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Review

Traditional Herbal Remedies Used for Managing Anxiety and Insomnia in Italy: An Ethnopharmacological Overview

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Abstract: Anxiety and insomnia are among the most common mental health disorders and are a major cause of disability around the world. Traditional herbal medicines are receiving significant attention in global health debates. Several Italian regions maintain rural traditions and are among the most extensively studied areas of Europe regarding medicinal plant uses. The present overview aims to highlight the use of wild and cultivated plants, specifically as sedatives and for insomnia treatment in Italy, and to collect, analyze, and summarize the available literature about their pharmacological activity as well as clinical and pre-clinical studies concerning the most cited plants. In total, 106 wild taxa are used in Italy for sedative purposes. The plant species belong to 76 genera and 32 families, of which the most cited are Asteraceae (24.2%) and Lamiaceae (21.1%). Leaves (29%) and flowers (27%) are the plant parts mostly used as infusion (70%) and decoction (25%). Out of 106 taxa documented, only the most cited are analyzed in this overview (*A. arvensis* L., *C. nepeta* L., *C. monogyna* Jacq., *H. lupulus* L., *L. nobilis* L., *L. angustifolia* Mill., *M. sylvestris* L., *M. chamomilla* L., *M. officinalis* L., *O. basilicum* L., *P. rhoeas* L., *P. somniferum* L., *R. officinalis* L., *T. platyphyllus* Scop., and *V. officinalis* L.). Among the fifteen species selected, only seven have been studied for their pharmacological activity as hypnotic-sedatives. Future pre-clinical and clinical studies are needed to better clarify the mechanism of action of bioactive compounds and confirm the potential of these alternative therapies.

Keywords: traditional herbal medicines; generalized anxiety disorder; sleep disorders; sedative; anxiolytic

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1. Introduction

Anxiety and insomnia are among the most common mental health disorders and are a major cause of disability around the world [1–4]. GAD (generalized anxiety disorder) [5] has received increasing attention in recent years as a prevalent disorder associated with significant impairment [6]. Patients with GAD complain that they worry excessively, are excessively aroused, have heightened muscle tension, and a have variety of autonomic symptoms [7]. The impact of the anxiety is not limited to consistent stress, which is associated with higher risk of cardiovascular and cerebrovascular diseases, but also has debilitating physical manifestations such as headaches, uncontrolled trembling, and sweating [8]. Insomnia symptoms are generally considered to encompass difficulty in initiating sleep, disrupted sleep, and early morning awakenings [9].

Gamma-aminobutyric acid (GABA), the main inhibitor neurotransmitter in the central nervous system (CNS), plays an important role in anxiety [10]. Anxiety and related neurological disorders often result from low GABA levels in CNS [11]. The anabolism and catabolism of GABA are regulated by two enzymes: glutamic acid decarboxylase (GluAD) and GABA transaminase (GABA-T), respectively. The most common strategies to increase GABA level in the brain are based on the affinity to the benzodiazepine (BZD) site of the $GABA_A$ receptors, the stimulation of GluAD, and the inhibition of GABA-T. Important pharmacotherapy agents used in GAD are the selective serotonin reuptake

inhibitors (SSRIs) and the serotonin and noradrenaline reuptake inhibitors (SNRIs) [12,13]. In most cases, the medications used in these limited treatment options for anxiety and insomnia (e.g., anxiolytics, sedative-hypnotics, antidepressants, and sleep aids drugs) are often associated with serious and unpleasant side effects such as dependence, nausea, tremors, cognitive impairment, increased risk of motor vehicle accidents, falls, weight gain, and fractures [14,15].

To overcome this issue, the use of natural products such as herbal medicines is becoming an appealing approach, especially for those individuals with mild to moderate symptoms of anxiety and sleep-disorders [16]. As defined by the World Health Organization, traditional herbal medicines are naturally occurring, plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices [17]. Over the past few years, the use of natural or herbal remedies as a form of self-treatment of various stress-related afflictions has become increasingly popular in Western societies [18,19]. Nowadays, herbal medicine represents one of the most frequently used complementary or alternative treatments of insomnia [20]. However, the efficacy of traditional medicinal herbs in complementary and alternative medicine of the mental health disorders has not been exhaustively explored yet, especially concerning the mechanism of actions of phytocomponents.

Ethnopharmacology can be defined as a multi-disciplinary area of research concerned with the observation, description, and experimental investigation of indigenous drugs and their biological activities [21,22] that also seeks to further develop the use of this local knowledge [23]. These types of research have great importance not only because of their contribution to healthcare but also for the preservation of biodiversity, for the raising of environmental consciousness, and because of different sociological and economic aspects [24].

European medicinal plants are of central interest to ethnographers, anthropologists, ethnobiologists, pharmacologists, and other scholars interested in wider health questions [25]. In the last decades, studies concerning the medicinal plants used among rural populations in industrialized countries have received growing attention, especially in south-eastern and central European countries [26–29]. In the Italian Peninsula, many ethnobotanical surveys have been carried out because of high biological and cultural diversity [26–33]. These studies have focused on plants' practical uses through traditional knowledge, with particular attention paid to medicinal plants. Despite this, the use of plants as remedies for anxiety and insomnia has received marginal attention so far and, to date, no systematic review has been conducted to investigate their use for GAD treatment in Italy.

In this context, the aim of this systematic review is (a) to highlight the use of wild and cultivated plants specifically for the treatment of anxiety and insomnia in Italy; and (b) collect, analyze, and summarize the available literature about the pharmacological activity of the most used plants.

2. Materials and Methods

Electronic literature searches were conducted using the following databases: Blackwell Synergy, Web of Science, Scopus, and Google Scholar, using the following key words and connectors: "Italy" OR "ethnobotany" OR "ethnobotanical", "ethnopharmacology" OR "medicinal plants" AND "stress" OR "anxiety" OR "anxiolytic" OR "sedative" OR "insomnia" OR "hypnotic". Besides the articles gathered from the online databases, further papers were selected from the references cited by the studies previously collected. The criteria for article selection were defined a priori to avoid personal bias. We searched both national and international journals published from 1967 to 2021. Publications were filtered for English and Italian languages, duplicates, document type (no patents), and full text availability. In all, 146 articles were found in both the databases as well as the previously collected papers, 49 of which contained reports of wild plants specifically used as sedative-hypnotic for anxiety and/or insomnia treatment. We used the same electronic

databases (included PubMed) to survey phytochemical and clinical studies supporting the effectiveness of plants for each use report. Based on the results obtained, we drafted a check list reporting the following data: plant name, family plant part(s) used, preparation, and references. The nomenclature follows the World Flora Online [34]. Families are organized according to APG IV for angiosperms [35]. Abbreviations of authors are standardized according to Brummitt and Powell (1992), as recommended by Rivera, et al. (2014) [36,37]. The obtained data were analyzed using descriptive statistics and presented in form of charts and tables.

3. Results and Discussion

Based on the 65 studies providing adequate and relevant data, 106 wild taxa used in Italy for sedative purposes have been documented (Table 1). The plant species belong to 32 families and 76 genera. Asteraceae (24.2%) and Lamiaceae (21.1%) are the most frequently cited families, followed by Apiaceae, Poaceae, Rosaceae (5.3%), and Malvaceae, Papaveraceae, Rutaceae, and Valerianaceae (4.2%). This could probably be attributed to the similar distribution, from both quantitative and qualitative points of view, of the analog active substances among species, especially those of families Lamiaceae and Asteraceae [38,39]. The families of Asteraceae and Lamiaceae have biosynthetic pathways that mainly produce phenols, terpenoids, and phenylpropanoids, as secondary metabolites, which are the main phytochemicals responsible for the sedative properties against sleep disorders and anxiety [40,41]. The major route of administration is oral (with decoction and infusion as main methods of preparation), although in some pre-clinical and clinical trials inhalation is also reported.

Table 1. Identified taxa (106 in total) used as traditional herbal remedies in Italy for managing anxiety and insomnia. The plant parts used and the preparation methods are indicated.

Botanical Name	Family	Parts Used	Preparation	References
Achillea moschata L.	Asteraceae	Aerial parts	Infusion	[42,43]
Adiantum capillus-veneris L.	Adiantaceae	Aerial parts	Decoction	[44–46]
Agrimonia eupatoria L.	Rosaceae	Aerial parts	Infusion	[43]
Alchemilla group *alpina* L.	Asteraceae	Leaves	Infusion	[33]
Alchemilla group *vulgaris* L.	Asteraceae	Leaves	Infusion	[33]
Aloysia citrodora Paláu (=*Lippia triphylla* (L'Hér.) Kuntze)	Verbenaceae	Leaves	Infusion	[31,45]
Angelica archangelica L.	Apiaceae	Roots	Extract	[47]
Angelica sylvestris L.	Apiaceae	Leaves	Infusion	[43]
Anthemis arvensis L.	Asteraceae	Flowers	Infusion	[44–46,48]
Artemisia absinthium L.	Asteraceae	Leaves	Infusion	[49]
Artemisia arborescens L.	Asteraceae	Flowers	Infusion	[50]
Artemisia vulgaris L.	Asteraceae	Leaves, roots		[47,51,52]
Arum italicum Miller	Araceae	Leaves	Infusion	[53]
Arum pictum L. f.	Araceae	Leaves	Infusion	[53]
Avena fatua L.	Poaceae	Fruits	Decoction	[54]
Avena sativa L.	Poaceae	Fruits	Decoction	[54]
Ballota nigra L.	Solanaceae	Whole plant		[47]
Borago officinalis L.	Boraginaceae	Leaves	Infusion	[43]
Calendula officinalis L.	Asteraceae	Whole plant		[47]
Centranthus ruber (L.) DC.	Valerianaceae	Whole plant, rhizome	Infusion	[31,55]
Chamaemelum nobilis All.	Asteraceae	Aerial parts	Infusion	[56]
Citrus aurantium L.	Rutaceae	Leaves	Infusion	[55]
Citrus limon L.	Rutaceae	Fruits	Juice	[57,58]
Citrus x *sinensis* (L.) Osbeck	Rutaceae	Flowers	Infusion	[59]

