Public Health Service Food and Drug Administration

E. R.C. Hillow Barrenson

# Memorandum

2012 FEB 28 P 2: 10

Date: February 16, 2012

- From: Fred Hines, Consumer Safety Officer, New Dietary Ingredient Review Team, Division of Dietary Supplement Programs, Office of Nutrition, Labeling and Dietary Supplements, HFS-810
- Subject: 75-Day Premarket Notification of New Dietary Ingredients

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To: Dockets Management Branch, HFA-305

Subject of the Notification: Syringa vulgaris extract

Firm: I.R.B. lstituto di Ricerche Biotecnologiche S.p.A.

Date Received by FDA: November 9, 2011

90-Day Date: February 7, 2012

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and

Cosmetic Act, the attached 75-day premarket notification and related correspondence for the

aforementioned substance should be placed on public display in docket number

**FDA-1995-S-0039** as soon possible since the 90-day date is February 7, 2012. Thank you for your assistance.

Fred A. Hines, DVM, CSO

PT737

FDA-1995-5-0039

#### DEPARTMENT OF HEALTH AND HUMAN SERVICES



Public Health Service

Food and Drug Administration 5100 Paint Branch Parkway College Park, Maryland 20740

JAN 2 3 2012

Mr. Roberto Dal Toso I.R.B. Istituto di Ricerche Biotecnologiche S.p.A. Via Lago di Tovel 7 36077 Altavilla Vicentina, Italy

Dear Mr. Dal Toso:

This is to inform you that the notification, dated November 4, 2011, that you submitted pursuant to 21 United States Code (U.S.C.) § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was received and filed by the Food and Drug Administration (FDA) on November 9, 2011. Your notification concerned "Dry extract of *Syringa vulgaris (Lilac)* titrated in verbascoside" derived from cell cultures of the plant, which you identify as a new dietary ingredient that you intend to market in dietary supplement products.

According to your notification, "The recommended dosage for "Dry extract of Syringa vulgaris (Lilac) titrated in verbascoside" is "between 2.5 mg and 25 mg of phenylpropanoids per day for an adult person. "The ingredient is intended for adults and children 12 years of age and older. Not to be given to children under the age of 12 without first consulting a paediatrician. Pregnant woman should not use this ingredient without prior consulting a physician."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary supplement, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

This letter is to inform you that FDA has completed the review of your notification concerning "Dry extract of *Syringa vulgaris (Lilac)* titrated in verbascoside". Your notification does not comply with the requirements of 21 CFR 190.6 and is incomplete. Under 21 CFR 190.6(b)(4), if

#### Page-2- Mr. Roberto Dal Toso

any part of the material submitted in support of the notification is in a foreign language, it shall be accompanied by an accurate and complete English translation. Your notification lacked the complete English translation of material submitted in a foreign language.

Nevertheless, FDA has carefully considered the information in your submission and the agency has significant concerns about the evidence on which you rely to support your conclusion that the dietary supplement product containing "Dry extract of *Syringa vulgaris (Lilac)* titrated in verbascoside" will reasonably be expected to be safe under the conditions of use described in your notification.

FDA was unable to establish the identity of your new dietary ingredient "Dry extract of *Syringa vulgaris* (Lilac) titrated in verbascoside" because you did not provide important information about the source of the plant used to make your new dietary ingredient. For example, you did not provide the part of the plant used to derive your tissue culture or the relationship of tissue cultures of *S. vulgaris* to the plant parts eaten. In addition, you did not describe the composition of your ingredient or the products to which you compare your ingredient. For example, you did not provide HPLC chromatograms to help explain the relationship between your extract and what has been historically consumed as food. In addition, you did not provide a description of the level of your extract in your dietary ingredient, you did not provide only a vague description of the manufacture, and you did not provide a specification for the product. Without such information, it is unclear how the product you intend to market is qualitatively and quantitatively similar to the substances described in the information that you rely on as evidence of safety or how that information forms the basis for a reasonable expectation of safety under the intended conditions of use.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that the dietary supplement containing "Dry extract of Syringa vulgaris (Lilac) titrated in verbascoside", when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of November 9, 2011. After the 90-day date, the notification will be placed on public display at FDA's Division of Docket Management in docket number FDA-1995-S-0039 (formerly docket number 95S-0316) as new dietary ingredient notification report number 737. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration. Page-3- Mr. Roberto Dal Toso

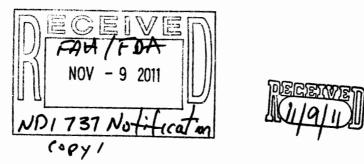
If you have any questions concerning this matter please contact Dr. Fred Hines, Consumer Safety Officer for the New Dietary Ingredient Review Team, at (240) 402-1756.

Sincerely yours,

Dan D. Levy, Ph.D. Microbiologist, Supervisor New Dietary Ingredient Review Team Division of Dietary Supplement Programs Office of Nutrition, Labeling and Dietary Supplements Center for Food Safety and Applied Nutrition



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Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800) Center for Food Safety and Applied Nutrition, Food and Drug Administration

5100 Paint Branch Parkway, College Park, MD 20740-3835 USA

# PRE-MARKET NOTIFICATION OF SYRINGA VULGARIS (Liliac) TISSUE CULTURE EXTRACT AS NEW DIETARY INGREDIENT

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Altavilla Vicentina, 4th November 2011



To:

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800) Center for Food Safety and Applied Nutrition, Food and Drug Administration

5100 Paint Branch Parkway, College Park, MD 20740-3835 USA

Altavilla Vicentina, November 4th, 2011

# Object: Pre-market Notification of Syringa vulgaris tissue culture extract as New Dietary Ingredient

Dear Sirs,

we are hereby submitting a pre-market notification of a new dietary ingredient according to US national regulatory requests.

#### 1) Name and full address of the Manufacturer of the New Dietary Ingredient:

I.R.B. Istituto di Ricerche Biotecnologiche S.p.A. Via Lago di Tovel 7 36077 Altavilla Vicentina, Italy

IRB is registered since 2009 in the FDA Registration of Food Facilities database N° 10876553138

#### 2) Name of the New Dietary Ingredient

Dermasyr 50 and Lilac 50 (for a more detailed description see Attachment 1)

3) Syringa vulgaris L. (common name: Lilac) is widely present in the USA, and was used as food or dietary ingredient before October 14<sup>th</sup>, 1994 (Herbs in Commerce List, revised 9-17-96). Syringa vulgaris extracts from many different tissues (leaves, flowers, buds and bark) are present in many products commercially available in the US market of nutritional supplements. Follows a short list of suppliers for products containing Syringa vulgaris extracts: Rockwell Nutrition, Boiron and Dolisos, Organic Pharmacy, Dynamic Nutritional Associates Labs, Nutraquest, NutritionGeeks, Wellnx Life Sciences and e-shops (Lilo by Hipernatural.com).

The Syringa vulgaris (Lilac) tissue culture extract has been notified to the Ministry of Health in Italy as food supplement (see **Attachment 12**). In Europe, the Dermasyr 50 ingredient from plant tissue culture is present as ingredient in dietary supplements registered in the Italian Registry of Dietary Products (see **Attachment 12**): Verbasyr (code M08 34019-Y) and Acteox (M06 15483-Y



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- 4) In dietary supplements, the recommended daily consumption of phenylpropanoids, expressed as verbascoside, present in the Syringa vulgaris tissue culture extract ingredient should range between 2,5 mg and 25 mg per adult person or above 12 years. Children below 12 years of age and pregnant women should seek medical advice prior to use.
- 5) In USA, there is a history of safe use as dietary supplement for many tissues of the *Syringa vulgaris* (Lilac) plant (bark, leaves, flowers and buds).

The analytical, nutritional and toxicological information that IRB has produced to support the safe use of the *Syringa vulgaris* tissue culture extract are described in **Attachment 1**.

A specific HPLC analysis for phenylpropanoids has been performed

Since the nutritional use of *Syringa vulgaris* (Lilac) plant tissues (blossoms, leaves and buds) extracts is considered to be safe based on a traditional and consolidated use as an ingredient in nutritional supplements, also the tissue culture extracts should be considered to be safe at the recommended conditions of use since the major active phenylpropanoids are the same in plants and tissue cultures and, at the recommended oral daily dosages, do not appear to provide significant toxicological risks.

No genetic modification has been made on the tissue culture.

Acute oral toxicological test performed by OECD 420 has shown no sign of toxicity up to 2g/kg of Syringa vulgaris tissue culture extracts with 50% w/w of phenylpropanoids (commercial name Dermasyr50) and a summary of the toxicological literature to structurally related molecules and metabolic derivatives shows no safety risk at the recommended usage conditions. (see Attachment 7)

A Salmonella typhimurium reverse mutation test with Syringa vulgaris tissue culture extract with 85% w/w of verbascoside resulted negative up to 5 mg/mL (see Attachment 9).

A micronucleus test on human lymphocytes resulted negative up to 62,5 mg/mL of Syringa vulgaris tissue culture extracts with 50% w/w of phenylpropanoids (Lilac 50) (see Attachment 10).

An analytical search for **common environmental pollutants** (pesticides, herbicides, heavy metals and aflatoxins) resulted to be **mostly undetectable** in the tissue culture extract (see **Attachment 11**).

Some **beneficial health biological properties** of *Syringa vulgaris* extracts have been reported and published (see *Mazzon et al 2009* in the Bibliography).

6) Notifications to and registration by the Italian Ministry of Health for commercial sale of Syringa vulgaris tissue culture extracts (Commercial names: Acteox and Dermasyr) are shown in Attachment 12 thus supporting that the new dietary ingredient, when used under the recommended conditions, will reasonably be expected to be safe.



7) Contact person designated by the manufacturer

Dr. Roberto Dal Toso IRB SpA, Via Lago di Tovel 7, 36077 Altavilla Vicentina, Italy Tel: +39-0444-371463 Fax: +39-0444-371465 e-mail: r.daltoso@irbtech.com

We are convinced that the information provided is sufficient supportive evidence that Syringa vulgaris (Lilac) tissue culture extracts are reasonably expected to be safe at the recommended conditions of use.

In any case we are open to provide any further information that might be required.

Kind Regards

Roberto Dal Toso

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# I.R.B. Istituto di Ricerche Biotecnologiche S.p.A. (Institute of Biotechnological Research Inc.)

# NDI PREMARKET SAFETY NOTIFICATION

### DIETARY INGREDIENT OF Syringa vulgaris EXTRACTS TITRATED IN VERBASCOSIDE DERIVED FROM PLANT TISSUE CULTURE

Altavilla Vicentina, 4th November 2011

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### INTRODUCTION

IRB is a **dietary ingredient supplier**, it commercializes through its distributors, plant tissue culture extracts to final nutritional supplement manufacturers. IRB will not commercialize any ingredient or product directly to the end consumer.

In this dossier, IRB intends to provide supportive evidence for the safe dietary use of *Syringa vulgaris* (*Lilac*) extracts obtained from plant tissue cultures **as dietary ingredient**.

The dry extract obtained either from the plant or the plant tissue culture of *Syringa vulgaris* can be titrated in phenylpropanoids, their active ingredient. It is upon the quali-quantitative presence of these compounds that the study of the extracts obtained by cell cultures with those obtained from fresh shoots of plants cultivated by traditional means is based.

Phenylpropanoids, mainly verbascoside and its analogues, extracted from *Syringa vulgaris* tissue culture and all the substances detectable by the HPLC analytical method employed were identified. None of the substances identified and none of the known potential metabolites and metabolic derivatives harbor a risk of toxicity at the recommended dosages.

Finally, manufacture by biotechnological fermentation permits a greater standardization, obviating seasonal variation and reducing the presence of endogenous undesirable substances and environmental contaminants. These characteristics constitute the basis of the substantial equivalence between the *Syringa vulgaris* extracts obtained by tissue culture fermentation and those traditionally in use.





# **1. ADMINISTRATIVE DETAILS OF THE APPLICANT**

Name:	I.R.B. Istituto di Ricerche Biotecnologiche S.p.A.
Address:	Via Lago di Tovel, 7
	36077 Altavilla Vicentina (VI)
Phone n°:	+39-0444-371463
Fax n°:	+39-0444-371465
Contact:	Dr. Roberto Dal Toso
E-mail:	r.daltoso@irbtech.com

Name of ingredient: Dry extract of Syringa vulgaris (Lilac) titrated in verbascoside

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### 2. COMPOSITION OF THE SYRINGA VULGARIS EXTRACT

#### 2.1. Botanical notes

Scientific denomination: Syringa vulgaris L.

