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Final Report on the Safety Assessment of *Piper Methysticum* Leaf/Root/Stem Extract and *Piper Methysticum* Root Extract

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Abstract

Piper methysticum leaf/root/stem extract is the cosmetic ingredient name for a material derived from the leaves, roots, and stems of the *Piper methysticum G. Forster* plant, commonly known as kava kava. This and other kava-derived ingredients are used as skin-conditioning agents at concentrations from 0.0001% to 0.1%. The Food and Drug Administration issued a consumer advisory in 2002 expressing concern about liver damage in individuals who have ingested kava products. The available oral toxicity data support the concern about liver damage on ingestion but do not resolve the question, for example, whether these ingredients would be substantially absorbed through the skin. Other data needs are described, including toxicology data for yangonin, methysticin, and kavain, which may be present in kava-derived ingredients. Accordingly, the available data are insufficient to support the safety of these ingredients in cosmetics.

Keywords

Piper methysticum leaf/root/stem extract and *Piper methysticum* root extract, cosmetics, safety

Piper methysticum leaf/root/stem extract and *Piper methysticum* root extract are botanical extracts used as skin-conditioning agents in cosmetics. In 2002, the US Food and Drug Administration (FDA) issued a consumer advisory and a letter to health care professionals expressing concern about liver damage in individuals who have ingested kava products.[1,2] The Cosmetic Ingredient Review (CIR) undertook this assessment to evaluate the safety of these plant extracts in cosmetics, concluding that there are insufficient data to support their safety in cosmetics.

Chemistry

Definition

The *International Cosmetic Ingredient Dictionary and Handbook* defines *Piper methysticum* leaf/root/stem extract and *Piper methysticum* root extract as cosmetic ingredients used as skin-conditioning agents.[3] In each case, the definition is circular; that is, the root extract is the extract of the root. Only *Piper methysticum* leaf/root/stem extract has a CAS number (84696-40-2); however, this CAS number may be associated with the root extract as well.

Common names for these extracts include ava, ava pepper, awa, intoxicating pepper, kava, kava kava, kava pepper, kava root, kawa, kawa kawa, kew, rauschpfeffer, sakau, tonga, wurzelstock, and yangona.[1]

Composition

The cosmetic ingredient, *Piper methysticum* root extract, is a mixture of 2 groups of related compounds: substituted α-pyrones or substituted 5,6-dihydro-α-pyrones; both groups collectively are known as kavalactones or kavapyrones.[4]

Most available data on kava composition come from analysis of extracts not prepared for use in cosmetics. Because these data demonstrate that other kava extracts contain principally kavalactones and kavapyrones, it is reasonable to assume that these constituents also would be found in cosmetic ingredients. Table 1 lists kava constituent chemicals and their structures.[5]

The methysticin group of derivatives vary as a function of the presence or absence of double bonds in the 5,6 position or the 7,8 position. A similar pattern exists for the kawain group, with the addition of methoxy and hydroxyl groups that may be present for others in this group. Yangonin's basic

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Table 1. Kavalactones Present in *Piper Methysticum* Leaf/Root/Stem Extract and *Piper Methysticum* Root Extract

