(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 August 2007 (30.08.2007)

PCT

(10) International Publication Number
WO 2007/095716 A1

(51) International Patent Classification:
A61K 36/18 (2006.01)

(21) International Application Number:
PCT/CA2006/001156

(22) International Filing Date: 14 July 2006 (14.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/776,325 23 February 2006 (23.02.2006) US

(71) Applicant *(for all designated States except US)*: **IOMEDIX SLEEP INTERNATIONAL SRL** [CA/BB]; #2 Rendezvous Road, Worthing, Christ Church, BB 15006 (BB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GARDINER, Paul** [CA/CA]; 5100 Spectrum Way, Mississauga, Ontario L4W 5S2 (CA). **HEUER, Marvin** [US/CA]; 5100 Spectrum Way, Mississauga, Ontario L4W 5S2 (CA). **CHAUDHURI, Shan,** [CA/CA]; 5100 Spectrum Way, Mississauga, Ontario L4W 5S2 (CA). **CLEMENT, Ken** [CA/CA]; 5100 Spectrum Way, Mississauga, Ontario L4W 5S2 (CA).

(74) Agent: **TORYS LLP**; Suite 3000, 79 Wellington Street West, Box 270, TD Centre, Toronto, Ontario MK5 1N2 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/095716 A1

(54) **Title:** COMPOSITIONS AND METHODS FOR THE INDUCTION AND MAINTENANCE OF QUALITY SLEEP

(57) **Abstract:** Supplemental compositions, and methods for administering same to a user, are provided for promoting a restful night's sleep by speedily inducing a person to fall asleep and to maintain sleep, as well as alleviating minor aches and pains so as to further improve the quality of a person sleep. The supplemental composition may include at least an extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof. The supplemental composition may be provided for consumption at least one time daily, e.g., prior to sleep.

Compositions and Methods for the Induction and Maintenance of Quality Sleep

Field of the Invention

The present invention relates to a composition to aid in the induction and maintenance of sleep in a user, e.g., human.

Background of the Invention

Sleep typically occupies about one-third of a person's life and affects a person's mental and physical well-being. It additionally affects mood, behavior and physiology. Sleep and the control of sleep is a complex process involving multiple chemicals and brain structures. It is a dynamic process involving distinct physiological changes and involves both positive and negative signaling. The regulation of sleep in humans is governed by three processes – each influenced by hormonal and environmental factors: a daily sleep-wake cycle influenced by a circadian rhythm (24 hour cycle) tied to light-dark cycles controlled by a cluster of about 10,000 neurons located in the hypothalamus behind the eyes, called the suprachiasmatic nuclei (Hastings MH. Central clocking. Trends Neurosci. 1997 Oct;20(10):459-64.); a separable oscillating sleep homeostatic process influenced by prior sleep (Dijk DJ, Lockley SW. Integration of human sleep-wake regulation and circadian rhythmicity. J Appl Physiol. 2002 Feb;92(2):852-62.); and an ultradian rhythm which occurs within the 24 hour circadian cycle.

The need for sleep is a biological drive similar to thirst or hunger. Interestingly though, the function of sleep is largely unknown, however some

evidence indicates that sleep is required for learning (Stickgold R, James L, Hobson JA. Visual discrimination learning requires sleep after training. Nat Neurosci. 2000 Dec;3(12):1237-8.; Gais S, Plihal W, Wagner U, Born J. Early sleep triggers memory for early visual discrimination skills. Nat Neurosci. 2000 Dec;3(12):1335-9.). Additionally, sleep deprivation studies in rats have shown that when rats are not allowed to sleep, the end-result is death apparently related to immune system failure (Everson CA. Sustained sleep deprivation impairs host defense. Am J Physiol. 1993 Nov;265(5 Pt 2):R1148-54.). In humans, similarly, mild sleep deprivation also results in indications of impaired immune system function (Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB J. 1996 Apr;10(5):643-53.). Although specific sleep requirements vary from individual to individual, sleeping less than six hours per day has been shown to increase the risk of glucose intolerance and diabetes (Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Nieto FJ. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med. 2005 Apr 25;165(8):863-7.). Insomnia has been estimated to affect 40% of North Americans per year (Stoller MK. Economic effects of insomnia. Clin Ther. 1994 Sep-Oct;16(5):873-97). A study by the U.S. National Sleep Foundation and the Gallup Organization involving 1,000 randomly selected Americans revealed that insomnia negatively impacts activities during waking function and effects quality of life (Roth T, Ancoli-Israel S. Daytime consequences and correlates of insomnia in the United States: results of the

1991 National Sleep Foundation Survey. II. Sleep. 1999 May 1;22 Suppl 2:S354-8.). Another study involving 261 insomnia sufferers and 101 individuals with no sleep complaints revealed that insomnia significantly impairs quality of life (Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep. 1999 May 1;22 Suppl 2:S379-85.).

The neurotransmitter Gamma Aminobutyric Acid (GABA) is a primary inhibitory neurotransmitter. One of its effects is to induce sleep. The GABA-receptors are associated with chloride ion channels – signaling through the GABA-receptor changes the electrochemical gradient of the neuron, leading to activity inhibition (Olsen RW, Tobin AJ. Molecular biology of GABAA receptors. FASEB J. 1990 Mar;4(5):1469-80). Benzodiazepines are thought to act via interaction with the GABA receptor; enhancing the inhibitory effects of GABA. As such, Benzodiazepines are a widely used class of drugs primarily used as tranquilizers, muscle-relaxants, hypnotics or sedatives (Valenstein M, Taylor KK, Austin K, Kales HC, McCarthy JF, Blow FC. Benzodiazepine use among depressed patients treated in mental health settings. Am J Psychiatry. 2004 Apr;161(4):654-61.). Additionally, Adenosine, a neuromodulator, may induce sleep by extracellular accumulation in specific brain regions such as the basal forebrain during prolonged wakefulness (Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ, Rainnie DG, Portas CM, Greene RW, McCarley RW. Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. Behav Brain Res. 2000 Nov;115(2):183-204.; Zeitzer JM, Morales-Villagran A,

Maidment NT, Behnke EJ, Ackerson LC, Lopez-Rodriguez F, Fried I, Engel J Jr, Wilson CL. Extracellular adenosine in the human brain during sleep and sleep deprivation: an in vivo microdialysis study. Sleep. 2006 Apr 1;29(4):455-61.). Actions on both the GABA-benzodiazepine receptor complex (Mendelson WB. Sleep-inducing effects of adenosine microinjections into the medial preoptic area are blocked by flumazenil. Brain Res. 2000 Jan 10;852(2):479-81.) and/or the adenosine A1 receptor (Thakkar MM, Winston S, McCarley RW. A1 receptor and adenosinergic homeostatic regulation of sleep-wakefulness: effects of antisense to the A1 receptor in the cholinergic basal forebrain. J Neurosci. 2003 May 15;23(10):4278-87.) can lead to the induction and maintenance of sleep. The stimulatory effects of caffeine are thought to be due to antagonism of adenosine A1 receptors (Sawynok J. Pharmacological rationale for the clinical use of caffeine. Drugs. 1995 Jan;49(1):37-50.), wherein an aroused state is observed.

