VENETUM* EXTRACT) FOR USE AS A FOOD INGREDIENT

tokiwa
PHYTOCHEMICAL

EXPERT CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VENETRON™ (*APOCYNUM VENETUM* EXTRACT) FOR USE AS A FOOD INGREDIENT

The undersigned, independent experts, qualified by scientific training and relevant national and international experience was commissioned by TOKIWA PHYTOCHEMICAL Co., Ltd (hereafter referred to as TOKIWA) to evaluate the safety of *Apocynum venetum* extract, VENETRON™, in support of TOKIWA's determination that VENETRON™ is Generally Recognized as Safe (GRAS) for general food use based on scientific procedures supported by a history of safe use.

A. venetum, known as 'Luobuma' in Chinese, is a wild shrub growing widely in the middle to northwestern regions of China. It distributes mainly in the Talim valley of Xinjiang, and its leaves have been used as a tea drink from ancient time in China. Nowadays it still has been used as a tradition herb tea and called as "Longevity tea". Some polyphenols, such as hyperoside, isoquercitrin and procyanidins was reported to be contained in the leaves of *A. venetum*.

VENETRON™ is extracted from *A. venetum* leaves and contains not less than 4% of hyperoside and isoquercitrin. VENETRON™ is incorporated into health food product, such as tablet or capsule, and used for anti-stress, anti-depression and sleep improvement.

VENETRON™ is used in foods in general at levels that would ensure a total daily intake of VENETRON™ of 50mg/person/day. The proposed daily intake was derived from the preclinical and clinical studies on the effectiveness of VENETRON™. The safety of this degree of intake is supported by the absence of major adverse effects in subjects receiving up to 150mg VENETRON™ /day in a clinical safety study. In addition, LD_{50} of VENETRON™ in mice is higher than 2000mg/kg, which is equivalent to 66.7mg/kg for human (approximately 4002mg/day of VENETRON™ for a 60kg person) by applying a conservative 30-fold safety factor. And the no-observe-adverse-effect-level (NOAEL) for VENETRON™ was concluded to be at least 250mg/kg bw/day for rats, which is equivalent to 8.33mg/kg for human (approximately 500mg/day of VENETRON™ for a 60kg person) by applying a conservative 30-fold safety factor.

The experts assessed the preclinical and clinical data, as well as a history of human intake, and concluded that the intake for VENETRON™ of 100mg/person/day raised no safety issues.

EXPERT CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VENETRON™ (*APOCYNUM VENETUM* EXTRACT) FOR USE AS A FOOD INGREDIENT

The experts considered the safety of VENETRON™ was supported firstly on the basis of the long experience of *A. venetum* leaves as a tea. *A. venetum* leaves is a traditional and popular herb from ancient China, especially in Xinjiang with a long history of use as a medicine and tea. It is known as "Luobuma" in Chinese and quite popular among the people living around Lop Lake, who have been using Luobuma as a longevity tea and to strength the body. Also, it has been contained in 'pharmacopeia of People's Republic of China, 2005' and used to treat neurasthenia, palpitation, insomnia, edema with oliguria, hypertension and nephritic edema. Pharmaceutical tablet containing *A. venetum* leaves is used as a drug for hypertension in China. And In Japan, *A. venetum* leaves import starts in 1985 and many tea products using *A. venetum* leaves had been sold under different brand name. In 1994, YANLONG tea was launched as a new tea product and the total quantity sold thorough May 2014 reached 650ton and 150,000,000 packs were sold since 1997. In additional, 'YANLONG Level Care', an aqueous extract of roasted *A. venetum* leaves, was permitted as a FOSHU (FOOD for Special Health Uses) for hypertension in Japan on August, 7th, 2007.

With respect to VENETRON™ safety, the experts carefully assessed the results of preclinical and clinical safety investigations conducted with VENETRON™. The experts assigned primary importance to the results of a safety study on 30 healthy male volunteers for consecutive 12 weeks intake. The intake dose was 50mg/day in 1-8 weeks, and 150mg/day in 9-12 weeks. This study included measurement of height, weight, blood pressure, pulse rate, urinalysis, hematology, and blood biochemical test at week 0, week 4, week 8 and week 12. No harmful conscious and objective symptoms related to VENETRON™ were observed in all of the volunteers throughout the trial period. VENETRON™ also did not cause any virtual changes in the blood and urine samples. From this result, the intake for VENETRON™ of 100mg/person/day was considered to be safe.

The experts also evaluated the results of a clinical study on 39 individuals with mild depression for 8 weeks intake (50mg/person/day). No subjects dropped out of the study due to side effects and use of VENETRON™ by individuals with mild depression is general safe, with few side effects.

The specifications for VENETRON™ were carefully reviewed by the experts to ensure that the product meet standards for food use. Heavy metal, arsenic and microbiological assays were performed.

tokiwa
PHYTOCHEMICAL

EXPERT CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VENETRON™ (*APOCYNUM VENETUM* EXTRACT) FOR USE AS A FOOD INGREDIENT

After a critical independent evaluation of the available safety and clinical information for VENETRON™, the undersigned experts conferred and unanimously concluded that VENETRON™, when used in foods in general at levels providing a daily total intake of 100mg/person/day, is safe and is Generally Recognized as Safe (GRAS) based on scientific procedures supported by a history of safe use.

V Butterweck June 12, 2014

Veronika Butterweck, Ph.D. Date
Professor
School of Life Sciences
Institute for Pharma Technology
University of Applied Sciences and Arts
Northwestern Switzerland

Sansei Nishibe June 13, 2014

Sansei Nishibe, Ph.D. Date
Professor Emeritus
Faculty of Pharmaceutical Sciences
Health Sciences University of Hokkaido

Kuo-Hsiung Lee May 28, 2014

Kuo-Hsiung Lee, Ph.D. Date
Kenan Distinguished Professor of Medicinal Chemistry
Director of Natural Products Research Laboratories
Eshelman School of Pharmacy
The University of North Carolina at Chapel Hill

tokiwa
PHYTOCHEMICAL

Summary of Data Supporting the Status of TOKIWA's VENETRON™ as a GRAS Food Ingredient

tokiwa
PHYTOCHEMICAL

Summary of Data Supporting the Status of TOKIWA's VENETRON™ as a GRAS Food Ingredient

Table of Contents

LIST OF APPENDICES

LIST OF TABLE AND FIGURES

GLOSSARY

ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
A. venetum	*Apocynum venetum*
BMI	Body mass index

tokiwa
PHYTOCHEMICAL

BP	**Blood pressure**
CYP	**Cytochrome P450**
FOSHU	**FOOD for special health uses**
GABA	**Gamma-amino butyric acid**
GRAS	**Generally recognized as safe**
γ-GTP	**γ-Glutamyl transpeptidase**
Hb	**Hemoglobin**
HPLC	**High performance liquid chromatography**
JSFA	**Japan's Specification and Standards for Food Additives**
LDH	**Lactate dehydrogenase**
Lot No. abcdefghi	**abc: code number**
	de: Manufacturing year
	fg: Manufacturing month
	hi: Number lot/year
MCH	**Mean corpuscular hemoglobin**
MCHC	**Mean corpuscular hemoglobin concentration**
MCV	**Hematocrit, mean corpuscular volume**
NMR	**Nuclear magnetic resonance**
NOAEL	**No-observe-adverse-effect-level**
P-gp	**P-glycoprotein**
PMS	**Premenstrual syndrome**
RSD	**Relative standard deviation**
TLC	**Thin-layer chromatography**
TOKIWA	**TOKIWA PHYTOCHEMICAL CO., LTD**
TP	**Total protein**
YANLONG Level Care	**Name of a FOSHU made from *Apocynum venetum* leaves**
YANLONG tea	**Name of a tea product made from *Apocynum venetum* leaves**
VENETRON™	**Brand name of TOKIWA's *Apocynum venetum* leaves extract**

tokiwa
PHYTOCHEMICAL

Summary of Data Supporting the Status of TOKIWA's VENETRON™ as a GRAS Food Ingredient

1.0 INTRODUCTION

1.1 Objectives

A. venetum, known as 'Luobuma' in Chinese, is a wild shrub growing widely in the middle to northwestern regions of China. It distributes mainly in the Talim valley of Xinjiang, and its leaves have been used as a tea drink from ancient time in China. Nowadays it still has been used as a tradition herb tea and called as "Longevity tea". Some polyphenols, such as hyperoside, isoquercitrin and procyanidins was reported to be contained in the leaves of *A. venetum* [1, 2].

VENETRON™ is extracted from *A. venetum* leaves and contains not less than 4% of hyperoside and isoquercitrin. VENETRON™ is incorporated into health food product, such as tablet or capsule, and used for anti-stress, anti-depression and sleep improvement.

VENETRON™ is used in foods in general at levels that would ensure a total daily intake of VENETRON™ of 50mg/person/day. The proposed daily intake was derived from the preclinical and clinical studies on the effectiveness of VENETRON™.

We are seeking confirmation from independent experts that the use of VENETRON™ in foods for the general population is indeed GRAS, based on scientific procedures supported by a safe use.

1.2 History of Safe use

The safety of VENETRON™ was supported firstly on the basis of the long experience of *A. venetum* leaves as a tea. *A. venetum* leaves is a traditional and popular herb from ancient China, especially in Xinjiang with a long history of use as a medicine and tea. It is known as "Luobuma" in Chinese and quite popular among the people living around Lop Lake, who have been using Luobuma as a longevity tea and to strength the body. Also, it has been contained in 'pharmacopeia of People's Republic of China, 2005' and used to treat neurasthenia, palpitation, insomnia, edema with oliguria, hypertension and nephritic edema [3]. Pharmaceutical tablet containing *A. venetum* leaves is used as a drug for hypertension in China [4].

In Japan, *A. venetum* import starts in 1985 and many tea products using *A. venetum* leaves had been

sold under different brand name. In 1994, YANLONG tea was launched as a new tea product and the total quantity sold thorough May 2014 reached 650ton and 150,000,000 packs were sold since 1997. In additional, 'YANLONG Level Care', an aqueous extract of roasted *A. venetum* leaves, was permitted as a FOSHU (FOOD for Special Health Uses) for hypertension in Japan on August, 7th, 2007. The recommended dosage of 'YANLONG Level Care' is 500ml/day, which contains 30mg of sum of hyperoside and isoquercitrin. No genetic toxicity was observed in comet assay, micronucleus assay, chromosomal aberration test both *in vitro* and *vivo* [5].

2.0 BASIS FOR GRAS DETERMINATION

2.1 Overview

According to Volume 62, Number 74 of the April 17, 1997 Federal Register, Pages 18937 to 18964 (Proposed Rules, 21 CFR Part 170, et al), in the United States, a substance exempt from the definition of food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts. General recognition of safety may be accomplished through: (1) scientific procedures or (2) experience based on common use in food prior to January 1, 1958, when the Food Additives Amendment was enacted. Whereas the former requires the same quantity and quality of scientific data as would be required for a food additive, a determination that the use of a substance in foods in generally recognized as safe (GRAS) through common use can be based solely on a substantial history of food use by a significant number of consumers prior to that date.

2.2 TOKIWA's VENETRON™ as a GRAS Substance

Pursuant to 21 CFR 170.30, we have determined VENETRON™ to be GRAS based on scientific procedures supported by a history of safe use. Our determination that VENETRON™ is GRAS was confirmed by experts who are qualified by scientific training and experience to evaluate the safety of VENETRON™ as a component of food. The safety of VENETRON™ is based on data document entitled **"EXPERT CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VENETRON™ (*APOCYNUM VENETUM* EXTRACT) FOR USE AS A FOOD INGREDIENT"**.

