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Amended Safety Assessment of *Hypericum Perforatum*-Derived Ingredients as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) has issued an amended safety assessment of 7 *Hypericum perforatum*-derived ingredients as used in cosmetics. A common name for this plant is St John wort. These ingredients function in cosmetics as skin-conditioning agents—miscellaneous and antimicrobial agents. The Panel reviewed relevant animal and human data related to the *H perforatum*-derived ingredients. Because formulators may use more than 1 botanical ingredient in a formulation, caution was urged to avoid levels of toxicological concern for constituent chemicals and impurities. The Panel concluded that *H perforatum*-derived ingredients were safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment.

Keywords

Hypericum perforatum

Introduction

Several cosmetic ingredients are derived from *Hypericum perforatum* L. One common name for this plant is St John wort. These ingredients function in cosmetics as skin-conditioning agents—miscellaneous and antimicrobial agents (Table 1).[1] The 7 ingredients in this safety assessment are:

- *H perforatum* extract;
- *H perforatum* flower extract;
- *H perforatum* flower/leaf extract;
- *H perforatum* flower/leaf/stem extract;
- *H perforatum* flower/twig extract;
- *H perforatum* leaf extract;
- *H perforatum* oil.

In 2001, the Cosmetic Ingredient Review (CIR) published a safety assessment of *H perforatum* extract and *H perforatum* oil as used in cosmetics,[2] finding insufficient data to determine that these ingredients were safe for use in cosmetics. Additional data needs were identified:

- current concentration of use data;
- function in cosmetics;
- photosensitization and phototoxicity data using visible light (550-610 nm; 5-10 J);
- gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures;
- dermal reproductive/developmental toxicity data;
- skin irritation/sensitization data in humans on *H perforatum* oil; and
- ocular irritation data, if available.

Additional data have been submitted and are summarized subsequently along with new data discovered in the literature. Data on the major constituents of *H perforatum* are also included.

Since the original report was published, the name of *H perforatum* extract was changed to *H perforatum* flower/leaf/stem extract.[3] Since then, another ingredient named *H perforatum* extract, defined as an extract of the whole plant, has been added to the *International Cosmetic Ingredient Dictionary and Handbook*.[1]

Original Safety Assessment

This is a summary of the data in the original safety assessment.

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Table 1. The Definitions and Functions of the *Hypericum Perforatum*-Derived Cosmetic Ingredients.

Ingredient, CAS #	Definition	Function
Hypericum perforatum extract	The extract of the whole plant, *Hypericum perforatum*	Skin-conditioning agent—miscellaneous
Hypericum perforatum flower extract	The extract of the flowers of *Hypericum perforatum*	Skin-conditioning agent—miscellaneous
Hypericum perforatum flower/leaf extract	The extract of the flowers and leaves of *Hypericum perforatum*	Skin-conditioning agent—miscellaneous
Hypericum perforatum flower/leaf/stem extract, 84082-80-4	The extract of the flowers, leaves and stems of *Hypericum perforatum*	Skin-conditioning agent—miscellaneous
Hypericum perforatum flower/twig extract	The extract of the flowers and twigs of *Hypericum perforatum*	Antimicrobial agent; skin-conditioning agent—miscellaneous
Hypericum perforatum leaf extract	The extract of the leaves of *Hypericum perforatum*	Skin-conditioning agent—miscellaneous
Hypericum perforatum oil, 68917-49-7	The fixed oil obtained from St. John's Wort, *Hypericum perforatum*	Skin-conditioning agent—miscellaneous

Hypericum perforatum extract is an extract of the capsules, flowers, leaves, and stem heads of the *Hypericum*, *H perforatum*. In 1998, it was reported to the Food and Drug Administration (FDA) that *H perforatum* extract and *H perforatum* oil were used in 64 and 11 cosmetic formulations, respectively.[2] One manufacturer reported that *H perforatum* extract is used at concentrations of $\leq$5%, and it was reported by another supplier that a mixture of *H perforatum* extract and propylene glycol is used at concentrations of 1% to 10%. In 1984, *H perforatum* extract and *H perforatum* oil were reported to be used at concentrations of $\leq$5% and unknown concentrations, respectively.

In male subjects, a single oral administration of *Hypericum* extract resulted in a nonlinear increase, with increasing dose in the amount of hypericin or pseudohypericin appearing in the plasma, and the increase was statistically significant for hypericin. With long-term dosing of *Hypericum* extract, steady state occurred after 14 days. The polyphenol fraction of *H perforatum* had immunostimulating activity on the mononuclear phagocyte system and cellular and humoral immunity, and the lipophilic portion had immunosuppressive activity on cellular and humoral immune responses.

The oral median lethal dose (LD_{50}) values for rats and mice of mixtures containing *H perforatum* extract were >20 mL/kg. The minimum lethal subcutaneous dose of *H perforatum* using guinea pigs was 0.1 mL. The intraperitoneal LD_{50} values of the polyphenol, lipophile, and water soluble fractions of *H perforatum* were 780, 4300, and 2800 mg/kg, respectively. Signs of toxicity were observed in Awasi sheep fed *H perforatum* flowers (4 g/kg) for 14 days. In a chronic study in which Long-Evans rats were fed *H perforatum* (5%), average daily weight gain was statistically significantly decreased when compared to control animals. Mixtures containing *H perforatum* extract and *H perforatum* oil were not irritants (up to 5%) or sensitizers (up to 5%) in animals. *Hypericum perforatum* is a primary photosensitizer in animals because of the pigment hypericin that causes photoactivated damage by absorbing visible light. A mixture containing *H perforatum* oil, butylene glycol, and water was not phototoxic. Mixtures containing *H perforatum* extract (0.5%) and *H perforatum* oil (0.1%) were non to slightly irritating, respectively, in rabbit eyes.

In an Ames test, a tincture of *Hypericum* had mutagenic effects at 20 mg/100 μL suspension, which the researchers attributed to flavonols. However, the origin of the plant and the mode of preparation of the tincture were considered to play a role in the mutagenic potential. In another Ames test, *H perforatum* (10 μL) had mutagenic activity; in testing fractions of 3 extracts, the mutagenic potential was found exclusively in quercetin, and hypericin was not mutagenic. *Hypericum* extract (500 μL) and hypericin were not genotoxic in unscheduled DNA synthesis assays using primary rat hepatocytes. *Hypericum* extract (4.00 μL/mg) was not mutagenic in a cell transformation assay using Syrian golden hamster embryo cells, and it was not genotoxic in a mouse fur spot test or in a chromosome aberration test.

A mixture of *H perforatum* oil, butylene glycol, and water was not irritating in clinical studies. In human testing, *Hypericum* extract did not appear to be toxic, although some undesirable drug interactions were observed.

Chemistry

Definition

The definitions and functions of these *H perforatum*-derived ingredients are provided in Table 1.

Constituents

Constituents of *H perforatum* are listed in Table 2.

Hypericum perforatum flower contains not less than 0.08% of total hypericins expressed as hypericin calculated with reference to the dried drug.[4-6] Constituents of *H perforatum* include:

- phloroglucinol derivatives: 0.2% to 4%, depending on the age of the herbal drug, mainly hyperforin and its homolog adhyperforin and furanohyperforin;
- naphthodianthrone: 0.06% to 0.4%, mainly pseudohypericin and hypericin, protohypericin, protopseudohypericin, cyclopseudohypericin, and skyrin derivatives; the amount of pseudohypericin is about 2 to 4 times higher than that of hypericin;
- flavonoids: 2% to 4%, mainly glycosides of the flavonol quercetin: hyperoside, rutin, isoquercitrin, quercitrin; also biflavones (I3, II8-biapigenin, amentoflavone);
- procyanidines: for example, procyanidine B2, tannins with catechin skeletal (6%-15%);

Table 2. Constituents Found in *Hypericum Perforatum*.[60]