Table 1. *Cont.*

Botanical Name	Family	Parts Used	Preparation	References
Clinopodium nepeta (L.) Kuntze (=*Calamintha nepeta* (L.) Savi)	Lamiaceae	Aerial parts	Decoction	[47,49,54,59–61]
Conium maculatum L.	Apiaceae	Leaves	Infusion	[62]
Corydalis cava (L.) Schweigg. and Körte	Papaveraceae	Tubers	Infusion	[47]
Crataegus laevigata (Poir.) DC.	Rosaceae	Flowers	Infusion	[43,63,64]
Crataegus monogyna Jacq.	Rosaceae	Flowers, leaves	Decoction	[31,43–45,49,54,65–68]
Crocus sativus L.	Iridaceae	Pistil	Infusion	[51]
Cydonia oblonga Mill.	Rosaceae	Fruits	Decoction	[44]
Cynodon dactylon (L.) Pers	Poaceae	Roots	Decoction	[60]
Dianthus seguieri Vill.	Caryophyllaceae			[69]
Ecballium elaterium (L.) A. Rich	Cucurbitaceae	Roots, fruits	Decoction	[54]
Foeniculum vulgare Miller	Apiaceae	Fruits	Decoction	[32,60]
Humulus lupulus L.	Cannabaceae	Flowers	Infusion	[32,43,53,55,60,70,71]
Hyoscyamus niger L.	Solanaceae	Seeds		[47]
Hypericum perforatum L.		Flowers	Infusion	[65]
Ilex aquifolium L.	Aquifoliaceae	Leaves	Infusion	[53,62]
Jacobaea delphiniifolia (Vahl) Pelser and Veldkamp	Asteraceae	Flowers	Infusion	[62]
Lactuca sativa L.	Asteraceae	Leaves	Decoction	[32,43,55]
Lactuca virosa L.	Asteraceae	Latex	Raw	[47]
Laurus nobilis L.	Lauraceae	Leaves	Infusion	[52,55,57,61,72]
Lavandula angustifolia Miller	Lamiaceae	Flowers	Infusion	[31,62,65,73]
Lavandula officinalis Chaix	Lamiaceae	Flowers	Infusion	[65]
Lavandula stoechas L.	Lamiaceae	Flowers	Infusion	[57,72]
Leucanthemum alpinum Lam.	Asteraceae	Leaves	Infusion	[43]
Lolium multiflorum Lam.	Poaceae	Fruits	Decoction	[51]
Lolium perenne L.	Poaceae	Fruits	Decoction	[51,74]
Lotus corniculatus L.	Fabaceae	Flowers	Infusion	[47,75,76]
Malva cretica Cav.	Malvaceae	Aerial parts	Decoction	[59]
Malva neglecta Wallr.	Malvaceae	Aerial parts	Decoction	[59]
Malva sylvestris L.	Malvaceae	Aerial parts	Decoction	[58–60,77]
Matricaria camomilla L. (=*Chamomilla recutita* (L.) Rauschert)	Asteraceae	Flowers	Infusion	[31,33,42,43,45,47,49–51,53,55–60,63–65,68,72–74,78–86]
Matricaria discoidea DC.	Asteraceae	Flowers	Infusion	[33]
Melilotus officinalis Pall.	Fabaceae	Flowers	Infusion	[43]
Melissa officinalis L.	Lamiaceae	Whole plant	Infusion	[33,43,45,49,57,59,61,63,73,87,88]
Melittis melissophyllum L.	Lamiaceae	Flowers	Infusion	[77]
Mentha aquatica L.	Lamiaceae	Aerial parts	Infusion	[59,62]
Mentha piperita L.	Lamiaceae	Whole plant	Infusion	[59,61]
Mentha spicata L. (=*M. spicata* L. subsp. glabrata (Lej. and Courtois) Lebeau)	Lamiaceae	Aerial parts	Infusion	[59,62]
Mentha suaveolens Ehrh. subsp. *suaveolens*	Lamiaceae	Aerial parts	Infusion	[62]
Mentha viridis L.	Lamiaceae	Whole plant	Infusion	[57]
Myrtus communis L.	Myrtaceae	Leaves	Infusion	[44]
Nepeta cataria L.	Lamiaceae	Aerial parts		[43,73,89]
Ocimum basilicum L.	Lamiaceae	Leaves, flowers	Infusion	[43,49,54,63,72,82,90]

Table 1. *Cont.*

Botanical Name	Family	Parts Used	Preparation	References
Olea europaea L.	Oleaceae	Leaves	Infusion	[90]
Opuntia ficus-indica (L.) Mill.	Cactaceae	Flowers	Infusion	[59]
Origanum majorana L.	Lamiaceae	Leaves	Infusion	[44]
Origanum vulgare L. subsp. *viridulum* (Martrin-Donos) Nyman	Lamiaceae	Leaves	Infusion	[43,86]
Paeonia mascula (L.) Mill.	Paeoniaceae			[91]
Papaver rhoeas L.	Papaveraceae	Petals, fruits	Infusion	[31,32,43–48,50,53,59–64,66,67,72,73,77,79,82,85,86,88,92]
Papaver setigerum DC.	Papaveraceae	Fruits	Decoction	[45,46]
Papaver somniferum L.	Papaveraceae	Fruits	Infusion	[46–48,53,68]
Passiflora caerulea L.	Passifloraceae	Fruits, seeds	Decoction	[32,45,46]
Pimpinella anisum L.	Apiaceae	Fruits	Infusion	[43,57]
Polypodium vulgare L.	Polypodiaceae	Leaves	Infusion	[43]
Primula veris L.	Primulaceae	Flowers, leaves	Infusion	[43,65]
Primula vulgaris Huds.	Primulaceae	Flowers	Decoction	[45,71]
Prunus persica (L.) Batsch	Rosaceae	Flowers	Decoction	[55]
Robinia pseudacacia L.	Fabaceae	Flowers	Decoction	[63]
Rosmarinus officinalis L.	Lamiaceae	Aerial parts	Infusion	[44,45,60,61,77]
Ruta chalepensis L.	Rutaceae	Leaves	Infusion	[82]
Salix alba L.	Salicaceae			[76]
Salvia officinalis L.	Lamiaceae	Leaves	Infusion	[49,54]
Santolina insularis (Gennari ex Fiori) Arrigoni	Asteraceae	Leaves	Infusion	[44]
Senecio delphinifolius Vahl.	Asteraceae	Aerial parts	Decoction	[68]
Solanum nigrum L.	Solanaceae			[91,93]
Sonchus oleraceus L.	Asteraceae	Leaves	Infusion	[94]
Stachys recta L.	Lamiaceae	Aerial parts	Infusion	[45,95]
Tanacetum balsamita L. (=*Balsamita major* Desf.)	Asteraceae	Leaves	Infusion	[43,47,76,96,97]
Tanacetum parthenium (L.) Sch.-Bip.	Asteraceae	Flowers	Infusion	[45,46]
Thalictrum aquilegiifolium L.	Ranunculaceae	Leaves		[47]
Thymbra capitata (L.) Cav.	Lamiaceae	Aerial parts		[89]
Thymus serpyllum L.	Lamiaceae	Aerial parts	Infusion	[65]
Tilia cordata Mill.	Malvaceae	Leaves	Infusion	[45,81,88]
Tilia platyphyllus Scop.	Malvaceae	Flowers	Infusion	[31,43,59,60,84]
Tilia sp.	Malvaceae	Flowers	Infusion	[42,66,82]
Tussilago farfara L.	Asteraceae	Flowers	Infusion	[98]
Urtica dioica L.	Urticaceae	Leaves	Infusion	[49]
Valeriana montana L.	Valerianaceae	Rhizome	Decoction	[51]
Valeriana officinalis L.	Valerianaceae	Rhizome, fruits	Decoction	[43,45,47,51,60,63,64,68,74]
Valeriana tripteris L.	Valerianaceae			[99]
Verbena officinalis L.	Verbenaceae	Flowers, leaves	Infusion	[44–46,100,101]
Zea mays L.	Poaceae	Stigmas and styles	Infusion	[53]
Ziziphus jujuba Mill. (=*Ziziphus sativa* Gaertn.)	Rhamnaceae	Fruits	Decoction	[44]

As shown in Figure 1, leaves (29%) and flowers (27%) are the most frequently used plant parts. This is probably due to do the fact that leaves, besides photosynthesis, are also used as synthetic and storage organs for secondary metabolites such as phenols and terpenoids (essential oil), while flowers, which often have an aromatic smell, are mainly composed of terpenes, flavonoids, and aromatic compounds [102]. These secondary metabolites are the most responsible for the sedative properties used to treat sleep disorders and anxiety. Additionally, harvesting of leaves, instead of roots or the whole plant, allows for the sustainable utilization of the plants, hence promoting their conservation [103].

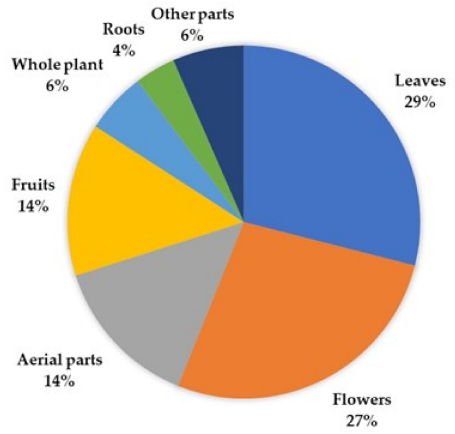

Figure 1. Plant parts used for medicinal applications in GAD in Italy.

From the analyses carried out at a regional scale, Campania has the highest number of records of plants used in GAD (39), followed by Lombardy (29) and Tuscany (25) (Figure 2).

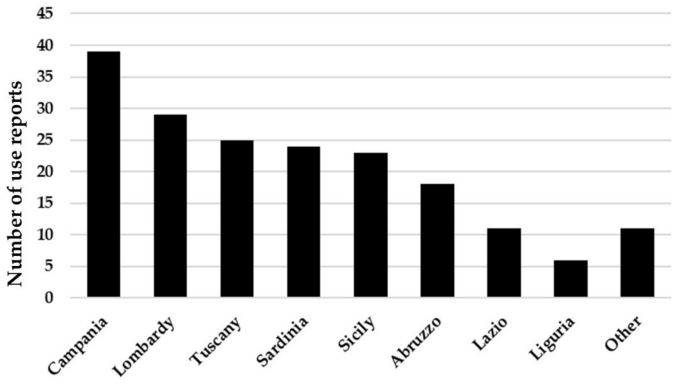

Figure 2. Number of use reports for each Italian region.

