

KAVALACTONE COMPOSITIONS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. application serial number 60/ 351,167, filed, January 22, 2002, U.S. application serial number 10/010,201, filed November 30, 2001, and U.S. application serial number 09/853,304, filed May 11, 2001, which are herein incorporated by reference in their entirety.

BACKGROUND

It is believed that the use of kava (*Piper methysticum* Forst.) predates written history. The origination of the plant is attributed to the New Guinea / Indonesia area and it is believed that Polynesian explorers were responsible for its spread from island to island. Oceania (i.e., the Pacific island communities of Micronesia, Melanesia and Polynesia) is an area where islanders have been known for centuries to consume a drink, also called kava and derived from the root of kava, in ceremonies and celebrations due to its reported calming effect and ability to promote sociability. The root and the drink were apparently first described in the Western world by Captain James Cook as a result of his exploration of the South Seas in 1768. Many myths and anecdotal stories surround the use of kava, and these vary from culture to culture.

The extract of the kava root is known to contain a class of structurally related chemical compounds known as kavalactones. At least sixteen different members of this chemical class are known to be present. A relaxing action (i.e., calming effect, sleep inducing effect) of the extract is attributed to certain members of this class. Kavalactones possess low bioavailability; in fact, they are practically insoluble in water. Thus, bioavailability in oral administration settings is always an issue that must be addressed. The mechanism of activity of the kavalactones remains uncertain, and their effect on cytokines, such as the interleukins is unclear.

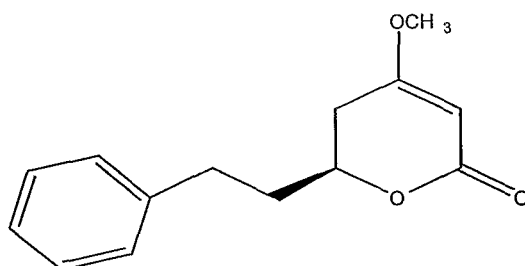
Cytokines such as interleukin-12 (IL-12) mediate the acute phase response to inflammatory stimuli, enhance the microbicidal functions of macrophages and other cells, and promote specific lymphocyte responses. See, e.g., Fearon and Locksley,

Science 272:50 (1996). Recently, in vivo studies implicate the inhibition of IL-12 production in therapeutic effects against inflammatory disorders such as sepsis (Zisman et al., Eur. J. Immunol. 27:2994 (1997)), collagen induced arthritis (Malfait et al., Clin. Exp. Immunol. 111:377 (1998)), established colitis (U.S. Patent No. 5,853,697), experimental autoimmune encephalomyelitis (Leonard et al., J. Exp. Med. 181:381 (1995)), experimental autoimmune uveoretinitis (Yokoi et al., Eur. J. Immunol. 27:641 (1997)), psoriasis (Turka et al., Mol. Med. 1:690 (1995)), and cyclophosphamide induced diabetes (Rothe et al., Diabetologia 40:641 (1997)). Thus, compounds having IL-12 inhibitory activity provide new approaches for therapeutic strategies to address these and other IL-12 mediated disease.

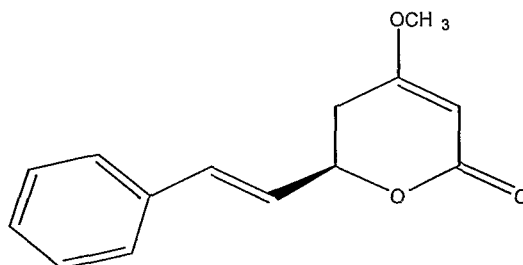
SUMMARY

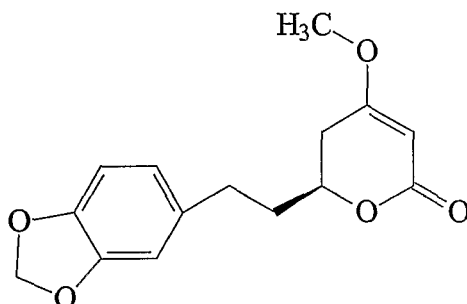
The invention is based in part on the unexpected discovery that three kavalactones, dihydrokawain, dihydromethysticin, and kawain (structures shown below), exhibit IL-12 inhibitory activity.

Dihydrokawain



Kawain



Dihydromethysticin

As such, the compounds, compositions and methods of this invention are useful in treating IL-12-mediated disease or disease symptoms (e.g., IL-12 overproduction-related disorders) in a subject. IL-12 mediated disease or disease symptoms refers to disease or disease symptoms in which IL-12 activity is involved, such as those wherein IL-12 is involved in signaling, mediation, modulation, or regulation of the disease process. IL-12 overproduction-related disorders involve those where overproduction of IL-12 is a basis for the disorder.

In one aspect, the invention relates to a medicinal ointment including 1% to 90% (e.g., 1% to 40%, 1.5% to 30%, 2% to 25%, or any range wherein the lower boundary is any integer % between 1% and 89%, inclusive, and the upper boundary is any integer % between 2% and 90%, inclusive) by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof, and a medicinally acceptable carrier. The term “active kavalactone” herein refers only to dihydrokawain, dihydromethysticin, kawain, or a combination of them. In other aspects, the compositions (e.g., medicinal ointment) and methods of use are those wherein the dihydrokawain and dihydromethysticin are synthetic, that is, are not directly derived from root extraction, rather are synthesized using one or more chemical transformation reactions.

In another aspect, the invention is a patch (see, for example, U.S. Patent 5,186,938) including an active kavalactone-containing material layer. More specifically, the material layer, e.g., a pad or a pressure-sensitive adhesive, serves as a substrate for receiving 1% to 90% (e.g., 1% to 40%, 1.5% to 30%, 2% to 25%, or any range wherein the lower boundary is any integer % between 1% and 89%, inclusive, and the upper boundary is any integer % between 2% and 90%, inclusive) by weight an active kavalactone selected from the group consisting of dihydrokawain,

dihydromethysticin, kawain, and a combination thereof. The active kavalactone can be in the form of a composition having 1% to 90% (e.g., 1% to 40%, 1.5% to 30%, 2% to 25%, or any range wherein the lower boundary is any integer % between 1% and 89%, inclusive, and the upper boundary is any integer % between 2% and 90%, inclusive) by weight an active kavalactone associated with the material layer (e.g., impregnated, embedded, or coated on the surface. A patch optionally has a protective layer intimately adhered to one side of the material layer, which is resistant to passage of the active kavalactone.

The invention also relates to a method for treating (e.g., curing, preventing, ameliorating) an IL-12 overproduction-related disorder, including administering to a subject (e.g., human, dog, cat) in need thereof an effective amount of an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof. The method of treating has an effect on the disease itself or on the symptom. The effect can be objective, that is, a measurable physical effect (e.g., greater range of motion, reduced swelling, reduced rash area), or subjective, that is, based on the feeling or perception of the subject (e.g., decreased irritation, decreased soreness, general feeling of relief). The disorder that can be treated by the method includes colitis, Crohn's disease, diabetes, encephalomyelitis, multiple sclerosis, osteoarthritis, periodontitis, psoriasis, rheumatoid arthritis, sepsis, and uveoretinitis.

The invention also relates to a method for treating (e.g., curing, preventing, relieving, or ameliorating) pain, including administering to a subject (e.g., mammal, human, dog, cat, horse) in need thereof an effective amount of an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof. The method of treating has an effect on the pain itself or on the symptom. The effect can be objective, that is, a measurable physical effect (e.g., reduced burning sensation, dulled pain, reduced swelling, improved mobility or range of motion), or subjective, that is, based on the feeling or perception of the subject (e.g., decreased irritation, decreased soreness, general feeling of relief). The disorder that can be treated by the method includes primary or secondary hyperalgesia, burning associated with capsaicin, myofascial pain, intractable myofascial pain, osteoarthritis pain, preemptive analgesia, neuropathic pain, and

inflammatory pain. The administration of the compounds and compositions delineated herein for treating pain can be topically, including via any patch comprising compounds or compositions as delineated herein. In one aspect, the methods provide between about 8 to about 24 hours of pain relief in a single application or administration of the compounds or compositions delineated herein.