Chemical	Plant part	Concentration, ppm
(+)-Catechin	Plant	
(+)-Epicatechin	Plant	
(-)-Epicatechin	Plant	
(E)-beta-farnesene	Plant	0.5-9
(E)-ocimene	Plant	0.1-2.25
(Z)-ocimene	Plant	0.25-4.5
1(3)-11(8)-biapigenin	Flower	
1(3)-11(8)-biapigenin	Shoot	72.5
1,3,6,7-tetrahydroxyxanthone	Leaf	
1,3,6,7-tetrahydroxyxanthone	Plant	
2,2-dimethyl-7-isobutyl-2h,5h-pyrano-(4,3-b)-pyran-5-one	Plant	1.5-27
2,2-dimethyl-7-sec-butyl-2h,5h-pyrano-(4,3-b)-pyran-5-one	Plant	1-18
2-methyl-butenol	Plant	
2-methyl-decane	Fruit essential oil	
2-methyl-decane	Leaf essential oil	
2-methyl-decane	Shoot	
2-methyl-octane	Fruit essential oil	
2-methyl-octane	Shoot	
2-methyl-octane	Leaf essential oil	
5-methylheptan-2,4-dione	Plant	0.25-4.5
6-methyl-hept-5-en-2-one	Plant	1-18
6-methylheptan-2,4-dione	Plant	0.25-4.5
Acetophenone	Plant	0.1-2.25
Acylphloroglucinols	Plant	
Adhyperfolin	Flower	
Adhyperfolin	Fruit	
Adhyperiforin	Plant	2000-19 000
Alkanes	Shoot	
Alkanols	Shoot	
Alpha-amorphene	Plant	0.25-4.5
Alpha-campholenol	Plant	0.05-0.9
Alpha-cuprenene	Plant	16-288
Alpha-eudesmol	Plant	2.5-45
Alpha-humulene	Plant	1-18
Alpha-phellandrene	Plant	0.3-5.4
Alpha-pinene	Shoot essential oil	
Alpha-pinene	Leaf essential oil	
Alpha-pinene	Plant	13-245
Alpha-pinene	Fruit essential oil	
Alpha-selinene	Plant	1-18
Alpha-terpinene	Plant	1-18
Alpha-terpineol	Plant	3-54
Alpha-terpinyl-acetate	Plant	0.1-1.8
Amentoflavone	Flower	100-500
Amentoflavone	Shoot	
Ar-curcumene	Plant	0.5-9
Ascorbic-acid	Leaf	
Ascorbic-acid	Seed	395
Ascorbic-acid	Shoot	16.5
Ascorbic-acid	Plant	1300
Beta-amyrin	Shoot	
Beta-bourbonene	Plant	0.25-4.5
Beta-carotene	Shoot	12.1
Beta-elemene	Plant	0.25-4.5
Beta-eudesmol	Plant	2-32
Beta-pinene	Fruit essential oil	
Beta-pinene	Shoot	
Beta-pinene	Plant	335-6055
Beta-pinene	Leaf essential oil	
Beta-selinene	Plant	1.5-27
Beta-sitosterol	Plant	
Beta-sitosterol	Shoot	
Biapigenin	Leaf	
Bicycloelemene	Plant	0.1-1.8
Borneol	Plant	0.15-2.7
Bornyl-acetate	Plant	0.2-3.6
Brenzcatechin	Plant	
Cadinene	Essential oil	
Cadmium	Leaf	1-7
Cadmium	Root	1-3
Cadmium	Plant	1-5
Caffeic-acid	Plant	1000
Caffeic-acid	Shoot	1000
Camphene	Plant	1-18
Carotene	Seed	165
Carotenoids	Plant	
Caryophyllene	Essential oil	
Caryophyllene	Plant	26-468
Caryophyllene-epoxide	Plant	0.5-9
Catechins	Plant	
Ceryl-alcohol	Plant	
Chlorogenic-acid	Leaf	
Chlorogenic-acid	Plant	
Chlorophyll	Plant	
Choline	Leaf	
Choline	Plant	
Choline	Shoot	34-1000
Cineole	Essential oil	
Cinnamic-acid	Plant	
Cis-trollixanthin	Flower	
Cyanidin	Plant	
Cyclopseudohypericin	Plant	
Cysteine	Plant	
Delta-cadinene	Plant	0.5-9
Dodecanol	Plant	
Elemol	Plant	0.25-4.5
Emodinanthranol	Plant	
Eo	Flower	2500
Eo	Shoot	700-1250
Eo	Seed	3300
Eo	Plant	500-9000
Fat	Seed	328 000
Fenchol	Plant	0.25-4.5

(continued)

Table 2. (continued)

(continued)

Table 2. (continued)

Chemical	Plant part	Concentration, ppm
Ferulic-acid	Plant	
Flavonoids	Flower	117 100
Flavonoids	Shoot	70 000-74 000
Gaba	Plant	700
Gallic-acid	Plant	
Gamma-curcumene	Plant	0.5-9
Gamma-eudesmol	Plant	1.5-27
Gamma-terpinene	Plant	1.5-27
Gentisic-acid	Plant	
Geranial	Plant	0.35-6.3
Geraniol	Plant	4-72
Geranyl-acetate	Plant	24-432
Glutamine	Plant	
Guaiol	Plant	1.5-27
Gurjunene	Plant	
Hexacosan-1-ol	Leaf	
Humulene	Essential oil	
Humulene	Plant	
Hyperesin-1	Plant	
Hyperesin-2	Plant	
Hyperforin	Flower	27 930
Hyperforin	Shoot	
Hyperforin	Plant	20 000-45 000
Hyperforin	Fruit	
Hyperforin	Leaf	
Hypericin	Cotyledon	14.5
Hypericin	Stem	40-210
Hypericin	Shoot	390-1780
Hypericin	Plant	5000-7000
Hypericin	Leaf	190-1950
Hypericin	Fruit	730
Hypericin	Flower	860-18 000
Hypericin	Flower essential oil	5-19
Hypericin	Essential oil	2200
Hypericins	Plant	95-4660
Hypericodihydroanthrone	Plant	
Hyperifolin	Plant	
Hyperin	Plant	3500-5500
Hyperoside	Flower	6570
Hyperoside	Stem	
Hyperoside	Shoot	5000-40 000
Hyperoside	Plant	3500-20 000
Hyperoside	Leaf	
I3, ii8-biapigenin	Flower	100-500
I3, ii8-biapigenin	Plant	2600
I3, ii8-biapigenin	Flower	1000-5000
Imanin	Plant	
Imanin	Shoot	
Ishwarane	Plant	0.5-9
Isoferulic-acid	Plant	
Isohypericin	Plant	
Isoquercetin	Plant	
Isoquercitin	Plant	
Isoquercitrin	Flower	
Isoquercitrin	Plant	3000

(continued)

Table 2. (continued)

Chemical	Plant part	Concentration, ppm
Isovalerianic-acid	Plant	
Isovaleric-acid-ester	Plant	
Kaempferol	Plant	
Kielcorin	Plant	
Kielcorin	Root	
Kilecorin	Plant	
Lead	Leaf	6-18
Lead	Plant	2-12
Lead	Root	4-5
Leucine	Plant	
Leucocyanidin	Plant	
Limonene	Fruit essential oil	
Limonene	Shoot	
Limonene	Plant	5-90
Limonene	Leaf essential oil	
Linalool	Plant	2.5-45
Lutein	Flower	
Luteolin	Plant	
Luteoxanthin	Flower	
Lysine	Plant	
Mangiferin	Plant	
Mangiferin	Shoot	
Mangiferin(sic)	Plant	
Mannitol	Plant	11 000-20 000
Methyl-2-decane	Plant	
Methyl-2-octane	Essential oil	164 000
Methyl-3-but-3-en-2-ol	Plant	
Methyl-geranate	Plant	0.3-5.4
Myrcene	Fruit essential oil	
Myrcene	Leaf essential oil	
Myrcene	Essential oil	
Myrcene	Plant	10-190
Myrcene	Shoot	
Myricetin	Plant	
Myricetin-3-o-beta-d-glucoside	Plant	
Myristic-acid	Plant	
N-decanal	Essential oil	
N-nonane	Fruit essential oil	
N-nonane	Shoot	
N-nonane	Essential oil	
N-nonane	Leaf essential oil	
N-octanal	Essential oil	
N-octanol	Essential oil	
N-undecane	Fruit essential oil	
N-undecane	Leaf essential oil	
N-undecane	Shoot	
Neo-alloocimene	Plant	0.3-5.4
Neral	Plant	0.35-6.3

(continued)

Table 2. (continued)