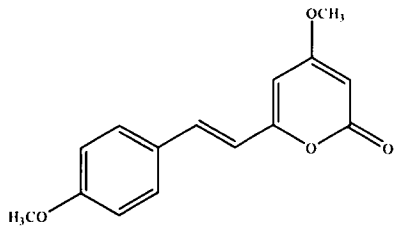
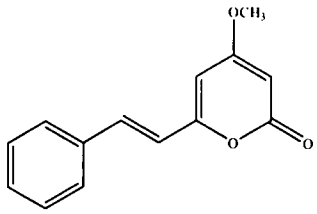
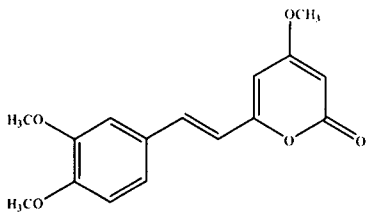
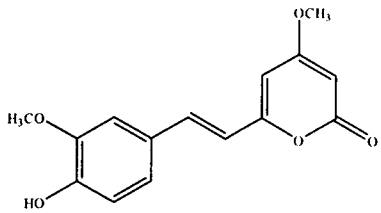
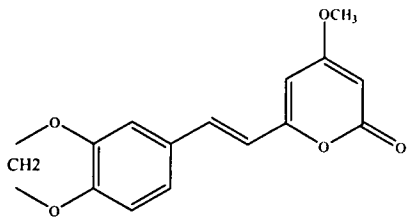
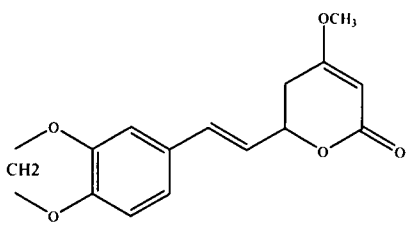
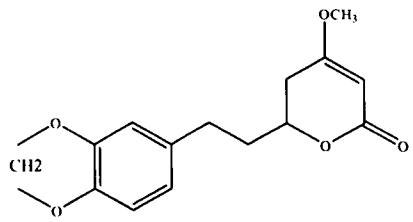
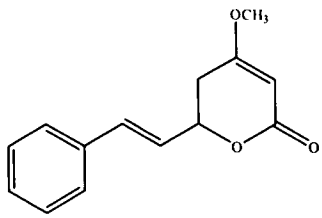
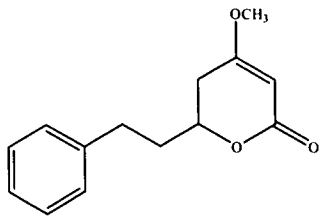
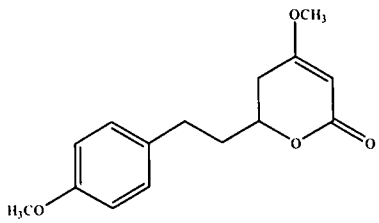
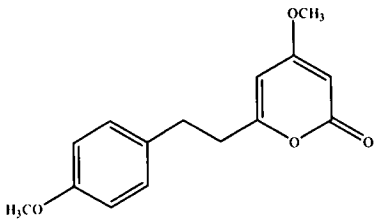
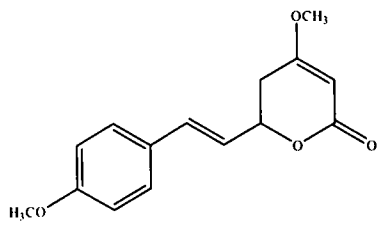
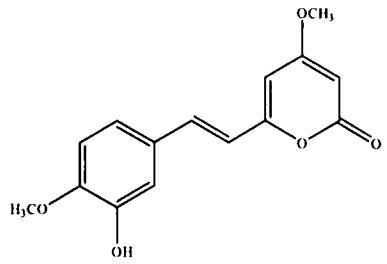
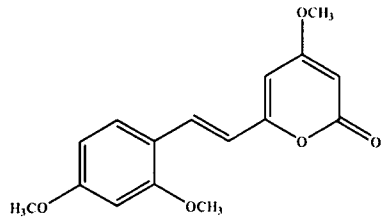
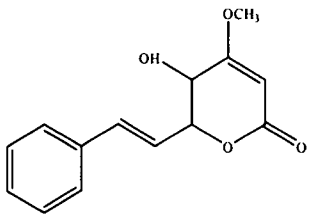
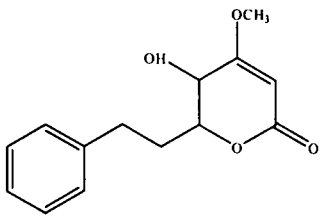
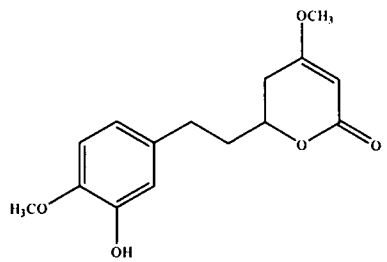
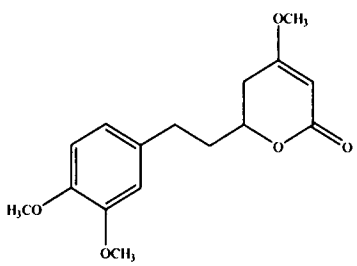
Name (CAS No.)	Structure	Reference
Yangonin (500-62-9)		Bilia et al 2002[67]
Desmethoxyyangonin[a] (15345-89-8)		Bilia et al 2002[67]
11-Methoxyyangonin		Singh 1992[4]
11-Methoxy-nor-yangonin		Singh 1992[4]
5,6-Dehydromethysticin		Bilia et al 2002[67]
Methysticin (495-85-2)		Bilia et al 2002[67]

Table 1. (continued)

Name (CAS No.)	Structure	Reference
Dihydromethysticin (19902-91-1)		Bilia et al 2002[67]
Kawain[b] (500-64-1)		Bilia et al 2002[67]
Dihydrokawain (587-63-3)		Bilia et al 2002 [67]
5, 6, 7, 8-Tetrahydroyangonin		Ramzan and Tran 2004[11]
7,8-Dihydroyangonin		Ramzan and Tran 2004[11]
5,6-Dihydroyangonin		Ramzan and Tran 2004 [11]

(continued)

Table 1. (continued)

Name (CAS No.)	Structure	Reference
11-Hydroxyyangonin		Ramzan and Tran 2004[11]
10-Methoxyyangonin		Ramzan and Tran 2004[11]
5-Hydroxykavain		Ramzan and Tran 2004[11]
5-Hydroxy-7,8-dihydrokavain		Ramzan and Tran 2004[11]
11-Hydroxy-12-methoy-7,8-dihydrokavain		Ramzan and Tran 2004[11]
11,12-Demethoxy-7,8-dihydrokavain		Ramzan and Tran 2004[11]

[a] 5,6-dehydrokawain is a synonym.
[b] 5,6-Deihydro-4-methoxy-6-(2-phenylethenyl)-2H-pyran-2-one is a synonym.

Table 2. Physical and Chemical Properties of Kavalactones[11]

Compound	Formula	Color	MP, °C	λ_{max}, nm	Log ε_{max}	Solubility	α^{20} D (solvent)
Kavain[a,12]	$C_{14}H_{14}O_3$	White	105-106	245	4.41	Practically insoluble in water. Soluble in acetone, ethanol, and methanol. Slightly soluble in hexane.[12]	+105 (EtOH)
7,8-Dihydrokavain	$C_{14}H_{16}O_3$	White	56-58	235, 260	4.04, 3.46	Practically insoluble in water. Soluble in alcohol and chloroform. Moderately soluble in ether.[12]	+30 (EtOH)
Methysticin	$C_{15}H_{14}O_5$	White	139-140	227, 267	4.39, 4.15	—	+95 (acetone)
7,8-Dihydromethysticin	$C_{15}H_{16}O_5$	White	117-118	235, 287	4.18, 3.61	—	+20.57 (MeOH)
Yangonin	$C_{15}H_{14}O_4$	Yellow	153-154	361	4.39	—	-
Desmethoxyyangonin	$C_{15}H_{12}O_3$	Yellow	138-140	231, 255, 344	4.24, 4.16, 4.42	—	-
5,6,7,8-Tetrahydro-yangonin	$C_{15}H_{18}O_4$	White	89-90	227, 278	4.29, 3.25	—	+20 ($CHCl_3$)
7,8-Dihydroyangonin	$C_{15}H_{16}O_4$	-	104-106	224, 278	4.10, 3.97	—	—
5,6-Dihydrohangonin	$C_{15}H_{16}O_4$	-	122-124	263	4.42	—	
11-Methoxyyangonin	$C_{16}H_{16}O_5$	Yellow	160-161	250, 365	4.16, 4.38	—	—
11-Hydroxyyangonin	$C_{15}H_{14}O_5$	—	198-200	—	—	—	—
10-Methoxyyangonin	C16H16O5	—	191-192	—	—	—	—
5-Hydroxykavain	$C_{14}H_{14}O_4$	—	120-122	—	—	—	—
5-Hydroxy-7,8-dihydrokavain	$C_{14}H_{16}O_4$	White	92	231, 260	4.11, 2.85	—	+73 ($CHCl_3$)
5,6-Dehhydromethystiicin	$C_{15}H_{12}O_5$	Yellow	229-230	222, 250, 361	4.41, 4.14, 4.40	—	—
11-Methoxynoryangonin	$C_{15}H_{14}O_5$	Yellow	218-119	221, 250, 373	4.36, 4.15, 4.47	—	—
11-Hydroxy-12-methoxy-7, 8-dihydrokavain	$C_{15}H_{18}O_5$	White	165-167	229, 275	—	—	+35 ($CHCl_3$)
11,12-Dimethoxy-7, 8-dihydrokavain	$C_{16}H_{20}O_5$	White	124-125	229, 275	—	—	+32 ($CHCl_3$)

