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The Medical use of Lemon Balm (*Melissa officinalis*) and Valerian (*Valeriana officinalis*) as Natural Sedatives: Insight into their Interactions with GABA Transmission

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Abstract

Lemon balm (*Melissa officinalis*) and valerian (*Valeriana officinalis*) have been consumed by humans since Antiquity, usually as herbal tea and brewing, for their sedative and relaxing capacities. These properties are associated with empirical observations of the effects of these plants on the body. But since the advent of phytotherapy as alternative medicine, it appeared on the market alcoholic extracts or essential oils, for which the same indications are claimed. It is therefore necessary to clarify or define the mechanisms of action of their various constituents to explain their effectiveness. We review here the current knowledge about the pharmacological properties – particularly the molecular targets – of the bioactive compounds of lemon balm and valerian. In this way, the activities of lemon balm and valerian, empirically observed throughout the body, can be explained and objectified at the molecular and cellular levels thanks to the mode of action of their molecular contents (terpenoids and phenolic derivatives). Our interest is to scientifically explain the pharmacological effects of these two plants in traditional medicine.

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Introduction: Traditional and Contemporary Use

According to the World Health Organization, in most industrialized countries, 70 to 95% of people use traditional medicine, including phytotherapy, representing a market of over 65 billion Euros in 2008 [1]. Nowadays, one of the main issues with herbal medicine is to highlight the efficiency of the plants used, not only to characterize their cellular and molecular targets, but also to understand and predict some side effects, and to precisely define the effective dose levels below which an active ingredient has no effect, and beyond which it becomes toxic. This constraint for companies selling herbal products - drugs and food supplements - requires important human, material and financial resources. In addition, since the beginning of the 21st century, the popularity in the Western population for herbal medicine imposes to bring new light on plants already known and used [2]. From now on, the only herbal drugs authorized in the European Union are those considered "traditional" that have proven their safety in normal conditions and with a history showing real benefits, without necessarily having undergone clinical trials [3]. An important feature is to prevent the marketing of products with non- or partially characterized properties that might be ineffective or even dangerous [4]. Better know compounds would allow to better target the requirements related to the content for these products. Lemon balm (*Melissa officinalis*) and valerian (*Valeriana officinalis*) are medicinal plants known since ancient times. We review here their chemical, pharmacological and medical properties to provide answers to their use in traditional medicine as relaxant cures. Some examples of their posology, according to the European Medicine Agencies [5,6] can be seen in the table 1.

The drugs used in medicines or food supplements is the dry extract of lemon balm leaves or the leaves themselves; the essential oil derived thereof may also be used. Lemon balm is known since ancient Greece and has been used in folk medicine of different countries [7]. Nowadays, several medications contain lemon balm. It is traditionally used in the symptomatic treatment of digestive disorders and their painful component, and in the symptomatic treatment of minor sleep disorders. A large body of evidence suggests that lemon balm could be used in the treatment of a variety of human health diseases, and associated to other uses including its pesticide activity (Figure 1). No interactions with other medicinal products have been reported so far in the use of lemon balm [6]. Concerning *V. officinalis*, the drug consists of valerian roots [8]. It is traditionally used orally in the symptomatic treatment of neurotonic statements of both adults and children, to manage minor sleep disorders. Herbal formulations containing valerian, usually in the form of root dry extract can be used alone or in combination with other herbs exhibiting sedative properties such as passionflower, hawthorn and horehound (Figure 1). No interactions with other medicinal products or other forms of interaction have been reported so far in the use of valerian [6].

Taxonomic and Botanical Description, Crop

Lemon balm

There are three subspecies of lemon balm: *officinalis, inodora* and *altissima* [9] but only the first is used therapeutically [10]. Lemon balm is a perennial herb with square stem, erect and branched, growing in clumps, measuring usually between 30 and 80 cm high (Figure 1). Leaves are stalked and located opposite and decussate on the rod. Their edges are heavily aliased. They are oval and heart-shaped, with very cross linked projecting ribs on the bottom face, giving this embossed appearance to the upper side. The surface is covered with fine short hairs.