Another chemical associated with sleep is Melatonin. It is a hormone produced by the pineal gland from the amino acid tryptophan. Production is rhythmic in keeping with an intrinsic cycle of approximately 24-hours in duration, wherein levels are low during the day and increasing towards the nighttime (Wyatt JK, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. Am J Physiol. 1999 Oct;277(4 Pt 2):R1152-63). Melatonin appears to have two distinct effects on the circadian clock: neuronal inhibition and phase-shifting of the sleep cycle (Liu C, Weaver DR, Jin X, Shearman LP, Pieschl RL, Gribkoff VK, Reppert SM. Molecular dissection of two distinct actions of

melatonin on the suprachiasmatic circadian clock. Neuron. 1997 Jul;19(1):91-102.). Oral administration of supplemental melatonin during the day induces sleepiness and improves night sleep (Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. Proc Natl Acad Sci U S A. 1994 Mar 1;91(5):1824-8.). Two types of melatonin G-protein coupled receptors have been classified in mammals and termed MT1 and MT2 (Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005 Jul;27(2):101-10.).

Serotonin (5-hydroxytryptamine, 5HT), like melatonin, also displays a diurnal pattern; however, it functions in an opposing rhythm with daytime levels being higher than nighttime levels Portas CM, Bjorvatn B, Fagerland S, Gronli J, Mundal V, Sorensen E, Ursin R. On-line detection of extracellular levels of serotonin in dorsal raphe nucleus and frontal cortex over the sleep/wake cycle in the freely moving rat. Neuroscience. 1998 Apr;83(3):807-1.). Three basic serotonin receptor types have been identified: 5HT-1, 5HT-2 and 5HT-3. Several subtypes of 5HT-1 have also been identified. The exact response of cells to serotonin depends on the receptor types expressed (Andrade R. of membrane excitability in the central nervous system by serotonin receptor subtypes. Ann N Y Acad Sci. 1998 Dec 15;861:190-203.) however, Serotonin has been shown to inhibit GABA receptors (Feng J, Cai X, Zhao J, Yan Z. Serotonin receptors modulate GABA(A) receptor channels through activation of anchored protein kinase C in prefrontal cortical neurons. J Neurosci. 2001 Sep 1;21(17):6502-11.),

likely contributing to the opposing actions of serotonin and GABA and play a role in sleep.

Summary of the Invention

The present invention according to one embodiment thereof, provides for a composition directed towards the induction of sleep. More specifically, the invention is directed towards a sleep-promoting and pain-relief composition. Advantageously, the sleep-promoting and pain-relief composition of the present invention may additionally provide for maintenance of sleep, thereby promoting a good quality, restful sleep as well as alleviating minor aches and pains, thus further improving the quality of the person's sleep. The composition of the present invention comprises an extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof. For example, the present invention may be effective in promoting a restful night's sleep by speedily inducing a person to fall asleep and maintain sleep as well as alleviating minor aches and pains further improving the quality of an individual's, e.g. a human or animal, sleep. Furthermore, the present invention advantageously provides a method for the maintenance of sleep thereby promoting a good quality, restful sleep as well as alleviating minor aches and pains, thus further improving the quality of an individual's, e.g. human or animal, sleep by administering to a human or a animal a composition comprising an extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof.

According to an embodiment, the present invention may provide a composition comprising an extract of Valerian Root, an extract of Willow Bark

and Melatonin or a derivative thereof. Additionally, the composition may include one or more of an extract of Hops cone, Lavender flower powder, an extract of Passionflower, Skullcap powder, an extract of Coenzyme Q10, a leaf of extract Lemon Balm. The composition may include a time-release mechanism, e.g., wherein the time-release mechanism provides 4 hours of active compound release. Also, the melatonin may be incorporated into a tablet coating to promote sleep more quickly, e.g., to promote instant or immediate sleep. Also, in an embodiment of the present invention, all or a portion of the melatonin may be fine-milled. Advantageously, the extract of Valerian Root, the extract of Willow Bark and the Melatonin or a derivative thereof, are provided in amounts effective to at least one of promote sleep and relieve pain.

Detailed Description of the Invention

The present invention according to an embodiment thereof is advantageously directed towards a sleep-promoting and pain-relief composition which, for example, may induce sleep and promote the maintenance of sleep leading to a restful night's sleep, as well as alleviate minor aches and pains, further improving the quality of a person's sleep. Compounds employed in various embodiments of the present invention have been shown to be active at receptor sites in the central nervous system that relate to the induction and maintenance of sleep. Moreover, the composition of the present invention also contains compounds shown to alleviate minor aches and pains.

In an embodiment, the present invention may include the use of combinations, wherein the combination includes, without being limited to, one or

more of the following: Melatonin, Coenzyme Q10, Lemon Balm leaf extract, Hops cone extract, Lavender flower extract, Passionflower extract, Skullcap, deodorized Valerian root and Willow bark extract. The supplement may be consumed in any form, e.g., a capsule, a tablet, a caplet, a liquid beverage, a powder beverage mix, or as a dietary gel. The preferred dosage form of the present embodiment is a timed release caplet.

As set forth above, the dosage form of the diet supplement, in accordance with the example embodiment set forth below, may be provided in accordance with customary processing techniques for herbal and/or dietary supplements, wherein the active ingredients are suitably processed into a desired form. In accordance with an embodiment of the present invention, one or more ingredients of the diet supplement are processed so as to form fine-milled particles. For instance, in an embodiment, one or more ingredients of the supplemental dietary composition is processed by a large-scale dry milling technique that produces fine particles, preferably known as fine-milled particles. The use of dry milling techniques, in combination with excipients and polymers, to form fine-milled particles has been shown to improve flow and dispersability, stability, resistance to moisture, bioavailability, and dissolution/release properties. Formulations may benefit by containing fine-milled particles because providing one or more ingredients in fine-milled particle sizes may optimize one or more of the flow and dispersability, stability, resistance to moisture, bioavailability, and dissolution/release properties of the one or more ingredients in a diet supplement. In vitro tests designed to simulate the environment of a stomach

were performed to test the dissolution rate of fine-milled particle tablets relative to tablets having particles that are not fine-milled. These test showed that in tablets produced from fine-milled particles the time to 100% dissolution was approximately 15 minutes. In the case of non-fine-milled particle compositions, only 90% dissolution was observed after 120 minutes. In a preferred embodiment, the supplemental composition contains fine-milled particles having an average size between about 2 nm and about 50 nm.