Chemical	Plant part	Concentration, ppm
Nerol	Plant	1-18
Neryl-acetate	Plant	1-18
Nicotinic-acid	Leaf	0.007-1200
Nonacosane	Plant	
Nonane	Plant	23-414
Nor-cyclopseudohypericin	Plant	
Novoimanin	Plant	
Novoimanin	Shoot	30 000-40 000
Oct-1-ene	Plant	1.5-17
Octacosan-1-ol	Leaf	
Opcs	Plant	
Ornithine	Plant	
P-coumaric-acid	Plant	
P-cymene	Plant	0.5-9
P-hydroxy-benzoic-acid	Plant	
Palmitic-acid	Plant	
Pectin	Plant	
Perflavit	Shoot	
Phenol	Plant	
Phlobaphene	Plant	
Phloroglucinol	Plant	
Phloroglucinol	Shoot	
Phytosterols	Plant	
Pinene	Essential oil	
Pinol	Plant	0.05-0.9
Proanthocyanidins	Plant	120 000
Procyanidins	Plant	
Proline	Plant	
Protein	Seed	181 000-207 000
Protohypericin	Plant	
Protopseudohypericin	Plant	
Provitamin-a	Plant	130
Pseudohypericin	Cotyledon	164.9
Pseudohypericin	Shoot	40
Pseudohypericin	Plant	
Pseudohypericin	Leaf	
Pseudohypericin	Flower	2260-5800
Pseudohypericodihydroanthrone	Plant	
Pyrogallol	Plant	
Quercetin	Flower	1000
Quercetin	Plant	20 000
Quercetin	Stem	
Quercetin	Shoot	
Quercetin	Leaf	
Quercetin-3-o-glucuronide	Plant	
Quercetin-3-o-glucuronide	Shoot	
Quercetin-3-o-xyloside	Plant	
Quercetin-3-o-xyloside	Shoot	
Quercitrin	Flower	3380
Quercitrin	Leaf	
Quercitrin	Plant	
Quercitrin	Shoot	3000-5240
Resorcynol	Plant	
Rhodan	Plant	
Rutin	Flower	1000-2800
Rutin	Leaf	2000-3000
Rutin	Stem	
Rutin	Shoot	10 000
Rutin	Plant	16 000
Saponin	Seed	
Scopoletin	Plant	
Selina-4,11-diene	Plant	0.15-2.7
Sitosterol	Plant	
Stearic-acid	Plant	
Tannins	Flower	162 000
Tannins	Stem	18 000
Tannins	Shoot	3300
Tannins	Plant	30 000-160 000
Tannins	Leaf	124 000
Tannins	Seed	121 000
Taraxasterol	Shoot	
Terpinen-4-ol	Plant	0.5-9
Terpineolene	Plant	1.5-27
Tetracosan-1-ol	Leaf	
Threonine	Plant	
Triacontan-1-ol	Leaf	
Trollichrome	Flower	
Umbelliferone	Plant	
Undecane	Plant	0.25-4.5
Vanillic-acid	Plant	
Violaxanthin	Flower	
Xanthones	Plant	12.8

- xanthones: in trace amounts;
- essential oil: 0.1% to 0.25%; the essential oil of dried flowering tops contains as main compounds 2-methyloctane (16%) and α-pinene (10.6%). In the essential oil of leaves of Indian origin, 58 components were identified, α-pinene (67%) being dominant; the other components included caryophyllene, geranyl acetate, and nonane (each about 5%);
- other constituents: include small amounts of chlorogenic acid and other caffeoylquinic and p-coumaroylquinic acids and also free amino acids.

Information on the characterization of different commercial *H perforatum* extracts with regard to hypericins, hyperforin, and flavonoids are provided in Table 3.

In a batch of St. John wort extract capsules, the label stated that they contained 300 mg of extract and 900 μg of hypericin.[7] Analysis found that the contents actually weighed 444 ± 20 mg and contained 840 ± 56 μg of hypericin and 11 ± 0.63 mg of hyperforin.

Method of Manufacture

It was reported that cosmetic grade *H perforatum* flower/leaf/stem extract is mostly extracted from the dried plant but may occasionally be extracted from fresh material.[3] Extraction

Table 3. Parameters/Characterization of Various Commercial *Hypericum perforatum* Extracts (These are Assumed to be Dietary Supplements).[61]

Parameter	Value
LI 160	
Extraction solvent	80% methanol
DER	3-6:1, initially 4-7:1
Total hypericins	0.12%-0.28%
Hyperforin	Approximately 4.5%
Flavonoids	Approximately 8.3%
Other	From several notes in publications it can be assumed that the content of hyperforin is in the range from 3% to 6%
WS 5570	
Extraction solvent	80% methanol
DER	3-7:1
Total hypericins	0.12%-0.28%
Hyperforin	3%-6%
Flavonoids	$\geq$6.0%
Other	The extraction solvent and the declared amount of *Hypericum* of this extract are identical with that of LI 160
Ze 117	
Extraction solvent	Solvents vary: 50% ethanol (m/m) or ethanol 49% m/m: 2-propanol (97.3:2.7)
DER	4-7:1
Total hypericins	0.2%
Hyperforin	nearly free of hyperforin (eg, 0.07%)
Other	Information on the refinement of the extract in order to reduce the content of hyperforin is not available
Hyperforat drops	
Extraction solvent	50% ethanol
DER	0.5:1
Total hypericins	2 mg/mL
Hyperforin	Not specified
Other	Liquid
STW 3	
Extraction solvent	50% ethanol
DER	5-8:1
Total hypericins	mean 0.2%
Hyperforin	mean 2%
Flavonoids	mean 9%
Esbericum	
Extraction solvent	60% ethanol
DER	2-5.5:1
Total hypericins	0.1%
Hyperforin	Not specified
Flavonoids	Not specified
STEI 300	
Extraction solvent	60% ethanol m/m
DER	5-7:1
Total hypericins	0.2%-0.3%
Hyperforin	2%-3%
Flavonoids	Not specified
LoHyp-57	
Extraction solvent	60% Ethanol
DER	5-7:1
Total hypericins	0.2%-0.3%
Hyperforin	2%-3%
Flavonoids	Not specified
STW3-VI	
Extraction solvent	80% Ethanol
DER	3-6:1
Total hypericins	Mean 0.2%
Hyperforin	Mean 2.0%
Flavonoids	Mean 9%
WS 5572	
Extraction solvent	60% ethanol
DER	2.5-5:1
Total hypericins	Not specified
Hyperforin	4%-5%, 5%, 1.5%
Calmigen	
Extraction solvent	Not specified
DER	Not specified
Total hypericins	0.3%
Hyperforin	Not specified
Hyperiforce	
Extraction solvent	Not specified
DER	4-5:1 (shoot tips)
Total hypericins	0.5%
Hyperforin	Not specified

Abbreviation: DER, dry extract ratio.

solvents include water/propylene glycol, propylene glycol, 86% ethanol, 50% butylene glycol, water, sunflower oil, olive oil, caprylic/capric triglycerides, or glycerin. Solids in these extracts measure 0.1% to 5%. The hypericin content from an 86% ethanol (3% solids) extract of fresh plant materials was reported to be 60 to 65 μg/mL, and the hyperforin content was 240 to 900 μg/mL.

Use

Cosmetic

Data on ingredient usage are provided to the FDA Voluntary Cosmetic Registration Program (VCRP; Table 4).[8] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group.[9]

Hypericum perforatum extract was reported to be used in 32 leave-on products (up to 0.01%), 3 rinse-off products (no use concentration reported), and 1 baby product (no use concentration reported). *Hypericum perforatum* flower was reported to be used in 1 leave-on product; maximum concentration of use was reported to be 0.005% in face and neck creams, lotions, and powders. *Hypericum perforatum* flower/leaf/stem extract is reported to be used in 49 leave-on products (up to 0.07% in body and hand creams, lotions, and powders) and in 25 rinse-off products (up to 0.00004% in shampoos and rinses), mostly in skin care products. The VCRP reports that it is also used in 2 products that are diluted for bath (no use concentration reported). There is 1 reported

Table 4. Frequency of Use According to Duration and Exposure of *Hypericum Perforatum*-Derived Cosmetic Ingredients.[8,9,a]

Use type	Uses	Maximum concentration (%)	Uses	Maximum concentration (%)	Uses	Maximum concentration (%)	Uses	Maximum concentration (%)
	Hypricum perforatum extract		*Hypericum perforatum* flower extract		*Hypericum perforatum* flower/leaf/stem extract		*Hypericum perforatum* oil	
Total/range	35	0.00005-0.01	1	0.005	76	0.00002-0.07	17	0.00005
Duration of use								
Leave on	32	0.00005-0.01	1	0.005	49	0.00002-0.07	13	0.00005
Rinse off	3	NR	NR	NR	25	0.00002-0.00004	4	NR
Diluted for (bath) use	NR	NR	NR	NR	2	NR	NR	NR
Exposure type								
Eye area	5	NR	1	NR	1	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	NR	1	NR	1	NR
Incidental inhalation powders	1	NR	NR	NR	1	NR	NR	NR
Dermal contact	31	0.00005-0.01	1	0.005	64	0.00002-0.07	16	0.00005
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair noncoloring	22	NR	NR	NR	12	0.00002-0.00004	1	NR
Hair coloring	1	NR	NR	NR	NR	0.00002	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	4	NR	NR	NR
Baby	1	NR	NR	NR	1	NR	NR	NR

Abbreviations: NR, not reported; Totals, rinse-off + leave-on product uses.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

use in baby lotions, powders, and creams. *Hypericum perforatum* oil is reported to be used in 13 leave-on products and in 4 rinse-off products. Use concentration was only reported for skin preparations up to 0.00005%.