Lemon balm is present in the wild in southern Europe and North America, and Asia Minor in slightly shady places such as the edge of a

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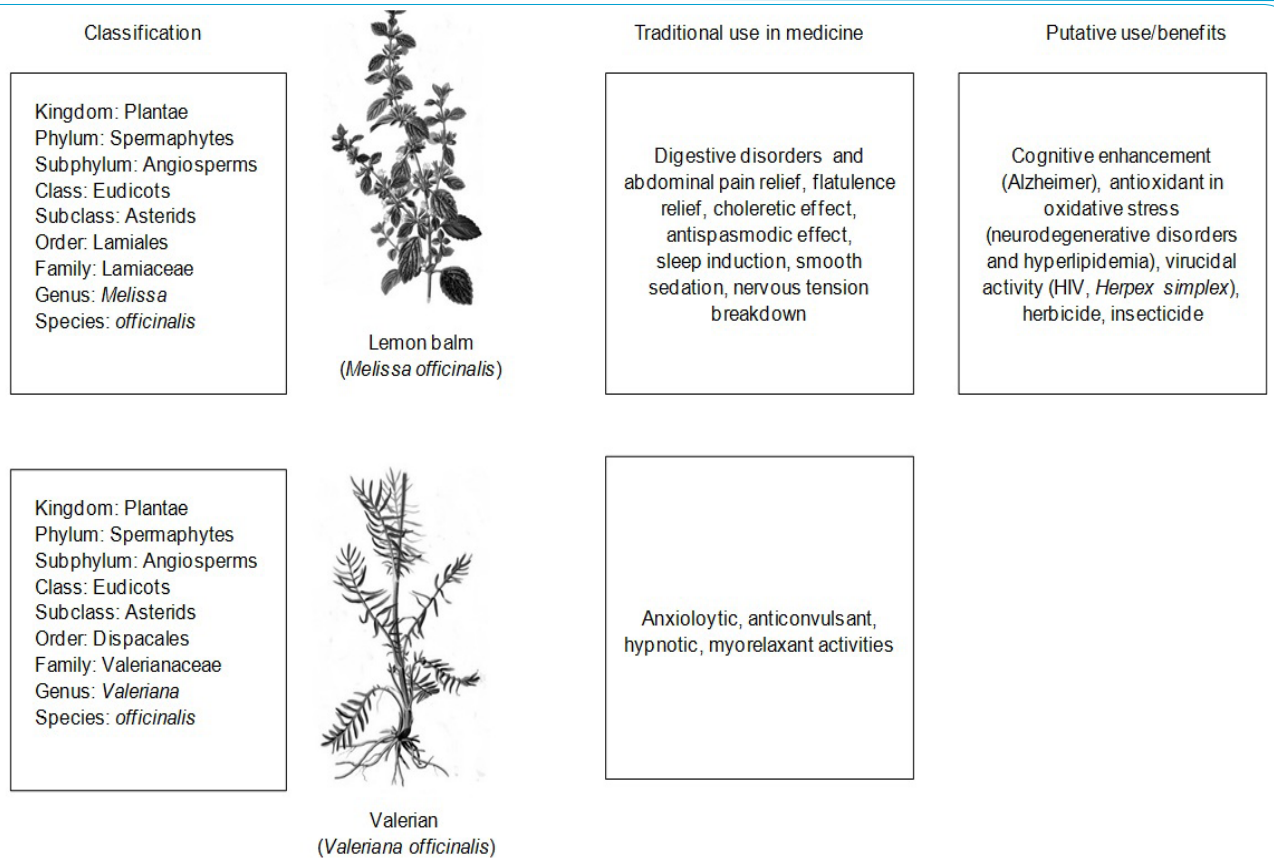


Figure 1: Lemon balm and valerian, and their main human uses. Pictures from Wikimedia commons.

hedge, a wood or uncultivated and cool place [9]. It is grown in central and western Europe and the United States [11]. The first normal harvest is done only after the second year of cultivation. Indeed, the first year, the producer can only expect 25% of a normal return. The leaves and stems are harvested before flowering, at the end of June to early July. A second harvest can take place in late August to early September. Originally, the collection was done with sickles but now there are mechanical harvesters, used especially when the surface of the field is important. Drying the plant must be performed soon completed picking because the plant is damaged very quickly. The drug used in medicines or food supplements is the dry extract of lemon balm leaves or dried lemon balm leaves. However, the essential oil derived thereof may also be used.