Figure 3 shows a summary of the 15 most commonly cited taxa used as sedative or for insomnia treatment in Italy. For each species, life form, chorology, phytochemical profiles, and clinical evidence are discussed in the paragraphs below following the alphabetic order of the plants' scientific names. The chemical composition for each plant may change depending on sources, cultivars, growing conditions, age of the plant and part of the plant used, country, storage conditions, and extraction procedures.

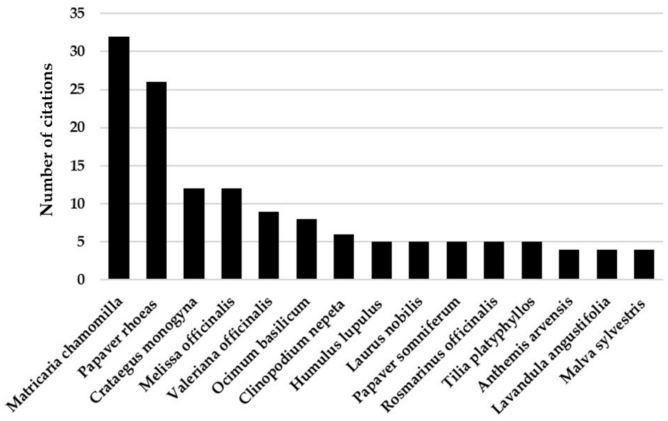

Figure 3. Most cited species in all Italian regions.

Table 2 shows the most cited species used as hypnotic-sedatives in Italy and summarizes the mechanism of actions, where reported, and the related bioactive compounds.

Table 2. Most cited species in Italy used as hypnotic-sedatives. Bioactive compounds responsible of the actions are indicated as well as their related mechanism of action.

Plants	Major Bioactive Compounds	Mechanism of Action	Actions	Clinical Evidence	References
Anthemis arvensis L.	n. a.	n. a.	S	N	[48]
Clinopodium nepeta L.	*Monoterpenoids:* pulegone, menthone, 1,8-cineole and carvone	n. a.	S	N	[104–106]
Crataegus monogyna Jacq.	*Polyphenol*: epicatechin *Flavonol*: hyperoside	n. a.	A, S	Y	[107–109]
Humulus lupulus L.	*Terpenes bitter acids:* humulone and lupulone *Chalcone*: Xanthohumol *Alcohol:* 2-methyl-3-buten-2-ol	- Molecules with GABA-like activity - Modulation of ML_1 and 5-HT_6 receptors	S	Only in combination with other herbs	[110–115]
Laurus nobilis L.	*Phenylpropanoids:* eugenol and methyl eugenol *Monoterpenoid:* 1,8-cineole	n. a.	S	N	[116,117]
Lavandula angustifolia Mill.	*Monoterpenoids*: linalool and linalyl acetate	- Interaction with NMDA receptor - Inhibition of SERT - Inhibition of VOOCs	A, S	Y	[118–126]
Malva sylvestris L.	*Flavonoids:* malvin, malonylmalvin, alvidin, apigenin *Monoterpenoid:* linalool	n. a.	A, S	N	[127,128]
Matricaria chamomilla L.	*Flavonoid*: apigenin	- Ligand for the BZD receptors - Molecules with benzodiazepine-like activity - Inhibition of GluAD activity	A, S	Y	[129–135]
Melissa officinalis L.	*Phenols:* rosmarinic acid, oleanolic acid, and ursolic acid	- Inhibition of GABA transaminase	A	Y	[135–138]
Ocimum basilicum L.	*Monoterpenoid*: linalool *Phenylpropanoid:* eugenol *Phenylpropene*: methyl chavicol	n. a.	A, S	N	[139–141]
Papaver rhoeas L.	*Flavonol:* hyperoside	n. a.	A, S	N	[142,143]

Table 2. *Cont.*

Plants	Major Bioactive Compounds	Mechanism of Action	Actions	Clinical Evidence	References
Papaver somniferum L.	*Alkaloids:* morphine, codeine, noscapine, and tubocurarine	- Modulation of opioids μ-receptors	S	N	[144,145]
Rosmarisus officinalis L.	*Phenols: r*osmarinic acid, caffeic acid *Flavones:* cirsimaritin, salvigenin *Monoterpenoid:* 1,8 cineole *Diterpenoids*: carnosic acid, carnosol, and rosmanol, *Triterpenoid:* ursolic acid	- Inhibition of T-type calcium channels - Mediation of GABAA receptors	A, S	Y	[146,147]
Tilia platyphyllus Scop.	*Flavonoids*: quercetin, isoquercitrin, and rutin	- Molecules with GABA-like and benzodiazepine-like activity - Modulation of GABAergic and serotonergic systems	A, S	N	[148–150]
Valeriana officinalis L.	*Sesquiterpenes*: valerenic acid and valerenol *Valepotriates*	- Modulation of GABAA receptor - Modulation of serotonergic system	A, S	Y	[135,151–154]

Abbreviations: n. a. = not applicable; S = sedative; A = anxiolytic; Y = yes; N = no.

3.1. *Anthemis arvensis* L.

Corn chamomile (*Anthemis arvensis* L.) is an annual herbaceous plant native to Europe. It differs from common chamomile due to its receptacle being internally full. In folk medicine, it is also used as an anti-inflammatory, emetic, antispasmodic, and digestive [44,155,156].

The phytochemical profile of genus Anthemis is characterized by sesquiterpene lactones belonging to germacranolides, eudesmanolides, and guaianolides [157]. In particular, two known sesquiterpene lactones, antheindurolides A and B, together with five new related lactones (5-Hydroxy-5,6-dihydro-6,13-dehydro-antheindurolide A; 5-Acetoxy-5,6-dihydro-6,13-dehydro-antheindurolide A; 6-Hydroxy-5,6-dihydro-4,5-dehydro-antheindurolide A; Antheindurolide A-5,6-oxide; and 6-hydroperoxy-5,6-dihydro-4,5-dehydro-antheindurolide A) with the same unusual skeleton, have been isolated from the aerial parts of *Anthemis arvensis* [158].

Despite the fact this plant belongs to the group of the most cited species in the Italian folk medicine for its sedative effects, to the best of our knowledge there are no scientific works about pre-clinical and clinical trials of corn chamomile for the treatment of insomnia and anxiety. In-vitro and in-vivo studies are needed to clarify its common use as sedative and its mechanism of action.

3.2. *Clinopodium nepeta* L.

Lesser calamint (*Clinopodium nepeta* (L.) Kuntze subsp. *nepeta*) is an erect herbaceous perennial species, sometimes woody at the base, native to southern Europe. Lesser calamint

is widely used as flavor in soups and salads [159–161]. In folk phytotherapy, lesser calamint, due to its sedative effects, is used against diarrhoea, toothache, and as emollient [59,63,162].

Bozovic and Ragno (2017) reported in detail the different compositions of essential oils extracted from lesser calamint in different countries all over the world and in particular from different regions of Italy. In general, three types of oil can be extracted from lesser calamint. The first one and the most widespread contains pulegone as the major component, associated with a wide range of other compounds, such as menthone, isomenthone, menthol and its isomers, piperitenone, piperitone, and piperitenone oxides. The second type is characterized by the predominance of piperitone oxide and/or piperitenone oxide, while the third chemotype is characterized by the predominance of carvone and 1,8-cineole [163].

Despite its well-known antifungal and antioxidant activities, lesser calamint has also been widely used in folk medicine against insomnia, depression, convulsion, and cramps [163–165]. The main factor responsible for these activities seems to be compounds present in the essential oil, in particular pulegone, menthone, 1,8-cineole, and carvone [105,106]. It has been proved that carvone reduces locomotor activity in mice and potentiates pentobarbital-induced sleeping time [104]. However, so far there no clinical evidence has been presented of sedative and anxiolytic effects of lesser calamint.

3.3. Crataegus monogyna Jacq.

Hawthorn (*Crataegus monogyna* Jacq.) is a flowering thorny shrub or small tree, native to Europe, west Asia, and northwest Africa, nowadays widespread in north America and in other parts of the world. Slightly scented flowers have five white petals, numerous red stamens, and are grouped in dense corymbs. Leaves are deeply lobed. The fruit is a red berry-like pome containing a single seed. In folk phytotherapy, hawthorn as well as a sedative is commonly used as hypotensive and for cardiovascular diseases [43,63].

Scientific evidence has demonstrated that *Crataegus* species are a source of nutrients, nutraceuticals, and bioactive compounds [166]. A complete chemical and bioactive characterization of different parts of the *C. monogyna* showed that flowers have the highest tocopherols (159.84 mg/100g of dry weight) and ascorbic acid (408.37 mg/100 g dry weight) contents, and the best n-6/n-3 fatty acids ratio; over-ripened fruits showed the highest levels of carbohydrates (glucose, fructose, sucrose, and trehalose) and SFA (saturated fatty acids); and unripe fruits presented the highest polyunsaturated fatty acids (PUFA) contents with the best PUFA/SFA ratio, and the highest levels of flavonoids (436.34 $\pm$ 43.36 mg CE/g extract) and phenols (701.65 $\pm$ 16.57 mg GAE/g extract), and the most promising antioxidant properties [167]. The main bioactive compounds detected in hawthorn included epicatechin, hyperoside, rutin, vitexin, vitexin 2-O-rhamnoside, chlorogenic acid, hydroxycinnamic acid derivatives, proanthocyanidins, anthocyanins and triterpenes including betulinic, and oleanolic and ursolic acids [168,169].