#### Family: Oleaceae

Common names: Lilac, Common lilac

*Etymology*: the scientific name originates in ancient Greece mythology. Syringa was a beautiful nymph of Arthemide with which the goddess used to hunt in the green and fragrant woods that in that period were covering the Peloponnese.

*Morphology*: Lilac is a perennial, deciduous shrub that grows between twelve to sixteen feet tall. The leaves are simple, ovate to broadly ovate, and five to twelve centimetres long. The flowers are mostly white, lilac, or purple, pleasantly fragrant in long terminal panicles.

Habitat and flowering: Common lilac is native of Europe, in the Balkan area, and naturalized in the United States, escapes from cultivation from New York to North Dakota, south to Georgia and Kansas. Lilac is easily grown on most soil types but prefers neutral to slightly acid soil. This species does not tolerate poorly drained soils. It performs best in a warm sunny position.

*Properties and uses*: Economic: A green dye is obtained from the flowers and the leaves and a yellow-orange dye is obtained from the twigs. An essential oil is obtained from the flowers and used in perfume fragrances.

Ethnobotanic: The bark and leaves has been chewed as a treatment for sore mouth.

Syringa vulgaris is widely used as a food and dietary supplement as well as glycerolic extracts for gemmo-therapy. Several dietary supplements coming from, or containing, a variety of *Syringa vulgaris* plant tissues are now, or have been, on the market in the USA provided by Rockwell Nutrition, Boiron, Organic Pharmacy, Dynamic Nutritional Associates Labs, Nutraquest, Dolisos, NutritionGeeks, Wellnx Life Sciences and e-shops (Lilo by Hipernatural.com).

All tissues of *Syringa vulgaris* plants are used in food natural and nutritional supplements preparations (University of Arkansas, Division of Agriculture), but buds are mainly used for glycerolic extracts (Unda Seroyal, USA). *Syringa vulgaris* has also been reported as in USA as dietary ingredient prior to October 14, 1994 (by American Herbal Products Association 1996).

Relevant web-pages of the quoted companies and documents are found in Attachment 2.



### 2.2. IRB technology for the production of plant tissue culture extracts

IRB obtains *Syringa vulgaris* botanical extracts by **plant tissue culture** biotechnology. A flow-chart illustrating this process is shown in *Figure 1*.

In brief, the first step in obtaining a new plant cell line is sterilization of the tissue from the desired species. This phase is necessary to remove all micro-organisms (bacteria, funguses and molds) that could alter or impede the development of the culture from the plant tissue. The sterilized plant tissue is then cut into minute fragments (explants) and deposited in Petri dishes containing a nutritious, antibiotic-free solid medium supplemented with growth regulators.

Culturing the explanted tissue results in the generation of disorganized aggregates of undifferentiated cells known as calluses, which are maintained by regular transfer to fresh medium. Via these repeated transfers, over time, aggregates of rapidly growing cells are obtained.

This procedure permits the generation of a **non-GM** plant cell culture in that no genetic engineering procedures to modify the plant genome are carried out.

The biomass expanded in a bioreactor containing the sterile liquid culture is then mechanically homogenized and filtered; the filtrate is extracted to concentrate the desired metabolites on an XAD4 resin and eluted with a hydroalcoholic solution (ethyl alcohol). The powder form of the final extract is obtained by evaporation of the hydroalcoholic solution and freeze-drying of the residual aqueous solution.

The technology of secondary metabolite production with plant cell cultures has been widely described (*Vanisree Mulabagal and Tsay H.S., Plant Cell Cultures - An Alternative and Efficient Source for the Production of Biologically Important Secondary Metabolites Int. J. Appl. Sci. Eng. 2004. 2, 1: 29-48*) and a brief outline of the process as performed in IRB, including the tissue culture medium, is described in **Attachment 3**.



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### 4. METABOLISM AND TOXICOLOGY

As reported by the Division of Agriculture of the University of Arkansas, the Lilac (Syringa vulgaris) has been classified to Toxicity Category 4 - plants are generally considered non-toxic to humans.

The extract of *Syringa vulgaris* produced by IRB from plant tissue cultures as well as containing the carbohydrates, lipids and proteins typical of the plant, contains 3 predominant species of phenylpropanoids which have been completely characterized and are known for their safety at the recommended dosages for oral administration.

The main phenylpropanoid, i.e. verbascoside, present may produce, via enzymatic digestion and gastroenteric, hematic or cellular metabolism, several functional residues, namely caffeic acid, ferulic acid and hydroxytyrosol, and the common monosaccharides glucose and rhamnose None of these substances have been shown to have adverse effects at the recommended dosage for use as a nutritional ingredient.

Furthermore, **verbascoside has a large structural similarity to echinacoside**, another widely used nutritional ingredient, due to the presence of the same monosaccharide molecules (glucose and rhamnose), as well as caffeic acid and hydroxytyrosol. As yet, no toxic effects linked to the oral administration of echinacoside at the recommended dosage for use as a nutritional supplement have been reported. Data from the literature (see **Attachment 6**) regarding the known compounds (verbascoside, caffeic acid, hydroxytyrosol, glucose, rhamnose and galactose).

Regarding extracts from *Syringa vulgaris* culture with 50% verbascoside (w/w) (Biolab Report SAM2075i, see Attachment 7), show the absence of acute oral toxicity, in the rat, of a single oral administration of 2 g/kg (Class 5/NC of GHS classification).

Long term (three months) clinical studies with 18 mg daily oral administration of verbascoside and 150 mg of echinacoside three times daily have been carried out by Oryza Oil&Fat Chemical Co in Japan with a food grade extract of *Cistanche tubulosa* (P25) with no sign of toxicity on the human subjects. Thus oral supplementation up to 54 mg of verbascoside and 450 mg of echinacoside a day for 3 months has proven to be non toxic (Attachment 8).

Another long term "life span" treatment with purified verbascoside dissolved at up to 2.56 mg/mL in the drinking water of fruit flies (*Drosophila melanogaster*) showed **no signs of toxicity** and actually resulted in a **statistically significant increase in the life span** of both male and female flies (Pan et al 2008)

A mutagenesis test performed by the **Salmonella typhimurium Reverse Mutation assay**, with an without S9 activiation, on a *Syringa vulgaris* extract with 85% verbascoside (w/w) (Biolab Report SAM4014i, see Attachment 8) was **negative up to 5 mg/mL (Attachment 9)**.

Furthermore, a **micronucleus test** has been performed with a lilac tissue culture extract 50% in verbascoside on human peripheral blood lymphocytes with **no evidence of genotoxic effects effect up to 62.5 mg/L** (31,2 mg/L of verbascoside) (AD34GV 349 BTL Final Report see **Attachment 10**).

Several scientific articles report for the anti-mutagenic and DNA repair activity of verbascoside (Shi et al. 2000; Gao et al. 2003; Zhang et al. 2008; Fabiani et al. 2008).



One scientific article by Santoro et al. 2008 reports that increased Sister Chromatid Exchange in cultured human lymphocytes by treatment with verbascoside, with the effects becoming apparent "in vitro" with treatments at 0.05 mM of pure verbascoside. This concentration is equivalent to 31.2 mg/L of verbascoside, which are respectively 80 and 8 times above the 2.5 mg to 25 mg (equivalent to 0.03 mg/kg to 0.43 mg/kg for a man of 70 kg of weight) daily oral dosage recommended. No genotoxic effect was apparent at 0.01mM (equivalent to 6.24 mg/L of verbascoside).

Santoro et al. 2008 also suggest that caffeic acid may be the main chemical residue mediating this effect. Caffeic acid is the typical phenolic residue present in verbascoside, as well as in echinacoside and chlorogenic acid. Echinacoside is widely used as food supplement in *Echinacea angustifolia* root extracts and in an epidemiological study no increase of teratogenic risk has been reported during pregnanacy (*Perri et al. 2006*). Furthermore, up to 220 mg of chlorogenic acids are present in each 200 mL cup of instant coffee (*Farrell et al. 2011*), and no general awareness of any genotoxic threat of chlorogenic acids is available when taken by oral administration. Caffeic acid itself, has also bee tested for "in vitro" genotoxicity and has been shown to produce no damage to DNA in a Comet test up to 1500 uM (i.e. 13.5 g/L of caffeic acid) and no effect on the micronucleus test in hepatocytes up to 50uM (9 mg/L of caffeic acid equivalent to 31.2 mg/L of verbascoside) (*Maistro et al. 2011*), in substantial agreement with the previously mentioned test made with lilac tissue culture extract 50% in verbascoside (AD34GV 349 BTL Final Report **Attachment 10**).

A similar, but even more evident discrepancy between "in vitro" genotoxic results and *in vivo* has been described for quercetin and green tea catechins, other polyphenols widely present in dietary products and food. For quercetin a number of *in vitro* genotoxic tests, including the Ames's test, have indicated a potential mutagenic activity of quercetin. Additionally, in hamster and mouse cells and human lymphocytes, quercetin exposure induced chromosomal aberrations, DNA single strand breaks, and micronucleus formation (*Harwood et al. 2007*). The main structural feature for these actions appears to be 1) the ortho-dihydroxy catechol group of the B-ring and 2) the 2-3 double bond in the C-ring. These chemical features appear to be very similar to the caffeic acid structure.

The results of quercetin-related mutagenicity/genotoxicity observed in vitro have not been confirmed by in vivo experiments. With oral administration to mice and rats, quercetin consistently did not induce any significant changes in several mutagenicity/genotoxicity endpoints (i.e., micronuclei, chromosomal aberrations, sister chromatid exchange, unscheduled DNA synthesis, and alkali-labile DNA damage) in somatic cells in comparison to untreated controls (*Harwood et al. 2007*). Analogously for green tea catechins, where positive *in vitro* tests (i.e. chromosomal aberration assay and mouse lymphoma L5178/tk assay), have not been confirmed to occur by *in vivo* assays up to daily dosages of 2000 mg/kg (*Ogura et al. 2008*).

As suggested by Long LH et al. 2007 for the apparent *in vitro* mutagenic and clastogenic effects of epigallocatechin gallate (EGCG) on CHO cells, one possible explanation is the formation of  $H_2O_2$  in the culture mediam by interaction of the test chemicals with components of the cell-culture media used, so that different tissue culture media result in different genotoxic effects.

A similar phenomenon has been observed for quercetin (*Long et al. 2000*) and for EGCG on HaCat cells by *Elbling et al. 2011*. In this later *in vitro* study, **the same concentration of EGCG was yielding different genotoxic outcomes depending on the ratio of cell number to medium working volume**.



Long LH 2007 also suggests that: "most or all of the apparent toxicity and clastogenicity of EGCG on CHO cells is an artifact" and a similar explanation might occur also for the apparent "in vitro" genotoxicity of other polyphenols (i.e. quercetin, caffeic acid and verbascoside).

Stability studies performed on the freeze-dried final product have demonstrated that phenylpropanoids are over 95% stable over three years of conservation in a dry environment at 25°C.

### 5. INTENDED USE

The consolidated traditional use of the *Syringa vulgaris* plant, in particular the young spring leaves, blossoms and bark, is for nutritional purposes and traditional medicinal applications. However, there is no general protocol for the preparation and use of *Syringa vularis* plant tissue extracts.

Specific final product application and health claims are to be provided by the nutritional supplement manufacturer.

The intended use of a *Syringa vulgaris* extract titrated in phenylpropanoids is as **an ingredient in nutritional supplements**. The recommended dosage for *Syringa vulgaris* extracts as a nutritional ingredient is between **2.5 mg and 25 mg of phenylpropanoids per day for an adult person** (if weight is 70 kg this equals to, approximately, 0.04 mg/kg and 0.28 mg/kg).

The ingredient can be provide both at 50% (w/w) and at 10% (w/w) and standardized by addition of food grade maltodextrins as required.