Valerian

There are three subspecies of *valerian: officinalis, sambucifolia* and *tenuifolia*. It is a biennial plant by its root measuring up to 1.50 meters. The strain is short and fibrous while the rod is hollow with fluted appearance. Leaves pinnate are arranged in rosette to the base of the stem and in an opposite manner along thereof. The flowers are white to pink and arranged in cymes at the end of the stem. The underground parts are made of a light gray-brown conical rhizome from which multiple long, thin roots (Figure 1). The plant, especially the dried underground part, exudes a particularly strong and unpleasant smell. Valerian grows naturally in temperate and sub polar regions of Eurasia, in moist woods and along streams [12]. It easily grows on the clay siliceous soil.

Valerian is cultivated for its root. Harvesting is done by pulling in the fall (October and November), from the second year of cultivation. The aerial parts of the plant are cut; the roots are dug mechanically and then washed. The root obtained is then cut and dried at less than 40°C [13]. The drug consists of valerian root, i.e the underground plant parts (rhizomes, roots and stolons) dried, whether whole or divided.

Therapeutic properties

The effects of lemon balm and valerian, in the form of plant powder or dry extract (mainly aqueous or hydro-alcoholic) have been extensively studied to determine their mechanism of action. Therefore, most studies were initially aimed to demonstrate the therapeutic efficacy assumed by the traditional use (Table 1). In addition, some have sought to discover new medical properties by *in vitro* or animal experiments or clinical observation in humans.

The uses of lemon balm in cases of nervousness and minor sleep disorders, and gastrointestinal disorders such as flatulence and abdominal pain, has been empirically established [7] (Table 1). The use of the plant to relieve abdominal pain is specific to *M. officinalis* and due to analgesic antispasmodic properties associated with stimulation of digestion, and particular to a choleretic effect. Valerian is also traditionally used to treat sleep disorders and soothe nervous tension especially when associated with muscle contractures [14]. Its use in the event of a state of mild nervousness and sleep difficulties is recognized, but is also a matter of debate [15]. In addition to its gastrointestinal properties, lemon balm exhibits interesting effects on the central nervous system. Particularly in rat brains, it inhibits the activity of GABA transaminase (GABA-T), the enzyme responsible of

	Persons concerned	Used forms	Posology
Lemon balm	Children over 12 years, adults, elderly*	Chopped dry leaves or powder	1.5 to 4.5 g, 1 to 3 times per day
		Herbal tea	1.5 to 4.5 g of dry leaves to 150 ml of boiling water, infused for 5 to 15 minutes, 1 to 3 times per day
		Tincture	2 to 6 ml, 1 to 3 times per day
		Liquid extract	2 to 4 ml, 1 to 3 times per day
		Aqueous or ethanol dry extract (45% v/v)	Doses equivalent to the posology of the infusion, tincture and liquid extract

Valerian	Adolescents over 12 years, adults, elderly*	Well-established use		
		Drug to Extract Ratio tincture [1:5] or aqueous or ethanol dry extract (70% v/v)	1 dose equivalent to 2-3 g of the herbal substance - 3 times a day in case of moderate nervousness - or 1 dose 1 hour before bedtime in case of sleep disorders or 1 additional dose at dinner if necessary Maximum 4 doses per day	
		Traditional use		
		Powder or dried valerian root herbal tea	0.3 to 3 g	3 times per day, if referred relaxing.
		Fresh plant juice	15 ml	
		Essential oil of valerian root	15 mg	1 dose 1 hour before bedtime in case of sleep disorders or 1 additional dose at dinner if necessary. Maximum 4 doses per day

Table 1: Examples of posology for the traditional use and recognized use of lemon balm and valerian. The oral route of administration is recommended. The treatment duration should be limited and if symptoms persist, a medical consultation should be considered. *The use in children under 12, pregnant or breastfeeding women is not recommended. Modified from EMA, 2013, 2015.

