

# SONG-YI MUSHROOM

# Tricholoma matsutake

# New biotech products for Cosmetics formulations

# **Skin Whitening Soaps**

- # Amino acids & polypeptides
- # 1,3-butylene glycol extracts
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CAMPO MATSUTAKE-KUSEI EXTRACT

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Song Yi Mushroom Extract



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#### SONGI YI MUSHROOM EXTRACTS

#### Song Yi mushroom derived ingredients for the cosmetics industry.

Products from the Song Yi mushroom listed in this brochure:

#### **Introduction:**

Song-Yi mushroom, *Tricholoma matsutake*, and its relatives are natural products emitting a pine musk odour. They are important dietary items for the musk deer, whose range of habitat stretches from the Korean-Siberia high mountain steppes to the Himalayan mountain chain. Musk is identical in structure and chemistry to the pheromones secreted by the human male and is a well-recognised sexual attractant.

In the male musk deer, musk is formed at puberty, and being a single, solitary animal roaming alone in the vast expanse of snow covered mountains, it utilises the odour to attract the female musk deer for mating and procreation of the species.

#### The products:

#### Song-Yi liquid powders, 1, 11 and 111

Campo's Song Yi protein derivatives offer a range of functional materials providing an excellent marketing concept. The term Song-Yi is widely recognised as a dietary supplement and conveys positive attribute such as a supple, delicate, smooth fruit bodies and luxurious - a sensory delight of aroma and to the touch.

It is recognised that to utilise its attractive marketing concept and to confer its useful functionalities in skin and hair care, a water-soluble form is needed.

#### Song-Yi mushroom 1, 3-BG extract

Campo Song-Yi extract in 1,3-butylene glycol

#### Songyic acid (Song-Yi ethanol fractionate extract)

A new and novel non-irritating, or cell damaging skin whitener, as a substitute for arbutin or kojic acid.

#### Song-Yi - Ceramide blend

The benefits of Song-Yi mushroom extract and Campo's novel biotechnologic human skin ceramide oil in one product.

#### SONGI YI MUSHROOM LIQUID POWDERS 1, 11 AND 111

- Amino acids and protein derivatives in Song-Yi mushroom liquid powders

Campo's Song-Yi protein derivatives offer a range of cross-functional bioactive materials providing an excellent marketing concept.

The terms Song-Yi (Korea) and Matsutake (Japan) are widely recognised and convey very positive attributes of smooth, supple, luxuriously expensive, a sensory delight to hold, touch and smell the unique fragrance.

The finely powdered Song-Yi / Matsutake has been found to be limited in use for cosmetics preparation. However, it is generally recognised that to utilise its attractive marketing concept and to confer its useful cross-functional bio-active properties to a wider range of cosmoceuticals, cosmetics and toiletries, water-soluble forms of Song-Yi are desirable.

Song-Yi liquid powders 1, 11 and 111 represent such a range of water-soluble Song-Yi derivatives. They are manufactured by the hydrolysis of the pure powdered mycelium under carefully controlled conditions and present a range of water soluble forms of Song-Yi from individual Song-Yi amino-acid blends to high molecular weight polypeptide. An alcohol soluble derivative, Song-Yi liquid powder AS can also be made available.

#### Song-Yi Liquid Powder 1

- Is composed principally of the free amino acids occurring in Song-Yi. Molecular weight is approximately 90

#### Song-Yi Liquid Powder 11

- Is a water-soluble hydrolysed Song-Yi protein of average molecular weight 10,000. It contains polypeptides with molecular weights up to 50,000 but predominantly the molecules fall within the range 5,000 - 30,000.

#### Song-Yi Liquid Powder 111

- Is a solution of hydrolysed Song-Yi protein showing a broad spectrum of molecular weight species from free amino acids to polypeptides of approximately 1,000 molecular weight.

Both Song-Yi Liquid powders 11 and 111 comply with the FDA definition of "protein" for labeling purposes, i.e., and molecular weight of 1,000 or above. The derivatives are produced from Song-Yi mushroom mycelium in a mass-cultured process (bio-technology) without endangering the wild population.

#### SONGI YI MUSHROOM LIQUID POWDERS

#### PRODUCT SPECIFICATIONS

Species: *Tricholoma matsutake*Part used: tissue cultured mycelium

Product: Appearance % Total solids % Ash % Nitrogen % Protein pH	Liquid Powder I	Liquid Powder II	Liquid Powder III
	yellow liquid	dark amber liquid	yellow liquid
	27 - 31	20 -30	25 - 28
	12 - 31	20 - 23	12 - 14
	2.0 - 2.5	1.6 - 2.4	1.8 - 2.4
	12.5 - 15.5	10.0 - 15.0	11.2 - 13.8
	3.7 - 4.5	4.0 - 6.0	4.0 - 6.0
Microbial specification Total count: Yeasts & moulds	ons < 100 opg < 100 opg	< 100 opg < 100 opg	< 100 opg < 100 opg

#### Other safety features:

Edible in small quantities, LD<sub>50</sub> rat, 25 g/kg body weight

#### SONG-YI AMINO ACIDS & PROTEINS IN SONG-YI LIQUID POWDERS

# AMINO ACID COMPOSITION Typical amino acid analysis on the 3 products are indicated below

Amino acid	song-yi lp I	song-yi lp II	song-yi lp III
Aspartic acid	4.7	13.3	5.6
Threonine	1.9	4.3	2.1
Serine	15.4	20.3	11.6
Glutamic acid	4.1	10.2	4.7
Proline	1.2	1.3	1.2
Glycine	34.7	16.1	32.8
Alanine	28.4	16.1	32.8
Cystine	0.1	0.1	0.1
Valine	2.0	2.6	2.1
Methionine	0.2	0.2	0.2
Isoleucine	1.2	1.1	1.2
Leucine	1.2	1.1	1.2
Tyrosine	0.6	4.7	1.0
Phenylalanine	0.9	1.0	0.9
Histidine	0.8	3.6	1.1
Lysine	1.4	4.4	1.7
Arginine	1.5	3.3	1.7

The limited solubility of tyrosine, as the free amino-acid, results in a lower tyrosine content in the liquid powder 1 than in the liquid powder 11, where tyrosine is present in the polypeptide chain. Other differences in the amino acid analyses may be ascribed to differences in the proportions of the two native novel Song-Yi proteins, fuibromatsutoin (Kampoyaki Patent pending) and Serisongyin (Kampoyaki Patent pending).

#### **PROPERTIES**

It has been shown that Song-Yi amino acids, in common with other amino-acid mixtures, possesses excellent moisture binding properties as shown in graph #1.

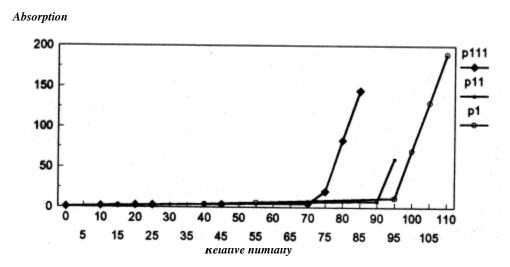
In common with other partially hydrolysed protein, Song-Yi liquid powder 11 also possesses useful moisture binding properties.

The high level of low molecular weight amino-acids in Song-Yi liquid powder 1 and Song-Yi liquid powder 111 can be expected to enhance its penetration of hair and skin where cross-functionalities of activities is required to facilitate repair of defects.

#### MOISTURE BINDING PROPERTIES OF SONG-YI AMINO ACIDS

#### Graph #1

Moisture absorption of Song-Yi liquid powders



#### RADIO ACTIVE TAGGING OF SONG-YI LIQUID POWDER 1

The three predominant water-soluble amino-acids, glycine, alanine and serine, representing approximately 85% of the amino acids of the Song-Yi liquid powder 1, were obtained from the Radiochemicals Division of Sigma Chemical Co., as  $C_{14}$  radioactive materials.