3.0 MANUFACTURING AND PRODUCT SPECIFICATIONS

3.1 VENETRON™ Composition and Specification

The proposed food grade specification for TOKIWA's VENETRON™, as well as the results of analyses performed on three lots of the final product, are summarized in Table3.1-1.

Table 3.1-1 VENETRON™ product specifications and independent lot analyses

	Item	Specification	Test Method	Lot number		
				Lot No. 797130401	Lot No. 797121205	Lot No. 797120904
Appearance	Form	Powder	-	Complies	Complies	Complies
	Color	Brown	Comparing with standard sample	Complies	Complies	Complies
	Taste	Bitter taste	Comparing with standard sample	Complies	Complies	Complies
Impurities Specifications	Heavy matals (as Pb)	Not more than 20 ppm	JSFA	Complies	Complies	Complies
	Arsenic (as As_2O_3)	Not more than 2 ppm	JSFA	Complies	Complies	Complies
Physical/Chemical Specifications	Loss on drying	Not more than 6.0 %	JSFA	3.6%	2.1%	2.3%
	Residue on ignition	Not more than 3.0 %	JSFA	0.3%	0.3%	0.5%
	Identification test	Positive	TLC method	Positive	Positive	Positive
	Content of sum of hyperoside and isoquercitrin	Not less than 4.0 %	HPLC method	8.2%	8.3%	8.7%
Microbiological Specifications	Total aerobic plate count	Not more than 1000 cfu/g	Standard methods of analysis in food safety regulation	Complies	Complies	Complies
	Escherichia coli	Negative	Standard methods of analysis in food safety regulation	Complies	Complies	Complies

JSFA: Japan's Specification and Standards for Food Additives.

Preparation of standard references from VENETRON™

Standard references of hyperoside and isoquercitrin were prepared from VENETRON™. VENETRON™ was suspended in water and partitioned with *n*-butanol. The yielded *n*-butanol fraction was subjected to a octadecyl-bonded silica (ODS) column and eluted with 15% acetonitril/water. The collected fraction containing hyperoside and isoquercitrin was crystallized with 99.5% ethanol to obtain the standard reference of hyperoside (HPLC purity 97.97%). The crystallizing mother solution was concentrated, and then dissolved in hot 20% ethanol/water. After cooling for one night, it was recrystallized with 40% ethanol to obtain the standard reference of isoquercitrin (HPLC purity 97.96%).

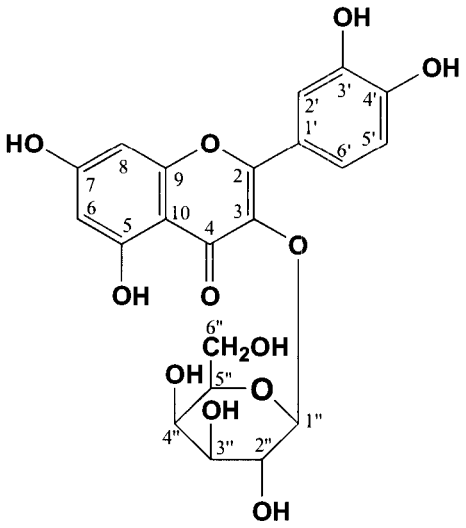
Structure confirmation of hyperoside and isoquercitrin prepared from VENETRON™

The Carbon-13 NMR spectroscopic data of hyperoside and isoquercitrin prepared from VENETRON™ were in good agreement with those of previously reported [6].

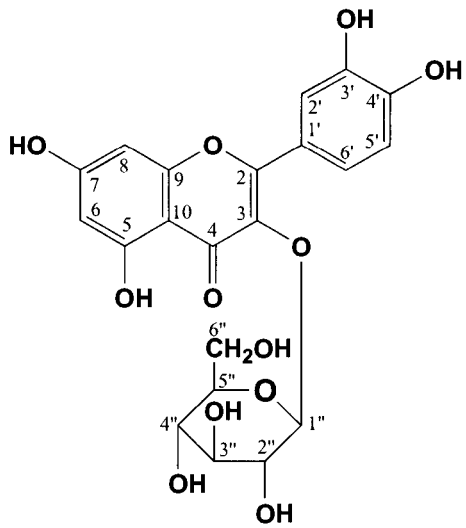
Table 3.1-2 Carbon-13 NMR spectroscopic data of hyperoside and isoquercitrin prepared from VENETRON™ and those in literature

Assignment	Hyperoside		Isoquercitrin	
	Observed	Literature [6]	Observed	Literature [6]
C-4	178.1	177.5	178.1	177.6
C-7	164.8	164.0	164.8	164.2
C-5	161.9	161.2	162.0	161.3
C-2	157.1	156.3	157.1	156.5
C-9	157.1	156.3	157.1	156.5
C-4'	149.0	148.3	149.0	148.5
C-3'	145.4	144.7	145.4	144.8
C-3	134.5	133.8	134.4	133.7
C-6'	122.5	121.8	122.2	121.6
C-1'	122.0	121.3	122.1	121.4
C-5'	116.9	116.2	117.1	116.5
C-2'	115.9	115.2	115.9	115.3
C-10	104.7	104.0	104.8	104.2
C-1"	103.1	102.3	102.3	101.4
C-6	99.3	98.6	99.3	98.8
C-8	94.2	93.4	94.2	93.6
C-5"	76.5	75.8	77.9	77.5
C-3"	74.1	73.4	77.4	76.8
C-2"	72.1	71.3	74.9	74.3
C-4"	68.7	68.0	70.9	70.3
C-6"	60.9	60.8	61.9	61.3

Figure 3.1-1 Structures of hyperoside and Isoquercitrin



Hyperoside



Isoquercitrin

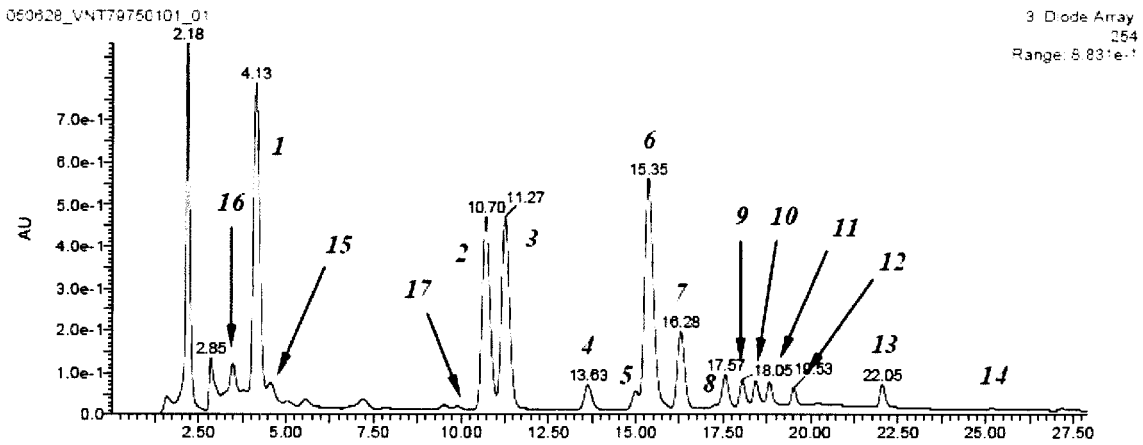
Specification sheet of VENETRON™ refers to Appendix 1.

CoA of standard references and validation data of HPLC analysis refer to Appendix 2.

Certificates of analysis of three lots refer to Appendix 3.

We also analyzed other compositions in *A. venetum* leaves. Chlorogenic acid, hyperoside-malonate and other polyphenols were found in VENETRON™ [7].

Figure 3.1-2 HPLC chromatograph of VENETRON™



Compound number	Compound name
1	Chlorogenic acid
2	Hyperoside
3	Isoquercitrin
4	Trifolin
5	Astragalin
6	Hyperoside-malonate
7	Hyperoside-acetate
8	Isoquercitrin-acetate
9	Trifolin-malonate
10	Isoquercitrin-malonate
11	Astragalin-malonate
12	Trifolin-/Astragalin-acetate
13	Quercetin
14	Kaempferol
15	Catechin/Epicatechin
16	Gallocatechin/Epigallocatechin
17	Gallocatechin-dimer

3.2 Stability

Table 3.2-1 showed the results of stability test when VENETRON™ was stored at ambient temperature in airtight and light-resistant containers. VENETRON™ was stable under the conditions of the study for 3 year and 3 months.

Table 3.2-1 Storage stability of three lots of VENETRON™

Lot No. 797050402	Loss on drying	Content		
		Total	Hyperoside	Isoquercitrin
Specification	Not more than 6.0%	Not less than 4.0%	-	-
Manufacturing date	3.1%	9.2%	4.7%	4.5%
3 months	3.2%	9.4%	4.7%	4.7%
6 months	3.6%	9.2%	4.6%	4.6%
1 year	3.4%	9.5%	4.8%	4.7%
2 year	3.5%	8.9%	4.5%	4.4%
3 year	3.8%	8.8%	4.4%	4.4%
3 year and 3 months	3.7%	9.5%	4.8%	4.7%

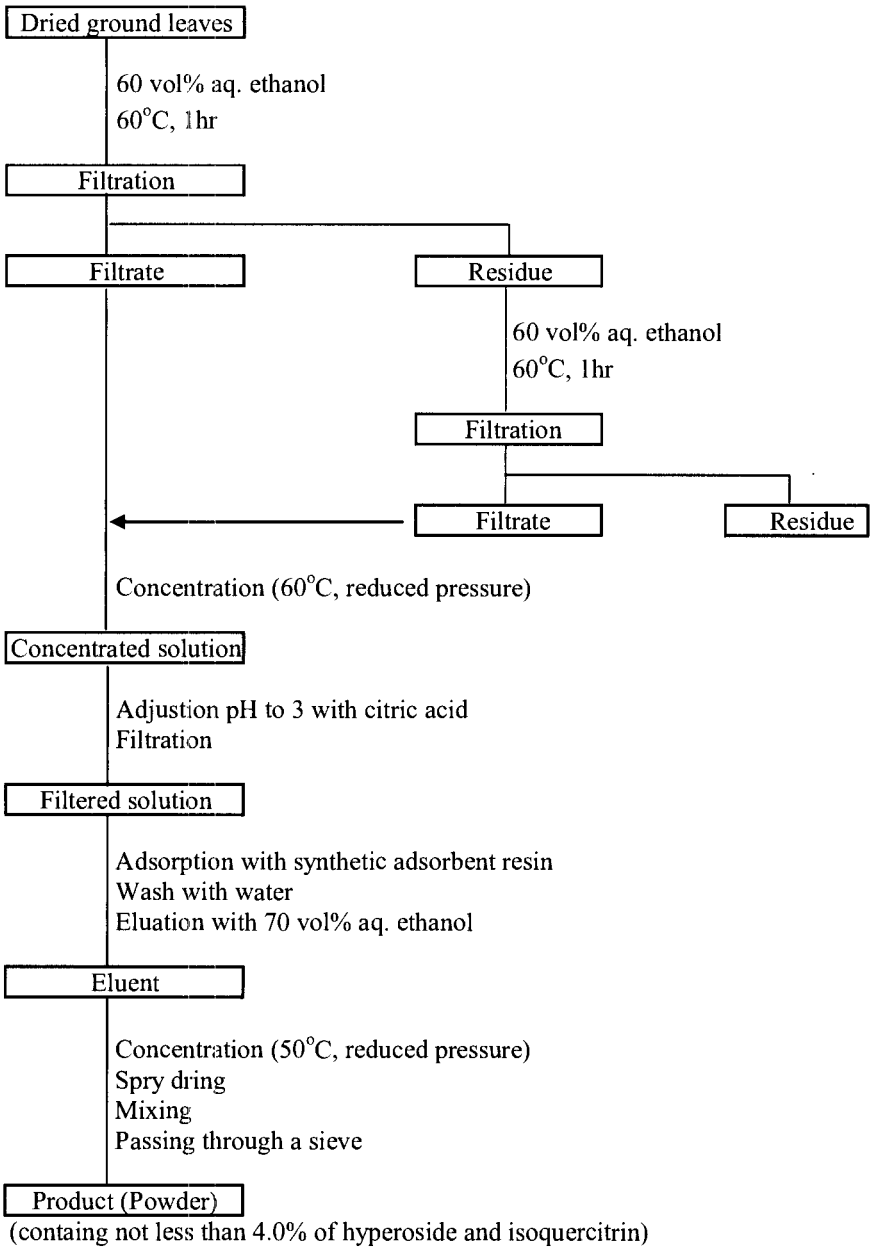
Lot No. 797050804	Loss on drying	Content		
		Total	Hyperoside	Isoquercitrin
Specification	Not more than 6.0%	Not less than 4.0%	-	-
Manufacturing date	2.5%	8.9%	4.3%	4.6%
3 months	2.4%	9.1%	4.4%	4.7%
6 months	2.6%	9.1%	4.4%	4.7%
1 year	2.9%	9.2%	4.5%	4.7%
2 year	3.0%	9.0%	4.4%	4.6%
3 year	3.5%	9.0%	4.3%	4.7%
3 year and 3 months	3.5%	9.1%	4.3%	4.8%