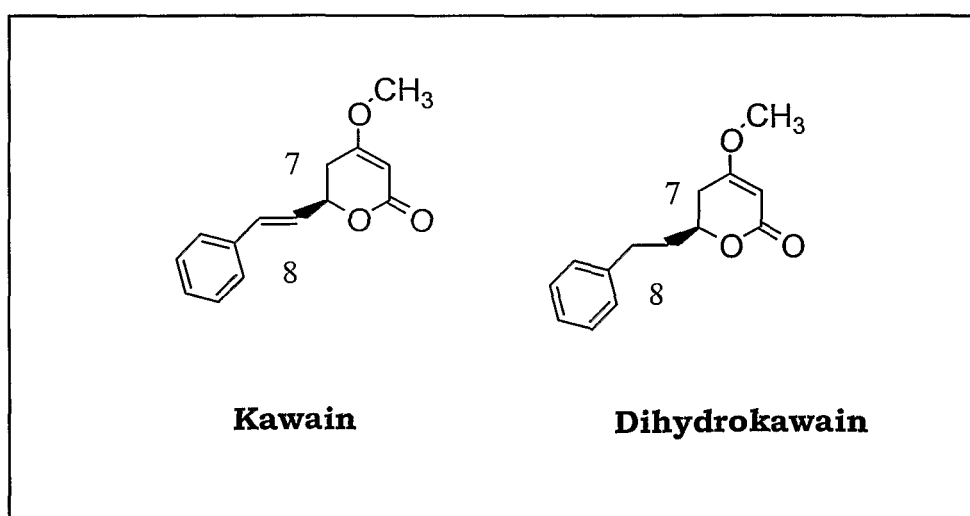
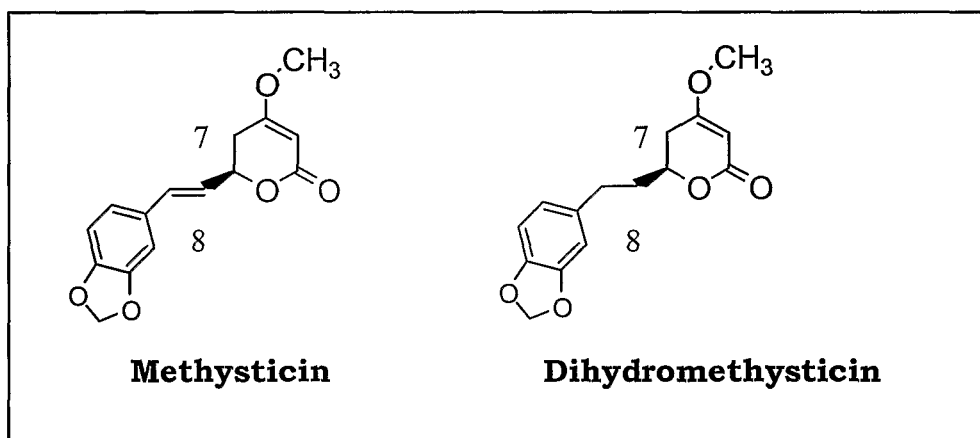
In another aspect, the invention relates to methods of treating pain in a subject (e.g., mammal, human, animal, dog, cat, horse) in need of pain relief by administering a composition (e.g., a topical composition) having any of the six major kavalactones (e.g., desmethoxyyangonin, dihydrokawain, dihydromethysticin, kawain, methysticin, and yangonin), or any combination thereof. In another aspect the methods herein include administering a composition (e.g., a topical composition) having any of the six major kavalactones (e.g., desmethoxyyangonin, dihydrokawain, dihydromethysticin, kawain, methysticin, and yangonin), or any combination thereof, wherein the composition is essentially void of (e.g., having less than 1%, less than 0.5%, less than any percentage between 0% and 1%, or 0%) any of para-aminobenzoic acid (PABA), calcium-d-pantothenate, or aloe. In another aspect the methods herein include administering a composition (e.g., a topical composition) having any of the six major kavalactones (e.g., desmethoxyyangonin, dihydrokawain, dihydromethysticin, kawain, methysticin, yangonin, or any combination thereof), wherein the composition further comprises any of petrolatum, beeswax, or vegetable oil (e.g., jojoba oil), or any combination thereof.

Another aspect of the invention relates to a packaged product including a container, a composition containing an active kavalactone disposed in the container, the kavalactone being selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof, and a label (e.g., sticker, product insert) with the container and having instructions for application of the active kavalactone for treating an IL-12 overproduction-related disorder.

Also within the invention are a composition herein for use in treating disease (e.g., IL-12 mediated diseases or disease symptoms (such as osteoarthritis), or other diseases (such as fibromyalgia), and use of such a composition for the manufacture of a medicament for the treatment of the aforementioned diseases or disease symptoms.

The invention relates compositions, and to methods for producing compositions, of high kavalactones content from rhizome of *Piper methysticum* Forst. (pepper intoxicant, Piperaceae family) called kava-kava. The compositions include those having a high content of kavalactones, and include those having high proportions of the kavalactones, 7,8-dihydrokawain and 7,8-dihydromethysticin. Additionally, the compositions and methods to produce them also reduce or eliminate certain chemical compounds present in kava kava extract, which may be associated with one or more detrimental side effects.

10



It is also an object of the invention to provide a method to converge four active kava kava components (e.g., kavalactones) to two active kavalactones, dihydrokawain and dihydromethysticin, by hydrogenation (e.g., catalytic) of the kavalactones. The present invention is based, in part, on the insight, that four active kavalactones can be
5 classified into two sets of compound groups and the difference between the two in each set is the presence in the molecule of a double bond (unsaturated) or a single bond (saturated bond) at the C-7 and C-8 (carbon-carbon bond) linkage. Kava extracts contain higher proportions of four kavalactones (kawain, methysticin, dihydrokawain and dihydromethysticin), which upon hydrogenation results in higher
10 proportions of dihydrokawain and dihydromethysticin. Additionally, the reduction process (e.g., hydrogenation) results in the reduction of the carbon-carbon double bond in the side chain of the flavokawains (or in other kava kava components) to give saturated flavokawain derivatives (or other derivatives of kava kava components that are less toxic or more easily isolated) that account, in part, for the change in color and
15 less irritating effects. Furthermore, the exposure of flavokawains or other kava kava components to aqueous base treatment (e.g., LiOH, NaOH) also results in conversion of the flavokawains or other kava kava components to water soluble derivatives that are either less colorful (and also less irritating) or are easier to separate (e.g., remove, extract, chromatograph, isolate) from other kavalactones than flavokawains with the
20 unsaturated side chain or kava kava components in their original form.

In one aspect, the invention is a 7,8-dihydrokawain and 7,8-dihydromethysticin enriched hydrogenated extract (e.g., kavalactone extract) from rhizome of *Piper methysticum* Forst., wherein said extract comprises 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% (e.g., at least 60%, at
25 least 70%, at least 80%, at least any integer % between 50% and 99%) of the total content of kavalactones by weight.

Another aspect of the invention is a 7,8-dihydrokawain and 7,8-dihydromethysticin enriched, reduced 7,8-epoxyyangonin- and 7,8-epoxy-5,6-dehydrokawain-containing, hydrogenated extract (e.g., kavalactone extract) from
30 rhizome of *Piper methysticum* Forst., wherein said extract comprises 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of

kavalactones by weight, and contains less than 0.01% (by weight) of each of 7,8-epoxyyangonin and 7,8-epoxy-5,6-dehydrokawain.

Another aspect of the invention is a 7,8-dihydrokawain and 7,8-dihydromethysticin enriched, reduced mycotoxin-containing, hydrogenated extract (e.g., kavalactone extract) from rhizome of *Piper methysticum* Forst., wherein said extract comprises 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight, and contains less than 0.1% (by weight) mycotoxins.

In another aspect, the invention is a process for the preparation of a dry extract from the rhizome of *Piper methysticum* Forst. comprising 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% (e.g., at least 60%, at least 70%, at least 80%, at least any integer % between 50% and 99%) of the total content of kavalactones by weight, comprising the chemical reduction (e.g., hydrogenation) of a raw kava extract solution in the presence of hydrogen gas with a catalyst. The processes delineated herein can further comprise extracting the pulverized rhizome of *Piper methysticum* Forst. (rhizoma Kava-kava) (by various extraction methods with organic solvent including supercritical fluid extraction) to obtain an extract solution. The extraction organic solvent can be any suitable organic solvent, including any of EtOH (80%-100%), MeOH (80%-100%), ethyl acetate, chloroform, acetone, or combination thereof. The processes delineated herein can further comprise chemically reducing an extract solution in a hydrogenation reaction to obtain a 7,8-Dihydrokawain and 7,8-Dihydromethysticin enriched hydrogenated mixture; filtering the hydrogenated mixture under vacuum to obtain a solution; and concentrating the solution to dryness to obtain the extract having 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight.