They were mixed in the correct ratio and then added to larger quantities of unlabelled Song-Y liquid powder 1 to give a suitable amount for handling.

#### HAIR TREATMENT

Virgin, brown hair, (DeMeo Brothers), was used exclusively. Duplicate hair swatches, 100mg, were treated with 10 ml portions of Song-Yi liquid powder 1 solution for 15 minutes, followed by Three 15 second rinses with 10-ml portions of distilled water to remove unbound amino acids.

The hair swatches were blotted on paper tissue hydrolysed with 10 ml concentrated hydrochloric acid (S.G. 1.18) in sealed tubes for 48 hrs.

#### SCINTILLATION COUNTING OF SAMPLES

0.05 ml quantities of hydrolysate were pipetted into 10 ml of scintillant and counted automatically on a Hewlett-Packard liquid scintillation counter.

The washings from the hair treatment were similarly checked to form that the washing procedure had been successful.

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#### **RESULTS**

	Test #1	test #2	test #3
2 % Liquid Powder 1	6.3 mg/g	6.7  mg/g	6.5 mg/g

The results demonstrate that Song-Yi liquid powder 1 is highly substantive to virgin hair.

#### **FUNCTIONS & APPLICATIONS**

Song-Yi liquid powders 1, 11 and 111 are a range of water soluble novel conditioning additives recommended for use in both hair care and skin care formulations.

Song-Yi liquid powder 1, low molecular weight indicates that the molecules can penetrate the cuticle in the undamaged hair and the surface layers of the epidermis. The unique properties combined with its outstanding moisture binding properties can be expected to produce a deeper and longer lasting conditioning effect when applied to the skin and hair.

The inclusion of Song-Yi liquid powder 1, 11 and 111 into shampoo and conditioner formulations will result in improvements to manageability, gloss, feel and texture.

Song-Yi liquid powder 11 has film-forming properties. This can be especially important for damaged hair since the P11 can coat the hair shaft and increase moisture retention at the hair surface. When applied to the skin, P11 will impact a smoothing effect in an analogous manner to other film formers. In addition, P11 will provide a protective effect helping to combat chapping and irritation caused by detergents.

P11 will also assist in the retention of moisture at the surface of the skin.

Song-Yi liquid powder 111 combines the moisturing properties of Song-Yi amino acids with the film forming properties of the hydrolysed Song-Yi protein.

#### PHYSIOLOGICAL PROPERTIES

Song-Yi liquid powders 1, 11 and 111 are considered to be acceptable cosmoceutical raw materials.

They present no special health hazards, are essentially non-irritating to the skin and eye, and are essentially non-toxic.

#### TECHNICAL SPECIFICATION

Product: song-yi mushroom, 1,3-BG extract

Product #: 95-001

Species: Tricholoma matsutake
Parts used: tissue cultured mycelium
Concentration: 1.0kg extract = 11.00 kg

Appearance: brown liquid Odour: characteristic

Solvent: 1,3-BG: water 50:50

Density (g/ml, 20°c): 1.210
Refractive index: 1.400
Preservative: none
Total germs: < 100 cfu/g
Heavy metals: 0.60 ppm

Pesticides: nil

Comments: specification may change without prior notice

Campo Research

Div. of JTC Kampoyaki

# JAPANESE MUSHROOM EXTRACTS

#### **CAMPO RESEARCH SYSTEMS**

product pd#0001

JAPANESE MEDICINAL MUSHROOM EXTRACTS FOR COSMETICS APPLICATIONS

#### PRODUCT TECHNICAL DATA SHEET

**Product name:** Campo Matsutake water-soluble

**INCI name:** 1,3-butylene glycol (and) Tricholama matsutake (proposed)

**Botanical name:** Tricholama matsutake (S.Ito et Imai) Singer

**Botanical synonym:** Armillaria matsutake S.Ito et Imai

**Japanese name:** Matsutake

Other names: Song-Yi (Korea), Korean Red pine mushroom (English)

**Plant parts used:** mycelium

Literature: Japanese Chuyaku Daijiten, Vol 1 - 8, Shoggakkan Co Ltd, Tokyo, Japan

Arora, David, Mushrooms Demystified (2nd ed.), Ten Speed Press,

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Pyo, M.y., Korean J Nutrition, 1975, <u>18</u>, (1), 47 - 59

Brian, P.W., Trans. of the British Mycocological Soc, 1972, 58, (3), 359 - 375

Active substances: S- matsutake alcohol stimulating fragance

2- octen- 1- ol circulatory stimulant/

bacteriostatic moisturising moisture retainer

methyl cis-  $\alpha$ - methylcinnamate

 $\alpha$ - and  $\beta$ - pinene cembrenes

stimulating fragance stimulating fragrance

#### Oriental traditional applications and medicinal status:

amino acids

#### **Ethnobotany**

This edible fungus is much sought after in Japan due to its unique fragrance, a sweet earthy pine-like mushroom odour. As such it provides a natural flavouring and fragrance to festive season delicacies where it is used as the main ingredient.

Cosmetically, it is used as a decoration, normally steeped overnight in water, the solution then being used as a facial wash, generally in Autumn, to remove summer sun darkened facial spots and for the tightening of facial wrinkles.

#### **Applications and dosage recommendations:**

Matsutake is recommended for incorporation in sensitive facial lotions, **moisturising** products, sensitive skin care products, hair care preparations and bath and shower products.

Usage levels: 10 - 15 %

#### **Applications code:**

#### **Specification:**

Standardised for:

Concentration: 1 kg extract = 80.00 kg **Matsutake** ( **dried** )

Appearance: brown liquid

Odour: characteristic, sweet earthy pine / mushroom odour

1,3-butylene glycol: 62 %

Refractive index d 20° C 1.425 - 1.520 Density d 20° C 1.005 - 1.345

pH: Refer to Technical Specification identification: positive, TLC specification solubility (water) soluble, clear to cloudy solubility (surfactants) soluble, clear to cloudy

preservative : nil antioxidant : nil

total germs: < 100 cfu / ml, no pathogenic organisms

pesticides: nil

heavy metals (Pb, Cd, Hg, As): < 0.60 ppm

storage: <20°C, closed containers in dark stability: under above conditions, up to 12 months

#### comments:

Due to the nature of this extract, sedimentation may occur, but this will have no effect on the efficacy of the extract.

This material has not been animal tested for efficiency, bioavailability or therapeutic content.

External use only. NOT FOR DRUG USE

#### SONG YI MUSHROOM extracts

songyic acid complex - a new, novel whitener for the horny layer of the skin

Conventional cosmetics skin whiteners have traditionally been based on hydroquinone and monobenzylether derivatives of hydroquinones such as arbutin and kojic acid. These function by inhibiting the formation of tyrosine in the melanogenesis stage of skin cell pigment formation. This chemical inhibition of normal human biological processes in the deeper skin layers damages dermal physiology and elicits undesirable side effects such as de-naturation of cells leading to contact dermatitis, a skin irritation, irreversible leukoderma, a pigment disorder which may be the first stage in a process ultimately leading to skin cancers, and pigment cell death. Statistically, these effects would be expected to be apparent in 30 % of all users.

The loss of cell pigments then opens the way to UV-A and UV-B afflictions of the skin, which would ordinarily be offered some protection from melanin, which in cases of post arbutin and kojic acid treatment is absent. There are many reported instances of skin melanoma gaining a foothold in arbutin and kojic whitened skin.