U.S. Provisional Patent Application 60/776,325 discloses a method for improving the absorption, palatability, taste, texture, and bioavailability of compounds by increasing the solubility of compounds in proprietary formulations for the purposes of enhancing or improving muscle size, growth and/or recovery time and/or weight loss. The increased bioavailability of the compound or ingredients is achieved by reducing the particle size via "fine-milling" thereby increasing the surface area-to-volume ratio of each particle, thus increasing the rate of dissolution. The compositions and methods disclosed promote increased bioavailability by increasing the total surface area of poorly soluble particles, thereby increasing the rate of absorption.

As used herein the, term "fine-milled" and/or "fine-milling" refers to the process of micronization. Micronization is a mechanical process that involves the application of force to a particle, thereby resulting in a reduction in the size of the particle. The force, in the case of micronization, may be applied in any manner such as, e.g., the collision of particles at high rates of speed, grinding, or by an air-jet micronizer. In a preferred embodiment, fine-milled particles are obtained

by jet-milling with nitrogen and compressed air.

As used herein, the term "particle size" refers to the diameter of the particle. The term "average particle size" means that at least 50% of the particles in a sample will have the specified particle size. Preferably, at least 80% of the particles in a sample will have the specified particle size, and more preferably, at least 90% of the particles in a given sample will have the specified particle size.

The size of a particle can be determined by any of the methods known within the art. Methods for particle size determination which may be employed are, e.g., sieves, sedimentation, electrozone sensing (Coulter counter), microscopy, and/or Low Angle Laser Light Scattering. The preferred methods for the particle size determination of the present invention are the methods which are most commonly used in the pharmaceutical industry, such as laser diffraction, e.g., via light scattering Coulter Delsa 440SX.

The fine-milling process may be employed in the processing of one or more of the ingredients of the present invention in the dosage forms of tablets (e.g., immediate-release film coated, modified-release and fast-dissolving), capsules (e.g., immediate-release and modified-release), liquid dispersions, powders, drink mixes, etc.

Furthermore, the dosage form of the nutritional supplement in accordance with the aforementioned embodiment or further embodiments as interpreted by one of skill in the art related to the present invention may be provided in accordance with customary processing techniques for herbal and/or dietary and/or nutritional supplements in any of the forms mentioned above.

Melatonin

Melatonin is a hormone produced by the pineal gland from tryptophan and is involved in sleep regulation (Reiter RJ. melatonin: cell biology of its synthesis and of its physiological interactions. Endocr Rev. 1991 May;12(2):151-80.). It is used to treat sleep disorders such as insomnia and 'jet lag' by stimulating the release of specific pituitary hormones (Ninomiya T, Iwatani N, Tomoda A, Miike T. Effects of exogenous melatonin on pituitary hormones in humans. Clin Physiol. 2001 May;21(3):292-9.) and adjusting the circadian rhythm to coincide with the local day and nighttime.

Melatonin supplementation has been demonstrated to be safe and effective at increasing the total amount of sleep time in healthy subjects (Matsumoto M. The hypnotic effects of melatonin treatment on diurnal sleep in humans. Psychiatry Clin Neurosci. 1999 Apr;53(2):243-5.). Moreover, Melatonin has also been shown to benefit individuals suffering from insomnia (Hughes RJ, Sack RL, Lewy AJ. The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: assessment in a clinical trial of melatonin replacement. Sleep. 1998;21(1):52-68.; Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab. 2001 Oct;86(10):4727-30.; Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, Ford I. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev. 2005 Feb;9(1):41-50.) by way of the induction of sleep. The most common effect of melatonin on sleep is a reduction in sleep latency, the time taken to fall asleep

(Zhdanova IV, Wurtman RJ, Lynch HJ, Ives JR, Dollins AB, Morabito C, Matheson JK, Schomer DL. Sleep-inducing effects of low doses of melatonin ingested in the evening. Clin Pharmacol Ther. 1995 May;57(5):552-8.; Nagtegaal JE, Kerkhof GA, Smits MG, Swart AC, Van Der Meer YG. Delayed sleep phase syndrome: A placebo-controlled cross-over study on the effects of melatonin administered five hours before the individual dim light melatonin onset. J Sleep Res. 1998 Jun;7(2):135-43.; Kayumov L, Brown G, Jindal R, Buttoo K, Shapiro CM. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. Psychosom Med. 2001 Jan-Feb;63(1):40-8.; Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Baker G, Klassen TP, Vohra S. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med. 2005 Dec;20(12):1151-8.), wherein it reduces the time it takes for an individual to fall asleep. Melatonin may also normalize the circadian rhythm and benefit shift workers and individuals with circadian rhythm disorders (Avery D, Lenz M, Landis C. Guidelines for prescribing melatonin. Ann Med. 1998 Feb;30(1):122-30.; Kunz D, Mahlberg R, Muller C, Tilmann A, Bes F. Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. J Clin Endocrinol Metab. 2004 Jan;89(1):128-34.; Mundey K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. Sleep. 2005 Oct 1;28(10):1271-8.).

Melatonin may also been shown to be effective in treating seasonal depression (Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of

winter depression: a pilot study. Psychiatry Res. 1998 Jan 16;77(1):57-61.) and migraines (Peres MF, Zukerman E, da Cunha Tanuri F, Moreira FR, Cipolla-Neto J. Melatonin, 3 mg, is effective for migraine prevention. Neurology. 2004 Aug 24;63(4):757.). Furthermore, blood pressure as well as stress hormones can be reduced by daily oral administration of melatonin in healthy men (Arangino S, Cagnacci A, Angiolucci M, Vacca AM, Longu G, Volpe A, Melis GB. Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. Am J Cardiol. 1999 May 1;83(9):1417-9.).

One aspect of the present invention includes the use of Melatonin for the regulation of sleep. U.S. Patent Nos. 6,703,412, 5,716,978, and 5,641,801 disclose methods of treating sleeplessness, sleep latency period, circadian rhythm disorders involving Melatonin.

For example, U.S. Patent No. 6,703,412, entitled "Method of Treating Sleeplessness with Melatonin on an Acute Basis" purports to describe a method of treating sleeplessness in a human comprising the administration of an effective amount of not greater than 10 mg of melatonin or a pharmaceutically acceptable salt thereof. The method further comprises the administration of melatonin after a person has tried and failed to go to sleep, or has awakened from sleep and is unable to return to sleep. The method may be employed up to one hour from the person's desired waking time.

U.S. Patent No. 5,716,978, entitled "Methods of Treating Circadian Rhythm Disorders" describes a method in which infants and blind humans employ the administration of Melatonin to produce a phase-shifting effect and

reinstate a proper circadian rhythm. The method involves the administration of Melatonin from about 6 hours to about 19 hours prior to when a normal sleep phase should begin. The administration of Melatonin is to be less than 1 mg and at a time prior to a person's endogenous Melatonin onset time.

