

## Herbal Drugs and Sleep: What can we Expect?

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### Abstract

Herbal drugs are increasingly being used in our setting as an alternative to, or to supplement, the conventional medication used in sleep disorders. By reviewing different herbal drugs, a description of their therapeutic and adverse effects is established in order to recognise them in a sleep unit and thus be able to establish a more effective approach to them.

**Keywords:** Herbal drugs; Insomnia; Sleep disorders

### Introduction

Phytotherapy is the use of natural plants or vegetable substances for the treatment of a wide range of symptoms and diseases, in order to improve organ and body system function. It is a widely used modality worldwide that forms part of other complete healthcare systems such as naturopathy, traditional Chinese medicine and homeopathy. Most of its widespread use is in the form of self-consumption. In many western countries like Spain, the production, authorisation, registration, distribution and dispensation of products of vegetable origin is regulated, either through food legislation or legislation applicable to plant-based traditional medicines. It is a natural therapy, in the subgroup called "biological practices", defined as those that use substances that are found in nature and used for their flavour, aroma or possible therapeutic properties, such as herbs, flowers, leaves, tree bark, fruit, seeds, stalks and roots, foodstuffs and vitamins. Some examples include the use of dietary supplements, some of them part of conventional medicine, herbal products and others known as "natural" [1].

The fourth section of Royal Decree 1345/2007 is related to traditional plant-based medicines, and establishes the requirement to register traditional plant-based medicines, the criteria to be met for the simplified procedure, the "per se" simplified registration procedure for traditional plant-based medicines, the causes for denial of registration and market recall when a substance or vegetable product, or a combination of the two, ceases to be included in the list edited by the European Medicines Agency Herbal Medicinal Products Committee.

According to the World Health Organisation, a medicinal plant is one which, in one or more of its organs, contains substances that can be used for preventive and/or therapeutic purposes, or are precursors for chemical-pharmaceutical synthesis. The Royal Spanish Pharmacopoeia establishes that "plants, parts of plants, fungi or lichens, whole, fragmented or cut, unprocessed, generally dried, although occasionally also fresh, are considered to be vegetable drugs. Some exudates that have not undergone specific treatment are also considered to be vegetable drugs". Medicinal or herbal products solely of vegetable origin are thus obtained from these plants and their active

substances (drugs, understood as the part of a medicinal plant used for therapeutic purposes).

The growing use of phytotherapy in Spain, together with greater monitoring by pharmacies, has enabled us to detect, analyse and interpret the possible side effects and interactions of these products, especially in polymedicated patients. The saying "not all green is healthy" is pertinent to this context. Although the therapeutic margin of this type of product is very broad, they are not free from undesired reactions, whether cross-reactions or otherwise, and this could in some cases lead to life-threatening patient intoxication. As a general rule, these medicinal products should be taken with plenty of water, and those that affect the CNS should not be mixed with alcohol.

### Background and Knowledge

In addition, in 2004, the Spanish Ministry of Health and Consumer Affairs published a Ministerial Order containing a list of plants for which sale to the public was restricted or forbidden because of their toxicity [2], which is part of Law 25/1990, of 20 December, on Medicinal Products, specifically section 2. The Spanish Society of Phytotherapy was consulted for the compilation of the list. However, in one of its journals, the society expressed its "surprise to find that our suggestions and proposals were not taken into consideration, and we would like to insist that the list should be reviewed by a committee of experts and updated at least once a year, based on scientific criteria" [3].

Medicinal plants, then, after the starting material has been collected in order to formulate and manufacture phytotherapy products, must be prescribed by a doctor, dispensed by a pharmacy and be subject to pharmacotherapeutic monitoring, to optimise the therapeutic results for a given condition in a target patient, thus preventing the side effects associated with their incorrect consumption.