In the case of Song-Yi mushroom extract, the skin whitening mechanism is operational at the skin surface, without penetration to the deeper layers. It is effective without inhibiting the function of tyrosinase or suppressing melanogenesis by the total prevention of tyrosinase formation. The mechanism involves formation of a leuco-melanin (a reduced form of melanin) on the surface cells which becomes semi-permanent in the subsequent natural process of keratinisation of the epidermis.

In addition to giving the skin a naturally lighter look when compared with the bleached look of arbutin treated skin, the presence of leuco-melanin gives effective UV protection. Although the natural lighter look of Song-Yi treated skin is an important factor; a further important effect is the protection of the skin from UV light by the leuco-melanin. Song -Yi also provides a physical UV blocking effect preventing melanin re-oxidation and subsequent re-darkening of the skin which is prevalent in the case of arbutin and kojic acid treatments.

Kojic acid and arbutin do not give any effective UV blocking, so that skin initially whitened by these agents can eventually have a darker look than pre-treatment, due to re-oxidation of the melanin.

Thus, Song-Yi mushroom ethanolic extracts provides an excellent and unique surface skin whitening effect without causing skin death and pigment denaturisation, whitening the epidermis keratin of the horny layer of the skin, producing functional leuco-melanin which is an effective UV protector and effectively prevents melanin re-oxidation. Due to the excellent UV blocking power of Song-Yi, all these action are enhanced without the attendant skin irritation experienced in other types of skin whiteners such as arbutin and kojic acid

#### TECHNICAL SPECIFICATION

Product: song-yi mushroom, ethanolic fraction extract

Product #: 95-003

Species: Tricholoma matsutake
Parts used: tissue cultured mycelium
Concentration: 1.0kg extract = 11.00 kg

Appearance: colourless to light yellow liquid

Odour: characteristic
Solvent: ethanol fractionate
Density (g/ml, 20°c): 0.700 - 0.800
Refractive index: 1.200 - 1.350

Preservative: none Total germs: <100 cfu/g Heavy metals: 0.60 ppm

Pesticides: nil

Comments: specification may change without prior notice

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#### PRODUCT SPECIFICATION

Product: song-yi - ethanolic extract

Product #: 01-05

Species: Tricholoma matsutake

Appearance: white or grey-white or pale yellowish crystalline

 Odour:
 odourless

 Assay:
 99.9 %

 m. Pt. (°C):
 186 - 189

 Loss on drying:
 < 0.3 %</td>

 Sulphated ash:
 < 0.3 %</td>

 Heavy metals:
 < 0.0001%</td>

(As Hg, Pb, As)

#### Solubility:

 1,3-butylene glycol
 7.0 - 9.0 %

 1,2-propylene glycol:
 7.5 - 9.6

 Ethanol 96%:
 10 - 12.7

 Water:
 0.05 %

 Glycerol:
 1%

 Isopropanol:
 5 %

Amazonian oil slightly soluble Campo cosmetic oils slightly soluble

Stability: good

LD<sub>50</sub> oral -mouse 6.3 g/kg body weight LD<sub>50</sub> oral-rat 18.9 g/kg body weight

Rhesus monkey mucous membrane test - good tolerance

#### Human volunteers skin tests:

No absorption through intact skin was detected for 15 days of continuous use in 100 % water, oil and ethanolic media.

There were no signs of photosensitisation or phototoxic properties.

#### **TECHNICAL SPECIFICATION**

Product: song-yi - ceramide oil

Product #: 95-005

Species: Tricholoma matsutake
Parts used: tissue cultured mycelium
Concentration: 1.0kg extract = 11.00 kg

Appearance: colourless to light yellow liquid

Odour: characteristic
Solvent: THS-ceramide oil
Density (g/ml, 20°c): 0.900 - 0.950
Refractive index: 1.200 - 1.350

Preservative: none
Total germs: < 100 cfu/g
Heavy metals: 0.60 ppm

Pesticides: nil

Comments: specification may change without prior notice

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Div. of JTC Kampoyaki

# SONG-YI MUSHROOM - CERAMIDE RW COMPLEX EXTRACT PRODUCT NUMBER 10/02/1995

The popularity of the Song-yi mushroom (Matsutake mushroom) in Korea and Japan is well known and much in demand.

This combination of biotechnologic Human Skin Ceramide RW and Songyi mushroom extract gives skin care products a novel silky soft feeling, and has an anti-inflammatory effect in sun-damaged and aged skin conditions.

The Biotechnological Human Skin Ceramide RW is the same version of our novel ceramide as in the Alpha-Ceramidein; providing formulators with a novel concept without the hassles of solubility of cloudy and poor soluble was-solid ceramides, This ceramide RW is clearly soluble in aqueous or ethanol phase of the formulation, as well as miscible in the oil phase.

As our other Campo THS Ceramide, Ceramide Munthru, this version of THS Ceramide RW Exhibits and increases the resistance of the skin against infections (among the other known TEWL properties), which is a true and an imperative of all Human Skin Ceramides of such exhibition of properties in the maintenance of young skin.

This version also aids in the growth and pigmentation of the hair.

#### **SPECIFICATION**

Appearance: clear colourless liquid

Odour: characteristic - Song-yi mushroom musky pine

 Specific density (20° C)
 1.040 - 1.150

 Refractive index (20° C)
 1.395 - 1.450

 pH value (20° C)
 6 - 8.5

 Dry residue (Mettler 160°C)
 10% - 30 %

Vehicle distilled water (ex-WHEY)

Preservation nil (in-vacuum magnetised chamber treated)

Microbiology

Germs < 100 cfu/ml non-pathogenic

Yeasts & molds < 100 cfu/ml

#### **Application**

As an additive for skin and hair care preparations, e.g. Skin creams, sun protection and after sun formulations, hand-gels, face & hair lotions, skin caring bath products and other skin care cosmeticeuticals.

**Dosage levels:** 1- 10 %

### CAMPO SONGYI MUSHROOM GEL EXTRACT

# Novel Skin Whitening Agent Songyi Gel Liquid (25%) Matsutake-Kuseki

Edible Songyi Mushrooms are used as body and facial skin fair/lightening complexion improvement remedy in ancient Chinese Imperial Palace households, mainly by the Imperial Queens and Royal Concubines.

The fresh mushrooms (in autumn) are steeped in wine and spring water blend combination for 3 full moons (approx. 84 days & nights) and the gelified mixture is steamed for 3 days and the resultant gel is kept in a container for daily applications on the facial and body skin for whitening purpose

This application is used in all seasons - against winter snow-glare (reflected UV) darkened skin, and summer sun darkened skin with great active results of natural skin-hued whitening of the skin.

In Japan, traditionally two Japanese names or terms call this remedy: "Matsutake-Origo" and "Matsutake Kuseki" which terms are used interminglingly and defines the same purpose and the meaning - of **WHITENING THE SKIN**.

Matsutake-Kuseki is a more dilute liquid version (25%) of the Matsutake-Origo - a gel.

Campo's active cosmetic additive version is manufactured from Tissue Cultured grade of Edible Songyi Mushroom and are extracted in aqueous and ethanol solution in a high steam distillation and the resultant gel, on cooling, is diluted with 1:1 part of Aqueous: Ethanol solution to produce - Matsutake Kuseki which has approximately 30-45% active whitening action compared to the air-exposed unstable and extremely skin irritating 'Arbutin' of which known action of whitening (Arbutin) is via skin pigment cell death.

Matsutake-origo is a gel-like compound and is in a very mega-concentration form. It has 45 times of active whitening power of Arbutin; and 100 times of the active whitening power of Kojic Acid. Matsutake-origo is non-skin irritating and stable in most skin whitening formulations.