a. Boiling point 195-197°C.
MP Melting Point, dash means not reported.

structure includes 2 methoxy groups, and the other members of this group are characterized by the presence or absence of double bonds in various positions and/or the addition of an hydroxyl group. The similarities between yangonin and kawain are manifested in that desmethoxyyangonin is a synonym for 5,6-dehydrokawain, and vice versa.

The relative amounts of each constituent may vary as a function of the plant part or source. For example, using a chloroform extraction, the average kawain content on a dry mass basis (% *m/m*) was 1.90% in root extracts, 1.17% from rhizomes, and 0.84% in commercial powders; for yangonin was 1.73% from roots, 0.70 from rhizomes, and 0.47% in commercial powders; and for methysticin was 2.12% from roots, 1.00% from rhizomes, and 0.69 in commercial powders.[5]

Variation also may be found between geographic regions or with the age of the plant. Commercial samples from Fiji were reported to contain significantly more yangonin with dichloromethane extraction than did samples from Vanuatu.[6] The overall kavalactone portion of the plant extract may vary depending on the age of the plant, from 3% to 20% in one report.[7,8]

Trace amounts of other compounds have been isolated from kava and include alkaloids (3α,4α-epoxy-5β-pipermethystine, kawain, methoxycinnamoylpyrolidine and pipermethystine), flavonoids, ketones (cinnamylidine-acetone and methylene 3,4-dioxycinnamylidine-acetone), phytosterols (stigmasterol, stigmastanol, β-sitoserol and campesterol), organic acids, and aliphatic alcohols.[9-11]

Physical and Chemical Properties

Table 2 presents the available chemical and physical properties of the principal constituent chemicals that may be extracted from kava. In general, kavapyrones are poorly soluble in water.[13]

Method of Manufacture

No information on the production of kava extracts for use in cosmetics was available.

Traditionally, lateral roots from the plant were cut from the root mass, cleaned, cut, and macerated into fine particles using a mortar and pestle to make kava powder. Commercially available *Piper methysticum* powder used to make kava beverage is mechanically ground. The powdered product is mixed with water, and the infusion is then strained before drinking.[13]

Medicinal extracts from kava are made by extracting the dried herb with an ethanol–water mixture (producing extracts containing about 30% kavapyrones) or with an acetone–water mixture (producing extracts containing about 70% kavapyrones).[14]

Table 3. Current Uses and Concentrations of *Piper Methysticum* Leaf/Root/Stem Extract and *Piper Methysticum* Root Extract

Product Category (Total No. of Formulations)	2005 Uses[69]	2006 Concentrations[16]
Piper methysticum leaf/root/stem extract		
Bath preparations		
Soaps and detergents (594)	—	0.01%
Noncoloring hair preparations		
Hair tonics, dressings (623)	—	0.01%
Shaving preparations		
Aftershave lotions (231)	2	—
Other shaving preparation products (63)	1	—
Skin care preparations		
Skin cleansing creams, lotions, liquids, and pads (1009)	—	0.1%
Body and hand skin care preparations (840)	—	0.01%
Moisturizers (1200)	—	0.0001-0.01%
Total uses/ranges for *Piper methysticum* leaf/root/stem extract	3	0.0001-0.01%
Piper methysticum root extract		
Noncoloring hair preparations		
Hair tonics, dressings (623)	—	0.01%
Bath preparations		
Soaps and detergents (594)	—	0.01%
Skin care preparations		
Body and hand skin care preparations (840)	—	0.01%
Moisturizers (1009)	—	0.01%
Total uses/ranges for *Piper methysticum* root extract	0	0.01%

Dash means not reported.

Stability

Duve and Prasad[15] reported that the major active constituents in basal stems begin to deteriorate after months of storage of the plant prior to extraction.

Use

Cosmetics

Piper methysticum leaf/root/stem extract and *Piper methysticum* root extract are used as skin-conditioning agents.[3] Table 3 shows available uses and concentrations of *Piper methysticum* leaf/root/stem extract in cosmetics provided by industry to FDA under the Voluntary Cosmetic Registration Program (VCRP). No use data from the VCRP were found for *Piper methysticum* root extract, but the Cosmetic, Toiletry, and Fragrance Association (CTFA) provided a use concentration range for *Piper methysticum* leaf/root/stem extract, which reflected a use concentration range of 0.0001% to 0.01%.[16] No uses were reported to the VCRP for *Piper methysticum* root extract, but CTFA provided a 0.1% use concentration.