Lot No. 797080301	Loss on drying	Content		
		Total	Hyperoside	Isoquercitrin
Specification	Not more than 6.0%	Not less than 4.0%	-	-
Manufacturing date	4.2%	10.2%	5.3%	4.9%
3 months	3.8%	10.2%	5.3%	4.9%
6 months	3.9%	10.1%	5.2%	4.9%
1 year	4.2%	9.8%	5.0%	4.8%
2 year	4.4%	9.9%	5.1%	4.8%
3 year	4.7%	10.4%	5.4%	5.0%
3 year and 3 months	4.9%	10.5%	5.4%	5.1%

3.3 VENETRON™ Manufacturing

Dried ground leaves of *A. venetum* were extracted with 60 vol% aqueous ethanol under 60°C for one hour, and then filtered. The residue was extracted again under the same conditions as above. The first and second filtrates were combined and concentrated at 60°C under reduced pressure. The concentrate was suspended in water and adjusted to pH=3 with citric acid. The obtained solution was filtered by filter cloths covered with diatomaceous earth as a filter aid to remove insoluble matters. The filtrate was passed through synthetic adsorbent resin to absorb active ingredients, and then wash the resin with water. The active ingredients were eluted with 70 vol% aqueous ethanol, and then the eluent was concentrated at 50°C under reduced pressure and spray dried. The obtained solid extract was mixed thoroughly and passed through a sieve to get equalized powder.

Figure 3.3-1 Manufacturing process of VENETRON™



4.0 PRECLINICAL SAFETY OF VENETRON™

4.1 Acute Toxicity [8]

The potential for adverse effects following short-term exposure to VENETRON™ (2000mg/kg bw) was investigated in a single-dose oral toxicity study in accordance with OECD guidelines for the testing of chemical 401 (1987). VENETRON™ (Lot No.000601) was dissolved in purified water to make a 100mg/mL test solution. Following a 4-hour fast, mice of the ICR strain (10/sex/group) received a single gavage dose of VENETRON™ test solution, equivalent to 2000mg/kg bw. A control group received the same volume of purified water (0.6mL). Animals were observed for 14 days. Endpoints evaluation included clinical signs, body weights, and mortality. At the end of the observation period (day 14), mice were euthanized and all organs were macroscopically examined. There were no treatment-related clinical signs or death of animals of either sex in any group throughout the observation period. Body weight changes in the VENETRON™ group were approximately the same as that noted in the control group. At necropsy, no abnormal changes were observed in any animal.

Based on these results, the authors concluded that the approximate 50% lethal dose (LD_{50}) of VENETRON™ under the conditions of this study was greater than 2000mg/kg bw for both male and female ICR mice, which is equivalent to 66.7mg/kg for human (approximately 4002mg/day of VENETRON™ for a 60kg person) by applying a conservative 30-fold safety factor.

Table 4.1-1 Body weights of mice treated orally with VENETRON™ for 14 days

	Body weight (g)		
Male	Day 0	Day 7	Day 14
Control	27.8±0.6	32.3±1.5	36.6±1.3
VENETRON™	27.8±0.6	32.8±1.3	37.4±1.5
Female	Day 0	Day 7	Day 14
Control	24.8±1.0	27.0±1.0	30.5±2.2
VENETRON™	24.5±1.1	26.6±1.8	29.8±1.5

Mean±SD

4.2 Subchronic Toxicity

We evaluated the potential toxicity of VENETRON™ following subchronic oral administration at the University of Münster, Germany, in year 2001. Five doses (15, 30, 60, 125, 250mg/kg bw) of VENETRON™ were administered as suspensions in purified water via gavages to rats (8-10/group), on a daily basis, 7 times weekly, for 8 weeks. Purified water was used in dosing the control animals. Body weights were measured before and after the study. At the end of the study, animals were euthanized and liver, kidney, heart, spleen and prostate were weighed.

The statistical significances of changes in body and organ weights were assessed.

No statistically significant, dose-related effects on body and organ weights were seen in any of the VENETRON™ groups in comparison to the control group.

The no-observe-adverse-effect-level (NOAEL) for VENETRON™ under the conditions of this study was concluded to be at least 250mg/kg bw/day for rats, which is equivalent to 8.33mg/kg for human (approximately 500mg/day of VENETRON™ for a 60kg person) by applying a conservative 30-fold safety factor.

Table 4.2-1 Body and organ weights of rats treated orally with VENETRON™ for 8 weeks

	Body	Body	Liver	Kidney	Prostate	Heart	Spleen
	(beginning)	(After 8 weeks)					
control	140.5±2.3	400.0±5.5	15.85±0.57	2.846±0.033	547.8±36.1	1.264±0.030	799.2±30.3
15mg/kg	142.5±3.0	402.1±5.5	16.09±0.46	2.892±0.105	561.4±19.1	1.256±0.036	802.1±38.6
30mg/kg	135.9±1.9	401.6±8.0	15.83±0.40	2.810±0.085	597.2±22.4	1.275±0.020	867.3±34.3
60mg/kg	144.3±2.2	396.2±8.0	15.20±0.37	2.871±0.065	592.2±20.5	1.208±0.020	826.4±21.3
125mg/kg	137.9±3.6	395.7±13.7	15.96±0.62	2.681±0.069	574.5±36.2	1.257±0.032	744.0±34.7
250mg/kg	137.5±2.7	372.9±10.1	15.70±0.48	2.676±0.067	595.6±28.8	1.215±0.034	811.0±29.9

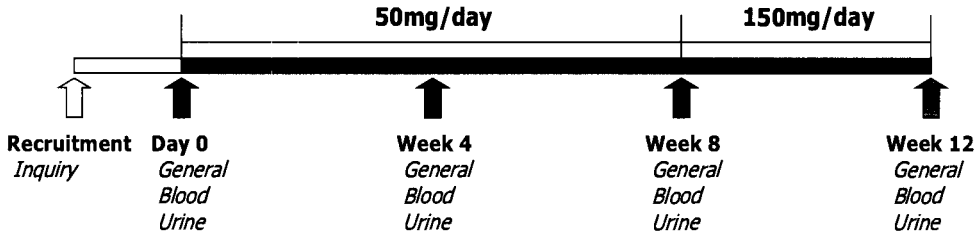
Mean±SE

5.0 CLINICAL DATA

Clinical studies were conducted to examine the safety of VENETRON™ in human. They provided supporting evidences that VENETRON™ at dose 100mg/day is generally safe since no significant adverse effects were reported in any of these studies.

5.1 Clinical safety study on healthy person [9]

We conducted a safety study on 30 healthy male volunteers for consecutive 12 weeks intake. The intake dose was 50mg/day in 1-8 weeks, and 150mg/day in 9-12 weeks. The following parameters, height, weight, blood pressure (BP), pulse rate, urinalysis (protein qualitative analysis, sugar, urobilinogen, bilirubin, specific gravity, pH, ketone body and occult bleeding reaction), hematology (leukocyte, erythrocyte and platelet, Hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), blood biochemical test (total protein (TP), Albumin (ALB), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ -glutamyl transpeptidase (γ-GTP), blood sugar, total cholesterol, neutral fat, urea nitrogen and creatine) were examined. The conscious and objective events were investigated according to the participant's diary.



No harmful conscious and objective symptoms related to VENETRON™ were observed in all of the participants throughout the trial period. VENETRON™ also did not cause any virtual changes in the blood and urine samples. Although pulse, total protein and albumin were significantly reduced, however, the variations were in the normal ranges. These results strongly indicate that VENETRON™ at dose 100mg/day is generally safe in healthy human.

Table 5.1-1 Changes on height, weight, blood pressure and pulse rate

Test items	Day 0	Week 4	Week 8	Week 12
BMI	24.9±2.9	24.7±2.8	24.6±2.8	24.7±2.9
Systolic BP (mmHg)	125.9±16.0	127.3±14.4	125.8±12.8	126.5±9.6
Diastolic BP (mmHg)	76.5±14.5	82.8±15.0	77.9±9.4	79.7±10.8
Pulse rate (beats/min)	74.3±7.9	71.0±6.4	69.8±5.2*	70.3±5.2

n=30, Mean±SD, *: P<0.05.

Table 5.1-2 Changes on hematological data

Test items	Day 0	Week 4	Week 8	Week 12
Leukocyte (/μl)	6314±1421	6146±1633	6050±1286	5948±1640
Erythrocyte ($\times 10^4$/μl)	502.7±36.0	503.9±29.8	497.2±29.6	496.2±38.7
Hb (g/dL)	15.77±0.92	15.83±0.91	15.52±0.78	15.52±0.96
Hematocrit (%)	47.01±2.64	47.11±2.25	46.11±1.95	46.00±2.76
MCV (fL)	93.74±5.59	93.68±5.42	92.90±5.14	92.97±5.62
MCH (pg)	31.45±1.60	31.48±2.06	31.27±1.81	31.37±1.97
MCHC (%)	33.56±0.70	33.61±0.98	33.65±0.64	33.74±0.77
Platelet ($\times 10^4$/μL)	25.48±5.54	24.94±5.46	24.98±4.97	25.33±5.38

n=30, Mean±SD

Table 5.1-3 Changes on blood biochemical data

Test items	Day 0	Week 4	Week 8	Week 12
AST (IU/L)	25.7±9.6	25.7±8.7	22.4±5.6	23.9±8.9
ALT (IU/L)	33.8±25.7	32.2±21.4	27.0±15.4	31.2±23.7
γ-GTP (IU/L)	62.5±59.1	57.4±54.6	47.6±38.8	51.9±45.8
ALP (IU/L)	235.5±85.3	219.3±61.0	219.7±61.6	220.0±65.5
LDH (IU/L)	186.9±29.7	189.6±28.9	180.2±28.0	183.5±28.2
Neutral fat (mg/dL)	116.7±97.2	123.1±85.5	106.8±49.6	115.1±77.5
Total cholesterol (%)	194.0±38.9	195.0±39.6	189.0±36.2	191.3±37.0
TP (g/dl)	7.62±0.39	7.50±0.31	7.37±0.29*	7.37±0.33*
ALB (g/dL)	4.82±0.29	4.72±0.26	4.57±0.21*	4.67±0.23
Bilirubin (mg/dL)	0.72±0.23	0.72±0.24	0.69±0.26	0.75±0.25
Urea nitrogen (mg/dL)	14.1±3.1	14.2±3.1	14.5±3.0	14.4±2.6
Creatinine (mg/dL)	0.840±0.081	0.835±0.090	0.832±0.086	0.880±0.088
Blood sugar (mg/dL)	89.7±10.9	90.5±10.5	90.1±11.2	90.0±10.0

n=30, Mean±SD, *: P<0.05.