In other aspects, the invention relates to any of the processes delineated herein wherein: the hydrogenation reaction is carried out in ethanol, the hydrogenation reaction is carried out in ethyl acetate; the hydrogenation reaction is carried out in a mixture having ethanol and ethyl acetate; the hydrogenation reaction is carried out in a mixture ethyl acetate and another solvent; or the hydrogenation reaction is carried out in a solvent other than methanol. In other aspects, the invention relates to any of the processes delineated herein wherein: the entire hydrogenation reaction is carried

out at room temperature; wherein the entire hydrogenation reaction is carried out at temperatures greater than 5 °C ; wherein the entire hydrogenation reaction is carried out at any range of degrees wherein the lower number in the range is an integer between about 5 and 39 °C and the upper number of the range is an integer between about 6 and 40 °C; or wherein the entire hydrogenation reaction is carried out between about 15 and 30 °C. In other aspects, the invention relates to any of the processes delineated herein wherein: the hydrogenation reaction is carried out at atmospheric pressure; or wherein the hydrogenation reaction is carried out under pressure (e.g., greater than atmospheric, 1 atmosphere, in a Parr hydrogenation apparatus). In another aspect, the invention relates to any of the processes delineated herein, wherein the reaction mixture (e.g., mixture of starting materials or reagents and solvent) at the initiation of the reaction is homogeneous (with the exception of the catalyst or its support) in nature.

Another aspect of the invention is any of the processes delineated herein: wherein the catalyst comprises a catalytic metal that is any of palladium, platinum, nickel, iron, or a combination thereof; wherein the catalytic metal is in an amount of from 0.001 to 5 weight percent, based on the weight of the catalyst; wherein the catalyst is palladium on a charcoal support; or wherein the palladium is in an amount of from about 1 to 30% (e.g., about 1 to 10, about any range wherein the lower number is an integer number between 1 and 29 and the upper number is an integer number between 2 and 30) weight percent, based on the weight of the palladium on a charcoal support.

Another aspect of the invention is any of the processes delineated herein wherein the filtering process is accomplished by using any filtration aid, including CELITE, alumina, silica gel, or FLORISIL. Another aspect of the invention is any of the processes delineated herein further comprising treating the solution with aqueous alkaline solution (e.g., 0.05 to 0.5 N, 0.05 to 1N, 0.05 to 3N, 0.05 to 5N, 0.05 to 10N) at room temperature to obtain a pure extract solution; and purifying said pure extract solution by chromatography using neutral alumina, silica gel, or FLORISIL. In other aspects, the processes are those delineated herein wherein the aqueous alkaline solution is any of LiOH, NaOH, or KOH solution.

In another aspect, the invention relates to any of the processes delineated herein further comprising introducing a second solvent to the extract solution. The second solvent can be ethyl acetate.

In another aspect, the invention relates to any of the processes delineated herein, wherein the resulting dry extract from the rhizome of *Piper methysticum* Forst. has lower mycotoxin (e.g., at least 50% less, at least an integer % between 10 and 90% less) content than the dry extract prior to chemical reduction treatment.

The invention also relates to a process for reducing the amount of mycotoxins in a dry extract from the rhizome of *Piper methysticum* Forst. comprising 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight, comprising the chemical reduction of a raw kava extract solution in the presence of hydrogen gas with a catalyst.

In another aspect, the invention relates a process of any of those delineated herein, wherein the resulting dry extract from the rhizome of *Piper methysticum* Forst. has lower (e.g., at least 50% less, at least an integer % between 10 and 90% less) 7,8-epoxyyangonin and 7,8-epoxy-5,6-dehydrokawain content than the dry extract prior to chemical reduction treatment.

The invention also relates to a process for reducing the amount of 7,8-epoxyyangonin and 7,8-epoxy-5,6-dehydrokawain in a dry extract from the rhizome of *Piper methysticum* Forst. comprising 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight, comprising the chemical reduction of a raw kava extract solution in the presence of hydrogen gas with a catalyst.

Kava kava extracts are known to be useful to soothe the nerves, to induce relaxation and sleep, to counteract fatigue, for urinary tract health, for asthma and rheumatism, and to reduce weight. The relaxing action (i.e., calming effect, sleep inducing effect), analgesic effect, and anti-microbial activity of the extracts are attributed to certain members of the extract. Kava's most popular application is as a natural anxiolytic, comparing favorably in several studies to a number prescription medications, including benzodiazepines. It is also known as a folk medicine that is used as phytotranquilizer for relaxing in cases of nervousness and overexcitement, as

an agent for including sleep. Kavalactones are responsible for many of the observed effects.

The extract of the kava root is known to contain a class of structurally related chemical compounds known as kavalactones. At least sixteen different members of this chemical class are known. However, four kavalactone molecules, kawain, dihydrokawain, methysticin and dihydromethysticin, have been found to have significant biological effects. (M. Greenwood-Robinson, Kava (Chapter 5) published by Dell Publishing, New York 1999). In particular, dihydrokawain and dihydromethysticin are useful as analgesics or pain relievers. (Kava an overview: Special review Herbalgram Vol. 39, (1998) The Journal of the American Botanical Council and the Herb Research Foundation). Thus, methods of securing increased amounts of these kavalactones can be useful.

It is desirable to make kava extracts containing increased proportions of the active constituents in order to derive maximum benefits from the natural herb. However, it is difficult from a practical standpoint to isolate certain active constituents via fractionation and /or other purification methods because many kavalactones have very similar functional groups, similar polarities, and very different appearances (e.g., oil, crystal). No separation and purification methods specifically for isolating dihydrokawain and dihydromethysticin kavalactones together from kavalactone extract mixtures have been reported in the literature.

The details of one or more aspects of the invention are set forth in the accompanying figure and the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DESCRIPTION OF DRAWING

FIG. 1 illustrates the IL-12 inhibitory activity of six kavalactones.

DETAILED DESCRIPTION

This invention is based in part on the unexpected discovery that specific kavalactones inhibit production of IL-12, whose overproduction is implicated in a number of diseases and disease symptoms. The IL-12 inhibitory activity of six major kavalactones (e.g., desmethoxyyangonin, dihydrokawain, dihydromethysticin,

kawain, methysticin, and yangonin) was measured using a cellular assay for determination of IL-12 cytokine inhibition. Among them, kawain, dihydrokawain, and dihydromethysticin were found to have much higher IL-12 inhibitory activity relative to the other kavalactones. These results are shown in Figure 1. Thus, compositions
5 containing one of the three active kavalactones, kawain, dihydrokawain, dihydromethysticin, or a combination thereof, are useful for treating disease or disease symptoms related to IL-12 overproduction.

The active kavalactones, kawain, dihydrokawain, dihydromethysticin, or a combination thereof, are also useful for treating pain or pain symptoms in a subject
10 (e.g., mammal, human, dog, cat, or horse), by administration (e.g., topical administration) of an effective amount of the compounds or compositions delineated herein. Alternatively, the six major kavalactones (e.g., desmethoxyyangonin, dihydrokawain, dihydromethysticin, kawain, methysticin, and yangonin), or any combination thereof, are useful in the methods of treating pain or pain symptoms
15 delineated herein. The use of the kavalactones in a topical ointment can provide a more efficient administration route than oral administration because the kavalactones are not subject to first-pass effects (e.g., metabolism, degradation) associated with oral bioavailability. Various enzymatic processes can degrade kavalactones within one hour of oral administration. Additionally, the topical carrier in a composition
20 delineated herein can work synergistically with the lipophilic properties of the kavalactones to provide a more advantageous delivery method of the kavalactones to the pain site (i.e., through the skin, without injection by needles) in a subject (e.g., mammal, human, dog, cat, horse).

Referring back to FIG. 1, six kavalactones were tested in an IL-12 inhibitory
25 assay as follows: Lipopolysaccharide (LPS, *Serratia marcescens*) was obtained from Sigma (St. Louis, MO). Human recombinant IFN γ was purchased from Boehringer Mannheim (Mannheim, Germany). Human peripheral blood mononuclear cells were isolated by centrifugation using Ficoll-Paque (Pharmacia Biotech, Uppsala, Sweden) and prepared in RPMI medium supplemented with 10% FCS and antibiotics in a 96-
30 well plate with 1×10^6 cells/well. Human PBMC were primed with IFN γ (30 U / mL) for 16 h and then stimulated with 1 mg/mL of LPS in the presence of different concentrations of test compound. Cell-free supernatants were taken 20 h later for

measurement of cytokines. Cell viability was assessed using the bio-reduction of MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium] (Promega, Madison, WI). Cell survival was estimated as the ratio of the absorbance in compound-treated groups versus compound-free control. Human IL-12 was assayed using ELISA kits (Endogen, Cambridge, MA), essentially according to the manufacturer's instructions. IL-12 inhibition can also be measured by other methods (e.g., *in vivo*, *in vitro*, animal models) of assaying for enzyme inhibition activity.