The actions of both Songyi Gel Liquids 25% (Matsutake Kuseki) and Songyi Gel (Matsutake-Origo) are as surface skin Whitening instead of highly inflammatory/irritating - pigment cell death as is the case with Arbutin and Kojic Acid.

Campo Research Singapore

### TECHNICAL SPECIFICATION

PRODUCT NAME: SONG YI MUSHROOM GEL LIQUID 25% CONC.

SYN. NAMES: MATSUTAKE KUSEKI EXTRACT

MATSUTAKE EXTRACT

Tricholoma matsutake (Singer) Extract Gel Liquid

INGREDIENT ACTIVITY: SURFACE SKIN WHITENING

PARTS USED: Whole mushroom-fresh

APPEARANCE: GELIFIED DILUTED LIQUID

SPECIFIC GRAVITY: 0.730 - 0.990

REFRACTIVE INDEX: 1.200 - 1.500

SOLVENT(S): WATER: ETHANOL 1:1

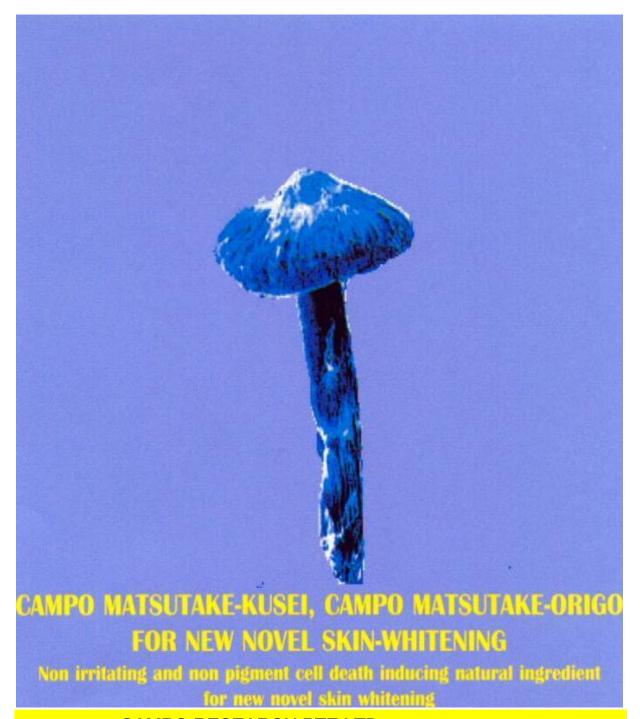
SOLUBILITY: WATER, ETHANOL, 1,3-BG, 1,2-PG

PRESERVATION: NONE

HEAVY METALS: NONE

Matsutake-Origo 100% (Songyi Gel 100%) is available only on custom request due to the its high-cost.

Campo Research





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CAMPO® Novel Functional Active Cosmetic Ingredient & Raw Materials

# CAMPO SONGYI GEL LIQUID 25% (Tricholoma matsutake-Singer Extract)

(CAMPO MATSUTAKE-KUSEI EXTRACT)

The increasing demands of skin whitening agents in the Asia Pacific markets over the past 3 years have created so much excitement and stimulation among the manufacturers of the cosmetic industry to come up with latest product development and innovation on this category of skin care. The explosion of skin whitening products, likewise, has led to the upsurge of research studies and the expansion of knowledge concerning skin care. Rapid growth rate on this product sector is expected to take the Asia Pacific, especially in developing countries, by storm.

Having pale whitened skin is beautiful and a sign of attractiveness. This is a common view among Asian women. For some women, it connotes being in a higher strata of society since most upper class women are observed to have fairer skin as they are not much exposed to sunlight and spend their time indoors. For some, it is the result of enticement from the fashion industry and just the feeling of being different, a fresh look, and a new transformation. Whatever may be the reasons, they resort to any ways and means, from the physical through the use of umbrellas to chemical through application of sunscreens and whitening agent, just to protect and shield the skin from the sun.

Available in the market today is 3 types of whitening products: those containing sunscreens; those containing light reflection ingredients; and those containing ingredients that actually produces a chemical change on the skin. Though the whitening effect of some agents is evident, some are also believed to damage skin, produce skin irritation and reddening. Hydroquinone, which became popular and the first product used widely, has the risk of irritation resulting in oedema, erythema and desquamation. Usages of these products were banned in many countries in Asia because of numerous of these side effects. The ramifications and diversity of the skin whiteners stirred up cosmetic analysts and researchers to investigate the nature of the active ingredients present on these products. Launching of the newly experimented and developed products has been a common trend in the Asia Pacific regions where the demand is very high. Many people are becoming more aware of products made from natural ingredients not only because of the abundance of these natural resources in their areas but people perceive the ingredients extracted out as good for them.

The development of products on this category has been geared towards the mechanism of action of the specific components. Recent formulations have resulted from considerable research and have been the outgrowth of innovative and thorough analysis of the biochemical pathways of the melanin synthesis and the biophysical considerations that affect its complex process. Promising developmental effort is on the area of sub-cellular action of whitening agents that affect the expression of the various melanogenic enzymes.

In line with the wide-range of Campo novel innovative products, Campo Research ventures into an exciting new functional active ingredients range (which are originally screened and evaluated for novel drug discovery program based on natural product chemistry) with consumer precievable immediate results,

These Campo novel ingredients that represents a 'step ahead' in the fast swelling product of skin tone lightening agents as these new novel cosmetic ingredients are well-known and accepted / identified with affulences and aristocracy; which were used empirically for many generations for skin-whitening in the Orient as dietary articles.

Campo Novel Skin-Whitening Active Ingredients for cosmetic formulations are:
Campo Pearl Powdered Extract-water-soluble, Campo Birds' Nest Extract, Campo Songyic acid complex™ whitening ingredients, Campo Ganoderma lucidum, Campo Organic Germanium from Ginseng root, Campo Pearl Guanine, Campo Snow-white Coral Algae Extract, Campo Pearl Powdered Extract and Campo Songyi Gel Liquid 25% were selected based on their identical and similar route of biosynthetic pathways in the active modes of whitening efficacies.

These new novel whitening ingredients acted individually in an adaptogenic manner as substrate(s), as biosynthesis by-products, as enzymatic principles (enzymes), as unusual new active metabolites and without any undue interferences or inhibiting classical actions with tyrosine biosynthesis or inhibition and/or (its) inhibited tyrosine mediated clinical complications such as Tyrosinemia I, Tyrosinemia II, Tyrosinemia III Phenylketonuria (PKU) and Alkaptonuria; with the strong possibility of Parkinsons' diease due to inhibition of tyrosine and its importance in numerous biosynthetic reactions including tyrosine as a substrate for formation of dopamine.

Campo Novel Active Skin-Whitening Ingredients including Campo Songyi Gel Liquid 25% introduced are specific extracts dietary/food articles, which are often used as for skin-whitening and other cosmetic purposes by the very rich and aristocratic families of the Orient,

In this product brochure: Campo Songyi Gel Liquid 25% is discussed as a novel cosmetic ingredient that proves unique and effective as a skin whitener/ lightener because of its combined active components derived from tissue-cultured high yield Songyi mushroom mycelium. It contains (as in all cases of other Campo Skin-whitening active ingredients-see above) numerous adaptogenic specific enzymatic principles, specific bio-available trace elements and specific substrates which functions are adaptogenic and specific supplementation in biosynthetic metabolism pathways with skin-whitening activity without irritation or pigment cell-death, in a very novel manner.

The exceptional beauty transformation that manifests from Songyi Gel extract (its) usage and other Campo Skin-whitening ingredients; is a result of considerable research and innovation based on the empirical knowledge and uses of the Imperial courtesans of the Middle Kingdom (China) and Imperial Japan. The outstanding features of the ingredient's (Songyi Gel extract or its dilute versions) active components lends itself to its ability to act on the subcellular and molecular level in the regulation of melanogenesis through partial-inhibition, re-supplementation and supplementation of various melanogenic enzymes.