Noncosmetics Use

Piper methysticum extracts have been widely used in the South Pacific for social, ritual, and medicinal purposes.[17,18] Elsewhere, *Piper methysticum* is generally available in capsules, powders, and teas or as liquids.[7]

General Biology

Absorption, Distribution, Metabolism, and Excretion

Meyer[19] investigated the absorption of 6 kavalactones—kawain, dihydrokawain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin—administered orally in a peanut oil solution to mice. Both kawain and dihydrokawain were rapidly absorbed from the gastrointestinal tract, the peak effect in mice being 10 minutes, as measured by a maximal electric shock test (no details provided about the maximal electric shock test). Methysticin and dihydromethysticin had a longer induction period, about 30 to 45 minutes, but also had a longer duration of action. Yangonin and desmethoxyyangonin were poorly absorbed from the gut peritoneum, and/or rapid elimination occurred.

Male albino Wistar rats (number not specified) were given 1 of 5 kavalactones (dihydrokawain, kawain, methysticin, 7,8-dihydroyangonin, and yangonin), either via stomach tube as suspensions in 1 mL of water with a small amount (not specified) of sodium deoxycholate (concentration not specified) or as intraperitoneal injections with solutions of compounds in dimethylsulphoxide. Urine, feces, and bile were assessed for metabolites.[20]

The urinary metabolites for each kavalactone as a function of route of exposure in the rat are listed in Table 4.

Other Effects

Studies examining possible antiviral effects of kava extract showed mixed results, and no conclusions could be drawn.[21,22]

Table 4. Urinary Metabolites of Kavalactones in Male Albino Wistar Rats[68]

Kavalactone	Dosage/Route	Metabolite
Dihydrokawain	400 mg/kg orally	4-hydroxy-6-phenylhexan-2-one 4-hydroxy-6-hydroxyphenylhexan-2-one 8-hydroxydihydrokawain Hydroxydihydrokawain *p*-hydroxydihydrokawain Dihydroxydihydrokawain *m,p*-Dihydroxydihydrokawain
Kawain	400 mg/kg orally and 100 mg/kg intraperitoneally	*p*-hydroxybenzoic acid 4-hydroxy-6-phenyl-5-hexen-2-one, hippuric acid 4-hydroxy-6-hydroxyphenyl-5-hexen-2-one *p*-hydroxydihydrokawain Hydroxykawain *p*-hydroxykawain *p*-hydroxy-5,6-dehydrokawain 2 unidentified metabolites
Methysticin	100 mg/kg intraperitoneally and 400 mg/kg orally	*m,p*-dihydroxykawain *m,p*-dihydroxydihydrokawain
7-8 Dihydroyangonin	100 mg/kg intraperitoneally and 400 mg/kg orally	*p*-hydroxy-5,6-dehydro-7,8-dihydrokawain dihydroxy-5,6-dehydro-7,8-dihydrokawain
Yangonin	400 mg/kg orally	*p*-hydroxy-5,6-dehydrokawain dihydroxy-5,6-dehydro-7,8-dihydrokawain *p*-hydroxy-5,6-dehydrokawain

Studies evaluating kava extract for bactericidal and antifungal effects also have been reported.[21]

Several authors reported study results suggesting that kavapyrones have muscle-relaxant effects.[2,23-30]

Analgesic effects of dihydrokavain and dihydromethysticum have also been examined.[25]

Considerable research studying the effect of aqueous and lipid soluble (resin) kava extracts administered intraperitoneally on behavioral responses in mice and rats has been reported.[31-33] The relevance of these data to cosmetic use cannot be evaluated without knowing whether kava is absorbed dermally.

According to Leung and Foster,[34] anodyne, anesthetic, analgesic, antimycotic, antiseptic, antispasmodic, diuretic, expectorant, sedative, stimulant, and tonic activities have been attributed to *Piper methysticum* leaf/root/stem extract. *Piper methysticum* leaf/root/stem extract was found to be a sedative, anticonvulsive, and spasmolytic in animal studies.

Enzyme Effects

Wu et al[35] isolated 6 cyclooxygenase enzyme (COX-I and COX-II) inhibitory compounds with antioxidant activities from *Piper methysticum* (kava kava) root. According to these authors, kavain is 1 of 6 major kavalactones present in *Piper methysticum* roots that was determined to have antithrombotic action in human platelets. These authors suggested that by inhibiting the action of COX and thromboxane synthase enzymes, kavain has a preventive effect on the formation of prostaglandin E_2 and thromboxane A_2.

Unger et al[36] investigated the influence of *Piper methysticum* root extract on the main drug-metabolizing enzyme cytochrome P450 3A4 (CYP3A4) because cytochrome P450 enzymes are involved in the hepatic metabolism and elimination of xenobiotics. The authors concluded that inhibitory activity increased with decreasing polarity of the extraction solvent. They suggested that this finding points to a stronger activity of lipophilic ingredients, which also suggests a potent inhibition of CYP34A by highly lipophilic *Piper methysticum* constituents such as kavalactones or flavokavines.

Matthews et al[37] concluded that these results suggest that compounds in *Piper methysticum* have a high potential for causing drug interactions through inhibition of P450 enzymes responsible for much of the metabolism of pharmaceutical agents.

Zou and Dike[38] studied whether components of *Piper methysticum* are bioactivated by cytochrome P450 enzymes to cytotoxic metabolites. The authors concluded that in vitro *Piper methysticum* compounds do not appear to be activated to toxic metabolites by enzymes known to be important in metabolic activation.

Effect on Tumor Necrosis Factor-α

Hashimoto et al[27] investigated the effect of kavalactones and *Piper methysticum* extract on tumor necrosis factor-α (TNF-α) release assay from BALB/3T3 cells treated with okadaic acid, a tumor inducer. In vitro, kava extract dose-dependently inhibited TNF-α release, as did all of the kavalactones. 5,6-Dehydrokawain and yangonin significantly inhibited TNF-α release with IC_{50} values of 17 μM and 40 μM, respectively. In vivo, kava extract and the kavalactones significantly decreased TNF-α production.