Commercial names of the ingredient: Dermasyr 50 and Lilac 50

Name of commercially available dietary supplements in Europe:

Verbasyr (code M 0834019-Y of Italian Reg Nutritionals) commercialized by Asleton and Acteox (code M 06 15483-Y of Italian Reg Nutritionals) commercialized by Biofarma. (See Attachment 12)

The ingredient is intended for adults and children 12 years of age and older. Not to be given to children under the age of 12 without first consulting a paediatrician. Pregnant woman should not use this ingredient without prior consulting a physician.

### 6. LEVEL OF UNDESIRABLE SUBSTANCES

Syringa vulgaris tissue cultures were assessed for the presence of a wide variety of insecticides, fungicides, herbicides, mycotoxins and heavy metals. All of the undesirable substances analyzed were **undetected** in the Syringa vulgaris tissue culture extract as a result of the production process (see **Attachment 11**).



### 7. OTHER RELEVANT INFORMATION

Syringa vulgaris tissue culture extract titrated in phenylpropanoids has been tested by oral administration (0.2 mg/kg and 2 mg/kg) in a rat model of colitis with significant normalization of all altered parameters (*Mazzon et al. 2009*).

Notifications of commercial nutritional supplements (Verbasyr and Acteox) to the Ministry of Health in Italy and the list of registered nutritional supplements in Italy are reported in **Attachment 12**.

#### CONCLUSIONS

From traditional use, scientific literature and toxicological data the Syringa vulgaris plant and Syringa vulgaris tissue culture extracts titrated in verbascoside, the main polyphenolic component, appear to be reasonably safe when used as dietary ingredients as recommended.

The reported data confirm that the Syringa vulgaris (Lilac) tissue culture extract titrated in verbascoside and developed by IRB appears to be well characterized for the qualitative and quantitative level of the phenylpropanoids present. Furthermore, thanks to the plant cell culture technology, the ingredient is highly standardized composition, reproducible in quality and free of environmental contaminants which further increases safety margins.





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Education of the

Attach2

### **Toxic Plants Listed on Plant Materials List**

From: A Rational Guide to Plant Toxicity by Richard Kingston, Phar. D., Minnesota Regional Poison Center, Ramsey Medical Center, St. Paul, Minnesota and professor at the University of Minnesota

Lilac (Syringa vulgaris)

Toxicity Category 4 - plants are generally considered non-toxic to humans.

Link to: http://www.aragriculture.org/horticulture/ornamentals/toxic\_plants.htm

## Herbs in Commerce in the United States as Dietary Ingredients prior to October 14, 1994

dealers a stark

### (Alphabetical Listing by Species Botanical Name)

### Prepared by the American Herbal Products Association (revised 9/17/96)

Abelmoschus esculentus Abelmoschus moschatus (Medik.) Abias webbiana Abrus precatorius Abutilon indicum Acacia catechu Willd Acacla concinna D.C. Acacia farnesiana Willd. Acacia leucophlaea Willd. Acacia senegal Acacia seyal Acacia vera Acacia arabica, Linn. Acalypha Indica Acanthopanax sessiliflorus Acanthopanax gracilistylus Acanthospermum hispidium Acanthus virilis Acer spicatum Achillea millefolium L. Achyranthes bidentata Bl. Achyranthus aspera Linn. Aconitum columbianum Aconitum ferox Wall. Aconitum heterophylium Wall. Aconitum nepellus L. Aconitum plamatum Aconitum carmichaelii Debx. Acorus calamus L. Acorus gramineus Soland. Adenophora tetraphylla (Thunb.) Fisch. Adenophorus stricta Miq. Adhatoda vasica Adiantum capillus - veneris L. Adiantum lunulatum Adiantum pedatum L. Adonis vernalis Aesculus hippocastanum L. Aframomum melegueta (Roscoe) ♠K. Schumann Agastache rugosa (Fisch. et Mey.) O. Ktze. Agalhosma betulina Agathosma crenulata Agati grandiflora Agave americana Agkistrodon aculus Aglala roxburghlana, Miq. Agrimonia gryposepala Agrimonia pilosa

4

Agrimonia eupatoria L. Agropyron repens Ailanthus altissima Ailanthus excelsa Akebia quinata Decne. Akebia trifoliata Alangium decapetalum Albizzia lebbek Benth. Albizzia julibrissin Durazz. Alcea rosea L. Alchemilia xanthochiora Rothm. Aichemilia vulgaris auct. non L. Alchornea rugosa Alchornea villosa Aletris farinosa L. Alhagi camelorum Fisch. Alisma orientale (Sam.) Juzepczuk Alisma plantago-aquatica L. var. orientale Sam Alkanna tinctoria (L.) Tausch Allium tuberosum Allium ascalonicum Allium cepa Linn. Allium sativum L. Allium schoenoprasum L. Aloe barbadensis Mill. Aloe vera (L.) N.L. Burm. Aloe ferox Mill. Aloe littoralis Aloe spicata Aloysia triphylla (L'HÅr.) Britton Alpinia chinensis Alpinia galanga (L.) Willd. Alpinia katsumadai Alpinia officinarum Hance Alpinia oxyphylla Alstonia boonel Alstonia scholaris R. Br. Alstornia constricta Althaea officinalis L. Amaranthus spinosus Amaryllis beliadona Linn. Ambrosia artemislilolia Ammi visnaga Amomum subulatum Amomum tsao-ko Crev. et. Lem. Amomum villosum Amomum xanthioides Amomum cardamomum Amomum krervanh Amomum melegueta Roscoe 2

Amorphophallus campanulatus Amorphophallus konjac Amyda sinensis Amygdalus persica Amygdalus communis Anacardium occidentale Anacycius pyrethrum Anagallis arvensis Ananas comosus Anaphalis margaritacea (L.) Benth. & J.D. Hook. Andrographis paniculata Andropogon citratus Andropogon gayanus Kunih. Andropogon jwarancusa Andropogon muricatus Andropogon aciculatus Anemarrhena asphodeloides Bge. Anemone pulsatilla Anemone hepatica Anemone pratensis Anemopsis californica (Nutt.) Hook. & Arn. Anethum graveolens L. Angelica pubescens Maxim. Angelica sinensis (Oliv.) Dies Angelica polymorpha Maxim. Angelica archangelica L. Angelica atropurpurea L. Angelica dahurica (Fischer ex Hoffm.)Franch. et Sav. Angelica glauca, Edgw. Anthemis cotula Anthemis nobilis Anthriscus cerefolium (L.) Hoffm. Apium graveolens L. Apocynum cannabinum L. Apocynum frutescens Apocynum androsaemifolium L. Apondanthera smllacifolia Aquilaria agallocha Aquilaria sinensis Arachis hypogaea Aralia nudicaulis L. Aralia racemosa L. Aralia californica Wats. Aralia hispida Arctium lappa L Arctium minus Arctostaphylos uva-ursi (L.) Spreng.

Stephania tetrandra S. Moore Sterculia acuminata Stereospermum suaveolens D.C. Stevia ivaefolia Stevia rebaudiana (Bertoni) Hemsi. Sticta pulmonaria Stillingia sylvatica Garden ex L. Strychnos nux-vomica, L. Strychnos potatorum Styrax benzoin Dryander Styrax paralleloneurum Perkins Styrax tonkinensis (Pierre) Cralb. et Hartw. Swertia chirayita Swertia radiata Symphytum officinale L. Symphytum x uplandicum Nyman Symplocarpus foetidus (L.) Salisb.ex Nutt. Symplocos theaefolia Symplocos racemosa, Roxb. Syringia vulgaris Syzygium jambolana Lam. Syzyglum jambos Syzygium aromaticum (L. M) err. & L. M. Perry Syzygium cumini Skeels Syzygium jambolana DC. Tabebula heptaphylla (Vell.) Toledo Tabebula impetiginosa (Mart. ex DC.) Standi. Tabebuia avellanedae auct. Tacca aspera Roxb. Tagates erecta Tagates lucida Tamarindus Indica Tamarlx gallica Tanacetum parthenium (L.) Schultz-Bip. Tanacetum vulgare L. Taraxacum mongolicum Taraxacum officinale G.H.Weber ex Wigg. Taraxacum densiconis Taxus baccata, Linn. Tecoma undulata **Tectona grandis** Tephrosia purpurea (Linn.) Pers. Tephrosia villosa Terminalla arjuna Bedd. Terminalia bellerica (Gaertn.) Roxb. Terminalia chebula (Gaertn.) Retz.. Temstroemia pringlel (Rose) Teucrium chamaedrys L. Teucrium scorodonia L. Thea sinensis Thelesperman trifidum Theobroma cacao L.

Thonningla sanguinea Thuja orientalis L., Thuja occidentalis L. Thuja plicata Thymus serpyllum Thymus vulgaris L. Thymus xcitrlodorus (Pers.) Schreb. Tilia x europaea L. Tilia platyphyllos Scop Tillandsia usneoides Timida Tsen et Lee Tinospora cordilolia Tinospora sinensis Trachyspermum ammi Tradescentia diuretica Trametes versicotor Tremella fuciformis Trianosperma tayuya Mart. Tribulus terrestris, Linn. Tribulus lenuginosus Tribulus aey Trichillia barraensis Trichosanthis Kirliowli Trifolium pratense L Trifolium repens Trigonella foenum-graecum L. Trillium erectum L. Trillium ovatum Tripterygium wilfordil Triticum aestivum L. Tropaeolum minus Turnera diffusa Willd. ex Schult. Turnera aphrodisiaca (Ward)Urban Turnera orpifera Tussilago fartara L. Tylophora asthmatica Tynnanthus elegans Ulmus rubra Muhl. Ulmus Julva Michx. Uncaria gambir (Hunter) Roxb. Uncaria rhyncholphylla Unicaria tomentosa (Wilid.) DC, Urtica californica Urtica dioica L. Urtiga urens Usnea barbata (L.) Wigg. Usnea californica Usnea longissima ach. Usnea subfloridiana Vaccaria segetalis Vaccinium corymbosum L. Vaccinlum myrtillus L. Vaccinium pallidum Alton Vaccinium angustilolium Aiton Vaccinum oxycoccos Valeriana officinalis L. Valeriana sitchensis Bong. Valeriana wallichil DC. Valeriana edulis Nutt, ex Torr. & A.

Gray Valeriana edulis procera (Kunth) F. G. Meyer Vanilla planifolia Andr. Vanilla tahitensis J. W. Moore Vascularis luffae Veratrum viride Aiton Verbascum thapsus L. Verbena hastata L. Verbena leucostachys Verbena officinalis L. Veronia cinerea Veronica officinalis L. Veronicastrum virginicum (L.) Farwell Vetiveria zizaniodes (L.) Nash Viburnum prunifolium L. Viburnum opulus L. Vinca major Vinca minor L. Vinca rosea Viola cucullata Viola odorata L Viola sororia Willd. Viola papilionacea Pursh pro parte Viola tricolor L. Viscum album L. Viscum flavescens Vitex agnus-castus L. Vitex negundo Linn. Vitis rotundifolia Vitis trifolia Vitis vinifera Withania somnilera Dunal. Wolfiporia cocos (Schwein.) Ryv. & Gilbn. Xanthium sibiricum Xanthorhiza simplicissima Marshall Xylaria nigripes Xylopla sethiopica Yucca glauca Nutt. Yucca whipplei Torr. in Emory Yucca aloitolia L. Yucca baccata Yucca brevilolla Engelm. in Wats. Zanthoxylum alatum, Roxb. Zanthoxylum americanum Mill. Zanthoxylum clava-herculis L. Zanthoxylum rhetsa, Llnn. Zanthoxylum simulans Hance Zea mays L. Zeyheria montana Zinglber officinale Roscoe Ziziphus joazeiro Ziziphus jujuba Mill. Ziziphus spinosa Hu Ziziphus jujuba var. spinosa Hu Ziziphus vulgaris, Linn.



January 12, 1998

Linda S. Kahl, Ph.D. Office of Special Nutritionals 1716 Center For Food Safety and Applied Nutrition Food and Drug Administration 200 "C" St., S.W. (HFS-450) Washington, D.C. 20204

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The herbal supplement for which the statement is made is Common Lilac (Syringa Vulgaris). The statement of nutritional support reads as follows:

Herbal support for the heart.