#### **HOW SKIN-WHITENING WORKS?**

In consideration as to how skin-lightening agents work, a basic understanding of the tanning process is essential (see Campo UVzymes™ literature volumes 1, 2 & 3). This phenomenon is the result of enhanced melanin production (enzymatic principles such as T4N5 and other similar acting enzymes) by the skin. The color pigmentation of the skin, hair bulbs, and eyes in humans and other mammals results from the synthesis and distribution of melanin. Melanin is a group of complex pigments made in specialized cells called melanocytes and subcellular organelles called melanosomes. Neither the exact structure of melanin pigment nor its biosynthetic pathway are completely understood. Studies have shown that the essential enzyme in the melanin biosynthetic pathway is tyrosinase. However it is not regulated solely by tyrosinase at enzymatic level and additional factors (eg: homogentisic – catalysed by dioxygenase enzyme) involved in the melanogenesis have been identified which can modulate pigmentation in either a positive or negative fashion.

Most commercially available skin-lightening agents work in various single mechanisms. There are chemical ingredients that absorb UV light, antioxidants that inhibit several oxidation steps during melanogenesis, reducing agents that reduce dopaquinone back to DOPA, indole-blocking factors which interrupt intermediates in melanin biosynthesis, agents that interfere with ribosomal protein synthesis, agents that block tyrosinase biosynthesis, those which inhibit the tyrosine-tyrosinase system, those that block melanin pigment transfer from melanosomes to keratinocytes, those that alter melanosomes organelles, agents which promptly scatter melanin granules, and those agents that selectively destroy melanocytes. The remarkable difference of Campo Songyi gel from other product category of skin lightening agents is Songyi gel extract's (its) multifunctional action in that the Extract specific actives affect a number of enzymes systems believed to participate in the pathway of melanogenesis. But the primary mode of action that significantly produced the desired result is through the ingredient's proprietary actives to inhibit tyrosinase activity, the enzyme behind the tan.

#### **MELANIN SYNTHESIS:**

Melanin is a complex pigment made up of yellow-red pheomelanins and brown-black eumelanins. Both types are synthesized from tyrosine though some require cysteine. The site of melanin synthesis is the melanosome, which is and an organelle found in specialized cells called melanocytes which are thin, elongated dendritic cells of the basal layer of the epidermis. The melanins synthesized and deposited on melanosomes include: eumelanins, pheomelanins and mixed melanins. Melanin provides much of the normal pigmentation of skin and hair. Normal skin pigmentation results from a mixture of several coloured pigments: haemoglobin, carotenoids and melanins. It is the amount of melanin produced that makes the differences in the racial skin colour, although other factors are involved such as the epidermal distribution and deposition of melanosomes. The principal function of melanin is to provide protection against the damaged cause by UV irradiation. Tanning is due to an increase in skin melanin.

The initial steps in melanin synthesis are catalyzed by tyrosinase. This enzyme catalyzes at least two different reactions in the biosynthetic pathway of melanogenesis and the quantity of melanin synthesized is directly proportional to the amount of activity of tyrosinase enzyme present in the cell. There is a good correlation as to its activity and the skin pigmentation in humans. Tyrosine is hydroxylated to DOPA and oxidized to dopaquinone. From there, the pathways for synthesis of eumelanin and pheomelanins diverge. Pheomelanins incorporate a cysteine, eumelanins cyclize to create an additional aromatic ring, called an indole ring.

Melanin pigmentation is a complex multi-step process involving both melanocytes and keratinocytes in the epidermal-melanin unit. Melanosomes are synthesized in melanocytes, transferred to keratinocytes and transported to the epidermal surface.

Mostly now, available skin-whitening ingredients' active functions are inhibition of the formation of tyrosine in the melanogensis stage of the skin cell pigment formation.

The results of these forms of chemical (bleach or semi-bleaching) inhibition of the normal human biological processes in the deeper skin layers damaged dermal physiology and elicits undesirable side effects such as: 'de-naturation of cells' leading to contact dermatitis, a skin irritation, irreversible leukoderma, a pigment disorder which may be the first stage in a process ultimately leading to skin cancers, and pigment cell death.

The loss of cell pigments then further opens the way to excess Solar UV-A and UV-B rays and these solar UV mediates afflictions (actinic keratosis, melanoma, and immuno-

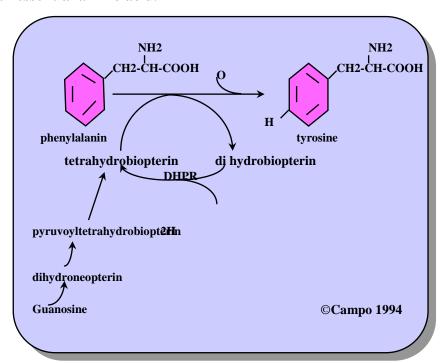
suppressions, etc), which would ordinarily being be offered some protection from melanin.

In most cases of where skin being post-treated- with chemical bleaches and whiteners (i.e. with hydroquinones, catechols, phenols, kojic, and arbutin), this UV protection is absent.

A new medical implication has been currently circulating with chemically bleached/whitened skin is classical PKU (phenyl ketonuria), which cause mental retardation (IQs lowering to or defecting to 30's or senility) due to tyrosine deficiency. Typically, dietary phenylalanine (an aromatic amino acid) is converted into tyrosine. Most of the cosmetically used chemical whitening agents is known to interfere with the functions of phenylananine hydroxylase (phase)(an enzyme) which convert the phenylananine (amino-acid) to tyrosine.

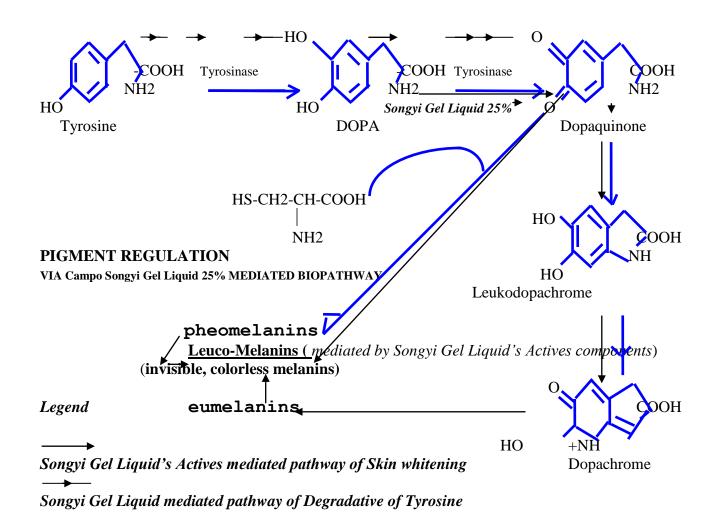
Any interference by chemical bleaching/whitening agents with the *phase* enzyme's functions, causes non-conversion of phenylananine into tyrosine and cause elevation in serum phenylananine.

In such cases of PKU, (the non-conversion of tyrosine from phenylananine), in general, the status of tyrosine is non-essential amino acid; but in this PKU cases it (tyrosine) becomes an essential amino acid.