Hawthorn extract has traditionally been used as herbal remedy in complementary and alternative medicine [170]. Nowadays, hawthorn preparations are mostly used for the treatment of angina, hypertension, arrhythmias, congestive heart failure, and hyperlipidemia [171,172]. Only a few publications have examined the effect of *C. monogyna* on CNS. Pulp and seed hawthorn extracts (at the dose range of 100–1000 mg/kg and 10–1000 mg/kg, respectively) showed analgesic activity in mice and decreased the exploratory behaviors in hole-board experiments and the spontaneous locomotor activities in activity cage tests, suggesting this plant may be appropriate to treat stress, anxiety, sleep disorders, and pain control [107]. A more recent study compared the effect of hawthorn and chlordiazepoxide on reducing anxiety of sixty female laboratory mice [108]. Animals were divided in 4 groups: control (no anxiety and no injection, n = 10); anxiety group (no injection, n = 10); chlordiazepoxide group (1.2 mg/kg of drug was injected intraperitoneal, n = 10); and treated group which received 50, 100, and 200 mg/kg of hawthorn extract intraperitoneal (n = 30). Anxiety was induced by dark boxes and then evaluated using plus evaluated maze. Results indicated that hawthorn extract reduces anxiety in

dose-dependent manner, and in particular 100 and 200 mg/kg doses can be proposed as a good replacement for chlordiazepoxide to reduce anxiety reflexes [108]. Very recently, a double-blind, placebo-controlled trial investigated the effect of hawthorn fruit extract on controlling the blood pressure in 60 patients with hypertension and sleep disorder. Data showed that after treatments, the intervention group had a significant improvement in systolic and diastolic blood pressure compared to placebo group; furthermore, results of the Pittsburgh questionnaire scores showed a significant decrease of sleep disorders severity in *C. monogyna* extract-treated group ($p = 0.001$) [109].

3.4. *Humulus lupulus* L.

Common hop (*Humulus lupulus* L.) is a dioecious, rhizomatous, perennial, herbaceous climbing plant, native to Europe, southwestern Asia, and North America. Leaves 3–5 are deeply lobed, and female flowers are grouped in cone-like structures. Young shoots are commonly used as ingredients in salads, soups, and omelettes [33,63,90]. Leaves are used for dysmenorrhea treatment [173], flower infusion as digestive, and to treat toothache [43].

The phytochemistry of *H. lupulus* is extensively reported in literature. Hops' essential oil is mainly composed of monoterpenes (with b-myrcene as the main representative, up to 57.9%) and sesquiterpenes (including α-humulene up to 51.2%, β-caryophyllene up to 14.7%, γ-elemene up to 14%, and β-selinene up to 10.5%) [174]. Akazawa, et al. (2012) reported some triterpenoids identified in hop' cones, including α-amyrin, β-amyrin, δ-amyrin, lupeol and ursa-9(11), and 12-dien-3b-ol [175]. Regarding the flavonoids and their derivatives, mostly present in seeds and bracts of female inflorescences, five groups have been determined in hops: chalcones (e.g., xanthohumol, desmethylxanthohumol), flavanones, flavonols (e.g., quercetin, kaempferol, morin, and myricetin), flavan-3-ols (e.g., catechin, epicatechin, and gallocatechin) and tannins, including some glycosides derivatives [174]. In hops, the most abundant hydroxycinnamic acids are caffeic acid, ferulic acid, and sinapic acid, while the main hydroxybenzoic acids are represented by gallic acid, syringic acid, and vanillic acid [176]. Phloroglucinol derivatives have also been found in hops, and they are mostly represented by numerous derivatives of humulone and lupulone, also known as bitter acids [174]. Bitter acids can be classified in two categories: α-acids (derived from humulone) and β-acids (derived from lupulone).

Zanoli, Rivasi, Zavatti, Brusiani and Baraldi (2005) investigated the effects of hops CO_2 extract and its fraction containing a-bitter acids on the central nervous system of rats [114]. Both extracts, orally administered, exerted a pentobarbital sleep-enhancing effect in a dose-dependent manner, starting from a minimal effective dose of 10 mg/kg. However, neither of two extracts affected the locomotor activity in the open field test or the anxious behavior of rats submitted to the elevated plus-maze test. This study suggested that the *H. lupulus* fraction containing α-acids can be considered as the major responsible for the enhanced pentobarbital effect.

Later, Schiller, Forster, Vonhoff, Hegger, Biller and Winterhoff (2006) obtained similar results using ethanolic and CO_2 extracts of *H. lupulus* at higher dosage (100 and 200 mg/kg) to test their sedative effects following oral application in mice [115]. In particular, they attributed the sedative activity to three categories of constituents of lipophilic hops extracts; α-bitter acids proved to the be most active constituents, followed by β-bitter acids and hop oil extract. It has been reported that the sedative activity of hops also depends on xanthohumol and 2-methyl-3-buten-2-ol [112,113].

Another experiment conducted on female young adult quails underlined an evident decline in motor activity after 14 days administration of hops dry extract at doses 3.80, 7.60, and 41.80 mg/kg body weight [177].

The mechanism of action for the neuropharmacological effects of hops dried extracts can be explained by the presence of molecules GABA-like activity and by the interaction of some hop's compounds with melatonin and serotonin receptors (ML_1 and 5-HT_6; IC_{50} 71 μg/mL and 21 μg/mL, respectively) [110,111].

Up to now, studies regarding the clinical evidence of hops as anxiolytic and sleep-promoting herbs have been conducted only using mixture of hops and other herbal products, such as valerian and rosemary [178–180]. There is still a lack of knowledge regarding the clinical evidence of the real effectiveness of hops in the treatment of sleep and mental disorders. However, the conclusions of Committee on Herbal Medicinal Products (HMPC) on the use of the hop strobile medicines for relief of mental stress and to aid sleep are based on their 'traditional use' [181]. This means that, although there is insufficient evidence from clinical trials, the effectiveness of these herbal medicines is plausible and there is evidence that they have been used safely in this way for at least 30 years (including at least 15 years within the EU) [181].

3.5. *Laurus nobilis* L.

Bay laurel (*Laurus nobilis* L.) is an aromatic broadleaf evergreen tree or large shrub native to the Northern Africa, western Asia, and southern Europe. Leaves are coriaceous with revolute, entire margins. Both male and female flowers are bright yellow-green and grouped on short racemes. Bay laurel is traditionally used to season many dishes [81,159,182]. Leaves and fruits decoctions are used orally or topically to treat a wide range of diseases, mainly for gastrointestinal and respiratory ailments [54,65,183].

A recent study reported 1,8-cineole (33.3%) as the main component of bay fruits essential oil from Bulgaria, followed by α-terpinyl acetate (10.3%), α-pinene (11.0%), β-elemene (7.5%), sabinene (6.3%), β-phellandrene (5.2%), bornyl acetate (4.4%), and camphene (4.3%), while the main constituents of bay leaves essential oil were reported to be 1,8-cineole (41.0%), α-terpinyl acetate (14.4%), sabinene (8.8%), methyl eugenol (6.0%), β-linalool (4.9%), eugenol (4.8%), and α-terpineol (3.1%) [184]. A comparison study reported that major compounds of *L. nobilis* leaves were 1, 8-cineole (57.05, 58.45, and 65.99%), α-pinene (3.00, 6.03, and 2.14), β-pinene (2.88, 4.17, and 2.51%), sabinene (9.74, 6.10, and 4.06%), and limonene (2.33, 2.50, and 1.18%) in the seacoast, the mountains, and the plains are of Lebanon, respectively [185].

Various biological and pharmacological properties have been reported for bay leaves such as antibacterial, antifungal, antioxidant, insecticidal, and nematicidal activities [186].

Sayyah, Valizadeh and Kamalinejad (2002) evaluated the anticonvulsant activity of bay leaves essential oil, and they reported a sedation effect and motor impairment in mice from dose of 0.75 mL/kg, reducing the time spent on rotarod and reaching the highest effect at dose of 1 mL/kg (endurance time on rotarod = 0 s) [117]. In this study, they obtained the LD_{50} value of the essential oil at 1.45 (1.22–1.71) ml/kg. Later, the same group evaluated also the analgesic and anti-inflammatory activity of bay leaves essential oil and, in this study, they reported slightly different doses for the sedative effect of *L. nobilis* (0.125 mL/kg and 0.5 mL/kg of essential oil produced moderate and severe sedation respectively) [187]. These effects may be due to the presence of eugenol and methyl eugenol with their related pharmacological activities [188]. However, it has been reported that these compounds are able to cause cytotoxicity [189]. Furthermore, it has been demonstrated that another important component of essential oil 1,8-cineole at dose 400 mg/kg potentiates (2–6 fold increase) the pentobarbital sleeping time in mice [116]. Despite the pre-clinical studies on *L. nobilis* previously cited, it seems that there is a lack of studies with clinical evidence about the sedative and anxiolytic effects of bay laurel.

3.6. *Lavandula angustifolia Mill.*

Lavender (*Lavandula angustifolia* Mill.) is a strongly aromatic, evergreen dwarf shrub native to the Mediterranean basin. Its leaves, clustered on leafy shoots, are linear to lanceolate-linear and densely gray stellate tomentose. Its pinkish-purple flowers are produced on spikes at the top of slender stems. In folk medicine, lavender is also used for the treatment of gastro-intestinal, urinary, and respiratory diseases and against headache [31,77,87].

L. angustifolia essential oil isolated from fresh inflorescences and analyzed by GC-MS had as its main components linalyl acetate (47.56%), linalool (28.06%), lavandulyl acetate (4.34%), α-terpineol (3.75%), geranyl acetate (1.94%), caryophyllene oxide (1.38%), and 1,8-cineole (1.14%) [190]. Other minor components identified in the oil were β-caryophyllene (0.93%), borneol (0.85%), epi-α-cadinol (0.70%), nerol (0.59%), terpinen-4-ol (0.56%), β-myrcene (0.55%), limonene (0.55%), and 1-octen-3-ol (0.53%) [190]. However, quantitative and qualitative results might change depending on several factors, as indicated by Da Porto, et al. (2009), who compared three different extraction methods: supercritical carbon dioxide extraction, ultrasound extraction, and conventional hydro-distillation extraction [191]. Authors found that the best methodology, in terms of number of isolated compounds, flavor quality, and stability, were those obtained with supercritical CO_2.