This invention is also based in part on another unexpected discovery: the active kavalactones, i.e., dihydrokawain, dihydromethysticin, and kawain, can be administered effectively in a transdermal fashion (e.g., as a medicinal ointment, massage oil). Upon homogeneous formulation in an inert carrier, the active kavalactones can be effectively administered in the absence of permeation enhancers (e.g., dimethyl sulfoxide, 1-dodecyloazacycloheptan-2-one, sodium guaiazulene-3-sulfonate). Thus, compositions of the invention can be administered as an ointment thus avoiding bioavailability problems associated with oral administration (e.g., first pass effects, short half-life in blood, degradation, cytochrome P450 metabolism, gut metabolism, liver or kidney metabolism, or absorption). Such administration techniques allow for systemic or local administration of the dihydrokawain, dihydromethysticin, kawain, or a combination thereof. A medicinal ointment of the invention includes allows for one or more active kavalactones to reach subcutaneous levels, and provides an effect beyond that of a cosmetic or dermapharmaceutical, which affects activities at skin level (e.g., skin cell respiration, regeneration, and hydration).

An ointment composition of the invention can be formulated with one or more of the active kavalactones suspended or dissolved in a carrier, such as mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, water, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetyl alcohol, 2-octyldodecanol, and stearyl alcohol. An acceptable carrier can include water, a solvent, an emollient, a surfactant, a preservative, or a combination thereof. Water, when present, can be in an amount of 5 to 80% by weight. Other than water, the acceptable carrier can also contain a

relatively volatile solvent such as a monohydric C1-C3 alkanol (e.g., methyl alcohol or ethyl alcohol) in an amount of 1 to 70% by weight, and an emollient such as those in the form of silicone oils and synthetic esters in an amount of 0.1 to 30% by weight. Other solvents that are acceptable carriers include any suitable for administration of dihydrokawain, dihydromethysticin, and kawain, for example, dimethyl sulfoxide, C1-C20 alcohols, glycols, and ethers. Anionic, nonionic, or cationic surfactants can also be included in the biological acceptable carrier. The concentration of total surfactants can be from 0.1 to 40% by weight. Examples of anionic surfactants include soap, alkyl ether sulfate and sulfonate, alkyl sulfate and sulfonate, alkylbenzene sulfonate, alkyl and dialkyl sulfosuccinate, C8-C20 acyl isethionate, acyl glutamate, C8-C20 alkyl ether phosphate, and a combination thereof. Examples of nonionic surfactants include C10-C20 fatty alcohol or acid hydrophobe condensed with from 2 to 100 moles of ethylene oxide or propylene oxide per mole of hydrophobe; C2-C10 alkyl phenol condensed with from 2 to 20 moles of alkylene oxide; mono and di-fatty acid ester of ethylene glycol; fatty acid monoglyceride; sorbitan, mono- and di- C8-C20 fatty acid; block co-polymer (ethylene oxide/propylene oxide); polyoxyethylene sorbitan, and a combination thereof. Preservatives can also be included in the biological acceptable carrier to prevent growth of potentially harmful microorganisms, and can be employed in an amount of 0.01 to 2% by weight. Examples of preservatives include alkyl ester of para-hydroxybenzoic acid, hydantoin derivative, propionate salt, and a variety of quaternary ammonium compounds. Each preservative should be selected based on its compatibility with other ingredients in the composition. An ointment of this invention can be applied to any particular surface area of the body (including gums).

Also within the scope of the invention is a method for treating an IL-12 overproduction-related disorder, or pain, including administering to a subject (e.g., human, dog, cat) in need thereof an effective amount of an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof. The effective amount of active kavalactone is between 0.01 and 100 mg/kg body weight per day, alternatively between 0.5 and 75 mg/kg body weight per day of dihydrokawain, dihydromethysticin, kawain, or a combination thereof. The effective amount can be any specific amount within the aforementioned range or any

range of amount of active kavalactone, wherein the lower boundary is any number of mg/kg body weight between 0.01 and 99.99, inclusive, and the upper boundary is any number of mg/kg body weight between 0.02 and 100, inclusive. The effective amount is useful in a monotherapy or in combination therapy for the treatment of IL-12 overproduction-related disease or disease symptoms, or pain or pain symptoms. As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Effective amounts and treatment regimens for any particular subject (e.g., human, dog, cat) will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician or veterinarian.

To practice the method of the present invention, an active kavalactone-containing composition can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, perineurally, epidurally, by iontophoresis, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

A sterile injectable preparation, for example, a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl

cellulose or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

5 A preparation for oral administration can be any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions (including, for example, beverages). In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral
10 administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation composition can be prepared according to
15 techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. An active kavalactone-containing composition can also be administered in the form of a suppository or an implantable
20 device. Implantable devices and related technology are known in the art and are useful as delivery systems where a continuous, or timed-release delivery of pure kavalactone compounds or compositions delineated herein is desired. Additionally, the implantable device delivery system is useful for targeting specific points of pure kavalactone compound or composition delivery (e.g., localized sites, or organs). See,
25 Negrin CM, Delgado A, Llabres M and Evora C., *Biomaterials* 22 (6), 563 (2001). Timed-release technology involving alternate delivery methods can also be used in this invention. For example, timed-release formulations based on polymer technologies, sustained-release techniques and encapsulation techniques (e.g., polymeric, or liposomal) can also be used for delivery of the pure kavalactone
30 compounds and compositions delineated herein. Topical-patches having pure dihydrokawain, dihydromethysticin, kawain or a combination thereof, or a composition thereof are also included in this invention.

Acceptable carriers that can be used to prepare active kavalactone-containing compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (such as d- α -tocopherol polyethyleneglycol 1000 succinate), surfactants used in pharmaceutical dosage forms (such as Tweens or other similar polymeric delivery matrices), buffer substances (such as phosphates), glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes (such as protamine sulfate), disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Other solubilizing agents can also be advantageously used to enhance delivery of dihydrokawain, dihydromethysticin, kawain, or a combination thereof.

Also within the invention is a patch to deliver active kavalactone. A patch includes a material layer (e.g., polymeric, cloth, gauze, bandage) and 1% to 90% (e.g., 1% to 40%, or any range wherein the lower boundary is any integer % between 1% and 89%, inclusive, and the upper boundary is any integer % between 2% and 90%, inclusive) by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof. One side of the material layer can have a protective layer adhered to it to resist passage of active kavalactone compositions. The patch can additionally include an adhesive to hold the patch in place on a subject. An adhesive is a composition, including those of either natural or synthetic origin, that when contacted with the skin of a subject, temporarily adheres to the skin. It can be water resistant. The adhesive can be placed on the patch to hold it in contact with the skin of the subject for an extended period of time. The adhesive can be made of a tackiness, or adhesive strength, such that it holds the device in place subject to incidental contact, however, upon an affirmative act (e.g., ripping, peeling, or other intentional removal) the adhesive gives way to the external pressure placed on the device or the adhesive itself, and allows for breaking of the adhesion contact. The adhesive can be pressure sensitive, that is, it can allow for positioning of the adhesive (and the device to be adhered to the skin) against the skin

by the application of pressure (e.g., pushing, rubbing,) on the adhesive or device. Also included are peelable masks that can be formulated by placing the composition as a gel or paste on a protective layer made of a film-forming polymer (e.g., polyvinyl alcohol) and an adhesive promoting polymer (e.g., hydrophobic acrylate or methacrylate polymer, such as Pemulen TR2.RTM. from the B.F. Goodrich Company). Alternatively, a hydrogel composition (see, for example, U.S. Patent 5,961,479 or U.S. Patent 5,306,504) including any one or more of the active kavalactones can be used.

The invention also covers a pharmaceutical composition having a pure active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, or a combination thereof. Such a composition is useful for treating IL-12 mediated disease or disease symptoms, or other diseases (such as fibromyalgia), or pain or pain symptoms. Also within this invention is a method of treating disease or disease symptoms, (including IL-12 mediated disease or disease symptoms, pain, or pain symptoms) in a subject by administering to the subject a pure kavalactone-containing composition. The subject can be a human or an animal (e.g., dog, cat). The term "pure" refers to a level of 90% or higher. Pure active kavalactone can be derived from natural (e.g., root extract and purification) or synthetic (e.g., synthesis from natural or synthetic materials) means, or a combination thereof.