There were no reported uses or concentration of use for *H perforatum* flower/leaf extract, *H perforatum* flower/twig extract, and *H perforatum* leaf extract. *Hypericum perforatum* flower and *Hypericum* flower/leaf/stem extract are used at concentrations up to 0.07% in cosmetic products that may include loose powders of which airborne particles may be inhaled. The size distribution of the particles in cosmetic powders has not been reported. However, particles incidentally inhaled from cosmetic aerosols would likely be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[10-15]

Noncosmetic

Oral therapeutic use *H perforatum* was reported to be safe up to 900 mg/d (~13 mg/kg/d) for humans.[16]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

Dermal/percutaneous

Hypericin. Hypericin is absorbed through the intestinal epithelium by passive transcellular diffusion.[17] There was no hypericin detected in the plasma of Balb/c mice after administration to the ear (0.1%-1% in Beeler base) for 24 hours.[18] The distribution of hypericin-related fluorescence in the skin after dermal administration (1%) was concentrated in the stratum corneum and epidermis with only faint fluorescence in the dermis observed. At lower concentrations (0.1% and 0.01%), the fluorescence was concentrated only in the stratum corneum and was faint in the epidermis.

Oral

Hypericum perforatum extract. After a single oral dose of *H perforatum* extract (300 mg; tablet form; 900 µg hypericin + pseudohypericin), the mean serum level in subjects (n = 12) of total hypericin + pseudohypericin was 43 ng/mL and the mean skin blister fluid level was 5.3 ng/mL at 6 hours.[19] After

steady state administration (1 tablet, 3×/d for 7 days), the mean serum level of total hypericin + pseudohypericin was 12.5 ng/mL and the mean skin blister fluid level was 2.8 ng/mL. The authors stated that these skin levels are far below hypericin skin levels that are estimated to be phototoxic (>100 ng/mL).

After a single oral dose of a *H perforatum* extract (1600 mg/kg in agarose gel; 1.35% isoquercitrin, 0.38% quercitrin, 3.26% rutin, 1.83% hyperoside) administered to male Sprague Dawley rats (n = 30; control n = 6), the quercetin plasma level increased rapidly and reached the maximum of about 700 ng/mL after 4 hours.[20] After 24 hours, 50% of the C_{max} was still measurable. In contrast, the concentration level of isorhamnetin/tamarixetin increased much slower; the maximum was reached after 24 hours with a C_{max} of 903 ng/mL. Repeated doses of *H perforatum* extract (1600 mg/kg/d for 8 days) caused a continuous increase in the plasma levels of quercetin and isorhamnetin for 5 days; after that time the concentration remained constant.

Short-term oral administration of *H perforatum* extract (300 mg, 3×/d) to humans resulted in a selective induction of CYP3A activity in the intestinal wall.[7] *Hypericum perforatum* did not alter the activities of CYP2C9, CYPlA2, or CYP2D6 after 2 weeks.

In 36 samples of breast milk from mothers (n = 5) who were taking *H perforatum* extract (300 mg times/d), hyperforin was present in the milk at 0.9% to 2.5% (infant hyperforin dose/kg body weight expressed as a percentage of the maternal hyperforin dose/kg body weight).[21] The plasma from 2 of the infants contained low levels of hyperforin (0.1 ng/mL).

Hyperforin was detected in the breast milk of a mother who took 3 *H perforatum* extract pills (3 × 300 mg/d; 0.12%-0.28% hypericins, ~4.5% hyperforin).[22] Hyperforin and hypericin were below the limits of detection in the infant's plasma.

Constituents. The half-lives for hypericin, pseudohypericin, hyperforin quercetin, and isorhamnetin were similar whether *H perforatum* extract (612 mg) was administered to subjects (n = 18) in 1 dose or daily for 14 days.[23]

The C_{max} of hyperforin was ~370 ng/mL (~690 nmol/L) at ~3 hours after oral administration of an ethanol/water extract of *H perforatum* (0, 300 mg/kg; 5% hyperforin) to Sprague-Dawley rats (n = 5 for each sampling interval).[24] Blood samples were taken at 15 and 30 minutes and 1, 2, 4, 6, 8, and 24 hours.

In humans, the maximum plasma levels of ~150 ng/mL hyperforin (~280 nmol/L) were reached 3.5 hours after oral administration of a *H perforatum* ethanol/water extract.[24] In an open, single-dose, 4-way crossover study, the same *H perforatum* extract (300, 600, 1200 mg; in pill form) or a second extract (0.5% hyperforin) was orally administered to subjects (n = 6) for 8 days. Blood samples were taken at 0, 15, 30, and 45 minutes and 1, 1.5, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours on days 1 and 8. Washout period was 3 days.

In a second human double-blind, placebo-controlled, parallel-group, 8-day study of *H perforatum* extract (300, 600, and 1200 mg; in pill form) or a second extract (0.5% hyperforin), the half-life and mean residence time were 9 and 12 hours, respectively. Hyperforin pharmacokinetics were linear up to the 600 mg dose. Increasing the doses to 900 or 1200 mg resulted in lower C_{max} and area under the curve values than those expected from linear extrapolation of data from lower doses. Plasma concentration curves in volunteers fitted well in an open 2-compartment model. In the repeated-dose study, there was no accumulation of hyperforin in the plasma. The estimated steady state of hyperforin in plasma was ~100 ng/mL (~180 nmol/L).

Intravenous

Hypericin. Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) to rhesus monkeys (*Maccaca mulatta*; n = 3) resulted in a mean peak plasma concentration of 142 ± 45 μmol/L; elimination was biexponential with an average α half-life of 2.8 ± 0.3 hours and terminal half-life of 26 ± 14 hours.[25] Hypericin was not detected in the cerebrospinal fluid of any animal.

In vitro. Using human colonic Caco-2 cells as a model for human intestinal absorption, porcine capillary endothelial cells for the blood–brain barrier, and plexus choriodei epithelial cells for the blood–cerebrospinal fluid barrier, it was shown that orally ingested miquelianin (quercetin 3-O-beta-D-glucuronopyranoside; a flavonoid with antidepressant activity) could possibly cross all 3 barriers and reach the central nervous system.[26] The permeability coefficients of miquelianin for these cell lines were $0.4 \pm 0.19 \times 10^{-6}$, $1.34 \pm 0.05 \times 10^{-6}$, and $2.0 \pm 0.33 \times 10^{-6}$ cm/sec, respectively.

Anti-Inflammatory Activity

Hypericum perforatum flower extract. *Hypericum perforatum* flower extracts (a hydroalcoholic extract, a lipophilic extract, and an ethylacetic fraction) provoked a dose-dependent reduction in Croton oil-induced ear edema in mice.[27] Inflammation was induced in the right ear of male albino Swiss mice (n = 10) by applying Croton oil, 80 mg dissolved in 15 mL vehicle with and without the test substances. The following vehicles were used: acetone for extracts, the ethylacetic fraction, hypericin, hyperforin dicyclohexylammonium salt, dicyclohexylamine and the relevant controls, ethanol:acetone (3:1, v/v) for hyperoside and its controls, ethanol:acetone (1:1, v/v) for adhyperforin, amentoflavone, isoquercitrin, and the relevant controls. The left ear remained untreated. Control animals were treated only with Croton oil.

The doses that inhibited by 50% (ID_{50}) the Croton oil-induced ear edema in mice had the following order of activity: lipophilic extract (ID_{50} = 220 mg/cm^2) > ethylacetic fraction (ID_{50} = 267 mg/cm^2) > hydroalcoholic extract (ID_{50} >1000 mg/cm^2). Amentoflavone (ID_{50} = 0.16 mmol/L/cm^2), hypericin (ID_{50} = 0.25 mmol/L/cm^2), hyperforin DHCA salt (ID_{50} = 0.25 mmol/L/cm^2), and adhyperforin (ID_{50} = 0.30 mmol/L/cm^2) had anti-inflammatory activity that was more potent or comparable to that of indomethacin (ID_{50} = 0.26 mmol/L/cm^2),

whereas isoquercitrin and hyperoside were less active ($ID_{50} \sim 1$ mmol/L/cm^2). As dicyclohexylamine alone was inactive, the effect of hyperforin DHCA salt can be attributed completely to the phloroglucinol moiety. The pharmacological activity and phytochemical profile of the tested extracts and fractions suggest that different constituents are involved in the topical antiphlogistic property of *H perforatum* in vivo.

Drug Interactions

Hypericin. In an open-label, fixed schedule study, subjects (n = 12) were administered tolbutamide (CYP2C9), caffeine (CYPlA2), dextromethorphan (CYP2D6), oral midazolam (intestinal wall and hepatic CYP3A), and intravenous midazolam (hepatic CYP3A).[7] Blood and urine samples were taken before and during treatment. Subjects continued to take the *H perforatum* extract for 14 days. There were no serious adverse events but some cases of hypoglycemia occurred during the study. The bioavailability of midazolam was reduced to 55% of the control value after 2 weeks of treatment. The authors conclude that *H perforatum* reduced the therapeutic efficacy of drugs metabolized by CYP3A, and this effect should be anticipated during long-term administration.