Table 5.1-4 Changes on urinalysis data

Test items	Day 0	Week 4	Week 8	Week 12
Protein	(-) 28	(-) 28	(-) 31	(-) 29
	(±) 3	(±) 1	(±) 0	(±) 1
	(+) 0	(+) 2	(+) 0	(+) 0
Sugar	(-) 29	(-) 31	(-) 31	(-) 30
	(±) 1	(±) 0	(±) 0	(±) 0
	(+) 1	(+) 0	(+) 0	(+) 0
Urobilinogen	(-) 0	(-) 0	(-) 0	(-) 0
	(±) 31	(±) 31	(±) 31	(±) 29
	(+) 0	(+) 0	(+) 0	(+) 0
	(2+) 0	(2+) 0	(2+) 0	(2+) 1
Bilirubin	(-) 31	(-) 31	(-) 31	(-) 30
	(±) 0	(±) 0	(±) 0	(±) 0
Keto body	(-) 31	(-) 31	(-) 31	(-) 29
	(±) 0	(±) 0	(±) 0	(±) 0
	(+) 0	(+) 0	(+) 0	(+) 0
	(2+) 0	(2+) 0	(2+) 0	(2+) 1
occult bleeding reaction	(-) 30	(-) 31	(-) 31	(-) 29
	(±) 1	(±) 0	(±) 0	(±) 1

Protein, sugar, bilirubin, ketone body, occult bleeding reaction:

Standard (-) Negative;

Out of standard (±) False positive; (+) Slightly positive; (2+) Positive

Urobilinogen:

Standard (±) False positive; (+) Slightly positve;

Out of standard (2+) Positive

Table 5.1-5 Changes on urine biochemical data

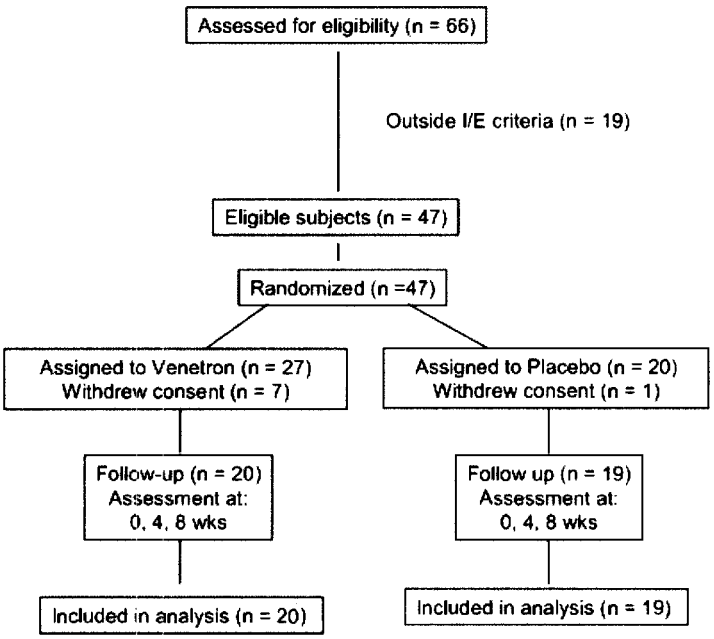
Test items	Day 0	Week 4	Week 8	Week 12
Specific gravity	1.019±0.007	1.019±0.006	1.018±0.006	1.020±0.006
pH	5.95±0.60	6.08±0.71	6.16±0.86	6.03±0.96

n=30, Mean±SD

5.2 Clinical study on individuals with mild depression [10]

We conducted a randomized 8-week study to determine the safety and therapeutic value of VENETRON™ after oral administration to mild depression subjects. The endpoints to be determined were weekly adverse effects, blood pressure, HAM-D, CGI scores and blood neurotransmitters. Here we focused on the appearance of adverse effects and changes of blood pressure, which were related with the safety of VENETRON™.

47 subjects were randomized to two groups and blindly assigned to VENETRON™ or to placebo. VENETRON™ was administered 50mg/day in tablet, and placebo was administered in tablets with the same color and appearance as active product.



There was no difference in the number of adverse events rated to be 'probably' and 'definitely' related to study product between the VENETRON™ and placebo groups. The total of 'possibly' related adverse events was higher in the VENETRON™ group.

The number of adverse events rated as moderate or severe were the same in the VENETRON™ group as the placebo group. The number of adverse events rated as mild was higher in the

VENETRON™ group.

In the VENETRON™ group, 47% of adverse events were gastrointestinal; other common ones were headache and dizziness. In the placebo group, the most common adverse events were gastrointestinal and dermatological.

Adverse events deemed to be possibly related to VENETRON™ include insomnia, decreased appetite, abnormal dreams, indigestion, chest pain, dizziness, increased appetite, diarrhea, nausea, shakiness, dry mouth, headache, acne, flatulence, burping, bloating, tinnitus, drowsiness, and decreased libido.

In addition, analysis of blood pressure at baseline, 4 weeks and at the end of the study showed no significant changes.

No subjects dropped out of the study due to side effects.

The results of this study suggest that use of VENETRON™ by individuals with mild depression is general safe, with few side effects.

Table 5.2-1 Frequencies of adverse events

	Venetron	Placebo
No. of adverse events	30	22
No. of patients reporting adverse events	9	9
Events rated as mild	28	20
Events rated as moderate	2	2
Events rated as severe	0	0
No. of adverse events explained as not related to study product	7	10
No. of adverse events rated to be 'possibly' related to study product	22	11
No. of adverse events rated to be 'probably' related to study product	1	1
No. of adverse events rated to be 'definitely' related to study product	0	0
Head, eyes, ears, nose, throat	1	1
Pulmonary/respiratory	0	3
Gastrointestinal	14	5
Metabolic/endocrine	0	1
Renal/genitourinary tract	1	1
Musculoskeletal	2	3
Dermatological	1	3
Neurological	9	4
Cardiovascular	2	1
Psychiatric	0	0
Others	0	0

Table 5.2-2 Effect of VENETRON™ on blood pressure

	Venetron			Placebo		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Systolic Blood Pressure (mmHg)	128±18	131±14	127±11	127±13	134±14	128±13
Diastolic Blood Pressure (mmHg)	77±10	79±10	78±10	80±7	78±12	79±10

Mean±SD

5.3 Additional supporting clinical studies

In addition to the abovementioned two clinical studies employing VENETRON™, we also conducted a few clinical studies examining the effects of dietary VENETRON™. Although these studies did not measure safety parameters, they provide additional supporting evidences that VENETRON™ is generally safe.

5.3-1 Concurrent use of GABA (gamma-amino butyric acid) and VENETRON™ on healthy human [11]

A double blind, crossover, placebo-controlled clinical trial was conducted on 12 healthy male volunteers. The volunteers were oral administered placebo, only GABA group (25mg/day/person), only VENETRON™ group (25mg/day/person), or GABA plus VENETRON™ (each 25mg/day/person) for 4 days.

No adverse effects were found in this clinical study.

5.3-2 Case report of VENETRON™ on premenstrual syndrome (PMS)

Case report of VENETRON™ on premenstrual syndrome (PMS) was conducted by Doctor: Kunihiko Tominaga MD, Director of the Lomalinda Clinic.

Patients with PMS intake VENETRON™ at the dose of 25-50mg/day/person, and no adverse effects are reported.

6.0 OTHERS STUDIES SUPPORTING SAFE USE

6.1 No influence on drug-metabolizing enzymes and P-glycoprotein [12]

The long intake of some health foods may induce hepatic cytochrome P450 (CYP) 3A and the intestinal P-glycoprotein (P-gp) in humans, and cause a decrease in the blood concentration of some drugs.

We investigated the influence of VENETRON™ on the drug disposition of the substrate drugs, nifedipine, for CYP3A in rats. There were no significant differences in the pharmacokinetic parameters of nifedipine between VENETRON™-treated and none-treated rats. Also, the intestinal absorption of methylprednisolone, which is a substrate for P-gp, was not affected by VENETRON™ treatment for two weeks.

This result indicates that VENETRON™ has no influence on drug-metabolizing enzymes and P-glycoprotein.

6.2 Absence of cardiotonic effect [13, 14]

Since *Apocynum* family plants usually contain cardiac glycoside, such as cymarin, we investigated the cardiotonic effect of VENETRON™ on the isolated guinea pig atrium and analyzed the content of cymarin in VENETRON™ by LC-MS/MS analysis.

The cardiotonic effect of VENETRON™ was found to be only one two hundredth of G-strophanthin, and the content of cymarin in VENETRON™ was less than 5ppm.

7.0 REFERENCES

[1] Nishibe S. et al. Flavonoid Content in *Apocynum* and *Poacynum* Leaves and Lipid-Peroxidation-Inhibiting Effect of Flavonoids. Natural Medicines, 48, 322 (1994).

[2] Kipker S, et al. Proanthocyanidins from *Apocynum venetum* L. International Congress on Natural Products Research (2004).

[3] Pharmacopeia of People's Republic of China, 2005.

[4] 中国国家基本药物目录 (2009).

[5] 特定保健用食品評価書　燕龍茶レベルケア　2006 年　食品安全委員会

[6] Markham K, et al. CARBON-13 NMR Studies of Flavonoids-III. Tetrahedron, 34, 1389 (1978).

[7] Kamata K, et al. Constituents from Leaves of *Apocynum venetum* L. J. Nat. Med., 62, 160 (2008).

[8] Acute Toxicity Study Report by Japan Food Research Laboratories.

[9] Li-Yang J. et al. Safety Study of *Apocynum venetum* L. Extract in Healthy Adults. Journal of Nutritional Food, 12(3), 1 (2010).

[10] KGK SYNERGIZE INC. Report, Effect of VENETRON™ on Symptoms of Depression in Individuals with Mild Depression (2006).

[11] Yoto A. et al. The Stress Reducing Effect of γ-Aminobutyric Acid and *Apocynum venetum* Leaf Extract on Changes in Concentration of Salivary Chromogranin A. Japanese Journal of Physiological Anthropology, 14(3), 55 (2009).

[12] Kobayashi M. et al. *Apocynum venetum* Extracts Does not Induce CYP3A and P-Glycoprotein in Rats. Bio. Pharm. Bull., 27, 1649 (2004).

[13] Irie K. et al. Cardiotonic Effect of *Apocynum venetum* L. Extract on Isolated Guinea Pig Atrium. J. Nat. Med., 63, 111 (2009).