A crude extract of the kava roots (obtained using various extraction methods (e.g., simple solvent soak, supercritical fluid extraction)) can be used as the source of active kavalactones for the preparation of a composition of this invention. If desired, the active kavalactones can be further purified by column chromatography. They can also be synthesized from readily available starting materials by conventional chemical methods. See, for example, Kostermans, Recl. Trav. Chim. Pays-Bas., 70, 79 (1951); Klohs et al., J. Org. Chem., 24, 1829 (1959); Spino, et al. Tetrahedron Lett., 37, 6503 (1996), and references cited in each. The active kavalactones present in a composition can be enriched by addition of those kavalactones (from either natural or synthetic sources). The three active kavalactones (e.g., dihydrokawain, dihydromethysticin, and kawain) contain one or more asymmetric centers and thus can occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. They can also occur in cis- or trans- or E- or Z- double bond isomeric

forms. All such isomeric forms can be tested using IL-12 assays to determine their inhibitory activity.

After various unsuccessful attempts for selective reduction of double bond between C-7 and C-8 without reduction of other functionalities in the molecules (e.g., the double bond in γ -pyrone ring), the desired reduction was accomplished by catalytic hydrogenation using a catalyst based on palladium, platinum or a combination thereof on a charcoal support. Thus, methods of producing kavalactones include those involving catalytic hydrogenation reactions of kavalactones (e.g., compounds, extracts of kava kava root, extracts of the rhizome of *Piper methysticum* Forst.) having unsaturated functional groups (e.g., carbon-carbon double bonds). In one aspect the hydrogenation reactions in the methods herein result in reduction (e.g., hydrogenation; catalytic hydrogenation; treatment with hydrogen gas, with or without a catalyst present) to give kavalactones, including those with saturated functional groups attached to the γ -pyrone ring, or lactone ring, of the compound.

A crude extract of the kava roots (obtained using various extraction methods (e.g., simple solvent soak, supercritical fluid extraction)) can be used as the source of active kavalactones for the preparation of a compositions and methods of this invention. Solvent soaks can be accomplished using any standard solvent such as alcohols (e.g., methanol, ethanol), ethyl acetate, chloroform, acetone, methylene chloride, ethers (e.g., ethyl ether) or combinations thereof. A supercritical fluid extraction method can be used including those described in the art (see for example, V.J. Krukonis, ACS Symposium Series 289 (1984), pp 155-175).

Kavalactones includes any chemical compound found in the kava kava root, or derived from an extract of kava kava having a lactone ring functionality in its structure. Kavalactones include, for example, any of (1) yangonin, (2) kawain, (3) methysticin, (4) 7,8-dihydromethysticin, (5) desmethoxyyangonin, (6) 7,8-dihydrokawain, (7) dihydrodesmethoxyyangonin, (8) 7,8-dihydroyangonin, (9) 11-hydroxyyangonin, (10) 7,8-dihydro desmethoxyyangonin, (11) 11-methoxy-12-hydroxydehydrokawain, (12) 10-methoxyyangonin, (13) 11-methoxyyangonin, (14) 11-, 12-dimethoxy 7,8-dihydrokawain, (15) 5,6-dihydroyangonin, (16) 5,6,7,8-tetrahydroxyyangonin, and (17) 5,6-dihydro-5-hydroxy-4-methoxy-6-(2-phenylethyl)-

2H-pyran-2-one. See, for example, Dictionary of Natural Products on CD-ROM, Chapman & Hall/CRC Press, ISBN/ISSN: 0412491508, v. 8.2.

These compounds can be identified using standard physicochemical and spectroscopic analytical techniques, including nuclear magnetic resonance (including
5 proton, carbon probes, 1-dimensional, 2-dimensional), infrared spectrometry, mass spectrometry, high performance liquid chromatography, thin-layer chromatography, elemental analysis, ultraviolet spectrometry, and the like.

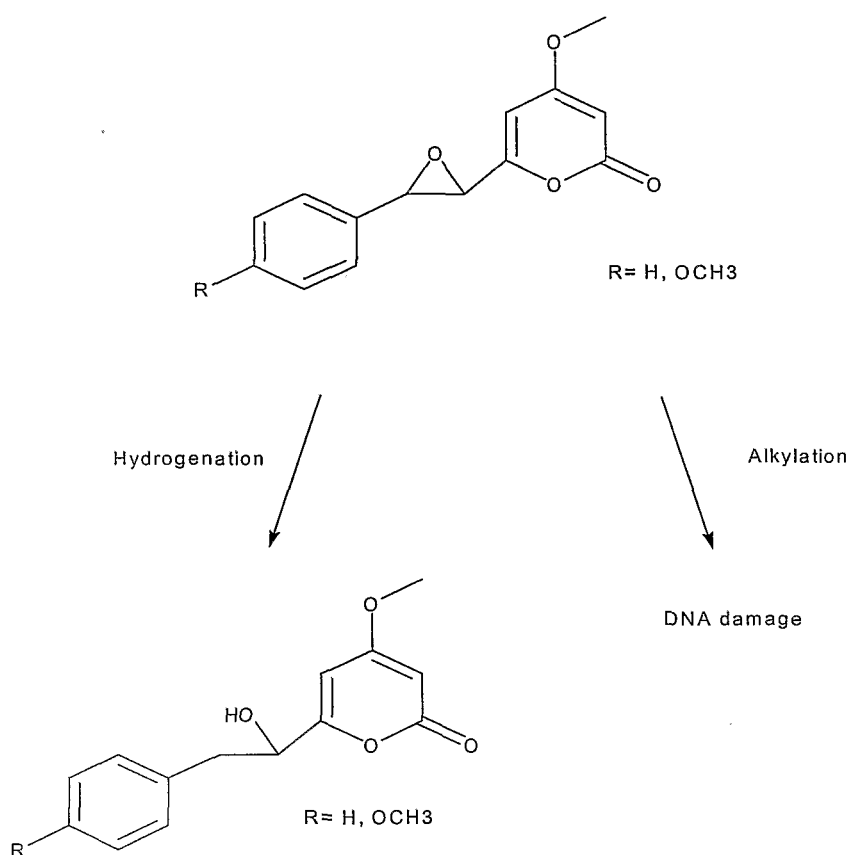
The invention also relates to methods for providing an essentially colorless kava extract, and the resulting essentially colorless kava extract produces thereby.

10 Usual extraction methods using organic solvents or aqueous organic solvents produce extracts having a strong yellow color, due mainly to the fact that the extracts have compounds known as flavokawains (including, e.g., flavokavins, flavokavains, flavokavin A, flavokavin B, dihydrokavain-5-ol) and other natural matrix pigments therein. These colored materials often induce undesirable secondary effects such as a
15 scaly skin rash called "kava dermatopathy", which appears when yellow crude kava extracts are consumed for long-terms or in large amounts. Extracts having these materials therein are also associated with undesirable (e.g., uncomfortable, unattractive, discoloration) staining when applied to the skin. In one aspect, these essentially colorless extract preparations have essentially no flavokawain content, that
20 is less than 1% (e.g., any percentage (in tenths of a percent) that is less than 1% flavokawains, by weight). These essentially colorless kava extracts, or preparations thereof, including those essentially void of flavokawains, are desirable for administering the health benefits of kavalactones, while avoiding the undesirable effects (e.g., dermatopathy, staining, skin irritation) associated with typical kava extract
25 preparations.

There have also been certain anecdotal reports of links of kava kava extract to certain hepatotoxicity events. While as yet not fully substantiated, one potential factor involved in such an event could be related to the presence of mycotoxins in the extract. The link between mycotoxins (naturally occurring toxins from fungal
30 sources, e.g., *Aspergillus*, and *Fusarium*) and liver disease is well known. Examples include Aflatoxin B1 (T. Asao et al., *J. Am Chem. Soc.*, 1963, 85, 1705), Aflatoxin G1 (B.E. Nesbitt et al., *Nature (London)*, 1962, 195, 1062), Aflatoxin GM1 (J.G.

Heathcote et al., *Tetrahedron*, 1969, 25, 1497), Aflatoxin M1 (C.W. Hozapfel et al.,
Tetrahedron Lett., 1966, 2799), Ochratoxin (K.J. Van der Merwe, *J. Chem. Soc.*,
1965, 7083), Sterigmatocystin (J.E. Davis, et al., 1962, 4179), Rubroskyrin (A.C.
Ghosh et al., *Appl. Environ. Microbiol.*, 1978, 35, 563), to name a few. See also,
5 C.W. Hesseltine, *Mycotoxins and Phycotoxins*, Elsevier: Amsterdam, (1986); and
references therein. Most of these compounds contain labile double bonds (which are
readily oxidized during normal metabolic processing into compounds (e.g., DNA
alkylating agents, carcinogens) that lead to toxicity and other disease processes)
and/or COOH substituents that are essential for their toxicity profile. Hydrogenation
10 of kava extract can convert the mycotoxins having the labile carbon-carbon double
bond to the corresponding dihydro forms that are less toxic or non-toxic, or are more
easily separable. Alkaline treatment also converts the COOH functional group in
mycotoxins into the dissociated form (COO^-) and this form can be easily extracted
and isolated. Thus, the current invention provides a convenient method to eliminate
15 and/or reduce mycotoxins causing unwanted adverse effect.

