Recommended Dosage

**Adults:** 1-2 capsules per night 30-60 minutes before sleeping or as directed by a health care practitioner.

**Uses**
- All natural herbal sleep and nervous system support formulation.
- Features Herbatonin® to reduce time falling asleep and promote a refreshing sleep.
- Relieves sleeplessness and restless sleep

**Other Uses**
- Traditionally used in Western Herbal Medicine for disturbed and restless sleep.
- Traditionally used in Western Herbal Medicine as a nervine for the relief of nervous tension, restlessness and excess nervous energy.

**Side Effects**
The long-term traditional use of hops, rice and alfalfa and their widespread current use demonstrate their safety and tolerability by humans with oral ingestion.1-3

Hops has a long history of use as a food, and has also been the subject of many clinical trials alone and in combination with other preparations and extensive toxicological investigations. No serious side effects have been observed or reported when used at doses up to 1000-fold the intended dose for clinical studies.1

Ingestion of hops extract by postmenopausal women for 5 consecutive days each month for 3 months did not adversely influence sex hormones or blood coagulation parameters, and animal toxicological studies have observed that the hops constituent xanthohumol is well tolerated and does not cause adverse effects on female reproduction or offspring development, organ function, or protein, lipid and carbohydrate metabolism.4,5

**Cautions**
Caution is advised regarding the use of hops during pregnancy due to potential hormonal effects. Caution is advised regarding use by individuals with depression and with oestrogenic-dependent tumours. If symptoms persist talk to your health care practitioner. Not for prolonged use. If symptoms persist seek the advice of a health care practitioner. Do not use if you are pregnant or likely to become pregnant or while breastfeeding. Keep out of reach of children. Children should not consume this product without medical advice.
Interactions
Animal and in vitro investigations indicate theoretical interactions with the concomitant use of hops with pharmaceutical sedatives and alcohol due to the herbs sedative properties.\textsuperscript{1,4}
The oestrogenic effects of hops may alter the efficacy of anti-oestrogenic medications.\textsuperscript{6}
Animal and in vitro data suggests hops constituents inhibited enzymes of the CYP2C family (CYP2C8, CYP2C9 and CYP2C19), potentially influence the effect of medications metabolized via these pathways including statins, non-steroidal anti-inflammatory drugs and anticoagulants.\textsuperscript{1,7,8}
Hops is reported to increase insulin sensitivity parameters in individuals with type 2 diabetes.\textsuperscript{1}
Alfalfa may interact with anticoagulant, birth control and hormone-replacement therapy.\textsuperscript{9}

Contraindications
• Contraindicated in individuals with a hypersensitivity to hops or its constituents.\textsuperscript{1,5}
• Alfalfa is contraindicated in individuals with a history of systemic lupus erythematosus.\textsuperscript{9}
• There is insufficient toxicity data to confirm the safety of these ingredients for use during pregnancy and lactation.\textsuperscript{3,9}

Mechanism of Action
HOPS:
• Sedative:
  o Binds to and increasing the function of GABA\textsubscript{A} receptors and modulating GABA-induced responses and potentiates GABAergic activity\textsuperscript{3,4,10-12}
  o Inhibition of glutamic acid decarboxylase activity.\textsuperscript{13}
  o Involvement of melatonergic system by binding to ML1 and ML2 receptors, inducing melatonin-like activity at receptor level and systemically\textsuperscript{5,11,14}
  o Reduces body temperature via activity on melatonin and oestrogen receptors.\textsuperscript{11,14,15}
  o Binds to serotoninergic 5-HT\textsubscript{6} receptors.\textsuperscript{11}
  o Acts on and enhances adenosine neuronal receptor activity.\textsuperscript{16,17}
• Anxiolytic:\textsuperscript{4,10}
  o Modulation and activation of GABA\textsubscript{A} \textsuperscript{a\textsubscript{2}} subunit receptors inducing a GABA response.\textsuperscript{10,14}
  o Binding to opioid receptors.\textsuperscript{18}
• Central nervous system modulation:
  o Neuroprotective via inhibition of inflammatory responses.\textsuperscript{4}
  o Improving cognitive flexibility and function.\textsuperscript{4,10}
  o Anti-depressant activity.\textsuperscript{11,13}
• Modulation of alpha and beta oestrogen receptors:
  o Induction of thermoregulatory effects including reducing body temperature (vasomotor disturbances can contribute to sleep disturbances during menopause).\textsuperscript{15,19}
  o Oestrogenic and progestogenic activity (low oestrogen and progesterone levels in menopause can cause sleep disturbances and mood symptoms including anxiety).\textsuperscript{19-21}
• Anti-inflammatory:
  o Inhibition of nitric oxide synthase-induced nitric oxide synthesis.\textsuperscript{4}
  o Suppression of nuclear-factor kappa-B (NF-\textsuperscript{KB}) activation.\textsuperscript{4}
  o Modulation of T cell-mediated synthesis of Th1 cytokines (interleukin-2, interferon-\gamma and tumour necrosis factor-\textalpha (TNF-\textalpha)).\textsuperscript{4}
RICE:
• Anxiolytic.\textsuperscript{22}