This statement is accompanied by the required disclaimer which is prominently displayed in **bold-faced type**.

This statement of nutritional support is based on data which renders these statements substantiated, truthful, and non-misleading.

Sincerely,

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William Nicoletti, R. Ph. President

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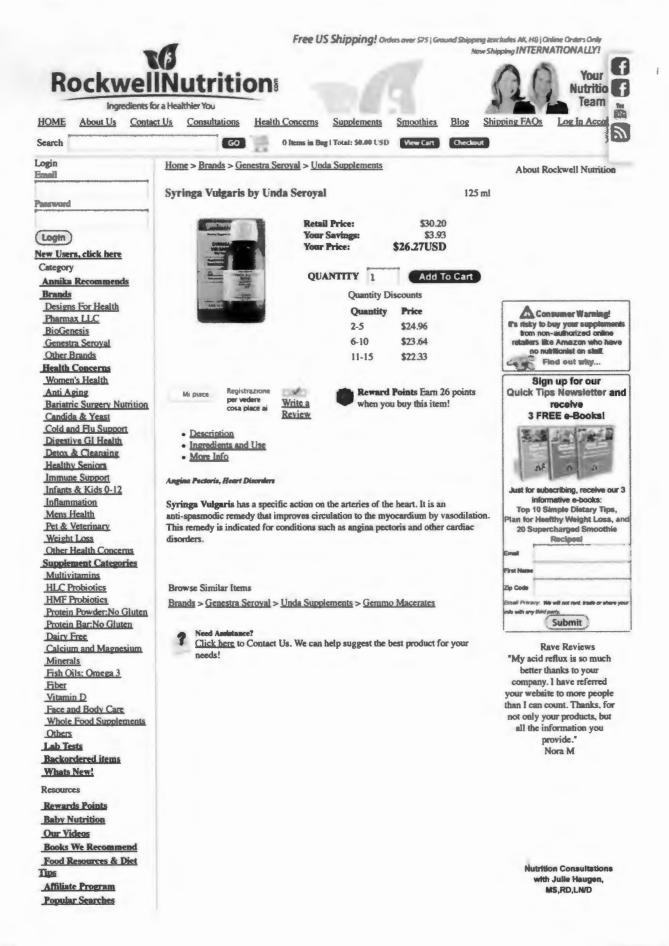
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EXTRACT NAME	INCI	CAS	EINECS	
LEMON FRUIT EXTRACT	Citrus Medica Limonum (Lemon) Fruit Extract	84929-31-7	284- 515-8	
LEMONGRASS EXTRACT	Cymbopogon Schoenanthus Extract	89998-16-3	289-754-1 (1)	
LEMON PEEL EXTRACT	Citrus Medica Limonum (Lemon) Peel Extract	84929-31-7	284- 515-8	
LEMON THYME EXTRACT	Thymus Citriodorus Extract	None	None	
LEMON VERBENA EXTRACT	Lippia Citriodora Flower Extract	85116-63-8	285-515-0	
LETTUCE EXTRACT	Lactuca Scariola Sativa (Lettuce Leaf) Extract	84776-66-9	283-995-6	
LICHEN EXTRACT	Usnea Barbata (Lichen) Extract	84696-53-7	283-658-3	
LIFE EVERLASTING EXTRACT	Helichrysum Stoechas Extract	None	None	
LILAC EXTRACT	Syringa Vulgaris (Lilac) Extract	90063-50-6	290-008-2	
LILY OF THE VALLEY EXTRACT	Convalleria Majalis Extract	None	None	
LIME FRUIT EXTRACT	Citrus Aurantifolia (Lime) Fruit Extract	90063-52-8	290-010-3	
LIME PEEL EXTRACT	Citrus Aurantifolia (Lime) Peel Extract	90063-52-8	290-010-3	
LINDEN FLOWER EXTRACT	Tilia Cordata Flower Extract	84929-52-2	284-536-2	
LICORICE EXTRACT	Glycynthiza Glabra (Licorice) Root Extract	84775-66-6	283-895-2	
LITCHI EXTRACT	Litchi Chinensis Fruit Extract	91722-81-5	294-483-7	
LOTUS FLOWER EXTRACT	Nelumbo Nucifera Flower Extract	85085-51-4	285-379-2	
LOVAGE EXTRACT	Levisticum Officinale Root Extract	None	None	
LYCIUM EXTRACT	Lycium Chinensis Fruit Extract	913545-16-1	None	
MACA EXTRACT	Lepidium Meyenii Root Extract	None	None	
MACADAMIA NUT EXTRACT	Macadamia Ternifolia Seed Extract	None	None	
MADDER ROOT EXTRACT	Rubia Tinctorum Root Extract	None	None	
MAGNOLIA EXTRACT	Magnolia Biondii Flower Extract	85085-47-8	285-376-6	
MAGNOLIA FLOWER EXTRACT	Magnolia Liliflora Extract	246536-69-6	None	
MAIDENHAIR FERN EXTRACT	Adiantum Capillus Veneris Leaf Extract	84649-72-9	283-457-0	
MALLOW EXTRACT	Maiva Syvestris (Mallow) Extract	84082-57-5	282-003-9	
MANDARIN EXTRACT	Citrus Nobilis (Mandarin Orange) Peel Extract	90063-83-5	N/A	
MANGO EXTRACT	Mangifera Indica (Mango) Fruit Extract	90063-86-8	290-045-4	
MANGOSTEEN EXTRACT	Garcinia Mangostana Peel Extract	90045-25-3	289-884-9 (1)	
MARIGOLD EXTRACT	Calendula Officinalis Flower Extract	84776-23-8	283-949-5	
MARJORAM EXTRACT	Origanum Majorana Leaf Extract	84082-58-6	282-004-4	
MARSHMALLOW EXTRACT	Althaea Officinalis Root Extract	73049-65-7	277-254-6	
MATE EXTRACT	llex Paraguariensis Leaf Extract	84082-59-7 / 73296-98-7	277-364-4	
MEADOW SWEET EXTRACT	Spiraea Ulmaria Extract	84775-57-5	283-886-3	
MELILOT EXTRACT	Melilotus Officinalis Extract	84082-81-5	282-028-5	
MELON EXTRACT	Cucumis Melo (Melon) Fruit Extract	90063-94-8	290-054-3	
MILK PROTEIN EXTRACT	Casein Extract	None	None	

Syringa Vulgaris by Unda Seroyal

http://www.rockwellnutrition.com/syringa-vulgaris-by-unda-s...



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Suggested Use

### Syringa vulgaris Lilac PFAF Plant Database

http://www.pfaf.org/user/Plant.aspx?LatinName=Syringa+vul ...

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The leaves and the fruit are antiperiodic, febrifuge, tonic and vermifuge[4]. The bank or leaves have been chewed by children as a treatment for sore mouth[257].

#### Syringa vulgaris Lilac PFAF Plant Database

#### Steet Water

the American Indian States States

An essential oil is obtained from the flowers. Used in perfumery(171). A green dye is obtained from the flowers(166), Green and brown dyes can be obtained from the terige(166). Plants can be grown as an informal hedge(200). The plant is often used as a rootstock for the various ornamental cultivers of liter. Its main disedventage is that it can sucker very freely(200).

#### Cultivation details

Succeeds in most soils, including chafk, but dislikes acid soils[11]. Prefers a deep stiff well-drained loam in a werm surmy position[11, 200]. A very ormamental plant[1], it does tand to sucker quite freely though[200]. There are many named variaties, developed for their ormamental value[162]. The flowers attract butterflies and moths[30]. Plants in this genus are notably susceptible to honey fungue[200].

#### Propagation

Seed - sow March in a north facing cold frame. Pre-treating the seed with 4 weeks warm then 3 weeks cold stratification improves garmination. It is probable that sowing the seed as soon as it is ripe in a cold frame would be a more reliable method[4]. Prick the seedings out into individual pots once they are large enough to handle. Plant them out in the summer if sufficient growth has been made, otherwise grow them on in a cold frame for their first winter and plant out in late spring of the following year. Cuttings of young shoots, 7cm with a heel, June in a frame[200]. Cuttings of half-ripe wood, 7cm with a heel, July/August in a frame[200]. Levering in spring before new growth begins. Takes 12 months[78]. Division of suckers in late winter. They can be planted straight out into their permanent positions.

Expert community

#adhor

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Betanical References

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Links / References

(K) Ken Fern Notes from observations, tasting etc at Plants For A Future and on field trips.

[1]F. Chittendon. RHS Dictionary of Plants plus Supplement. 1956

Comprehensive listing of species and how to grow them. Somewhat outdated, it has been replaces in 1982 by a new dictionary (see [200]). (4)Grieve. A Modern Herbel.

Not so modern (1930's?) but lots of information, mainly temperate plants.

[11]Bean. W. Trees and Shrubs Hardy in Great Britain. Vol 1 - 4 and Supplement.

A classic with a weelth of information on the plants, but poor on pictures.

(17)Clapham, Tootin and Warburg. Flora of the British Isles.

A very comprehensive flora, the standard reference book but it has no pictures.

(30)Carter D. Butterflies and Moths in Britain and Europe.

#### Readers comment.

#### Elizabeth H.

Etienne Van Rattingen Thu Apr 22 09:16:38 2004 coronairsciercees, angine pectoris, techycardia, aritmic heart, decompensatio cordia.

#### Eizebeth H.

Dr. Sudhir Mestri Fri Jun 3 04:45:13 2005

If you can suggest me a supplier of genuine liles flower all (Syringe Vulgeris), pieces let me know. I am interested in buying the all. You can send me the details on admestri@bateera.com. Thenks. Dr. Suchir Meetri

Elizabeth H.

Deidre Wille Wed Apr 16 2008

Syringe vulgeris grows in zones 4b, 4e and 3b in the USA.

Elizabeth H. Mon Apr 27 2009

They bloom in the epring

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#### syringa vulgaris

Plant Biology Researchers Corn and plant experts needed With experie Fresh Flowers Wholesale? Fresh Quality Flowers for florists and restaur Tibetan Organic Cordyceps Best Quality 100% Guaranteed Order Now,



English name: Lilac

#### **Description:**

Shrub of the family of oleáceas that reaches up to 4 mt. tall, very petiolated segments with leaves, whole, ACORAZONADO and pointy, soft tissue and nerve; purple flowers of course, except in the variety that has white, fragrant, tubular corolla of heading into four equal lobes and large bouquets upright and Conical and capsular fruit, compressed, black coriaceous, with two seeds. The leaves are used medicinally, fruit and bark.

#### Habitat:

Originates in Turkey and Persia and is cultivated in temperate zones of Europe



### BetaStax Review | Buy It, User Reviews, Forum, Ratings

	etspotlight						Like Dietap	ollight For Special Offers1 -> Mi place
860	3 Diet Articles and Counting						Over 21	2 Thousand Trusted Vistor Reviews & Opinion
owse Diets A-Z	BetaStax Review					siglia	this on Google	You may also like
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Reviews C	Nuchedrine P99X	22221	(4.6) (4.5)	NA		1	4	TOP AS TONSE
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Reviews F	website, which is helpful. There i	s also a pag	e of test	imonials v	with before	and after	photos.	today and noticed that (more)
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Reviews T-V	Product Features							weighed in at 177 (more)
Reviews V-Y	As with many other dietary sup morning and afternoon meals, a							
Reviews Y-2	is also encouraged. Two caps container). Unfortunately the cos is noted that BetaStax can be pu	ules of Bet at of this proc	aStax is fuct is n	s a servis lot reveale	ng (60 ca ad on the	psules in vebsite. H	a single	
	Continue Your Weight Loss Res							
	Advantages							
	There are stores listed out or     There are some testimonials				n be purch	ased.		
	Disadvantages							
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	Conclusion							
	The official websile for BetaStat be nice to see some clinical downside, there is no price quo this diet product does contain	trial results ted for Beta	pertain Stax, wh	ing to the	is weight raise a fe	loss drug v eyebrow	on the	



SlimQuick Appetite Control

http://www.supplementworld.co.za/slimquick-appetite-control ...



You will earn 70 Points for buying this product

Control Appetite

Appetite suppressant designed specifically for a woman's body.