γ-aminobutyric acid (GABA) degradation with an *in vitro* IC_{50} of 0.35mg/ml. This is due to rosmarinic acid, ursolic acid and oleanolic acid [16,17]. However, *in vivo* studies would be necessary to determine whether the inhibition of GABA-T also appears. In addition, neither a methanol extract nor an aqueous extract of lemon balm moves the benzodiazepine (BZD) antagonist flumazenil from its GABA type A receptor (GABAAR) binding site [18]. This suggests that these extracts do not act on BZD receptor sites, and may not share with BZDs the same side effects. Currently, there are two main anxiolytic families: BZDs, which gather the majority of molecules, and H1 antihistaminics. BZDs facilitate GABA transmission which results in anxiolytic effects, muscle relaxation, anticonvulsant properties and sedation. But BZDs induce physical and psychic dependence as many adverse effects proportional to the dose administered such as drowsiness, anterograde amnesia and impaired concentration [19]. The anxiolytic effect of an ethanol extract of valerian root has been shown in rats up to 3 ml/kg ip. The effect was comparable with the BZD diazepam (1ml/kg). In the *Elevated Plus Maze* test, to evaluate the anxiety level, valerian root extracts administered to rats significantly decreased the anxiety [20,21]. In addition to its anxiolytic capacity, valerian has proved anticonvulsant effects. In fact, valerian has long been used for its antiepileptic properties in Iran. In adults, temporal lobe seizure is the most common form of epilepsy. Extracts of valerian roots were tested on a model of animal epilepsy obtained after a lesion in the temporal lobe. The antiepileptic effects observed would be partly due to the activation of the adenosine system. The activation of presynaptic A1 adenosine receptors by valerian root components decreases neurotransmitter release. They are therefore a potential target for the treatment of epilepsy.

Besides, a meta-analysis of randomized placebo-controlled studies found that valerian improves sleep quality if it is assessed qualitatively, which implies that volunteers were asked if their sleep is improved or not. However, these data were not quantitatively correlated through a visual scale [14,15]. The sedative properties of valerian would be linked to its strong anxiolytic potential than any hypnotic effect. Thus, sleep can be induced and/or enhanced in patients with anxiety as the cause of such disorders [20]. This might explain why valerian does not induce drowsiness in healthy subjects. Finally, valerian extracts have a dose-dependent myorelaxant effect on the guinea pig ileum stimulated at 0.1 Hz, a test used as an *in vitro* model of bowel movements. This type of contraction was due to the release of acetylcholine, and could be alleviated by administration of atropine. This suggests that the valerian extract may have anti-cholinergic activity [23].

A treatment with valerian root and alcohol-dry extract of lemon balm leaves was tested on hyperactive children diagnosed suffering from sleep disorders. The improvement of sleep disorders and symptoms related to hyperactivity was recorded. The treatment revealed no side effects: no case has been suspended for reasons of poor tolerance [24]. Complementarily, when tested on human volunteers in a clinical study vs placebo, the combination of lemon balm and valerian decreased the anxiety induced by a stress test. An excessive quantity of this association resulted in the opposite observation [25]. The association of valerian root extract and lemon balm leaf was well tolerated and without side effects in a study on healthy volunteers vs placebo. The combination was well tolerated by 97% of the volunteers. In both groups, 28% of subjects reported side effects like fatigue and sleep disorders. It showed that the use of these two treatment plants is at low risk and that their tolerance is very good [26].

Neuroactive components

Lemon balm and valerian have a diverse chemical composition, but a large amount of molecules have been identified in both plants. The constituents of the whole drug and those of the essential oil are

different. Some compounds are common to both plants, especially in their essential oil. Indeed, lemon balm and valerian are derived from the same sub-class of *Asteridae*. It is therefore not surprising to find similarities in their composition. Lemon balm leaves are rich in phenolic acids and flavonoids. About ten molecules can be distinguished for their capacity to act on the GABA network, thus promoting a decrease in the activity of the central nervous system. We here quote which molecules found in lemon balm and/or valerians were described as sedatives (Table 2).