Nowadays, lavender essential oil and its major components linalool and linalyl acetate are used in aromatherapy. The sedative properties of lavender essential oil and its main constituents, linalool (37.3%) and linalyl acetate (41.6%), were investigated by Buchbauer, Jirovetz, Jager, Dietrich and Plank (1991) in mice after inhalative absorption. After 6–8 weeks, a clear decrease of the motility of young mice was found after inhalation. In detail, after 30, 60, and 90 min of inhalative exposure, the motor activity decreases to: 22%, 0%, and 0% for lavender oil; 32%, 8%, and 0% for linalool; and 42%, 11%, and 0% for linalyl acetate [121]. Results of more recent studies confirmed the anxiolytic and sedative activity of lavender [122,123]. A chronic exposure to lavender essential oils (daily, for 7 continuous days) significantly reduced anxiety-like behavior and inhibited depression in elevated plus-maze and forced swimming tests, suggesting both anxiolytic and antidepressant activity [192]. Lavender oil (0.1–1.0 mL exposure for 30 min and 60 min) exhibited anxiolytic properties similar to those of chlordiazepoxide (10 mg/kg i.p.), used as a reference anxiolytic with well-known effects on open-field behavior [123].

Inhalation of lavender essential oil increased the immobility of over-agitated mice artificially induced by intraperitoneal injection of caffeine [193].

Not only the lavender essential oil has been investigated for its hypnotic-sedative effects. Alnamer, Alaoui, Bouidida, Benjouad and Cherrah (2011) found that the methanolic extract of stems and flowers of lavender produced significant sedative effect in mice at doses of 200, 400, and 600 mg/kg (by oral route), compared to reference substance diazepam, and a hypnotic effect at doses of 800 and 1000 mg/kg [125]. More recently, another study conducted by Ghadim, Neisy, Sisakht and Khoshdel (2020) showed the anxiolytic and antidepressant-like properties of lavender flower aqueous extract in chronic mild stress model of rats [124].

There is clinical evidence that Lavandula oil preparation has significant beneficial influence on quality and duration of sleep and alleviates anxiety disorders. Kasper, Gastpar, Muller, Volz, Moller, Dienel and Schlafke (2010) investigated the anxiolytic efficacy of lavender oil in capsule preparation, called silexan, on 221 adults suffering from anxiety disorder [126]. Patients were randomized in a double-blind, placebo-controlled trial and received 80 mg/day of orally administered preparation from Lavandula species or placebo for 10 weeks. The HAMA (Hamilton Anxiety Scale) score and the PSQI (Pittsburgh Sleep Quality Index) were acquired, and both total scores decreased between baseline and week 10. Patients treated with silexan showed a total score decrease of 59.3% for the HAMA and of 44.7% for the PSQI compared to 35.4% and 30.9% in the placebo group ($p < 0.01$) [126]. Similar results were obtained in another double-blind, randomized study of 6-week-intake of silexan compared to lorazepam [194]. Bradley, et al. (2009) investigated the effect of orally administered lavender capsules (containing sunflower oil and 100 or 200 µL of organic *Lavandula angustifolia* oil) on responses to anxiety-provoking film clips (low anxiety). Compared to the placebo group, which received capsules with sunflower oil only, a 200 µL dose caused a greater reduction of self-reported state anxiety, heart rate, and galvanic skin response from baseline [195].

Regarding the use of lavender for insomnia, a clinical trial on 64 patients (male and female) with ischemic heart disease showed that aromatherapy with lavender oil significantly

improved the mean scores of sleep quality compared to control group ($p < 0.001$) [196]. Lavender aromatherapy has been tested also in sixty-seven midlife women with insomnia [197]. Data revealed that women, after receiving aromatherapy, experienced a significant improvement in sleep quality up to 1 week after the end of the intervention. However, lavender aromatherapy does not appear to confer benefits on HRV (heart rate variability) in the long-term follow-up [197]. Similar results were previously obtained by Lewith, et al. (2005) in a pilot study based on ten volunteers [198].

Very little research has been done on the mechanisms of action of lavender on CNS. Schuwald, Noldner, Wilmes, Klugbauer, Leuner and Muller (2013) studied the effect of lavender aromatherapy as potent anxiolytic and its molecular mechanism [120]. Authors found that lavender oil, at nanomolar concentrations, inhibits voltage-dependent calcium channels (VOCCs) in murine synaptosomes and primary hippocampal neurons. They also found that, compared to pregabalin, which is an established anxiolytic, lavender oil does not interact with the binding site of pregabalin—the a2d subunit of VOCCs—but unselectively reduces the calcium influx through several different types of VOCCs such as N-type and P/Q-type [120]. Lopez, Nielsen, Solas, Ramirez and Jager (2017) studied the effects of lavender essential oil and its isolated monoterpenes (linalool, linalyl acetate) on different pharmacological targets, such as MAO-A (monoamine oxidases A), serotonin transporter (SERT), $GABA_{A,}$ and NMDA (*N*-methyl-D-aspartate) receptors, involved in anxiolytic and antidepressant properties [119]. Results indicated that lavender essential oil and its main components exert affinity for the glutamate NMDA-receptor in a dose-dependent manner with an IC_{50} value of 0.04 µL/mL for lavender oil. In addition, lavender and linalool were able to inhibit the serotonin transporter, whereas they did not show inhibition of MAO-A and did not show affinity for $GABA_A$-benzodiazepine receptor. This result is in agreement with a previous study conducted by Chioca, Ferro, Baretta, Oliveira, Silva, Ferreira, Losso and Andreatini (2013), who found that lavender essential oil did not alter [^{3}H] flunitrazepam binding to the benzodiazepine site on the $GABA_A$ receptor, but its anxiolytic-like effect is related to serotonergic neurotransmission, likely mediated by $5\text{-}HT_{1A}$ receptors [118].

3.7. *Malva sylvestris* L.

Common mallow (*Malva sylvestris* L.) is an annual or perennial herb native to Europe, northern Africa, and southwestern Asia and is widespread almost throughout the world. Rough-hairy leaves are deeply 3–7 lobed. The bright rose-purple flowers bloom singly or in 3–5 flowered axillary clusters. In the folk medicine, common mallow has a variety of uses due to its important therapeutic properties [87,199].

Different parts of *Malva sylvestris* (leaves, flowers, immature fruits, and leafy flowered stems) were compared for their chemical composition [200]. Leaves methanolic extract revealed the highest content of phenolics (386.45 mg/g of extract), flavonoids (210.81 mg/g), and carotenoids (0.19 mg/g), while the flowers revealed the highest amount of ascorbic acid (1.11 mg/g of extract). Authors quantified α,β,γ,δ-tocopherols that reached the highest level in the leaves. Regarding the fatty acids fraction, the major compounds found in all samples were linolenic, linoleic, and palmitic acid [200]. The major flavonoids identified in mallow leaves are gossypin and hypolaetin 3′-sulphate, whereas flowers have as major flavonoids malvin, malonylmalvin, oenin, malvidin, delphinidin, genistein, myricetin, apigenin derivatives, quercetin, kaempferol, 5,7-dimeth-oxycoumarin, and scopoletin [201–204]. Terpenoids identified from fresh leaves were linalool, 3,7,11,15-tetramethylhexadeca-1,6,10-trien-3,8,14,15-tetraol, and blumenol A [205].

Very little research has been done on pre-clinical evidence of sedative and anxiolytic properties of *Malva sylvestris*. Rezaei, Pashazadeh, Alizadeh, Mirzazadeh and Javanian (2013) found that the doses of 450 mg/kg body weight of mallow's extract exerted better sedation and anti-anxiety effects in Wistar rats than diazepam ($p < 0.01$) [128]. Modaresi and Lohrasbi (2017) investigated the effects of hydroalcoholic mallow's extract on reducing dark anxiety in forty mice divided into five groups: control (received only physiological

serum injections); dark anxiety (experienced anxiety by being in dark boxes); and 50, 100, and 200 mg/kg doses of the mallow's extract [127]. Data indicated that 100 and 200 mg/kg of mallow extract could reduce the anxiety in a dose-dependent way.

To the best of our knowledge, so far there is no clinical evidence of sedative and anxiolytic effects of common mallow.

3.8. Matricaria chamomilla L.

Chamomile (*Matricaria chamomilla* L.) is an annual herbaceous plant native to South-West Asia and South-Eastern Europe and nowadays widely naturalized on all continents. Flowerheads, called capitula, have white ligulate peripheral flowers (ray flowers) and yellow tubulose flowers in the central disc. They have a conical receptacle and are internally hollow. Leaves are bi-or tripinnate with lanceolate shape reduced to linear laciniae. In folk phytotherapy, the plant parts used to prepare infusions are inflorescences.

Chamomile flowers contain a large group of biologically active molecules, and more than 120 metabolites have been identified belonging to different classes of compounds such as amino acids, carbohydrates, flavonoids, coumarins, vitamins, and fatty acids [206]. The essential oil extracted from *M. chamomilla* flowers is mainly composed of sesquiterpenes and their derivatives, including β-farnesene (29.8%), α-farnesene (9.3%), α-bisabolol and its oxide (15.7%), chamazulene (6.4%), germacrene D (6.2%), and spiroether (5.6%) [207]. The chamomile's phenolic fraction is most commonly analyzed by liquid chromatography and it contains coumarins (herniarin and umbelliferone), phenylpropanoids (chlorogenic acid and caffeic acid), flavones (apigenin, luteolin, and their glucoside), flavonols (quercetin and rutin), and flavanone (naringenin) [208].