**Manufacturer's Description** 

SLIMQUICK® Appetite Control packets are an appetite suppressant designed specifically for a woman's body in a delicious Pink Lemonade flavour Designed for Women. Helps address 6 weys for controlling appetite; promotes a longer feeling of fullness, reduces appetite, provides an excellent source of fibre, provides a good source of protein, improves digestion and provides problotics. Contains 5 g of protein and 5 g of fiber. Caffeine free.

Promote a longer feeling of FULLNESS- Promoting feelings of fullness are vital to successfully controlling appetite and supporting weight-loss efforts. SLIMQUICK® Appetite
Control helps promote a feeling of fullness to control portion size and reduce caloric intake.

Reduce APPETITE- Reduced caloric intake is a key factor in any weight-loss program. Ingredients used for Appetite Control have been included in SLIMQUICK® Appetite
Control to help women reduce their delity calorie consumption and stick to a healthy eating plan.

Provide an excellent source of FIBER- Increased fibre intaks is an important strategy for any weight-loss program to help reduce appetite throughout the day. SLIMQUICK®
Appetite Control is an excellent source of fibre, providing 5 g of fibre per serving.

Provide a good source of PROTEIN- Increasing the amount of protein in your diet has a beneficial effect on suppressing appetite. SLIMQUICK® Appetite Control is a good source of protein, providing 5 g of protein per serving.

Improve DIGESTION- A healthy, properly functioning digestive tract is more in tune with the body's signals for hunger and thirst, and is better able to control food intake.
 SLIMQUICKB Appstite Control contains ingredients to help improve digestion.

Provide PREBIOTICS- Prebiotics help improve the ecology of the digestive tract, which benefits overall health SLIMQUICK® Appetite Control is formulated with prebiotic fibre to help improve the overall health of the digestive tract.

#### **Recommended Usage**

 As a dietary supplement, slowly pour 1 powder packet (15 g) of SLIMQUICK® Appetite Control and 16.9 ft.oz. (500 mL) of cold water into a leak resistant container and shake vigorously until mixed, let ait briefly, re-shake and enjoy.

• If adding to a full bottle of water, take a few big sips (removing approximately 2 fl.oz. or 60 mL) prior to adding contents, shake vigorously until mixed, let sit briefly, re-shake

#### and enjoy.

For the first 3 days take one serving 30-80 minutes prior to dinner. On the 4th day and onward, take one serving 30-60 minutes prior to lunch and one serving 30-60 minutes prior to dinner.

· Do not exceed 3 servings in a 24-hour period.

- SLIMQUICK® Appetite Control should be used as part of a sensible low-fat diet high in protein and fibre, and regular exercise program.

#### **Nutritional Values**

Nutritional Information:	Serving Size: 15 grams (1 pecket) Servings per Container: 14		
	Amount per Berving	1% Daily Value	
Calories	35		
Total Carbohydrates	8g	3%	
Distary Fiber	59	20%	
Sugars	<1g	t	
Protein	5g	10%	
Folais (as Folic Acid)	200 mcg	50%	
Chromium (as Chromium Trichtoride Hexahydrate)	300mcg	250%	
Simquick Appetite Control 6 ways Natural weight loss support blend	12.2g	t	
Whey Protein Concentrate (milk)		t	
leulin (Estishation trighna) (noit)		t	
Synetrim [Rice Extract (Oryza sativa) (bran) [10% Fatty Acids], Fenugreek Extract (Trigonella foenum graecum) (seed) [8% Gelectomernen], Astragelus membranaceus L.) (root) [5% polysaccherides], Tribulus Extract (Tribulus terrestria) (fruit) [5% Seponins], Megnolia Extract (Magnolia officinalis) (seria parts) [2% Honotiol], Lilac extract (Syringa vulgaria) (whole plent) [5% seponins], Goat's Rue (Galega officinalist) (whole plant) [5% Seponins], Jojoba Extract (Simmondsia chinensist) (fruit), Phellodendron Extract(Phellodendron amurenee) (leaf and stem) ]2% Berberine], Eurycoma longifolia Extract (whole plant) [1% Seponins], Rice Extract (Oryza sativa) (bran)		Ť	
Gineeng Extract (Panex gineeng) (root) [10% Gineenoeides]		t†	
Chase Tree Extract (View agnus-cestus) (fruit)		1	

#### Ingredients

Other Ingredients: Maltodextrin, citric acid, natural and artificial flavore, tri-calcium phosphate, sorbitol, acesultame potassium, natural color, sucratose, allicon dioxide.

#### Disclaimer

#### KEEP OUT OF REACH OF CHILDREN.

Do not use if you are pregnant or nursing. Not intended for use by persons under 19. Consult a physician before using this product if you have been treated for or diagnosed with, or have a family history of any medical condition including but not limited to diabetes, or are taking monoamine coldese (NAO) inhibitors or anti-congulants or if you are taking any prescription drug or over-the-counter medication.

Use only as directed. Do not exceed recommended serving, as improper use of this product does not enhance results. Do not use if powder packet has been opened. Store in a cool dry place.

Healthy Indulgence Slender Nutrition - Hero Nutritionals

http://www.akins.com/shop/product\_view.asp?id=260739&St ....



for carbohydrates, protein, fibers, polyphenols, polysaccharides and fatty acids), Astragalus Root (Astragalus membranaceus L.) Extract (standardized for polysaccharides), Vegetable Wax (Oryza sativa) extract (standardized for galactomannan), Jojoba Fruit (Simmondsia chinensis) Extract (standardized for phenolics), Tribulus Fruit (Tribulus terrestris) Extract (standardized for phenolics), Tribulus Fruit (Tribulus terrestris) Extract (standardized for saponins), Lilac Whole Plant (Syringa vulgaris) Extract, Goat's Rue (Galega officinalis) Extract (standardized for saponins), Magnolia Bark (Magnolia officinalis) Extract (standardized for honokid), Phellodendron Leaf and Stem (Phellodendron amurense) Extract (standardized for saponins). Other Ingredients: Dark chocolate (cocoa liquor,

#### Who Says You Can't Eat The Flowers : Morgan Botanicals

#### http://www.localharvest.org/blog/25051/entry/eating\_the\_flowers



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#### Morgan Botanicals (Tehachapi, California)

Herbal Information and Recipes

[Member listing]

« Sea Kale: The Perenn.. | Main | Basil: The Beneficia... »

15 Oct · Thu 2009

#### Who Says You Can't Eat The Flowers



There are so many flowers that can be eaten. The culinary use of flowers dates back thousands of years to the Chinese, Greek and Romans. Today there is a resurgence of interest in edible flowers, and I can see why. Flowers add texture, interest, and beauty to dishes that could otherwise be simply boring.

Collect your flowers at the optimum time. Pick them when they are fully open in the coolest part of the day. Flowers that are not fully open (unless buds are desired) or those starting to wilt should be avoided. Sample a flower or two for flavor before harvesting. Remove the pistils and stamens because the pollen can detract from the flavor of the flower as well as cause allergic reactions in susceptible individuals.

After harvest, place long-stemmed flowers in water and then in a cool location. Short stemmed flowers should be placed between layers of damp paper toweling or in a plastic bag in the refrigerator. Immediately before using, gently wash the flowers to remove dirt and check for insects.

It is important to know what part of the flower is edible before consuming. Only the petals of some flowers such as Rose, Tulip, Yucca and Lavender are edible. Separate the flower petals from the rest of the flower just prior to use to keep wilting to a minimum. Roses, Dianthus, English daisies, and Marigolds have a bitter white area at the base of the petal where it was attached to the flower. Break or cut off this portion before using. With a little research and a cutinary imagination, you can change your ordinary dish into a culinary masterpiece!

#### Here's a list of flowers known for culinary use:

- Calendula (Calendula officinalis)
- · Carnations (Dianthus caryophyllus
- · Chrysanthemums (Chrysanthemum coronarium)
- Clover (Trifolium species)
- · Comflower (Centaurea cynaus)
- · Dame's Rocket (Hesperis matronalis)
- · Dandelions (Taraxacum officinalis)
- Day Lilies (Hemerocallis species)
- · English Daisy (Bellis perennis)
- Apple Blossoms (Malus species)
- Banana Blossoms (Musa paradisiaca)
- · Citrus Blossoms (orange, lemon, lime, grapefruit, kumquat)
- · Elderberry Blossoms (Sembucus spp)
- · Fuchsia (Fuchsia X hybrida)
- · Garden Sorrel (Rumex acetosa)
- · Gladiolus (Gladiolus spp)
- · Alliums (leeks, chives, garlic, garlic chives)
- Angelica (Angelica archangelica)
- Anise Hyssop (Agastache foeniculum)
- Basil (Oclmum basilicum)
- · Bee Balm (Monarda didyma)
- · Borage (Borago officinalis)
- · Burnet (Sanquisorba minor)
- · Chervil (Anthriscus cerefolium)

Calendar

« October 2011										
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#### Who Says You Can't Eat The Flowers : Morgan Botanicals

- · Chicory (Cichorium mtybus)
- Cilantro/Conander (Coriander sativum)
- · Chamomile (Chamaemelum noblis)
- · Dill (Anethum)
- · Fennel (Foeniculum vulgare)
- Ginger (Zingiber officinale)
- · Jasmine (jasmine officinale)
- Lavender (Lavandula angustifolia)
- · Lemon Verbena (Aloysia triphylla)
- Marjoram (Origanum majorana)
- · Mint (Mentha spp)
- · Oregano (Origanum vulgare)
- Rosemary (Rosmarinus officinalis)
- · Safflower (Carthamus tinctonus)
- Sage (Salvia officinalis)
- · Savory (Satureja hortensis)
- · Thyme (Thymus spp.)
- Hibiscus (Hibiscus rosa-sinensis)
- Hollyhock (Alcea rosea)
- Honeysuckle (Lonicers japonica)
- Hyacinth (Brodiaea douglasii)
- Impatiens (Impatiens wallerans)
- Johnny-Jump-Ups (Viola tricolor)
- Lilac (Syringa vulgaris)
- Linden (Tilla spp.)
- · Marigold (Tagetes tenuifolia aka T. signata)
- Nasturtiums Tropaeolum majus)
- · Pansy (Viola X wittrockiana)
- · Peony (Paeonia lactifiora)
- · Phlox, Perrennial Phlox (Phlox paniculata)
- · Pineapple Guave (Feijoa sellowians)
- · Primose (Primule vulgaris)
- Queen Anne's Lace (Daucus carot
- · Roses (Rosa rugosa or R. gallica officinalis)
- Scented Geraniums (Pelargonium species)
- Snap Dragon (Antimhinum majus)
- · Sunflower (Helianthus annus)
- Sweet Woodruff (Galium odoratum)
- Tulip Petals (Tulipe)
- · Arugula (Eruca vesicaria)
- Radish Flowers (Raphanus sativus)
- Scarlet Runner Beans (Phaseolus vulgaris)
- · Pea Blossoms (Pisum species)
- Squash Blossoms (Curcubita pepo)
- · Violets (Viola species)
- Yucca Petals (Yucca species)

Only eat flowers that have been positively identified and you are sure they are edible. If uncertain, consult a good reference book on edible flowers prior to consumption.

Please email any questions to herbalist@morganbotanicals.com.

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BetaStax<sup>na</sup> provides a powerful blo-chemical edge to help you achieve serious results from your diet and training program. Its cutting edge PUREWAYSLIM® blend has been shown to promote significant weight-loss results in as early as 2 weeks in a recent university clinical study.\*\* Suggested Use: Take 2 capsules prior to morning meat and 2 capsules prior to mid-attempon meal with 8 ounces of water. Do not take in the evening. Do not exceed 4 capsules per day. Begin use with one half the suggested serving for the first week (1 capsule twice per day). For best results, use as part of a sensible diet and exercise program. Consult your medical doctor prior to beginning any diet or exercise program.

#### KEEP OUT OF REACH OF CHILDREN

Wall, NJ 07719

#### CAUTION: READ AND FOLLOW ALL LABEL INSTRUCTIONS PRIOR TO USE. NOT FOR USE BY INDIVIDUALS UNDER 18.

WARNING: Do not use if pregnant or nursing. Consult your medical doctor before use if you are taking any prescription or over-the-counter medications, or if you have been treated for or have a family history of any medical conditions including, but not limited to, hypertension. One serving of this product contains as much calielne as approximately 2 cupe of collee. Do not consume



synephrine or catteine from other sources including but not limited to coffee, lea, soda, and other dietary supplements or medications containing phenylephrine, or other stimulants. Recommended cycle length is 8 weeks, followed by a 1 week break. Discontinue use and consult your doctor immediately if any adverse reactions occur. Discontinue 2 weeks prior to surgery. Use only as directed. Do not use if imprinted seal under cap is broken or missing.