This PKU condition is further mutated at the genetic level (mutation of the phenylananine hydroxylase genes ) of the chemical skin bleach/whitener and such mutations is carried forth as hereditary genetic make-up of PKU (from PKU afflicted users) to the users' children and their off-springs

(See also illustration Fates of Tyrosine via Songyi Gel Liquid 25% mediated degradation)
Songyi Gel Liquid 25%
Songyi Gel liquid 25%



#### **PIGMENT REGULATION:**

The nature of melanogenesis is a complex process involving different levels of organization and a concerted mechanism of biochemical and biophysical events. In humans, the regulation of pigmentation, though its not completely understood, operates in cellular and subcellular levels, each level having its own complexity. Hence, at present, little is known concerning the precise action of any step-regulating substances that affect its numerous pathways to melanogenesis. The nature of inhibitors that acts and controls at many different levels is varied. However, inhibition of the synthesis of the enzymes involved in the pathway leads to inhibition in the production of melanin.

The regulation of pigmentation is regulated at the cellular level by melanocytes synthesizing melanin within melanosomes, which can be produced in varying amounts, in different sizes and densities (leuco-melanins- see Campo Songyic acid literature available on contractual project basis).

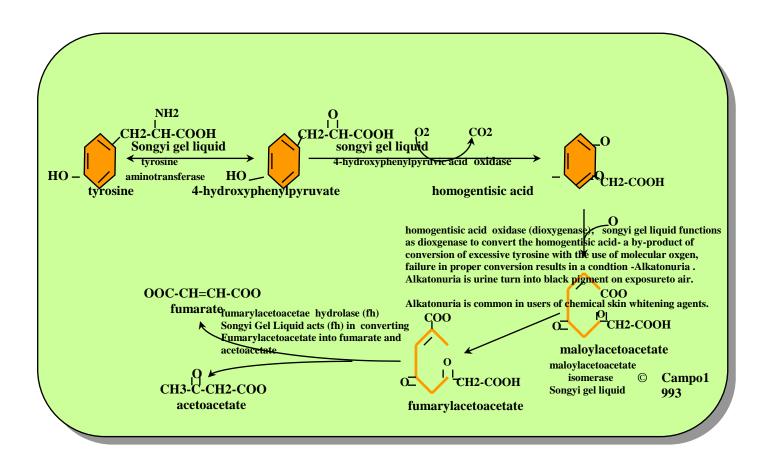
Also, regulation operates at the subcellular level where the synthesis and the interplay of the various melanogenic enzymes and inhibitors play a vital role.

The skin pigmentation process can be seen as one unit in the entire panorama of melanin synthesis. The end result is attributed to the organization and distribution of melanosomesthat contains the melanin, its quantity and function. Moreover, it is dependent on several separate but related events such as:

- ➤ The migration of the primitive cell melanoblast from the neural crest.
- ➤ The differentiation and proliferation of melanoblast to its mature form melanocytes.
- ➤ The dimension of melanosomes and its rate of synthesis and melanization.
- ➤ The synthesis of melanin in the melanosomes.
- The transport efficiency of melanosomes to keratinocytes.
- ➤ The rate of melanosome degradation within the keratinocytes.
- The activity of the enzyme tyrosinase: its rate of synthesis, inhibition and decay (Tyrosine degradation).

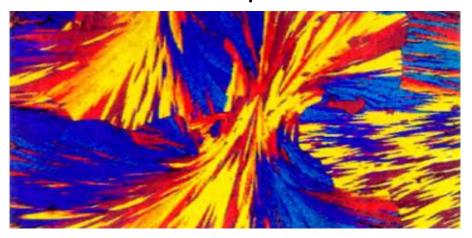
#### FATES OF EXCESS TYROSINE IN THE SKIN-WHITENING PROCESS

Degradative pathway of excess Tyrosine —as mediated by the Active components of Songyi Gel Liquid 25%, in the formation of Leuco-melanins



# Tyrosine-Melanin reduction enzyme (s) Which convert melanin in to Leuco-Melanin\*

Tyosine-Melanin reduction enzymes which are responsible for the catalyst & formation of Leuco-melanin are isolated, stabilized and optimized; and are optimized bio-available from the following natural products-cosmetic functional active extracts for new novel range of skin-whitening personal-care products:

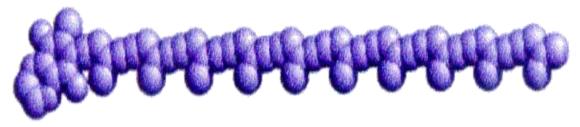


- Campo Snow White Coral Algae Extract
- Campo Pearl Extract Pws
- Campo Pearl Bezoar Acid Extract-pbaws
- \* Campo Pearl Powder Extract
- \* Campo Pearl Organic Germanium Extract-pogws
- \* Campo Ginseng Organic Germanium Extract
- \* Campo Garlic Organic Germanium Extract
- Campo Songyic Acid Complex
- Campo Songyi Gel Liquid 25% (Matsutake-Kuseki)
- \* Campo Songyi Ethanol Fraction Extract and Campo Bird's Nest Extract

Novel Structure of a Leuco-Melanin reduction catalyst Enzyme (S) as found in our Campo Novel-Skin-Whitening Actives.

<sup>\*</sup>Leuco-melanin, a colorless, invisible melanin which is functional as photoprotection without darken skin pigment

# Essential Biomolecule-CoEnzyme Q10 (Ubiquinone)



An important point should be noted here on CoEnzyme Q10 – an Essential Biomolecule that is produced in all mammalian tissues; and any lackings in the levels of CoEnzymes Q10 manufacture is related with myriads of physiological dysfuctions. The formation of CoEnzymes Q10's quinone ring is synthesized from the Amino Acids Tyrosine and phenylalanin.

Total and complete in hibition of the amino acid Tyrosine and its formation as experienced with most of the presently available Skin Whitening Agents can be implicated is skin Aging and other complications.

#### Literature Ref:

Ernster, L. and Daliner,G (1995) Biochemical, Physiological and medical Aspects of Ubiquinone Function. Biochima 'et Biophysica Acta, 1271, 195-204.

(More literature references available on request)

© 1995 copyright CAMPO tyrosine-melanin reduction enzyem(s) **pictomicrograph(s) of structure(s)** series

#### CAMPO SONGYI GEL LIQUID 25%: A BREAKTHROUGH IN SKIN WHITENING AND LIGHTENING.

Campo Songyi Gel Liquid 25% has been designed not only to provide a better, fairer skin but also to impart a pleasant skin feeling. Unlike other conventional lightening products, this novel liquid extract was bio-engineered and extracted- so as not to leave a tingling sensation on the skin, which is the telltale sign of pigment cell death. Campo Songyi Gel Liquid 25% 's unique blend of the active components to whiten/lighten skin tone and reduce the already present (previously-formed)melanins into leuco-melanins (invisible, colorless melanins which are functional as true dark pigmented melanin in photo-protection) while further mediating formation of leuco-melanins instead of new dark melanin pigments (see illustration-pigment regulation), and reducing degradatively the excessive tyrosine (see illustration-degradative (decay) of Tyrosine) and to enhance vitality and freshness of the skin makes Campo Songyi Gel Liquid 25% an extraordinary skin whitening/lightening agent from among the existing products of this category in the market today.

# CAMPO Songyi Gel Liquid 25% Novel Skin Whitening Agent

MATSUTAKE KUSEKI

Songyi Gel is used as facial and body skin fair complexion improving remedy in ancient Chinese Imperial Palace households, mainly by the Imperial Queens and Royal Concubines.

The Songyi mushrooms were soaked in wine and spring water combination for 3 full moons (approx. 84 days & nights) and the gellified mixture is steamed for 3 days and the resultant gel is kept in a container for daily applications on the facial and body skin for whitening purpose This application is used in all seasons - against winter snow-glare darkened skin, and summer sun darken skin with great active results of natural skin-hued whitening of the skin.

In Japan, traditionally this remedy is called by two Japanese names or terms: "MATSUTAKE-ORIGO" and "MATSUTAKE-KUSEKI" which terms are used interminglingly and defines the same purpose -of WHITENING THE SKIN.