Toxicological Studies

Acute Toxicity

Intravenous

Hypericin. Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) was well tolerated by rhesus monkeys (n = 3).[25] At a dose of 5 mg/kg, a transient severe photosensitivity rash was observed at 12 hours that resolved within 12 days. Edema and a pruritic erythematous rash with evolution to eschar were observed on the face and light-exposed skin. Mild anorexia and transient elevation in hepatic transaminases were observed.

Repeated-Dose Toxicity

Oral: nonhuman

Hypericum perforatum extract. *Hypericum perforatum* extract (900 and 2700 mg/kg) was orally administered to rats and dogs daily for 26 weeks.[16] Decreased body weight, slight changes in the hematological parameters, and changes in the clinical chemistry parameters, which indicate a slight load damage to the liver and kidneys, were observed in both dose groups. A mild hypertrophy of the zona glomerulosa of the adrenals was observed.

Oral: human

Hypericum perforatum extract. In a randomized, double-blind, crossover study, *H perforatum* extract (255-285 mg; 900 μg hypericin content) orally administered to healthy male subjects (n = 12) 3 times/day for 13 days had no effect on vasoconstrictor responses (VRs) of cutaneous blood flow or skin conductance response (SR).[28] The VR and SR were measured before treatment and at 0.5, 3, and 5 hours after the last dose was given. Systolic and diastolic blood pressures were monitored before the start of medication as well as on treatment days 11 and 14. *Hypericum perforatum* extract and the controls (25 mg amitriptyline, and placebo) were administered to the subjects with at least a 14-day wash out period between treatments.

Reproductive and Developmental Toxicity

Animal

Hypericum perforatum extract. There were no reproductive or developmental effects observed in a 2-generational study of *H perforatum* extract using CD-1 mice (n = 20).[29] The female mice were administered *H perforatum* (180 mg/kg in feed) for 2 weeks prior to mating through gestation. Males were not treated. Increases in body weight, body length, and head circumference (measurements taken from postnatal day 3 through adulthood) were similar between the 2 groups of offspring, regardless of gender. No differences in reaching physical milestones (ie, teeth eruptions, eye opening, external genitalia) were noted between the 2 groups. Reproductive capability, perinatal outcomes, and growth and development of the second-generation offspring were unaffected by parental exposure to *H perforatum* extract.

There were no clinical signs of maternal or developmental toxicity when pregnant Wistar rats (n = 15) were orally administered *H perforatum* extract (36 mg/kg/d in saline; 0.4% hypericin) during gestation days 9 to 15.[30] Maternal toxicity was evaluated through water and food intake, body weight gain, piloerection, locomotor activity, diarrhea, and mortality. Animals were killed on day 21 of gestation and necropsied. The indices of implantation and resorption were calculated.

Examination of the liver, kidney, heart, lungs, brain, and small intestine of the pups of Wistar rats (n = 6) orally treated with *H perforatum* extract (methanol extraction solution containing 0.3% hypericin; 0, 100, 1000 mg/kg/d) showed severe damage to the liver and kidneys of animals killed postnatally on days 0 and 21.[31] Three dams were treated starting 2 weeks prior to mating through 21 days of lactating. The other 3 were treated from delivery through 21 days of lactation. Maternal body weights, gestation time, number of live pups, and weight of pups at birth were similar between the groups. The livers of newborn pups of dams in the low-dose group treated before and during pregnancy showed focal hepatocyte damage was apparent, with vacuolization of cells. In the high-dose group, these lesions were much more evident, with hepatocyte hyaline degeneration, lobular fibrosis, and disorganization of hepatocyte arrays. In the low-dose group, the kidneys showed a decrease in glomerular size with decrease in Bowman space and hyaline tubular degeneration, and in the high-dose group, these lesions were more severe. The same lesions, but much more diffuse and serious, were observed in pups killed after 21 days of ingesting milk from dams that were exposed to the test material throughout pregnancy and lactation. The same lesions

were evident also in pups that were exposed to the substance only through nursing.

There were no effects on maternal weight gain or gestation length nor any effect on offspring body weights (up to postnatal day 56) observed behavior or whole and regional brain weights in Sprague-Dawley rats (n = 35) fed diets containing *H perforatum* extract (0, 180, 900, 1800, 4500 ppm; 0, 0.18, 0.90, 1.80, 4.50 g/kg; 0.3% hypericin) from gestation day 3 to postnatal day 21.[32] Offspring body weights in the treated groups were lower than tin controls at post natal days 56 (180, 900, 1800 ppm groups) and 78 (180, 1800 ppm groups). Offspring were tested using the open field test, acoustic startle response test, complex maze test, Morris water maze test, and the elevated plus maze activity test.

There were no behavioral effects to the offspring of CD-1 mice (n = 45) orally administered *H perforatum* extract (0.75 mg/g/d in feed; 0.3% hypericin) for 2 weeks before and through gestation.[29] There were also no effects on reproductive behavior or success in the next 3 generations of offspring. In the male pups, the treatment group weighed less than the controls. The offspring were tested with homing, locomotor activity, exploratory, forced swim, and anxiety tests.

Hypericum perforatum flower extract. In an in vitro study, the contractility of the vas deferens of Wistar rats exposed to the hydromethanolic extract of the flowering tops of *H perforatum* (1-300 μg/mL; 0.3% hypericin) and hyperforin (10^{-8} to 10^{-4}mol/L was inhibited in a concentration-dependent manner.[33] Stimulation for the contractions was through electrical field stimulation or exposure to α,β-methylene adenosine triphosphate. Hypericin, quercitrin rutin, and kaempferol did not inhibit phenylephrine-induced contractions.

Hypericin. Sprague-Dawley rat embryos explanted into a culture of hypericin (0-142 ng/mL) for 2 days exhibited morphological changes when compared to controls starting at 71.0 ng/mL.[34] Embryos were explanted at gestational day 9.5 and were examined on day 11.5. The embryos exposed to high concentrations of hypericin (71.0 and 142.0 ng/mL) had lower total morphological score and number of somites compared with the control group. There was a negative linear trend in total morphological score, yolk sac diameter, and number of somites, indicating a progressive reduction in these parameters with increasing concentration of hypericin. There were no differences detected in crown-rump length. There were no adverse effects up 28.4 ng/mL.

Human

The frequency of live births and premature births in women in Canada who were taking St John wort (*H perforatum*; n = 54; average age = 32.6 ± 5.3) during their pregnancy were similar to those with no exposure (n = 108; average age = 32.5 ± 4.9).[35] Women were interviewed during pregnancy and followed for 5 to 7 years after birth. *Hypericum perforatum* was consumed by 76% of the pregnant women during the first trimester, 5.5% during the first and second trimester, 7.3% during the entire pregnancy, and 9.1% during some combination of the second and third trimester. Their average daily dose as reported by the subjects was 615 mg among those using tablets. The dose could not be estimated for a few of the subjects because they took *H perforatum* in the form of teas (3), tincture (1), or granules (1).

There were no differences in milk production, maternal adverse events, and infant weight over the first year of life observed when breastfeeding women (n = 33) were orally administered *H perforatum* extract (704.9 ± 463.6 mg/day, no further characterization) compared to disease-matched controls (n = 101) and age- and parity-matched nondisease controls (n = 33).[36]

In 36 samples of breast milk from mothers (n = 5) who were taking *H perforatum* extract (300 mg times/d), hyperforin was present in the milk at 0.9% to 2.5%.[21] The plasma from 2 of the infants contained low levels of hyperforin (0.1 ng/mL). No side effects were seen in the mothers or infants. The authors concluded that these results add to the evidence of the relative safety of St John wort while breastfeeding. Hyperforin was detected in the breast milk of a mother took 3 *Hypericum* extract pills (3 × 300 mg/d; 0.12%-0.28% *Hypericum*, ~4.5% hyperforin).[22] No clinical effects were observed in the mother and infant.

Hypericum perforatum flower extract. The above-mentioned contractility experiment was repeated with segments (3-4 cm) of the epididymal part of the vas deferens taken from subjects (n = 15) who underwent prostatectomy (9 who were 60-72 years old) or orchiectomy (3 who were 28-35 years old). *Hypericum perforatum* flower extract and hyperforin inhibited contractions stimulated by phenylephrine (3 × 10^{-6} mol/L).[33] The IC_{50} values were 13.9 ± 2.0 and 0.45 ± 0.04 μmol/L, respectively.

Genotoxicity

There were no new published genotoxicity studies discovered and no additional data were provided.