Besides its sedative effects, chamomile is among the most commonly used herbal remedies for dysmenorrhea disorders [173,209,210] and as spasmolytic and carminative [211,212]. The hydro-alcoholic extracts of *M. chamomilla* inflorescences not only have sedative and antispasmodic effects but also antioxidant, hypoglycaemic, and anticancer activities [134,213–215]. There is still a lack of knowledge regarding the mechanisms of action of chamomile flowers extracts used as alternative or complementary remedies for anxiety and insomnia. So far, reports have been in some cases controversial. The anxiolytic effects of chamomile may be attributed to the flavonoid apigenin, which is a ligand for central BZD receptors [131]. This flavonoid competitively inhibited the binding of flunitrazepam with a K_i of 4 μM but had no effect on muscarinic receptors, α1-adrenoceptors, or on the binding of muscimol to $GABA_A$ receptors, suggesting its use as anxiolytic and sedative but not as anticonvulsant or myorelaxant [133]. However, in contrast with previous reports, the study presented by Avallone, Zanoli, Puia, Kleinschnitz, Schreier and Baraldi (2000) showed that the sedative effect of apigenin is not mediated by BZD receptors since the affinity between them is very low. In addition, electrophysiological studies performed on cultured cerebellar granule cells showed that apigenin reduced GABA-activated Cl^- currents, suggesting that the sedative effect of *M. chamomilla* extracts can be ascribed to other compounds with BZD-like activity [134,216]. Similar finding were presented by Zanoli, Avallone and Baraldi (2000), who investigated the sedative and anxiolytic activities of apigenin contained in chamomile [132]. However, in this study apigenin failed to exert anxiolytic activity, it reduced locomotor behavior when injected in rats with a minimal effective dose of 25 mg/kg. Later, Awad, Levac, Cybulska, Merali, Trudeau and Arnason (2007) performed in vitro assay on rat brain homogenate to determine whether anxiolytic plants (such as *M. chamomilla, Centella asiatica, Eschscholtzia californica, Humulus lupulus, Hypericum perforatum, Melissa officinalis, Passiflora incarnata, Piper methysticum, Scutellaria lateriflora,* and *Valeriana officinalis*) interact with GluAD or GABA-T, consequently altering the level of GABA in the brain [135]. Results showed that *M. officinalis* extract exhibited the greatest inhibition of GABA-T activity (IC_{50} = 0.35 mg/mL), while *C. asiatica* and *V. officinalis* extracts (1 mg/mL) stimulated GluAD activity by over 40%. In contrast, chamomile and hops extracts showed significant inhibition of GluAD activity (0.11–0.65 mg/mL), suggesting that the anxiolytic effect of *M. chamomilla* likely does not involve GABA metabolism. Few

studies have been reported on controlled clinical trials of chamomile's anxiolytic efficacy. The first randomized, double-blind study was conducted for 8 weeks on 61 patients with mild to moderate generalized anxiety disorder [129]. Authors observed a reduction in mean of total HAMA (Hamilton Anxiety Rating) score during chamomile versus placebo therapy ($p = 0.047$), suggesting a modest anxiolytic activity of *M. chamomilla*. A few years later, the same research group evaluated long-term chamomile use for prevention of GAD symptom relapse on 179 patients enrolled in this study between March 2010 and June 2015. Data showed that the mean time to relapse was 11.4 ± 8.4 weeks for chamomile and 6.3 ± 3.9 weeks for placebo, and chamomile participants maintained significantly lower GAD symptoms than placebo ($p = 0.0032$) [130]. There is a need to continue in vitro, pre-clinical, and clinical trials in order to clarify the mechanisms of action of chamomile flowers extract for the treatment of anxiety and insomnia.

3.9. Melissa officinalis L.

Lemon balm (*Melissa officinalis* L.) is a perennial herbaceous plant native to central Europe, the Mediterranean Basin, and Central Asia that is now naturalized in the Americas and elsewhere [217]. Its flowers are white, with double-lipped corolla, and its leaves are wrinkled, ovate, and lemon-scented. Its leaves and flowers are eaten raw in salads or used for flavoring meat [71,218]. In folk phytotherapy, lemon balm is also used for gynaecological disorders [42], as digestive [219], lenitive [44], for wound healing [220], and as blood depurative and memory booster [33].

The chemical composition of lemon balm has been extensively studied, and the main constituents are reported to be hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acid and chlorogenic acid, tannins, flavonoids (including luteolin, luteolin 7-O-beta-D-glucopyranoside, luteolin 3-O-beta-D-glucuronopyranoside, and apigenin 7-O-beta-D-glucopyranoside) sesquiterpenes (including β-caryophyllene and germacrene), triterpenes, and volatile oils [221]. The main components of volatile oil (0.5–0.1% of the plant by weight) are citronellal, geranial, and neral, followed by methyl citronellate, ocimene, citronellol, geraniol, nerol, β-caryophyllene, β-caryophyllene oxide, and linalool [222–225]. The chemical composition of flower oil has also been studied, and trans-carveol (28.89%) is the major component, followed by citronellol (25.24%), δ-3-carene (5.26%), citronellal (4.9%), geraniol (2.2%), 1-octene-3-ol (2.03%), and spathulenol (2.06%) [226].

Numerous pharmacological activities have been associated with lemon balm for its anti-viral and anti-HIV effects; antioxidant, anti-inflammatory, and antimicrobial activity; anticancer and anti-tumour effects; and anxiolytic and antidepressant effects, and it is also used in the treatment of patients with Alzheimer's and cardiovascular diseases and to improve memory and concentration [221]. No side effects have been reported so far [138].

Although the mechanisms of action of lemon balm are poorly understood, it has been shown that the active components extracted from leaves are mainly flavonoids, terpenoids, and phenolic compounds. Clinical evidence of the effects on cognition, mood, and stress of *M. officinalis* extract have been reported in the literature.

In a survey of ten anxiolytic botanicals, the extract of *M. officinalis* was found to be the best inhibitor of GABA transaminase, one of the enzyme targets in the therapy of anxiety [135]. The inhibition of GABA-T increases the availability of GABA in CNS. To explore the mechanism of action of the anxiolytic herb *Melissa officinalis* L. in more detail, Awad, Muhammad, Durst, Trudeau and Arnason (2009) performed a bioassay-guided fractionation of the dried leaves using in vitro measure of GABA-T activity [136]. The methanol extract showed the greatest inhibition against GABA-T, followed by water extract, ethyl acetate extract, and hexane extract. Therefore, the methanol extract was chosen for further phytochemical characterization by HPLC-DAD and LC-MS. Rosmarinic acid, ursolic acid, and oleanolic acid were identified as active principles. In particular, in vitro assays of standard compounds showed that rosmarinic acid was the main responsible of GABA-T inhibition (40% inhibition at 100 μg/mL), followed by oleanolic acid (20% inhibition at 10 μg/mL) and ursolic acid (20% inhibition at 100 μg/mL) [136], suggesting

further analysis such as animal studies are necessary to confirm the GABA-T inhibition by *M. officinalis* extract. Based on this finding, Ibarra, et al. (2010) evaluated the reduction of anxiety-like reactivity in mice treated for 15 consecutive days with *M. officinalis* under stressful situations (e.g., the elevated plus maze and the open field task) [227]. They demonstrated that the plant extract (240 mg/kg and 360 mg/kg) has anxiolytic-like effects under moderate stress conditions (elevated plus maze).

In a double-blind, placebo-controlled, randomized experiment, 18 healthy volunteers received two separate single doses of *M. officinalis* extract (300 mg and 600 mg) and a placebo, on separate days separated by a 7-day washout period [137]. The 600 mg dose was associated both with significantly improved calmness and significantly decreased alertness in comparison to placebo during the post-dose completion of the defined intensity stressor simulation (DISS) battery. Another study demonstrated that chronic administration of *Melissa officinalis* L. (600 mg of Cyracos, Naturex, SA, France) in 20 healthy volunteers affected by mild-to-moderate anxiety disorders and sleep disturbances improves anxiety-associated symptoms, including emotional instability, intellectual disturbance, psychosomatic symptoms, and speech problems [138].

3.10. Ocimum basilicum L.

Basil (*Ocimum basilicum* L.) is an herbaceous annual plant native to Asia. The scented leaves are opposite to entire or toothed margins. Flowers with a white bilabiate corolla. Usually used as condiment, basil decoction is also used as digestive, carminative, and to treat headaches [59,82,85].

Ocimum basilicum is rich in essential oils; a total of 36 metabolites were identified by GC-MS analysis, and among them, linalool (69.87%) was the major constituent, followed by geraniol (9.75%), p-allylanisole (6.02%), 1,8-cineole (4.90%), trans-α-bergamotene (2.36%), and neryl acetate (1.24%) [228]. Other compounds detected in the essential oil were estragole, sesquiterpene hydrocarbons, oxygenated monoterpenes, phenylpropanoids, linoleic acid, methyl eugenol, and α-cadinol [229,230]. However, the amount and the composition of essential oil might change depending on several factors such as varieties, country, age of plants, etc. [231,232]. The aqueous extract of leaves showed high content of polyphenols (146.31 μg/mg) and flavonoids (28.63 μg/mg); in particular, UPLC-ESI-MS/MS analysis revealed that the major flavonoid was apigenin-O-glucoside (7.53%), followed by luteolin (5.94%), while rosmarinic acid was the major polyphenol (15.76%), followed by caftaric acid (9.39%) [233].

Several pharmacological activities and therapeutic applications of *O. basilicum* have been documented. Its well-established properties include analgesic, anti-inflammatory, antioxidant, antimicrobial, hypoglycaemic, hepatoprotective, hypolipidemic, antiulcerative, hypotensive, immunomodulatory, neuroprotective, anti-convulsant, chemo preventative, chemo modulatory, and anti-cancer [231].

Moreover, several studies established the sedative and anxiolytic effect of this plant. An experiment conducted on 72 mice showed that intraperitoneal injection of hydro-alcoholic extract increased the duration of pentobarbital-induced sleep at doses of 25 and 50 mg/kg; the hypnotic effect of this leaf extract was comparable to that induced by diazepam in the positive control group [234]. Among the different fractions of hydro-alcoholic leaf extract (water fraction, ethyl-acetate fraction, and n-butanol fraction), authors found n-butanol fraction to be mainly responsible for the hypnotic effect of *O. basilicum*, suggesting that non-polar metabolites, such as linalool and eugenol, may play an important role in sedative-hypnotic effects of this plant [139].

Similar results were obtained by Rabbani, Sajjadi and Vaezi (2015), who tested intraperitoneal injections of both hydro-alcoholic extract and the essential oil of *O. basilicum* in mice by utilizing an elevated plus maze and locomotor activity meter [140]. Their study showed that the anxiolytic and sedative effects of essential oil were higher in comparison to the whole plant extract at the same doses (200 mg/kg). According to their GC-MS analysis,

the main components of the essential oil were methyl chavicol (42.8%), geranial (13.0%), neral (12.2%), and β-caryophyllene (7.2%).

More recently, the sedative effect released by the essential oil and headspace air of basil was tested in mice using inhalation as administration route [141]. Data indicated that direct inhalation of the headspace air from the hydronic chamber containing nine plants resulted in a 45.4% decrease in mouse activity versus the 47.1% decrease observed with the administration of basil essential oil via the inhalation route at a dose of 4.0×10^{-3} mg per cage. The GC-MS analysis of the essential oil extracted from basil revealed eugenol (44.5%), linalool (21.2%), methyl eugenol (10.0%), eucalyptol (6.7%), and α-bergamotene (3.9%) as main components [141].