In 1990, 2.5% of the population of the United States used one or more herbal drugs. In 1997, 42% of the American population was using some sort of medicine other than conventional medicine, and 12% were using herbal medicine concomitantly with other prescribed drugs or in monotherapy [4]. Despite the high documented prevalence of the use of herbal products by patients, less than half of them tell their doctors that they are taking them. It is therefore important for healthcare professionals to discuss herbal drugs with their patients [5].

But just as or even more important than discussing the use of herbal drugs in a GP practice, and in a sleep unit in particular, is the fact that pharmacists know enough to discern whether taking these drugs could be having an impact on the onset and/or perpetuation of the nosological conditions that caused the patient to seek medical care. So it is essential not to take a trivial or frivolous approach due to ignorance or limited knowledge of a socially accepted and increasingly widespread therapy.

As with any drug or chemically active ingredient, the toxicity of a herbal drug depends on dose, form, what it is taken with and the underlying condition being treated. In general, most commonly-used herbal drugs have a relatively good safety profile and a low incidence of adverse events. The U.K. Medicines Control Agency published a report establishing that, "in general, it is unlikely that a herbal drug will represent an important threat to human health" [6]. A 5-year study, conducted from 1991 to 1995, by the U.K. National Poisons Unit, on the side effects that could arise from the use of complementary medicines and food supplements, received 1,297 reports, but directly related adverse effects were only found on 38 occasions [7]. In addition, according to the World Health Organisation, there were approximately 8,000 reports of adverse events of herbal drugs from 1968 to 1997, although most of the signs were anecdotal and usually not due to the supplement itself, but to its contaminants [8].

The "modern" use of a herbal remedy may not reflect its use in "ancient" medicine. For example, an excellent safety record for an "ancient" oral product may have no relevance for the same product's use in a "modern" concentrated product at a high dose. On the other hand, herbal drugs that are apparently safe in healthy conditions, can be more dangerous in specific conditions (pregnancy, renal or hepatic function disorders, etc.), in special circumstances (during perioperative periods, etc.) or when combined with some conventional medicines [9].

## Herbal Drugs and Sleep

There are numerous herbal drugs that affect the nervous system. Note that in most cases, the active substances in herbal drugs that affect the nervous system are very active even at very low doses, especially alkaloids. In general, they are potentially very toxic substances with numerous collateral effects, and dosage must be closely monitored in all cases [10].

### Central stimulants

Central nervous system stimulants increase the activity of different nerve centres. From the perspective of their therapeutic application, and with the exception of antidepressants, they are not very widely used as they involve two important disadvantages: firstly, the central nervous system cannot effectively be stimulated for a long time, as temporary stimulation is followed by depression (except with some antidepressants) that can be even more intense than before the stimulant is administered; and secondly, stimulants usually present numerous side effects that limit their use. Pharmacologically, central stimulants can be divided into three groups:

**predominantly cerebral stimulants.**

**predominantly bulbar stimulants.**

**predominantly medullary stimulants.**

Stimulants that are predominantly cerebral or neocortical are also known as psychotropic drugs. They can be considered to have a tranquilliser antagonistic effect. They can cause seizures at high doses.

All psychic or psychomotor stimulant herbal drugs contain xanthic bases (caffeine, theophylline and theobromine) that act as stimulants of the cerebral cortex, and they can stimulate the spinal cord at high (toxic) doses [11]. At therapeutic doses, they stimulate mental function, increasing the ability to concentrate and pay attention, while at high doses they cause restlessness and insomnia, and can stimulate the respiratory, vasomotor and vagal bulbar centres, especially when they are depressed [12]. They also act as diuretics, as they increase glomerular filtration and reduce tubular resorption, thereby increasing the excretion of water and ions such as sodium, chlorine and, to a lesser extent, potassium.

#### Drugs rich in xanthic bases are:

**Coffee (*Coffea arabica*):** It is also choleric. Tree originating in Ethiopia. The seeds of the fruit constitute the drug. It contains up to 3% of xanthic bases, especially caffeine.