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DIETARY SUPPLEMENT 120 LIQUID CAPS

Amount Per Serving	70 LJ	aily Vi	HUØ**
Calories		7	
Calories from Fat		7	+
Calories from Saturated Fat		0	7
Total Fat		0.7 g	
Saturated Fat		0.1 g	1%
Trans Fat		0 g	†
Monounsaturated Fat		0.2 g	+
Polyunsaturated Fat		0.4 g	Ť
Vitamin 8-1 (as Sulbutiamine)			0,000%
Chromium (as Chromemate® chromium polynic	obnate) 21	0 mcg	167%
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Food and cosmetic ingredients with tonics, memory improving, anti-aging, anti-fatigue, anti-sex dysfunction, immune boosting and fat metabolism accelerating properties

# I STANDE TUBLICEA EXTRACT-P25

(Walter-soluble Rowder, Food Grade)

I STANDE TUBLICEA EXTRACT-PC25

(Water-soluble Powder, Cosmetic Grade)

ORYZA OIL & FAT CHEMICAL CO., LTD.

Ver. 1.0 JT

Attach 8



# Improve Memory Anti-aging,-fatigue CISTANCHE TUBULOSA EXTRACT

### 1. Introduction

Cistanche Tubulosa (Schenk) R. Wight is a plant that parasitizes the roots of Tamarix. Since it has no root or chloroplast, it cannot photosynthesize (Fig. 1). Therefore, it grows by absorbing the nutrition out of plants it parasitizes. In China, Cistanche Tubulosa is known as a rare Panax ginseng found in deserts and used as a pharmaceutical to cure Alzheimer's disease. In Japan, Cistanche Tubulosa has been categorized as a food after its food/pharmaceutical classification was revised by the Health, Labor and Welfare Ministry in 2005. It belongs to Cistanche, Orobanchaceae, same as the parasitic plant Cistanche salsa used in Chinese herbal medicine. According to the Chinese Comprehensive Pharmaceutical Dictionary, it supplements renal function, increases sexual power, and smoothes the intestines. The dictionary also states that it treats impotence, infertility, menstrual disorder, and psychroalgia of the back and knees. Cistanche salsa has been widely used clinically as a prescribed drug for supplementing renal function and nutritional fortification in China. However, collecting the valuable crude drug Cistanche salsa (certified as a class 2 national protected plant) has become difficult recently. Therefore, there is a growing awareness about Cistanche Tubulosa which belongs to the same family and has been reported to have similar effects and functions as Cistanche salsa.

Cistanche Tubulosa grows in the Takla Makan Desert in Hsinchiang Uighur Autonomous Region, China. It has a very strong vital energy to flower and fruit under severe desert conditions (Fig. 2). Its host tamarix grows to 6 meters tall and has small, dark pink flowers. This plant is used to protect against wind and sand (prevents the spread of yellow sand) in desert regions. Cistanche Tubulosa is now considered to be the key to greenification of deserts and prevention of global warming and the Chinese government recommends the incubation of Cistanche Tubulosa to stimulate local industries.

According to Mr. Keiichi Morishita's report, the Hotan region, an oasis in the Takla Makan Desert, has one of the four longest life expectancies in the world. The percentage of elderly people that live to be over one-hundred years old in this region is the highest in China, over three times that of Okinawa Prefecture in Japan which is famous for its people's longevity. Per 100,000 people, Okinawa has 51 people aged over 100 and Hotan has 183 such people. People of the Hotan region eat Cistanche Tubulosa daily and prepare it by slicing and then boiling with mutton in a pot or pickling it in tea or liquor in order to survive the harsh environmental conditions of the region. This habit is believed to be the key of people's longevity in the region.

Oryza Oil & Chemical Co., Ltd. studied Cistanche Tubulosa extract jointly with Sinphar Pharmaceutical Co., Ltd. (pharmaceutical company in Taiwan) with the assistance of Peking University. Sinphar Pharmaceutical Co., Ltd. established a raw

ingredient production base and also a subsidiary 新疆天力砂生薬物有限公司 in Hotan. The company implements GAP plantation of Cistanche Tubulosa to stably provide high-quality, pesticide-free raw material. The company's products are safe and extremely stable in quality. Moreover, its products have been certified as organic foods by the government and raised in GMP facilities. Through joint research, we have discovered that Cistanche Tubulosa extract has activities to prevent aging of the brain and skin, increase sexual power, and accelerate fat metabolism in addition to its known activities. Sinphar Pharmaceutical Co., Ltd. and Peking University have also discovered that the extract has activities to improve brain functions, prevent aging or fatigue, and boost immune strength from test data accumulated in their long-term study.

Our Cistanche Tubulosa extract is the highest concentration ever (echinacoside 25% min, acteoside 9% min). We believe that the extract can be used in a wide variety of foods and cosmetics as a new ingredient to improve brain functions, vitalize the body, and enhance beauty.



#### Fig. 1 Cistanche Tubulosa



Fig. 2 Hsinchiang Uighur Autonomous Region (GAP plantation)

# 2. Functional Components of Cistanche Tubulosa

The main effective ingredients of Cistanche Tubulosa extract are phenylethanoid glycosides, especially echinacoside and acteoside (Fig. 3). Although echinacoside is known as the main component of the herb Echinacea, Cistanche Tubulosa contains a higher amount of echinacoside than any other plant. Acteoside (a type of polyphenols) has an extremely strong antioxidative property which is reported to be 15 times stronger than resveratrol (polyphenols contained in grapes) and 5 times stronger than vitamin  $C^{1}$ . In recent study, new compounds (kankanoside and others) have been isolated<sup>2)</sup> and

been vasorelaxing activity has reported as a pharmacological action of the new compounds, echinacoside, and acteoside<sup>3)</sup>. Active constituents in extracts of Cistanche salsa and Cistanche Tubulosa that belong to the same family, were compared and it was clarified that Cistanche Tubulosa has more active constituents (Fig. 4). Cistanche Tubulosa extract with high active quantity of constituents performs various bioactive functions as described below.

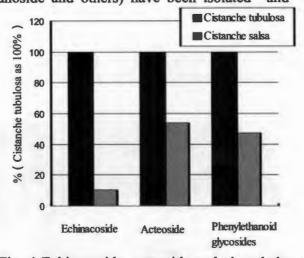
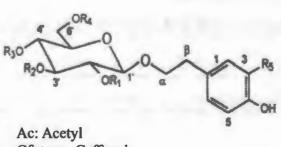


Fig. 4 Echinacoside, acteoside and phenylethanoid glycosides content of Cistanche salsa and Cistanche tubulosa

Compound Name	RI	R2	R3	R4	RS
2'-Acetylacteoside	Ac	Rha	Cľ	H	OH
Acteoside	H	Rha	Cf	H	OH
Cistanoside A	H	Rha	Cf	Glc	OMe
Cistanoside C	H	Rha	Cf	H	OMe
Echinacoside	H	Rha	Cf	Glc	OH
Isoacteoside	H	Rha	H	Cf	OH
Tubuloside A	Ac	Rha	Cf	Gl¢	OH



Cf: trans-Caffeoyl Glc: β -D-Glucopyranose Rha: α -L-Rhamnopyranose

Fig. 3 Components of Cistanche Tubulosa Extract

#### References

- 1) Kanebo : news release, 2005.
- 2) Haihui Xie et al., Chem. Pharm. Bull., 54(5), 669-675, 2006.
- 3) Yoshikawa M., et al., Bioorg. Med. Chem., 14(22), 7468-7475, 2006.

# **Bioactivities of Cistanche Tubulosa Extract**

# (1) Improvement of brain function

1) Improvement of learning and memory (in vivo)
2) Anti-apoptosis activity (in vitro) p.8
3) Rescue human fibroblasts (in vitro)
4) Prevent aging of the brain (in vitro)
5) Influence on cerebral ischemia-reperfusion (in vivo)
6) Increase the amount of brain neurotransmitters (in vivo)
7) Prevent cerebral infarction and myocardial infarction (in vivo)
8) Clinical Trial (Phase I-III) ······p.18

# (2) Anti-aging effect

1) Free Radical Scavenging Ability (in vitro) p.23
2) Enhances SOD activity and prevent lipid peroxidation (in vivo)
3) Cistanche species on peroxidation (in vitro, in vivo)
4) Anti-aging effect on aging mouse model (in vivo)

# (3) Skin beautifying effect

1) Inhibition of hyaluronidase (in vitro) · · · · · · · · · · · · · · · · · · p.2	28
2) Prevention of Photo-ageing of Skin (in vivo)	29

# (4) Anti-fatigue

Anti-fatigue of	mice (in	vivo)·····	p.31
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# (5) Aphrodisiac effect

1) Effects of the constituents of Cistanchis herba on sex behavior in stressed mice (in	
vivo)p.33	
2) Enhance male hormone production (in vitro, in vivo)	

# (6) Immune boosting effect

The effect of Cistanche Tubulosa extract on mouse lymphatic cells (in vivo) · · · · p.38

# (7) Metabolism enhancing effect

1)	e effect on cholesterol metabolism (in vivo) · · · · · · · · · · · · · · · · · · p.	.39
2)	e Effect of Cistanche Tubulosa Extract on Fatty Acid Metabolism (in vivo) . p.	.41

# (8) Antioxidant Activities

SOD-like Activity and DPPH Radical Scavenger Activity (in vitro) ..... p.43



#### 8) Clinical Trial (Phase I-III, Data from Sinphar group)

#### **OPhase I**

<b>Experimental Group</b>	1	2	3	4	5	6	7
Dosage (mg, single)	150	300	600	900	1500	1800	2400
Increasing times	1	2	4	6	10	12	16
Nos. of subject	2	4	6	6	4	4	4

1.1 Toxicity Test on Single Dose Administration (Oral)

Nos. of subject : 30

Method : Oral (Echinacoside 25%, Acteoside 3%)

Result :

There was no abnormal change in body temperature, breathing frequency, heart rate, systolic arterial pressure, diastolic pressure, hepatic/renal functions, fasting blood glucose level, blood in general, urine in general, stool in general, or electrocardiogram on any subject people. There was no side effect on groups during the test. The result confirmed the safety of the extract in single administration on normal persons.

1.2 Toxicity Test on Continuous Administration (Oral)

Nos. of subject : 12

105. 01 Subject . 12	Gloup	1	7	
Research centers:成都漢方医薬大学付属病院	Dosage (mg/times)	600	900	
Duration: 10days (Start: 2001.11)	Nos. of subject	6	6	

Group

Dosage : Oral Administration (three times a day) (Echinacoside 25%, Acteoside 3%) Result :

There was no abnormal change in body temperature, breathing frequency, heart rate, systolic arterial pressure, diastolic pressure, hepatic/renal functions, fasting blood glucose level, blood in general, urine in general, stool in general, or electrocardiogram on any subject people. There was no side effect on groups during the test. The result confirmed the safety of the extract in continuous administration on normal persons.

#### 1.3 Conclusion

There was no side effect or abnormal change in observation parameters during single and continuous administration safety tests conducted in phase I of Cistanche Tubulosa extract clinical test. This clarified that the extract would be safe to use in further clinical tests (Phase II, III). In phase II and III of the clinical tests, the extract was orally given to subject people three times a day. The dose was 600 mg per time (echinacoside 25% min, acteoside 3% min).



#### **@Phase II**

2.1 Method : According to the test method approved by the Ethics Committee, double blind tests were carried out at five research institutions. Subject patients were separated into two groups: a group to take Cistanche Tubulosa extract and another group to take the positive control (pharmaceutical product, Hydergine<sup>1</sup>). Administration was carried out over three months. Through the observation of subjects' cognitive functions (mini mental state examination: MMSE), social ability (berg balance scale: BBS), and ability of daily living (ADL) and physical examination by a doctor before and after the administration, the influence of Cistanche Tubulosa extract on clinical treatment of vascular dementia was evaluated, comparing to the positive control group. Safety of the extract for clinical treatments was evaluated at the same time.