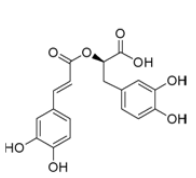
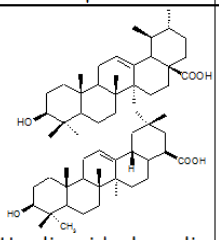
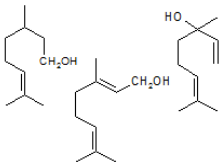
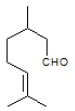
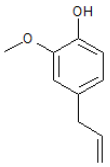
From lemon balm

Rosmarinic acid has been isolated and identified for the first time from rosemary (*Rosmarinus officinalis*) [27]. Yet this phenolic acid is present in greater amounts in the leaves of lemon balm, where its concentration is 3.9% against 2.5% in rosemary [28]. Rosmarinic acid is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid [27]. This is a polar molecule, which explains its solubility in water and ethanol (Table 2). It is present among *Lamiaceae, Borraginaceae* and *Apiaceae* and is expected to participate in the defense mechanisms of the plant [29].

Triterpenes are C30 compounds from the cyclization of squalene or epoxysqualene. These are highly lipophilic molecules, specific to the plant world, while steroids derived from them are common to the two kingdoms. The ursolic acid and oleanolic acid are triterpenes contained in the leaves of lemon balm (Table 2). These are two isomers widespread in plants [30]. As for the essential oil of lemon balm, it contains monoterpene hydrocarbons: ocimene and α-pinene. The ocimene is an acyclic monoterpene, it refers to the two cis-β-ocimene and trans-β-ocimene isomers. The α-pinene is a cyclic monoterpene. It is a phytoncide, a volatile substance released from the trees. It has sedative, anxiolytic and anticonvulsant properties, which would explain the calming effect of a walk in forest [31]. The essential oil of lemon balm also contains acyclic monoterpene alcohols such as citronellol , geraniol, and linalol present at up to 5% [32]. The essential oil of lemon balm contains citronellal made up of nearly 98% of the (+)-enantiomer and 2% of the (-)-enantiomer (Table 2). It represents with citral 40 to 75% of the essential oil, and is responsible for its lemony aroma [13].

From valerian

Valerian shares some chemical similarities with lemon balm. Sesquiterpenes produced by valerian are cyclopentane carboxylic acids chemically stable and non-volatile. Among them, there is valerenic acid, which is a qualitative and quantitative marker of valerian, and its derivatives. GABA was also isolated from

		Phenol acids	Triterpen acids	Hydrocarbures	Alcohols	Aldehyds	Aromatic compounds
Lemon balm	Leaf	 Rosmarinic acid (3.9 to 4.7%)	 Ursolic acid, oleanolic acid				
	Essential oil			 α-pinene	 Citronellol, geraniol, linalol (up to 5% altogether)	 Citronellal (40 to 75%)	 Eugenol

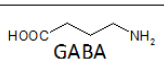
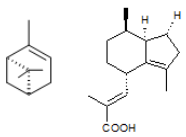
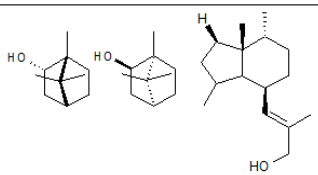
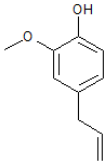
		Amino acids	Hydrocarbures	Alcohols	Aromatic compounds
Valerian	Root	 GABA	Valerenic acid (0.2 to 0.9%)		
	Essential oil		 α-pinene (2.2%), valerinic acid (0.3 to 3%)	 (+)-and (-)-borneol (0.1 to 0.6%), valerenol	 Eugenol

Table 2: Main neuroactive components of lemon balm or valerian. The list is restricted to molecules that exhibit a sedative effect on the central nervous system through their interaction with the GABA transmission. The chemical structure of each molecule and their presence in the leaf, root or essential oil is shown. When available, the amount of each compound is indicated in parentheses as a % of the total.

the roots of valerian (Table 2). As in the majority of plants, other amino acids were identified such as glutamine, tyrosine and arginine. The terpenoïd borneol is present in the essential oil of valerian, up to 0.1 to 0.6% [33]. The essential oil of many medicinal plants also contains borneol, such as that of German chamomile (*Matricaria chamomilla*) and lavender (*Lavandula officinalis*). It has two enantiomers: the (+) - borneol and the (-) - borneol [34] (table 2). The valerenic acid is 0.3 to 3% of the essential oil valerian. The sesquiterpene xanthorrhizol is also present in the ginger rhizome, *Turmeric xanthorrhiza*, an Asian plant which is associated to numerous benefits including antioxidant properties [35]. Other sesquiterpene alcohols are also present in the essential oil of valerian, including valerenol. Finally, eugenol is an aromatic present in its esterified form (Table 2).