ALFALFA:
• Anxiolytic.\textsuperscript{2}
Pharmaceutical Commentary

Hops’ generic name ‘Humulus’ is thought to come from the Slavic word for hops ‘chmele’, while the species name ‘lupulus’ is derived from the Latin word ‘lupus’, translating to ‘wolf’ in reference to the plants’ growing pattern of climbing onto other plants as a wolf climbs onto a sheep. The common name ‘hops’ is suggested to originate from either the Anglo-Saxon word ‘hoppan’ meaning ‘to climb’ or the Norwegian word ‘hupp’ meaning ‘tassel’ or ‘tuft’.\textsuperscript{13,23,24}

Native to the Northern Hemisphere and Eurasia and cultivated for more than 1000 years in Europe, Germany and North America, hops’ initial use from the Middle Ages was associated with its flavouring and preservative properties in beer.\textsuperscript{13,23,25}

Historical references to the medicinal use of hops were made by Paracelsus (1493-1541) as a digestive aid, and also by several authors including Bock (1498-1554) and Lonicerus (1528-1586) as a cleanser of the blood, liver and spleen, Hecker (1814) as a bitter tonic and calming herb, and Clarus (1864), Stephenson and Churchill (1834) Maton (1860) as a promoter of sleep. It has been recorded that King George III used hops pillows as a calming strategy.\textsuperscript{23}

Hops also has a long history of use in many traditional cultures including Chinese, Indian-Ayurvedic, Native American Indian and Western medicinal systems and is considered to have hypnotic, relaxant, sedative, antispasmodic, analgesic, bitter tonic and gynaecological-supporting properties.\textsuperscript{1,6,23,24} It has been used in such traditions for conditions including insomnia and sleep disturbances and nervous system and mood imbalances (restlessness, anxiety, nervous tension, nervousness, headache), with the traditional use of hops as a sedative connected to observations of tiredness and fatigue experienced by hops pickers.\textsuperscript{1,6,14,24} The German Commission E has approved the hops for the treatment of mood disturbances including anxiety and disturbed sleep.\textsuperscript{24}

Herbatonin® is a herbal mixture that supports sleep and the nervous system.*

Rice, also known in traditional Chinese medicine (TCM) as Dao ya, is thought to have spleen-invigorating properties, with spleen deficiency one of the patterns in TCM thought to contribute to restless sleep and insomnia.\textsuperscript{26,27}

Alfalfa has a long history of use in many traditional systems including TCM, Iraq, Mexican and Ayurvedic medicine for a broad range of conditions including for central nervous system disorders, and is considered to have restorative, anxiolytic, body strengthening, nutritive and tonic properties.\textsuperscript{1,2,9,28}

The most significant active constituents naturally occurring in hops are the resinous bitter acids, classified as alpha- (humulone, cohumulone and adhumulone) and beta- (lupulone, colupulone and adlupulone) acids, and volatile oils (myrcene, $\beta$-caryophyllene, farnesene, humulene).\textsuperscript{1,5,6,23} Other compounds present in hops include flavonoids, (isoxanthohumol, kaempferol, quercetin and rutin), prenylated flavonoids (xanthohumol, desmethyloxanthohumol and dehydrocycloxanthohumol), phenolic acids, catechins (catechin gallate, epicatechin gallate), polysaccharides, amino acids and minerals.\textsuperscript{1,6,23}
Melatonin, a key regulator of the sleep/wake cycle, is produced by the pineal gland under the direction of the hypothalamus and is secreted into the bloodstream and stored in the central nervous system with the onset of dark at night. As a hormone it acts by interacting with receptors, specifically melatonin 1 and 2 (ML1 and ML2) located in both the central nervous system and peripheral tissues. It also stimulates the synthesis of tryptophan and its conversion to serotonin. Hops has a similar effect to melatonin locally (in terms of binding to ML1 and ML2 receptors) and systemically, as well as enhancing the endogenous melatonin-mediated effects on sleep. The sedative and anxiolytic effects of hops is also significantly associated with its modulation of GABA and effects on GABAergic neurotransmission and serotonin, which also activates melatonin.

Rice constituents include flavonoids (tricin, tricinin), phenolic acids (ferulic, coumaric, sinapic, protocatechuic, chlorogenic, vanillic, caffeic and gallic acids), sterols, vitamins and minerals (thiamine, riboflavin, niacin, potassium and magnesium). Alfalfa also contains flavonoids as well as saponins, alkaloids, phenolic compounds, amino acids, coumarins, fatty acids and essential oils.