U.S. Patent No. 5,641,801 entitled "Method of Reducing the Period before the Onset of Sleep" purports to describe a method of inducing sleep in an individual via the administration of a single dose of Melatonin comprising less than 1 mg to raise the peak plasma Melatonin levels to within physiological nocturnal levels of normal untreated individuals.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Melatonin. A serving of the supplemental composition may include from about 0.001 g to about 0.01g of Melatonin. The preferred dosage of a serving of the supplemental composition comprises about 0.0040 g of Melatonin.

Furthermore, in an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include fine-milled Melatonin. A serving of the supplemental composition may include from about 0.0001 g to about 0.01 g of fine-milled Melatonin. The preferred dosage of a serving of the supplemental composition comprises about 0.0010 g of fine-milled Melatonin.

CoQ10

Coenzyme Q10 (CoQ10, ubiquinone) is found in the mitochondria of all cells and is involved in energy production. It is found at its highest

concentrations in the heart, liver, kidney and pancreas. CoQ10 is a potent antioxidant in human blood (Weber C, Sejersgard Jakobsen T, Mortensen SA, Paulsen G, Holmer G. Antioxidative effect of dietary coenzyme Q10 in human blood plasma.. Int J Vitam Nutr Res. 1994;64(4):311-5.) where it also acts to preserve vitamin E, another major antioxidant (Thomas SR, Neuzil J, Stocker R. Inhibition of LDL oxidation by ubiquinol-10. A protective mechanism for coenzyme Q in atherogenesis? Mol Aspects Med. 1997;18 Suppl:S85-103).

Due to its high concentrations in the heart, CoQ10 is believed to benefit and strengthen the heart. Many heart-related diseases are thought to result from defective myocardial energy production and numerous studies have suggested that supplementation with CoQ10 is beneficial (Mortensen SA. Perspectives on therapy of cardiovascular diseases with coenzyme Q10 (ubiquinone). Clin Investig. 1993;71(8 Suppl):S116-23.). A meta-analysis of eight clinical trials supports the efficacy of CoQ10 for the treatment of congestive heart failure (Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. Mol Aspects Med. 1997;18 Suppl:S159-68.). Another study has shown that individuals suffering from angina were able to exercise for longer periods when receiving CoQ10 (Kamikawa T, Kobayashi A, Yamashita T, Hayashi H, Yamazaki N. Effects of coenzyme Q10 on exercise tolerance in chronic stable angina pectoris. Am J Cardiol. 1985 Aug 1;56(4):247-51.) as compared to untreated groups. Moreover, myocardial function was improved by CoQ10 in patients with disease conditions known to involve energy production deficits (Folkers K, Wolaniuk J, Simonsen R, Morishita

M, Vadhanavikit S. Biochemical rationale and the cardiac response of patients with muscle disease to therapy with coenzyme Q10. Proc Natl Acad Sci U S A. 1985 Jul;82(13):4513-6.) wherein these patients also reported a 'subjective' improved sense of well-being. CoQ10 supplemented with iron and vitamin B6 has also appeared to prevent the progression of Alzheimer's disease, a neurological disease often associated with impaired mitochondrial function (Imagawa M, Naruse S, Tsuji S, Fujioka A, Yamaguchi H. Coenzyme Q10, iron, and vitamin B6 in genetically-confirmed Alzheimer's disease. Lancet. 1992 Sep 12;340(8820):671.). Moreover, in another neurological disorder, CoQ10 in a phase II clinical trial was reported to slow the progression of Parkinson's disease (Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmutter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M; Parkinson Study Group. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol. 2002 Oct;59(10):1541-50.) which often results in disturbed sleep and has been shown to involve impaired mitochondrial function and low levels of CoQ10 (Shults CW, Haas RH, Passov D, Beal MF. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. Ann Neurol. 1997 Aug;42(2):261-4.).

Furthermore, CoQ10 has been successfully used to treat high blood pressure, eliminating the need for medication in many cases (Langsjoen P, Langsjoen P, Willis R, Folkers K. Treatment of essential hypertension with coenzyme Q10. Mol Aspects Med. 1994;15 Suppl:S265-72.). Migraines have

also been successfully and safely treated with CoQ10 (Sandor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology. 2005 Feb 22;64(4):713-5.) most likely due its effects on blood pressure.

In a Japanese study, CoQ10 was shown to provide relieve from snoring in about half of the subjects, displaying a decrease in the sound level of their snoring (Takasaki Y, Yoshida H, Kaneko Y, Kaneda R, Kurosaki S, Yamadera Y., An Analysis of Effectiveness of Activated Co-enzyme Q10 on Subjects by Using Acoustic Technology. Biopharma Ltd. Tokyo Japan). Specifically, about 44% of subjects displayed a decrease in the sound level of their snoring during the REM stage of sleep, about 40% of subjects showed a decrease in the sound level of their snoring during non-REM sleep stages I/II, and about 33% of subjects showed a decrease in the sound level of their snoring during non-REM sleep stages III/IV. Furthermore, subjects reported in questionnaires that their feeling of restfulness was improved upon waking.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include CoEnzyme Q10. A serving of the supplemental composition may include from about 0.0005 g to about 0.1000 g of CoEnzyme Q10. The preferred dosage of a serving of the supplemental composition comprises about 0.0010 g of CoEnzyme Q10.

Lemon Balm Leaf Extract

The plant Melissa officinalis, commonly known as Lemon balm is a member of the mint family and is often referred to as 'the calming herb". Lemon balm extract has proven antioxidant activity which likely contributes to its beneficial effects (Hohmann J, Zupko I, Redei D, Csanyi M, Falkay G, Mathe I, Janicsak G. Protective effects of the aerial parts of Salvia officinalis, Melissa Officinalis and Lavandula angustifolia and their constituents against enzyme-dependent and enzyme-independent lipid peroxidation. Planta Med. 1999 Aug;65(6):576-8.). However, in the central nervous system, it possesses acetylcholine receptor activity (Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E. acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. J Ethnopharmacol. 2000 Feb;69(2):105-14.), therefore suggesting that it may have another possible mechanism of action relating to cell-signaling.

Randomized, placebo-controlled, double-blind clinical studies investigating the acute effects of Lemon balm extract on cognition and mood have demonstrated a calming effect (Kennedy DO, Scholey AB, Tildesley NT, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). Pharmacol Biochem Behav. 2002 Jul;72(4):953-64.) in addition to the effect of improved mood (Kennedy DO, Wake G, Savelev S, Tildesley NT, Perry EK, Wesnes KA, Scholey AB. Modulation of mood and cognitive performance following acute administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. Neuropsychopharmacology. 2003

Oct;28(10):1871-81.). Lemon balm extract has also shown potential in reducing the negative mood effects of stress in clinical trials (Kennedy DO, Little W, Scholey AB. Attenuation of laboratory-induced stress in humans after acute administration of Melissa officinalis (Lemon Balm). Psychosom Med. 2004 Jul-Aug;66(4):607-13.).