Two epoxide-containing derivatives were isolated from Kava extract fractions.
One is 7,7-epoxyyangonine ($\text{R}=\text{OCH}_3$) (see, Japan *KOKAI* 2001-316260A). The
other is 7,8-epoxy-5, 6-dihydrokawain ($\text{R}=\text{H}$) (see, *J. Indian Chem. Soc.*, 63, 1986
p.780). See, formula below. Both molecules have a very reactive epoxide moieties at
20 benzylic positions, which have been implicated as a cause of hepatic damage. These
two natural kavalactones have the potential to cause hepatotoxicity in long and heavy
usage. These reactive kavalactones can form covalent bonds with DNA, enzymes and
proteins to cause liver necrosis. Thus, the methods of this invention also convert these
unwanted natural kavalactone epoxides (via hydrogenation) to hydroxy forms ($\text{R}=\text{H}$,
25 OCH_3), which are less toxic and isolable or separable.



Hydrogenation refers to the chemical reaction (e.g., hydrogenation) by exposing a chemical compound to hydrogen gas. This can be performed in the presence or absence of a catalyst, and can be performed at atmospheric or under high pressure (e.g., in a Parr generator). A catalyst is any chemical composition that is capable of facilitating the reaction at issue, for example, hydrogenation catalysts include palladium metal on carbon, palladium acetate, ruthenium dichloride, platinum oxide, rhodium chloride tri-(triphenylphosphine), and the like. The catalyst can include a catalytic metal which include any metal capable of facilitating the desired reaction such as palladium, ruthenium, nickel, rhodium, platinum, and the like. See, also, P.N. Rylander, *Hydrogenation Methods*, Academic Press, New York, 1985. Standard conditions and catalysts are known in the art, including those delineated in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3d. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic*

Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995); and subsequent editions thereof. Filtration aids are any suitable filter that is capable of separating one component of a mixture from another, including paper, CELITE, alumina, FLORISIL, silica, glass (fritted), and the like. Alkaline substances include any basic substance or salt, such as lithium hydroxide, potassium hydroxide, or sodium hydroxide. The equipment, solvents, chemicals, and catalysts suitable for these processes are readily available from commercial sources, including for example, Aldrich Chemical Company, Fluka AG, and Tokyo Chemical Industry.

The kavalactones (e.g., dihydrokawain, dihydromethysticin,) contain one or more asymmetric centers and thus can occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. They can also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms are included in the description of kavalactones.

In order that the invention described herein may be more readily understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner. All references cited herein are expressly incorporated by reference in their entirety.

Example 1

Kawain is synthesized essentially as follows. N-Bromosuccinimide (1 eq.) is slowly added to a 2.3M solution of ethyl β -methoxycrotonate (1 eq.) in carbon tetrachloride. Upon allowing the reaction to equilibrate, the mixture is heated at reflux for ca. 4 h. The mixture is then cooled (0 °C) and filtered, followed by washing of the precipitate with cold CCl₄. The combined filtrates are concentrated (*in vacuo*, rotovap) and the residue distilled to give the desired product, ethyl γ -bromo- β -methoxycrotonate, whose identity is confirmed by various means including proton nuclear magnetic resonance spectrometry and mass spectrometry.

A 0.5M solution of ethyl γ -bromo- β -methoxycrotonate (1 eq.) in benzene is poured into a flask containing zinc filings (1.2 eq.). Cinnamic aldehyde (1.2 eq.) is added. Upon gentle warming to initiate the reaction, the mixture is refluxed for ca. 1

hr. The mixture is cooled, poured into cooled saturated aqueous ammonium chloride, and the aqueous phase extracted three times with ethyl ether. The combined extracts are dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue is recrystallized (MeOH) to give to give the desired product whose identity is confirmed by various means including proton nuclear magnetic resonance spectrometry and mass spectrometry.

Example 2

Dihydrokawain is synthesized essentially as follows. Methyl 3-hydroxy-5-phenylpentanoate (1 eq.) in tetrahydrofuran is added to a solution of the lithium enolate of t-butyl acetate (3 eq., from lithium diisopropylamine and t-butyl acetate) at -78 °C and allowed to slowly warm to 0 °C. The mixture is quenched with 1N HCl solution and extracted with dichloromethane. The combined extracts are washed with aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a residue. The residue can be purified (silica gel chromatography) or converted directly. The resulting β -diketone is hydrolyzed with subsequent lactonization essentially according to the procedure of Tabuchi et al. (trifluoroacetic acid, dichloromethane; *J. Org. Chem.* 59, 4749, (1994)) to give the desired product, whose identity is confirmed by various means including proton nuclear magnetic resonance spectrometry and mass spectrometry.

Example 3

Dihydromethysticin is synthesized essentially as follows. 10% Palladium on carbon (0.03 wt. eq.) is added to a 1M solution of methysticin (1 eq.) in tetrahydrofuran. The mixture is subjected to hydrogenation using a Parr apparatus at ca. 35 p.s.i. The mixture is filtered and the combined filtrates are concentrated (*in vacuo*, rotovap) to give a solid. The solid material is recrystallized (¹PrOH) to give the desired product, whose identity is confirmed by various means including proton nuclear magnetic resonance spectrometry and mass spectrometry.

Example 4

A crude EtOH extract of kava-kava (100 g) containing about 40 g of kavalactones (PureWorld botanicals, NJ) was suspended into a mixture of water (300 mL) and ethyl acetate (200 mL). After removal of insoluble residues, the organic layer was separated from the aqueous layer. The aqueous layer was further extracted with ethyl acetate (200 mL x 2) to produce organic extracts. All organic extracts were combined to obtain an organic solution, which was washed with a saturated NaCl solution (200 mL x 2), dried over anhydrous NaSO₄, and dried. The resulting dark brown oil (45 g) was purified by column chromatography with 800 g of Kieselgel 60 (230-400 mesh ASTM, EM Science, Germany), n-hexane/ethyl acetate (2:1) being the eluting solvent. Pale yellow kavalactone fractions were collected and dried to produce a partially crystallized amorphous oil (36 g). The total content of the kavalactones in the product thus obtained was about 93% by weight. Each of the three kavalactones, dihydrokawain, dihydromethysticin, and kawain, was identified by high pressure liquid chromatography.

Example 5

A crude EtOH extract of kava-kava (100 mL) containing about 15g of kavalactones (PureWorld botanicals, NJ) was concentrated under reduced pressure to remove excess EtOH. The concentrated extract (60 mL) was purified by column chromatography with 500 g of Florisil (200mesh, Aldrich), n-hexane/ethyl acetate (2:1) being the eluting solvent. Yellow kavalactone fractions were collected and dried to produce a pale yellow amorphous oil (13 g). The total content of the kavalactones in the product thus obtained was about 95% by weight.

Example 6

A light yellow kava-kava extract (10 g) containing about 5 g of kavalactones (extracted by Phasex Corp., MA) obtained by a supercritical fluid extraction method (V.J. Krukonsis, ACS Symposium Series 289 (1984), pp 155-175) was purified by column chromatography with 300 g Aluminum Oxide, Neutral (J. T. Barker, NJ), with n-hexane/ethyl acetate (2:1) being the eluting solvent. Pale yellow kavalactone

fractions were collected and dried to produce a partially crystallized amorphous oil (4.2 g). The total content of the kavalactones in the product thus obtained was about 95% by weight.