The essential oil acute toxicity of basil was investigated by [235]. Results revealed no signs of toxicity or mortality under 250 mg/kg. The LD_{50} was 532 mg/kg and may be related to the higher content of linalool as reported in literature [236].

To the best of our knowledge, so far there are no clinical evidence of sedative and anxiolytic effects of basil.

3.11. Papaver rhoeas L.

Corn poppy (*Papaver rhoeas* L.) is a cosmopolitan annual herbaceous weed. This species has been associated with agriculture in the Old World since early times, and its diffusion is linked to the cultivation of cereals [237]. It has solitary flowers with four red petals that often have a black-purple dot at the base of each one, emerging from drooping hairy buds. Basal leaves form a rosette of pinnatipartite leaves with 7–9 lanceolate or elliptic segments and serrate or dentate margins, while apical leaves are smaller but more dissected [238]. The fruit is an egg-shaped, hairless capsule. Stem and fruit exude a white to yellowish latex when cut.

Various phytochemical components have been identified in corn poppy petals (e.g., alkaloids, flavonoids, vitamins, anthocyanins, and essential oils). The main class of compounds of *P. rhoeas* is represented by alkaloids, including rhoeadine, isorhoeadine, allocryptopine, coulteropine, berberine, epiberberine, coptisine, sinactine, isocorydine, roemerine, rhoeagenine, isorhoeagenine, sanguinarine, mecambrine, salutaridine, glaucamine, epiglaucamine, glaudine, stylopine, and canadine [239,240]. The flavonoids kaempferol, quercetin, hypolaetin, and luteolin, along with the flavonoid glycosides isoquercitrin, astragaline, and hyperoside, were isolated from the methanol petals extract by Hillenbrand, Zapp and Becker (2004), who also identified two new depsides, 2-O-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxyphenylacetic acid and 2-O-(4-hydroxybenzoyl)- 2,4,6-trihydroxyphenylacetic acid, along with p-hydroxybenzoic acid and its methyl ester, protocatechuic acid, 2-(4-hydroxyphenyl)- ethanol, 2-(3,4-dihydroxyphenyl)-ethanol [142]. Corn poppy is a good source of vitamins, including ascorbic acid, dehydroascorbic acid, tocopherols, and tocotrienols [241]. The essential oil of *P. rhoeas* aerial parts has been investigated using GC-MS by [242]. Authors identified, in total, twenty-one constituents, and among them sesquiterpenes were shown to be the main group. *P. rhoeas* petals are rich in anthocyanins responsible for the red color of poppy. The most represented anthocyanins in the extracts of *Papaver rhoeas* L. were found to be delphinidin-3-O-glucoside, cyanidin-3-O-glucoside, cyanidin-3-O-rutinoside, peonidin-3-O-glucoside, petunidin-3-O-glucoside, petunidin-3-acetylglucoside, and delphinidin-3-p-coumaroylglucoside [243].

In recent past decades, the biological activity of this plant has been widely studied to elucidate its use for pharmacological purposes. Different parts of the plant (roots, stems, leaves, and petals) exhibited several biological activities, including antidepressant, antimicrobial, antioxidant, antiulcerogenic, and cytotoxic [143]. Behavioral and pharmacological studies showed that hydro-alcoholic extracts of poppy petals reduced locomotory, exploratory, and postural behavior of mice at 100 mg/kg dose, while sedative effect was obtained at 400 mg/kg dosage [244]. Toxicological analysis on mice revealed that the toxic effects of hydroalcoholic extracts of *P. rhoeas* are observed from a dose of 2000 mg/kg with an LD_{50} situated approximately at 4000 mg/kg [244]. The effect of poppy hydro-

alcoholic extract on the reduction of acute stress induced by electro foot shock in mice was also evaluated [245]. Different doses of the plant extracts (15–60 mg/kg) were injected intraperitoneally in the treated group 30 min before the stress. Results indicated that stress increased corticosterone level in both control group (saline injections) and treated group. However, in a later study, *P. rhoeas* alcoholic extract reduced anxiety levels without increasing corticosterone levels in male rats after intraperitoneal injections at 100, 200, and 400 mg/kg [246]. This controversial results may be due to the higher doses that Hosseini, Hamzavi and Aghababa (2015) administered to rats during the experiment. Regarding the clinical evidence, so far no studies have been conducted on the sedative and anxiolytic effects of corn poppy.

3.12. Papaver somniferum L.

The opium poppy (*Papaver somniferum* L.) is an annual herb probably native to Asia Minor or the Western Mediterranean region; nowadays, it is widely cultivated in many parts of the world with temperate climates [237]. Its aerial parts are glaucous, leaves are lobed, the upper stem clasping the stem. Its large flowers are white, pinkish or violet, and its fruit is a capsule. All parts of the plant exude latex when wounded. The latex was named *opion* by the ancient Greeks, derived from *opos* (meaning juice); later opium became its name. The ancient Greeks associated various divinities with opium (e.g., Hypnos, Morpheus, Nyx, and Thanatos), due to its soporific and sedative activities [247].

The most important secondary metabolites of opium are benzylisoquinoline alkaloids (BIAs); among them, morphine has the most prominent effect on CNS [145]. The alkaloids are synthesized, stored, and metabolized in the latex but they can be found in other parts of the plant. Other important BIAs with related pharmacological activity are codeine (narcotic analgesics), papaverine (vasodilator), noscapine (cough suppressant and potential anticancer), sanguinarine (antimicrobial), and tubocurarine (muscle relaxant) [144].

High amount of tocopherol was detected in poppy seeds, in the study of Özcan and Atalay (2006); b-tocopherol is the main representative, followed by a-tocopherol and Δ-tocopherol, and the total tocopherol contents range from 348.76 ppm to 623.14 ppm. Poppy seeds contain up to 50% oil, and authors identified as main fatty acids linolenic, oleic, palmitic, stearic, and linoleic acids [248].

Different parts of the plant, seeds, fruits, and latex are used for their nutritional and pharmacological properties. The opium poppy is used as diuretic or against toothaches in traditional medicine [53,85]. In popular phytotherapy of the Campidano Valley of Cagliari and the Urzulei district (Italy) fruits, infusions of *P. somniferum* are traditionally used as general and cough sedative [53].

3.13. Rosmarinus officinalis L.

Rosemary (*Rosmarinus officinalis* L.) is an evergreen shrub native to the Mediterranean region and naturalized throughout much of Europe. The linear leaves resemble small, curved pine needles and are fragrant when crushed. Bluish flowers are borne in axillary clusters. Leaves are used to flavor baked potatoes or meat dishes [89].

Rosemary is traditionally used in folk medicine as a galactagogue or to treat renal colic and dysmenorrhea, mood and nervous system disorders, and physical and mental fatigue [173,249]. It is also used to relieve symptoms caused by respiratory disorders and to counteract hypercholesterolaemia [59,82,83].

Maceration, hydrodistillation, distillation, and Soxhlet by supercritical fluid extraction are the most used methods to extract bioactive compounds from *R. officinalis* [250]. The major compounds found in rosemary extract include carnosic acid, carnosol, and rosmarinic acid, while the main constituents of rosemary essential oil are camphor (5.0–21%), 1,8-cineole (15–55%), α-pinene (9.0–26%), borneol (1.5–5.0%), camphene (2.5–12%), β-pinene (2.0–9.0%), and limonene (1.5–5.0%) [250]. Other important bioactive components are ursolic acid, betulinic acid, apigenin, diosmin, luteolin, chlorogenic acid, epirosmanol, and oleanolic acid [250].

Rosemary has been found to have several biological activities, such as antioxidant, anti-inflammatory, antimicrobial, and anti-cancer properties, as well as being useful for anxiety, stress, and memory [251]. Rosemary extract is often used in aromatherapy to treat anxiety-related conditions and increase alertness [252,253].

Rosemary leaf infusion (2 g into 100 mL of hot water) has been evaluated on adult male mice to test its effect on anxiety/fear, depression-like behavior, memory/learning, and cerebral and liver cholinesterase [254]. Authors, using LC-MS analysis, identified 16 compounds in rosemary tea, with rosmarinic acid, caffeic acid, and 7-O-glucuronide as major components. Data of behavioral tests revealed that daily oral administration of rosemary to adult mice significantly reduced both the anxiety ($p < 0.05$), the depression-like behavior ($p < 0.05$), and the cholinesterase isoforms activity ($p < 0.05$), while memory/learning was unaffected [254]. Noori Ahmad Abadi, et al. (2016) evaluated the effect of the hydroalcoholic extract of *R. officinalis* L. on anxiety in 50 mice randomly divided into five groups (the control group received normal saline; the positive control group received 1 mg/kg diazepam; and the experimental groups received doses of 100, 200, and 400 mg/kg body weight of rosemary extract) [255]. Results of the elevated plus maze test showed that rosemary extract dose-dependently increases the mice spending time and the entries number of mice in plus maze open arms (indicating less stress), and that the dose of 400 mg/kg was similar to diazepam [255]. In another study, authors performed fractionation and purification of salvigenin, rosmanol, cirsimaritin, ursolic acid, carnosol, hesperidin, and nepitrin from the dried plant of *R. officinalis* obtained from commercial retailer [147]. Authors investigated the effects of these non-volatile components of rosemary on CNS function, and they found that at dose 10–100 mg/kg, rosmanol, cirsimaritin, and salvigenin elicited anxiolytic effect on mice in both elevated plus maze and light/dark tests. Moreover, since the anxiolytic activity was not ameliorated by flumazenil but was inhibited by pentylenetetrazol, authors suggested that a possible mechanism of action is likely to be mediated via $GABA_A$ receptors at a site other than the high affinity benzodiazepine binding site [147].

No liver toxicity was found in rats after one month administration of rosemary water extract at doses of 100, 200, and 500 mg/kg body weight [256]. However, the HMPC published a very detailed report on safety and toxicological data of different rosemary extracts [257].

In a clinical study, inhalation of rosemary and lavender essential oil sachets reduced anxiety, and, in particular, rosemary increased focus and concentration and promoted a sense of clarity [258]. Solhi, et al. (2013) demonstrated the effectiveness of rosemary in the improvement of sleep and reduction of insomnia in a clinical trial of 81 patients with opium withdrawal syndrome divided into control group (treated with methadone and placebo for 4 weeks) and case group (treated with methadone and rosemary capsules filled with 300 mg of dried powdered leaves) [259].