Moreover, the cognitive function of Alzheimer's patients has been shown to be improved by the use Lemon balm extract (Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry. 2003 Jul;74(7):863-6.). In this study, the treatment group also displayed less agitation than the placebo group, suggesting an improvement in mood. Furthermore, clinical trials have demonstrated that Lemon balm can be effective at reducing stress and anxiety when used in combination with Valeriana (Kennedy DO, Little W, Haskell CF, Scholey AB. Anxiolytic effects of a combination of Melissa officinalis and Valeriana officinalis during laboratory induced stress. Phytother Res. 2006 Feb;20(2):96-102.). Another study has shown that when presented in a lozenge also containing Lavender oil and hops, Lemon balm can alter brain-waves related to working memory, leading to the induction of a state of relaxation and an improved ability to cope with emotional and physiological stress (Dimpfel W, Pischel I, Lehnfeld R. Effects of lozenge containing lavender oil, extracts from hops, lemon balm and oat on electrical brain activity of volunteers. Eur J Med Res. 2004 Sep 29;9(9):423-31.).

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Lemon Balm leaf extract. A serving of the supplemental composition may include from about 0.0010 g to about 0.1000 g of Lemon Balm leaf extract. The preferred dosage of a serving of the supplemental composition comprises about 0.0800 g of Lemon Balm leaf extract.

Hops cone extract (Humulus lupulus)

The hop plant (Humulus lupulus) is a flowering vine used traditionally as a sedative to assist with anxiety reduction and sleep difficulties. In mice, hops extract displays sleep-enhancing and antidepressant activities (Zanoli P, Rivasi M, Zavatti M, Brusiani F, Baraldi M. New insight in the neuropharmacological activity of Humulus lupulus L. J Ethnopharmacol. 2005 Oct 31;102(1):102-6.).

In vitro tests have shown that hops contain compounds with antioxidant and chemoprotective activity as well as compounds that can induce detoxification enzymes (Dietz BM, Kang YH, Liu G, Eggler AL, Yao P, Chadwick LR, Pauli GF, Farnsworth NR, Mesecar AD, van Breemen RB, Bolton JL. Xanthohumol isolated from Humulus lupulus Inhibits menadione-induced DNA damage through induction of quinone reductase. Chem Res Toxicol. 2005 Aug;18(8):1296-305.).

A combination of valerian and hops has been shown to interact with adenosine receptors (Muller CE, Schumacher B, Brattstrom A, Abourashed EA, Koetter U. Interactions of valerian extracts and a fixed valerian-hop extract combination with adenosine receptors. Life Sci. 2002 Sep 6;71(16):1939-49.) to aid in the maintenance of sleep. Moreover, binding of the valerian-hop

combination to melatonin and serotonin receptors has also been shown (Abourashed EA, Koetter U, Brattstrom A. In vitro binding experiments with a Valerian, hops and their fixed combination extract (Ze91019) to selected central nervous system receptors. Phytomedicine. 2004 Nov;11(7-8):633-8.). These two receptor types are also known to be involved in the sleep process. Furthermore, hop extract has been shown to modulate the gamma-aminobutyric acid receptor (GABA(A) receptors) and display GABA-like activity (Aoshima H, Takeda K, Okita Y, Hossain SJ, Koda H, Kiso Y. Effects of beer and hop on ionotropic gamma-aminobutyric acid receptors. J Agric Food Chem. 2006 Apr 5;54(7):2514-9.) relating to sleep. GABA is an inhibitory neurotransmitter that can induce relaxation and sleep. Modulation of any or all of these receptors may mediate the sleep-inducing activity of hops.

Most of the studies examining the efficacy of hops to aid sleep employ hops in combination with other compounds acting on various receptors known to be involved in sleep regulation. A combination of valerian and hops has been shown to reduce the time taken to fall asleep and results in a more refreshed feeling in the morning in subjects suffering from mild to moderate insomnia (Fussel A, Wolf A, Brattstrom A. Effect of a fixed valerian-Hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study. Eur J Med Res. 2000 Sep 18;5(9):385-90.).

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Hops cone extract. A serving of the supplemental composition may include from about

0.0010 g to about 0.1000 g of Hops cone extract. The preferred dosage of a serving of the supplemental composition comprises about 0.0200 g of Hops cone extract.

Lavender Flower (Lavandula officinalis)

Oil from Lavandula officinalis, commonly known as the Lavender plant is frequently used in aromatherapy as a mode to induce relaxation. The mild sedative effects of Lavender have been demonstrated in animals and humans (Lis-Balchin M, Hart S. Studies on the mode of action of the essential oil of lavender (Lavandula angustifolia P. Miller). Phytother Res. 1999 Sep;13(6):540-2.). Further to the sedative effect, Lavender oil has been shown to reduce agitation of patients suffering from dementia (Holmes C, Hopkins V, Hensford C, MacLaughlin V, Wilkinson D, Rosenvinge H. Lavender oil as a treatment for agitated behaviour in severe dementia: a placebo controlled study. Int J Geriatr Psychiatry. 2002 Apr;17(4):305-8.). Moreover, Lavender has also been shown be beneficial for treating depression (Akhondzadeh S, Kashani L, Fotouhi A, Jarvandi S, Mobaseri M, Moin M, Khani M, Jamshidi AH, Baghalian K, Taghizadeh M. Comparison of Lavandula angustifolia Mill. tincture and imipramine in the treatment of mild to moderate depression: a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry. 2003 Feb;27(1):123-7.). Additionally, the sleep-inducing effects of other compounds may be increased by Lavender (Gyllenhaal C, Merritt SL, Peterson SD, Block KI, Gochenour T. Efficacy and safety of herbal stimulants and sedatives in sleep disorders. Sleep Med Rev. 2000 Jun;4(3):229-251.).

U.S. Patent No. 5,958,462, entitled "Therapeutic Bath Salts and Method of Use," describes a composition comprising magnesium, carbonate and copper compounds and optionally essential oils including that of Lavender. The composition comprises bath salts purported to be helpful in the relaxation of muscles, elimination or reduction of muscle spasms, and the overall enhancement of a person's mood when used as an aromatherapy.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Lavender Flower powder. A serving of the supplemental composition may include from about 0.0010 g to about 0.0100 g of Lavender Flower powder. The preferred dosage of a serving of the supplemental composition comprises about 0.0050 g of Lavender Flower powder.