MATSUTAKE-KUSEKI is a more dilute liquid but high activity skin-whitening version of the Matsutake-Origo - a gel.

Campo's active cosmetic additive version is manufactured from tissue-cultured —edible mycelium of Tricholoma matsutake; are extracted in aqueous and ethanol solution in a high steam

distillation and the resultant gel on cooling is diluted with 1:1 part of Aqueous: Ethanol solution to produce –Matsutake-Kuseki which has approximately 30-45% active whitening action compared to the air-exposure unstable and extremely skin irritating 'Arbutin' which action of whitening is via skin pigment cell death.

Matsutake-origo is a gel-like compound and is in a very megaconcentration form. It has 45 times of active whitening power of Arbutin, and 100 times of the active whitening power of Kojic Acid.

Matsutake-origo is non-skin irritating and stable in most skin whitening formulations.

### **TECHNICAL SPECIFICATION**

PRODUCT NAME: Songyi Gel Liquid 25%

SYN. NAMES: Matsutake Kuseki Extract

Diluted Kokuto-Origo Extract,

Tricholoma matsutake Singer Extract (INCI name)

INGREDIENT ACTIVITY: SURFACE SKIN- WHITENING WITHOUT IRRITATION

PARTS USED: **Mycelium** of whole fresh mushrooms

SPECIFIC GRAVITY: 0.730 – 0..990 (Hitachi U-2010)\*

REFRACTIVE INDEX: 1.200 - 1.500 (Atago RX-5000)\*

SOLVENT(S): WATER :ETHANOL 1:1

SOLUBILITY: WATER, ETHANOL, 1,3BG, 1,2-PG

PRESERVATION: NONE HEAVY METALS: NONE

Comments: These hi-tech equipments' results and reading may differ

slightly with standard conventional equipments.

#### **RAW MATERIAL'S ORIGIN:**

Campo Songyi Gel Liquid 25% is manufactured from mycelium of whole fresh Matsutake / Songyi mushroom.

#### THE COMPOSITION:

	200/
Polysaccharides	90%
Gelatin	0.01%
C. Amino Acids	
C.1. Phenylalanine	1%
C.2. L-Tyrosine	1%
C.3 Cysteine	0.5%
ENZYMES	
(thermophilic heat-stable Enzymes)	
D.1. Phenolase EC 1.14.18.1 (Monophenol monooxenase)	1.5%
D.2. Polyphenol Oxidase EC 1.10.3.1	1.5%
D.3. Catechol Oxidase EC 1.1.3.14	1.5%
D.4. Phenylalanine hydroxylase EC 1. 14. 16.1	0.05%
D.5. p-hydroxyphenylpyrutate hydrolase	0.05%
D.6. Homogenitisic acid oxidase EC 1.13.11.5	0.05%
D.7. Maleylacetoacetate isomerase EC 5.2.1.2	0.05%
D.8. Fumarylacetoacetate hydrolase	0.05%
D.9. Tyrosine aminotransferase EC.2.6.1.5	0.05%
D.10 EC 1.6.5.3	0.05%
E. Vitamins and Co-Factors	
E.1. L-Ascorbic Acids	2.0%
E.2 Tetrahydrobiopterin	0.01%
E.3 Bioterpin	0.05%
E.4 Ubiquinone (Q10)	0.10%
E.5 Ubiquinone Homologue (Q9)	0.15%



Photo 1 \_10% Songyi Gel Oil based Skin-Whitening Liquid Soap and 0.10% & Songyi Gel Liquid 25% & 10% Songyi Gel Ceramide Extract based de-pigmentation cream was applied 3 x a day for 7 days on the subject's facial areas.

Results: 25% success in de-pigmentation; appearance of rosy lighten skin tone and removal of acne induced blemishes from the subject's facial application areas.

Photo 2 10%Songyi Gel Oil based Skin whitening Soap bar's rich lather and 0.5% Songyi Gel Liquid 25%& 10% Songyi Gel Ceramide Extract based Skin depigmentation cream was applied 3 x a day for 7 days on the subject's facial areas.

Results:75% success in de-pigmentation, natural lighten skin tone, removal of acne induced blemishes and dark age spots from the subject's facial application areas.

#### **Special Conditions monitored:**

- Urine samples of human volunteers were daily taken and exposure to air, to evaluated any existence of Alkaptonuria.
   Results: None observed
- 2. Examination of the external ears of the human subjects were conducted daily to evaluate any existence of Alkaptonuria

#### **RIPT ASSAY**

Songyi Gel Liquid 25% was also safety tested using a variety of in vivo and vitro protocols. The CAMVA was used to determine irritancy. This in vitro assay determines the irritancy of a test compound based on its ability to induce hemorrhage on the chorioallantoic membrane of a chicken egg. Two other in vitro tests were run on Campo Songyi Gel Liquid 25% - EpiDerm and Epi-Ocular. EpiDerm is a three - dimensional system composed of human epithelial cells to which the test compound is applied. After incubation, the number of viable cells is measured using the MTT conversion assay.

An  $ET_{50}$  is determined, which gives an idea of potential skin toxicity. EpiOcular is a three- dimensional system composed of stratified human keratinocytes to which the test material is applied. After incubation , the number of viable cells is measured using the MTT conversion assay. An  $ET_{50}$  is determined, which gives idea of possible ocular irritation . Results are shown in Figure I.

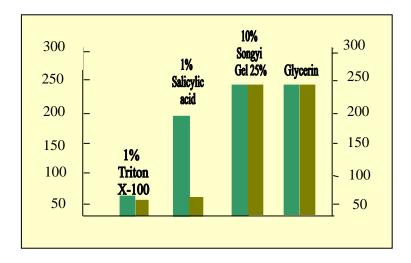


Figure 1. in vitro Toxicology

A sixty -person RIPT was run on Campo Songyi Gel Liquid 25% to assess its ability to induce skin irritation and sensitization. The method is modified from the 200 person methodology cited in the reference Appraisal of the Safety of Chemicals in Food, Drugs, and Cosmetics. The material was tested at 100% concentration and underwent nine inductive patchings.

#### **Results**

The CAMVA gave an  $RC_{50}$  value of 27%. This value is indicative of a material that is not a primary irritant. The results for EpiDerm and EpiOcular are detailed in Figure I. For Campo Songyi Gel Liquid 25%, the  $ET_{50}$  for the EpiDerm was >24 hours and for the EpiOcular it was >240 minutes. In comparison, salicylic acid yielded  $ET_{50}$  values of 19.3 hours for EpiDerm and 14.8 minutes for EpiOcular . Campo Songyi Gel Liquid 25% gave scores similar to the scores of glycerine, whereas salicylic acid scored more closely to Triton X-100 , the positive control for the system.

#### **Discussion**

Campo Songyi Gel Liquid 25% has less irritation potential than salicylic acid 10%. The safety testings done on Campo Songyi Gel Liquid 25% clearly shows this. The EpiDerm and The EpiOcular Assays made actual comparisons between Campo Songyi Gel Liquid 25% and salicylic acid 10%, and the Campo natural extract proved to be much less irritating.

#### Conclusion

Campo Songyi Gel Liquid 25% is safe, efficacious natural extracts for use in a variety of cosmetic formulations.