[14] 入江かおる　ラフマ抽出物（ベネトロン）のモルモット摘出心房に対する作用 日本薬学会第 129 年会 (2006).

Appendix 1 Specification of VENETRON™

Specification of VENETRON™ (Rafuma extract)

VENETRON™ (Rafuma extract) is extracted from Rafuma (*Apocynum venetum* L.) leaves. It contains not less than 4.0 % of Hyperoside and Isoquercitrin, calculated on the dried basis.

Description Brown powder with bitter taste.

Identification test
Dissolve about 0.1 g of VENETRON™ in 50 mL of 50 % ethanol, and use this solution as the sample solution. Dissolve about 3 mg of dried standard hyperoside and isoquercitrin in 50 mL of 50% ethanol respectively. Use these solutions as the standard solutions. Perform the test with these solutions under thin-layer chromatography. Spot 5 μL each of the sample and standard solutions on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixed solvent of Ethyl acetate / Formic acid / Acetic acid / Water (100:11:11:26). Examine the plate under ultraviolet light (wavelength 254 nm), and the spots obtained from the sample solution shows the same Rf values as the spot from the standard solutions.

Purity test
(1) Heavy metals — Not more than 20 ppm (1.0 g, Method 2, Standard solution 2.0 mL).
(2) Arsenic — Not more than 4 ppm (0.5 g, Method 3, Equipment B).

Loss on drying Not more than 6.0 % (1 g, 80 °C, reduced pressure, 3 hours).

Residue on ignition Not more than 3.0 % (1 g).

Content of sum of Hyperoside and Isoquercitrin Not less than 4.0 %
Weigh accurately about 50 mg of VENETRON™, dissolve in 50 % ethanol to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 3 mg of previously dried standard hyperoside and isoquerctirin, dissolve in 50 % ethanol to make exactly 50 mL, respectively, and use these solutions as the standard solutions.
Pipet 10 μL each of the sample solution and the standard solutions, and perform the test as directed under the Liquid Chromatography (HPLC) according to the following conditions. Determine the peak areas of hyperoside and isoquercitrin in the sample solution (A_{HT} and A_{IT}) and standard solutions (A_{HS} and A_{IS}).

Operating conditions—

Detector : UV Absorption 330 nm
Column : ODS Column
Column temperature : 35 °C
Mobile phase : Water / Acetonitrile / Trifluoroacetic acid solution = 85 : 15 : 0.1
Flow rate : Adjust the flow rate so that the retention time of isoquerctirin is about 10 minutes.

Amount (mg) of hyperoside

$$= \text{amount (mg) of hyperoside standard calculated on the dried basis} \times \frac{A_{HT}}{A_{HS}}$$

Amount (mg) of isoquercitrin

$$= \text{amount (mg) of isoquercitrin standard calculated on the dried basis} \times \frac{A_{IT}}{A_{IS}}$$

Determine the content of hyperoside and isoquercitrin (%) in the VENETRON™ using the values obtained as above.

Microbiological test

(1) Total aerobic microbial count—Not more than 1000 cfu/g.
(2) Escherichia coli—Negative.

Test method is according to *Japan's Specifications and Standards for Food Additives.*

Appendix 2 CoA of standard references and validation data of HPLC analysis

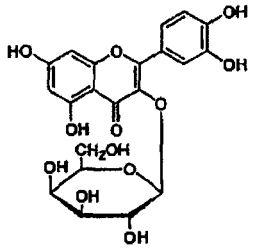
tokiwa
PHYTOCHEMICAL

Natural Alternatives for a Healthier Tomorrow
TOKIWA PHYTOCHEMICAL

ANALYSIS REPORT

Hyperoside

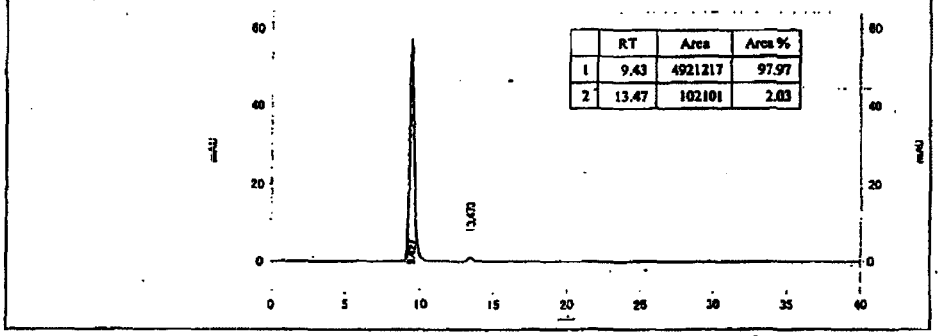
Code No.	P2202
Lot No.	20270901
CAS number	[482-36-0]
Other name	Quercetin 3-galactoside
Molecular formula	$C_{21}H_{20}O_{12}$
Molecular weight	464.4
Appearance	Powder
Purity	≧95% (HPLC)



Storage: Store at 4℃ in a dry and dark place. Place in a desiccator under vacuum for 48 hours before use.

HPLC Analysis

Column	SHISEIDO Capcell PAK C18 UG120, 3 μm, ϕ 2.0 x 150 mm
Solvent	acetonitrile / water / trifluoroacetic acid (15 / 85 / 0.1, v / v / v)
Flow rate	0.2 ml / min
Detector	352 nm
Sample	3.01mg / 50ml (50% EtOH) 2μl
Column temp.	35 ℃



	RT	Area	Area %
1	9.43	4921217	97.97
2	13.47	102101	2.03

(09 / 29 / 2008) (M/D/Y)

Kazutaka kataoka
Manager of Q.C.

(09 / 29 / 2008) (M/D/Y)

T. Yamashita
Tadatoshi Yamashita
Analyst

TOKIWA PHYTOCHEMICAL CO., LTD.

HEAD OFFICE / LAB / PLANT : 158 Kinoko, Sakura-shi , Chiba, 285-0801, JAPAN
TEL : 81-43-498-0007 FAX : 81-43-498-0561
Web Page: www.tokiwaph.co.jp
TOKYO BRANCH / SALES : Uriyama Bldg. 6F, 4-4-16 Nihombashi Hon-cho, Chuo-ku, Tokyo, 103-0023, JAPAN
TEL : 81-3-5200-1251 FAX : 81-3-5200-1256 E-mail: pureproducts@tokiwaph.co.jp

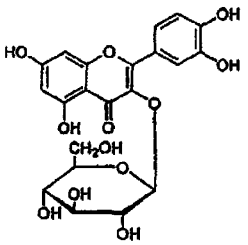
tokiwa
PHYTOCHEMICAL

Natural Abundance for a Healthier Tomorrow
TOKIWA PHYTOCHEMICAL

ANALYSIS REPORT

Isoquercitrin

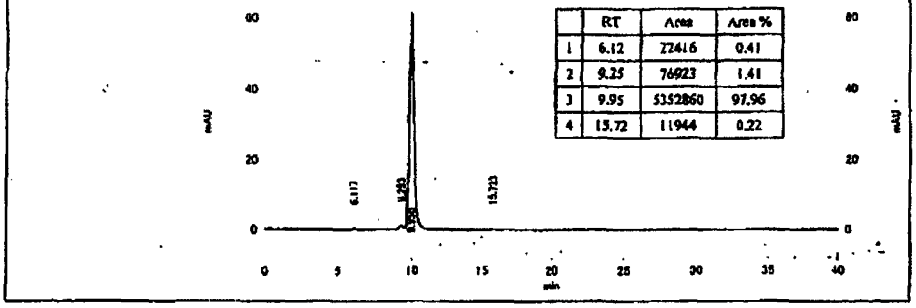
Code No.	P2203
Lot No.	20370903
CAS number	[482-35-9]
Other name	Quercetin 3-glucoside
Molecular formula	$C_{21}H_{20}O_{12}$
Molecular weight	464.4
Appearance	Powder
Purity	≧95% (HPLC)



Storage: Store at 4°C in a dry and dark place. Place in a desiccator under vacuum for 48 hours before use.

HPLC Analysis

Column	SHISEIDO Capcell PAK C18 UG120, 3 μm, ϕ 2.0 x 150 mm
Solvent	acetonitrile / water / trifluoroacetic acid (15 / 85 / 0.1, v / v / v)
Flow rate	0.2 ml/min
Detector	352 nm
Sample	3.0 mg / 50ml (50% EtOH) 2μl
Column temp.	35 °C



	RT	Area	Area %
1	6.12	22416	0.41
2	9.25	76923	1.41
3	9.95	5352860	97.96
4	15.72	11944	0.22

(09 / 29 / 2008) (M/D/Y)

Kazutaka kataoka
Manager of Q.C.

(09 / 29 / 2008) (M/D/Y)

Tadatoshi Yamashita
Analyst

TOKIWA PHYTOCHEMICAL CO., LTD.

HEAD OFFICE / LAB / PLANT : 158 Kinoko, Sakura-shi, Chiba, 285-0801, JAPAN
TEL : 81-43-498-0007 FAX : 81-43-498-0561
Web Page: www.tokiwaph.co.jp
TOKYO BRANCH / SALES : Uchiyama Bldg. 6F, 1-4-16 Nihombashi Hon-chu, Chuo-ku, Tokyo, 103-0023, JAPAN
TEL : 81-3-5200-1251 FAX : 81-3-5200-1256 E-mail: pureproducts@tokiwaph.co.jp

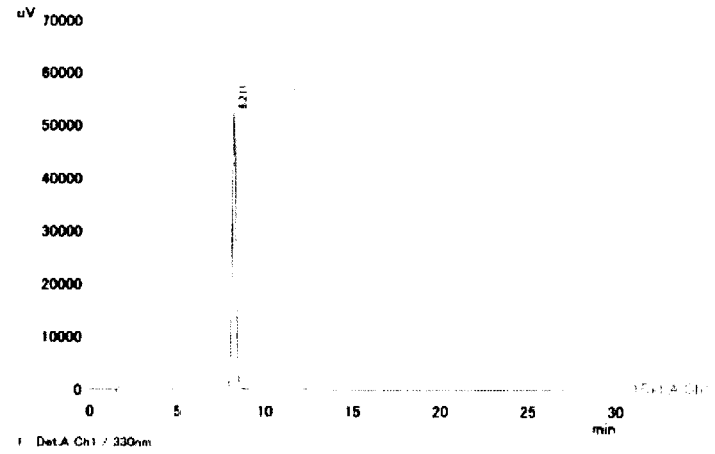
tokiwa
PHYTOCHEMICAL

Analysis Data of VENETRON

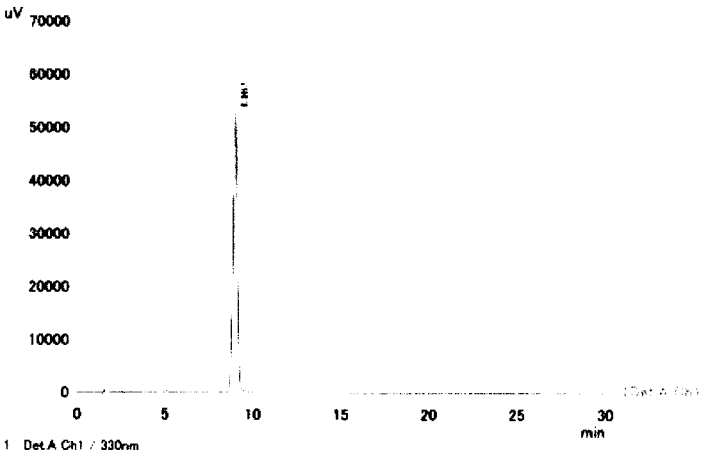
1. Specificity (see attached chromatograms)