Physiological and molecular targets in the central nervous system

GABA transmission

The components of lemon balm and valerian were mainly studied to determine if they contribute to the sedative properties of the two plants. Scientific studies are therefore particularly focused on the characterization of their mode of action. The issues addressed by the traditional use of these plants are the assumptions of such studies. These studies also allow a glimpse of other purposes of these plants and to understand their potential toxicity. We examined the interaction of lemon balm and valerian compounds on the central nervous system to objectify their traditional and medical use. Studies have focused on the mode of action of each of these plants on the GABAergic system to explain their relaxing and anxiolytic properties (Figure 2). Several molecules from both plants potentiate the response of GABAARs *in vitro* or *in vivo* by allosteric modulation or by agonist effect. GABA binding on its receptors induces a greater inhibition of neuronal activity. Several plant compounds have therefore been studied to determine scientifically their mechanism of action. The valerenic acid is responsible for the effects of *V. officinalis* on GABAARs [36]. However, its site of action remains unknown. Therefore, Khom et al. [37] studied its effects of 13 stoechiometric arrangements of GABAARs. The binding of valerenic acid is not displaced by flumazenil and therefore it does not interact with the BZD site [38]. Valerenic acid is a specific modulator of GABAAR $\beta_{2/3}$ subunits, giving it an anxiolytic potential [37]. Moreover, valerenic acid, like valerenol, promote the binding of BZD on their site *in vitro* [39].

In addition, borneol, which is present in the essential oil of valerian, acts on GABAAR as a positive modulator. Such allosteric modulators (barbiturates, BZD, neurosteroids, alcohol etc.) are able to produce anxiolytic, sedative, anesthetic effects or muscle relaxation, as a function of the GABAAR subtype they bind to (Figure 2). Both (+)- and (-)-borneol enantiomers (Table 2), induce a dose-dependent positive modulation of GABA current, from 0.1 µM, on human $\alpha_1\beta_2\gamma_2L$ GABAARs, the predominant subtype in the human brain [40]. The (+)-borneol was more active than the (-)-borneol, and this difference in activity is observed at very low and very high concentrations. Besides, borneol also acts as a partial agonist of GABAARs. Flumazenil does not inhibit the action of the (+)-borneol, suggesting that the latter does not bind to the same site as BZDs [34]. This accredits the use of (+)-borneol in Chinese and Japanese medicine as an anesthetic and analgesic and why it causes mild sedation in mice in inhalation [41].