The predominant hops constituents that have been the subject of pharmacokinetic investigations are flavonoids and bitter acids. After remaining intact when passing through the stomach, the flavonoid isoxanthohumol, which has demonstrated good but relatively slow bioavailability in human subjects (maximum serum concentrations reached in 2-7 hours), can be subsequently converted via colonic bacteria or hepatic glucuronic and CYP1A2 metabolism to 8-prenylnaringenin. Xanthohumol intestinal absorption is subject to a saturation effect at a threshold dose, while alpha bitter acids were better absorbed than beta-acids in Caco-2 models. These compounds are extensively conjugated with glucuronic acid and to a lesser extent, sulphate, before undergoing enterohepatic recirculation (excreted in the bile, metabolised in the gut microbiome and reabsorbed) before being extensively distributed in body tissues and also crossing the blood brain barrier. They are largely excreted via biliary secretion, with minimal quantities excreted via the urine.

The traditional and current clinical use of hops for sleep and nervous system imbalances is supported by the mechanisms of action demonstrated by the herb and its constituents. Specifically, in vitro and animal investigations have found that by modulating and binding to gamma-amino butyric acid (GABA), melatonin, serotonin and adenosine receptors, hops and its constituents promote sedative and anxiolytic effects by subsequently influencing the endogenous levels and activity of GABA, melatonin, serotonin and adenosine.

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Diurnal variations of melatonin levels. The hormone secretion increases soon after the onset of darkness, peaks in the middle of the night, between 2 and 4 a.m., and gradually falls during the second half of the night.  

Sleep

These underlying mechanisms and the well-established clinical benefits observed with the use of hops to support sleep have also been demonstrated in human clinical trials.  

In healthy female nurses experiencing work-stress associated with night-shift working patterns, the impact of hops on work-stress, anxiety and sleep was investigated.  

Prior to the 14-day intervention period, all subjects (n=17) completed the Effort Reward Imbalance Model and State-Trait Anxiety Inventory Questionnaires to assess baseline work-stress and anxiety levels, respectively. During the intervention period, subjects wore Actimeters to assess sleep parameters (time in bed, assumed sleep, actual sleep time, sleep latency, sleep efficiency, total activity), and ingested approximately 1g/day of hops in non-alcoholic beer with their supper meal. It was observed that ingestion of hops resulted in improvements in sleep quality, particularly sleep latency (12.01 + 1.19 vs 20.50 + 4.21 minutes, p<0.05) and total activity (5284.78 vs 7258.78 activity pulses) and anxiety (18.0963.8 vs 20.6962.14 State-Trait Anxiety Inventory scores).

Similar results were observed in a separate clinical trial by the same research group investigating the impact of hops on sleep quality in a university student population experiencing exam-induced stress. Conducted over a 3-week period, the first week was the control phase where subjects did not have any active treatment, while during the subsequent 2-weeks all subjects ingested approximately 1g/day of hops in non-alcoholic beer. Stress levels were assessed using the State-Trait Anxiety Inventory Questionnaire and sleep quality, latency, duration and efficiency were measured using the Pittsburgh Sleep Quality Index (PSQI). Hops ingestion was associated with significant improvements in sleep and sleep latency (both p<0.05). The authors concluded that hops ingested in non-alcoholic beer was beneficial for improving sleep quality in individuals under stress.
**Nervous System Support**

Clinical evidence also supports the long traditional use of hops for supporting nervous system imbalances.\(^{12,40,41}\)

In a randomised, double-blind, placebo-controlled, crossover study, the impact of hops on young generally healthy adults with mild depression, anxiety and stress levels was investigated.\(^{40}\) Over 4-weeks, subjects (n=36) orally ingested either placebo or 200mg of hops daily followed by a 2-week washout period before undergoing the alternative treatment (active or placebo). Assessments performed included the Depression Anxiety Stress Scale-21 (DASS-21) to determine depression, anxiety and stress symptomatology and morning blood cortisol levels, conducted at the beginning and end of each 4-week intervention period. Compared with placebo, hops resulted in significant decreases in DASS-21 anxiety (9.2+7.3 vs 5.1+5.9), depression (11.9+7.9 vs 9.2+7.4) and stress scores (19.1+8.1 vs 11.6+8.1, all p values <0.05). The authors concluded that the results indicated that hops may have overall mood-enhancing effects.

A separate randomised placebo-controlled trial investigated the impact of hops on menopause-induced symptoms including mood and anxiety.\(^{41}\) For 12 weeks, subjects (n=120) ingested either placebo or hops (equivalent to 500mg dried flowering part daily), with assessments of symptom severity taken at 4, 8 and 12 weeks (Greene Scale which assessed physical and psychological symptoms (anxiety, depression). Compared with placebo, the mean score for mental symptoms was lower in the hops group at 4 (-1.6, -1.2, -2.0 vs -2.0, -2.9, -3.0), 8 (-3.4, -2.9, -3.9 vs -6.1, -5.5, -6.7) and 12 weeks (-4.3, -3.7, -4.8 vs -7.9, -7.2, -8.6) (all p<0.001).

A 2017 systematic review of phytomedicines with GABA-modulating effects for anxiety also found that based on preclinical evidence, hops induced anxiolytic effects by interacting and modulating the hops GABA system.\(^{12}\)

*For more information, please visit the Herbatonin® website at www.herbatonin.com*
References

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