Irritation and Sensitization

Irritation

Dermal: human

Hypericum perforatum extract. In an irritation test (n = 18), a bath oil containing *H perforatum* extract (concentration not provided; 50 μL) did not cause irritation and was similar to the control of distilled water.[37] The test material was administered to the volar surface of the arm under occlusion for 24 hours. After an hour, the test areas were evaluated and the test substance readministered for another 24 hours and evaluated again. The evaluations were transepidermal water loss, photometric measurements of skin erythema, and visual scoring.

Sensitization

No dermal sensitization studies were discovered or submitted.

Phototoxicity

Dermal administration

Hypericum perforatum extract . A product containing *H perforatum* extract (1.1%) was not photosensitizing to the backs of guinea pigs when applied to tape-stripped skin.[38] The backs of the guinea pigs were irradiated (320-400 nm; 10.2 J/cm^2) for 5 consecutive days after the product (1, 5, 10, and 20% in distilled water; 0.011%, 0.055%, 0.11%, 0.22%) was administered. Two weeks later, the product (0.1% and 1%) was applied and the skin irradiated. The test sites were observed at 24 and 48 hours.

Incubation in methanolic extract of *H perforatum* (> 50 μg/mL; 0.3% hypericin-like derivatives) was phototoxic to human keratinocyte HaCaT cells in ultraviolet A (UVA) light.[39] The cells were incubated for 4 hours then irradiated (1 J/cm^2 UVA or 150 mJ/cm^2 ultraviolet B [UVB]) for 3 hours. The test substance was not phototoxic in UVB light.

Hypericum perforatum oil. Hypericum perforatum oil (110 μg/mL) and an ointment containing Hypericum oil (30 μg/mL) were not phototoxic when administered to subjects (n = 8) with skin types II and III and no history of skin disease or photosensitivity.[40] There was no change in the minimal erythema dose (MED) after administration of the test materials. There was an increase in the erythema index after treatment with *H perforatum* oil using a more sensitive photometric measurement. The light doses were 24, 48, 96, and 144 J/cm^2 (290-2500 nm), and the treated area was observed at treatment and after 24 and 48 hours.

Hypericin. Dermal administration of hypericin (n = 5-10; 0.1%-1%) resulted in minimal photosensitization to the ears of Balb/c mice at the highest concentration.[18] Hypericin acetate (n = 5-10; 0.015%-1.5%) induced more severe and prolonged response after irradiation characterized by intense erythema and ear swelling at all concentrations; skin damage was healed in 14 days with no scar formation. Residual photosensitization effects declined to almost nondetectable at day 7. Radiation exposure (586 and 589 nm) was performed 24 hours after administration of the test material.

Oral administration

Hypericum perforatum extract. In an oral study of 2 different *H perforatum* extracts (STW3, 80% ethanol extract, 612 mg, 1.4 mg hypericin; STW3-VI, 50% ethanol extract, 900 mg, 1.75 hypericin), male subjects (n = 20) had no change in minimum erythema dose of irradiation after administration of the test substances for 2 weeks.[41] Plasma steady state of hypericin/pseudohypericin was obtained before day 14 of treatment. The UV dose was adjusted for skin type. Two adverse events were reported, both described as hypersensitivity to light in mild intensity

In the presence of a stable plasma concentration of hypericin (6.72 ng/mL) the MED values did not differ from controls.[42] *Hypericum perforatum* extract (three 60 mg capsules) was orally administered twice daily for 2 weeks. Photosensitivity was tested before and after administration of the test material.

Oral administration of *H perforatum* extract in a single dose (5400 and 10 800 μg hypericin; n = 12) or over 7 days (5400 μg initial dose, 2700 μg /d; n = 24) did not increase dermal erythema or pigmentation when subjects were exposed to UVB, UVA, visible light, or solar simulated radiation.[43] There was no evidence of phototoxicity. Phototesting was performed prior to first dose and 6 hours after last administration of hypericin tablets. The postadministration erythema index and melanin index were similar to preadministration measurements in all cases except for visible light where there was an increase in the erythema index in the single dose study at both dose levels.

The single dose (5400 and 10 800 μg hypericin; n = 48) and steady state (5400 μg initial dose, 2700 μg /d hypericin; n = 24) studies were repeated with similar results.[44]

In vitro

Hypericum perforatum extract, hypericin, quercetin, and pseudohypericin. *Hypericum perforatum* extracts (0, 30, 40, 50, 60, 70, 90, 100 μg/mL) from 3 different sources and hypericin (0, 0.1, 0.3 μg/mL) were cytotoxic to human keratinocyte cells (HaCaT cells) after incubation and exposure to UVA radiation (250-700 mJ/cm^2) in a concentration- and UVA dose-dependent manner.[45] The cells were incubated in the test substances for 24 hours, irradiated, and then tested for viability using a neutral red assay. As for other constituents, quercetin was cytotoxic without radiation, rutin was phototoxic, and quercitrin had antiphototoxic properties. The UVA irradiation by itself was not cytotoxic up to 1000 mJ/cm^2, where it was mildly cytotoxic.

Hypericin combined with *H perforatum* extracts (plant parts not specified) or constituents exerted less phototoxicity than pure hypericin to HaCaT keratinocytes.[46] The keratinocytes were exposed to 2 *H perforatum* extracts, (1) an ethanol reextraction of residue following a chloroform extraction (3.35 μmol/L hypericin and 124.0 μmol/L total flavonoids) and (2) a chloroform extract (hypericin and flavonoids not detected) supplemented with hypericin (20 μmol/L) and hypericin (20 μmol/L). Each plate was exposed to ambient light provided by fluorescent light bulbs that supplied 5.2 ± 5% J/cm^2 after 30 minutes of exposure to the test materials at room temperature. The extracts showed 24% and 40% less phototoxicity to the keratinocytes, respectively, than to those exposed to hypericin.

In a neutral red uptake assay of HaCAT keratinocytes exposed to UVA light (320-400 nm) after incubation in hypericin (0.1, 0.5, and 1 μmol/L) for up to 60 minutes, there was a dose-dependent increase in DNA damage as irradiation dose increased.[47] However, the authors stated that although the results show that the combination of hypericin and UVA light increased the genotoxic burden, when all factors are taken into account, the risk of significant photogenotoxic damage

incurred by the combination of *H perforatum* extracts and UVA phototherapy may be low in the majority of individuals.

Treatment with both photoactivated hypericin and pseudohypericin resulted in a dose-dependent inhibition of proliferation of human acute T leukemic lymphoma cells; nonphotoactivated plant pigments had no effect on cell proliferation.[48] The IC_{50} of irradiated hypericin was 100 and 200 ng/mL for pseudohypericin.

In a test of the protective effect of quercetin, a natural antioxidant compound, on hypericin-induced cytotoxicity under light conditions using human promyelocytic leukemia cells (HL-60), hypericin (10^{-5} mol/L) alone decreased cell survival to 21%.[49] The combination of quercetin (10^{-5} mol/L) increased survival to 46%. Lower concentrations of quercetin had no protective effect. The authors suggested that these results indicate that oxygen radicals can play a role in hypericin-induced phototoxic effects.

Ocular

Hypericin. Human lens epithelial cells incubated in hypericin (0.1-10 μmol/L) and irradiated (4 J/cm^2 UVA or 0.9 J/cm^2 visible light) had increased necrosis and apoptosis.[50] Neither hypericin exposure alone nor light exposure alone reduced cell viability. The addition of the ocular antioxidants lutein and N-acetyl cysteine did not prevent the damage. The authors concluded that ingested *H perforatum* extract is potentially phototoxic to the eye and could contribute to early cataractogenesis.

Photosensitized photopolymerization was induced in lens alpha-crystalline, isolated from calf lenses, after irradiation (>300 nm, 24 mW/cm^2) in the presence of hypericin (5×10^{-5} mol/L in 10 mmol/L ammonium bicarbonate; pH 7.0).[51] Further analysis of the oxidative changes using mass spectrometry showed specific oxidation of methionine, tryptophan, and histidine residues, which increased with time of irradiation. Hypericin did not damage the lens protein without irradiation. Damage to alpha-crystalline could undermine the integrity of the lens directly by protein denaturation and indirectly by disturbing chaperone function. The authors suggest that in the presence of light, hypericin can induce changes in lens protein that could lead to the formation of cataracts.

Human retinal pigment epithelial (hRPE) cells exposed to hypericin (10^{-7} to 10^{-5} mol/L) and irradiated (0.72 J/cm^2) reduced cell viability compared to untreated cells and cells that were either just exposed to the test material or irradiated.[52] Viability was measured by (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) and lactate dehydrogenase assays after 1.5 hours incubation in hypericin and irradiated for 1, 3, 5, and 10 minutes. The presence of hypericin in irradiated hRPE cells significantly changed the redox equilibrium of glutathione and a decrease in the activity of glutathione reductase. Increased lipid peroxidation as measured by the 2-thiobarbituric acid reactive substances assay correlated with hypericin concentration in hRPE cells and visible light radiation.