Coté et al[39] compared the activity of commercial kava extract (prepared by acetone, ethanol, or methanol extraction) with traditional kava extract (water extraction). The authors noted that commercial preparations have been linked to hepatotoxicity, whereas no such effects are seen with traditional preparations. The extracts were compared for their inhibition of the major drug-metabolizing P450 enzymes. For specific P450 enzymes (CYP3A4, CYP1A2, CYP2C9, and CYP2C19), the inhibition was more pronounced for the commercial preparation. The authors suggested that the variations in the health effects reported for kava extracts may result from the different preparation protocols used.

Hematologic Effects

Gleitz et al[40] tested the effects of kavain (10-400 μmol/L) in dimethyl sulfoxide (DMSO) on platelet aggregation. Platelets from healthy human volunteers were treated with arachidonic acid (AA) in DMSO, followed by varying amounts of kavain 5 minutes later. AA stimulated platelet aggregation, adenosine triphosphate (ATP)-exocytosis, and the synthesis of prostaglandin E_2 and thromboxane A_2 by platelets. Kavain dose-dependently inhibited all of these effects. Pretreatment with kavain also dose-dependently inhibited the effects of AA.

Uebelhack et al[41] reported on a study where *Piper methysticum* extract and individual kavalactones were tested using platelets from the blood of healthy human subjects. Blood was centrifuged to form platelet-rich plasma and pellets. The monoamine oxidase (MAO) assay was used for testing. *Piper methysticum* extract was made up of kavain (13.9%), dihydrokavain (15.9%), yangonin (9.3%), desmethoxyyangonin (3.8%), dihydromethysticin (13.1%), and methysticin (11.6%). Concentrations of kavalactones in extract tested were 0.25 to 45 μM and 2 to 225 μM for intact and disrupted platelets, respectively. All 6 kavalactones were tested individually at concentrations of 20 μM with intact platelets. Kavain, desmethoxyyangonin, and methysticin were tested at 0.05 to 200 μM to determine IC_{50} values. Extract and kavalactones were diluted with saline or phosphate buffer. For MAO inhibition studies, assays were incubated for up to 60 minutes at 37°C. *Piper methysticum* extract disrupted platelet homogenates (IC_{50} 1.4 μM) and reversibly inhibited MAO-B in intact platelets (IC_{50} 24 μM) dose dependently. All 6 kavalactones inhibited MAO-B at different levels. Desmethoxyyangonin and methysticin were the most potent, with IC_{50} values of 1.2×10^{-7} and 6.7×10^{-7}, respectively, and a mean K_i of 0.28 μM and 1.14 μM, respectively. The order of potency of all lactones was desmethoxyyangonin > methysticin > yangonin > dihydromethysticin > dihydrokavain > kavain.

Cytotoxicity

Nerurkar et al[42] studied the in vitro effects of the kava alkaloid pipermethystine, found mostly leaves and stem of kava, and kavalactones such as 7,8-dihydromethysticin and desmethoxyyangonin, which are abundant in the root. Human hepatoma cells (HepG2) were treated with kavalactones and kava alkaloid at concentrations of 1, 10, 25, 50, 100, and 200 μM for up to 24 hours. The kavalactones and alkaloid were dissolved in DMSO and added to the culture media according to their molecular weights. The final concentration of DMSO in the media was 0.1%. All compounds were soluble in the media and did not precipitate over time. Long-term toxicity was measured for up to 15 days by changing the media with fresh test compounds every 2 days. Controls were treated with equivalent concentrations of DMSO. Media were harvested to determine the release of lactate dehydrogenase, and cells were harvested to determine caspase-3, mitochondrial membrane potential, cellular ATP content, and production of reactive oxygen species.

HepG2 exposure to 100 μM and 50 μM of pipermethystine resulted in a 90% and 65% loss in cell viability within 24 hours, respectively. Kavalactones at similar concentrations had no effect on cell viability for up to 8 days of treatment. The authors mentioned that according to mechanistic studies, pipermethystine significantly decreased cellular ATP levels, decreased mitochondrial membrane potential, and induced apoptosis as measured by the release of caspase-3 after 24 hours of treatment in contrast to kavalactones. The authors suggested that pipermethystine, as opposed to kavalactones, was capable of causing cell death, partly by disrupting mitochondrial function. Therefore, pipermethystine may contribute to rare but severe hepatotoxic reactions to *Piper methysticum*.

Mechanism of Action

Steiner[43] reported that *Piper methysticum* leaf/root/stem extract's neurological effects are mediated through dopaminergic neurons of the nucleus accumbens in the mesocorticolimbic dopamine reward system. As early as 1959, Klohs et al asserted that the main action of all kavalactones (and, presumably, those found in kava extracts) was muscle relaxation.

In neither case can the relevance to cosmetic use be determined without knowing whether kava ingredients are absorbed dermally.

Animal Toxicology

Acute Oral Toxicity

Male rats were administered several different samples of *Piper methysticum Forster*, either from different cultivars or from different areas of 1 plant.[44] The samples (40 g of dry powder) were extracted with 500 mL of ether for about 6 hours. The solvent was evaporated and the residue was emulsified in 25 mL of water and 25 mL of arachis oil with some (not defined) lecithin. This emulsion was immediately administered to rats as a single dose via stomach tube at a dose range of 0.5 to 3 g per 100 kg of body weight. Four of the 8 different kinds of *Piper methysticum Forster* produced unconsciousness and paralysis when administered at a dose equal to 20 g of dried *Piper methysticum Forster* per kilogram of body weight. This dose also caused occasional death. Less toxic samples caused

some signs but to a lesser extent. No further details were provided.