5 Example 7

Composition of a kavalactones-containing cream of this invention:

	chemical name	wt. %
10	kavalactones	10
	glycerin	1
	propylene glycol	1
	polyglycerylmethacrylate	1
	hydroxyethylcellulose	0.5
15	magnesium aluminum silicate	0.5
	imidazolidinyl urea	0.5
	disodium EDTA	0.05
	petrolatum	2
	isopropyl palmitate	5
20	dimethicone	0.5
	cetyl alcohol	0.5
	isostearic acid	3
	PEG-40 stearate	1
	PEG-100 stearate	1
25	sorbitan stearate	1
	glycolic acid	7
	ammonium hydroxide	pH adjusted to 4.4
	deionized water	qs to 100%

30

Example 8

Composition of another kavalactones-containing cream of this invention:

5	chemical name	wt. %
	kavalactones	10
	Isostearyl Isononanoate	2.5
	propylene glycol	1
10	hydroxyethylcellulose	0.5
	magnesium aluminum silicate	0.75
	cocoa butter	1.2
	petrolatum	2
	isopropyl palmitate	5
15	dimethicone	0.5
	stearic acid	3
	isostearic acid	1.5
	glycerol stearate	1.5
	PEG-40 stearate	1
20	PEG-100 stearate	1
	cetyl /stearyl alcohol	2.5
	glycerin	2.5
	glycolic acid	10
	propylparaben	0.1
25	ammonium hydroxide	pH adjusted to 3.8
	deionized water	qs to 100%

30 Example 9

Composition of another kavalactones-containing cream of this invention:

	chemical name	wt. %
	beeswax	24.5
5	kavalactones	5
	vegetable oil (jojoba oil)	70
	propylparaben	0.5

.10

Example 10

Composition of a cream, to which various amounts of kavalactones can be added:

15	ingredient	wt (%)
	petrolatum	2
	stearyl alcohol	0.5
	isopropyl myristate	5
20	sorbitan monooleate	5
	polyoxyl 40 stearate	5
	propylene glycol	5
	methylparaben	0.3
	ammonium hydroxide	pH adjusted to 4.4
25	deionized water	qs to 100%

Example 11

Composition of a kavalactones-containing jelly of this invention:

chemical name	wt. %
white petrolatum, USP	90
kavalactones	10

Example 12

Composition of an oil-in-water emulsion, to which various amounts of kavalactones can be added:

chemical name	wt. %
xanthan gum	0.2
disodium EDTA	0.1
sodium PCA	0.5
diazodinyI urea	0.3
titanium dioxide	1
stearic acid	3
cyclomethicone	0.3
cetyl alcohol	0.5
glyceryl stearate	0.5
PEG-100 stearate	0.5
steareth-2	0.2
lecithin	0.5
tocopherol	0.2
octyl methoxycinnamate	6
glucono-1,5-lactone	6
glycolic acid	3

	malic acid	2
	lactic acid	2
	green tea extract	1
	triethanolamine	pH adjusted to 3.8
5	deionized water	qs to 100%

Example 13

10 A patient with rheumatoid arthritis (left leg, joint) was unresponsive to several oral medications. A composition containing 5 g of cream (as described in Example 10) and 500 mg of kavalactones (as extract prepared according to Example 4) was administrated to the joint three times a day. Substantial relief of the rheumatoid arthritis symptoms was achieved 30 min after topically applying the kavalactones-
 15 containing cream to the joint.

Example 14

A patient suffered from chronic lower back problems, which could not be relieved by oral drugs (such as aspirin and ibuprofen). Substantial relief of the
 20 symptoms (e.g., relief from burning sensation in the affected area, general relief to resume daily activity (e.g., walking) was achieved 10 min after applying the kavalactones-containing cream described in Example 13 to the back.

Example 15

25 A patient suffers from fibromyalgia symptoms in the left knee. Ten minutes after applying the kavalactones-containing cream described in Example 13 to the knee, the patient felt relief from discomfort.

Example 16

30 A patient suffers from periodontitis (molars). Ten minutes after applying a kavalactones-containing jelly described in Example 11 (using kavalactone extract

prepared according to Example 4) to the gum area, the symptoms were ameliorated, including reduced redness of the affected area and relief from discomfort.

Example 17

5 Four subjects were exposed to topical capsaicin at 1% in two extremities. After approximately 1 hour, when the burning became quite intense, either placebo or 30 % kava was applied to the effective area in a blinded fashion. All subjects reported a marked reduction in the burning associated with capsaicin in the side receiving capsaicin but not in the side receiving the placebo. This indicates that kava (e.g.,
10 kavalactones) were able to counteract the burning (secondary and primary hyperalgesia) associated with capsaicin.

Example 18

Topical kava was applied to three individuals with intractable myofascial and
15 osteoarthritis pain. All patients had a complete reduction in pain. This pain relief lasted 8 – 24 hours with a single application.

Example 19

A 1% capsaicin cream was prepared by mixing of 455g of EUCERIN crème
20 with 10ml of EtOH solution and 5g natural capsaicin (trans-8-methyl-N-vanilyl-6-noneamide) (purchased from Aldrich Chemical Company, Inc., Milwaukee, WI).

Example 20

Crude pulverized Kava root powder (500 g) (cultivar name: Mo'i (purchased
25 through Botanical Liaisons, 1180 Crestmoor Drive, Boulder, CO 80303) was extracted with refluxing EtOAc (1.8 L) under mechanical stirring for 3 hours, cooled to rt, filtered, and washed with EtOAc (500 mL). The filtrate and washings were combined and evaporated to leave crude extract (60g). The crude material was dissolved into ethyl acetate (300 mL) and 5% Pd/C (6.0 g) and charcoal (6.0 g) were
30 added. The mixture was then hydrogenated on a Parr hydrogenator at 40 psi H₂ for 60 min. Catalyst and carbon were filtered off. Removal of the solvent afforded the final

Kava extract as an off-white paste. (50 g, 10 % yield from Kava root). Total content of 7,8-Dihydrokawain (38%) and 7,8-Dihydromethysticin (24%) by weight is 62%.

Example 21

5 Kava dry root powder (500 g) (cultivar name: Nene ele ele purchased through Botanical Liaisons, 1180 Crestmoor Drive, Boulder, CO 80303) was stirred with 95% EtOH (1.8 L) under reflux for 3 hours, cooled to rt, filtered, and washed with 95% EtOH (800 mL). The filtrate and washings were combined and was treated with charcoal (20 g) at 80 °C for 30 – 60 min, cooled to rt and filtered through a layer of
10 Al₂O₃ (neutral, activated, 120 g) and CELITE (100 g), washed with 95% EtOH (2 x 500 mL). Combined filtrate and washings were evaporated to leave crude extract (38g). To a 300 mL solution of the crude extract was slowly added 5% Pd/C (3.8 g). The mixture was then hydrogenated on a Parr hydrogenator at 40 psi H₂ for 30 min. Catalyst and carbon were filtered off through a layer of CELITE. Removal of the
15 solvent afforded the final Kava mixture as an off-white paste. (30 g, 6% yield from Kava root). Total content of 7,8-Dihydrokawain (48%) and 7,8-Dihydromethysticin (20%) by weight is 68%.

Example 22

20 Dry pulverized Kava root (500 g) (origin: Vanuatu, purchased through Botanical Liaisons, 1180 Crestmoor Drive, Boulder, CO 80303) was stirred with Acetone (1.8 L) under reflux for 3 - 5 hours, cooled to rt, filtered, and washed with Acetone (800 mL). The filtrate and washings were combined and was treated with charcoal (10 g) at 45 °C for 60 min, cooled to rt and filtered through a layer of Al₂O₃
25 (neutral, activated, 90 g) and CELITE (50 g), washed with Acetone (2 x 500 mL). Combined filtrate and washings were evaporated to leave crude extract (40g). To a 300 mL Ethyl acetate solution of the crude extract 5% Pd/C (4.3 g) was added. The mixture was then hydrogenated on a Parr hydrogenator at 40 psi H₂ for 30 min. Catalyst and carbon were filtered off through a layer of CELITE. Removal of the
30 solvent afforded the final Kava mixture as an off-white paste. (33 g, 6.6 % yield from Kava root).

Example 23

Crude powdered Kava root (500 g) (Calivar name: Mo'i purchased through Botanical Liaisons, 1180 Crestmoor Drive, Boulder, CO 80303) was extracted with refluxing EtOAc (1.8 L) under mechanical stirring for 3 hours, cooled to rt, filtered, and washed with EtOAc (500 mL). The filtrate and washings were combined and evaporated to leave crude extract (35g). To a 300 mL ethyl acetate solution of the crude extract 5% Pd/C (3.5 g) and charcoal (3.5 g) were added. The mixture was then hydrogenated on a Parr hydrogenator at 40 psi H₂ for 60 min. Catalyst and carbon were filtered off. The filtrate was treated with 0.2 N LiOH (2 x 150 mL). Organic layers were separated. After removal of the solvent, the final Kava lactone mixture as obtained as an off-white paste. (32 g, 6.4 % yield from Kava root). Total content of 7,8-Dihydrokawain (38%) and 7,8-Dihydromethysticin (23%) by weight is 61%.

Example 24

Kava yellow extract (100 g) containing 84% kavalactones (Kaviar +80, purchased from Cosmopolitan Trading, P.O.Box 85840, Seattle, WA 98145) was dissolved in EtOAc (150 ml). The solution was then hydrogenated with 5% Pd/C (5 g) on a Parr hydrogenator at 40 psi H₂ for 60 min. Catalyst and carbon were filtered off through a layer of CELITE. Removal of the solvent afforded the final Kava mixture as a pale-green paste. (95 g.). Total content of 7,8-Dihydrokawain (47%) and 7,8-Dihydromethysticin (20%) by weight is 67%.