Another double-blinded randomized controlled trial was based on 68 participating students who randomly received 500 mg of dried powdered rosemary aerial parts and placebo twice daily for one month [260]. Authors proved that rosemary can be used to boost prospective and retrospective memory, reduce anxiety and depression, and improve sleep quality [260]. A very recent study investigated the effect of rosemary tea consumption on the plasma levels of anxiety and depression biomarkers in twenty-two healthy volunteers aged between 20 and 50 years old [261]. The tea was prepared from 5 g of dried rosemary in 100 mL boiled water, and the main polyphenols were found to be rosmarinic acid, caffeic acid derivatives, luteolin-3′-O-(2″-O-acetyl)-b-D-glucuronide, luteolin-3-O-glucuronide, rosmarinic acid-3-O-glucoside, nepitrin, syringic acid, feruloylnepitrin, luteolin-7-O-rutinoside, caffeic acid, vanillic acid, and luteolin. The tea was administered once a day for ten days, and results indicated the anxiolytic and/or antidepressant effects of rosemary tea consumption since it increases the level of the most reliable depression biomarker, including brain-derived neurotrophic factor and TNF-a [261]. Although further studies are needed to better understand the mechanism of action of rosemary extract as sedative-hypnotic, previous work suggested that the inhibition of T-type calcium channels

(TTCCs) might contribute to the neuroprotective, sleep-promoting, and anxiolytic effects of *R. officinalis* [146].

3.14. Tilia platyphyllos Scop.

Broad-leaved linden (or bigleaf linden) (*Tilia platyphyllos* Scop.) is a large deciduous tree native to Europe and southwestern Asia. Its leaves are round-ovate, with acuminate tips, serrate margins, cordate bases, and pubescent below. Its flowers fragrant, pale yellow, and arranged in pendant cymose clusters. In Italy, besides its sedative use, this species is used to treat coughs, sore throats, and bronchitis, and as febrifuge [33,43,78].

A detailed phytochemical profile of *Tilia platyphyllos* Scop inflorescences revealed the presence of flavonoids, mainly quercetin glycosides (rutin, hyperosid, quercitrin, isoquercitrin, quercetin-3,7-di-O-rhamnoside, quercetin-rhamno-xyloside, and quercetin-3-O-gluco-7-O-rhamnoside) and kaempferol glycosides (astragalin, tilirosid, kaempferol-3-O-gluco-7-O-rhamnoside, and kaempferol-3,7-di-O-rhamnoside) [262]. High content of oligomeric and polymeric procyanidins, mainly composed of catechin and epicatechin building blocks such as prodelphinidin C and procyanidin B4, have been identified [262,263]. Essential oils from flowers, bracts, and leaves of *T. platyohyllos* were analyzed by GC-MS and compared to those obtained from *T. rubra* DC. and *T. arqentea* Desf. [264]. The oils are characterized by a high percentage of hydrocarbons (tricosane, heneicosane, pentacosane, and nonacosane), aliphatic acids (hexadecanoic acid, tetradecanoic acid, and nonanoic acid), and terpenes (camphor, linalool, carvacrol, anethole, pulegone, menthol, citronellol, geraniol, carvone, 1,8 cineole, b-ionone, terpinen-4-ol, and geranyl acetone) [264]. Very recently, novel piperidine alkaloids (named tiliamines A and B, and their acetylated derivatives tilacetines A and B) and 3,4-dihydro-2H-pyrrole alkaloids (named tiliines A and B) were detected in *T. cordata* and *T. platyphyllos* flowers [265].

According to HMPC, *T. platyphyllos* Scop., along with *T. cordata* Miller and *T. x vulgaris* Heyne, are traditional herbal medicinal products used for the relief of mild symptoms of mental stress, administered as herbal tea in boiling water or as tincture (not recommended for children) [266]. However, so far there have been no scientific studies on the hypnotic-sedative property of *T. platyphyllos* extract, although many studies have been carried out on the sedative and anxiolytic effects of other Tilia genera, in particular, *T. americana*, *T. tomentosa,* and *T. europea* [148–150,267–271]. An in-vitro study investigated the interaction of *Tilia europeae* L. aqueous extract with $GABA_A$ receptors in rat brain [150]. Data suggested that the extract of *T. europeae* contains GABA and probably other benzodiazepine-like substances that displace the [^{3}H] flunitrazepam binding and counteract the expected GABA-induced increase in [^{3}H] flunitrazepam binding [150]. Similarly, the action of *T. tomentosa* as anxiolytic and sedative in in vitro hippocampal neurons has been reported, and data suggested that *T. tomentosa* extract binds to both $GABA_A$ and BDZ receptor sites [149]. Furthermore, another study reported that both the methanol extract and a flavonoid mixture of *T. americana* (composed of quercetin, isoquercitrin, and rutin) produce anxiolytic and sedative-like effects through GABAergic and serotonergic systems [148]. Although the mechanism of action has been proposed only for other species of Tilia, this might be attributable also for *T. platyphyllos* Scop., due to similarity of their chemical profiles. However, more in-vitro and in-vivo studies are needed to shed a light on the use of *T. platyphyllos* for the treatment of GAD.

3.15. Valeriana officinalis L.

Valerian (*Valeriana officinalis* L.) is a perennial herbaceous plant native to Europe and Asia. The leaves are odd-pinnate, with each leaf having 7–10 pairs (plus terminal) of lance-shaped leaflets, which are aromatic when bruised. Its corolla has four white fused petals, and its stamens three. Its fruit is accompanied by a plumy pappus. In traditional phytotherapy, valerian is also used to treat cramps, tachycardia, headache, colitis, toothache, and hypertension [43,78,272].

Over 150 chemical constituents have been identified in valerian extract, and many of them are physiologically active, such as alkaloids, terpenes, free amino acids, organic acids, valepotriates, and flavones [273]. The main alkaloids (0.01–0.05% of root dry weight) found in valerian's root are actinidine, chatinine, valerianine, valerine, alpha-methyl pyrryl ketone, and naphthyridin methyl ketone [274,275]. Terpenes and organic acids represent 0.2–2.8% of root dry weight, and they are mainly composed of valeric, isovaleric, valerenic, isovalerenic, and acetoxyvalerenic acids; bornyl acetate; bornyl isovalerenate; 1-pinene; 1-comphene; 1-borneol; terpineol; valeranone; and cryptofauronol [276]. Other important active compounds are valepotriates (iridoid molecules), which are exclusively found in valerian extracts [277]. However, in *V. officinalis,* valepotriates represent only 0.3–1.7% of roots and rhizome DW compared to *V. edulis,* in which they represent 8.0–12.0% DW, and compared to *V. kilimandschari,* in which they were found in roots, leaves, stems, and flowers at high amounts (5.2%, 5.9%, 3.2%, and 3.8%, respectively) [278]. The principal valepotriates are valtrate, isovaltrate, 7-desisovaleroyl-7-acetylvaltrate, 7-homovaltrate, didrovaltrate, and isovaleroxy-hydroxy-didrovaltrate [276].

Valerian is a mild sedative and sleep-promoting agent, often used as complementary or alternative medicine in the treatment of anxiety-induced sleep disturbance [279].

Constituents of *V. officinalis* roots, such as valepotriates and valerenic acid, activate GABAergic system and to a lesser extent the serotonergic system, which are both involved in sleep promotion and regulation [135,151,152]. In particular, valerenic acid is a specific allosteric modulator of $GABA_A$ receptors [280]. Benke, Barberis, Kopp, Altmann, Schubiger, Vogt, Rudolph and Mohler (2009) described specific binding sites on $GABA_A$ receptors with nM affinity for synthetic valerenic acid and valerenol, which then would largely account for the anxiolytic action of valerian extracts [153].

It was demonstrated, using the elevated plus maze method, that a significant reduction occurred in anxious behavior of rats when valerian-extract- (3 mL/kg) or valerenic-acid-(75 µg/kg) exposed subjects were compared to the ethanol control group (1 mL/kg) [281].

In a randomized, controlled trial conducted by Aliakbari and Rafieian (2018) on eighty patients, it was shown that *Valeriana officinalis* improves the quality of sleep in patient with chronic heart failure [154]. However, five meta-analysis reviews published in 2000, 2006, 2007, 2010, and 2020 revealed that the effect of *V. officinalis* in treating sleep problems and associated disorders might vary, and in some cases the outcomes do not support its use in treating insomnia [282–286]. Stevinson and Ernst (2000) analyzed nine randomized, placebo-controlled, double-blind trials measuring the effect of valerian on sleep in human participants [285]. Results were contradictory, and there was inconsistency in terms of patients, experimental design, and methodology among the trials. Another meta-analysis study included 16 randomized clinical trials on valerian monotherapy or in combination with other herbal medicines [282]. Data showed significant methodologic problems between trials, and the valerian doses, preparations, and length of treatment varied considerably. Nine studies out of sixteen did not have positive outcomes in regard to improvement of sleep quality. In another meta-analysis of 37 trials, authors found in most of studies no significant differences between valerian and placebo either in healthy individuals or in persons with general sleep disturbance or insomnia [286]. The meta-analysis of 18 randomized placebo-controlled trials published by [283] showed that *Valeriana* spp. interventions reduced sleep latency over placebo by only 0.70 min. The authors of [284] performed a meta-analysis on sixty studies to evaluate the effectiveness of *Valeriana* spp. (*V. officinalis* and *V. edulis*) to improve sleep quality and to reduce anxiety. Results produced inconsistent outcomes, most probably due to the quality of herbal extracts; therefore, authors suggest that it may be necessary to revise the quality control processes, including standardization methods and shelf life of valerian extracts [284].

4. Conclusions

The studies we included in this review demonstrate the established tradition in Italy of using wild plants as additional or alternative treatments to conventional medicine in

order to cure anxiety and insomnia. The role of ethnobotanical research is to avoid the loss of traditional knowledge concerning medicinal plant lore and, at the same time, provide a basis for developing new drugs from phytochemical and biochemical research. For the latter, it is crucial to investigate chemical and biological properties on a larger scale, including the toxicity evaluation of the plant extracts and phytochemicals. In addition, pre-clinical and clinical studies are needed to better clarify the mechanism of action of bioactive compounds and to confirm the potential of these alternative therapies.

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