**Tea (*Thea sinensis*):** Tree growing in tropical African and American countries. Its young leaves are used, which contain up to 4% caffeine bound to polyphenols (giving its characteristic delayed release in the body), tannins and flavonoids [13].

**Mate (*Ilex paraguensis*):** Tree originating in Brazil and Paraguay. Its leaves contain up to 2.3% caffeine.

**Cola (*Cola nitida*):** Tree originating in equatorial Africa. It contains up to 2.5% caffeine and also has a delayed effect [14].

**Guarana (*Paullinia cupana*):** Native to the Amazon rain forest and grown in Brazil. Its seeds, which contain up to 5% caffeine, tannins and flavonoids, are chewed and used to make a social beverage; where they are consumed they represent a public health problem, as their high tannin content makes them highly carcinogenic [15].

Caffeine in particular, the most consumed in our setting, is used as a stimulating social beverage. In case of drunkenness due to excessive alcohol intake, they partially neutralise the effects of ethyl alcohol. Depending on the doses consumed, they can cause insomnia, anxiety, restlessness and vagal symptoms that should be considered in our medical history [16]. It causes addiction, and at low doses stimulates the CNS, reducing the sensation of fatigue and tiredness.

Predominantly bulbar stimulants are known as analeptic, and can also cause seizures at high doses. They act primarily on the bulbar respiratory centre and to a lesser extent on the vasomotor centre.

#### The following are analeptic drugs:

**Camphor (*Cinnamomum camphora*):** Tree from the wood of which camphor is obtained.

**Rosemary (*Rosmarinus officinalis*):** Mediterranean bush, the essential oil of which is also rich in camphor.

**Lobelia (*Lobelia Inflata*):** North American herbaceous herb, the stalks and leaves of which contain lobeline as the most abundant alkaloid; a piperidine derivative that is used as a respiratory stimulant in bulbar syncope derived from epidural anaesthesia, and in barbiturate, morphine and carbon monoxide intoxication. The mechanism of action is caused by reflex bulbar excitation by stimulation of the cardio-aortic and carotid sinus nerve endings. Indeed, its overdose can cause respiratory centre paralysis [17].

The main predominantly medullary stimulant is strychnine (*Strychnos nux-vomica*).

**Strychnine** (*Strychnos nux-vomica*): Asian tree, the seeds of which contain strychnine as the most abundant alkaloid, which causes hyperexcitability followed by reflex seizures in response to all kinds of external stimuli. Strychnine does not limit its effect to the spinal cord and at high doses it acts on the bulb, causing increased respiratory rate, vasoconstriction and bradycardia [18].

### Central depressants

They are a heterogeneous group of drugs that are capable of reducing the activity of different nerve centres.

According to their effect, they are classified as:

- 1) Hypnotic agents.
- 2) Sedatives.
- 3) Tranquillisers (neuroleptic agents, minor tranquilisers and anxiolytic agents)
- 4) Antineuralgic agents.
- 5) Centrally-acting muscle relaxants.
- 6) Analgesics.

### Hypnotic agents

These drugs induce sleep, and occasionally act synergically as sedatives, depending on the doses used. They are used in the treatment of psychophysiological or simple insomnia of undetermined cause, of which three modalities can be described: sleep onset insomnia or with elongated sleep onset latency, most common in middle-aged or young people with nervous hyperexcitability and an anxious component, and early-morning awakening insomnia and sleep-maintenance insomnia, related to a greater anxious-emotional burden and more common in older people.

A hypnotic agent is a drug capable of causing physiological-like sleep; that is, a state of unconsciousness that can be reversed by sensitive or sensory stimuli. In this respect, an ideal hypnotic agent must meet the following conditions:

- 1) Act rapidly, reducing sleep latency time.
- 2) Not qualitatively and quantitatively alter sleep macrostructure.
- 3) Not cause side effects that have an impact on the patient's health.
- 4) Provide a broad therapeutic safety margin.
- 5) Not cause drug addiction.
- 6) The most used hypnotic drugs are benzodiazepines, Z-drugs and chloral hydrate; according to the premises described above, they are far from ideal agents [19].