Example 25

The pale green paste (30g) produced in Example 5 was then treated with 0.2N LiOH solution (200ml x 2). The organic layer was washed with water (200ml x 2) and dried over Na₂SO₄. Organic solvent was evaporated to leave a pale green paste (27g) Total content of 7,8-Dihydrokawain (49%) and 7,8-Dihydromethysticin (22%) by weight is 71%.

Example 26

A pale green paste (20g) produced in Example 6 was then subjected to column chromatography (hexane/ethyl acetate =2:1) on 200g of neutral alumina to yield 15g

of 7,8-Dihydrokawain (64%) and 7,8-Dihydromethysticin (30%) by weight as a mixture.

Example 27

5 Dry pulverized Kava root (500 g) (cultivar name: Nene purchased through Botanical Liaisons, 1180 Crestmoor Drive, Boulder, CO 80303) was stirred with 95% EtOH (1.8 L) under reflux for 3 - 5 hours, cooled to rt, filtered, and washed with 95% EtOH (800 mL). The filtrate and washings were combined and was treated with charcoal (8 g) at 80 °C for 30 min, cooled to rt and filtered through a layer of Al₂O₃
10 (neutral, activated, 120 g) and CELITE (50 g), washed with 95% EtOH (2 x 500 mL). Combined filtrate and washings were evaporated to leave crude extract (43g). To a 300ml ethyl acetate solution of the crude extract was added 5% Pd/C (3.2 g). The mixture was then hydrogenated on a Parr hydrogenator at 40 psi H₂ for 60 min. Catalyst and carbon were filtered off through a layer of CELITE. Removal of the
15 solvent afforded the final Kava mixture as an off-white paste. (39g, 7.8 % yield from Kava root). Total content of 7,8-Dihydrokawain (37%) and 7,8-Dihydromethysticin (27%) by weight is 64%.

Example 28

20 Pulverized Kava root (500 g) (cultivar name: Molokai green purchased through Botanical Liaisons, 1180 Crestmoor Drive, Boulder, CO 80303) was stirred with 95% EtOH (1.8 L) under reflux for 3 hours, cooled to rt, filtered, and washed with 95% EtOH (800 mL). The filtrate and washings were combined and was treated with charcoal (10 g) at 80 °C for 30 min, cooled to rt and filtered through a layer of Al₂O₃
25 (neutral, activated, 90 g) and CELITE (50 g), washed with 95% EtOH (2 x 500 mL). Combined filtrate and washings were evaporated to leave crude extract (32g). The crude extract was then dissolved in EtOAc (300 mL), 5% Pd/C (3.2 g) was added. The mixture was then hydrogenated on a Parr hydrogenator at 40 psi H₂ for 30 min. Catalyst and carbon were filtered off through a layer of CELITE. The filtrate was
30 shaken with 0.2 N LiOH (2 x 150 mL) and then with H₂O (150 mL). Organic layers were separated and concentrated in vacuo to afford the final Kava lactone mixture as

an off-white paste. (30 g, 6% yield from Kava root). Total content of 7,8-Dihydrokawain (46%) and 7,8-Dihydromethysticin (19%) by weight is 65%.

5 All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, technical data sheets, internet web sites, databases, patents, patent applications, and patent publications.

A number of embodiments of the invention have been described.
10 Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A medicinal ointment comprising 1% to 90% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof; and a medicinally acceptable carrier.
2. The medicinal ointment of claim 1, wherein the active kavalactone is dihydrokawain.
3. The medicinal ointment of claim 1, wherein the active kavalactone is dihydromethysticin.
4. The medicinal ointment of claim 1, wherein the active kavalactone is a combination of dihydromethysticin, dihydrokawain, and kawain.
5. The medicinal ointment of claim 1, wherein the ointment comprises 1.5% to 30% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof; and a medicinally acceptable carrier.
6. The medicinal ointment of claim 5, wherein the active kavalactone is dihydrokawain.
7. The medicinal ointment of claim 5, wherein the active kavalactone is dihydromethysticin.
8. The medicinal ointment of claim 5, wherein the active kavalactone is a combination of dihydromethysticin, dihydrokawain, and kawain.
9. The medicinal ointment of claim 1, wherein the ointment comprises 2% to 25% by weight an active kavalactone selected from the group consisting of

dihydrokawain, dihydromethysticin, kawain, and a combination thereof; and a medicinally acceptable carrier.

10. The medicinal ointment of claim 9, wherein the active kavalactone is dihydrokawain.
11. The medicinal ointment of claim 9 wherein the active kavalactone is dihydromethysticin.
12. The medicinal ointment of claim 9, wherein the active kavalactone is a combination of dihydromethysticin, dihydrokawain, and kawain.
13. A patch comprising a material layer and a composition associated with the material layer; the composition having 1% to 90% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof, associated with the material layer.
14. The patch of claim 13, further comprising a protective layer intimately adhered to one side of the material layer which is resistant to passage of the active kavalactone.
15. The patch of claim 14, wherein the material layer includes a pressure-sensitive adhesive.
16. The patch of claim 15, wherein the active kavalactone is dihydrokawain.
17. The patch of claim 15, wherein the active kavalactone is dihydromethysticin.
18. The patch of claim 15, wherein the active kavalactone is a combination of dihydromethysticin, dihydrokawain, and kawain.

19. The patch of claim 15, wherein the adhesive layer includes 1.5% to 30% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof; and a medicinally acceptable carrier.
20. The patch of claim 19, wherein the active kavalactone is dihydrokawain.
21. The patch of claim 19, wherein the active kavalactone is dihydromethysticin.
22. The patch of claim 19, wherein the active kavalactone is a combination of dihydromethysticin, dihydrokawain, and kawain.
23. The patch of claim 15, wherein the adhesive layer includes 2% to 25% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof; and a medicinally acceptable carrier.
24. The patch of claim 23, wherein the active kavalactone is dihydrokawain.
25. The patch of claim 23, wherein the active kavalactone is dihydromethysticin.
26. The patch of claim 23, wherein the active kavalactone is a combination of dihydromethysticin, dihydrokawain, and kawain.
27. A method for treating pain comprising administering to a subject in need of pain relief a medicinal ointment comprising 1% to 90% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof; and a medicinally acceptable carrier.
28. A method for treating pain comprising administering to a subject in need of pain relief a patch comprising a material layer and a composition associated with the

material layer; the composition having 1% to 90% by weight an active kavalactone selected from the group consisting of dihydrokawain, dihydromethysticin, kawain, and a combination thereof, associated with the material layer.

5

29. A method of treating pain comprising administering to a subject in need of pain relief a medicinal ointment comprising 1% to 90% by weight a kavalactone selected from the group consisting of desmethoxyyangonin, dihydrokawain, dihydromethysticin, kawain, methysticin, and yangonin, and a combination thereof; and a medicinally acceptable carrier.

10

30. The method of claim 27, wherein the pain is myofascial pain.

31. The method of claim 27, wherein the pain is hyperalgesia.

15

32. The method of claim 27, wherein the pain is preemptive analgesia.

33. The method of claim 27, wherein the pain is osteoarthritis pain.

20

34. The method of claim 27, wherein the pain is inflammatory pain.

35. The method of claim 27, wherein the pain is neuropathic pain.

36. The method of claim 27, wherein the medicinal ointment further comprises petrolatum, beeswax, vegetable oil, or combination thereof.

25

37. The method of claim 27, wherein the medicinal ointment is essentially devoid of para-aminobenzoic acid.

30

38. The medicinal ointment of claim 1, wherein the dihydrokawain and dihydromethysticin are synthetic.

39. The medicinal ointment of claim 1, wherein the active kavalactones are derived from a hydrogenated kava extract.
40. A 7,8-dihydrokawain and 7,8-dihydromethysticin enriched hydrogenated extract from rhizome of *Piper methysticum* Forst., wherein said extract comprises 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight.
41. A process for the preparation of a dry extract from the rhizome of *Piper methysticum* Forst. comprising 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight, comprising the chemical reduction of a raw kava extract solution in the presence of hydrogen gas with a catalyst.
42. A process for the reducing the amount of mycotoxins in a dry extract from the rhizome of *Piper methysticum* Forst. comprising 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight, comprising the chemical reduction of a raw kava extract solution in the presence of hydrogen gas with a catalyst.
43. A 7,8-dihydrokawain and 7,8-dihydromethysticin enriched, reduced mycotoxin-containing, hydrogenated extract from rhizome of *Piper methysticum* Forst., wherein said extract comprises 7,8-Dihydrokawain and 7,8-Dihydromethysticin in at least 50% of the total content of kavalactones by weight, and contains less than 0.1% mycotoxins.