Passion Flower Extract

Passion flower has been used traditionally for relaxation and as a sleep-aid as well as a treatment for anxiety. The main active component of Passionflower is thought to by chrysin, one of several flavonoids which have been isolated from this plant (Menghini A, Mancini LA. TLC determination of flavonoid accumulation in clonal populations of Passiflora incarnata L. Pharmacol Res Commun. 1988 Dec;20 Suppl 5:113-6.; Pereira CA, Yariwake JH, Lancas FM, Wauters JN, Tits M, Angenot L. A HPTLC densitometric determination of flavonoids from Passiflora alata, P. edulis, P. incarnata and P. caerulea and comparison with HPLC method. Phytochem Anal. 2004 Jul-Aug;15(4):241-8.). In mice, chrysin has been shown to act as an agonist of benzodiazepine receptors

and also possess anti-anxiety activity (Wolfman C, Viola H, Paladini A, Dajas F, Medina JH. Possible anxiolytic effects of chrysin, a central benzodiazepine receptor ligand isolated from Passiflora coerulea. Pharmacol Biochem Behav. 1994 Jan;47(1):1-4.). Studies have shown that, in mice, Passionflower extract reduces anxiety and induces sleep (Soulimani R, Younos C, Jarmouni S, Bousta D, Misslin R, Mortier F. Behavioural effects of Passiflora incarnata L. and its indole alkaloid and flavonoid derivatives and maltol in the mouse. J Ethnopharmacol. 1997 Jun;57(1):11-20.). Clinical trials in humans have further demonstrated that Passionflower is effective in the treatment of anxiety (Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther. 2001 Oct;26(5):363-7.).

One aspect of the present invention includes the use of Passionflower extract for the reduction of stress and anxiety. U.S. Patent Nos. 6,080,410 and 5,681,578 describe a method and composition, respectively, employing Passionflower extracts for the reduction of stress and anxiety.

U.S. Patent No. 6,080,410, entitled "Method for Reducing Daily Stress and Anxiety in Adults," describes a method of employing a novel dietary supplement which serves a general relaxant comprised of Kava root extract, and at least one of Passionflower, Chamomile Flower, Hops, and Schizandra Fruit. The method claims to reduce daily stress and anxiety in adults. It is administered in capsule format.

U.S. Patent No. 5,681,578, entitled "Composition for Relieving Stress Anxiety, Grief, And Depression," describes a composition comprising gamma Aminobutyric acid, glutamine, glycine, magnesium, passionflower, primal officinalis and vitamin B6. The composition is purported to relieve stress, anxiety, grief and depression.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Passionflower extract. A serving of the supplemental composition may include from about 0.0010 g to about 0.0100 g of Passionflower extract. The preferred dosage of a serving of the supplemental composition comprises about 0.0020 g of Passionflower extract.

Skullcap (*Scutellaria lateriflora*)

Scutellaria, also known commonly as Skullcap, is a member of the mint family and has been used traditionally to treat depression and stress. Studies in mice indicate that Skullcap reduces anxiety (Awad R, Arnason JT, Trudeau V, Bergeron C, Budzinski JW, Foster BC, Merali Z. Phytochemical and biological analysis of skullcap (Scutellaria lateriflora L.): a medicinal plant with anxiolytic properties. Phytomedicine. 2003 Nov;10(8):640-9.). The effects of Skullcap may be at least partially mediated by antagonism of serotonin receptors (Gafner S, Bergeron C, Batcha LL, Reich J, Arnason JT, Burdette JE, Pezzuto JM, Angerhofer CK. Inhibition of [3H]-LSD binding to 5-HT7 receptors by flavonoids from Scutellaria lateriflora. J Nat Prod. 2003 Apr;66(4):535-7.). A clinical study involving healthy volunteers also demonstrated that Skullcap reduces anxiety

(Wolfson P, Hoffmann DL. An investigation into the efficacy of Scutellaria lateriflora in healthy volunteers. Altern Ther Health Med. 2003 Mar-Apr;9(2):74-8.).

U.S. Patent No. 7,045,158, entitled "Standardized Extracts of *Scutellaria Laterifloa,*" describes an improved extract of *Scutellaria Laterifloa* and relates to a pharmaceutical composition prepared from said extract wherein it is suitable for treating anxiety, insomnia, convulsions, muscle tension and spasms.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Skullcap powder. A serving of the supplemental composition may include from about 0.0001 g to about 0.0100 g of Skullcap powder. The preferred dosage of a serving of the supplemental composition comprises about 0.0010 g of Skullcap powder.

Valerian Root (Valeriana officinalis)

Valeriana officinalis, wherein the root, normally called Valerian root, is a perennial herb traditionally used as a sedative and sleep-aid. Compounds from Valerian interact with GABA, melatonin, and/or adenosine systems through binding to certain melatonin and serotonin receptor subtypes (Abourashed EA, Koetter U, Brattstrom A. In vitro binding experiments with a Valerian, hops and their fixed combination extract (Ze91019) to selected central nervous system receptors. Phytomedicine. 2004 Nov;11(7-8):633-8.), particularly the 5-HT_{5A} subtype (Dietz BM, Mahady GB, Pauli GF, Farnsworth NR. Valerian extract and valerenic acid are partial agonists of the 5-HT5a receptor in vitro. Brain Res Mol

Brain Res. 2005 Aug 18;138(2):191-7.). Interaction with this receptor is thought to be responsible for the sleep-inducing and maintenance effect of Valerian root extract.

Valerian root extract has proven to be useful in several clinical trials. Subjective self-evaluation of sleep quality improved in a valerian supplemented group as part of a randomized controlled trial (Leathwood PD, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. Pharmacol Biochem Behav. 1982 Jul;17(1):65-71.), compared to control groups. In another clinical trial, the valerian group reported improved sleep over the placebo group, with 89% of participants reporting improved sleep (Lindahl O, Lindwall L. Double blind study of a valerian preparation. Pharmacol Biochem Behav. 1989 Apr;32(4):1065-6.). Sleep was additionally improved in children with various intellectual deficits, particularly those with hyperactivity (Francis AJ, Dempster RJ. Effect of valerian, Valeriana edulis, on sleep difficulties in children with intellectual deficits: randomised trial. Phytomedicine. 2002 May;9(4):273-9.).

One aspect of the present invention includes the use of Valerian for improving the quality of sleep and reducing minor aches and pains. U.S. Patent Nos. 6,869,622 and 6,383,527 describe respective compositions for improving the quality of sleep and alleviating muscular aches and strains, particularly with respect to those in the lower back.

For example, U.S. Patent No. 6,869,622, entitled "Composition for Improving Sleep Quality and Efficiency, And Method of Preparing and Using the

Composition," describes a pharmaceutically active extract of the plant root family of Valerianaceae and its usefulness in improving sleep quality and efficiency. The patent purports to relate to a method for reducing the number of times a patient wakes after sleep onset, comprising administering to the patient a pharmaceutically-active extract of the root of a plant of the family Valerianaceae, wherein it is processed via an ethanolic and water extraction. Furthermore, a single dosage is administered between the range of 50 mg and 5000 mg approximately one-half and two hours prior to bedtime.