The UVB irradiation of bovine lenses exposed to hypericin (10^{-6} mol/L) caused an increase in focal length variability and protein leakage compared to lenses that were only UVB irradiated.[53] The lenses were placed in tissue culture wells and irradiated (0.2 J/cm^2) then followed for 7 days. Lenses treated with hypericin and irradiated had an increase in focal length variability as compared with the lenses that were only UVB irradiated. Lenses without UVB irradiation had lower focal length variability than irradiated lenses. For nonhypericin-treated lenses, UVB-irradiated lenses had a larger variability (4.58 mm) than the unirradiated lenses (1.78 mm). The lenses incubated in elevated glucose concentrations had a focal length variability (3.23 mm) equivalent to that of the unirradiated hypericin-treated lenses (3.54 mm). The authors concluded that photooxidative damage by hypericin results in changes in the optical properties of the lens, protein leakage, and finally cataract formation. This is evidence that people should protect their eyes from intense sunlight when taking *H perforatum*-derived substances.

Using the data collected in questionnaires by the National Center for Complementary and Alternative Medicine and Alternative Health/Complementary and Alternative Medicine Supplement (ALT; a total of 120 142 753 responses), an association between the oral use of *H perforatum* among person 40 years of age and older and the presence of cataracts was reported to have an odds ratio of 1.59 (05% confidence interval 1.02-2.46) or that persons with cataracts are 59% more likely to report St. John's wort use.[54] The authors stated that *Hypericum perforatum* may increase the risk of cataracts but the mechanism is not established.

Clinical Use

Oral

There are many clinical studies of the oral use of *H perforatum* extracts for effectiveness as an antidepressant and for safety. Table 5 is a summary of adverse effects that have been reported with the oral administration of *H perforatum* extracts. Adverse events included nausea, headache, dizziness abdominal pain, insomnia/sleep disturbance, cold symptoms, and diarrhea. Except for sleep disturbance, and to a lesser extent headache, the adverse events were reported in low percentages of the subjects.

Dermal

In a half-side comparison study of a cream with and without *H perforatum* extract (1.5% hyperforin), there were 4 reported adverse events in 3 subjects that were classified as not serious but resulted in not finishing the study.[55] One subject developed contact eczema to the vehicle. In the subjects, all with atopic dermatitis, that finished the 4-week study (n = 18), both sides of the skin lesions improved, with fewer skin colonies of *Staphylococcus aureus* on the *H. perforatum* extract side on days 7, 14, and 28.

Table 5. Reported Adverse Events in Oral Clinical Trials.

Extract[a]	Daily dose	Adverse events	Reference
WS 5570	3 × 300 mg	n = 21 of 186; nausea (4.8%), headache (1.6%), dizziness (2.2%), abdominal pain (1.1%), insomnia (1.6%)	62
WS 5572	3 × 300 mg	Sinusitis, bronchitis, common cold	63
Ze 117	2 × 250 mg	n = 6 (7.4%) of 81; abdominal pain (2), moderate diarrhea (1), moderate; melancholia (1), moderate acute deterioration of patient's condition (1), moderate dry mouth (1)	64
Ze 117	2 × 250 mg	8% of 240 subjects; only GI disturbances (5%) with an incidence greater than 2%	65
PM235, (Cederroth International AB, Sweden)	3 × 270 mg	n = 150; mild, mainly headache, gastrointestinal symptoms	66
WS 5570	900 or 1800 mg	26.8% of 71; no "typical adverse events (except: 1 allergic reaction to sunlight → early study termination); 0.006 AE/d	67
Ze 117	2 × 250 mg	62 (39%) of 157; dry mouth (13), headache (3), sweating (2), asthenia (2), nausea (1)	68
STEI 300	3 × 350 mg	0.5 events per subject (22%); n = 263; most frequently reported adverse event: nausea	69
STW3	612 mg	9.8% related to study medication; n = 123; diarrhea (1); serious adverse events that caused leaving the study (3) somatic disorder, cerebral hemorrhage, unrelated accident	70
LI 160	3 × 300 mg	Adverse events: 38; n = 163; subjects with adverse events: 35.1%; adverse events possibly related to study medication: 24; body as a whole (13), gastrointestinal system disorders (6), autonomic nervous system disorders (10), central and peripheral nervous system disorders (10), skin and appendages disorders (9), psychiatric disorders (2), others (5)	71
WS 570	600 or 1200 mg (2 × 600 mg)	All adverse events. 49 (39.8%); n = 123, 127; serious events 1 (tendon rupture attributable to accidental injury); ear and labyrinth disorders 3 (2.4%), gastrointestinal disorders 24 (19.5%), general disorders and administration site conditions 2 (1.6%), infection and infestations 7 (5.7%), injury, poisoning, and procedural complications 1 (0.8%), investigations 1 (0.8%), metabolism and nutrition disorders 1 (0.8%), musculoskeletal and connective tissue disorder 1 (0.8%), nervous system disorder 6 (4.9%), psychiatric disorders 2 (1.6%), renal and urinary disorders 1 (0.8%), reproductive system and breast disorders 1 (0.8%), respiratory, thoracic, and mediastinal disorders 4 (3.3%), skin and subcutaneous disorders 4 (3.3%), vascular disorders 1 (0.8%)	72
LI 160	3 × 300 mg	n = 90; most common adverse events: headache (42%), dry mouth (22%), nausea (20%), gastrointestinal upset (20%), sleepiness (18%)	73
LI 160	900 mg/d for 4 weeks, after this period no adequate response, new dose 1200 mg/d	n = 98; headache (41%), abdominal pain (≥10%)	74
LI 160	900-1500 mg (3-5 × 300 mg)	n = ∼110; diarrhea (21%), nausea (19%), anorgasmia (25%), forgetfulness (25%), frequent urination (27%), sweating (18%), swelling (19%)	75
WS 5570	900 mg (3 × 300 mg)-1800 mg (3 × 600 mg)	n = ∼125; upper abdominal pain (9.6%), diarrhea (9.6%), dry mouth (12.8%), nausea (7.2%), fatigue (11.2%), dizziness (7.2%), headache (10.4%), sleep disorder (4%), increased sweating (7.2%); highest incidence: gastrointestinal disorders (59 events in 42 subjects), nervous system disorders (35 events in 29 subjects), 2 serious adverse events (psychic decompensation attributable to social problems, hypertensive crisis), both not caused by *Hypericum*	76

(continued)

Table 5. (continued)

Extract[a]	Daily dose	Adverse events	Reference
Not specified	900-1800 mg/d	n = 22-23; sleep disturbance (54.8%), anxiety (42.9%); sexual problems (11.9%), headaches (42.9%), dizziness (11.9%), tremor (19.1%), sweating (16.7%), dry mouth (38.1%), muscle spasms (11.9%), muscle or joint stiffness (19.1%), urinary problems (16.7%), difficulty digesting (19.1%), nausea or vomiting (9.5%), diarrhea (23.8%), lack of appetite (23.8%), heart palpitations (9.5%), fatigue (45.2%), pain (11.9%), blurred vision (14.3%); 1 serious adverse reaction (acute manic reaction)	77
WS 5573	3 × 300 mg	WS 5573 (28.6% of 49 subjects); bronchitis (3/1), influenza-like symptoms (2/0), cough (2/0), infection (1/0)	78
Ze 117	2 × 250 mg	8% *Hypericum*, GI disturbances (5%)	65
Hyperiforce (provided by Bioforce AG, Roggwil, Switzerland)	3 × 1 tablet (standardized to either 0.17, 0.33, or 1 mg total hypericin per day)	n = 114-119; there is no difference in AE with possible or probable causality in the 3 treatment groups; Probable/possible relation to study medication: skin (0/3), nerves (2/5), psyche (1/1), gastrointestinal tract (4/0), organism as a whole (0/2)	79
LoHyp 57	2 × 400 mg	n = 149 (withdrawn for AEs: 6)	80
STW3-VI	900 mg	n = 129; total AEs. 58 (17.2%); rRelated: 10; gastrointestinal disorders (6), ear and labyrinth disorders (1), skin and subcutaneous tissue disorders (1)	81
LI 160	3 × 300 mg	n = 165;37% of the subjects; dry mouth (5%), drowsiness (1%), sleepiness (2%), dizziness (1%), lethargy (1%), nausea/ vomiting (7%), headache (7%), constipation (5%), pruritus (2%)	82
LI 160	3 × 600 mg	23% of the subjects; n = 37; dry mouth (3); gastric symptoms (5), tiredness/sedation (5), restlessness (6), tremor (2), dizziness (5), allergic skin reaction (1)	83
WS 5572	600 mg/1200 mg	17 subjects; n = 21 (13 with relation to *Hypericum*); AEs frequency < 1%; skin irritation, pruritus, allergic exanthema, nervousness, restlessness, gastrointestinal disorders (4), diarrhea, insomnia	84

Abbreviations: AE, adverse event; GI, gastrointestinal.
[a] See Table 3 for parameters/characterizations of these extracts.