HPLC chromatogram of standard solution

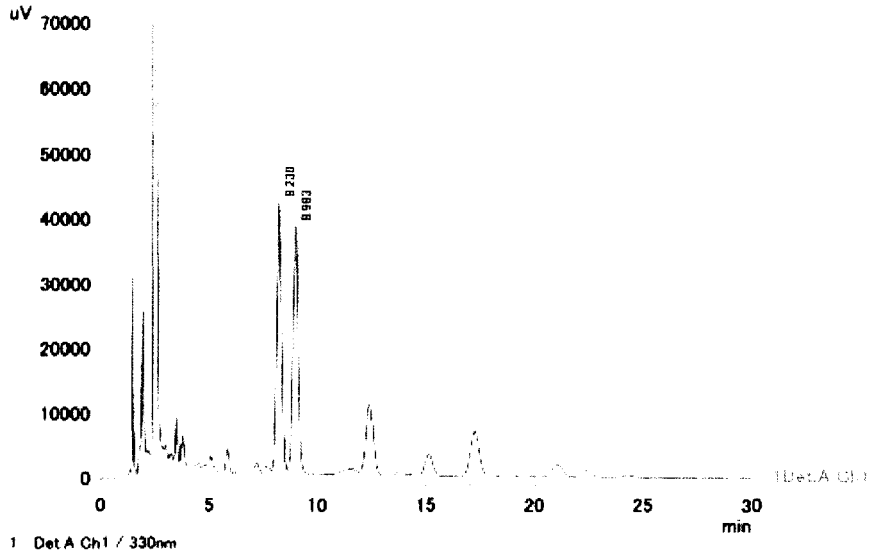
Hyperoside standard



Isoquercitrin standard



HPLC chromatogram of Sample solution



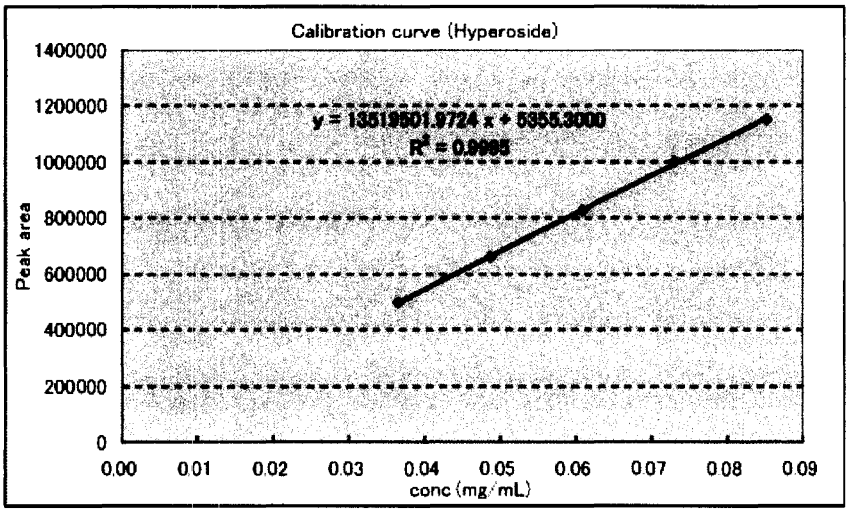
Chromatogram	Retention time (Hyperoside)	Retention time (Isoquercitrin)
Hyperoside standard	8.211	
Isoquercitrin standard		8.967
Sample	8.230	8.983

2. Linearity

Standard Data

Hyperoside Standard

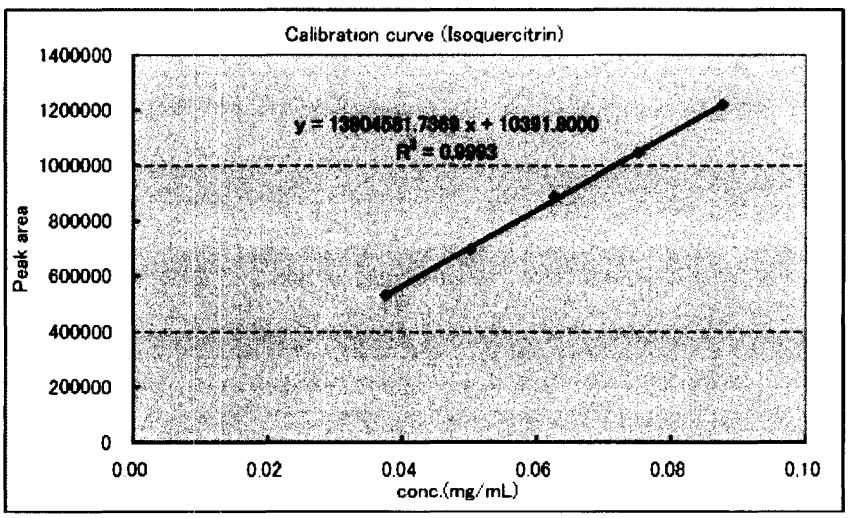
conc. (mg/mL)	0.03650	0.04867	0.06084	0.07301	0.08518
Peak area	499014	661101	826379	1001648	1151267



Standard Linearity: 0.9995

Isoquercitrin Standard

conc. (mg/mL)	0.03758	0.05011	0.06264	0.07517	0.08770
Peak area	529781	694493	886969	1045129	1219182



Standard Linearity: 0.9993

3. Accuracy

Sample Deta

・3conc, 3times analysis data

Hyperoside

Weight Conc. (%)	70	100	130
Recovery(%)	98.7	99.9	100.5
	99.0	99.8	100.8
	99.3	100.3	100.4
Average(%)	99.0	100.0	100.6
RS	0.3008	0.2564	0.2369
RSD(%)	0.3038	0.2564	0.2356

AVG Recovery: 99.9%

Isoquercitrin

Weight Conc. (%)	70	100	130
Recovery(%)	98.7	100.0	100.7
	99.0	99.8	101.0
	99.1	100.3	100.5
Average(%)	98.9	100.0	100.7
RS	0.2146	0.2496	0.2411
RSD(%)	0.2169	0.2496	0.2394

AVG Recovery: 99.9%

4. Precision (repeatability)

sample date

・3conc, 3times analysis data

Wight Conc.		Peak Area	Peak Area	Hyperoside	Isoquercitrin	Total
mg/50mL	%	(Hyperoside)	(Isoquercitrin)	(%)	(%)	(%)
35.5	70	455623	450000	4.75	4.49	9.24
36.4		468004	462335	4.76	4.50	9.26
34.6		441848	435728	4.78	4.51	9.29
Average		455158	449354	4.76	4.50	9.26
RS		13084	13315	0.0163	0.0115	0.0277
RSD(%)		2.8746	2.9632	0.3422	0.2558	0.2995

Wight Conc.		Peak Area	Peak Area	Hyperoside	Isoquercitrin	Total
mg/50mL	%	(Hyperoside)	(Isoquercitrin)	(%)	(%)	(%)
50.0	100	646040	637438	4.78	4.51	9.30
50.2		647482	638653	4.77	4.50	9.28
49.7		644317	635492	4.80	4.53	9.33
Average		645946	637194	4.79	4.51	9.30
RS		1585	1595	0.0124	0.0115	0.0239
RSD(%)		0.2453	0.2502	0.2597	0.2537	0.2566

Wight Conc.		Peak Area	Peak Area	Hyperoside	Isoquercitrin	Total
mg/50mL	%	(Hyperoside)	(Isoquercitrin)	(%)	(%)	(%)
64.7	130	838222	827609	4.80	4.53	9.32
66.6		865354	853996	4.81	4.54	9.35
65.0		840946	829822	4.79	4.52	9.31
Average		848174	837142	4.80	4.53	9.33
RS		14941	14638	0.0105	0.0100	0.0205
RSD(%)		1.7615	1.7485	0.2193	0.2204	0.2193

AVG RSD: 0.2585%

5. Summary

		Result
Specificity		Complies
Linearity (standard)	R^2>0.998	Complies (0.999)
Accuracy	98-102%	Complies (99.9%)
Precision	RSD≤2.0%	Complies (0.26%)
Range	80-120%	Complies (70-130%)

Appendix 3 Certificates of analysis of three lots

tokiwa
PHYTOCHEMICAL

Certificate of analysis

Product name: VENETRON™(Rafuma extract)
Lot No. 797130401
Manufacturing date : April 26, 2013
Expiry date : March, 2016

	Specification	Result
Description	Brown powder with bitter taste	Complies
Identification test	Positive	Complies
Purity test		
(1) Heavy metals	Not more than 20 ppm	Complies
(2) Arsenic	Not more than 2 ppm	Complies
Loss on drying	Not more than 6.0 %	3.6 %
Residue on ignition	Not more than 3.0 %	0.3 %
Content of sum of Hyperoside and Isoquercitrin	Not less than 4.0 %	8.2 %
Microbiological test		
(1) Total aerobic plate count	Not more than 1000 cfu/g	Complies
(2) Escherichia coli	Negative	Complies

Date: May 7, 2013

K. Kataoka
Manager of Q.C.

tokiwa
PHYTOCHEMICAL

Certificate of analysis

Product name: VENETRON™(Rafuma extract)
Lot No. 797121205
Manufacturing date : December 7, 2012
Expiry date : November, 2015

	Specification	Result
Description	Brown powder with bitter taste	Complies
Identification test	Positive	Complies
Purity test		
(1) Heavy metals	Not more than 20 ppm	Complies
(2) Arsenic	Not more than 2 ppm	Complies
Loss on drying	Not more than 6.0 %	2.1 %
Residue on ignition	Not more than 3.0 %	0.3 %
Content of sum of Hyperoside and Isoquercitrin	Not less than 4.0 %	8.3 %
Microbiological test		
(1) Total aerobic plate count	Not more than 1000 cfu/g	Complies
(2) Escherichia coli	Negative	Complies

Date: December 14, 2012

K. Kataoka
Manager of Q.C.

000046

tokiwa
PHYTOCHEMICAL

Certificate of analysis

Product name: VENETRON™(Rafuma extract)
Lot No. 797120904
Manufacturing date : September 20, 2012
Expiry date : August, 2015

	Specification	Result
Description	Brown powder with bitter taste	Complies
Identification test	Positive	Complies
Purity test		
(1) Heavy metals	Not more than 20 ppm	Complies
(2) Arsenic	Not more than 2 ppm	Complies
Loss on drying	Not more than 6.0 %	2.3 %
Residue on ignition	Not more than 3.0 %	0.5 %
Content of sum of Hyperoside and Isoquercitrin	Not less than 4.0 %	8.7 %
Microbiological test		
(1) Total aerobic plate count	Not more than 1000 cfu/g	Complies
(2) Escherichia coli	Negative	Complies

Date: September 27, 2012

K. Kataoka
Manager of Q.C.

SUBMISSION END

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

August 21, 2014

Mr. Jin Tatsuzaki
President
Tokiwa Phytochemical Co., Ltd.
158, Kinoko, Sakura-Shi
Chiba 285-0801
JAPAN

Re: GRAS Notice No. GRN 000530

Dear Mr. Tatsuzaki:

The Food and Drug Administration (FDA) has received the notice, dated June 30, 2014, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received this notice on July 17, 2014, filed it on August 8, 2014, and designated it as GRAS Notice No. GRN 000530.

