

SLEEP⁸ is elaborated with ingredients attributed with anxiolytic, sedative, relaxing and hypnotic effects, which act naturally in synergy to help one fall asleep and recover refreshing sleep. They act on the CNS, binding to GABA-ergic receptors, decreasing anxiety and nervousness without the usual side effects of hypnotic medications. SLEEP⁸ increases REM sleep, improving the duration and quality of sleep. It acts on the circadian rhythm, regulating periods of wakefulness and sleep.

Ingredients: Magnesium bisglycinate, passionflower flower extract (*Passiflora incarnata*), hops strobile extract (*Humulus lupulus*), skullcap root extract (*Scutellaria lateriflora*), chamomile flower extract (*Matricaria chamomilla*), qiye shen'an pian leaf extract (*Panax notoginseng*), catnip herb top (*Nepeta cataria*), anticaking agents: vegetable magnesium stearate and silicon dioxide, melatonin, vegetable capsule (glazing agent: hydroxypropylmethylcellulose; purified water).

Nutritional information:	1 capsule (360 mg)
Passionflower (4% flavonoids)	35 mg (**)
Hops (3,5% flavonoids)	35 mg (**)
Skullcap (12,5% flavonoids)	35 mg (**)
Chamomile (5% flavonoids)	35 mg (**)
<i>Panax notoginseng</i>	25 mg (**)
Catnip	15 mg (**)
Melatonin	0,5 mg (**)
Magnesium	20 mg (5%*)

*NRV: Nutrient Reference Value in % / **NRV not established

Contains no: Preservatives, artificial flavour or colour, sugar, milk or milk products, starch, wheat, corn, or yeast.

Size and format:
90 vegetable capsules

Recommended daily dose:
1-3 capsules daily before bedtime. The effect of the product may begin within 3-7 days.

Do not exceed the stated recommended daily dose.

Indications and uses:

Different studies have shown that the ingredients in SLEEP⁸ have proven efficacy as sedative, relaxing or sleep-inducing agents. SLEEP⁸ can help induce sleep and prolong sleep naturally, without the usual side effects of hypnotic drugs. It is effective for insomnia, sleep disorders associated with anxiety, nervousness and stress, jet-lag and sleep alterations in shift workers.

Cautions:

Do not use if you are pregnant, breastfeeding, taking immunosuppressive drugs or cyclosporine, or allergic to plants of the Asteraceae/Compositae/daisy family. Should not be given to children under the age of 12 years.

Consult a health care practitioner prior to use if you have depression, a hormonal disorder, diabetes, liver disease, kidney disease, cancer, endometriosis, cerebral palsy, seizure disorders, migraine, or hypertension. Consult a health-care practitioner if you are treated with oral anticoagulants, antidiabetic or antiplatelet medication because a dose adjustment might be necessary.

Concomitant use with other sedative/hypnotic and/or anxiolytic medication can enhance the sedative effect for which it should be avoided without supervision.

Interaction between *Panax Notoginseng* and the MAOIs have been described.

Simultaneous use of SLEEP⁸ and alcohol or antidepressant medications can enhance the sedative effect.

PASSION FLOWER: The active part of this plant lies in the uppermost pistils. Passion flower contains flavonoids (vitexin, isovitexin, orientin), flavones and flavonols such as apigenin, luteolin and quercetol, alpha-pyrone derivatives (maltol and ethyl maltol), coumarins and phenolic acids, among other compounds.

Experimental studies show its sedative and anxiolytic action. The results suggest that it strengthens and prolongs sleep, and in a study carried out on patients with general anxiety disorders, passion flower was proven effective. It is not known exactly which compound(s) are responsible for this activity, although it is possibly due to a synergic effect between its diverse components^(1-3,6).

HOPS: For therapy, the female flower parts are used, which contain a resin rich in bitter compounds, humulones and lupulones. They also possess essential oil, mineral salts, tannins and different types of flavonoids (flavones, isoflavones and chalcones). The effect of hops on the central nervous system, especially in sleep alterations, has been well studied, above all in experimental trials. It has sedative, anxiolytic and sleep-inducing activity.