Research institutions: 福建省漢方医薬研究院, 戸州医学院付属漢方病院, 陜 西漢方医薬大学付属病院, 西安市漢方病院, 成都漢方医薬大学付属病院。 Duration: 2002.3~2002.10

2.2 Nos. of subject : Cistanche Tubulosa extract : 120

Positive control (pharmaceutical product, Hydergine) : 120 Dosing period : Three months Dosage : Oral Administration (600 mg, three times a day)

- 2.3 Result
- 2.3.1 Efficacy result

Efficacy ratio	MMSE	BBS	ADL	Symptoms
Cistanche Tubulosa Extract	75.66%	66.09%	50.43%	84.35%
Positive control	72.32%	54.46%	40.18%	70.54%

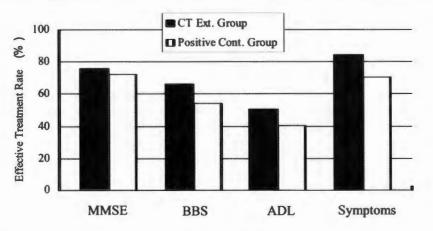


Fig. 21. The Treatment Effect of Cistanche Tubulosa Extract (CT Ext.) vs. Positive Control Group (Phase II)



#### CISTANCHE TUBULOSA EXTRACT CATALOG ver.1.0 JT

Cardiovascular Disease / Patient's Review	Treatment Rate	Improve	No changes	Worse
Mild (46 subjects)	63.04%	-	34.78%	2.17%
Moderate (61 subjects)	34.43%	44.26%	21.31%	0.00%
High (9 subjects)	22.22%	55.56%	22.22%	-

2.3.2 Analysis on the Efficacy & Safety of Cistanche Tubulosa on Vascular Dementia

1. Cistanche Tubulosa Extract demonstrated effective treatment rate in patients with moderate symptoms of the diseases compared with positive control group.

2. Treatment rate of Cistanche Tubulosa Extract is similar to that in positive control group in patients with severe symptoms of the diseases.

2.3.3 Efficacy result of each facility

In the phase II of Cistanche Tubulosa extract clinical test on vascular dementia patients, there was no significant difference in results among the five research institutions (p>0.05). This indicates that the effectiveness of the extract was the same in each research institution.

#### 2.4 Long-term efficacy

Three months after the completion of the phase II clinical test, a survey was carried out to learn about Cistanche Tubulosa extract's long-term effectiveness on vascular dementia. The subject patients' cognitive function was examined at their homes. As a result, cognitive function of the subjects who took Cistanche Tubulosa extract remained the same or even improved three months later. The efficacy rate was 90.32%. The efficacy rate of the positive control was 78.05%. At the survey visiting the patients who took Cistanche Tubulosa extract, the score to evaluate their cognitive function was 7.89±4.40 points higher than the score before the administration and  $0.35\pm2.95$  points higher than the score at the completion of the administration. The score to evaluate cognitive function of the patients who took the positive control was  $5.73\pm3.23$  points higher than the score at the completion of the administration. The score was  $0.80\pm1.58$ points lower than the score at the completion of the administration. The results show a significant difference between the two groups (p<0.05) and indicate that long-term effectiveness of Cistanche Tubulosa extract is higher than the positive control.

#### 2.5 Safety evaluation

Before and after the administration, blood in general, urine in general, stool in general, hepatic function (ALT), renal function (BUN, Cr), and electrocardiogram of subjects of both groups were analyzed. As a result, Cistanche Tubulosa extract was confirmed to have no negative influence on safety indexes. Although there was a significant difference in the influence on electrocardiogram (p<0.05) as compared to the positive control (Hydergine), there was no significant difference in other safety indexes (p>0.05).

#### 2.6 Conclusion

Results of the clinical tests described above indicate that Cistanche Tubulosa extract is effective for treatment of vascular dementia. Since no toxicity or side effect was seen during the clinical tests, Cistanche Tubulosa extract was confirmed to be safe for treatment of vascular dementia as well.



#### **③Phase III**

3.1 Method : According to the test method approved by the Ethics Committee, double blind tests were carried out at four research institutions. Subject patients were separated into two groups: a group to take Cistanche Tubulosa extract and another group to take the positive control (Hydergine). Administration was carried out over three months. Through the observation of subjects' cognitive functions (mini mental state examination: MMSE), social ability (berg balance scale: BBS), and ability of daily living (ADL) and physical examination by a doctor before and after the administration, the influence of Cistanche Tubulosa extract on clinical treatment of vascular dementia was evaluated, comparing to the positive control group. Safety of the extract for clinical treatments was evaluated at the same time.

Research institutions:成都漢方医薬大学付属病院,西安市漢方病院,戸州医学院付属漢方病院,福建省漢方医薬研究院。

Duration : 2002.12~2003.8

3.2 Nos. of subject : Cistanche Tubulosa extract : 333

Positive control (pharmaceutical product, Hydergine) : 111

Dosing period : Three months

Dosage : Oral Administration (600 mg, three times a day)

- 3.3 Result
- 3.3.1 Efficacy result

Efficacy ratio	MMSE	BBS	ADL	Symptoms
Cistanche Tubulosa Extract	77.74%	72.10%	57.37%	91.19%
Positive control	64.15%	62.26%	38.68%	66.98%

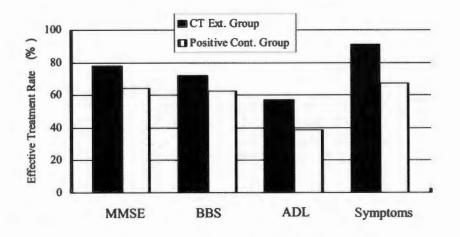


Fig. 22. The Treatment Effect of Cistanche Tubulosa Extract (CT Ext.) vs. Positive Control Group (Phase III)



#### CISTANCHE TUBULOSA EXTRACT CATALOG ver.1.0 JT

Cardiovascular Disease / Patient's Review	Treatment Rate	Improve	No changes	Worse
Mild (137 subjects)	83.94%	-	16.06%	0.00%
Moderate (182 subjects)	37.36%	49.45%	13.19%	0.00%
High (3 subjects)	66.67%	33.33%	0.00%	-

3.3.2 Analysis on the Efficacy & Safety of Cistanche Tubulosa on Vascular Dementia

1. Cistanche Tubulosa Extract is more effective in patients with moderate symptoms of the diseases compared with positive control group.

2. No significant difference was observed on patients with severe symptoms when compared with positive control group.

#### 3.3.3 Efficacy result of each facility

In the phase III of Cistanche Tubulosa extract clinical test on vascular dementia patients, there was no significant difference in results among the four research institutions (p>0.05). This indicates that the effectiveness of the extract was the same in each research institution.

#### 3.4 Long-term efficacy

Three months after the completion of the phase III clinical test, a survey was carried out to learn about Cistanche Tubulosa extract's long-term effectiveness on vascular dementia. The subject patients' cognitive function was examined at their homes. As a result, cognitive function of the subjects who took Cistanche Tubulosa extract remained the same or even improved three months later. The efficacy rate was 64.71%. The efficacy rate of the positive control was 69.77%. At the survey visiting the patients who took Cistanche Tubulosa extract, the score to evaluate their cognitive function was  $5.39\pm3.26$  points higher than the score before the administration and  $1.71\pm2.43$  points higher than the score at the completion of the positive control was  $4.47\pm2.70$  points higher than the score before the administration. The score was  $1.47\pm1.84$ points lower than the score at the completion of the administration.

#### 3.5 Safety evaluation

As a result, Cistanche Tubulosa extract was confirmed to have no negative influence on safety indexes.

#### 3.6 Conclusion

Results of the clinical tests described above indicate that Cistanche Tubulosa extract is effective for treatment of vascular dementia. Since no toxicity or side effect was seen during the clinical tests, Cistanche Tubulosa extract was confirmed to be safe for treatment of vascular dementia as well.

#### \*1: Hydergine (Nonproprietary name : Dihydroergotoxine mesylate)

A drug to improve brain metabolism and peripheral blood circulation. It improves blood flow by releasing vascular tone and dilating blood vessels. It also accelerates oxygen and blood supply to the brain and improves metabolism of brain cells.

**CISTANCHE TUBULOSA EXTRACT CATALOG ver.1.0 JT** 

#### (3) Acute toxicity test (LD<sub>50</sub>)

Acute Toxicity test was conducted according to the Guidelines for Single-Dose Toxicity Tests for Pharmaceutical Products. Cistanche Tubulosa Extract was orally administered to male and female mice at 26.4 g/kg and kept for 8 days. No abnormalities and fatal event observed at 26.4 g/kg. Upon autopsy no abnormalities were observed. Thus,  $LD_{50}$  of Cistanche Tubulosa Extract is deduced to be >26.4 g/kg in both male and female mice.

Furthermore,  $LD_{50}$  of Cistanche Tubulosa Extract is deduced to be >17.6 g/kg in both male and female rats.

#### (4) Genotoxicity

#### 1 Ames test

Ames test showed no difference of the colony counting in TA97, TA98, TA100 and TA102 strains with or without Cistanche Tubulosa Extract (8-5000  $\mu$ g/plate).

② Micronucleus test

Micronucleus test of polychromatic erythrocyte in mice marrow showed that Cistanche Tubulosa Extract (2.5-10 g/kg) has no damage effects to bone marrow cells.

#### ③ Teratogenicity test

Teratogenic test showed Cistanche Tubulosa Extract (2.5-10 g/kg) has no teratogenesis to mice spermatozoon.

#### (5) Sub-acute Toxicity

Cistanche Tubulosa Extract was orally administered to male and female rats at 0.65-1.30 g/kg and kept for 30 days. No abnormalities and fatal event were observed at 0.65-1.30 g/kg. Upon autopsy no abnormalities were observed.

#### (6) Long-term toxicity

Cistanche Tubulosa Extract was orally administered to male and female rats at 1.65 g/kg and kept for 180 days. No abnormalities and fatal event were observed at 1.65 g/kg. Upon autopsy no abnormalities were observed.

Furthermore, Cistanche Tubulosa Extract was orally administered to male and female beagle dogs at 1.50 g/kg and kept for 180 days. No abnormalities and fatal event were observed at 1.50 g/kg. Upon autopsy no abnormalities were observed.

CISTANCHE TUBULOSA EXTRACT CATALOG ver.1.0 JT

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# 7. Recommended Daily Dosage

The recommended daily dosage for Cistanche Tubulosa Extract-P25 is 100-400 mg/day.

# 8. Applications

	Applications	Claims	Examples
Foods	Brain function improving food Tonic food Beauty food	<ol> <li>Improve of brain function</li> <li>Tonic</li> <li>Anti-aging</li> <li>Anti- fatigue</li> </ol>	Beverages, hard & soft capsules, tablets, candies, chewing gums, chocolates, wafers, jellies etc
Cosmetics	Beauty cosmetic	5) Aphrodisiac 6) Beauty	Body lotions, body gel etc.

# 9. Packaging

CISTANCHE TUBULOSA EXTRACT-P25 (Water-soluble, for food) CISTANCHE TUBULOSA EXTRACT-PC25 (Water-soluble, for cosmetic) 5kg Interior packaging : Aluminum bag

Exterior packaging : Cardboard

# 10. Storage

Store in cool and dry dark place.