Case Studies

Hypericum perforatum extract. A 45-year-old female subject developed large blisters that resolved with some hyperpigmentation after laser treatment at 532 nm at 1.5 J/cm^2.[56] She had received a previous treatment with no ill effects. It was discovered that the subject had started taking medication that contained St John wort (*H perforatum*). Another treatment a month after stopping the medication resulted in no ill effects.

A case of an overdose of *H perforatum* extract in a suicidal attempt of a 16-year-old girl resulted in seizures and confusion that resolved after 6 days.[57] It has been reported that the girl had taken up to fifteen 300-μg tablets/day for 2 weeks and 50 tablets just before hospitalization. After 6 days, the electroencephalogram was normal and no further seizures occurred in the following 6 months.

A case of acute neuropathy was reported in a woman after taking powdered *H perforatum* extract (500 mg/d) and exposure to sunlight.[58] The pain started after 4 weeks of use and increased over time and after sunbathing. Symptoms decreased with discontinuation of use after 3 weeks and disappeared after 2 months.

Two pregnant women taking *Hypericum* extract (not characterized as to plant part, 900 mg/day) had no signs of toxicity or other harmful effects.[59] The authors stated concern about the use of *H perforatum* instead of an established effective treatment because safety of *H perforatum* in pregnancy and lactation has not been established.

Summary

Hypericum perforatum (aka St. John's wort)-derived ingredients function in cosmetics as skin-conditioning agents—miscellaneous, skin-conditioning agents—humectants; skin protectants; antioxidants, hai-conditioning agents; and antimicrobial agents. New information has been submitted to meet the data needs that were identified because of the insufficient conclusion of the previous report.

Since the original report was published, the name of *H perforatum* extract was changed to *H perforatum* flower/leaf/stem extract and *H perforatum* extract is now defined as an extract of the whole plant.

Hypericum perforatum extract was reported to be used in 32 leave-on products, 3 rinse-off products, and 1 baby product in concentrations of up to 0.003%. *Hypericum perforatum* flower was reported to be used in 1 leave-on product; maximum concentration of use was reported to be 0.005%. *Hypericum perforatum* flower/leaf/stem extract is reported to be used in 49 leave-on products and in 25 rinse-off products, mostly in skin care products and 2 products that are diluted for bath up to 0.07%. *Hypericum perforatum* oil is reported to be used in 13 leave-on products and in 4 rinse-off products. Use concentration was only reported for skin fresheners up to 0.00005%.

Hypericin, the most active constituent of *H perforatum*, penetrated the stratum corneum and epidermis of mouse ear skin, with little evidence of penetration into the dermis at 1%, with less penetration into the skin at 0.1% and 0.01%. Hypericin, pseudohypericin, hyperforin quercetin, and isorhamnetin were observed in the plasma after oral administration of *H perforatum* extract. Hyperforin was detected in human breast milk but not in the feeding infant's plasma in mothers that ingested *H perforatum* extract.

Orally administered *H perforatum* extract at 900 and 2700 mg/kg to rats and dogs resulted in signs of load damage to the liver and kidneys at the high doses. Orally administered *H perforatum* extract at 255 to 285 mg to healthy male subjects 3 times/day for 13 days had no effect on vasoconstrictor responses of cutaneous blood flow or SR.

There was liver damage to the pups of rats orally treated with *H perforatum* extract at 100 and 1000 mg/kg/d. Lower doses had no effects on rat and mice dams or pups and had no effect on the cognitive abilities of pups. Rat embryos incubated in hypericin at 71.0 and 142 ng/mL had a negative linear trend in total morphological score, yolk sac diameter, and number of somites.

No effects were reported or observed in women who ingested *H perforatum* during pregnancy nor any effects to their infants. No effects were observed in breast feeding infants of mothers who took *H perforatum*.

There was inhibited contractile response in rat and human vas deferens exposed to *H perforatum* up to 300 μg/mL. Human sperm had DNA denaturation when exposed to *H perforatum* extract.

Hypericin demonstrated antiviral, anti-inflammatory, and antitumor effects to human leukocytes.

A bath oil with an unknown concentration of *H perforatum* extracts was nonirritating to humans.

Dermal administration of *H perforatum* extract was not photosensitizing to the backs of guinea pigs at 1.1%. *Hypericum perforatum* oil in a product was not phototoxic to humans at 110 μg/mL. Hypericin at 0.1% and hypericin acetate at 0.015% caused more severe and prolonged dermal response when mouse skin was irradiated. Single dose and short-term oral administration of *H perforatum* extract did not increase photosensitization in humans. Human keratinocyte cells incubated in *H perforatum* extracts and constituents demonstrated increased cytotoxic and photogenotoxic effects when exposed to UVA. Human and bovine ocular cells/lens epitheliums had increased apoptosis and reduced cell viability after incubation in hypericin and exposure to UVA. A survey showed a connection between *H perforatum* use and the development of cataracts.

Adverse events in oral efficacy clinical trials included nausea, headache, dizziness abdominal pain, insomnia/sleep disturbance, cold symptoms, and diarrhea.

Discussion

Although an earlier safety assessment of *H perforatum* extract and oil found the available data insufficient to support safety, additional data were submitted addressing the concentration of use and function in cosmetics and providing photosensitization/phototoxicity, reproductive/developmental toxicity, irritation/sensitization, and ocular irritation data.

Although there are data gaps in this report, the relatedness of constituents, physicochemical properties, functions, and concentrations in cosmetics allowed grouping these ingredients together and extrapolating the available toxicological data to support the safety of the entire group.

The Cosmetic Ingredient Review Expert Panel (Panel) expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

A cosmetic formulation may contain multiple botanical ingredients, each of which can contribute to the total concentration of constituents of concern in the botanical ingredients. For example, the Panel noted that 1 constituent of *Hypericin perforatum*-derived ingredients is hypericin. Hypericin has been shown to be a photosensitizer in visible light and to have possible teratogenic effects in an in vitro study in rats. Hypericin was reported to be present in the various plant parts at 5 to 18,000 ppm. Another constituent is quercetin. Quercetin may be genotoxic and is reported to be in *H perforatum* plant parts at 1000 to 20 000 ppm. Because the maximum concentration of use in cosmetics that contain these *H perforatum* extracts was reported to be 0.07%, the Panel concluded that the amount of exposure to these constituents would be below the threshold of toxicological concern.

The Panel also noted that the use of other botanical ingredients that may contain hypericin and/or quercetin, in combination with *H perforatum*-derived ingredients in a single formulation, could result in exposures that exceed levels of toxicological concern. Potential sensitizers are also constituents of concern that may be present. Thus, cosmetic products containing multiple botanical ingredients should be formulated to ensure that total exposures to such constituents remain below levels of toxicological concern when used as intended.

The Panel discussed the issue of incidental inhalation exposure from face and neck powders. There were no inhalation toxicity data available. The sizes of a substantial majority of the particles of these ingredients, as manufactured, would be expected to be larger than the respirable range (ie, aerodynamic equivalent diameters > 10 μm) and to aggregate and agglomerate to form much larger particles in formulation and would not be respirable to any appreciable amount. Furthermore, particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used (at concentrations up to 0.07% in cosmetic products that may become airborne), the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

The Panel considered other data available to characterize the potential for *H perforatum*-derived ingredients to cause irritation and sensitization, systemic toxicity, and reproductive/developmental toxicity. They noted the lack of systemic toxicity at doses much higher than any cosmetic exposure in acute and subchronic oral exposure studies. There was also little or no irritation or sensitization in multiple tests of dermal and ocular exposure. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The Panel concluded that the following *H perforatum*-derived ingredients were found safe in the present practices of use and concentration in cosmetics:

- *H perforatum* extract;
- *Hperforatum* flower extract;
- *H perforatum* flower/leaf extract*;
- *H perforatum* flower/leaf/stem extract;
- *H perforatum* flower/twig extract*;
- *H perforatum* leaf extract*;
- *H perforatum* oil.

indicates not in current use. Were the ingredients not in current use to be used in the future, the expectation is that they would be used in products categories and at concentrations comparable to others in the group.

Authors' Note

Unpublished sources cited in this report are available from Lillian J. Gill, Director, Cosmetic Ingredient Review, 1620L Street, NW, Suite 1200, Washington, DC 20036, USA.

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