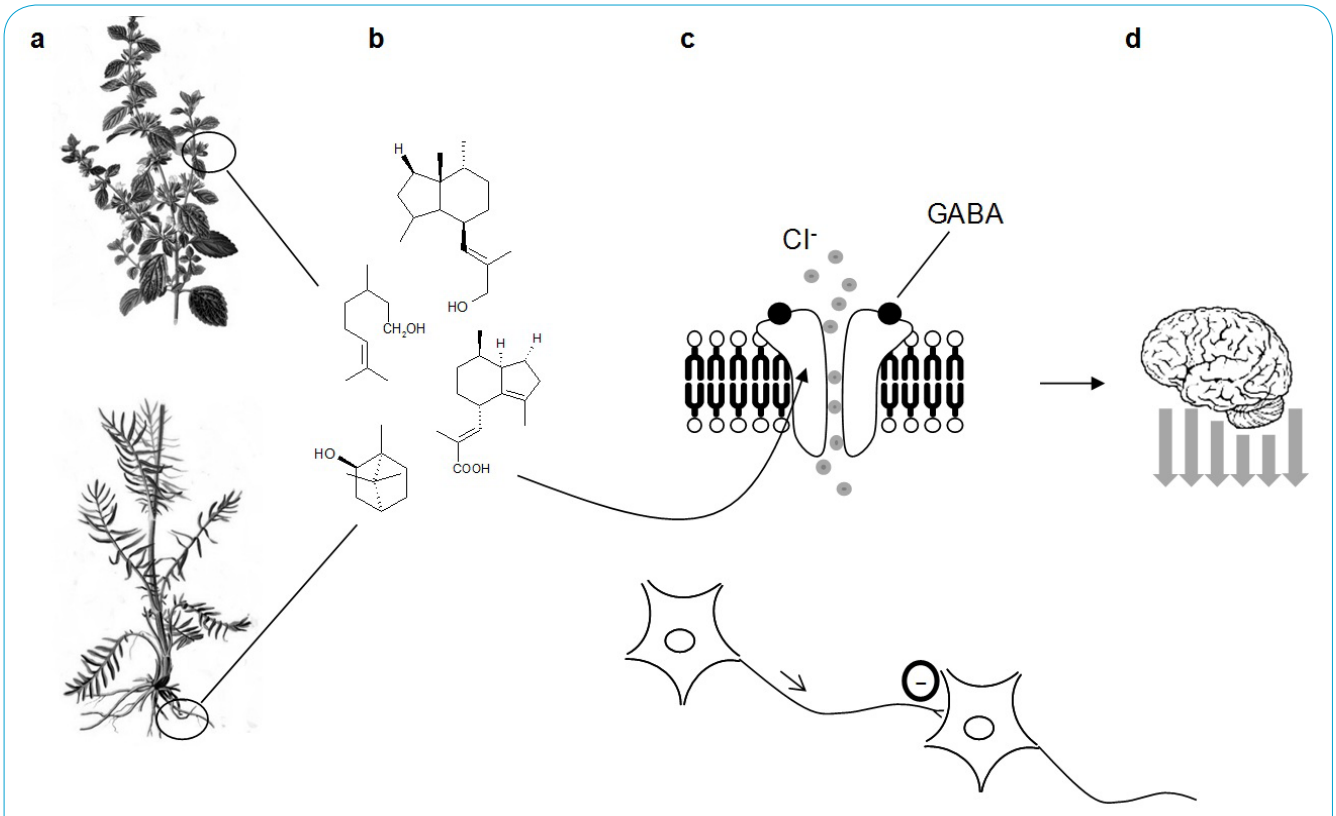


Figure 2: From plants to human therapies. Molecules shown (b) are examples of pharmacologically active constituents of lemon balm leaves or valerian roots (a), shown to act on GABAARs as positive modulators (c). This reinforces the GABA-induced neuronal inhibition (c) and facilitates the decrease of brain activity, thus ending in either sedation, anxiolysis, muscle relaxation, sleep enhancement or anticonvulsant activity (d).

Eugenol, pinene (both the α and β forms), citronellol and citronellal (Table 2) also potentiate the effects of GABA on rat brain GABAARs expressed in Xenopus oocytes [31]. This was also observed with linalol and geraniol with the GABAAR subunits α1 and β1 [43].

The inhibition of GABA-T by a methanolic extract of lemon balm is attributed to rosmarinic acid, ursolic acid and oleanolic acid. This inhibition reaches 40% with 100 µg/ml rosmarinic acid. The latter is present at this concentration in the methanol extract, suggesting that it is the cause of the observed inhibitory activity. The inhibition of GABA-T is 13% and 20% to 10 µg/ml ursolic acid and oleanolic acid respectively [16]. The observed activity is likely due to a synergy between these compounds and optionally other unknown molecules.

Other targets

Adenosine appears as one of the main sedative neurotransmitters in the brain. It would allow the induction of sleep through its interaction with A1 and $A2_A$ receptors after accumulation in the brain during the day. A1 adenosine receptors are abundant in the brain, but can also be found at the peripheral level in much more negligible quantity. $A2_A$ receptors are also widespread in the brain while $A2_B$ and A3 receptors are little present [43]. Valerian root extracts showed a high affinity for A1 receptors. However, it turns out that hydrophilic extracts rather act as partial agonists whereas lipophilic extracts rather act as antagonists. Based on this finding, Lacher et al. [43] sought to identify the compounds in valerian roots that could explain the antagonist effect of lipophilic extracts. Isovaltrate possesses an inverse agonist activity, which means its binding leads to the opposite effect to that caused by adenosine. This would result in *in vivo* excitation rather than sedation [43]. As valerian is traditionally drunk as an infusion, which is lacking in lipophilic isovaltrate, these excitatory effects have not been observed. The hydrophilic extracts act as partial agonists of A1 receptors, which may explain the sedative effect of the herbal tea.