The subject of the notice is extract of *Apocynum venetum* leaves. The notice informs FDA of the view of Tokiwa Phytochemical Co., Ltd. (Tokiwa) that extract of *Apocynum venetum* leaves is GRAS, through scientific procedures, for use as an ingredient in food. Tokiwa intends to use extract of *Apocynum venetum* leaves at levels up to 100 milligrams per day.

In accordance with proposed 21 CFR 170.36(f), a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)) is available for public review and copying at www.fda.gov/grasnoticeinventory. If you have any questions about the notice, contact me by electronic mail at judith.dausch@fda.hhs.gov or by telephone at (240) 402-2040.

Sincerely yours,

judith.dausch@fda.hhs.gov
Digitally signed by judith.dausch@fda.hhs.gov
DN: cn=judith.dausch@fda.hhs.gov
Date: 2014.08.21 15:20:28 -04'00'

Judith G. Dausch, Ph.D.
Division of Biotechnology and
GRAS Notice Review
Center for Food Safety
and Applied Nutrition

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

August 21, 2014

Mr. Jin Tatsuzaki
President
Tokiwa Phytochemical Co., Ltd.
158, Kinoko, Sakura-Shi
Chiba 285-0801
JAPAN

Re: GRAS Notice No. GRN 000530

Dear Mr. Tatsuzaki:

The Food and Drug Administration (FDA) has received the notice, dated June 30, 2014, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received this notice on July 17, 2014, filed it on August 8, 2014, and designated it as GRAS Notice No. GRN 000530.

The subject of the notice is extract of *Apocynum venetum* leaves. The notice informs FDA of the view of Tokiwa Phytochemical Co., Ltd. (Tokiwa) that extract of *Apocynum venetum* leaves is GRAS, through scientific procedures, for use as an ingredient in food. Tokiwa intends to use extract of *Apocynum venetum* leaves at levels up to 100 milligrams per day.

In accordance with proposed 21 CFR 170.36(f), a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)) is available for public review and copying at www.fda.gov/grasnoticeinventory. If you have any questions about the notice, contact me by electronic mail at judith.dausch@fda.hhs.gov or by telephone at (240) 402-2040.

Sincerely yours,

judith.dausch@fda.hhs.gov
Digitally signed by judith.dausch@fda.hhs.gov
DN: cn=judith.dausch@fda.hhs.gov
Date: 2014.08.21 15:20:28 -04'00'

Judith G. Dausch, Ph.D.
Division of Biotechnology and
GRAS Notice Review
Center for Food Safety
and Applied Nutrition

Hard copy cc: GRN 000530 (1 copy)
R/D:JDausch:HFS-255:8/20/14
Edit/Init:SWestBarnette:HFS-255:8/21/14
F/T:JDausch:8/21/14

From: Dausch, Judith
To: Tatsuzaki Jin
Subject: Questions Regarding GRN 530 - Extract of Apocynum venetum leaves
Date: Thursday, October 02, 2014 2:48:39 PM

Hello Mr. Tatsuzaki,

In reviewing your GRAS notice, GRN 530 extract of *Apocynum venetum* leaves we had some questions. Please provide a response to the following:

1. Is *Apocynum venetum* extract intended to be used in conventional foods or is the intended use as a dietary supplement? Please explain.

2. If the intended use of *Apocynum venetum* extract is intended for use in conventional foods, please indicate the intended foods.

Please provide us with a phone number so that we may discuss the notice with you or your designated contact person.

Thank you. We look forward to hearing from you.

Judith G. Dausch, Ph.D., R.D.
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety, Rm. 2058
5100 Paint Branch Parkway
College Park, MD 20740-3835
E-mail: Judith.Dausch@fda.hhs.gov
Tel: 240-402-2040 Fax: 301-436-2965

From:	Dausch, Judith
To:	"Tatsuzaki Jin"
Cc:	"楊 金　"
Bcc:	Dausch, Judith
Subject:	GRN 530 - Extract of Apocynum venetum leaves - Please Send Request for us to Cease GRAS Evaluation
Date:	Tuesday, October 07, 2014 3:24:00 PM

Dear Mr. Tatsuzaki,

Thank you for clarifying that GRN 530 extract of *Apocynum venetum* leaves is intended to be used as a dietary supplement.

The Office of Food Additive Safety Division of Biotechnology and GRAS Notice Review, to which you sent your submission, does not handle dietary supplement ingredients. Dietary supplements are regulated through FDA's Office of Nutrition, Labeling, and Dietary Supplements. You may read about their program here: http://www.fda.gov/Food/DietarySupplements/default.htm. If you click on the bullet that says New Dietary Ingredients Notification Process, you will find a bullet on How to Submit Notifications. An address is provided for submitting notifications for a new dietary ingredient. You may contact their program by calling: 240-402-1761.

Given that we don't evaluate dietary supplement ingredients, we intend to stop evaluation of your GRAS notice.

Please send a request for us to cease our safety evaluation of GRN 530 via email within one week.

Judith G. Dausch, Ph.D., R.D.
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety, Rm. 2058
5100 Paint Branch Parkway
College Park, MD 20740-3835
E-mail: Judith.Dausch@fda.hhs.gov

From:	Dausch, Judith
To:	Tatsuzaki Jin
Cc:	"楊 金 "; West-Barnette, Shayla
Subject:	Conference Call to Discuss Questions Regarding GRN 530 - Extract of Apocynum venetum leaves
Date:	Tuesday, October 21, 2014 10:22:39 AM

Hello Mr. Tatsuzaki,

We look forward to talking with you about your GRAS notice on Thursday, October 23rd from 10 – 11:00 am Eastern Standard Time. We do not have Skype capability and will need to talk by conference call.

Please have your participants dial in to the number below. It is a toll number.

Dial In Number: 1-203-607-6889
Passcode: 4161014

I will follow up our call with an e-mail summary of our teleconference discussion.

Does this work for you?

Thank you.

Judy Dausch

Judy Dausch, Ph.D.
FDA/OFAS/DBGNR
(240) 402-2040

Memorandum of Telephone Conversation

Date: October 23, 2014

Place: FDA, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, 4300 River Road, College Park, MD 20740

Between:

Ron Chanderbhan	HFS-255
Judith Dausch	HFS-255
Mike DiNovi	HFS-255
Jeremy Milohov	HFS-255
Tim Twaroski	HFS-255
Shayla West-Barnette	HFS-255
Romina Shah	HFS-255

and

Jin Tatsuzaki	Tokiwa Phytochemical Co., Ltd.
Dr. Jinwel Yang	Tokiwa Phytochemical Co., Ltd.
Schinchiro Shinkai	Tokiwa Phytochemical Co., Ltd.
Tsutomu Sasaki	Tokiwa Phytochemical Co., Ltd.

Subject: GRAS Notice 530 – Extract of *Apocynum venetum* Leaves

FDA requested a meeting with Tokiwa to discuss issues pertaining to an insufficient GRAS notice that does not meet the GRAS standard.

FDA received the submission on July 17, 2014. The intended use is stated as an ingredient in food at levels of up to 100 milligrams per day.

We explained to Mr. Tatsuzaki that we requested the meeting to inform him that the submission does not meet the GRAS standard due to FDA's classification of the substance as a new drug. We explained to him that Tokiwa has promoted the substance for use in treating health conditions that classify it as a drug according to the U.S. regulatory system. In addition, we discussed the elements of a safety data package that form the basis of an adequate GRAS determination.

Comments from the review team included chemistry and toxicology issues. FDA explained that the discussion of intended use should include information on specific food categories or per serving use levels. An explanation of how an intake level of 50 mg/p/day would be achieved was also recommended. FDA also addressed the lack of detailed composition of the substance and explained that it is desirable to try and account for 100% of the chemical composition. A more complete discussion of the components present in the extract was recommended. Other chemistry issues discussed included the need to identify the adsorbent resin used in the manufacturing process and whether it is approved for use in food.

With regard to toxicology issues, FDA discussed the lack of a safety discussion of the major components, including hyperoside, isoquercitrin, quercetin, and catechins and recommended that a specific discussion be included for each component. FDA also indicated that the reference in the notice to a safety factor of 30 may not be conservative and that our regulations currently identify a 100-fold safety factor and recommended in FDA's Redbook. Another concern highlighted by FDA relevant to the safety determination was the need to provide a certified translation of the articles in the GRAS notice.

Tokiwa inquired about using human clinical data that supports treatment of health conditions as the basis for the safety discussion. FDA staff clarified that we specifically seek safety studies with specific endpoints, and that health benefits or efficacy of the substance is not relevant to the safety discussion. Tokiwa requested that FDA cease its review of the GRAS notice and that a follow up list of the issues discussed be provided after the call. FDA agreed to provide the list of concerns and suggested that Tokiwa consider securing a consultant who is familiar with U.S. food and dietary supplement regulations.

Judith G. Dausch, Ph.D.

cc: SBJ 001379
R/D:HFS-255:JDausch:10/23/14
F/T:HFS-255:JDausch:2/18/15

From: Dausch, Judith
To: Tatsuzaki Jin
Cc: "楊 金 "; West-Barnette, Shayla
Subject: Summary of Issues for GRN 530 - Extract of Apocynum Venetum Leaves
Date: Tuesday, October 28, 2014 5:09:28 PM

Hello Mr. Tatsuzaki,

Thank you for providing the names of the participants on the call on October 23, 2014.

Please see a list of issues that our safety review team has identified. Given the issues we discussed, we suggest that Tokiwa withdraw the notice as the best option since we are not in a position to provide a favorable safety review. If a withdrawal is not requested, FDA will issue a No-Basis letter that summarizes why we disagree with the safety determination and post it on our website.

Please see the link to FDA's Redbook, the guidance to industry that addresses toxicology issues.

http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm

Issues for GRN 530: Extract of *Apocynum venetum* leaves

Issue	Notes
FD&C Act, Section 301(ll)	
Drug claims – literature points to drug effects • Used in China to treat neurasthenia, palpitation, insomnia, edema w/oliguria, hypertension and nephritic edema (2005) • Permitted for treatment of hypertension in Japan (2007) • Clinical trial on 47 individuals w/mild depression. Website shows patent for use as an anti-depressant and considers it alternative to St. John's Wort.	Section 301(ll) prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the Food, Drug &Cosmetic Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies.
References	
• Unpublished internal report on clinical study • Foreign language without translations	
Chemistry	
Notice only accounts for about 10% of the ingredient composition	Could rely on the literature, but data composition in the papers is not always quantitative. Provide data to account for 95% of the composition.
Intended use: • No information on food categories or per serving use levels • Exposure calculations needed to achieve 50 mg/day	Tokiwa could provide food categories An explanation is needed on how they would limit the total daily intake to 50 mg/p/d (p. 1). Statement needed on

	whether this level is for 1 serving and how this would be achieved. They also give consensus GRAS statement that substance is safe in foods at total daily intake of 100 mg/p/d (p. 3).
Manufacturing Process: • No statement on adsorption resins being food grade • Regulatory status	Need to identify the adsorbent resin and refer to the approved use in food ("synthetic adsorbent resin," p. 9 – could be an unapproved resin and possible source of contamination to food). (p. 4 - food grade spec for final product)
Specifications • No lead spec • No residual ethanol spec	Provide lead specification. Heavy metal specications of <20 ppm, arsenic <2 ppm are provided. State residual ethanol in final product and provide a specified limit for ethanol
Toxicology	
Lack of safety discussion: • Hyperoside – reproductive effects • Isoquercitrin – effects on Ca+ regulation, bw • Quercetin – NTP tests positive in genetic toxicology tests and possible carcinogenicity in rats • Catechins	Published study is cited in Chinese There is a chronic study on rutin (quercetin glycoside) that be used for discussion Could reference existing GRAS notice (GRN 341 – quercetin) if similar use levels Catechins are discussed in a previous GRAS notice - green tea extract ECGC (epigallocatechin gallate)
Statement that safety factor of 30 is conservative, contradicts our regulation stating a recommended100-fold safety factor	Re-do of the calculation is needed

-

I look forward to your response.