Meyer[45] stated that available data show that large doses of kawain, dihydrokawain, methysticin, and dihydromethysticin produce ataxia and paralysis without loss of consciousness, followed by complete recovery. These kavalactones caused the most paralyses when given at doses of 10 to 30 mg/kg intravenously; the same effect was seen with an oral dose that was 10 times higher. Kavalactones produced depressed polysynaptic responses in the flexor, crossed extensor, skin twitch, and pinna in animals. Also, a rapid intravenous injection of 10 to 30 mg/kg of dihydromethysticin caused a transient drop in blood pressure. This effect was dependent on the speed of injection; the authors attributed this effect to peripheral vasodilation. This effect was also observed in both cats and rabbits where decreased blood pressure was followed by bradycardia that lasted several hours. Experimental results showed that yangonin and desmethoxyyangonin were synergistic with the other 4 kavalactones studied in producing muscle relaxation and hypothermia. No further details were provided. The authors suggest that the 6 kavalactones are all pharmacologically active and differences in action are due to their dosage.

Short-Term Toxicity

A 2.5-month study carried out by Van Dam-Bakker et al[44] investigated a dose of emulsion (described above) equal to 8 g of dry substance per kilogram of body weight.[44] *Piper methysticum* leaf/root/stem extract was administered via a stomach tube twice a week to 12 young adult male rats. Generally, the emulsion came from 1 sample. Control rats received a mixture of oil and water with some lecithin. Five animals in the test group died, compared with none in the control group. No further details were provided.

Singh and Devkota[46] described an experiment where groups of 6 male Sprague-Dawley rats (225-250 g) were given a daily oral dose of 200 or 500 mg/kg/d of *Piper methysticum* extract or a saline placebo for 2 or 4 weeks. High-performance liquid chromatography revealed relative amounts of the major kavalactones in the extract: kavain (37.97%), dihydrokavain (12.72%), methysticin (23.08%), dihydromethysticin (9.25%), yangonin (11.20%), and desmethoxyyangonin (5.66%). At the end of each treatment period, blood was drawn and serum was assayed to determine enzyme activity levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase, all of which are considered to be markers for liver toxicity. Also, liver homogenates were prepared to determine malondialdehyde formation. After 2 weeks of treatment, all enzyme activity levels were decreased in the treated animals (both doses) by 500 mg/kg for ALT and AST and 200 mg/kg for ALP. At 4 weeks, ALT levels were lower by 500 mg/kg in treated animals. Malondialdehyde levels were comparable to those in control animals.

Lim et al[47] compared short-term toxic effects of pipermethystine in male Fischer F344 rats (200-220 g) to acetone–water extracts of kava rhizome.[47] The rats were divided into 4 groups with 5 animals per group. The control group received corn oil (3.33 mL/kg/d), the second group received pipermethystine (10 mg/kg/d), the third group was treated with kava rhizome extract (100 mg/kg/d equivalent to 63 mg total kavalactone/kg/d), and the fourth group received both pipermethystine and kava rhizome extract. Pipermethystine and kava rhizome were mixed in corn oil and administered via intragastric gavage daily for 2 weeks. The animals were fasted overnight prior to being sacrificed in a carbon dioxide chamber. Blood was obtained, and ALT and AST were analyzed. Livers were then excised, weighed, and examined. Pipermethystine and kava rhizome extract had no effect on daily food intake and liver weight in comparison to control rats. Rats in all experimental groups lost overall body weight; however, kava rhizome caused the most significant weight loss (42 g) compared with the control group. Treatment of F-344 rats with pipermethystine (10 mg/kg) and kava rhizome (100 mg/kg) during the test period did not elicit any significant changes in liver function tests or cause severe hepatic toxicity. However, pipermethystine and kava rhizome extract–treated rats exhibited a significant increase in hepatic glutathione, cytosolic superoxide dismutase, TNF-α, mRNA expression, and cytochrome P450 2E1 and 1A2.

Subchronic Oral Toxicity

Hapke et al[48] performed subchronic toxicological studies on a preparation containing 50 mg of d,l-kavain and 200 mg of magnesium orotate in rats and dogs.[48] Male and female Wistar rats received daily oral doses of 10, 100, or 400 mg/kg for 91 days. After 8 weeks, the high dose was increased to 1000 mg/kg. Male and female mongrel dogs received daily oral doses of 10, 100, or 200 mg/kg for 3 months. Serum glutamate pyruvate transaminase levels were significantly increased in high-dose rats; however, liver cell damage was not confirmed by histological examination. In high-dose dogs, the preparation was mildly toxic; proliferation of the small cells of the thyroid epithelium and a multicentric necrosis of the parenchyma of the liver were observed in 1 high-dose dog.

DiSilvestro et al[49] examined kava extract–induced liver damage and galactosamine-induced hepatitis enhancement using male Sprague-Dawley rats (150-174 g). Acetone and ethanol extracts of Samoan kava cultivar Ava Laau were prepared at doses ranging from 31 to 133 mg/kg diet. Under the conditions of this experiment, kava did not enhance the effects of the hepatotoxin galactosamine (500 mg/kg intraperitoneally); some kava doses even showed modest protection against liver damage. Liver histology analysis showed no signs of kava causing or enhancing liver injury.

Chronic Toxicity

Chronic toxicity data are presented in the Carcinogenicity section.

No published studies were found and no unpublished studies were made available relating to ocular toxicity, dermal irritation or sensitization, or phototoxicty.

Neurotoxicity

Jamieson and Duffield[50] observed the positive interaction of intraperitoneally administered alcohol ethanol and orally administered kava resin in male Balb/c mice (20-25 g body weight). The authors stated that kava resin significantly increased alcohol hypnosis. The authors noted that 300 mg/kg kava resin also proved to be lethal to 3 of 6 mice treated with 4 g/kg ethanol, therefore indicating that toxicity and hypnosis were increased.

Reproductive and Developmental Toxicity

No published studies were found, and no unpublished studies were made available.

Genotoxicity

Hsu et al[51] reported that desmethoxyyangonin was negative in the Ames assay.

The National Toxicology Program (NTP)[52] reported that kava kava extract was negative in a micronucleus test, in *Salmonella* assays, and, in vivo, in male and female mice.