# 11. Expression

<Food>

CISTANCHE TUBULOSA EXTRACT-P25 Expression: CISTANCHE TUBULOSA EXTRACT

# AktuchR

REGISTRO INTEGRATORI PER PROD PRODOTTO (FASE 0)V8.0 LA FORMULA INTEGRAL ANTIOXIDANTE		CODICE
(FASE 0)V8.1 LA FORMULA INTEGRAL NUTRITIVA	SEPAI BEAUTICEUTICAL DIVISIO	N M 10 44040 1
+ 3/	SEPAI BEAUTICEUTICAL DIVISIO	N N 10 44040 M
01 TISANA PREPASTO	ERBORISTERIA DOTT. CECCHIN	E 06 22130-Y
02 TISANA DURVILLEA GLACIALE	GIANLUCA MECH	E 11 45903-Y
04 TISANA BALSAMICA	GIANLUCA MECH	E 11 45747-Y
05	GIANLUCA MECH	E 11 45740 V
05 BOMBER	LABORATORIO TERAPEUTICO M.	R. N 11 51993-Y
1 AL GIORNO	CLOROFILLA	X AD 09803-Y
1 P	INDEL	X AD 01032-Y
100% CREAPURE DEGUSSA	ERBA VITA ITALIA	E 08 35501-Y
100% CREATINA MONOIDRATA	ASOLI FARMACEUTICI	X AD 07383-Y
100% CREATINA MONOIDRATA	VITAMIN SHOP	X AD 09262-Y
100% CREATINA PURE	BODY EVOLUTION	1 07 04501-Y
100% DESTOCK	FITNESS PRODUCTS	X AD 09472-Y
100% EGG PRO EXTRA vg	LABORATOIRES FORTE' PHARMA	M 07 31649-Y
100% ISO WHEY	EUROSUP	
100% L-GLUTAMINE	NEWTRITIONS	X AD 03547-Y
100% MALTODEX	NEWTRITIONS	N 09 40118-Y
100% PREMIUM MELATONIN	ULTIMATE ITALIA	N 08 31834-Y
100% PREMIUM SAW PALMETTO	INTERPHARM HERBES	X AD 03157-Y
100% PURE CREATINE POLVERE	INTERPHARM HERBES	1 07 30545-Y
100% PURE PLATINUM WHEY	VIVINFORMA	E 07 30546-Y
100% SIERO ISOLATE	NEWTRITIONS	N 10 46138-Y
100% WHEY	DIETA & FITNESS	N 09 38800-Y
100% WHEY DELITE	ULTIMATE ITALIA	N 07 32885-Y
100% WHEY GOLD STANDARD	SCITEC NUTRITION	I 06 19388-Y
100% WHEY GOLD STANDARD VARI GUSTI	NUTRIZEN	I 06 15475-Y
100% WHEY PROTEIN	NUTRICA	N 08 35736-Y
00% WHEY PROTEIN	SPORT E FITNESS	N 08 35430-Y
00% WHEY PROTEIN	JUST NATURAL	N 09 38814-Y
00% WHEY PROTEIN FUEL	BOOSTER	X AD 08705-Y
	FAST ENERGY	I 06 18526-Y
	ABS	I 06 15830-Y
00% WHEY PROTEIN NUTREND 2 ERBE & FIBRA	NUTRI TRADE	I 06 19973-Y
	EQUILIBRA	N 11 47344-Y
	PHARMA GREEN	E 10 45477-Y
	ZERMAT LIMITED	E 08 33210-Y
	MOLDES	E 06 19083-Y
	ARIX LABORATORI	N 09 41262-Y
	AST ENERGY	E 09 40372-Y
	IONELLI	1 06 18409-Y
	A RO	X AD 05418-Y
	HARMATEAM	M 07 33944-Y
	TI	N 09 42682-Y
	ILTE ITALIA	M 10 42965-Y
2		I 06 19939-Y
3		X AD 00315-Y
5		X AD 00303-Y
5 OT		X AD 00550-Y
	WTRITIONS	M 05 06504-Y
		N 08 37658-Y
A - TRICREATINE MALATE CAPSULE	BORATORIO TERAPEUTICO M.R.	N 11 48354-Y
	ITEC NUTRITION TRISYSTEM	N 09 42779-Y

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ACIDRASE	NYL LABORATORIES	N 11 45330-Y
ACIFOLIN R	SIIT	X AD 04520-Y
ACILAT	HASSELT	X AD 03858-Y
ACILIN	STAR DUST ITALIA	E 07 30060-Y
ACILIP 600 COMPRESSE	CORYPHARMA	N 11 43872-Y
ACIMIRT	LABORATORIO TERAPEUTICO M.R.	X AD 10906-Y
ACINORM	LABORATOIRES ORTIS	E 06 14584-Y
ACINORM 12	LABORATOIRES ORTIS	E 06 14463-Y
ACISAN CPR	FARMACIA SANTINI	E 08 16659-Y
ACISTOM	HERBOPLANET	105 13684-Y
ACL	HUMANUTRITION	N 08 33660-Y
ACL	EUDINAMIS	X AD 00910-Y
ACL 1200 FORTE	PROGETTO NUTRIZIONE	N 11 51562-Y
ACMOS ACMOMETALLO	MANENTIS	E 07 14040-Y
ACMOS ACMOSEL	MANENTIS	E 07 14617-Y
ACMOS CALCIO	MANENTIS	I 06 14616-Y
ACMOS FERRO	MANENTIS	1 05 14041-Y
ACMOS MAGNESIO	MANENTIS	1 05 14618-Y
ACMOS MANGANESE	MANENTIS	1 05 14042-Y
ACMOS SELENIO	MANENTIS	1 05 14615-Y
ACMOS YIN	MANENTIS	E 06 14044-Y
ACMOS ZINCO	MANENTIS	1 05 14043-Y
ACNET	ICIM INTERNATIONAL	M 06 11691-Y
ACNO'	ROEDER 1956 FARM	X AD 04024-Y
ACQUA D'ALOE IL DEPURATIVO GIORNO	SOCIETA' DEL KARITE'	X AD 13480-Y
ACQUA D'ALOE IL DEPURATIVO SERA	SOCIETA' DEL KARITE'	X AD 13481-Y
ACQUA D'ERBE SOLUZIONE ACQUOSA	PRINCIPIO ATTIVO	E 09 41928-Y
ACQUA DI MELISSA	ERBORISTERIA DOTT, CECCHINI	E 06 21999-Y
ACQUA DI MELISSA SOL. IDROALCOLICA COMPOSTA	POLCARO FITOPREPARAZIONI	E 09 41082-Y
ACQUA DIUR	GREEN REMEDIES	M 11 47957-Y
ACQUA MILLEFOGLIE	SOLERBE FARM	E 10 42753-Y
ACQUACELL CON FINOCCHIO E FRASSINO	DOMENICI	E 10 44481-Y
ACQUADREN DRENA	BIOS LINE	E 10 43960-Y
ACQUADREN LINEA CONF.250 ML	BIOS LINE	E 10 43700-Y
ACQUADREN LINFODRENA CONF.30 TAVOLETTE	BIOS LINE	E 10 43701-Y
ACQUARETIX	AMAZZONIA FITOPREPARATI	E 08 33716-Y
ACQUARIS	ERBORISTERIA CASA DELLA SALUTE	E 10 44140-Y
ACRONELLE	BROMATECH	X AD 08885-Y
ACS 500	NOVASALUS FITOLAB	N 11 49663-Y
ACTAEA RACEMOSA COMPOSITUM	LABOR VILLA STODDARD	E 06 24649-Y
ACTENACOL JUNIOR	DICOFARM	E 08 33507-Y
ACTENACOL SCIROPPO	DICOFARM	E 08 17774-Y
ACTEOX	BIOFARMA	M 06 15483-Y
ACTICEL	MOLDES	X AD 09270-Y
ACTICELL CON IOTRINA F	SYRIO PHARMA	X AD 03128-Y
ACTICIR PLUS	IBERSAN	E 09 39082-Y
ACTICIR VENOSAN FIALE	IBERSAN	M 11 47319-Y
ACTICOLON	AVD REFORM	X AD 03587-Y
ACTICOLON 0-12	AVD REFORM	X AD 02839-Y
ACTIDIET	RICERCA	X AD 03462-Y
ACTIDREN	EDONE' PHARMA	X AD 03582-Y
ACTIDREN OPERCOLI	ABOCA	E 08 36828-Y
ACTIFERROPLUS	LAMPUGNANI FARMACEUTICI	X AD 12888-Y
ACTIFIBRA	NATURANDO	M 06 18999-Y
ACTIFIT	BY SB	X AD 03798-Y

VERBASCUM SIGMA	OMEOPIACENZA	E 10 41434-Y
VERBASYR	ASLETON	M 08 34019-Y
VERBENA BK	ALMA	E 07 24865-Y
VERBENA CPS	ERBA VITA ITALIA	E 06 23142-Y
VERBENA DELTA	OMEOPIACENZA	X AD 03207-Y
VERBENA E.F.	ERBA VITA ITALIA	E 06 22847-Y
VERBENA ODOROSA ES. IDR.	NCE NUOVO CENTRO ERBORISTICO	E 07 25311-Y
VERBENA ODOROSA SOL. IDR.	FITOFARMACEUTICA MEDICA	E 06 23643-Y
VERBENA ODOROSA SOL. IDR.	ERBORISTERIA DOTT. CECCHINI	E 06 22006-Y
VERBENA PLUS	ROSALIA PICCIOTTO	E 10 26223-Y
VERBENA SOL. IDR.	ERBA VITA ITALIA	E 06 22930-Y
VERBENA SOL. IDR.	ERBORISTERIA DOTT. CECCHINI	E 06 22005-Y
VERBENA SOL. IDR.	FITOFARMACEUTICA MEDICA	E 06 23642-Y
VERBENA TINTURA MADRE	POLCARO FITOPREPARAZIONI	E 09 41078-Y
VERGA D'ORO	VITALIS DR.JOSEPH	E 11 51611-Y
VERGA D'ORO	SAURO LABORATORIO D'ERBE	X AD 04328-Y
VERGA D'ORO COMPOSTA CAPSULE	CENTRO NATURALIA	E 11 20834-Y
VERGA D'ORO ES. IDR.	NCE NUOVO CENTRO ERBORISTICO	E 07 25312-Y
VERGA D'ORO ESTRATTO IDROALCOLICO	ERBAMEA	E 10 43098-Y
VERGA D'ORO PIANTA		E 09 40324-Y
VERGA D'ORO SOL. IDR.	ERBORISTERIA DOTT, CECCHINI	E 06 22004-Y
VERGA D'ORO SOL. IDR.		E 06 22004-1
VERGA D'ORO SOL. IDRO		E 05 12496-Y
VERGA D'ORO T.M.	NCE NUOVO CENTRO ERBORISTICO	E 07 25385-Y
	POLCARO FITOPREPARAZIONI	E 09 41079-Y
VE-RIL	ERBORISTERIA TEMPO VERDE	E 06 22245-Y
VERITROL	IBP	X AD 05875-Y
VERONICA E.F.		E 06 22848-Y
VERONICA E.F.	LABOR VILLA STODDARD	
VERONICA SOL. IDR.	FITOFARMACEUTICA MEDICA	E 06 24665-Y E 06 23645-Y
VERONICA SOL. IDR.		E 06 23045-1 E 06 22931-Y
VERONICA SOL. IDR. VERONICA TARASSACO ROSMARINO		
VERONICA TARASSACO ROSMARINO		E 06 20813-Y
	BRADERM	N 11 50312-Y
VERTIGINKGO	NSH	X AD 07548-Y
		X AD 00805-Y
VERTILENE	BIEMME PHARMA	M 06 19057-Y
VERTUSS	MADAUS	X AD 03756-Y
		X AD 09390-Y
	PLANTA MEDICA	X AD 07329-Y
VERUM PLANTA FIBRA FLUIDO CONCENTRATO		E 08 34299-Y
	FARMADERBE	X AD 07168-Y
	FITOFARMACEUTICA MEDICA	E 06 23788-Y
VESUGEN	PROF. DOMENICO CUCINOTTA	N 09 37271-Y
	ERBORISTERIA MAGENTINA	E 10 43218-Y
	ERBAMEA	E 05 12881-Y
VEXTRAGO	INTERNATIONAL SPORT NUTRITION	N 08 35863-Y
	VITAMIN CENTER	M 10 45920-Y
	GTA NUTRISPORT	I 05 12644-Y
VI MACA	SORAYA	M 09 42281-Y
VIA GAS	A & D	E 07 20007-Y
VIA GAS	PHYTO GARDA	E 06 19822-Y
	GIANLUCA MECH	E 11 45343-Y
VIACELL	AF UNITED	X AD 03951-Y
VIADAM	REGIFLOR NATURA	E 09 39997-Y
VIADOL	SAN BONE'	E 09 35642-Y
VIADOL	LINDASERVICE	M 10 40220-Y

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