In phytotherapy, two drugs are basically used as hypnotic agents:

**Kava-kava** (*Piper methysticum*): Bush originating in the Pacific Islands (Micronesia), the roots of which contain kavalactones that have a neurosedative and hypnotic effect, which appears to be due to their effect on the limbic structures, particularly the amygdala complex. At low doses it has an anxiolytic effect that, in double-blind trials, has been shown to be similar to that of oxazepam with no adverse reactions [20]; it is often used to treat benzodiazepine

dependency. As a hypnotic agent, it is usually combined with magnesium orotate in order to enhance its effect. It also has a myorelaxant effect.

**California poppy** (*Eschscholzia californica*): Herbaceous plant native to California. The whole of the plant is used as it contains a complex of different isoquinoline alkaloids belonging to 5 different series: protopine, pavine, aporphine, protoberberine and 5-benzyl tetrahydroisoquinoline. It has a hypnotic (100 mg/kg), sedative or anxiolytic (25 mg/kg) effect, depending on the administered dose [21]. It is also used in the treatment of benzodiazepine dependency.

### Sedatives

These drugs are used in states of anxiety and nervous tension, as they cause sedation, and even occasionally a degree of analgesia, by mitigating nervous hyperexcitability. Sedation is usually accompanied by intellectual depression and "numbed" consciousness, with a tendency to sleep even with regular therapeutic doses. This characteristic differentiates sedatives from tranquilisers, as the latter calm nervous excitability with no tendency to sleep or mental numbness. There are numerous herbal sedatives, and they can be classified according to the chemical structure of the substance responsible for the sedative effect

**Essential oil or oleoresins:** hop, lavender, valeriana.

**Alkaloids:** passiflora

**Glucosides, bitter substances or resins:** motherwort.

**Hop** (*Humulus lupulus*): Eurosiberian climbing herbaceous plant of which the female seed cones are used with an oleoresin in which the resinous fraction contains bitter substances (humulone and lupulone); its volatile or oily fraction is rich in methylbutenol, which experimentally has sedative effects [22] It is currently used in phytotherapy in the treatment of insomnia [23].

**Lavender** (*Lavandula angustifolia*): Mediterranean bush, the flowers of which contain an essential oil rich in linalyl acetate and linalool. These products have been experimentally shown to inhibit caffeine stimulation by up to 50%, largely through olfactory receptors [24]. It is used in phytotherapy to treat neuroleptic and benzodiazepine dependency, especially in geriatric patients [25].

**Valerian** (*Valeriana officinalis*): Eurosiberian herbaceous plant, the roots of which contain 0.3-0.8% essential oil. The plant's characteristic "sweaty feet" smell is due to its high content of isovalerianic and acetoxy valerianic acids of essential oil. It also contains 1% valepotriates. It has a sedative and anti-seizure effect [26]. *In vitro*, valerianic acid inhibits 3H-GABA uptake and stimulates its release in the synaptosomes, independently of Na-KATPase activity and membrane potential [27]. GABA is considered to be an important neurotransmission inhibitor involved in processes that coincide with stress and anxiety. This causes the chloride channels to open, so its conductivity increases through the cell membranes, reducing the reaction to depolarising stimuli. Isovalerianic acid increases the affinity of GABA for their receptors, thus resulting in greater bonding with the receptor and a more intense effect. All this leads to a reduction in nerve cell excitability. Pharmacodynamic studies have shown that liquid valerian extract (1200 mg) has a sedative effect comparable to that of diazepam (10 mg) [28]. Valerian is currently basically used in the treatment of insomnia and as an alternative to hypnotic-sedative agents such as benzodiazepines and/or Z-drugs in patients with nervous disorders (anxiety, palpitations, tension

migraines, etc.). It is important when guiding patients who are taking valerian to warn them that its continued use leads to dependency, so it should be prescribed discontinuously [29]. When administered immediately before going to bed to induce sleep, it creates some initial anxiety or restless sleep. To avoid these unpleasant effects, it is advisable to take the valerian-based product at least one hour before dinner.