#### TOXICOLOGICAL PROFILE: LD50 Dose

Rat oral > 36,000 mg/ kg body weightMucous membrane sublingual > 10,000 mg/ kg body weight

Mice oral > 23,000 mg/ kg body weight

Human volunteers 50 7 days repeat patch insult test - non-erythema

- Non-irritating

Human volunteers 100 oral ingestion of 100 grams @ day - essentially non toxic edible

For 30 days as grain alcohol USP (5%)

Based drink

### Tolerance exhibited by Campo Songyi Gel Liquid 25%

So as to ensure a good level of innocuity Campo Songyi Gel Liquid 25% was tested invitro as follows:

- Irritation potential of the chorio-allantoic membrance of an egg. When tested on the chorio-allantoic membrane of a chicken egg, according to The technique developed by *LUEPKE* in a 10% active aqueous solution. Campo Songyi Gel Liquid 25% is classified as non-irritant.
- LUEPKE, N.P., Hen's egg chorio-allantoic membrane test for irritation potention. Fd.Chem.1986, 24, 6-7, 495-496.

#### \* Cytotoxicity on human fibroblasts

When tested on human fibroblasts using a method patented by *BIOGIR*, (which can be applied to hydrosoluble products as well as to liposoluble). **Campo Songyi Gel Liquid 25%** in a 10% active aqueous phase or oily phase <u>does not</u> show any signs of Toxicity towards fibroblasts in a culture.

#### \* Eyetex

According to this technique, in a 10% active solution. **Campo Songyi Gel Liquid 25%** is classified as non-irritant.

#### Skintex

According to this technique, in a 10% active solution, *Campo Songyi Gel Liquid* 25% is not irritant.

This tolerance data is confirmed by the tests carried out in vivo on healthy humans.

#### \* Test on healthy humans

When patch tests were carried out at increasing concentrations (0.5%, 1.1%, 2.2%, 4.7%, 10% and 100%) on 10 subjects, **Campo Songyi Gel Liquid 25%** did not show any significant irritation reaction. *Its tolerance is satisfactory*.

#### **COMEDOGENESIS**

Campo Songyi Gel Liquid 25% tested in a 10% active solution on human volunteers, according to the usual protocols has proved to be free of comedogenic effect. Because of its good level of innocuity, Campo Songyi Gel Liquid 25% has proved to be a first class skin-whitening for very many skin-whitening formulae where tolerance is imperative (dermatological cream, anti-acne cream, baby cream, face whitening cream, whitening essence, whitening lotion, etc.)

#### **BIODEGRADABILITY**

The ultimate aerobic biodegradability of **Campo Songyi Gel Liquid 25%** is measured according to STURM test (OCDE 301 B, guideline EEC 84/449, Annex V, Method C5). Under these conditions a level of biodegradability of **Campo Songyi Gel Liquid 25%** is 100%, in 28 days, at 500 mg/l.

The level of biodegradability of **Campo Songyi Gel Liquid 25**% is considered to be excellent.



Songyi / Matsutake / Tricholoma matsutake Singer In the Pinewoods timberline, near Mt. Fuji, Japan (autunm) Where high level solar UV radiation is a daily occurrence.

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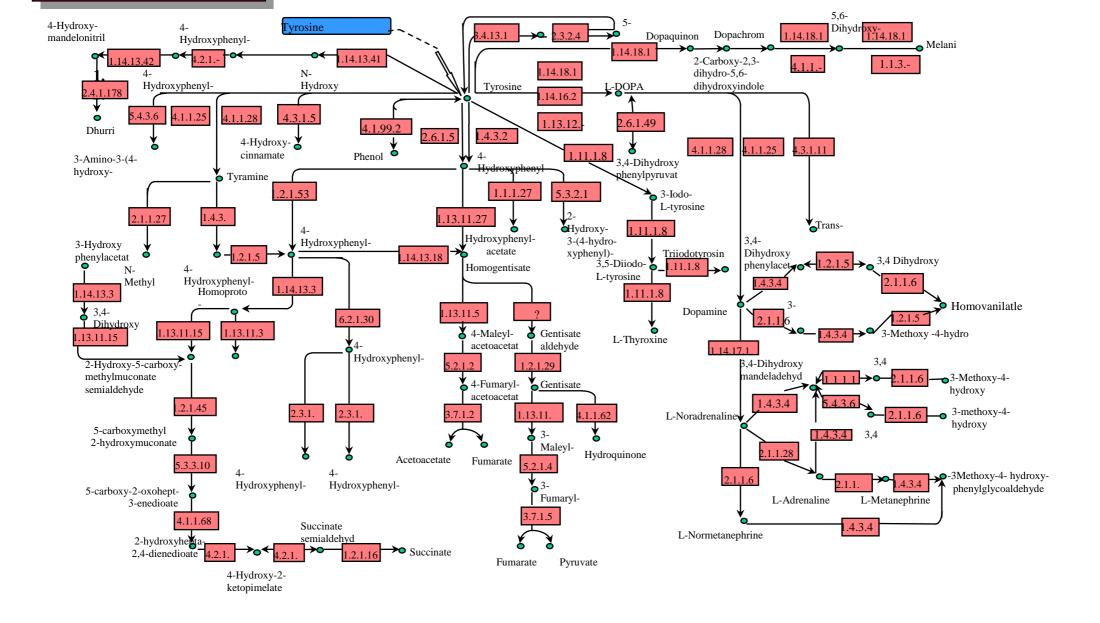
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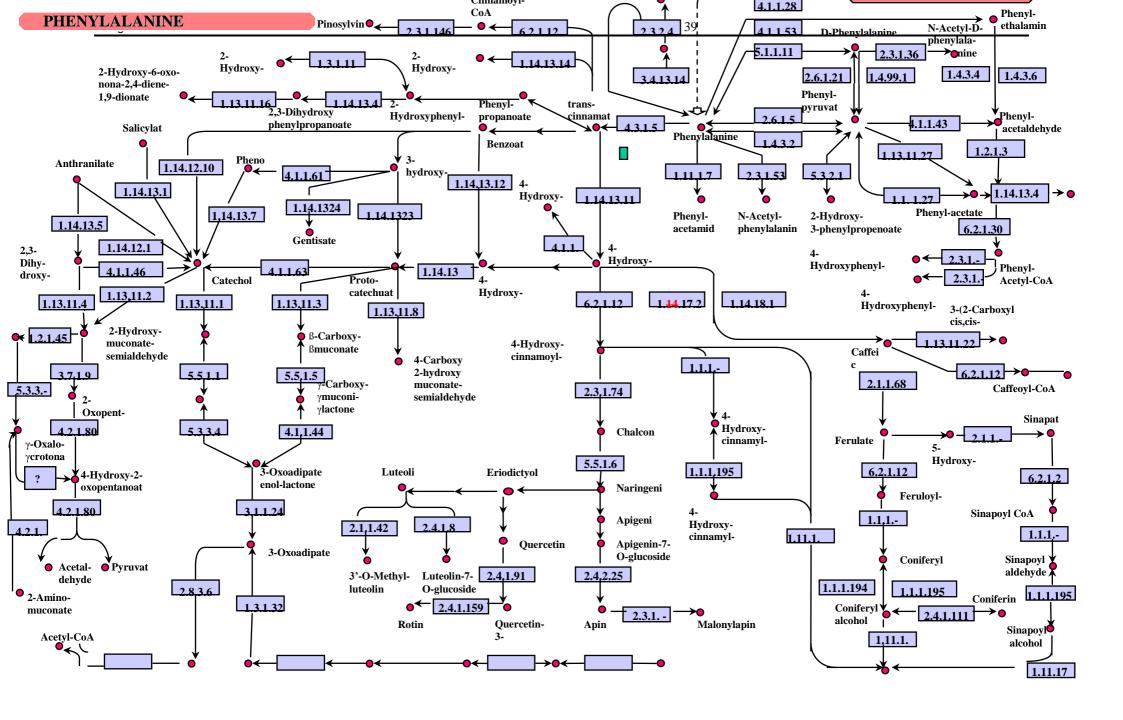
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Other reference available on request (approx. 189 page X A4 page)





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