Carcinogenicity

A 2-year NTP carcinogenicity study is in progress using kava kava extract at doses of 0, 0.1, 0.3, or 1 g/kg (rats) and 0, 0.25, 0.5, or 1.0 g/kg (mice) in both sexes.[52] Results are not yet available.

Clinical Assessment of Safety

A number of studies of the efficacy of kava kava extracts in the treatment of various conditions have been conducted. These studies did not provide information relevant to the safety of kava kava extracts in cosmetics.

Case Reports

Neurological effects. Schelosky et al[53] reported that 1 man (28 years old) and 3 women (22-76 years old) developed clinical signs of dopaminergic antagonism (oral and lingual dyskinesia, motor oscillations) following exposure to various *Piper methysticum* extracts (100-150 mg/d; up to 3 times per day). The onset of signs occurred from 45 minutes to 10 days after taking the extract. The use of other medications in addition to the herbal extract was verified in all but 1 case. All of the subjects abstained from the herbal preparation after the onset of clinical signs; the signs spontaneously subsided in 2 of the cases, whereas the other 2 required the use of an anticholinergic drug. The authors suggested that the sedative effects of *Piper methysticum* extract may result from dopamine antagonistic properties of the extracts.

Spillane et al[54] reported a case of an acute neurological syndrome associated with heavy kava use. A 27-year-old Aboriginal Australian man was admitted 3 times because of generalized choreoathetosis, which was believed to be secondary to kava binging. With each episode, the patient remained conscious and the symptoms decreased following the administration of intravenous diazepam. Within 12 hours his symptoms had subsided and he appeared to be normal on examination, an indication of an acute intoxication syndrome.

Liver toxicity. Eschar et al[14] reported on a 50-year-old man who had been taking 3 to 4 capsules of *Piper methysticum* extract per day for 2 months. This corresponds to a dose of 210 to 280 mg of lactones. His liver function tests revealed a 60-fold and 70-fold increase in AST and ALT concentrations, respectively. ALP activity was 430 IU/L (normal range, 30-125 IU/L), γ-glutamyltransferase was 691 IU/L (normal range, 9-35 IU/L), lactate dehydrogenase was 1132 IU/L (normal range, 125-240 IU/L, total bilirubin was 27 902 μmol/L (normal range, 6.8-25 μmol/L), and conjugated bilirubin was 212.3 μmol/L (normal range, 1.7-8.6 μmol/L). Prothrombin time was 25%. Ultrasound results showed that there was a slight increase in liver size but no ascites or portal vein thrombosis. The patient was negative for hepatitis A, B, C, and E; HIV; cytomegalovirus; and Epstein-Barr virus.

The patient developed stage IV encephalopathy, underwent a liver transplant, and recovered uneventfully. Upon examination, the liver was atrophic and the subhepatic and portal veins were free. Severely extensive hepatocellular necrosis and extensive lobular and portal infiltration of lymphocytes and numerous eosinophils were noted histologically.[14]

Russman and Helbling[55] reported on a 33-year-old female who had been taking the drug Laitan, which contains 210 mg of kavalactones, once per day for 3 weeks. Alcohol use was also noted in this patient. The patient developed malaise, jaundice, and decreased appetite, and her aminotransferases, bilirubin, and ALP levels were increased 60-, 15-, and 3-fold, respectively. Prothrombin time was normal, and serological tests for viral infections were negative, with the exception of low titers of Epstein-Barr virus IgM. A liver biopsy revealed infiltration of the portal tracts, bridging necrosis, destruction of the interlobular bile ducts, and canalicular cholestasis. Within 8 weeks of abstaining from the drug, liver function tests returned to normal. There was a strong and concentrated-dependent T-cell reactivity to Laitan as a result of a lymphocyte transformation test performed after recovery. It was also noted that the patient was a poor metabolizer of debrisoquin. The authors stated that in humans kavalactones are metabolized through hydroxylation; however, the enzymes involved have not been determined. The data, according to the authors, strongly suggest that *Piper methysticum* preparations may be hepatotoxic and that CYP2D6 deficiency is a risk factor.

The CDC has reported 2 US cases and 8 European cases of hepatic transplants due to kava-related liver failure.[56] The 2 US cases involved females (14 and 45 years old) who were taking kava-containing dietary supplements for 8 weeks to 4 months and who subsequently suffered liver failure and required a liver transplant. The 8 European cases involved 2 males (32 and 50 years old) and 6 females (22-61 years old) who used kava-containing products in doses of 60 to 240 mg/d for 8 weeks to 12 months. Each patient subsequently suffered liver failure and underwent, liver transplant.

Humberston and Krenzelok[57] reported on a 14-year-old female who had been taking Tension Tamers (Celestial Seasonings) tablets, which contain 100 mg of *Piper methysticum* extract, twice a day for 4 months. The patient subsequently suffered liver failure and underwent an orthotopic liver transplant.

Additional cases reporting visual disturbances, lethargy and disorientation, and possible drug interactions are available in the literature; however, the exact product and/or the doses of the substance ingested are not described.[8,58,59]

Additional reports describing adverse effects such as liver toxicity, liver failure, visual disturbances, lethargy, and disorientation and possible drug interactions following the use of various preparations of kava are available in the literature; however, the exact product and/or the doses of the substance ingested are not described.[58-60]

Adverse dermal effects. Consumption of heavy amounts of kava has been linked to a characteristic skin disease, termed kani, which consists of rough and scaly skin.[61-63] It is possible that this dermopathy is due to altered cholesterol metabolism; however, the exact cause is unknown.[63,64]

Jappe et al[65] reported that 1 man (70 years old) and 1 woman (52 years old) developed drug-induced skin eruptions after the consumption of *Piper methysticum* extract for 3 weeks (dose and times per day not reported). The use of other medications in addition to the herbal extract was verified in 1 of the 2 cases. In both cases, antinuclear and anti-extractable nuclear antibody titers, as well as direct immunofluorescence, were negative. In the male subject, infiltrating cells were $CD8^+$ and $CD4^-$, and the lymphocyte-transformation test with suspected drugs in serial dilution (0.1-1000 μg/mL) revealed significant proliferation with *Piper methysticum* extract only. In the female subject, a *Piper methysticum* extract patch test was positive (compared with a group of 20 controls), and the lymphocyte-transformation test was negative.