U.S. Patent No. 6,383,527, entitled "Compositions Comprising Valerian Extracts, Isovaleric Acid or Derivatives Thereof with a NSAID," purports to describe a combination of valerian extract or isovaleric acid or a derivative in with a non-steroidal anti-inflammatory compound for treating acute muscular aches, strains and sprains, and in particular lower back pain.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Valerian Root. A serving of the supplemental composition may include from about 0.1000 g to about 1.000 g of Valerian Root. The preferred dosage of a serving of the supplemental composition comprises about 0.1200 g of Valerian Root.

Willow bark extract (providing salicin) (Salix alba) 25% salicin

Willow bark (Salix alba) is a source of salicin, a precursor of acetylsalicylic acid (aspirin) traditionally used to treat pain, fever and inflammation. In a blind clinical trial, willow bark was demonstrated to be effective at relieving back pain (Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C.

Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med. 2000 Jul;109(1):9-14.). After four weeks, 39% of the high salicin group (n=65) were pain-free, 21% of the low salicin group (n=67) were pain-free, and only 6% of the placebo group (n=59) were pain-free. Willow bark extract has also been shown to effectively reduce arthritis pain (Schmid B, Ludtke R, Selbmann HK, Kotter I, Tschirdewahn B, Schaffner W, Heide L. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. Phytother Res. 2001 Jun;15(4):344-50.).

The diminishment of bodily pain is an integral part of quality sleep. The inclusion of Willow Back Extract aids in the alleviation of minor bodily pains, leading to an improvement in sleep quality and a reduction in sleep disruption due to discomfort.

One aspect of the present invention includes the use of Willow bark for the attenuation of minor aches and pains, leading to an improved quality of sleep. U.S. Patent Nos. 6,770,263 and 6,312,736 describe compositions for the treatment, e.g., alleviation, of aches and pains.

For example, U.S. Patent No. 6,770,263, entitled "Compositions and Methods for the Treatment of Aches and Pains," purports to describe methods and compositions useful for treating aches and/or pains. The composition comprises an aqueous medium having dispersed or dissolved therein an analgesic selected from the group consisting of white willow bark, aspirin,

ibuprofen, naproxen, and any combination thereof. The composition is then administered in an effective amount across a mucosal membrane.

U.S. Patent No. 6,312,736, entitled "Herbal Composition to Relieve Pain," describes a composition used to relieve pain and other symptoms associated with migraines and other types of headaches. The composition comprises a combination of White Willow bark extract, Kava Kava root extract, Feverfew extract, Ginger root extract, Guarana extract, and Vitamin B6 wherein the composition may be combined with liposomes to carry the composition in a sublingual dosage for fast pain relief.

In an embodiment of the present invention, which is set forth in greater detail in Example 1 below, the supplemental composition may include Willow bark extract. A serving of the supplemental composition may include from about 0.1000 g to about 1.000 g of Willow bark extract. The preferred dosage of a serving of the supplemental composition comprises about 0.1500 g Willow bark extract.

The present invention, according to an embodiment thereof, provides a method which includes the step of consuming a composition, wherein the method may, for example, alleviate minor aches and pains, speedily induce sleep, as well as provide for maintenance of sleep thereby promoting a good quality, restful sleep. In an embodiment of the present invention, the method includes the daily consumption, prior to going to sleep with the intent of a full night's sleep, of a sleep-promoting and pain-relief composition that may include at least an extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof.

Furthermore, the sleep-promoting and pain-relief composition may further comprise Coenzyme Q10, Lemon Balm leaf extract, Hops cone extract, Lavender flower extract, Passionflower extract, and Skullcap powder.

The present supplemental composition, or those similarly envisioned by one of skill in the art, may be utilized in methods to alleviate minor aches and pains, speedily induce sleep, as well as provide for maintenance of sleep thereby promoting a good quality, restful sleep in a formulation designed to be consumed on a daily basis prior to going to sleep with the intent of a night's rest.

In an embodiment of the present invention, the composition may include a time-release mechanism, e.g., wherein the time-release mechanism provides 4 hours of active compound release. Also, in various embodiments, the melatonin may be incorporated into a tablet coating to promote sleep more quickly, e.g., to promote instant or immediate sleep.

Although the following example illustrates the practice of the present invention one of its embodiments the example should not be interpreted as limiting the scope of the invention. Other embodiments of the present invention will be apparent to those of skill in the art form consideration of the specification and example.

Example 1

A supplemental composition is provided on a daily basis, prior to going to sleep with the intent on a full night's rest, the composition utilizing a dual-release caplet formulation comprising Melatonin (0.0040 g), fine-milled Melatonin (0.0010

g), Coenzyme Q10 (0.0010 g), Hops cone extract (0.0200 g), Lavender flower powder (0.0050 g), Passionflower extract (0.0020 g), Skullcap powder (0.0010 g), Lemon Balm leaf extract (0.0800 g), deodorized Valerian root (0.1200 g) and Willow bark extract (0.1500 g).

Directions: As a supplemental composition, 1 caplet is orally administered with an 8 oz. glass of water once daily prior to going to sleep. Preferably, the supplemental composition is consumed with the intent of a full night's sleep.

Claims

What is claimed:

1. A composition comprising an extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof.
2. The composition of claim 1, further comprising an extract of Hops cone.
3. The composition of claim 2, further comprising Lavender flower powder.
4. The composition of claim 3, further comprising an extract of Passionflower.
5. The composition of claim 4, further comprising Skullcap powder.
6. The composition of claim 5, further comprising an extract of Coenzyme Q10.
7. The composition of claim 6, further comprising a leaf of extract Lemon Balm.
8. The composition of claim 7, further comprising a time-release mechanism.
9. The composition of claim 8, wherein at least a portion of the melatonin is fine-milled.
10. The composition of claim 1, wherein the extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof, are provided in amounts effective to at least one of promote sleep and relieve pain.
11. The composition of claim 1, wherein the composition is provided in a tablet form.

12. The composition of claim 11, wherein the melatonin or derivative thereof is incorporated into a coating of the tablet, so as to promote sleep more quickly.

13. A composition comprising:

about 0.1200 g of an extract of Valerian Root per serving;

about 0.1500 g of an extract of Willow Bark per serving;

about 0.0040 g of Melatonin per serving;

about 0.0010 g of fine-milled Melatonin per serving;

about 0.0200g of an extract of Hops cone per serving;

about 0.0050 g of Lavender flower powder per serving;

about 0.0020 g of an extract of Passionflower per serving;

about 0.0010 g of Skullcap powder per serving;

about 0.0010 g of Coenzyme Q10 per serving; and

about 0.0800 g of an extract of Lemon Balm per serving.