It appears that the serotonin receptors 5-HT5A and 5-HT7 play a role in controlling circadian rhythm, which disturbance can cause insomnia. The antagonists of 5-HT3 receptor would prevent withdrawal symptoms associated with nicotine, alcohol, cocaine and the BZD diazepam [44]. The valerenic acid is a partial agonist of 5-HT5A receptor in human CHO-KI cells and these receptors are involved in the regulation of the sleep-wake cycle [45]. The valerenic acid might therefore fight against sleep disorders by enabling the restoration of a normal circadian rhythm.

Secondary effects

Before considering any use in the pharmaceutical field, one should ensure the effectiveness of lemon balm and valerian above all and rule out potential toxicity. For if these plants showed no side effects when taken over limited periods, what about a repeated intake or chronic exposure?

Valerian could be the cause of long-term liver toxicity because of the presence of valepotriates. These are experimentally sedative and antispasmodic, which earned them being long regarded as the active ingredients of valerian [46]. However they are also cytotoxic and mutagenic. They possess an alkylating potential due to the presence of an epoxide ring in their structure, making them highly unstable and thus highly reactive. The cytotoxicity of these components was tested on human tumor cells GLC4 and Colo 320. Still, it is likely that most commercial forms of valerian root are free of valepotriates because they hydrolyze rapidly in baldrinals that would be 10 to 30 times less toxic than the molecules from which they derive [46]. But as a precaution, the aqueous extracts or low alcohol content are preferred. It also appears *in vitro* and *in vivo*, an aqueous extract of lemon balm inhibits the activity of the Thyroid Stimulating Hormone (TSH) by preventing its binding to its receptor, inducing hypothyroidism, but this has not been shown in clinical studies [47]. Finally, the caryophyllene oxide, produced from the oxidation of β-caryophyllene present in the essential oil of lemon balm and valerian, is causing a skin sensitization in guinea pigs. The allergenic activity, however, is low because it is rapidly degraded into a more stable and less reactive molecule [48]. Similarly, local application of citral at a concentration greater than 1% causes skin sensitization [49]. Like all essential oils, it should be diluted before any external application to limit the risk of skin irritation.

Conclusion and Future Directions

Lemon balm and valerian have proven their efficiency. However, it can be difficult to use these therapeutic plants because their composition is highly variable and depends on many factors including their mode of culture, location, season, etc. Now it is necessary to have consistency in the product mix in order to obtain a reliable therapeutic result. Perhaps it would be more sensible to use the aqueous extracts, because they are the ones who are closest to the traditional use and therefore offer a better perspective. Whether whole plant powder or extract, these must be normalized, for their composition to be stable from one batch to another. In this case, it must be determined which molecule) constitute the active ingredient of the plant in order to agree on a minimum content to be included in the drug to ensure its effectiveness. Many of the compounds identified in lemon balm and valerian have a demonstrated pharmacological activity on the central nervous system. This is the case of valerenic acid, which exhibits a high affinity for GABAARs, and confers to valerian roots a natural sedative activity. It is the same for rosmarinic acid in the lemon balm leaves and its inhibitory activity on GABA-T. Moreover, other molecules appear to have similar or complementary pharmacological properties. Therefore, the activities described here can surely be explained, not by one or two active compounds, but rather a synergy between the components of the plant. However, within the plant or extracts may also be interactions between the compounds, making them less available and therefore less effective, even toxic.

GABAA receptors are the main target of synthetic molecules with sedative properties. Their pharmacology is relatively well developed, and the structure of a homopentamer receptor has recently been described [50]. Among the issues on plant compounds active on this receptor, it will be necessary to identify their binding site because it is clearly different from that of BZDs, and this will explain the differences in activity between natural and synthetic molecules [51]. In addition, the stoichiometry of GABAARs is often a crucial factor in the mode of action of pharmacologically active agents. A research tracks will include understanding what subunits promote allosteric binding compounds of valerian and lemon balm, to determine whether they modulate neuronal tonic or phasic inhibition [52]. Finally, understanding of synergistic mechanisms of plant compounds to GABA transmission should lead to formulate herbal products less concentrated and with greater efficiency, while reducing their side effects.

Competing Interests

The authors declare that they have no competing ointerests.

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