**Passiflora (*Passiflora incarnata*):** North American creeper, the aerial part of which contains flavonoids, notably vitexin, orientin, lucenin, coumarin and umbelliferone. It also contains maltol, responsible for its myorelaxant effect [30]. In humans, both the oral and peritoneal administration of *passiflora* extracts causes a sedative or hypnotic effect, depending on the administered dose [31]. Its long-term use is not free from hepatotoxic and pancreatotoxic effects, and the drug or its pharmaceutical derivatives can cause vomiting because of its strong bitter flavour. In a related plant, *Passiflora coerulea*, used ethnopharmacologically as a sedative, it has been shown that its anxiolytic and myorelaxant effect is due to its flavonoid content, especially chrysin (5- and 7-hydroxyflavone), which acts as a partial agonist of the central receptors for benzodiazepines [32]. It appears that the resulting sedative effect is due to the pharmacological interaction and synergy between flavonoids, maltol and indole alkaloids. Cardiac arrhythmias, long QTc, vomiting and hypersomnia have been described as side effects of this drug [33], hence the importance of learning whether our patients are self-medicating with the plant. It is currently used in phytotherapy in sedative, hypnotic, myorelaxant and anxiolytic products.

**Motherwort (*Leonurus cardiaca*):** Herbaceous plant native to Asia, the aerial part of which contains bitter glucosides with a structure similar to that of bufadienolides, alkaloids (leonurine) and essential oil. It is used as a sedative in the treatment of nervous disorders. It is contraindicated in patients treated with cardiotonic agents as it could enhance their effect, and the dose should be carefully calculated in all cases, due to these bufadienolides' high affinity for and effect on the myocardium.

## Tranquillisers

Tranquillisers or ataraxic drugs are those that have a calming effect on nervous hyperexcitability, without "numbing" consciousness and without inducing sleep tendency at the usual doses. They are selective central nervous system depressants that primarily act on a subcortical level, particularly the hypothalamus, the mesodiencephalic activating system and the limbic system, with no predominant effect on the cerebral cortex. The patient can thus reorganise his or her superior neurological functions. In phytotherapy, this group of drugs is divided into:

- 1) Neuroleptic agents or major tranquillisers.
- 2) Minor tranquillisers.
- 3) Anxiolytic agents.

Neuroleptic agents (*Rauwolfia* alkaloids (*Rauwolfia serpentina*): Bush native to Africa, the roots of which contain different alkaloids, primarily reserpine, which reduces irritability and anxiety without inducing sleep or "mental numbness". One side effect is clear extrapyramidal symptoms, even at therapeutic doses in long-term therapy. It is almost exclusively used on highly-agitated psychiatric patients in order to facilitate their cooperation and social reintegration.

**Minor tranquillisers:** They have a gentle calming effect. In phytotherapy, a series of drugs are used as minor tranquillisers, including: small-leaved lime (*Tilia cordata* and *Tilia platyphyllos*), sweet camomile (*Matricaria chamomilla*), Roman camomile (*Chamaemelum nobile*), lemon balm (*Melissa officinalis*), bitter orange (*Citrus aurantium*), boldo (*Boldea fragrans*) and bogbean (*Menyanthes trifoliata*).

**Anxiolytic agents:** In phytotherapy, both vegetable hypnotic agents and sedatives are used, occasionally in combination with antidepressants (St John's Wort, *Hypericum perforatum*). Examples are common hawthorn (*Crataegus monogyna*) and black horehound (*Ballota nigra*)

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