It contains 8-prenylnaringenin, a flavanone with powerful oestrogenic activity, making it useful in cases of sleep alteration associated with menopause⁽⁴⁻⁶⁾.

SKULLCAP: The dried root of skullcap has been used traditionally in Chinese medicine. Among its active principles are flavonoids such as baicalin and baicalein, wogonin and wogonoside. There is scientific evidence associating skullcap with anxiolytic and wakefulness-sleep phase regulating effects, as it seems that these flavonoids modulate the GABA(A) receptor which is involved in neuron balance⁽⁷⁻¹⁰⁾.

CHAMOMILE: The active part is the flower which contains essential oil and flavonoids, among which apigenin and sesquiterpene lactones stand out. Its mild sedative effect and anxiolytic action have been well studied, and it is apigenin that is responsible for binding to benzodiazepine receptors, causing this effect. Different revised monographs point out that chamomile is a good option for the treatment of nervous disorders such as anxiety and mild insomnia^(11,12).

PANAX NOTOGINSENG: Widely used in traditional Chinese medicine, this is known as Tienchi ginseng. Among its active components are ginsenosides, polysaccharides and saponins. Scientific literature on its anti-inflammatory activity, its cardioprotective action and its phytoestrogenic capacity. Its use for improving mental function and treating insomnia and anxiety has also been described. A recent study showed that this improvement was related to the saponin content of the plant. Concerning mental function, it improves memory and learning ability upon protecting neurons from oxidative damage and exerting a neuroregenerative action, which could compensate for the neuron damage that occurs in certain types of dementia^(13,14,15).

MAGNESIUM: The adult body contains between 20 and 28 grams of magnesium, of which about 60% is found in the bones, 26% in muscles and the rest in soft tissue and bodily fluids. Extracellular magnesium intervenes in neuromuscular transmission and proper cardiac function, and has a primordial role in muscle relaxation. Intracellular magnesium forms part of the bone matrix. It is an essential macroelement for the assimilation of calcium and vitamin C.

It is also considered an anti-stress mineral since diverse studies have shown that it decreases anxiety, and given that it relaxes muscles, it can be used for treating chronic stress and improving resistance to fatigue. Its nutritional deficit causes anxiety, fatigue, insomnia and trembling, among other manifestations. In our formula, magnesium has been joined to 2 glycine molecules to increase its absorption and bioavailability, so its absorption is 4 times faster than that of other magnesium formulas^(16,17).

CATNIP: The parts of this plant used for therapeutic purposes are the leaves and floral tips. It is found in Europe and North America. Among its main components are flavonoids, phenolic acids and terpenoids, which have been described as responsible for its mild sedative action. In another study, it was the nepetalactones contained in the plant that were found to be responsible for its sedative effect^(18,19).

MELATONIN: This hormone, found naturally in the body, is generally used to adjust the inner clock, regulating wakefulness-sleep cycles. It is used to treat the inability to fall asleep as well as insomnia associated with attention deficit and hyperactivity disorder^(20,21).

References:

- 1) Giménez, N. M., & Corberá, E. M. (2008). Fitoterapia del insomnio: consejos desde la farmacia. *Offarm: farmacia y sociedad*, 27(10), 94-101.
- 2) García-Borreguero, D., Navarro, C., & Ortega, T. (2008). Plantas medicinales para el insomnio: Centro de investigación sobre fitoterapia.
- 3) Fitoterapia.net. *Pasiflora* Disponible: www.fitoterapia.net, [13.02.2016].
- 4) Heilpflanzen-Welt Bibliothek. List of German Commission E Monographs. Disponible: <http://buecher.heilpflanzen-welt.de/BGA-Commission-E-Monographs/0270.htm> [13.02.2016].
- 5) Cañigual, S., Vila, R., & Wichtl, M. (Eds.). (1998). *Plantas medicinales y drogas vegetales para infusión y tisana: un manual de base científica para Farmacéuticos y Médicos*. OEMF International.
- 6) Consejo General de Colegios de Farmacéuticos (CGCF), (2002). Monografías de plantas.
- 7) World Health Organization (WHO) (2001). *Radix Scutellariae*. *Monographs on selected medicinal plants* Vol 3, 314-27.
- 8) Hui, K. M., Huen, M. S., Wang, H. Y., Zheng, H., Sigel, E., Baur, R., ... & Xue, H. (2002). Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi. *Biochemical pharmacology*, 64(9), 1415-1424.
- 9) de Carvalho, R. S. M., Duarte, F. S., & de Lima, T. C. M. (2011). Involvement of GABAergic non-benzodiazepine sites in the anxiolytic-like and sedative effects of the flavonoid baicalin in mice. *Behavioural brain research*, 221(1), 75-82.
- 10) Chang, H. H., Yi, P. L., Cheng, C. H., Lu, C. Y., Hsiao, Y. T., Tsai, Y. F., ... & Chang, F. C. (2011). Biphasic effects of baicalin, an active constituent of *Scutellaria baicalensis* Georgi, in the spontaneous sleep-wake regulation. *Journal of ethnopharmacology*, 135(2), 359-368.
- 11) World Health Organization (WHO) (1999). *Flos Chamomillae*. *Monographs on selected medicinal plants*. Vol 1, 86-94.
- 12) Viola, H., Wasowski, C., De Stein, M. L., Wolfman, C., Silveira, R., Dajas, F., ... & Paladini, A. C. (1995). Apigenin, a component of *Matricaria recutita* flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. *Planta medica*, 61(03), 213-216.
- 13) Xiang, H., Liu, Y., Zhang, B., Huang, J., Li, Y., Yang, B., ... & Zhang, H. (2011). The antidepressant effects and mechanism of action of total saponins from the caudexes and leaves of *Panax notoginseng* in animal models of depression. *Phytomedicine*, 18(8), 731-738.
- 14) Zheng, M., Qu, L., & Lou, Y. (2008). Effects of icariin combined with *Panax notoginseng* saponins on ischemia reperfusion-induced cognitive impairments related with oxidative stress and CA1 of hippocampal neurons in rat. *Phytotherapy Research*, 22(5), 597-604.
- 15) Tohda, C., Matsumoto, N., Zou, K., Meselhy, M. R., & Komatsu, K. (2002). Axonal and dendritic extension by protopanaxadiol-type saponins from ginseng drugs in SK-N-SH cells. *The Japanese Journal of Pharmacology*, 90(3), 254-262.
- 16) Boyle, Neil Bernard, Clare Lawton, and Louise Dye. "The effects of magnesium supplementation on subjective anxiety and stress—a systematic review." *Nutrients* 9.5 (2017): 429.
- 17) Brilli, E., et al. "Magnesium bioavailability after administration of sucrosomial® magnesium: Results of an ex-vivo study and a comparative, double-blinded, crossover study in healthy subjects." *Eur. Rev. Med. Pharmacol. Sci* 22 (2018): 1843-1851.
- 18) Stansbury, Jill, Paul R. Saunders, and David Winston. "The Calming Actions of *Anemone Pulsatilla*, *Nepeta*, and *Rauwolfia*." *Journal of Restorative Medicine* 2.1 (2013): 109-113.
- 19) Süntar, Ipek, et al. "Pharmacological and chemical features of *Nepeta* L. genus: Its importance as a therapeutic agent." *Phytotherapy research* 32.2 (2018): 185-198.
- 20) Scheer, Frank AJL, et al. "Repeated melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers: a randomized controlled trial." *Sleep* 35.10 (2012): 1395-1402.
- 21) Xie, Zizhen, et al. "A review of sleep disorders and melatonin." *Neurological research* 39.6 (2017): 559-565.