14. A method for at least one of promoting sleep and relieving pain, the method comprising the step of:

administering to a human or animal a composition comprising an extract of Valerian Root, an extract of Willow Bark and Melatonin or a derivative thereof.

15. The method of claim 14, wherein promoting sleep includes at least one of inducing sleep and maintaining sleep.

16. The method of claim 14, wherein the composition is administered to a user once daily prior to the user going to sleep.

17. The method of claim 16, wherein the composition is provided with a time-release mechanism.

18. The method of claim 17, wherein the time-release mechanism provides about 4 hours of active compound release.

19. The method of claim 18, wherein composition is provided in the form of a tablet, and the melatonin or derivative thereof is incorporated into a coating of the tablet to promote sleep more quickly.

20. The method of claim 14, wherein the composition further comprises an extract of Hops cone.

21. The method of claim 20, wherein the composition further comprises Lavender flower powder.

22. The method of claim 21, wherein the composition further comprises an extract of Passionflower.

23. The method of claim 22, wherein the composition further comprises Skullcap powder.

24. The method of claim 23, wherein the composition further comprises an extract of Coenzyme Q10.

25. The method of claim 24, wherein the composition further comprises a leaf of extract Lemon Balm.

26. The method of claim 25, wherein the composition further comprises a time-release mechanism.

27. The method of claim 26, wherein at least a portion of the melatonin is fine-milled.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001156

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 36/18*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion, Pubmed, Scopus, CAPlus, Biosis Keywords: Valerian, Valeriana officinalis, Willow, Salix alba, Melatonin, Hops, Humulus lupulus, Lavender, Lavandula officinalis, Passionflower, Skullcap, Scutellaria lateriflora, Coenzyme Q10, Lemon balm, Melissa officinalis, sleep, SleepMD, Iovate, Iomedix

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant	Relevant to claim No.
X	US 2005/0129783 A1 (MCLEARY, E.L. ET AL.) 16 June 2005, whole document.	1, 10-12
X	US 2004/0234544 A1 (JAGER, R. ET AL.) 25 November 2004, whole document.	1, 10-12
Y	US 6,869,622 B2 (ANCILE PHARMACEUTICALS, INC.) 22 March 2005, whole document.	1-27
Y	DOLLINS, A. B. et al. "Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance." PROC. NATL. ACAC. SCI. USA. March 1994. Vol. 91, pages 1824-1828, ISSN: 0027-8424, whole document.	1-27
Y	US 6,770,263 B1 (NATUREWELL, INCORPORATED) 3 August 2004, whole document.	1-27

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 October 2006 (06-10-2006)	20 November 2006 (20-11-2006)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Kathleen Pound 819 - 953-9757

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001156

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 14 to 27

because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 14 to 27 encompass a method of treatment of the human body which this Authority is not obliged to examine under Rule 39.1(iv) of the PCT, the search has been established on the basis of the alleged effects of the compositions referred to therein.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001156

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FÜSSEL, A. et. al. "Effect of a fixed valerian-hop extract combination (Ze 91019) on sleep polygraphy in patients with non-organic insomnia: a pilot study." EUROPEAN JOURNAL OF MEDICAL RESEARCH. 18 September 2000. Vol. 5, pages 385-390, ISSN: 0949-2321, whole document.	2-9, 13, 20-27
Y	LIS-BALCHIN, M. et. al. "Studies on the mode of action of the essential oil of lavender (*Lavendula angustifolia* P. Miller)." PHYTOTHERAPY RESEARCH. 1999. Vol. 13, pages 540-542, ISSN: 0951-418X, whole document.	3-9, 13, 21-27
Y	SOULIMANI, R. et. al. "Behavioural effects of *Passiflora incarnata* L. and its indole alkaloid and flavenoid derivatives and maltol in the mouse." JOURNAL OF ETHNOPHARMACOLOGY. 1997. Vol. 57, pages 11-20, ISSN: 0378-8741, whole document.	4-9, 13, 22-27
Y	AWAD, R. et. al. "Phytochemical and biological analysis of Skullcap (*Scutellaria lateriflora* L.): A medicinal plant with anxiolytic properties." PHYTOMEDICINE. 2003. Vol. 10, pages 640-649, ISSN: 0944-7113, whole document.	5-9, 13, 23-27
Y	BALDWIN, C. M. et. al. "Antioxidant nutrient intake and supplements as potential moderators of cognitive decline and cardiovascular disease in obstructive sleep apnea." SLEEP MEDICINE REVIEWS. December 2005. Vol. 9, pages 459-476, ISSN: 1087-0792, whole document.	6-9, 13, 24-27
Y	KENNEDY, D. O. et. al. "Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm)." PHARMACOLOGY, BIOCHEMISTRY, AND BEHAVIOR. 2002. Vol. 72, pages 953-964, ISSN: 0091-3057, whole document.	7-9, 13, 25-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2006/001156

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US6869622 B2	22-03-2005	AU6366800 A	13-02-2001
		CA2379395 A1	01-02-2001
		EP1235583 A1	04-09-2002
		IL147333D D0	14-08-2002
		JP2003505426T T	12-02-2003
		MXPA02000643 A	21-07-2003
		NZ516531 A	25-10-2002
		US6383526 B1	07-05-2002
		US6913770 B2	05-07-2005
		US20030017220 A1	23-01-2003
		US20030096865 A1	22-05-2003
		WO0107063 A1	01-02-2001
		WO02092113 A1	21-11-2002
US6770263 B1	03-08-2004	US2005036952 A1	17-02-2005
US2005129783 A1	16-06-2005	AU2004257756 A1	27-01-2005
		EP1643863 A2	12-04-2006
		US6579866 B2	17-06-2003
		US6964969 B2	15-11-2005
		US2002182196 A1	05-12-2002
		US2004043013 A1	04-03-2004
		US2005002992 A1	06-01-2005
		US2005025812 A1	03-02-2005
		US2005095233 A1	05-05-2005
		US2005181069 A1	18-08-2005
		US2006014773 A1	19-01-2006
		US2006062864 A1	23-03-2006
		US2006105062 A1	18-05-2006
		US2006110477 A1	25-05-2006
		US2006110478 A1	25-05-2006
		WO2005006890 A2	27-01-2005
		WO2005006890 A3	14-07-2005
		WO2006053217 A1	18-05-2006
		WO2006057893 A2	01-06-2006
		WO2006101663 A1	28-09-2006
US2004234544 A1	25-11-2004	BR0211814 A	08-09-2004
		CN1625406 A	08-06-2005
		DE10139250 A1	27-02-2003
		DE10235760 A1	06-03-2003
		EP1414469 A2	06-05-2004
		JP2004537577T T	16-12-2004
		NZ530981 A	30-06-2006
		WO03013549 A2	20-02-2003
		WO03013549 A3	06-11-2003
		ZA200400830 A	21-09-2004