Governmental Safety Concerns

In December 2001, the FDA posted a letter to health care professionals to announce an investigation into whether the use of dietary supplements containing kava extract is associated with liver toxicity.[66] The letter asked health care workers to review cases of liver toxicity and determine whether they could be related to kava extract supplements. Another letter, posted in March 2002, aimed to make sure health care professionals were aware of the consumer advisory the FDA issued the same day.[2] The consumer advisory warned of the potential severe liver injury associated with the use of dietary supplements that contained kava extract.[1] The advisory stated that other countries, including Germany, Switzerland, France, Canada, and the United Kingdom, have warned consumers of the risks of kava extract and some have removed products from the market. The advisory is also stated that liver damage is rare.

Summary

Piper methysticum leaf/root/stem extract and *Piper methysticum* root extract are derived from the leaves, roots, rhizome (rootstock), and stems of the *Piper methysticum* G. *Forster* plant. The exact composition of a given preparation will vary according to the growth conditions of the plant, the constituents used, and the method of extraction. The composition of the most commonly used product in industry is unknown.

A number of countries have issued warnings or bans regarding the use of kava products because of reports of liver toxicity, for which the mechanism is not currently understood.

Piper methysticum leaf/root/stem extract and *Piper methysticum* root extract are used as skin-conditioning agents. *Piper methysticum* leaf/root/stem extract in used in hair, shaving, skincare, and bath preparations at a concentration range of 0.0001% to 0.01%. No use data were reported to the FDA for *Piper methysticum* extract; however, the concentration of use provided by CTFA was 0.01% for the reported use categories (hair tonics, dressings, soaps and detergents, and body and hand moisturizers).

Piper methysticum leaf/root/stem extract has a number of reported medicinal uses.

Kava is readily absorbed following oral administration, but there is no information available on its absorption following dermal application. Various metabolites have been identified following administration of both whole preparations and isolated components. Approximately 40% of the administered dose is usually recovered in the urine.

The various components of kava are distributed throughout the body, including to the brain, and have been reported to have an effect on end points such as stress, addiction, muscle relaxation, and enzyme levels.

Kava extracts had no antiviral activity but did show antibacterial and antifungal activity in the systems tested. Select components were tested and found to be negative in mutagenicity assays.

Cytotoxicity studies in human hepatoma cells were positive for 1 kava extract component.

LD_{50} values have not been reported. Subchronic studies found changes in enzyme levels and changes in indicators of liver function, but pathological follow-up was not performed. Very high doses, up to 1000 mg/kg/d for rats and 200 mg/kg/d for dogs, did produce liver damage. The mechanism of action for these effects is not known.

No data are available on the chronic toxicity, ocular irritation, dermal irritation or sensitization, reproductive and developmental toxicity, or phototoxicity. An NTP 2-year long-term carcinogenicity study is in progress using kava kava extract at doses of 0, 0.1, 0.3, or 1 g/kg (rats) and 0, 0.25, 0.5, or 1.0 g/kg (mice) in both sexes. Several case study reports are available of individuals with a history of oral kava extract consumption who became seriously ill as a result of liver damage. Many of these individuals required liver transplants. Other effects reported in the case study literature include visual disturbances, antidopaminergic signs, and lethargy and disorientation.

Discussion

The CIR Expert Panel noted that the concerns expressed by FDA regarding liver toxicity when kava kava is taken as an herbal supplement led to FDA's request that CIR review the cosmetic use of ingredients made from this plant.

Certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is unknown. In still other cases, an ingredient is not in current use but may be used in the future.

Although some data are available on effects following oral ingestion of kava containing supplements, there are a lack of data to address dermal absorption and metabolism.

The Expert Panel released a Notice of Insufficient Data Announcement outlining the data needed to assess the safety of *Piper methysticum* leaf/root/stem extract and *Piper methysticum* root extract and issued a tentative report with an insufficient data conclusion.

The types of data required for each ingredient include the following (all testing is to be performed on cosmetic-grade ingredients):

1. Current concentration of use data, where not currently available (eg, hair care and coloring products, shaving products, and suntan products)
2. Confirmation that principal kavalactones present would be yangonin, methysticin, and kavain compounds
3. Toxicological profile of yangonin, methysticin, and kavain compounds
4. Dermal absorption of these compounds (if significantly absorbed, reproductive and developmental toxicity data may be needed)
5. Genotoxicity data from 2 assay systems, at least 1 of which is a mammalian system (if genotoxic, carcinogenicity data may be needed)
6. Dermal irritation and sensitization
7. Photoirritation and photosensitization for yangonin

No offer to supply the data was received; the Expert Panel has issued a Final Report—Insufficient Data. When the requested data are available, the Expert Panel will reconsider the final report.

Conclusion

The CIR Expert Panel concluded that the available data are insufficient to support the safety of *Piper methysticum* leaf/root/stem extract and *Piper methysticum* root extract.

Authors' Note

The 2009 Cosmetic Ingredient Review Expert Panel members are Wilma F. Bergfeld, MD, FACP, Chair; Donald V. Belsito, MD; Curtis D. Klaassen, PhD; James G. Marks, Jr., MD, Ronald C. Shank, PhD; Thomas J. Slaga, PhD; and Paul W. Snyder, DVM, PhD. The CIR director is F. Alan Andersen, PhD. Valerie Robinson, CIR scientific analyst, prepared this report.

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036, USA.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported. F. Alan Andersen, PhD, and Valerie Robinson are employed by the Cosmetic Ingredient Review.

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