Judith G. Dausch, Ph.D., R.D.
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety, Rm. 2058
5100 Paint Branch Parkway
College Park, MD 20740-3835
E-mail: Judith.Dausch@fda.hhs.gov
Tel: 240-402-2040 Fax: 301-436-2965

From: Dausch, Judith
To: Tatsuzaki Jin
Cc: West-Barnette, Shayla; manta415@tkm.att.ne.jp; k-you@tokiwaph.co.jp
Subject: RE: Withdraw GRN 530 from FDA review
Date: Monday, November 10, 2014 9:00:21 AM

Hello Mr. Tatsuzaki,

Thank you for contacting me regarding your request to withdraw GRN 530 from FDA review. We will honor this request.

We appreciate your attention to the issues discussed in the summary that was provided to you on October 28, 2014.

Best regards,

Judy Dausch

Judith G. Dausch, Ph.D., R.D.
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety, Rm. 2058
5100 Paint Branch Parkway
College Park, MD 20740-3835
E-mail: Judith.Dausch@fda.hhs.gov
Tel: 240-402-2040 Fax: 301-436-2965

From: Dausch, Judith
To: Tatsuzaki Jin
Cc: manta415@tkm.att.ne.jp; k-you@tokiwaph.co.jp
Subject: Withdrawal of GRN 530 - Extract of Apocynum Venetum Leaves - from FDA review
Date: Tuesday, December 02, 2014 4:35:16 PM
Attachments: 2014-12-2_Withdrawal_letter_0530_JDausch, Signed, Transmittal copy.pdf

---

Dear Mr. Tatsuzaki,

Please see the attached letter that officially acknowledges Tokiwa's request for FDA to cease its evaluation of your GRAS notice.

Thank you.

Judith G. Dausch, Ph.D., R.D.
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety, Rm. 2058
5100 Paint Branch Parkway
College Park, MD 20740-3835
E-mail: Judith.Dausch@fda.hhs.gov
Tel: 240-402-2040 Fax: 301-436-2965

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

Mr. Jin Tatsuzaki
President
Tokiwa Phytochemical Co., Ltd.
158, Kinoko, Sakura-Shi
Chiba 285-0801
JAPAN

Re: GRAS Notice No. GRN 000530

Dear Mr. Tatsuzaki:

The Food and Drug Administration (FDA) is responding to the notice, dated June 30, 2014, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on July 17, 2014, filed it on August 8, 2014, and designated it as GRAS Notice No. GRN 000530.

The subject of the notice is extract of *Apocynum venetum* leaves. The notice informs FDA of the view of Tokiwa Phytochemical Co., Ltd., that extract of *Apocynum venetum* leaves is GRAS, through scientific procedures, for use as an ingredient in food.

In an electronic mail message dated November 5, 2014, you asked that FDA cease to evaluate your GRAS notice. Given your request, we ceased to evaluate your GRAS notice, effective November 5, 2014, the date that we received your electronic mail message.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000530, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov/grasnoticeinventory.

Sincerely,

Antonia Mattia -S

Digitally signed by Antonia Mattia -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Antonia Mattia -S, 0.9.2342.19200300.100.1.1=13000715 80
Date: 2014.12.02 15:59:25 -05'00'

Antonia Mattia, Ph.D.
Director
Division of Biotechnology
and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

Mr. Jin Tatsuzaki
President
Tokiwa Phytochemical Co., Ltd.
158, Kinoko, Sakura-Shi
Chiba 285-0801
JAPAN

Re: GRAS Notice No. GRN 000530

Dear Mr. Tatsuzaki:

The Food and Drug Administration (FDA) is responding to the notice, dated June 30, 2014, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on July 17, 2014, filed it on August 8, 2014, and designated it as GRAS Notice No. GRN 000530.

The subject of the notice is extract of *Apocynum venetum* leaves. The notice informs FDA of the view of Tokiwa Phytochemical Co., Ltd., that extract of *Apocynum venetum* leaves is GRAS, through scientific procedures, for use as an ingredient in food.

In an electronic mail message dated November 5, 2014, you asked that FDA cease to evaluate your GRAS notice. Given your request, we ceased to evaluate your GRAS notice, effective November 5, 2014, the date that we received your electronic mail message.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000530, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov/grasnoticeinventory.

Sincerely,

Antonia Mattia, Ph.D.
Director
Division of Biotechnology
and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

Hard copy cc: **GRN 000530** (1 copy)
Electronic mail cc:PBeckerman (GCF-1)
HFS-200:DKeefe, MAdams
HFS-255:AMattia, RFChanderbhan, MDiNovi, SCarlson, RIMerker, SWestBarnette, PMGaynor, JMihalov, TTwaroski, PGaynor, and LShepherd

HFS-850 (CAssar)

Filename:GRN 000530

R/D:HFS-255:JDausch:12/2/14
Edit/Init:HFS-255:SWestBarnette:11/26/14,12/2/14
Edit/Comment/Init:HFS-255:CMcMahon for PMGaynor:11/26/2014
Edit/Comment/Init:HFS-255:AMattia:12/1/14
F/T:JDausch:12/2/14

NAME	ELECTRONIC SIGN-OFF	ACTING?
Judith Dausch Consumer Safety Officer	Judith G. Dausch -S Digitally signed by Judith G. Dausch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000375513, cn=Judith G. Dausch -S Date: 2014.12.02 11:18:10 -05'00'	☐
Carrie McMahon Consumer Safety Officer		☒
Antonia Mattia Director, Division of Biotechnology & GRAS Notice Review		☐

From:	Tatsuzaki Jin
To:	Dausch, Judith
Cc:	"楊 金 "
Subject:	Re: Questions Regarding GRN 530 - Extract of Apocynum venetum leaves
Date:	Tuesday, October 07, 2014 8:23:17 AM

Dear Dr. Judith Dausch,

Thanks for your comment on our GRAS notice, GRN 530 extract of Apocynum venetum leaves.
Apocynum venetum extract is intended to be used as a dietary supplement.
And Dr. Jinwei Yang (k-you@tokiwaph.co.jp), the director of our R&D, can discuss the notice with you. Her Tel. is 0081-43-498-0025.
If you think it is necessary to hold a phone meeting, we will call you at your convenient time.

Please feel free to contact us.

Sincerely yours,

Jin Tatsuzaki / President
Tokiwa Phytochemical Co., Ltd.

From:	Tatsuzaki Jin
To:	Dausch, Judith
Cc:	"楊 金 "
Subject:	Re: Questions Regarding GRN 530 - Extract of Apocynum venetum leaves
Date:	Friday, October 10, 2014 8:06:29 PM

Dear Dr. Judith G. Dausch,

Thank for your information.
GRN 530-extract of Apocynum venetum leaves is intended to be used in conventional food, such as beverage, Jelly, as well as supplemnt. Therefore, we hope you will continue the evaluation of our notice.

Sincerely yours,

Jin Tatsuzaki / President
Tokiwa Phytochemical Co., Ltd.

From:	Tatsuzaki Jin
To:	Dausch, Judith
Cc:	"楊 金 "; West-Barnette, Shayla
Subject:	Re: Please Request that FDA Cease Evaluation of GRN 530
Date:	Sunday, October 26, 2014 11:51:39 PM

Dear Dr. Judith G. Dausch,

Thank you for setting up a teleconference to discuss our GRAS Notice for the extract of Apocynum venetum leaves. The following three members from Tokiwa attended the teleconference on 23, October, 2014.

1. Jin Tatsuzaki
2. Shinichiro Shinkai
3. Jinwei Yang
4. Tsutomu Sasaki

Before sending a cease review letter, we want to make an exact judgment on the present condition. Would you please send us the summary of the conference call at first? Based on the summary, we will consider again, and make a conclusion.

Sincerely yours,

Jin Tatsuzaki / President
Tokiwa Phytochemical Co., Ltd.
158, KINOKO, SAKURA-SHI, CHIBA 285-0801 JAPAN
Tel. 043-498-0025;FAX.043-498-2397

Dausch, Judith wrote:

> Hello Mr. Tatsuzaki,
>
> Thank you for your participation on the call today to discuss the safety review issues with GRN 530 – Extract of *Apocynum venetum* Leaves. Please send me a list of the names of participants from Tokiwa on the call.
>
> **As we discussed, please send me an email requesting that we cease evaluation of GRN 530.** We will then send you a withdrawal letter as a response.
>
> I am working on a summary of the issues we discussed and will be involved in a week-long training all next week, so please allow some time for this follow up summary.

Thank you.

Judy

Judith G. Dausch, Ph.D., R.D.

U.S. Food and Drug Administration

Center for Food Safety and Applied Nutrition

Office of Food Additive Safety, Rm. 2058

5100 Paint Branch Parkway

College Park, MD 20740-3835

E-mail: Judith.Dausch@fda.hhs.gov

Tel: 240-402-2040 Fax: 301-436-2965

From:	Tatsuzaki Jin
To:	Dausch, Judith
Cc:	West-Barnette, Shayla; manta415@tkm.att.ne.jp; k-you@tokiwaph.co.jp
Subject:	Withdraw GRN 530 from FDA review
Date:	Wednesday, November 05, 2014 8:34:23 PM

Dear Dr. Judith G. Dausch,

Thank you for sending us the summary of the previous teleconference.

We appreciate your kind advice on our submitting GRAS Notice. We want to withdraw this GRAS Notice (GRN 530 -for the extract of Apocynum venetum leaves) for FDA review.

We will revise our application document according to the summary, and submit again in the future.

Sincerely yours,

Jin Tatsuzaki / President
Tokiwa Phytochemical Co., Ltd.
158, KINOKO, SAKURA-SHI, CHIBA 285-0801 JAPAN
Tel. +81-43-498-0025 ; FAX. +81-43-498-2397

From:	Tatsuzaki Jin
To:	Dausch, Judith
Cc:	manta415@tkm.att.ne.jp; k-you@tokiwaph.co.jp
Subject:	Re: Withdrawal of GRN 530 - Extract of Apocynum Venetum Leaves - from FDA review
Date:	Wednesday, December 03, 2014 2:19:44 AM

Dear Dr. Judith G. Dausch,

We recieved the letter. Thanks again for all of your supports.

Jin Tatsuzaki / President
Tokiwa Phytochemical Co., Ltd.

Dausch, Judith wrote:

> Dear Mr. Tatsuzaki,
>
> Please see the attached letter that officially acknowledges Tokiwa's request for FDA to cease its evaluation of your GRAS notice.
>
> Thank you.
>
> Judith G. Dausch, Ph.D., R.D.
>
> U.S. Food and Drug Administration
>
> Center for Food Safety and Applied Nutrition
>
> Office of Food Additive Safety, Rm. 2058
>
> 5100 Paint Branch Parkway
>
> College Park, MD 20740-3835
>
> E-mail: Judith.Dausch@fda.hhs.gov
>
> Tel: 240-402-2040 Fax: 301-436-2965